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Pharmacological interventions for the prevention of acute postoperative pain in adults following brain surgery (Review)

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[Intervention Review]

Pharmacological interventions for the prevention of acute postoperative pain in adults following brain surgery

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ABSTRACT

Background

Pain following brain surgery can compromise recovery. Several pharmacological interventions have been used to prevent pain after craniotomy; however, there is currently a lack of evidence regarding which interventions are most effective.

Objectives

The objectives are to assess the effectiveness of pharmacological interventions for prevention of acute postoperative pain in adults undergoing brain surgery; compare them in terms of additional analgesic requirements, incidence of chronic headache, sedative effects, length of hospital stay and adverse events; and determine whether these characteristics are different for certain subgroups.

Search methods

We searched MEDLINE, Embase, CINAHL, CENTRAL, Web of Science and two trial registries together with reference checking and citation searching on 28th of November 2018.

Selection criteria

We included blinded and non-blinded, randomized controlled trials evaluating pharmacological interventions for the prevention of acute postoperative pain in adults undergoing neurosurgery, which had at least one validated pain score outcome measure.

Data collection and analysis

We used standard Cochrane methodological procedures. We calculated mean differences for the primary outcome of pain intensity; any pain scores reported on a 0 to 100 scale were converted to a 0 to 10 scale.

Main results

We included 42 completed studies (3548 participants) and identified one ongoing study.

Nonsteroidal anti-inflammatories (NSAIDs)

Nonsteroidal anti-inflammatories (NSAIDs) reduce pain up to 24 hours (0 to 6 hours, MD −1.16, 95% CI −1.57 to −0.76; 12 hours, MD −0.62, 95% CI −1.11 to −0.14; 24 hours, MD −0.66, 95% CI −1.18 to −0.13; 6 studies, 742 participants; all high-quality evidence). Results for other

outcomes were imprecise (additional analgesic requirements: MD 1.29 mg, 95% CI −5.0 to 2.46, 4 studies, 265 participants; nausea and vomiting RR 1.34, 95% CI 0.30 to 5.94, 2 studies, 345 participants; both low-quality evidence).

Dexmedetomidine reduces pain up to 12 hours (0 to 6 hours, MD −0.89, 95% CI −1.27 to −0.51, moderate-quality evidence; 12 hours, MD −0.81, 95% CI −1.21 to −0.42, low-quality evidence). It did not show efficacy at 24 hours (MD −0.08, 95% CI −0.32 to 0.16; 2 studies, 128 participants; low-quality evidence). Dexmedetomidine may decrease additional analgesic requirements (MD −21.36 mg, 95% CI −34.63 to −8.1 mg, 2 studies, 128 participants, low-quality evidence). Results for other outcomes were imprecise (nausea and vomiting RR −0.43, 95% CI 0.06 to 3.08, 3 studies, 261 participants; hypotension RR 0.5, 95% CI 0.05 to 5.28, 3 studies, 184 participants; both low-quality evidence).

Scalp blocks may reduce pain up to 48 hours (0 to 6 hours, MD −0.98, 95% CI −1.66 to −0.3, 10 studies, 414 participants; 12 hours, MD −0.95, 95% CI −1.53 to −0.37, 8 studies, 294 participants; 24 hours, MD −0.78, 95% CI −1.52 to −0.05, 9 studies, 433 participants, all low-quality evidence; 48 hours, MD −1.34, 95% CI −2.57 to −0.11, 4 studies, 135 participants, very low-quality evidence. When studies with high risk of bias were excluded, significance remained at 12 hours only. Scalp blocks may decrease additional analgesia requirements (SMD −1.11, 95% CI −1.97 to −0.25, 7 studies, 314 participants). Results for other outcomes were imprecise (nausea and vomiting RR 0.66, 95% CI 0.33 to 1.32, 4 studies, 165 participants, very low-quality evidence).

Scalp Infiltration may reduce pain postoperatively but efficacy was inconsistent, with a significant effect at 12 and 48 hours only (12 hours, MD −0.71, 95% CI −1.34 to −0.08, 7 studies, 309 participants, low-quality evidence; 48 hours, MD - 1.09, 95% CI -2.13 to - 0.06, 3 studies, 128 participants, moderate-quality evidence). No benefit was observed at other times (0 to 6 hours, MD −0.64, 95% CI −1.28 to −0.00, 9 studies, 475 participants, moderate-quality evidence; 24 hours, MD −0.39, 95% CI −1.06 to 0.27,6 studies, 260 participants, low-quality evidence. Scalp infiltration may reduce additional analgesia requirements MD −9.56 mg, 95% CI −15.64 to −3.49, 6 studies, 345 participants, very low-quality evidence). When studies with high risk of bias were excluded, scalp infiltration lost the pain benefit at 12 hours and effects on additional analgesia requirements, but retained the pain-reducing benefit at 48 hours (MD −0.56, 95% CI −1.20 to -0.32, 2 studies, 100 participants, very low-quality evidence). Results for other outcomes were imprecise (nausea and vomiting, RR 0.74, 95% CI 0.48 to 1.41, 4 studies, 318 participants, low-quality evidence).

Pregabalin or gabapentin may reduce pain up to 6 hours (2 studies, 202 participants), MD -1.15,95% CI −1.66 to −0.6, 2 studies, 202 participants, low-quality evidence). One study examined analgesic efficacy at 12 hours showing significant benefit. No analgesia efficacy was shown at later times (24 hours, MD -0.29, 95% CI -0.78 to -0.19; 48 hours, MD - 0.06, 95% CI -0.86 to 0.77, 2 studies, 202 participants, low-quality evidence). Additional analgesia requirements were not significantly less (MD −0.37 (95% CI −1.10 to 0.35, 3 studies, 234 participants, low-quality evidence). Risk of nausea and vomiting was significantly reduced (RR 0.51, 95% CI 0.29 to 0.89, 3 studies, 273 participants, low-quality evidence). Results for other outcomes were imprecise (additional analgesia requirements: MD −0.37, 95% CI −1.10 to 0.35, 3 studies, 234 participants, low-quality evidence).

Acetaminophen did not show analgesic benefit (0 to 6 hours, MD −0.35, 95% CI −1.00 to 0.30; 12 hours, MD −0.51, 95% CI −1.04 to 0.03, 3 studies, 332 participants, moderate-quality evidence; 24 hours, MD -0.34, 95% CI -1.20 to 0.52, 4 studies, 439 participants, high-quality evidence). Results for other outcomes remained imprecise (additional analgesia requirements, MD 0.07, 95% CI −0.86 to 0.99, 4 studies, 459 participants, high-quality evidence; length of hospitalizations, MD −3.71, 95% CI −14.12 to 6.7, 2 studies, 335 participants, moderate-quality evidence).

Authors' conclusions

There is high-quality evidence that NSAIDs reduce pain up to 24 hours postoperatively. The evidence for reductions in pain with dexmedetomidine, pregabalin or gabapentin, scalp blocks, and scalp infiltration is less certain and of very low to moderate quality. There is low-quality evidence that scalp blocks and dexmedetomidine may reduce additional analgesics requirements. There is low-quality evidence that gabapentin or pregabalin may decrease nausea and vomiting, with the caveat that the total number of events for this comparison was low.

PLAIN LANGUAGE SUMMARY

Preventing pain after brain surgery

The problem

There is increasing evidence that people who have undergone brain surgery experience significant pain. This pain can have serious consequences including raised blood pressure, agitation, prolonged recovery time and an increased risk of long-term headaches. Research studies have looked at different drugs in an attempt to reduce the risk of pain for these people. There is now more evidence about pain reduction options for adults undergoing brain surgery but there remains uncertainty as to which options work best.

The question

This review aimed to determine which drugs provide the best chance of reducing pain for adults undergoing brain surgery, by collecting and combining the results of studies that looked at pain-relieving drugs for this patient group. To provide an accurate answer to this

question, only studies conducted in accordance with an approved high standard were included. Studies published in different languages and countries were included in order to obtain as much information as possible.

In addition to determining which drugs were best at preventing or reducing pain after brain surgery, this review attempted to determine additional information such as how much additional pain-relieving treatment was required in addition to the treatment under study; whether participants' pain was adequately controlled or not; how drowsy the participants were; what side effects they experienced; and how long they needed to stay in intensive care and in hospital. This review also considered whether some treatments worked better when given before or after surgery or for people undergoing different approaches to brain surgery.

The results

A total of 43 eligible studies, (42 complete and one still in progress), were found. Of the 42 completed studies (3548 participants), 10 studied injections of local anaesthetic into the scalp, 12 studied injection of local anaesthetic around specific scalp nerves, 8 studied nonsteroidal anti-inflammatory drugs (NSAIDs), 4 studied dexmedetomidine, 4 studied acetaminophen aka paracetamol), 2 studied opioid drugs, 3 studied gabapentin or pregabalin (anti-seizure drugs that can also be used for pain relief) together with 1 study each of local anaesthetic injected into the veins, local anaesthetic injected into the jaw and the drug flupirtine.

Sufficient information was abstracted to calculate the overall pain-preventing effects of the following: local anaesthetic injections around the surgical wound, local anaesthetic injections around specific scalp nerves, NSAIDs, acetaminophen, dexmedetomidine and pregabalin or gabapentin. When only high-quality studies were examined: NSAIDs reduced pain up to 24 hours after surgery, dexmedetomidine and local anaesthetics injected around specific scalp nerves reduced pain in the first 12 hours after surgery, pregabalin or gabapentin reduced pain in the first 6 hours after surgery and local anaesthetic injections around the surgical wound significantly reduced pain 48 hours after surgery, but did not affect pain at earlier time points.

When the timing of injection of local anaesthetics was examined, local anaesthetics injected around specific scalp nerves provided better early pain relief (first 6 hours) when injected after surgery and better late pain relief (12 and 24 hours) when injected before surgery.

The following interventions were also found to reduce the need for additional pain-relieving drugs: local anaesthetics injected around specific scalp nerves and dexmedetomidine. Gabapentin or pregabalin was found to reduce the risk of nausea and vomiting after surgery.

Acetaminophen was not found to prevent pain after brain surgery or reduce the need for additional pain-relieving drugs.

Insufficient evidence was found to determine whether any of these drugs made the participants more or less drowsy, affected how long they needed to stay in intensive care or whether different drugs worked better for adults undergoing different approaches to brain surgery.

The overall quality of the evidence that contributed to the results of this review was assessed and judged to be 'high' for pain-reducing effects of NSAIDs, 'moderate' to 'low' for pain-reducing effects of dexmedetomidine, acetaminophen, pregabalin and gabapentin and local anaesthetics injected around specific scalp nerves and ' low' to ' very low' for pain-reducing effects of local anaesthetic injections around the surgical wound, additional pain relief requirements and risk of nausea and vomiting after surgery .

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Nonsteroidal anti-inflammatory drugs (NSAIDs) compared with control or placebo medications for prevention of pain in adults undergoing brain surgery

NSAIDs compared with control or placebo medications for prevention of pain in adults undergoing brain surgery

Patient or population: adults undergoing brain surgery

Settings: hospitals, countries: Australia, Hungary, Turkey and India

Intervention: NSAIDs

Comparison: control or placebo medications

Outcomes	Absolute Effects (95% CI)		Relative Effect, Risk Ratio (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed Risk	Corresponding Risk				
Acute postoperative pain **0 to 6 hours** (Score 0 to 10, VAS or NRS Scale)	The mean pain scores in the control group ranged from 1.5 to 4.4	Mean difference in pain intensity was 1.11 points lower in those who received NSAIDS when compared with those who received control or placebo medications (1.64 points lower to 0.58 points lower)	Not applicable	742 (6)	⊕⊕⊕⊕ **high**	
Acute postoperative pain at 12 hours (Score 0 to 10, VAS or NRS Scale)	The mean pain scores in the control group ranged from 1.5 to 4.4	Mean difference in pain intensity was 0.74 points lower in those who received NSAIDS when compared with those who received control or placebo medications (1.22 points lower to 0.26 points lower)	Not applicable	742 (6)	⊕⊕⊕⊕ **high**	
Acute postoperative pain at 24 hours (Score 0 to 10, VAS or NRS Scale)	The mean pain scores in the control group ranged from 1.16 to 5.6	Mean difference in pain intensity was 0.70 points lower in those who received NSAIDS when compared with those who received control or placebo medications (1.26 points lower to 0.14 points lower)	Not applicable	742 (6)	⊕⊕⊕⊕ **high**	
Acute postoperative pain at 48 hours (Score 0 to 10, VAS or NRS Scale)	The mean pain score in the control group was 1.0	The mean pain score in the treatment group was 1.0, the same as the mean pain score in the control group so there was no mean difference in pain intensity between the two groups	Not applicable	149 (1)	⊕⊖⊖⊖ very **low**[1]	Only 1 study reported this outcome

Additional analgesia requirements 0 to 24 hours (Milligrams)	Mean analgesia requirement in the control group ranged from 16 to 28.4 mg	Mean difference in additional analgesia requirements in the first 24 hours after surgery 1.07 mg less in those who received NSAIDS when compared with those who received control or placebo medications (4.88 mg less to 2.72 mg more)	Not applicable	265 (4)	⊕⊕⊖⊖ **low** [2]	
Analgesic Success	27 percent of patients in the control group had no worse than mild pain at 12 hours	48 percent of patients in the treatment group had no worse than mild pain at 12 hours	Not applicable	Not applicable	⊕⊖⊖⊖ very **low**[1]	Only 1 study reported this outcome
Sedation	Not calculated	Not calculated	Not applicable	Not applicable	Not applicable	No eligible study addressed this outcome
Chronic Headache	Not calculated	Not calculated	Not applicable	Not applicable	Not applicable	No eligible study addressed this outcome
Length of critical care stay (hours)	Not calculated	Not calculated	Not applicable	Not applicable	Not applicable	No eligible study addressed this outcome
Length of hospital stay (hours)	Not calculated	Not calculated	Not applicable	Not applicable	Not applicable	No eligible study addressed this outcome
Adverse event **nausea and vomiting** (0 to 24 hours)	17 per 1000	23 per 1000	Risk of nausea and vomiting was 1.34 times greater in those who received NSAIDS when compared with those who received control or placebo medications (0.30 to 5.94)	345 (2)	⊕⊕⊖ **low** [3]	

CI: confidence interval; **RR:** risk ratio; **VAS:** visual analogue scale; **NRS:** numerical rating scale; **NSAIDS:** nonsteroidal anti-inflammatory drugs

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

1. The evidence was downgraded three levels due to the fact that all the evidence came from one small study.
2. The evidence was downgraded two levels due to a small pooled sample size and imprecision as the 95% CI for the effect estimate was wide and included the possibility of either no benefit or increased analgesic requirements in those who received NSAIDs.
3. The evidence was downgraded two levels due to imprecision of results i.e. a low number of total events and a wide 95% confidence that included the possibility of less, equal or greater risk of nausea and vomiting in those who received NSAIDS when compared with those who received control or placebo medication

Summary of findings 2. Dexmedetomidine compared with control or placebo medications for prevention of pain in adults undergoing brain surgery

Dexmedetomidine compared with control or placebo medications for prevention of pain in adults undergoing brain surgery

Patient or population: adults undergoing brain surgery

Settings: hospitals, countries: China, USA

Intervention: dexmedetomidine

Comparison: control or placebo medications

Outcomes	Absolute Effects (95% CI)		Relative effect, Risk Ratio (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed Risk	Corresponding Risk				
Acute postoperative pain **0 to 6 hours** (Score 0 to 10, VAS or NRS Scale)	The mean pain scores in the control group ranged from 3.0 to 3.6	Mean difference in pain intensity was 0.89 points lower in those who received dexmedetomidine when compared with those who received control or placebo medication (1.27 points lower to 0.51 points lower)	Not applicable	128 (2)	⊕⊕⊕⊖ **moderate**[1]	
Acute postoperative pain at 12 hours (Score 0 to 10, VAS or NRS Scale)	The mean pain scores in the control group ranged from 3.0 to 3.1	Mean difference in pain intensity was 0.81 points lower in those who received dexmedetomidine when compared with those who received control or placebo	Not applicable	128 (2)	⊕⊕⊖⊖ **low** [2]	

		medication (1.21 points lower to 0.42 points lower)				
Acute postoperative pain at 24 hours (Score 0 to 10, VAS or NRS Scale)	The mean pain scores in the control group ranged from 2.0 to 2.7	Mean difference in pain intensity was 0.08 points lower in those who received dexmedetomidine when compared with those who received control or placebo medication (0.32 points lower to 0.16 points greater)	Not applicable	128 (2)	⊕⊕⊖⊖ **low** [3]	
Acute postoperative pain at 48 hours	Not calculated	Not calculated	Not applicable	Not applicable	Not applicable	No study reported this outcome
Additional analgesia requirements 0 to 24 hours (Milligrams)	Mean analgesia requirement in the control group ranged from 52 to 170 mg	Mean difference in additional analgesia requirements in the first 24 hours after surgery 21.36 mg less in those who received dexmedetomidine when compared with those who received control or placebo medication (34 mg less to 8.1 mg less)	Not applicable	128 (2)	⊕⊕⊖⊖ **low** [2]	
Analgesic Success	Not calculated	Not calculated	Not applicable	Not applicable	Not applicable	No eligible study addressed this outcome
Sedation	Mean sedation score at 24 hours was 2.2 in the control group	Mean sedation score at 24 hours was 2.4 in the treatment group	Not applicable	52 (1)	⊕⊖⊖⊖ very **low** [4]	Only one eligible study addressed this outcome
Chronic Headache	Not calculated	Not calculated	Not applicable	Not applicable	Not applicable	No eligible study addressed this outcome
Length of hospital stay (hours)	Not calculated	Not calculated	Not applicable	Not applicable	Not applicable	No eligible study addressed this outcome
Adverse event nausea and vomiting	152 per 1000	67 per 1000	Risk of nausea and vomiting was 0.43 times less in those who received dexmedetomidine	261 (3)	⊕⊕⊖⊖ **low** [5]	

(0 to 24 hours)			when compared with those who received control or placebo medication (0.06 to 3.08)		
Adverse event **hypotension** (0 to 24 hours)	22 per 1000	11 per 1000	Risk of hypotension was 0.5 times less in those who received dexmedetomidine when compared with those who received control or placebo medication (0.05 to 5.28	184 (3)	⊕⊕⊖⊖ **low**[6]

CI: Confidence interval; **RR:** Risk Ratio; **VAS:** Visual Analogue Scale; **NRS:** Numerical Rating Scale

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

1. The evidence was downgraded by one level due to imprecision due a small pooled sample size i.e. 128 participants.
2. The evidence was downgraded by two levels due to imprecision due to a small pooled sample size and inconsistency of results in the form of unexplained important heterogeneity.
3. The evidence was downgraded two levels due to imprecision due to a small pooled sample size and a wide 95% CI which included the possibility of either no effect or greater pain intensity in those who received dexmedetomidine.
4. The evidence was downgraded three levels as it came from one small study.
5. The evidence was downgraded by two levels due imprecision due to a small total number of events and a wide 95% CI which included the possibility of less, equal or greater risk of nausea and vomiting in those who received dexmedetomidine when compared with those who received control or placebo medication.
6. The evidence was downgraded two levels due to imprecision due to a small total number of events and a wide 95% CI which included the possibility of less, equal or greater risk of hypotension in those who received dexmedetomidine when compared with those who received control or placebo medication.

Summary of findings 3. Pregabalin or Gabapentin compared with control or placebo medications for prevention of pain in adults undergoing brain surgery

0.9 Pregabalin or gabapentin compared with control or placebo medications for prevention of pain in adults undergoing brain surgery

Patient or population: adults undergoing brain surgery

Settings: hospitals, countries: Israel, India

Intervention: gabapentin or pregabalin

Comparison: control or placebo medication

Outcomes	Absolute Effects (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed Risk	Corresponding Risk				
Acute postoperative Pain **0 to 6 hours**	The mean pain scores in the control group ranged from 2.9 to 3.9	Mean difference in pain intensity was 1.15 points lower in those who received gabapentin or pregabalin when compared to those who received control or placebo medication (1.66 points lower to 0.6 points lower) *	Not applicable	202 (2)	⊕⊕⊖⊖ **low [1]**	* These results were measured as standardized mean differences and re-expressed as mean differences
Acute postoperative pain at 12 hours	The mean pain score in the control group was 2.26	Mean pain score in those who received pregabalin was 1.5 which was 1.1 times lower than the mean score in the control group	Not calculated	100 (1)	⊕⊖⊖⊖ very **low[2]**	Only 1 study reported this outcome
Acute postoperative pain at 24 hours	The mean pain scores in the control group ranged from 1.47 to 3.0	Mean difference in pain intensity was 0.29 points lower in those who received gabapentin or pregabalin when compared to those who received control or placebo medication (0.78 points lower to 0.19 points lower) *	Not applicable	202 (2)	⊕⊕⊖⊖ **low [1]**	* These results were measured as standardized mean differences and re-expressed as mean differences
Acute postoperative pain at 48 hours	The mean pain scores in the control group ranged from 1.13 to 2.0	Mean difference in pain intensity was 0.06 points lower in those who received gabapentin or pregabalin when compared to those who received control or placebo medication (0.86 points lower to 0.77 points higher) *	Not applicable	202 (2)	⊕⊕⊖⊖ **low [1]**	* These results were measured as standardized mean differences and re-expressed as mean differences
Additional analgesia requirements at 0 to 24 hours	Mean additional analgesia requirement in the control group ranged from 0.34 to 9.40 mg with agents used being fentanyl and morphine	Standardized mean difference in additional analgesia requirements in the first 24 hours after surgery 0.37 less in those who received gabapentin or pregabalin when compared with those who received control or placebo medications (1.10 less to 0.35 more)	Not applicable	234 (3)	⊕⊕⊖⊖ **low [1]**	Using Cohens rule of thumb: an effect size of 0.37 represents a small, non-significant effect size
Analgesic Success	Not calculated	Not calculated	Not applicable	Not applicable	Not applicable	No eligible study addressed this outcome

Sedation	Not calculated	Not calculated	Not applicable	Not applicable	Not applicable	No eligible study addressed this outcome
Chronic Headache	Mean pain score at 3 months of 1.51 in the control group	Mean pain score at 3 months of 1.28 in the control group	Not applicable	54 [1]	⊕⊖⊖⊖ very **low**[2]	Only one study addressed this outcome
Length of critical care stay (hours)	Not calculated	Not calculated	Not applicable	Not applicable	Not applicable	No eligible study addressed this outcome
Length of hospital stay (hours)	Mean length of stay in hospital in the control group was 8.3 days	Mean length of stay in hospital in those who received pregabalin group was 7.9 days	Not applicable	100 (1)	⊕⊖⊖⊖ very **low**[2]	Only one study reported this outcome
Adverse event **nausea and vomiting** (0 to 24 hours)	379 per 1000	203 per 1000	Risk of nausea and vomiting was 0.51 times less in those who received gabapentin or pregabalin when compared with those who received control or placebo medications (0.29 to 0.89)	273 (3)	⊕⊕⊖⊖ **low**[3]	

CI: Confidence interval; **RR:** Risk Ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

1. The evidence was downgraded by two levels due to small pooled sample size and possible indirectness of effect as the two drugs studied (pregabalin and gabapentin) differ somewhat in their pharmacological properties.
2. The evidence was downgraded three levels due to the fact that all the evidence came from one small study.
3. The evidence was downgraded by two levels due to imprecision as the number of total events were small and indirectness as the two drugs differ somewhat in their pharmacological properties.

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Summary of findings 4. Acetaminophen compared with control or placebo medications for prevention of pain in adults undergoing brain surgery

Acetaminophen compared with control or placebo medications for prevention of pain in adults undergoing brain surgery

Patient or population: adults undergoing brain surgery

Settings: hospitals, countries: Turkey, India, United States of America

Intervention: acetaminophen

Comparison: control or placebo medication

Outcomes	Absolute Effects (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed Risk	Corresponding Risk				
Acute postoperative pain **0 to 6 hours**	The mean pain scores in the control group ranged from 1.5 to 5,6	Mean difference in pain intensity was 0.35 points lower in those who received acetaminophen when compared to those who received control or placebo medication (1.00 points lower to 0.30 points higher)	Not applicable	332 (3)	⊕⊕⊕⊖ **moderate**[1]	
Acute postoperative pain at 12 hours	The mean pain scores in the control group ranged from 2.0 to 5.8	Mean difference in pain intensity was 0.51 points lower in those who received acetaminophen when compared to those who received control or placebo medication (1.04 points lower to 0.03 points higher)	Not applicable	332 (3)	⊕⊕⊕⊖ **moderate** [1]	
Acute postoperative pain at 24 hours	The mean pain scores in the control group ranged from 1.16 to 5.4	Mean difference in pain intensity was 0.34 points lower in those who received acetaminophen when compared with those who received control or placebo medication (1.20 points lower to 0.52 points higher)	Not applicable	459 (4)	⊕⊕⊕⊕ **high**	
Acute postoperative pain at 48 hours	The mean pain scores in the control group was 5.5	The mean pain scores in the control group was 5.5, with no significant difference between the groups	Not applicable	202 (1)	⊕⊖⊖⊖ very **low**[2]	Only 1 study reported this outcome
Additional analgesia requirements 0 to 24 hours	Mean additional analgesia requirement in the control group ranged from 1.75 mg to 85.5 mg	Mean difference in additional analgesia requirements in the first 24 hours after surgery 0.07 mg less in those who received acetaminophen when compared with those who re-	Not applicable	459 (4)	⊕⊕⊕⊕ **high**	

(milligrams)		ceived control or placebo medication (0.86 mg less to 0.99 mg more)				
Analgesic Success	Not calculated	Not calculated	Not applicable	Not applicable	Not applicable	No eligible study addressed this outcome
Sedation score at 24 hours (Richmond Agitation Sedation scale)	Mean sedation score in the control group was zero	Mean sedation score in the acetaminophen group was zero	Not applicable	131 (1)	⊕⊖⊖⊖ very **low**[2]	Only 1 study reported this outcome
Chronic headache	Not calculated	Not calculated	Not applicable	Not applicable	Not applicable	No eligible study addressed this outcome
Length of critical care stay (hours)	The median length of stay in the control group was 28 hours	The median length of stay in the acetaminophen group was 26 hours	Not applicable	131 (1)	⊕⊖⊖⊖ very **low**[2]	Only 1 study reported this outcome
Length of hospital stay (hours)	Mean length of stay in hospital in the control group ranged from 75.5 to 137 days	Mean difference in length of stay in hospital of 3.71 hours less in those who received acetaminophen when compared with those who received control or placebo medication (14.12 hours less to 6.7 hours more)	Not applicable	335 (2)	⊕⊕⊕⊖ **moderate**[1]	
Adverse events	Not calculated	Not calculated	Not calculated	Not applicable	Not applicable	No two studies reported comparable adverse events

CI: Confidence interval; **RR:** Risk Ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

1. The evidence was downgraded by one level due to a small pooled sample size.
2. The evidence was downgraded three levels due to the fact that all the evidence came from one small study.

Summary of findings 5. Scalp infiltration compared with control or placebo intervention for prevention of pain in adults undergoing brain surgery

Scalp infiltration compared with control or placebo intervention for prevention of pain in adults undergoing brain surgery

Patient or population: adults undergoing brain surgery

Settings: hospitals, countries: France, India, USA, Saudi Arabia, Greece, Thailand and China

Intervention: scalp Infiltration

Comparison: control or placebo Intervention

Outcomes	Absolute Effect (95% CI)		Relative Effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Asuumed Risk	Corresponding Risk				
Acute postoperative pain **0 to 6 hours** (Score 0 to 10, VAS or NRS Scale)	The mean pain scores in the control group ranged from 2.0 to 5.4	Mean difference in pain intensity was 0.64 points lower in those who received scalp infiltration when compared with those who received control or placebo interventions (1.28 points lower to 0.00 points lower)	Not applicable	475 (9)	⊕⊕⊕⊖ **moderate** [1]	
Acute postoperative pain at 12 hours (Score 0 to 10, VAS or NRS Scale)	The mean pain scores in the control group ranged from 1.6 to 5.0	Mean difference in pain intensity was 0.71 points lower in those who received scalp infiltration when compared with those who received control or placebo interventions (1.34 points lower to 0.08 points lower)	Not applicable	309 (7)	⊕⊕⊖⊖ **low** [2]	
Acute postoperative pain at 24 hours (Score 0 to 10, VAS or NRS Scale)	The mean pain scores in the control group ranged from 1.1 to 5.0	Mean difference in pain intensity was 0.39 points lower in those who received scalp infiltration when compared with those who received control or placebo interventions (1.06 points lower to 0.27 points higher)	Not applicable	260 (6)	⊕⊕⊕⊖ **moderate** [1]	
Acute postoperative pain at 48 hours (score 0 to 10, VAS or NRS scale)	The mean pain scores in the control group ranged from 2.3 to 3.8	Mean difference in pain intensity was 1.09 points lower in those who received scalp infiltration when compared with those who received control or placebo interventions (2.13 points lower to 0.06 points lower)	Not applicable	128 (3)	⊕⊕⊕⊖ **moderate** [3]	

Additional analgesia requirements 0 to 24 hours (milligrams)	Mean additional analgesia requirement in the control group ranged from 13 mg to 58 mg	Mean difference in additional analgesia requirements in the first 24 hours after surgery 9.56 mg less in those who received scalp infiltration when compared with those who received control or placebo interventions (15.64 mg less to 3.49 mg less)	Not applicable	345 (6)	⊕⊖⊖⊖ **very low** [4]	
Analgesic Success	8 percent of patients in the control group were pain-free at 6 hours	4 percent of patients in the treatment group were pain-free at 6 hours	Not applicable	49 (1)	⊕⊖⊖⊖ **very low** [5]	Only one study addressed this outcome
Sedation	Not calculated	Not calculated	Not applicable	Not applicable	Not applicable	No eligible study addressed this outcome
Chronic headache	Not calculated	Not calculated	Not applicable	Not applicable	Not applicable	No eligible study addressed this outcome
Length of critical care stay (hours)	Not calculated	Not calculated	Not calculated	Not applicable	Not applicable	No eligible study addressed this outcome
Length of hospital stay (hours)	Not calculated	Not calculated	Not calculated	Not applicable	Not applicable	No eligible study addressed this outcome
Adverse event nausea and vomiting (0 to 24 hours)	236 per 1000	174 per 1000	Risk of nausea and vomiting was 0.74 times less in those who received scalp infiltration when compared with those who received control or placebo in-	318 (4)	⊕⊕⊖⊖ **low** [6]	

		terventions (0.48 to 1.41)

CI: Confidence interval; **RR:** Risk Ratio; **VAS:** Visual Analogue Scale; **NRS:** Numerical Rating Scale

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

1. Consistency, precision, directness was rated high. The evidence was downgraded by one level due to inconsistency in the form of unexplained important heterogeneity.
2. The evidence was downgraded by two levels due to imprecision due to a small pooled sample size and loss of significance of results on sensitivity analysis.
3. The evidence was downgraded by one level due to a small pooled sample size.
4. The evidence was downgraded three levels due to imprecision due to a small pooled sample size, inconsistency in the form of unexplained important heterogeneity and loss of significance of results on sensitivity analysis.
5. The evidence was downgraded by three levels as the results came from one small study.
6. The evidence was downgraded two levels level due to imprecision i.e. a small number of total events and a wide 95% confidence that included the possibility of either no effect or increased nausea and vomiting in the intervention group.

Summary of findings 6. Scalp block compared with control or placebo intervention for prevention of pain in adults undergoing brain surgery

Scalp block compared with control or placebo intervention for prevention of pain in adults undergoing brain surgery

Patient or population: adults undergoing brain surgery

Settings: hospitals, countries: USA, India, Korea, Canada, Thailand, China and Spain

Intervention: scalp block

Comparison: control or placebo intervention

Outcomes	Absolute Effect (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed Risk	Corresponding Risk				
Acute postoperative pain **0 to 6 hours** (Score 0 to 10, VAS or NRS Scale)	The mean pain scores in the control group ranged from 2.0 to 5.7	Mean difference in pain intensity was 0.98 points lower in those who received scalp block when compared with those who received control or placebo interventions (1.66 points lower to 0.39 points lower)	Not applicable	414 (10)	⊕⊕⊖⊖ **low** [1]	

Acute postoperative pain at 12 hours (Score 0 to 10, VAS or NRS Scale)	The mean pain scores in the control group ranged from 2.3 to 5.0	Mean difference in pain intensity was 0.95 points lower in those who received scalp block when compared with those who received control or placebo interventions (1.53 points lower to 0.37 points lower)	Not applicable	294 (8)	⊕⊕⊖⊖ **low** [2]	
Acute postoperative pain at 24 hours (Score 0 to 10, VAS or NRS Scale)	The mean pain scores in the control group ranged from 1.7 to 4.2	Mean difference in pain intensity was 0.78 points lower in those who received scalp block when compared with those who received control or placebo interventions (1.52 points lower to 0.05 points lower)	Not applicable	433 (9)	⊕⊕⊖⊖ **low** [1]	
Acute postoperative pain at 48 hours (Score 0 to 10, VAS or NRS Scale)	The mean pain scores in the control group ranged from 1.6 to 4.0	Mean difference in pain intensity was 1.34 points lower in those who received scalp block when compared with those who received control or placebo interventions (2.57 points lower to 0.11 points lower)	Not applicable	135 (4)	⊕⊖⊖⊖ **very low** [3]	
Additional analgesia requirements 0 to 24 hours	The mean additional analgesia requirement in the control group was 0.3 mg to 15 mg with agents used being fentanyl and morphine	Standardized mean difference in additional analgesia requirements in the first 24 hours after surgery 1.11 less in those who received scalp block when compared with those who received control or placebo interventions (1.97 less to 0.25 less)	Not applicable	314 (7)	⊕⊕⊖⊖ **low** [2]	Using Cohens rule of thumb: an effect size of 1.11 represents a large effect size
Analgesic success	10 percent of patients in the control group were pain-free at 12 hours after surgery	15 percent of patients who had scalp blocks were pain-free at 12 hours after surgery	Not applicable	40 (1)	⊕⊕⊖⊖ **very low** [4]	Only one eligible study addressed this outcome
Sedation	Not calculated	Not calculated	Not applicable	Not applicable	Not applicable	No eligible study addressed this outcome
Chronic headache	Not calculated	Not calculated	Not applicable	Not applicable	Not applicable	No study addressed pain at 3 months
Length of critical care stay (hours)	Not calculated	Not calculated	Not calculated	Not applicable	Not applicable	No eligible study ad-

						dressed this outcome
Length of hospital stay (hours)	Not calculated	Not calculated	Not calculated	Not applicable	Not applicable	No eligible study addressed this outcome
Adverse event **nausea and vomiting** (0 to 24 hours)	514 per 1000	308 per 1000	Risk of nausea and vomiting was 0.66 times less in those who received scalp block when compared with those who received control or placebo interventions (0.33 to 1.32)	165 (4)	⊕⊕⊖⊖ **very low** [4]	

CI: Confidence interval; **RR:** Risk Ratio; **VAS:** Visual Analogue Scale; **NRS:** Numerical Rating Scale

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

1. The evidence was downgraded two levels due to inconsistency in the form of unexplained important heterogeneity and failure to retain significance on sensitivity analysis.
2. The evidence was downgraded two levels due to imprecision due to a small pooled sample size and inconsistency in the form of unexplained important heterogeneity.
3. The evidence was downgraded three levels as there was imprecision due to a sample pooled sample size, inconsistency in the form of unexplained important heterogeneity and failure to retain significance on sensitivity analysis and small pooled sample size.
4. The evidence was downgraded three levels as it came from one small study.
5. The evidence was downgraded three levels as there was inconsistency in the form of unexplained important heterogeneity and imprecision due to a small number of total events and a wide 95% CI which included the possibility of either no benefit or increased nausea and vomiting in the intervention group.

BACKGROUND

Description of the condition

Craniotomy (brain surgery) was previously considered less painful than other surgical procedures because the brain tissue lacks pain receptors and the relative immobility of the soft tissues of the head protects against pain due to tension and traction in the postoperative period (Dunbar 1999). Concern regarding the side effects of pain medication in this population, that is, impaired postoperative neurological assessment with opioids and increased risk of bleeding with nonsteroidal medication, also contributed to limited use of analgesics in those undergoing brain surgery.

Evidence now suggests that these patients experience significant postoperative pain. A prospective study of 256 participants undergoing elective craniotomy showed that 87% of patients reported pain in the first 24 hours after surgery with 55% reporting moderate to severe pain (Mordhorst 2009). Other similar studies showed high rates of postoperative pain in this population (De Oliveria Riberio 2013; Hansen 2013). Aside from the obvious patient discomfort, pain can delay recovery and increase length of hospital stay. It can also increase the risk of postoperative complications including hypertension, agitation and vomiting (Molnar 2014). These complications can be particularly problematic in neurosurgical populations as they can mimic, obscure and increase the risk of other neurosurgical complications such as raised intracranial pressure (pressure in the brain) and intracranial haemorrhage (bleeding into the brain).

Acute postoperative pain may also play a role in central sensitization and up-regulation of pain receptors, factors implicated in the development of chronic post-craniotomy headache. While the incidence of chronic headache varies with type of brain surgery, it can be as high as 23% to 34% at three months and 12% to 16% at one year after surgery (Harner 1993; Schaller 2003). For those who develop it, it is a debilitating and difficult-to-treat condition that can significantly impair quality of life and social functioning (Imayev 2013; Molnar 2014). Much of the data about post-craniotomy headache relates more to its epidemiology and treatment once established, than to the efficacy of interventions aimed at its prevention, making it difficult to elucidate the benefit of any particular analgesic strategy in reducing the incidence of chronic post-craniotomy headache. However, the fact that chronic post-craniotomy headache becomes evident as failure of resolution of postoperative headache rather than the de novo appearance of a new condition, supports a common etiologic pathway with acute post-craniotomy pain and hence a reasonable likelihood that interventions aimed at preventing acute headache may also be beneficial in reducing the risk of chronic headache (De Gray 2005). Evidence from wider surgical populations suggests that local and regional anaesthetic techniques rather than conventional analgesics may help reduce the incidence of chronic postoperative pain: whether this is true for patients undergoing brain surgery remains unknown as none of the studies included in that systematic review were conducted in this population (Weinstein 2018).

Description of the intervention

Several pharmacological interventions are currently available for the management of pain following craniotomy, although evidence suggests that opioid derivatives and nonsteroidal anti-inflammatory drugs (NSAIDs) are the most commonly used (De Oliveria Riberio 2013; Kotak 2009). In line with increasing awareness of the problem of post-craniotomy pain, there has been a sharp increase in the number of studies of interventions aimed at its prevention (Hwang 2015; Morad 2009; Williams 2011). A wide variety of strategies have been evaluated including various NSAIDs, scalp infiltration, regional scalp block and novel agents (Hwang 2015; Morad 2009; Williams 2011; Yadav 2014). While these interventions work through different mechanisms, the timing of their administration may be a factor in determining both the incidence and intensity of pain experienced after surgery.

The concept of 'pre-emptive analgesia'' was first proposed in the 1980s (Wall 1988), and centres on the theory that analgesia given before pain becomes established may ameliorate the mechanisms involved in the development of both acute and chronic postoperative pain. Pre-emptive, as opposed to rescue analgesia, may be particularly relevant to those undergoing brain surgery for the following reasons: the very nature of the surgery itself can impede the patient's ability to report pain, making it more difficult to achieve effective postoperative analgesia in this population (Hansen 2013; Kotak 2009); the need for accurate postoperative neurological assessment limits the analgesic options suitable for the relief of pain in the postoperative period in these patients (Gottschalk 2009; Molnar 2014); non-sedating analgesic options including scalp blocks and local anaesthetic infiltration may be technically easier and more tolerable for the patient when performed before the end of the operation and hence before pain is reported; systemic consequences of established pain including hypertension, vomiting and haemorrhage can be particularly undesirable in those who have had recent brain surgery and so prevention of acute pain in the postoperative period may help to reduce the risk of these problems (Basali 2000; Molnar 2014). Finally, prevention of acute pain after brain surgery might help to decrease the risk of chronic headache (De Gray 2005).

How the intervention might work

Pharmacological interventions used in the management of craniotomy pain act through different mechanisms.

Opioids

Opioids mediate their analgesic effects through central opioid receptors, blocking neurotransmitter (chemical) release and nociceptive (pain-transmitting) pathways (Martin 1983). While they are currently a mainstay of analgesia for craniotomy, their popularity is based more on tradition and familiarity than on evidence. A recent survey showed that 70% of neurosurgical units used codeine as the first-line opioid in the management of craniotomy pain (Kotak 2009). While codeine is not commonly used for postoperative pain in other forms of surgery, its popularity in neurosurgery centres on its minimal sedative properties in comparison to stronger opioids like morphine (Molnar 2014). Concerns about morphine's sedating properties and consequent impediment of neurological assessment have limited its use. Tramadol is generally used as a third- or fourth-line agent but has some important side effects including nausea, vomiting and reduction in the seizure threshold (Kotak 2009).

Acetaminophen

Acetaminophen inhibits cyclo-oxygenase and prostaglandin production. It is rarely used as a sole agent for the prevention

of post-craniotomy pain as it is generally not adequate alone (Molnar 2014). However, it has been shown to reduce morphine requirements by 20% in the postoperative period (Remy 2005).

Nonsteroidal anti-inflammatory drugs (NSAIDs)

Nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit cyclo-oxygenase and consequently prostaglandin production with resultant analgesic and anti-inflammatory effects (Higgs 1980). While NSAIDs have been shown to be effective for the relief of headache, their usefulness has been limited by their antiplatelet (platelet-inhibiting) action with concerns about an increased risk of intracerebral bleeding in neurosurgical patients (Imayev 2013). This led to an increasing interest in selective cyclo-oxygenase inhibitors, which are free of antiplatelet effects (Williams 2011).

Local anaesthetics-scalp infiltration and scalp blocks

Local anaesthetics produce a localized reversible block of pain fibres preventing propagation of the pain impulse (Becker 2012), and have been shown to provide effective analgesia through several different routes of administration and across a wide range of surgical populations (Tayeb 2017; Weinstein 2018), although their efficacy is yet not proven when given by more novel routes of administration (i.e. intravenous) (Weibel 2018). Common routes of administration of local anaesthetics in patients undergoing brain surgery are scalp infiltration and scalp block. Scalp infiltration addresses no specific sensory pathways, while regional scalp block involves infiltration of local anaesthetic at well-defined anatomical sites targeting the major sensory innervation (nerve) pathways of the scalp. Early results of regional scalp block are promising but inconclusive (Gilfoyle 2012).

Flupirtine

Flupirtine is a novel, centrally-acting analgesic that has N-methyl-D-aspartate receptor antagonist (opposing) properties. It has not yet been studied extensively in patients undergoing brain surgery but at least one study reported it to be as effective as diclofenac sodium for postoperative pain reduction in this population (Yadav 2014).

Dexmedetomidine

This is a highly selective alpha 2-agonist with no central respiratory depressive effects, anti-delirium and analgesic properties making it an increasingly popular choice for sedation of patients at high risk of respiratory compromise or delirium and for anaesthesia for awake brain surgery. While it has very few side effects, it is known to increase the risk of bradycardia (abnormally slow heart rate) and hypotension (abnormally low blood pressure) (Dunn 2016). Recently its analgesic effects in those undergoing brain surgery are being explored (Peng 2015; Song 2016).

Pregabalin or Gabapentin

These anti-convulsant medications inhibit central neurotransmitter release, reducing pain perception. They have found a role both in the management of acute postoperative pain and relief of chronic pain. There are concerns, however, that they may be associated with sedating effects and delayed extubation (removal of breathing tube) (Haldar 2015).

Why it is important to do this review

Postoperative pain relief is frequently suboptimal in this population (Hansen 2013). This is likely due to a number of factors. Firstly, the need for prompt and accurate neurologic assessment following brain surgery means healthcare providers are reluctant to use sedating analgesics which may impede that assessment. Secondly, despite the availability of a wide variety of analgesic options, the lack of robust evidence of the superiority of one over another contributes to a reliance on traditional and perhaps less efficacious forms of pain relief. Thirdly, there is still a lack of appreciation among healthcare providers of the frequency and severity of post-craniotomy pain (Ribeiro 2012). Finally, many of these patients may not be able to express their pain verbally and require a more proactive approach to pain evaluation and treatment than other surgical populations.

Given the challenges in achieving adequate postoperative pain relief and the particularly undesirable systemic consequences of pain in this population, studies have been increasingly focusing on the effectiveness of analgesia administered either before emergence from anaesthesia or before pain has become established (Hwang 2015; Williams 2011; Yadav 2014). Such an approach is supported by evidence of the role of pre-emptive analgesia in postoperative pain prevention in other surgical populations (Inanoglu 2007), and in children undergoing craniotomy in whom scheduled analgesia achieved significantly lower acute postoperative pain scores than 'as required' analgesia (Smyth 2004). However, pre-emptive analgesia carries its own risks, including exposure to analgesia-related adverse events and over-treatment of those who may otherwise have developed mild pain at worst.

Combining data from individual studies and addressing patient-relevant outcomes is key to establishing the relative efficacy and risk/benefit balance of pain prevention measures (McQuay 1995). While reviews of the effectiveness of some of these pharmacological interventions exist for neurosurgical patients, they are either confined to single interventions or studies which were published in English and for which the full-text papers were readily available (Gilfoyle 2012; Hansen 2011). As yet, there is no comprehensive review that attempts to quantify and synthesize the effectiveness and safety profiles of all the evaluated interventions. Without this process, we do not know which pharmacological interventions are most effective and how additional analgesic requirements and adverse effects compare between interventions. This review attempts to determine the current overall state of knowledge in this regard.

There is an increasing realization that patients consider good pain control to be the achievement of 'no worse than mild pain' (Moore 2013). This outcome measure has yet to be widely adopted in trials of analgesia for prevention of pain following brain surgery, however, where the data permits, this review will attempt to address this outcome, using the same definitions of 'no worse than mild pain' used in a recent Cochrane review of oral morphine for the relief of cancer pain (Wiffen 2016).

OBJECTIVES

The objectives of this review are to assess the effectiveness of pharmacological interventions for prevention of acute postoperative pain in adults undergoing brain surgery; compare

them in terms of additional analgesic requirements, incidence of chronic headache, sedative effects, length of hospital stay and adverse events; and determine whether these characteristics are different for certain subgroups

METHODS

Criteria for considering studies for this review

Types of studies

We included blinded and non-blinded, controlled, randomized trials evaluating the effectiveness of any pharmacological drug or technique for the prevention of acute postoperative pain in adults undergoing neurosurgery, which have at least one validated pain score as an outcome measure.

We excluded review articles, observational studies, case reports, case series, non-randomized studies and studies that had no control groups. We also excluded studies that investigated the use of agents with analgesic potential for non-analgesic purposes. The rationale for this decision was based on a high likelihood of important differences — in inclusion and exclusion criteria, dosages, timing, ancillary analgesic usage and attributable side effects — between studies that investigated these agents for their analgesic efficacy and studies that investigated them for their non-analgesic effects.

Types of participants

We included adults (defined as more than or equal to 18 years of age at the time of study enrolment), undergoing either supratentorial or infratentorial craniotomy or craniectomy either as an elective or emergency procedure. We excluded those undergoing neurosurgical procedures that did not involve accessing the brain such as spinal operations.

Types of interventions

We included any pharmacological drug or pharmacological technique evaluated against a control for the prevention of acute postoperative pain in adults undergoing neurosurgery. We excluded interventions that were specifically given for the relief of established acute pain after brain surgery as opposed to those given before pain had become established.

Types of outcome measures

Primary outcomes

1. Mean differences in validated measures of acute postoperative pain intensity measured at the following times:
   a. anytime in the first six hours postoperatively;
   b. 12 hours postoperatively
   c. 24 hours postoperatively;
   d. 48 hours postoperatively

Secondary outcomes

1. Analgesic success as measured by achievement of 'no worse than mild pain' with 'no worse then mild pain' being defined as a score of ≤ 30/100 mm on a visual analogue scale or ≤ 3/10 on a numerical rating scale.
2. Mean difference in additional analgesia requirement at the same time points.
3. Mean difference in validated measures of sedation at the same time points.
4. Mean difference in incidence of chronic post-craniotomy headache with chronic post-craniotomy headache being defined as headache persisting three months or more after surgery.
5. Mean difference in length of critical care unit stay.
6. Mean difference in length of hospital stay.
7. Rate of the adverse events in the perioperative period (intraoperatively until four days postoperatively) including, but not confined to, the following: respiratory depression, hypercapnia, elevated intracranial pressure, hypotension, nausea, vomiting, gastrointestinal bleeding, haematoma formation, nerve injury, local anaesthetic toxicity, local or systemic infection and death from any cause.

To capture all reported adverse events, we did not predefine each event but instead provided information in the review regarding how included studies defined these events and how those definitions varied in their wording and application between studies.

Our primary and secondary outcomes differed somewhat from those stated in the original protocol (Galvin 2015). Those differences and the reasons for those differences are detailed in the section entitled Differences between protocol and review.

Search methods for identification of studies

The search strategy used in this review was based on both Joanna Briggs Institute 2011, and the Institute of Medicine of the National Academics, and involved three steps. An initial search of MEDLINE was developed by a librarian (Amanda Ross, Bracken Health Sciences Library, Queens University, Kingston), in collaboration with the lead author (IMG) and sent for feedback from all authors. We included any changes suggested by the authors along with a text-word and index term analysis to better refine the search and ensure a more complete recall. In this second stage, we conducted a search, using all identified keywords and index terms, in MEDLINE, Embase, CINAHL, CENTRAL, and Web of Science's Citation Index. We completed the initial search in the week of 12 September 2016. We conducted an updated search using the same search strategy on 24 October 2017 and a further updated search on 28 November 2018.

In the third search stage, we searched the reference lists of all identified reports and articles for additional studies. We placed no language limits on the search. The initial MeSH terms we used were: craniotomy, decompressive craniectomy, trephining, brain neoplasms, narcotics, analgesics, local anaesthetics, local anaesthetics, aminopyridines, flupirtine, acetaminophen, morphine, tramadol, codeine, paracetamol, postoperative pain, pain, acute pain, headache, and slit ventricle syndrome. We also used the Controlled Clinical Trials hedge outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Our full strategy can be found in Appendix 1. We then uploaded the results to Covidence, systematic review software, for review by the authors as to relevance and whether a priori criteria were met.

Electronic searches

We identified RCTs through literature searching with systematic and sensitive search strategies as outlined in Chapter 6.4 of the *Cochrane Handbook of Systematic Reviews of Interventions* (Higgins

2011). We did not apply restrictions to language or publication status.

We searched the following databases for relevant trials:

1. Cochrane Central Register of Controlled Trials (CENTRAL; Issue 9 2017);
2. MEDLINE (Ovid SP, 1966 to 28 November 2018);
3. Embase (Ovid SP, 1988 to 28 November 2018);
4. CINAHL (Ovid SP,1982 to 28 November2018);
5. Web of Science (1990 to 28 November 2018).

We developed a subject-specific search strategy in MEDLINE and used that as the basis for the search strategies in the other databases listed. Where appropriate, the search strategy was expanded with search terms for identifying RCTs. All search strategies can be found in Appendix 1.

Searching other resources

We scanned the following trials registries for ongoing and unpublished trials (28 November 2018).

1. The World Health Organization International Clinical Trials Registry Platform (WHOICTRP) (http://apps.who.int/trialsearch/).
2. ClinicalTrials.gov.

We scanned the reference lists and citations of included trials and any relevant systematic reviews identified for further references to additional trials.

We searched conference abstracts to identify unpublished or ongoing studies.

When necessary, we contacted trial authors for additional information.

Data collection and analysis

Selection of studies

We uploaded the search results to Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia (Covidence), from where two authors (IMG, RL), independently screened the citations. This was done in two stages.

In the first stage, the two review authors (IMG, RL) independently examined the abstracts of all studies arising from the literature search and voted 'Yes', 'No', or 'Maybe' using the Covidence blinded voting system. We excluded studies which were clearly ineligible (e.g. in vitro studies, animal studies, studies in children, case reports) at this stage.

In the second stage, the same two review authors (IMG and RL) independently examined the full-text version of the studies selected in the first stage, and, where applicable, completed the study selection form for each study to determine its eligibility (Appendix 2). We resolved any conflicts identified by Covidence by discussion between both authors. At this stage in the screening process, any studies found by both authors (IMG and RL) to be eligible for inclusion, proceeded to the data extraction stage as described in the next section (Data extraction and management), while those found to be ineligible for inclusion were listed in the Characteristics of excluded studies table.

Data extraction and management

Two review authors (IMG and RL) independently extracted data from the studies selected above using a comprehensive data extraction form (Appendix 3). We resolved any conflicts by discussion between both authors.

Assessment of risk of bias in included studies

Two authors (IMG, RL), independently assessed the risk of bias in included studies using Cochrane's tool for assessing risk of bias as described in the *Cochrane Handbook of Systematic Reviews for Interventions* (Higgins 2011). We resolved any discrepancies by discussion. For each included primary study, we assessed bias in the following seven domains:

1. random sequence generation;
2. allocation concealment;
3. performance bias;
4. detection bias;
5. attrition bias;
6. reporting bias; and
7. other bias.

For each domain, we determined the risk of bias as low, unclear or high, according to methods used to ensure the minimization of each form of bias. In general, we categorized the level of risk of bias as follows. See 'Sensitivity analysis' for further information on the approach used for making overall risk of bias judgements.

1. Low risk: where information was available that clearly demonstrated that efforts were made to ensure minimal bias in that domain and the described methods were robust enough to have a high likelihood of being effective.
2. Unclear risk: when the information available was insufficient to be confident that the method used to minimize bias was robust enough to be effective.
3. High risk: when the study did not report any method to minimize bias in that domain.

We choose to include unblinded, single-blinded and double-blinded studies in this review to provide a comprehensive summary of the overall available evidence. In doing so, we accepted a greater level of overall 'performance' bias than if we had included only double-blinded studies.

Measures of treatment effect

We measured pooled estimates of effect for primary and secondary outcomes, providing these were reported at the relevant time points by two or more studies of any eligible intervention.

Where no more than one study of an eligible intervention reported an outcome of interest, we did not calculate a pooled estimate of effect.

For continuous outcomes, we calculated the mean differences (MDs), and standardized mean differences (SMDs), where studies used the same and different scales of measurement, respectively. For the primary outcome of pain intensity, we rescaled any pain scores that were reported on a 0 to 100 scale to a 0 to 10

scale and for studies where standardized mean differences were used to calculate pain outcomes, we re-expressed these as mean differences using the methods described in section 12 of the *Cochrane Handbook* (Higgins 2011). For the secondary outcome of additional analgesia requirement, we calculated MDs for analyses in which all included studies used additional analgesics solely in either milligram or microgram amounts, and we calculated SMDs for analyses including studies which used additional analgesics in both milligram and microgram amounts. Where standardized mean differences were used to measure additional analgesia requirements, we used Cohen's rule of thumb to provide an indication of effect size, where a standard mean difference of 0.2 to 0.49 represents a small effect size, 0.5 to 0.79, a moderate effect size and 0.8 or greater, a large effect size. (Higgins 2011).

For dichotomous outcomes, we calculated the risk ratios (RRs).

We presented all pooled estimates of effect with their respective P values and 95% confidence intervals (CIs).

Unit of analysis issues

Due to the high possibility of carry-over effects, we did not include cross-over studies in this review. For studies with more than one treatment arm, we included only the relevant arms, i.e. arms where a pharmacological analgesic intervention was assessed for its efficacy in terms of prevention of acute postoperative pain after brain surgery. Where more than one treatment arm in any one trial was eligible for inclusion in the same meta-analysis, then we divided the control group equally between the two arms, to avoid double counting. For example, for a trial evaluating 'Drug A' versus placebo versus 'Drug B' versus placebo for the prevention of acute postoperative pain after craniotomy, we divided the placebo control group equally between the group assigned to 'Drug A' and the group assigned to 'Drug B' for the meta-analysis of each outcome for which both groups were eligible.

Dealing with missing data

We handled missing data as follows:

Missing pain intensity outcome data

For missing pain scores, we planned to impute missing data using the last observation carried forward method. No missing pain scores were identified (among studies eligible for inclusion in the meta-analysis for this outcome), so we did not have to employ this technique. However, since the vast majority of studies reporting pain intensity outcomes, reported these at discrete time points as opposed to over time periods, we amended the way in which we analysed and reported the primary outcome 'pain intensity', to reflect the time points reported in the included studies. Further details of this amendment and its rationale are provided in the sections Types of outcome measures and Differences between protocol and review. The timing of 'pain intensity' measurements were not reported by two studies (which would otherwise have been eligible for inclusion in the meta-analysis for this outcome) (Rahimi 2006; Rahimi 2010). We excluded these two studies from the main comparison for this outcome as it was impossible to determine with any certainty when these measurements were made. No absolute values for pain scores were reported by another study (Ryan 2005), and so we excluded this study from the analysis as there were no data to base any imputed value on.

Missing additional analgesia consumption data

We excluded one study, which would otherwise have been eligible for inclusion in the meta-analysis for this outcome, as the time period over which the outcome was measured was not reported (Rahimi 2006).

Missing sedation scores

For missing sedation scores, we planned to impute missing data using the last observation carried forward method. Sedation scores were not widely measured in the included studies and, where absolute values were not reported, the authors did report that no significant difference was observed, therefore no imputation was required.

Missing adverse event data

For missing adverse event outcome data, we planned to analyse the data based on a worst and best case scenario (and present both analyses in the review), assuming that all and none of those whose data were missing developed the adverse event in question. No missing results for reported adverse events were identified. Some studies did not report absolute values for certain adverse events but reported that no significant difference was observed (Batoz 2009; Dilmen 2016; Jones 2009; Rigamonti 2013). These studies were not included in the calculation of the pooled estimate of effect for this outcome.

Missing standard deviations

Where standard deviations (SDs) were missing, they were calculated, where possible, from CIs and standard errors (SEs) as described in the *Cochrane Handbook of Systematic Reviews for Interventions* (Higgins 2011). Where P values only were reported, standard deviations were calculated using the method described in the *Cochrane Handbook of Systematic Reviews for Interventions* section 7.7.3.3 (Higgins 2011). Where none of the above data were available, standard deviations were imputed using the mean of SDs for the same continuous outcome measure, measured at the same time point for studies of the same intervention in this review.

Assessment of heterogeneity

We assessed clinical heterogeneity by comparing the following factors between studies: participants, setting, surgical techniques, intervention types, timing and dosages, outcomes assessed and ancillary treatments.

We assessed methodological heterogeneity by comparing the risk of bias in the included studies.

We assessed statistical heterogeneity by visual inspection of forest plots, the Chi ^{2} test, and calculation of the I^2 statistic. We considered a P value < 0.1 in the Chi ^{2} test and an I^2 statistic > 50% as indicative of significant statistical heterogeneity.

Assessment of reporting biases

To determine the presence or absence of reporting bias, we planned to examine funnel plots for each meta-analysis that included 10 or more studies to determine the degree of symmetry. However, no meta-analysis in this review included 10 or more studies. As the majority of studies eligible for inclusion in this review were small studies (typically including fewer than 100 participants), we cannot be confident that publication bias was insignificant. However, by

conducting a robust and comprehensive search for all eligible studies and by applying no language restrictions, we hope to have reduced the likelihood of not including studies whose results were not reported in the mainstream literature.

Data synthesis

We calculated pooled estimates of effect for the above outcomes and subgroups if all of the following conditions were met:

1. absence of substantial clinical or methodological heterogeneity between included studies;
2. inclusion of at least two eligible studies deemed to have either a low or unclear risk of bias;
3. absence of substantial publication bias.

Where significant statistical heterogeneity was present, we presented the pooled estimate of effect with subsequent discussion as to the likely impact of heterogeneity on the accuracy and quality of the estimate in the 'quality of evidence' section (Quality of the evidence).

We performed meta-analysis using Cochrane statistical software, (Review Manager 2014). We used a random-effects model to best represent the differences in treatment effects across studies (Results).

Subgroup analysis and investigation of heterogeneity

Where sufficient numbers of eligible studies (two or more) reporting relevant data were identified, we planned to perform the following subgroup analyses to determine the efficacy and safety of each evaluated intervention.

1. Participants undergoing infratentorial versus supratentorial craniotomy. The basis for this subgroup analysis was that the infratentorial approach is associated with higher postoperative pain scores (De Gray 2005).
2. Participants in whom the intervention was administered pre or intraoperatively versus postoperatively based on the rationale that early administration of analgesia may have greater preventative potential.
3. Participants who received inhalational versus total intravenous anaesthesia based on current controversy regarding the benefit of one form of anaesthesia over the other with some evidence showing a higher intensity of post-craniotomy pain in those who received inhalation anaesthesia (Mordhorst 2009), while other evidence suggesting no significant difference (Prabhakar 2016).
4. Participants who received steroids in the perioperative period based on evidence showing that the intraoperative administration of steroids reduced pain intensity after craniotomy (Mordhorst 2009).

Sensitivity analysis

Where appropriate, we performed the following sensitivity analyses:

1. Analysis excluding trials with a high risk of bias. A study was judged to have an overall high risk of bias if it had a high risk of bias in four or more of the seven domains of bias or a high risk of bias in three or more of the seven domains of bias with an unclear risk of bias in one or more domain. The rationale for choosing these criteria were based on author agreement that high or high and unclear risks of bias across multiple domains raised doubt about the overall methodological rigour of that study and was likely a reasonable way to determine an overall high risk of bias in a consistent manner for studies in a review of interventions that were given at different times relative to surgery and anaesthesia and by different routes of administration.
2. Analysis excluding studies with missing data considered to be missing for reasons likely related to either the intervention or outcomes studied.

'Summary of findings' table and GRADE

We constructed a 'Summary of findings' table for each evaluated pharmacological intervention:

1. NSAIDs (Summary of findings for the main comparison);
2. dexmedetomidine (Summary of findings 2);
3. gabapentin or pregabalin (Summary of findings 3);
4. acetaminophen (Summary of findings 4);
5. scalp infiltration (Summary of findings 5); and
6. scalp blocks (Summary of findings 6);

using GRADEpro GDT. For each comparison, we used the principles of the GRADE system to assess the quality of the body of evidence associated with the following outcomes (Guyatt 2008):

1. acute postoperative pain intensity during the first six hours;
2. acute postoperative pain intensity at 12 hours;
3. acute postoperative pain intensity at 24 hours;
4. acute postoperative pain intensity at 48 hours;
5. additional analgesia requirement from 0 to 24 hours postoperatively;
6. adverse events.

We took the following factors into account when evaluating the quality of the evidence: risk of bias among studies contributing to each outcome measure, inconsistency, imprecision, indirectness of results and the likelihood of publication bias.

We used the criteria below to downgrade evidence for a particular outcome:

1. no serious limitation in any of the above factors: evidence was not downgraded;
2. serious limitation in any of the above factors: evidence was downgraded by one point;
3. serious limitation in two or more of the above factors or very serious limitation in any one of the above factors: evidence was downgraded by two points.

One review author (IG) initially applied the GRADE system and then discussed the quality of evidence ratings for each outcome with a second author (RL). We reached final decisions on the ratings through discussion and consensus. It is important to note that the choice of outcomes included in our 'Summary of Findings' tables differed from those stated in our original protocol (Galvin 2015). The differences and the rationale for these differences are explained in the Differences between protocol and review.

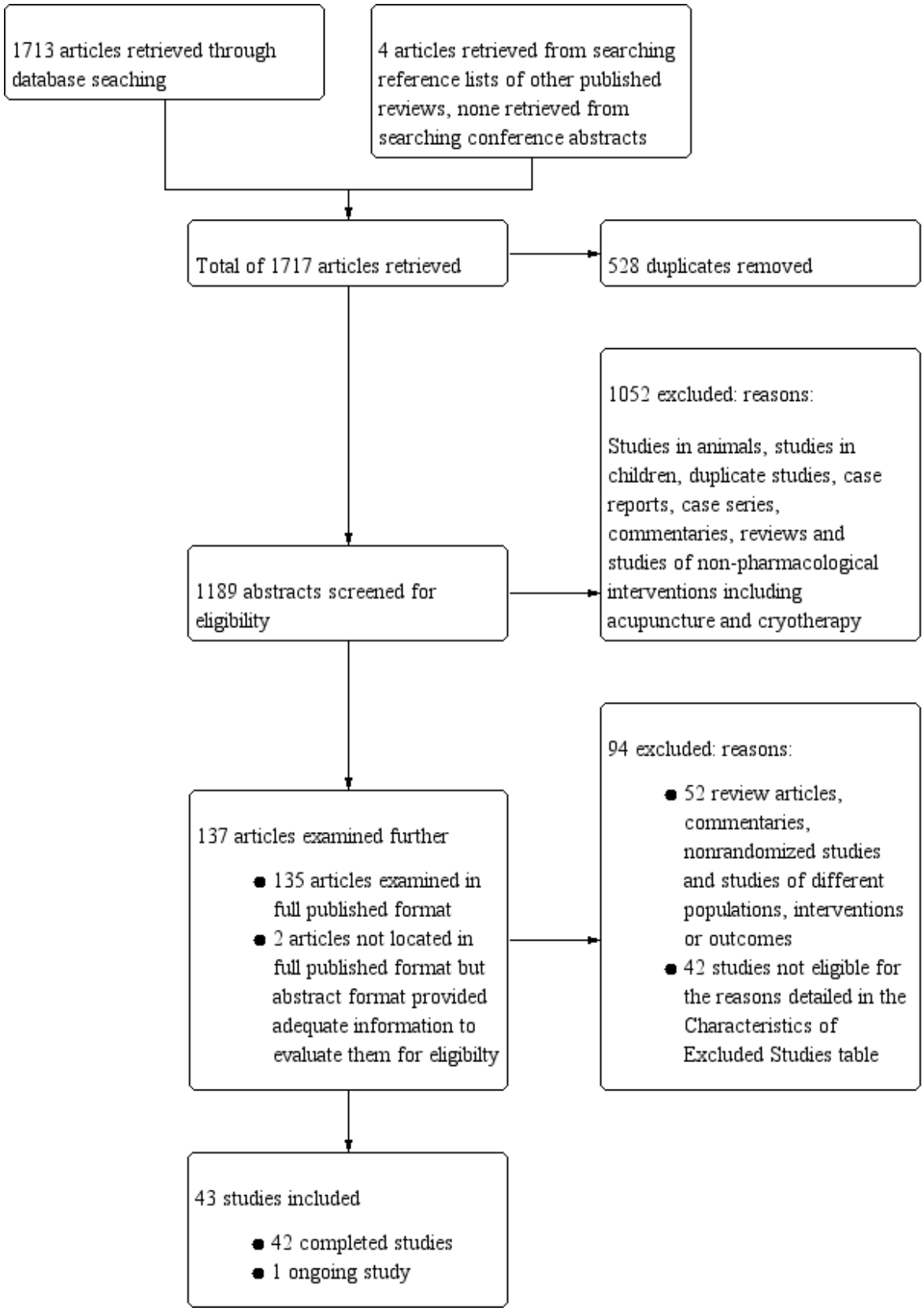
RESULTS

Description of studies

Results of the search

The initial search conducted on 12 September 2016 returned 1149 articles and another 4 articles were identified from searching the reference list of other published reviews. An updated search conducted on 24 October 2017 identified a further 62 articles and a further updated search on 28 November 2018 identified 502 articles making a total of 1717 articles. The identification and selection of eligible studies are described in the next paragraph and detailed in Figure 1.

Figure 1. Search results



Of the1717 articles retrieved: 528 were found to be duplicates, leaving 1189 articles, of which 1052 were excluded on initial screening. Excluded studies at this stage included animal studies, studies conducted in those < 18 years of age, case reports, commentaries, narrative reviews, duplicate reports etc.

Of the remaining 137 articles: 135 were available in full-text format and 2 were only available in abstract format but there was still enough information in the abstract to evaluate them for eligibility. We excluded 94 of these 137 articles, 52 having been found to be either review articles, commentaries or non-randomized studies and 42 having been found to be studies which were ineligible for the reasons detailed in the Characteristics of excluded studies table. Of the 43 eligible studies we found, 42 of these were completed studies and 1 was an ongoing study (see: Characteristics of ongoing studies).

Included studies

A summary of the included studies is provided in the characteristics of included studies table (Characteristics of included studies).

Participants

All participants were adults (≥ 18 years of age), ASA classification I to ASA classification III who were undergoing elective craniotomy. Not all studies provided details of the indication for surgery but among those that did, the commonest indication was for resection of intracranial tumour. The vast majority of completed studies included only participants who were undergoing supratentorial craniotomy, 14 studies either did not specify surgical approach or included participants undergoing either supra or infratentorial craniotomy (Batoz 2009; Bekker 2008; Can 2017; Choi 2009; Cokay 2013; Greenberg 2017; Jones 2009; Misra 2013; Molnár 2015; Rahimi 2010; Ryan 2005; Shimony 2016; Sivakumar 2018; Yardav 2014), and three studies included only those undergoing infratentorial surgery (Akcil 2017; Jellish 2006; Zeng 2019). Common exclusion criteria included an inability to understand the pain scoring system, decreased level of consciousness, known or suspected allergies to study medications, previous scalp incisions and pre-existing long-term opioid usage or chronic pain.

Interventions

Scalp infiltration

Ten studies examined the efficacy of infiltration versus saline placebo or no intervention in preventing pain after craniotomy (Akcil 2017; Batoz 2009; Biswaz 2003; Bloomfield 1998; El-Dawlatly 2007; Kiskira 2006; Law-Koune 2005; Saringcarinkul 2015; Zhang 2003; Zhou 2016). The local anaesthetics used to infiltrate around the surgical wound site included: bupivacaine 0.5% (Akcil 2017), bupivacaine 0.25% (Biswaz 2003; El-Dawlatly 2007), bupivacaine 0.25% with added epinephrine (Bloomfield 1998; Kiskira 2006), bupivacaine 0.375% with added epinephrine (Law-Koune 2005), bupivacaine 0.5% with added epinephrine (Saringcarinkul 2015), ropivacaine 0.75% (Batoz 2009; Zhang 2003), and ropivacaine 0.5% (Zhou 2016).

In four studies, scalp infiltration was performed before surgical incision (Akcil 2017; Biswaz 2003; El-Dawlatly 2007; Zhou 2016). In four, it was performed at the end of surgery before skin closure (Batoz 2009; Law-Koune 2005; Saringcarinkul 2015; Zhang 2003), and in two, it was performed pre- and again post-incision (Bloomfield 1998; Kiskira 2006).

Scalp block

Twelve included studies examined scalp block versus either saline placebo or no intervention (Akcil 2017; Bala 2006; Can 2017; Choi 2009; Cokay 2013; Ganzoni 2008; Hernández Palazón 2007; Hwang 2015; Nguygen 2001; Rigamonti 2013; Tucinda 2010; Zhang 2003). Local anaesthetics used included bupivacaine 0.25% with added epinephrine (Hernández Palazón 2007; Tucinda 2010), bupivacaine 0.5% without added epinephrine (Akcil 2017; Can 2017; Cokay 2013; Rigamonti 2013), and with added epinephrine (Bala 2006; Tucinda 2010), bupivacaine 0.75% with added epinephrine (Hwang 2015), ropivacaine 0.5% (Ganzoni 2008), ropivacaine 0.75% (Choi 2009; Nguygen 2001; Zhang 2003), and levo-bupivacaine 0.5% (Can 2017) .

Ten studies provided details of the nerves blocked and in these studies the nerves targeted were the supraorbital, supratrochlear, zygomaticotemporal, auriculotemporal, postauricular branches of the greater auricular nerves and the greater, lesser and third occipital nerves (Akcil 2017; Bala 2006; Can 2017; Choi 2009; Ganzoni 2008; Hernández Palazón 2007; Hwang 2015; Nguygen 2001; Rigamonti 2013; Tucinda 2010). Two studies did not provide specific details of the nerves blocked (Cokay 2013; Zhang 2003).

In six studies, scalp block was performed before surgical incision (Akcil 2017; Can 2017; Cokay 2013; Ganzoni 2008; Rigamonti 2013; Tucinda 2010), and in six, it was performed at the end of surgery (Bala 2006; Choi 2009; Hernández Palazón 2007; Hwang 2015; Nguygen 2001; Zhang 2003).

Pregabalin or Gabapentin

Two studies addressed gabapentin (Misra 2013: Zeng 2019), and one addressed pregabalin (Shimony 2016). The dosages of gabapentin used were 600 mg given the night before and again on the morning of surgery (Zeng 2019), and 600 mg given two hours prior to surgery (Misra 2013). The dosage of pregabalin was 150 mg given the evening prior to surgery, 90 minutes before surgery, two hours after surgery and every 12 hours thereafter until 72 hours postoperatively (Shimony 2016).

NSAIDs

Eight studies addressed the role of NSAIDs in this population (Dilmen 2016; Jones 2009; Molnár 2015; Rahimi 2006; Ryan 2005; Shepherd 2018; Willams 2011; Yardav 2014).

The agents studied included:

1. parecoxib 40 mg versus saline placebo, given orally at dural closure (Jones 2009; Willams 2011). In the study by Williams and colleagues, all participants in both the intervention and control group received scalp infiltration as well (Willams 2011);
2. rofecoxib 50 mg versus placebo, given orally one hour before surgery (Ryan 2005);
3. COX 2 Inhibitor 25 mg orally twice daily started postoperatively. No placebo medication was used in the control group (Rahimi 2006);
4. diclofenac 50 mg orally versus placebo, every eight hours from the second postoperative day, until 48 hours postoperatively (Yardav 2014);
5. diclofenac 100 mg orally one hour before surgery. No placebo medication was used in the control group (Molnár 2015);

6. dexketoprofen 50 mg intravenously versus placebo, given at skin closure and every 8 hours thereafter (Dilmen 2016);
7. metamizole 1 gram intravenously versus placebo, given at skin closure and every six hours thereafter (Dilmen 2016);
8. ibuprofen 800 mg intravenously every 8 hours with the first dose given intraoperatively (Shepherd 2018).

Opioids

Two studies addressed the role of opioids in this context (Jellish 2006; Rahimi 2010). Jellish and colleagues looked at the role of morphine patient-controlled analgesia with or without added ondansetron versus placebo in reducing the incidence of pain in those undergoing skull base surgery (Jellish 2006). Rahimi and colleagues addressed the role of tramadol versus no tramadol in reducing the intensity of pain after elective craniotomy for vascular lesions, tumour resection or epilepsy surgery (Rahimi 2010).

Dexmedetomidine

Four studies looked at dexmedetomidine versus placebo (Bekker 2008; Peng 2015; Song 2016; Yun 2016). Intravenous infusion dosages ranged from 0.5 to 0.8 mcg/kg/hr with one study including a 1 mcg/kg bolus loading dose (Bekker 2008). The timing and duration of infusions varied from after induction of anaesthesia until the start of skin closure (Bekker 2008; Peng 2015; Song 2016), to a brief infusion for 10 minutes, one hour before surgery ended (Bekker 2008).

Acetaminophen

Four studies addressed acetaminophen versus placebo (Artime 2018; Dilmen 2016; Greenberg 2017; Sivakumar 2018). The dosage used in all studies was one gram given intravenously. In Artime 2018, the first dose was given before skin incision. In the other three studies, it was given after surgery (Dilmen 2016; Greenberg 2017; Sivakumar 2018). In Sivakumar 2018, it was repeated every 8 hours postoperatively for a total of 24 hours. In Dilmen 2016, it was repeated every six hours postoperatively. In Greenberg 2017, it was repeated every 6 hours until 18 hours after surgery, and in Artime 2018, it was repeated every 6 hours postoperatively for a total of 24 hours.

Lidocaine

Only one study addressed intravenous lidocaine infusion versus placebo as a potential agent in the prevention of postoperative pain in this population (Peng 2016). A bolus of 1.5 mg/kg was given after induction of anaesthesia, followed by an infusion of 2 mcg/kg/hr.

Flupirtine

One study addressed this medication versus placebo (Yardav 2014). The dose used was 100 mg and it was given orally every eight hours from the second postoperative day until 48 hours postoperatively.

Sphenopalatine ganglion blocks

There was one eligible study of the role of sphenopalatine ganglion blockade versus placebo in reducing postoperative pain in those undergoing endoscopic transnasal resection of pituitary tumours (Ali 2010). Bilateral blocks were performed with 0.5% bupivacaine after induction of anaesthesia.

Outcomes

Acute postoperative pain intensity

Forty studies measured postoperative pain intensity. The 10 cm (100 mm) visual analogue scale was the most commonly used tool to measure pain intensity, being used in 30 studies (Akcil 2017; Ali 2010; Artime 2018; Batoz 2009; Biswaz 2003; Bloomfield 1998; Can 2017; Choi 2009; Cokay 2013; Dilmen 2016; El-Dawlatly 2007; Ganzoni 2008; Greenberg 2017; Hernández Palazón 2007; Jones 2009; Kiskira 2006; Law-Koune 2005; Molnár 2015; Nguygen 2001; Rahimi 2006; Rahimi 2010; Rigamonti 2013; Ryan 2005; Shepherd 2018; Sivakumar 2018; Tucinda 2010; Yardav 2014; Zeng 2019; Zhang 2003). The 0 to 10 or 0 to 100 numerical rating scale was used in nine studies (Bala 2006; Hwang 2015; Jellish 2006; Peng 2015; Peng 2016; Saringcarinkul 2015; Shimony 2016; Song 2016; Willams 2011), with one study using a pain rating between 0 and 3 (Misra 2013).

Seven studies measured pain beyond 48 hours postoperatively (Batoz 2009; Hwang 2015; Misra 2013; Molnár 2015; Rigamonti 2013; Shimony 2016; Zhou 2016). Of these, there were only four studies that measured pain anytime between 48 hours and one month postoperatively (Hwang 2015; Misra 2013; Molnár 2015; Rigamonti 2013).

Two studies reported no timing of their pain intensity measurements (Rahimi 2006; Rahimi 2010)

While most studies that measured pain intensity reported this outcome in terms of absolute numbers, four did not (Cokay 2013; Misra 2013; Peng 2016; Ryan 2005); of these, pain intensity was either reported as being above or below a threshold value (Misra 2013; Peng 2016), in terms of the overall statistical significance of the results (Cokay 2013), or not reported at all (Ryan 2005).

Analgesic success

This outcome was not widely reported with only six studies measuring it (Bala 2006; Jellish 2006; Misra 2013; Molnár 2015; Peng 2016; Saringcarinkul 2015). it was reported as numbers free of pain or with no worse than mild pain at various time points or it was possible to calculate from reports of those experiencing moderate or severe pain.

Additional analgesic requirements

Thirty-one studies reported this outcome (Akcil 2017; Artime 2018; Batoz 2009; Biswaz 2003; Can 2017; Choi 2009; Dilmen 2016; Ganzoni 2008; Greenberg 2017; Hernández Palazón 2007; Hwang 2015; Jellish 2006; Jones 2009; Kiskira 2006; Law-Koune 2005; Misra 2013; Nguygen 2001; Peng 2015; Rahimi 2006; Rahimi 2010; Rigamonti 2013; Ryan 2005; Saringcarinkul 2015; Shepherd 2018; Shimony 2016; Sivakumar 2018; Song 2016; Tucinda 2010; Willams 2011; Zeng 2019; Zhou 2016). All of these studies measured additional analgesia consumption in terms of quantity of analgesic required, with the exception of one study which measured it in terms of the number of patients requiring additional analgesia (Can 2017). Of rescue analgesic consumption, opioids were the most commonly measured agents including morphine, hydromorphone, fentanyl, tramadol and nalbuphine. Non-opioid analgesics used included acetaminophen and diclofenac.

Sedation

Sixteen studies measured the level of postoperative sedation (Artime 2018; Batoz 2009; Greenberg 2017; Hernández Palazón 2007; Hwang 2015; Jones 2009; Law-Koune 2005; Peng 2015; Saringcarinkul 2015; Shepherd 2018; Song 2016; Tucinda 2010; Willams 2011; Yardav 2014; Zeng 2019; Zhou 2016). The scales and methods used to measure sedation varied with four studies using the Ramsey sedation scale (Greenberg 2017; Peng 2015; Yardav 2014; Zeng 2019), with the remainder using either 4 or 5-point scales or patient-reported levels of drowsiness.

Chronic headache

This outcome was reported by only three studies with much variation in the time points used. It was measured as persistent pain at three months by one study (Shimony 2016), and persistent pain at two months by two studies (Batoz 2009; Rigamonti 2013).

Length of stay in critical care or hospital

Two studies measured length of stay in critical care (Greenberg 2017; Sivakumar 2018), but only one reported their results (Greenberg 2017). Six studies measured length of stay in hospital (Greenberg 2017; Rahimi 2006; Rahimi 2010; Shepherd 2018; Shimony 2016; Sivakumar 2018).

Adverse events

The commonest adverse event measured was the incidence of nausea and vomiting, being reported by 25 studies (Akcil 2017; Ali 2010; Artime 2018; Batoz 2009; Can 2017; Dilmen 2016; El-Dawlatly 2007; Ganzoni 2008; Hernández Palazón 2007; Hwang 2015; Jellish 2006; Jones 2009; Law-Koune 2005; Misra 2013; Peng 2015; Rigamonti 2013; Saringcarinkul 2015; Shimony 2016; Song 2016; Tucinda 2010; Willams 2011; Yardav 2014; Yun 2016; Zhou 2016; Zeng 2019). Other less commonly measured adverse events measured included hypotension, hypertension, bleeding, delirium, visual disturbances, agitation, respiratory depression, pruritis, diarrhoea and constipation. Few studies provided definitions for adverse events or measures of their severity.

Subgroups

Infratentorial versus supratentorial craniotomy

Only one eligible study (Molnár 2015), analysed pain outcomes separately in those undergoing supra versus infratentorial craniotomy and only one measured pain outcomes in those undergoing supratentorial versus supra and infratentorial craniotomy (Greenberg 2017).

Intervention timing

Of the 42 included completed studies, 21 commenced or completed the intervention before skin incision (Akcil 2017; Ali 2010; Artime 2018; Biswaz 2003; Bloomfield 1998; Can 2017; Cokay 2013; El-Dawlatly 2007; Ganzoni 2008; Misra 2013; Molnár 2015; Peng 2015; Peng 2016; Rigamonti 2013; Ryan 2005; Saringcarinkul 2015; Shimony 2016; Song 2016; Tucinda 2010; Yun 2016; Zeng 2019), and 21 after skin incision (Bala 2006; Batoz 2009; Bekker 2008; Choi 2009; Dilmen 2016; Greenberg 2017; Hernández Palazón 2007; Hwang 2015; Jellish 2006; Jones 2009; Kiskira 2006; Law-Koune 2005; Nguygen 2001; Rahimi 2006; Rahimi 2010; Shepherd 2018; Sivakumar 2018; Willams 2011; Yardav 2014; Zhang 2003; Zhou 2016).

Inhalation versus total intravenous anaesthesia

Only four studies of four different interventions used an exclusively total intravenous anaesthetic technique (Batoz 2009; Can 2017; Song 2016; Willams 2011).

Preoperative steroids

Only two studies of two different interventions included participants who had received preoperative steroids (Bloomfield 1998; Misra 2013).

Excluded studies

We excluded 42 studies.

The reasons for exclusion were as follows:

1. no postoperative pain outcome: three studies (Bajaj 2017; Bishnoi 2016; Doumiri 2015). These studies used agents that can also be used for analgesia i.e. clonidine, dexmedetomidine and lidocaine, however, the focus of these studies was on their efficacy for nonanalgesic outcomes including operating conditions and intraoperative haemodynamics. Although these agents have analgesic potential, these studies were excluded on the basis that the agents investigated were not used with analgesic intent or investigated for their analgesic potential or side effect profile in the context of use as analgesic agents.
2. no distinction between intraoperative and postoperative pain outcomes: one study (Soliman 2011);
3. no control group: 32 studies (Ackil 2018; Ayoub 2006; Citerio 2012; Domenech 2006; Dudko 2014; El Dahab 2009; Ferber 2000; Girard 2010; Goldsack 1996; Graham 1999; Hassani 2015; Honnma 2002; Imaev 2008; Imaev 2010; Jayaram 2016; Jeffrey 1999; Jose 2017; Luo 2014; Mohamed 2018; Morad 2009; Na 2011; Palazón 2006; Rajan 2016; Reddy 2018; Simon 2012; Stoneham 1996; Sudheer 2007; Tanskanen 1999; Theerth 2018; Ture 2009; Vallapu 2018; Verchere 2002);
4. different patient populations studied: four studies (Lu 2009; Venkatraghavan 2016; Wu 2014; Zhao 2013);
5. cross-over trial (Stone 2018).

Of the 42 excluded studies, most were published in English, one was published in French (Doumiri 2015), two were published in Chinese (Lu 2009; Luo 2014), one in Japanese (Honnma 2002), one in Spanish (Palazón 2006), and one in Russian (Imaev 2010).

Forty-one of the excluded studies had been completed, and one was an ongoing study (Wu 2014).

Details are provided in the Characteristics of excluded studies table.

Ongoing studies

We identified one ongoing study (KCT0000274). Details of this study are provided in the table, Characteristics of ongoing studies.

Studies awaiting classification

There are no studies awaiting classification.

Risk of bias in included studies

For each included study, a detailed 'Risk of bias' assessment is provided in the Characteristics of Included Studies table (Characteristics of included studies). A summary of the risk of bias

among included studies is provided in (Figure 2), and a graphical representation of overall risk of bias in each domain for all included studies is provided in (Figure 3).

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

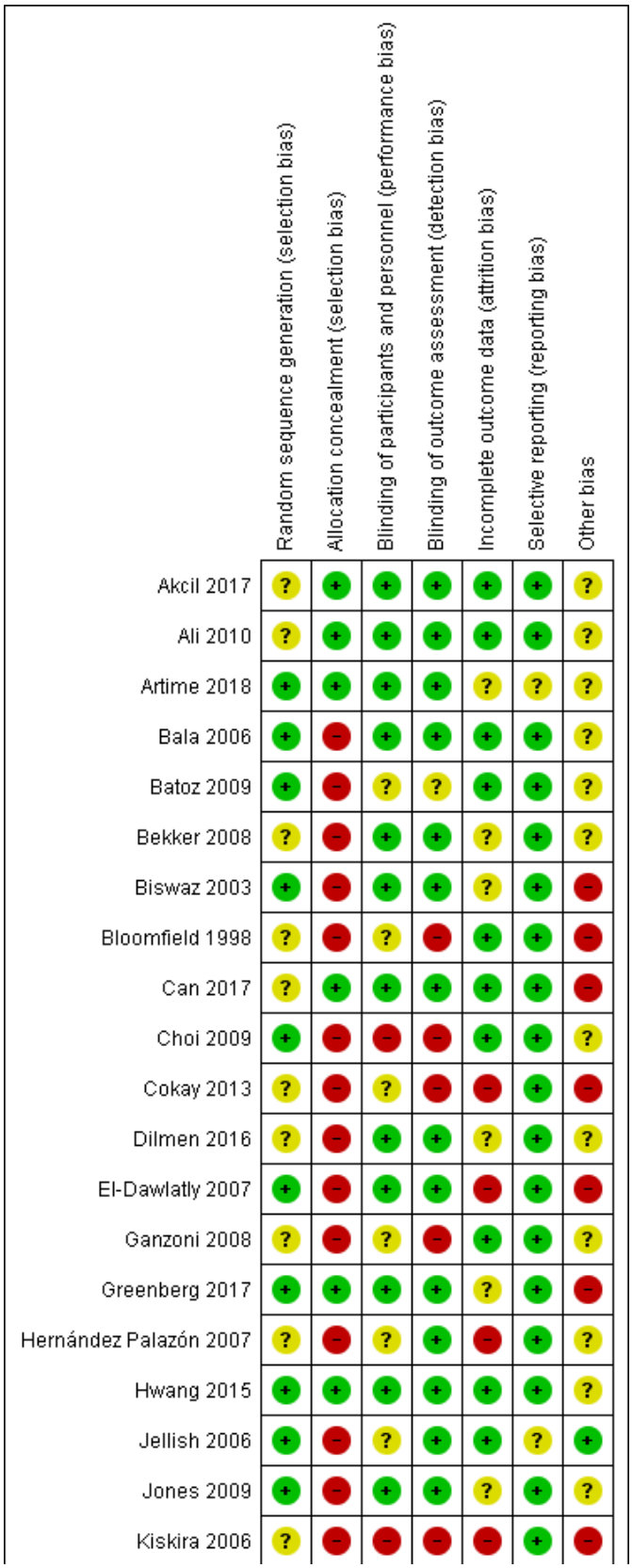


Figure 2. (Continued)

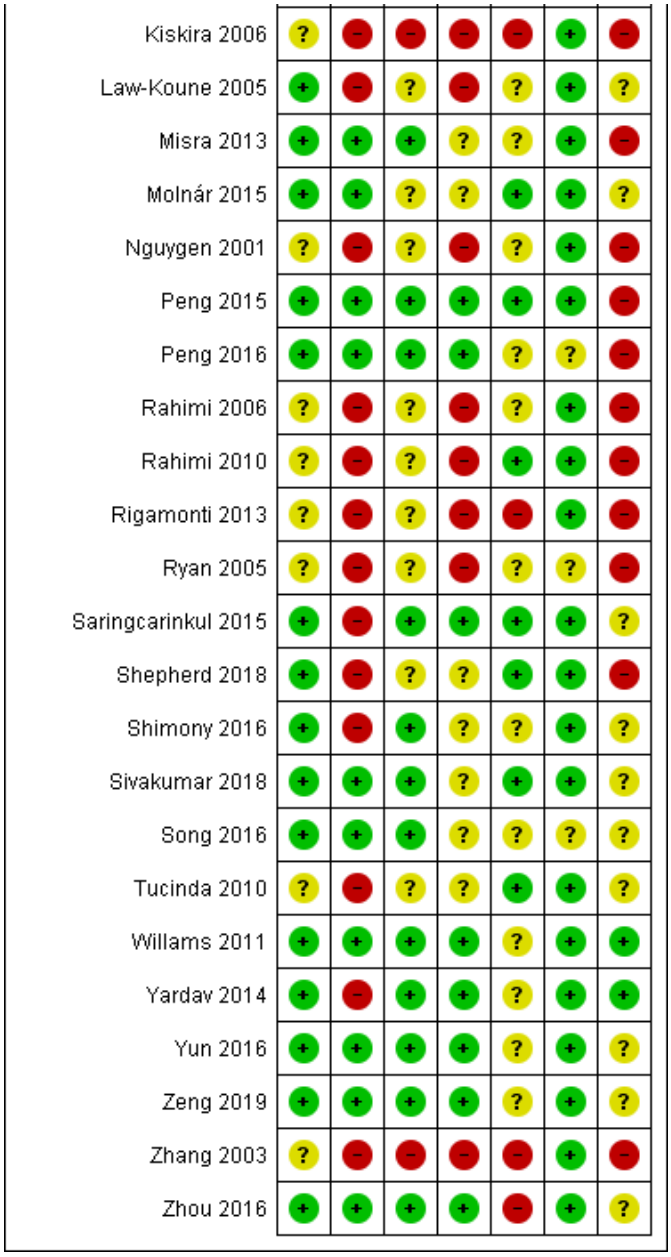
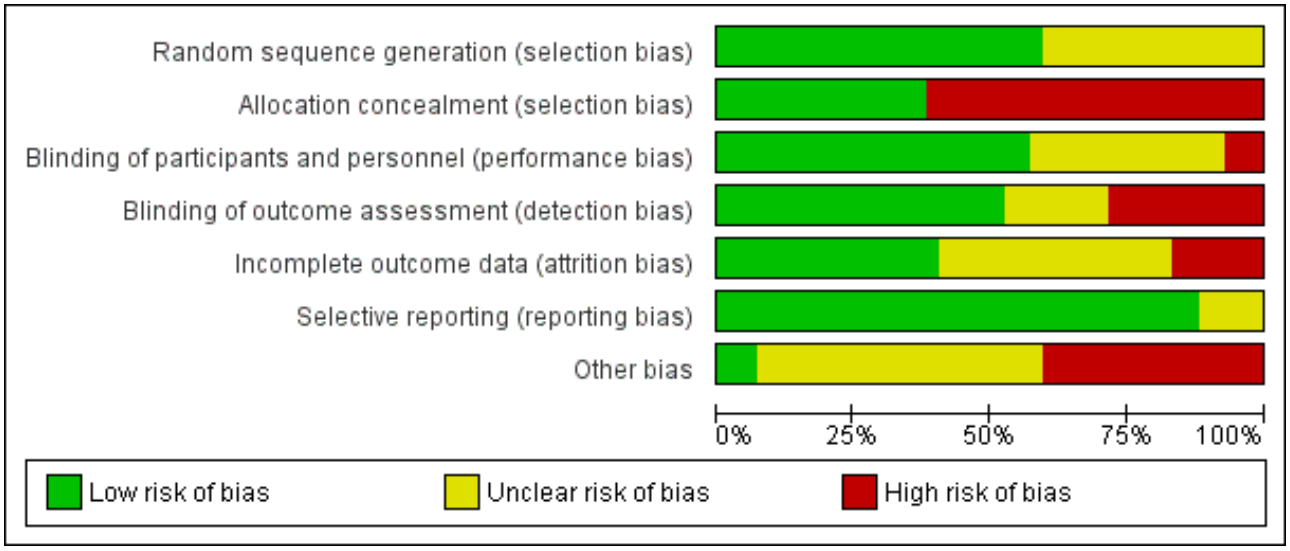


Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Allocation

Random sequence generation

Of the 42 completed studies included in the review, 25 were deemed to have a low risk, 17 were deemed to have an unclear risk and none were deemed to have a high risk of bias in this domain. Where authors reported the trial as randomized and provided detail regarding the method of randomization used, the study was judged to have a low risk of bias in that domain. Where authors reported the trial as randomized but did not describe the method of randomization used, the study was judged to have an unclear risk of bias in that domain.

Allocation concealment

Sixteen of the 42 completed studies which were included in the review were judged to have a low risk of bias in this domain, the remaining 26 being judged to have a high risk of bias. Studies assigned to the low risk category included those that provided details of the methods used to prevent those enrolling participants from guessing upcoming assignments; these methods included the use of sealed envelopes to conceal the treatment allocation (Akcil 2017; Ali 2010; Can 2017; Greenberg 2017; Misra 2013; Molnár 2015; Willams 2011; Yun 2016; Zhao 2013), and the use of coded vials which were assigned according to the randomization table (Peng 2016). A low risk judgement was also given to those studies reporting the performance of randomization, and study drug preparation by personnel who were not involved in treatment allocation (Hwang 2015; Peng 2015; Sivakumar 2018; Song 2016). While this method alone is not guarantee that those assigning the treatments were always unaware of the upcoming assignment, it does imply that methods were taken to conceal both the randomization sequence and the treatment being allocated. A high risk judgement was applied to all studies which did not describe any method of allocation concealment, or described a method that allowed those assigning interventions to predict which participant would receive which intervention.

Blinding

Performance bias

Blinding of participants and study personnel to the treatment administered was judged separately.

Blinding of participants

For the subjective outcome of pain, blinding of participants to treatment received is vital to validity. Of the 17 included completed studies which provided either 'no' or an 'inadequate' description of the methods used to blind participants, in 15 of these studies, the impact on validity was lessened significantly by the use of placebo medications or interventions or the intraoperative timing of the procedure, or both (Bekker 2008; Choi 2009; Cokay 2013; Ganzoni 2008; Hernández Palazón 2007; Jellish 2006; Kiskira 2006; Law-Koune 2005; Nguygen 2001; Rigamonti 2013; Ryan 2005; Shepherd 2018; Tucinda 2010; Zhang 2003). Three studies that did not use placebo medications and did not administer the study medication under anaesthesia, reported that they were blinded but provided inadequate details about the blinding method used. (Molnár 2015; Rahimi 2006; Rahimi 2010), These studies were judged to have an unclear risk of bias in this domain due to the possibility that patients may have reported pain outcomes differently based on the knowledge that they had or had not received the active treatment.

Blinding of study personnel

Of the 42 completed included studies, nine provided either 'no' or 'inadequate' details of the methods used to blind those administering scalp infiltration or scalp block (Batoz 2009; Choi 2009; Cokay 2013; Ganzoni 2008; Hernández Palazón 2007; Rigamonti 2013; Shepherd 2018; Tucinda 2010; Zhang 2003). While inadequate blinding of those administering pain medications or interventions is unlikely to have a significant effect on the way patients report pain outcomes or the way in which additional analgesic consumption is measured, it may have implications for the adequacy of performance of a scalp block or scalp infiltration even if a saline placebo is used. An operator who knows that they are blocking nerves or infiltrating the scalp with an inert saline

placebo may be less rigorous in their attention to detail than one who knows that they are using an active medication, with important implications for intervention efficacy and study validity.

Detection bias

Twenty of the 42 included studies provided either 'no' or 'inadequate' details regarding how those assessing pain outcomes were blinded to treatment received (Batoz 2009; Bloomfield 1998; Choi 2009; Cokay 2013; Ganzoni 2008; Kiskira 2006; Law-Koune 2005; Misra 2013; Molnár 2015; Nguygen 2001; Rahimi 2006; Rahimi 2010; Rigamonti 2013; Ryan 2005; Shepherd 2018; Shimony 2016; Sivakumar 2018; Song 2016; Tucinda 2010; Zhang 2003). For the outcomes of patient-rated pain using validated measuring tools, this is unlikely to have had a serious impact on the effect estimates. Similarly, for defined adverse events, length of stay in hospital and incidence of patient-reported chronic headache, the impact of this bias is likely to be minimal.

Incomplete outcome data

Bias due to incomplete outcome data was judged to be 'serious' for seven studies (Cokay 2013; El-Dawlatly 2007; Hernández Palazón 2007; Kiskira 2006; Rigamonti 2013; Zhang 2003; Zhou 2016). For six of the studies, the reason for this judgement was on the basis of a lack of information in the study reports regarding numbers followed up and numbers included in the final analysis (Cokay 2013; El-Dawlatly 2007; Hernández Palazón 2007; Kiskira 2006; Rigamonti 2013; Zhang 2003), while for one (Zhao 2013), it was due to a very high proportion (31%) of enrolled participants being lost to follow-up for the primary outcome of postoperative analgesic consumption, without the subsequent performance of an intention-to-treat analysis.

A large number of studies (17) were judged to be at unclear risk of attrition bias due to losses to follow-up of up to 22% of enrolled participants without a subsequent intention-to-treat analysis (Artime 2018; Bekker 2008; Biswaz 2003; Dilmen 2016; Greenberg 2017; Jones 2009; Law-Koune 2005; Misra 2013; Nguygen 2001; Peng 2016; Rahimi 2010; Ryan 2005; Song 2016; Willams 2011; Yardav 2014; Yun 2016; Zeng 2019). In only one study, in which 12 of the recruited participants were lost to follow-up, was an intention-to-treat analysis conducted (Shimony 2016). Often no reasons were provided for losses to follow-up but, where they were provided, they most commonly included the need for ongoing postoperative intubation and inability to communicate after surgery due to reduced level of consciousness. While these postoperative problems are common in patients undergoing brain surgery and while assessing patient-reported pain in these circumstances is virtually impossible, the exclusion of these participants from the analysis, makes it difficult to judge the efficacy of any pain-preventing intervention accurately.

Selective reporting

Five of the 42 included completed studies were judged to be at 'unclear risk' of selective reporting bias (Artime 2018; Jellish 2006; Peng 2016; Ryan 2005; Song 2016) .

The reasons for an unclear risk rating included lack of clarity regarding outcome priorities, with two studies failing to define which of their reported outcomes were primary and which were secondary (Peng 2016; Song 2016). In Song 2016, four outcomes were reported (postoperative pain, morphine consumption, sedation scores and adverse events), however, the authors did not report which outcome was primary although their sample size calculation implied that it was' morphine consumption'. In Peng 2016, several outcomes were reported (differences in physiological parameters, pain scores, dysphoria, nausea and vomiting), again with no definition of which outcome was primary and unfortunately no sample size calculation to assist the author in determining what the primary outcome may have been.

An unclear risk rating was also applied to a study which provided no absolute figures for its primary outcome of 'postoperative pain', reporting only those of its secondary outcome of 'morphine consumption' and to studies that gave greater priority in their reports to statistically significant secondary outcomes rather than statistically insignificant primary outcomes (Artime 2018; Jellish 2006; Ryan 2005).

The remaining studies were judged to be at low risk as outcomes were reported in the order specified in the methods section of their reports, so overall, bias due to selective reporting of outcomes was unlikely to have had a significant effect on the findings of this review.

Other potential sources of bias

Twenty-three studies were judged to be at unclear risk of other sources of bias. These included small studies with total enrolled numbers of fewer than 100 participants, studies that did not prespecify their subgroup analyses, studies that did not achieve target sample size, studies that did not adequately adjust for multiple data testing and those funded by pharmaceutical companies (Akcil 2017; Ali 2010; Artime 2018; Bala 2006; Batoz 2009; Bekker 2008; Choi 2009; Dilmen 2016; Ganzoni 2008; Hernández Palazón 2007; Hwang 2015; Jones 2009; Law-Koune 2005; Molnár 2015; Saringcarinkul 2015; Shepherd 2018; Shimony 2016; Sivakumar 2018; Song 2016; Tucinda 2010; Yun 2016; Zeng 2019; Zhou 2016).

Sixteen studies were judged to be at high risk of other sources of bias. These included studies reported in abstract format only where there was an overall lack of information regarding methods and analysis, making it difficult for the reader to judge the rigour of their methodology (Cokay 2013; Kiskira 2006; Rigamonti 2013; Ryan 2005), studies which provided either none or an unclear sample size calculation, making it difficult to determine whether they were adequately powered for their primary outcomes (Biswaz 2003; Bloomfield 1998; El-Dawlatly 2007; Misra 2013; Nguygen 2001; Peng 2015; Peng 2016; Rahimi 2006; Rahimi 2010; Zhang 2003), and studies with a long duration between completion and publication (Can 2017; Greenberg 2017).

Effects of interventions

See: **Summary of findings for the main comparison** Nonsteroidal anti-inflammatory drugs (NSAIDs) compared with control or placebo medications for prevention of pain in adults undergoing brain surgery; **Summary of findings 2** Dexmedetomidine compared with control or placebo medications for prevention of pain in adults undergoing brain surgery; **Summary of findings 3** Pregabalin or Gabapentin compared with control or placebo medications for prevention of pain in adults undergoing brain surgery; **Summary of findings 4** Acetaminophen compared with control or placebo medications for prevention of pain in adults undergoing brain surgery; **Summary of findings 5** Scalp infiltration

compared with control or placebo intervention for prevention of pain in adults undergoing brain surgery; **Summary of findings 6** Scalp block compared with control or placebo intervention for prevention of pain in adults undergoing brain surgery

1. NSAIDs

Summary of findings for the main comparison

Primary outcome

Acute postoperative pain intensity

We included six studies (742 participants) in the meta-analysis for this outcome (Dilmen 2016; Jones 2009; Molnár 2015; Shepherd 2018; Willams 2011; Yardav 2014). Five different NSAIDs (diclofenac, parecoxib, dexketoprofen, methimazole and ibuprofen) were included. We excluded two relevant studies from the analysis, as one did not provide any timing for the pain outcome measures (Rahimi 2006), and the other study provided no absolute figures in its reported results (Ryan 2005).

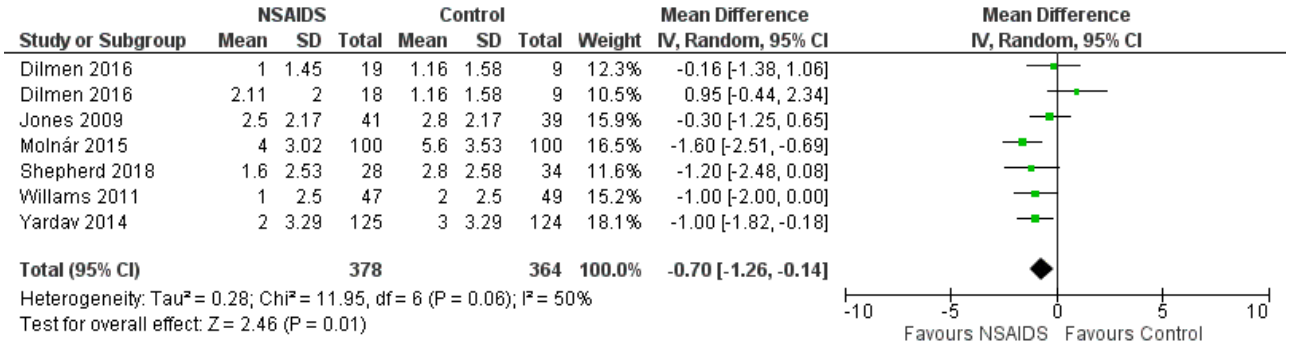
0 to 12 hours

The pooled estimate of effect for MD in pain intensity was −1.11 (95% CI −1.64 to −0.58, P < 0.0001), in the first six hours postoperatively (Analysis 1.1) and −0.74 (95% CI −1.22 to −0.26, P = 0.02) at 12 hours postoperatively (Analysis 1.2). We judged the quality of the evidence to be high.

24 to 48 hours

The pooled estimate of effect for the MD in pain intensity at 24 hours was −0.70 (95% CI −1.26 to − 0.14, P = 0.01, Figure 4). Again, we judged the quality of the evidence to be high. Only one study measured pain at 48 hours and reported a mean pain score of 1 in both groups at 48 hours (Yardav 2014). As this was the only study that reported pain at 48 hours, we did not calculate a pooled estimate of effect for this time point (Yardav 2014). The quality of the evidence was judged to be very low on the basis of these results coming from a single small study.

Figure 4. Forest plot of comparison: 1 NSAIDs versus control, outcome: 1.3 Acute pain at 24 hours.



Secondary outcomes

1. Analgesic success as measured by achievement of 'no worse than mild pain' with 'no worse then mild pain' being defined as a score of ≤ 30/100 mm on a visual analogue scale or ≤ 3/10 on a numerical rating scale

Only one eligible study addressed this outcome (Molnár 2015), and so we did not calculate a pooled estimate of effect**.** This study reported a significant difference in numbers of patients who experienced no worse than mild pain 12 hours after surgery with 48 percent of patients who received diclofenac having either no or mild pain versus 27 percent of patients who received the control.

2. Additional analgesia requirements

We included four studies (265 participants) in the pooled estimate of effect for this outcome (Dilmen 2016; Jones 2009; Ryan 2005; Willams 2011). We included one study twice (with the control group divided between both arms) as it studied this outcome for two different NSAIDs (Dilmen 2016). All of the studies used morphine or morphine equivalents measured in milligrams. The pooled estimate of effect for the MD in additional analgesic requirements was −1.07 (95% CI −4.85 to 2.72, P = 0.58, Analysis 1.4). We judged the quality of the evidence to be low. This was due to imprecision as the pooled sample size was less than 400, and the 95% CI for the effect estimate was wide and included the possibility of either no benefit or increased analgesic requirements in those who received NSAIDs.

3. Sedation

Of the four eligible studies that measured postoperative sedation (Jones 2009; Shepherd 2018; Willams 2011; Yardav 2014), none measured it using comparable scales and at relevant comparable time points, so we did not calculate a pooled estimate of effect.

4. Chronic headache

No eligible study reported this outcome.

5. Length of stay in a critical care unit

No eligible study reported this outcome.

6. Length of stay in hospital

Two studies addressed this outcome but only one reported P values and standard deviations (Shepherd 2018); the other reported neither a P value nor a standard deviation, so a pooled estimate of effect was not calculated for this outcome (Rahimi 2006).

7. Adverse events

Nausea and vomiting

Two studies (345 participants) compared the incidence of nausea and vomiting in those given NSAIDs versus control medication

(Willams 2011; Yardav 2014). The pooled estimate of effect for the risk ratio for nausea and vomiting was 1.34 (95% CI 0.30 to 5.94, P = 0.70, Analysis 1.5), with 70% of the weight coming from the study by Yardav and colleagues (Yardav 2014). We judged the quality of the evidence to be low due to imprecision of the results, i.e. a small number of total events and a wide 95% CI that included the possibility of decreased, equivocal or increased risk of nausea or vomiting in those who received NSAIDs.

Subgroup analyses

Infratentorial versus supratentorial craniotomy

As only one eligible study analysed pain outcomes separately in those undergoing supra versus infratentorial craniotomy we did not perform this subgroup analysis (Molnár 2015).

Intervention timing: pre- versus post-incision

In two studies, NSAIDs were administered prior to surgical skin incision (Molnár 2015; Ryan 2005). In five studies, they were given some time after surgical skin incision (Dilmen 2016; Jones 2009; Shepherd 2018; Willams 2011; Yardav 2014;). Subgroup analysis was not performed as only one study of pre-incision NSAIDs reported pain outcome figures (Molnár 2015).

Inhalation versus total intravenous anaesthesia

As only one eligible study used an exclusively total intravenous anaesthetic technique, there were not enough eligible studies to enable us to calculate a pooled estimate for the effect for this subgroup analysis (Willams 2011).

Preoperative steroids

No eligible studies addressed this outcome.

Sensitivity analyses

We did not conduct sensitivity analysis. This was because no eligible studies were judged to be either at high risk of bias or to have missing data considered to be missing for reasons likely related to either the intervention or the outcomes studied.

2. Dexmedetomidine

Summary of findings 2

Primary outcomes

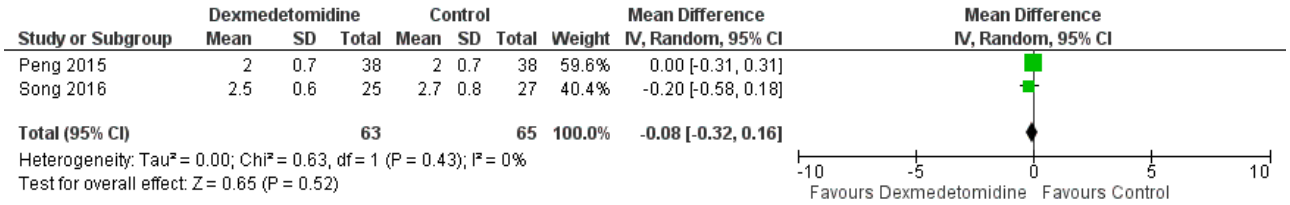
Acute postoperative pain intensity

We included two studies (128 participants) measuring postoperative pain intensity in the meta-analysis for this outcome (Peng 2015; Song 2016). Both studies used dexmedetomidine in similar ways, using infusions of up to 0.5 mcg/kg/hr or placebo infusions intraoperatively.

0 to12 hours

The pooled estimate of effect for the MD in pain intensity was −0.89 (95% CI −1.27 to −0.51, P < 0.00001, Analysis 2.1), during the first six hours postoperatively and −0.81 (95% CI −1.21 to −0.42, P = 0.0004 at 12 hours postoperatively; Analysis 2.2, Figure 5). We downgraded the quality of the evidence by one level for pain intensity at 0 to 6 hours, to a final grade of moderate quality, as the total number of studies and participants was small. We downgraded the quality of the evidence by two levels for pain intensity at 12 hours, to a final grade of low quality, due to the small total number of participants and inconsistency in the form of unexplained important heterogeneity.

Figure 5. Forest plot of comparison: 2 Dexmedetomidine versus control, outcome: 2.3 Acute pain at 24 hours.



24 to 48 hours

The pooled estimate of effect for the MD in pain intensity at 24 hours was −0.08 (95% CI −0.32 to 0.16, P = 0.52, Analysis 2.3), which was not statistically significant. We downgraded the evidence by two levels, to a final grade of low quality, due to the small total number of participants and due to imprecision, i.e. the 95 % CI was wide, including the possibility of either lesser, equivocal or greater pain intensity in those who received dexmedetomidine.

No relevant studies addressed pain intensity beyond 24 hours.

Secondary outcomes

1. Analgesic success as measured by achievement of 'no worse than mild pain' with 'no worse then mild pain' being defined as a score of ≤ 30/100 mm on a visual analogue scale or ≤ 3/10 on a numerical rating scale.

No eligible studies addressed this outcome.

2. Additional analgesia requirements

Two studies (128 participants) contributed to this outcome (Peng 2015; Song 2016). Both studies used morphine to provide additional analgesia. The pooled estimate of effect for the MD in additional analgesia requirement was −21.36 (95% CI −34.63 to −8.1, P = 0.002, Analysis 2.4), with 65% of the weight coming from Song 2016. We downgraded the quality of the evidence by two levels to a final grade of low quality, due to the small total number of participants and due to unexplained important heterogeneity.

3. Sedation

Only one eligible study addressed this outcome and so no pooled estimate of effect was calculated (Song 2016). This study reported a mean Ramsey Sedation score of 2.4 in the treatment group and 2.2 in the control group at 24 hours with no significant differences between the groups.

4. Chronic headache

No eligible studies reported this outcome.

5. Length of stay in a critical care unit

No eligible studies reported this outcome.

6. Length of stay in hospital

No eligible studies reported this outcome.

7. Adverse events

Nausea and vomiting

Three studies (261 participants) were included in the pooled estimate of effect for this outcome (Peng 2015; Song 2016; Yun 2016). The risk ratio for nausea and vomiting in those receiving dexmedetomidine versus control was 0.43 (95% CI 0.06 to 3.08, P = 0.40, Analysis 2.5). We judged the quality of the evidence to be low due to imprecision due to the small number of total events and a wide 95% CI that included the possibility of less, equal or greater risk of nausea and vomiting in those who received dexmedetomidine.

Hypotension

Three studies (184 participants) were included in the pooled estimate of effect for this outcome (Bekker 2008; Peng 2015; Song 2016). The risk ratio for hypotension in those receiving dexmedetomidine versus control was 0.50 (95% CI 0.05 to 5.28, P = 0.56, Analysis 2.6), with all the events occurring in only one study (Peng 2015). We judged the quality of the evidence to be low on the basis of a small number of total participants and a wide 95% CI that included the possibility of less, equal or greater risk of hypotension in those who received dexmedetomidine.

Subgroup analyses

We did not conduct subgroup analyses. This was because no eligible studies addressed the effects of either intervention timing, surgical approach or preoperative steroids on the relevant outcomes, and only one eligible study used an exclusively intravenous anaesthetic technique (Song 2016).

Sensitivity analyses

We did not conduct sensitivity analysis. This was because no eligible studies were judged to be either at high risk of bias or to have missing data considered to be missing for reasons likely related to either the intervention or outcomes studied.

3. Pregabalin or Gabapentin

Summary of findings 3

Primary outcomes

Acute postoperative pain intensity

Two studies (202 participants) addressed this outcome (Shimony 2016; Zeng 2019) using the numerical rating scale and the visual analogue scale, respectively. One study examined the efficacy of gabapentin (Zeng 2019), while the other examined the efficacy of pregabalin (Shimony 2016).

0 to 6 hours

The pooled estimate of effect was a SMD in pain intensity of −0.62 (95% CI −0.90 to −0.34, P < 0.0001, Analysis 3.1). When re-expressed as the mean difference in pain scores, these values were as follows; MD -1.15 (95% CI −1.66 to −0.6). The quality of the evidence was downgraded by two levels to a final level of low, due to a small pooled sample size and possible indirectness of effect as the two drugs studied (pregabalin and gabapentin) differ somewhat in their pharmacological properties.

12 hours

Only one study reported this outcome (Shimony 2016), so a pooled estimate of effect was not calculated. The study found a significant difference in pain at 12 hours in those who received pregabalin versus those who did not, with a mean score of 1.5 in the pregabalin group and mean score of 2.26 in the control group, with a P value of < 0.01.

24 hours

The pooled estimate of effect was a SMD in pain intensity of −0.78 (95% CI −2.06 to −0.51), P = 0.24, Analysis 3.2). When re-expressed as the mean difference in pain scores, these values were as follows; MD −0.29 (95% CI −0.78 to −0.19). The quality of the evidence was downgraded by two levels to a final level of low, due to a small pooled sample size and possible indirectness of effect as the two drugs studied (pregabalin and gabapentin) differ somewhat in their pharmacological properties.

48 hours

The pooled estimate of effect was a SMD in pain intensity of −0.02 (95% CI −0.29 to 0.26, P value 0.91, Analysis 3.3). When re-expressed as the mean difference in pain scores, these values were as follows; MD −0.06 (95% CI −0.86 to 0.77). The quality of the evidence was downgraded by two levels to a final level of low, due to a small pooled sample size and possible indirectness of effect as the two drugs studied (pregabalin and gabapentin) differ somewhat in their pharmacological properties

Secondary outcomes

1. Analgesic success as measured by achievement of 'no worse than mild pain' with 'no worse then mild pain' being defined as a score of ≤ 30/100 mm on a visual analogue scale or ≤ 3/10 on a numerical rating scale

Only one eligible study addressed this outcome, so no pooled estimate of effect was calculated (Misra 2013).

2. Additional analgesia requirements

Three studies including 235 participants addressed this outcome: one study of pregabalin (Shimony 2016), and two studies of gabapentin (Misra 2013; Zeng 2019). Agents used were morphine and fentanyl. The pooled estimate of effect for the SMD in additional analgesia requirement was −0.37 (95% CI −1.10 to −0.35, P = 0.31, Analysis 3.4). Using Cohen's rule of thumb, this represents a small, non-significant effect size. The quality of the evidence was downgraded by two levels to a final level of low, due to a small pooled sample size and possible indirectness of effect as the two drugs studied (pregabalin and gabapentin) differ somewhat in their pharmacological properties

3. Sedation

No eligible study addressed this outcome.

4. Chronic headache

Only one eligible study reported this outcome and so no pooled estimate of effect was calculated (Shimony 2016). That study found a mean pain score three months after surgery of 1.28 in the treatment group and 1.51 in the placebo group, with no statistical difference between groups.

5. Length of stay in a critical care unit

No eligible study reported this outcome.

6. Length of stay in hospital

Only one eligible study reported this outcome and so no pooled estimate of effect was calculated (Shimony 2016). This one study reported a non-significant difference in the number of days spent in hospital, with those who received pregabalin spending a mean of 7.9 days in hospital and those in the control group spending a mean of 8.3 days in hospital.

7. Adverse events

Nausea and vomiting

Three studies (275 participants) were included in the pooled estimate of effect for this outcome (Misra 2013; Shimony 2016; Zeng 2019). The risk ratio for nausea and vomiting was found to be significantly less in those treated with either gabapentin or pregabalin versus control interventions, risk ratio 0.51 (95% CI 0.29 to 0.89, P = 0.02, Analysis 3.5). The quality of the evidence was judged to be low due to imprecision as the number of total events was small and due to indirectness as the two medications differ somewhat in their pharmacologic properties.

Subgroup analyses

No subgroup analyses were conducted as no eligible studies addressed the effects of either intervention timing, surgical approach, preoperative steroids or anaesthetic technique on the relevant outcomes.

Sensitivity analyses

No sensitivity analyses were conducted as no eligible studies were judged to be either at high risk of bias or to have missing data considered to be missing for reasons likely related to either the intervention or outcomes studied.

4. Acetaminophen

Summary of findings 4

Primary outcomes

Acute postoperative pain intensity

0 to 6 hours

Three studies (332 participants) contributed to a pooled estimate of effect for the MD in acute pain intensity in the first six hours after surgery, of −0.35 (95% CI −1.00 to 0.30, P = 0.29, Analysis 4.1) (Artime 2018; Dilmen 2016; Sivakumar 2018). The quality of the evidence was judged to be moderate due to a small pooled sample size.

12 hours

Three studies (332 participants) contributed to a pooled estimate of effect for the MD in acute pain intensity at 12 hours, of −0.51 (95% CI −1.04 to 0.03, P = 0.06, Analysis 4.2) (Artime 2018; Dilmen 2016; Sivakumar 2018). The quality of the evidence was judged to be moderate due to a small pooled sample size.

24 hours

Four studies (439 participants) contributed to a pooled estimate of effect for MD in acute pain intensity at 24 hours, of 0.34 (95% CI −1.20 to 0.52, P = 0.44, Analysis 4.3) (Artime 2018; Dilmen 2016; Greenberg 2017; Sivakumar 2018). The quality of the evidence was judged to be high.

48 hours

Only one study addressed this outcome (Sivakumar 2018) and showed a mean pain score of 5.5 in the control group and 4.5 in the treatment group, with no significant differences between the groups.

Secondary outcomes

1. Analgesic Success. Analgesic success as measured by achievement of 'no worse than mild pain' with 'no worse then mild pain' being defined as a score of ≤ 30/100 mm on a visual analogue scale or ≤ 3/10 on a numerical rating scale

No eligible study addressed this outcome.

2. Additional analgesia requirements

Four studies (459 participants) contributed to a pooled estimate effect for MD in additional analgesia requirement, of −0.07 (95% CI −0.86 to 0.99, P = 0.89, Analysis 4.4), (Artime 2018; Dilmen 2016; Greenberg 2017; Sivakumar 2018). The quality of the evidence was judged to be high.

3. Sedation

Only one eligible study addressed this outcome using a validated scale, and so no pooled estimate of effect was calculated (Greenberg 2017). That study reported a Richmond Agitation Sedation score of zero in both groups at 24 hours.

4. Chronic headache

No eligible studies addressed this outcome.

5. Length of stay in a critical care unit

Only one eligible study reported this outcome, and so no pooled estimate of effect was calculated (Greenberg 2017). That study reported a median length of stay in critical care of 28 hours in the control group and 26 hours in the acetaminophen group with no significant differences between the groups.

6. Length of stay in hospital

Two studies (335 participants) contributed to a pooled estimate of effect for MD in length of hospital stay of −3.71 hours (95% CI −14.12 to 6.7, P 0.48, Analysis 4.5) (Greenberg 2017; Sivakumar 2018). The quality of the evidence was judged to be moderate, being downgraded one level due to a small pooled sample size.

7. Adverse events

No two studies addressed comparable adverse events, and so a pooled estimate of effect was not calculated.

Subgroup analyses

We did not conduct subgroup analyses as only one study addressed pain outcomes separately in those undergoing supratentorial craniotomy (Greenberg 2017), and no eligible studies addressed the effects of intervention timing, preoperative steroids or anaesthetic technique on the relevant outcomes.

Sensitivity analyses

No studies were judged to be at a high risk of bias.

5. Scalp infiltration

Summary of findings 5

Primary outcomes

Acute postoperative pain intensity

0 to12 hours

Pain in the first six hours: nine studies, including a total of 475 participants, contributed to this estimate (Akcil 2017: Biswaz 2003; Bloomfield 1998; El-Dawlatly 2007; Kiskira 2006; Law-Koune 2005; Saringcarinkul 2015; Zhang 2003; Zhou 2016). The effect estimate for the MD in pain intensity was - 0.64 (95% CI −1.28 to −0.00, P = 0.05) supporting a non-statistically significant benefit of scalp infiltration in terms of reduction in early postoperative pain intensity (Analysis 5.1). We downgraded the evidence by one level to a final grade of moderate quality, due to unexplained important heterogeneity.

Pain at 12 hours: seven studies, including 309 participants, measured pain at 12 hours, producing a pooled effect estimate for SMD in pain intensity of −0.71 (95% CI −1.34 to −0.08, P = 0.03, Analysis 5.3) with non-significant statistical heterogeneity (Akcil 2017; Batoz 2009; Biswaz 2003; El-Dawlatly 2007; Kiskira 2006; Saringcarinkul 2015; Zhang 2003). We downgraded the evidence by two levels to a final grade of low quality, due to a small pooled sample size and loss of significance of results on sensitivity analysis.

24 to 48 hours

Pain at 24 hours: six studies including 260 participants, measured pain at 24 hours using comparable pain scales, producing a pooled estimate of effect for MD in pain intensity of −0.39 (95% CI −1.06 to 0.27, P = 0.24, Analysis 5.5), which was not statistically significant (Akcil 2017; Batoz 2009; Biswaz 2003; El-Dawlatly 2007; Kiskira 2006; Zhang 2003). We downgraded the evidence two levels to a final grade of low quality, due to a small pooled sample size and unexplained important heterogeneity.

Pain at 48 hours: only three studies (128 participants) contributed to this outcome (Biswaz 2003; El-Dawlatly 2007; Zhang 2003). The effect estimate for the MD in pain intensity was −1.09 (95% CI −2.13 to -0.06, P = 0.04, Analysis 5.7). We downgraded the evidence by one level, to a final grade of moderate quality, due to a small pooled sample size.

Secondary outcomes

1. Analgesic success as measured by achievement of 'no worse than mild pain' with 'no worse then mild pain' being defined as a score of ≤ 30/100 mm on a visual analogue scale or ≤ 3/10 on a numerical rating scale

Only one eligible study addressed this outcome, so no pooled estimate of effect was calculated (Saringcarinkul 2015). That study showed no significant difference in the numbers of patients who were pain-free six hours after surgery with 4% of patients who received scalp infiltration being free of pain versus 8% of patient who received control.

2. Additional analgesia requirements

Six studies (345 participants) measured this outcome (Akcil 2017; Batoz 2009; Biswaz 2003; Kiskira 2006; Law-Koune 2005; Zhou 2016). The agents used to provide supplementary analgesia included diclofenac, morphine and nalbuphine. Dosages were all calculated in milligrams and so MD was used to calculate the pooled estimate of the effect of −9.56 (95% CI −15.64 to −3.49, P = 0.002, Analysis 5.10). There was moderate statistical heterogeneity which was unexplained, a small pooled sample size and the result lost significance when studies were included in a sensitivity analysis, so we downgraded the evidence by three levels to a final grade of very low quality.

3. Sedation

Of the four studies (337 participants) of scalp infiltration that measured postoperative sedation, none measured it using comparable scales and at relevant comparable time points so no pooled estimate of effect was calculated (Batoz 2009; Law-Koune 2005; Saringcarinkul 2015; Zhou 2016).

4. Chronic headache

Only two studies reported this outcome (Batoz 2009; Zhou 2016); as neither reported it at the same time point, no pooled estimate of effect was calculated.

5. Length of stay in a critical care unit

No eligible study reported this outcome.

6. Length of stay in hospital

No eligible study reported this outcome.

7. Adverse events

Nausea and vomiting

Four studies (318 participants) reported this outcome (El-Dawlatly 2007; Law-Koune 2005; Saringcarinkul 2015; Zhou 2016). The pooled estimate of effect for the risk ratio for nausea and vomiting was 0.74 (95% CI 0.48 to 1.14, P = 0.17, Analysis 5.9). We downgraded the evidence by two levels to a final grade of low quality, due to imprecision, i.e. a small total number of events, and a wide 95% CI that included the possibility of either less, equal or greater risk of nausea and vomiting in those who received scalp infiltration.

Subgroup analyses

Infratentorial versus supratentorial craniotomy

No eligible studies addressed these subgroups.

Intervention timing: pre- versus post-incision

Pooled estimates of effect were calculated for acute postoperative pain intensity and additional analgesic consumption for those who received scalp infiltration before surgical incision and for those who

received scalp infiltration some time after surgery had commenced. The results were as follows:

Mean difference in pain intensity in the first 6 hours was −0.14 (95% CI −0.08 to 0.52, P = 0.68) for those who received pre-incision scalp infiltration (5 studies, 216 participants) (Akcil 2017; Biswaz 2003; Bloomfield 1998; El-Dawlatly 2007; Saringcarinkul 2015), and −0.98 (95% CI −1.84 to −0.12, P = 0.03) for those who received post-incision scalp infiltration (4 studies, 259 participants) (Kiskira 2006; Law-Koune 2005; Zhang 2003; Zhou 2016), (Analysis 5.1).

Mean difference in pain intensity at 12 hours was −0.52 (95% CI −1.46 to 0.41, P = 0.27) for those who received pre-incision scalp infiltration (4 studies, 180 participants) (Akcil 2017;Biswaz 2003; El-Dawlatly 2007; Saringcarinkul 2015), and −1.14 (95% CI −1.77 to −0.50, P = 0.004) for those who received post-incision scalp infiltration (3 studies, 129 participants) (Batoz 2009; Kiskira 2006; Zhang 2003), (Analysis 5.3).

Mean difference in pain intensity at 24 hours was −0.01 (95% CI −0.84 to 0.81, P = 0.98) for those who received pre-incision scalp infiltration (3 studies, 131 participants) (Akcil 2017;Biswaz 2003; El-Dawlatly 2007), and −1.78 (95% CI −1.72 to 0.17, P = 0.11) for those who received post-incision scalp infiltration (3 studies, 129 participants) (Batoz 2009; Kiskira 2006; Zhang 2003), (Analysis 5.5).

Mean difference in additional analgesia requirement was −12.54 (95% CI −25.20 to 0.13, P = 0.05) for those who received pre-incision scalp infiltration (4 studies, 217 participants) (Akcil 2017; Biswaz 2003; Kiskira 2006; Zhou 2016), and −8.57 (95% CI −13.26 to −3.87, P = 0.0003) for those who received post-incision scalp infiltration (2 studies, 128 participants) (Batoz 2009; Law-Koune 2005) (Analysis 5.10).

Inhalation versus total intravenous anaesthesia

This subgroup analysis was not conducted as only one eligible study used an exclusively intravenous anaesthetic technique (Batoz 2009).

Preoperative steroids

Only one eligible study addressed this outcome so no subgroup analysis was conducted (Bloomfield 1998).

Sensitivity analyses

Excluding studies with a high risk of bias

We determined a study to have an overall 'high risk' of bias if it was judged to have a high risk of bias in four or more of the seven domains of bias or a high risk of bias in three or more of the seven domains of bias with an unclear risk of bias in one or more domain (Figure 2). Three studies of scalp infiltration fulfilled these criteria (Bloomfield 1998; Kiskira 2006; Zhang 2003), and so sensitivity analysis excluding these studies was conducted for the following outcomes:

Acute postoperative pain intensity

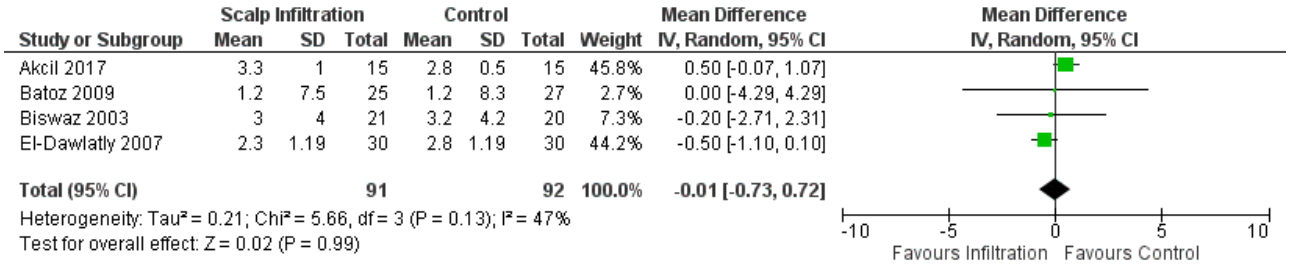
Exclusion of these studies changed the pooled estimate of effect for the MD in acute pain intensity as follows:

Mean difference in acute pain intensity in the first 6 hours became −0.04 (95% CI −0.43 to 0.35, P = 0.85, Analysis 5.2). Mean difference in pain intensity became 0.20 (95% CI −0.13 to 0.52, P = 0.24) for those who received scalp infiltration pre-surgical incision and −0.39 (95% CI −1.22 to 0.44, P = 0.36) for those who received it post-incision.

Mean difference in acute pain intensity at 12 hours became −0.35 (95% CI −1.31 to 0.61, P = 0.48, Analysis 5.4), with insufficient studies to analyse the effects of pre- versus post-incision scalp infiltration.

Mean difference in acute pain intensity at 24 hours became −0.01 (95% CI −0.75 to 0.73, P = 0.99, Figure 6), with insufficient studies to analyse the effects of pre- versus post-incision scalp infiltration.

Figure 6. Forest plot of comparison: 5 Scalp infiltration versus control, outcome: 5.6 Acute Pain at 24 hours (Excluding Studies with a High Risk of Bias).



Mean difference in acute pain intensity at 48 hours became −0.76 (95% CI −1.20 to −0.32, P = 0.0007, Analysis 5.8), with insufficient studies to analyse the effects of pre- versus post-incision scalp infiltration.

For the 12-hour time period, the exclusion of studies with a high risk of bias changed the initially significant result to non-significant and for the 48-hour time period, the exclusion of studies with a high risk of bias changed the initially non-significant result to significant, with virtually all the weight for the pooled estimate of effect coming from one study (El-Dawlatly 2007). For the 0- to 6-hour and 12-hour time periods, sensitivity analysis did not change the significance of the results.

Additional analgesia requirements

Sensitivity analysis changed the effect estimate to −8.16 (95% CI −16.5 to 0.18, P = 0.06), making the initial statistically significant result insignificant (Analysis 5.11).

Excluding studies with missing data considered to be missing for reasons likely related to either the intervention or outcomes studied

No studies were found where missing data was thought to be missing for reasons related to the intervention or outcomes being measured, so this analysis was not conducted.

6. Scalp blocks

Summary of findings 6

Primary outcomes

Acute postoperative pain intensity

0 to 12 hours

Pain in the first 6 hours: 10 studies (414 participants) used comparable pain scales to measure pain in the first 6 hours, producing a pooled estimate of effect for MD in pain intensity of −0.98 (95% CI −1.66 to −0.30, P = 0.005, Analysis 6.1), in favour of scalp block producing a statistically significant reduction in pain intensity (Akcil 2017; Bala 2006; Can 2017; Choi 2009; Ganzoni 2008; Hernández Palazón 2007; Hwang 2015; Nguygen 2001; Tucinda 2010; Zhang 2003). We judged the quality of the evidence to be low due failure to retain significance when studies with a high risk of bias were excluded and important unexplained heterogeneity.

Pain at 12 hours: 8 studies (294 participants) contributed to a pooled estimate of effect of for MD in pain intensity of −0.95 (95% CI −1.53 to −0.37, P = 0.001, Analysis 6.3), again in favour of scalp block producing a statistically significant reduction in pain intensity but with the limitation, important unexplained heterogeneity and a small pooled sample size (Akcil 2017; Batoz 2009; Choi 2009; Hernández Palazón 2007; Hwang 2015; Nguygen 2001; Tucinda 2010; Zhang 2003). We judged the quality of the evidence to be low, because of imprecision due to a small pooled sample size and inconsistency due to unexplained important heterogeneity.

24 to 48 hours

Pain at 24 hours: 9 studies (433 participants) contributed to a pooled estimate of effect for MD in pain intensity of −0.78 (95% CI −1.52 to −0.05, P = 0.04, Analysis 6.5), in favour of scalp block producing a statistically significant reduction in pain intensity but with the limitation of significant statistical heterogeneity (Akcil 2017; Can 2017; Choi 2009; Hernández Palazón 2007; Hwang 2015; Nguygen 2001; Rigamonti 2013; Tucinda 2010; Zhang 2003). We downgraded the evidence by two levels to a final grading of low quality, due to failure to retain significance when studies with a high risk of bias were excluded and due to important unexplained heterogeneity.

Pain at 48 hours: 4 studies (135 participants) contributed to a pooled estimate of effect for SMD in pain intensity of −1.34 (95% CI −2.57 to −0.11, P = 0.03, Analysis 6.7), in favour of scalp block producing a statistically significant reduction in pain intensity (Choi 2009; Hwang 2015; Nguygen 2001; Zhang 2003). We downgraded the evidence by three levels to a final grade of very low quality, as there was inconsistency in the form of important unexplained heterogeneity, the beneficial effect of scalp block on postoperative pain intensity as 48 hours was not sustained when studies deemed to have a high overall risk of bias were excluded, and the pooled sample size was small.

Secondary outcomes

1. Analgesic success as measured by achievement of 'no worse than mild pain' with 'no worse then mild pain' being defined as a score of ≤ 30/100 mm on a visual analogue scale or ≤ 3/10 on a numerical rating scale

Only one eligible study addressed this outcome, so no pooled estimate of effect was calculated (Bala 2006).

2. Additional analgesia requirements

Seven studies (314 participants) contributed to this outcome (Akcil 2017; Ganzoni 2008; Hernández Palazón 2007; Hwang 2015; Nguygen 2001; Rigamonti 2013; Tucinda 2010). The medications used to provide additional analgesia included morphine, morphine equivalents and codeine which were measured in milligrams, and fentanyl which was measured in micrograms. The pooled estimate of effect for the SMD in additional analgesic requirement was −1.11 (95% CI −1.97 to −0.25, P = 0.01, Analysis 6.9). Using Cohen's rule of thumb, this represents a large effect size. We downgraded the evidence by two levels to a final grade of low quality, due to a small pooled sample size and important unexplained heterogeneity.

3. Sedation

Of the three studies of scalp blocks that measured postoperative sedation (142 participants), none measured it using comparable scales and at relevant comparable time points, so no pooled estimate of effect was calculated (Hernández Palazón 2007; Hwang 2015; Tucinda 2010;).

4. Chronic headache

Only one study of scalp blocks reported pain at 2 months (Rigamonti 2013) and none reported pain at 3 months.

5. Length of stay in a critical care unit

No eligible study reported this outcome.

6. Length of stay in hospital

No eligible study reported this outcome.

7. Adverse events

Nausea and vomiting

Four studies (165 participants) contributed to a pooled estimate of effect for the risk ratio of nausea and vomiting of 0.66 (95% CI 0.33 to 1.32, P = 0.24, Analysis 6.10), (Ganzoni 2008; Hernández Palazón 2007; Hwang 2015; Tucinda 2010). We downgraded the evidence by three levels to a final grade of very low quality, as there was inconsistency in the form of important unexplained heterogeneity and imprecision, i.e. a wide 95% CI that included the possibility of either no benefit or increased nausea and vomiting in the intervention group and a small number of total events.

Subgroup analyses

Infratentorial versus supratentorial craniotomy

No eligible studies addressed these subgroups.

Intervention timing: pre- versus post-incision

We calculated pooled estimates of effect for acute pain intensity for those who received scalp blocks before surgical incision and for those who received scalp blocks some time after surgery had commenced. The results were as follows:

Mean difference in acute pain intensity in the first 6 hours was −0.19 (95% CI −0.53 to 0.15, P = 0.28) for those who received pre-incision scalp block (4 studies, 209 participants) (Akcil 2017; Can 2017; Ganzoni 2008; Tucinda 2010), and −1.92 (95% CI −3.08 to −0.76, P = 0.001) for those who received post-incision scalp block (6 studies, 205 participants) (Bala 2006; Choi 2009; Hernández Palazón 2007; Hwang 2015; Nguygen 2001; Zhang 2003) (Analysis 6.1).

Mean difference in acute pain intensity at 12 hours was −0.46 (95% CI −0.8 to −0.11, P = 0.01) for those who received pre-incision scalp block (2 studies, 89 participants) (Akcil 2017; Tucinda 2010), and −1.54 (95% CI −2.64 to −0.44, P = 0.006) for those who received post-incision scalp block (6 studies, 205 participants) (Bala 2006; Choi 2009; Hernández Palazón 2007; Hwang 2015; Nguygen 2001; Zhang 2003), (Analysis 6.3).

Mean difference in acute pain intensity at 24 hours was 0.01 (95% CI −1.07 to 1.09, P = 0.99) for those who received pre-incision scalp blocks (4 studies, 268 participants) (Akcil 2017; Can 2017; Rigamonti 2013; Tucinda 2010), and −1.80 (95% CI −3.00 to −0.59, P = 0.003) for those who received post-incision scalp infiltration (5 studies, 165 participants) (Choi 2009; Hernández Palazón 2007; Hwang 2015; Nguygen 2001; Zhang 2003), (Analysis 6.5).

Pooled estimates of effect were calculated for additional analgesia requirements in those who received pre- versus post-incision scalp blocks. The results were as follows:

Standardized mean difference in additional analgesia requirements in the first 24 hours postoperatively were −0.62 (95% CI −1.52 to 0.28, P = 0.18) for those who received pre-incision scalp blocks (4 studies, 208 participants) (Akcil 2017; Ganzoni 2008; Rigamonti 2013; Tucinda 2010), and −2.12 (95% CI −4.27 to 0.03, P = 0.05) for those who received post-incision scalp blocks (3 studies, 106 participants) (Hwang 2015; Hernández Palazón 2007; Nguygen 2001), (Analysis 6.9). Using Cohen's rule of thumb, this represents a moderate and large effect size respectively; however, neither achieved statistical significance.

Inhalation versus total intravenous anaesthesia

No subgroup analysis was conducted as only one eligible study used an intravenous anaesthetic technique (Can 2017).

Preoperative steroids

No subgroup analysis was conducted as no eligible studies were found.

Sensitivity analyses

Excluding studies with a high risk of bias

We determined a study to have an overall high risk of bias if it was judged to have a high risk of bias in four or more of the seven domains of bias or a high risk of bias in three or more of the seven domains of bias with an unclear risk of bias in one or more domain (Figure 2). Five studies of scalp blocks fulfilled these criteria (Choi 2009; Cokay 2013; Rigamonti 2013; Nguygen 2001; Zhang 2003).

Sensitivity analyses (excluding these studies) were therefore performed for the relevant following outcomes:

Acute postoperative pain intensity

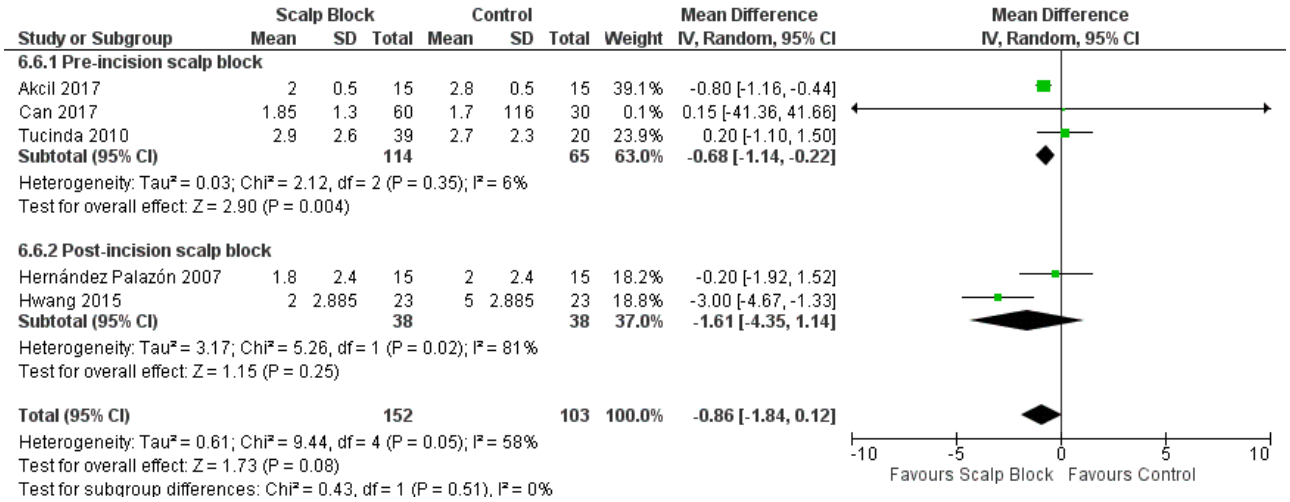
Exclusion of studies with a high risk of bias changed the pooled estimate of effect for the MD in acute pain intensity as follows:

Mean difference in acute pain intensity in the first 6 hours became −0.97 (95% CI −1.98 to 0.05, P = 0.06, Analysis 6.2). Mean difference in acute pain intensity in the first 6 hours became −0.19 (95% CI −0.54 to 0.15, P = 0.27) for those who received pre-incision scalp block and −1.71 (95% CI −2.44 to −0.98, P < 0.00001) for those who received post-incision scalp block.

Mean difference in acute pain intensity at 12 hours became −0.64 (95% CI −1.21 to −0.07, P = 0.03, Analysis 6.4). Mean difference in acute pain intensity at 12 hours became −0.46 (95% CI −8.0 to −0.11, P = 0.01) for those who received pre-incision scalp block and −1.54 (95% CI −3.33 to 0.26, P = 0.09) for those who received post-incision scalp block.

Mean difference in acute pain intensity at 24 hours became −0.86 (95% CI −1.84 to 0.12, P = 0.08, Figure 7). Mean difference in acute pain intensity at 24 hours became −0.63 (95% CI −1.14 to −0.22, P = 0.004) for those who received pre-incision scalp block and −1.61 (95% CI -4.35 to 1.14, P = 0.25) for those who received post-incision scalp block.

Figure 7. Forest plot of comparison: 6 Scalp block versus control, outcome: 6.6 Acute pain at 24 hours (excluding studies with a high risk of bias).



Mean difference in acute pain intensity at 48 hours became −0.91 (95% CI −3.04 to 1.25, P = 0.41, Analysis 6.8).

Additional analgesia requirements

Exclusion of studies with a high risk of bias, changed the pooled estimate of effect to −1.71 (95% CI −2.95 to −0.46, P = 0.007, Analysis 6.11). Using Cohen's rule of thumb, this represents a large effect size. Neither pre- or post-incision scalp blocks showed superiority.

Excluding studies with missing data considered to be missing for reasons likely related to either the intervention or outcomes studied

No studies were found where missing data was thought to be missing for reasons related to the intervention or outcomes being measured, so this analysis was not conducted.

Other pharmacological interventions

No other pharmacological interventions were found to have two or more eligible studies addressing relevant comparable outcomes so no pooled estimates of effect could be calculated for studies of opioids, flupirtine, intravenous lidocaine or sphenopalatine ganglion blocks.

DISCUSSION

Summary of main results

Pain intensity

For the primary outcome of postoperative pain intensity, nonsteroidal anti-inflammatories (NSAIDs) were beneficial up to 24 hours, dexmedetomidine was effective in the first 12 hours and pregabalin or gabapentin were effective in the first six hours after surgery.

When studies with a high risk of bias were excluded, scalp blocks were effective at 12 hours and scalp infiltration at 48 hours but not at earlier time points.

Acetaminophen did not show any benefit.

Additional analgesia requirements

In the first 24 hours after surgery, dexmedetomidine and scalp blocks significantly reduced additional analgesia requirements with the limitation of the quality of the evidence being low to very low. Nonsteroidal anti-inflammatories (NSAIDs), scalp infiltration, gabapentin or pregabalin and acetaminophen did not show any benefit.

Intervention timing

When studies with a high risk of bias were excluded, post-incision scalp blocks were effective at reducing early acute postoperative pain (0 to 6 hours), and pre-incision scalp blocks were effective at reducing postoperative pain at 12 and 24 hours.

Adverse events

The only significant difference detected was low-quality evidence for a lower risk of nausea and vomiting in those treated with pregabalin or gabapentin.

Length of hospital stay

Acetaminophen did not alter length of stay in hospital (this was the only intervention in which this outcome was studied),

Other outcomes and interventions

There were insufficient data to:

1. make accurate conclusions regarding the effects of the included interventions on overall analgesic success, sedative effects, the incidence of chronic headache or length of stay in critical care;
2. determine the effect of the following interventions on the intensity of postoperative pain: opioids, flupirtine, intravenous lidocaine and sphenopalatine ganglion blocks.

Overall completeness and applicability of evidence

The evidence obtained from this review provides a reasonably comprehensive picture of the potential role of several common pharmacological interventions in the prevention of post-craniotomy pain up to 48 hours postoperatively, helping clinicians

to choose which interventions may provide the best analgesic benefit for patients. The strengths of this review include its broad search strategy without language restriction, the inclusion of unblinded, as well as blinded trials, the capture of a wide range of pharmacological interventions, and the focus on patient-centred outcomes.

There are, however, some very important limitations to the completeness of this evidence, which in turn limit its clinical applicability. These include data quality, data quantity and heterogeneity, as detailed below.

Data quantity

There were not enough data to provide an overall measure of the effect in this population for the following outcomes:

1. prevention of postoperative pain: opioids, flupirtine, intravenous lidocaine, sphenopalatine ganglion blocks;
2. analgesic success;
3. additional analgesic requirement: opioids, flupirtine, intravenous lidocaine, sphenopalatine ganglion blocks;
4. sedation;
5. chronic headache;
6. length of stay in critical care;
7. adverse events, other than hypotension and nausea and vomiting;
8. effects of site of surgery, steroids and anaesthetic technique on the pain prevention effects of any interventions or medications.

Data quality

This is discussed in the next section (Quality of the evidence).

Heterogeneity

While several pharmacological interventions (scalp infiltration, scalp blocks, acetaminophen and dexmedetomidine) were relatively clinically homogenous in terms of their components and methods of administration, some interventions (NSAIDs, gabapentin and pregabalin) were not. Several different medications (diclofenac, ibuprofen, parecoxib, dexketoprofen and metamizole) were grouped together to provide an estimate of the overall efficacy of NSAIDs; while these drugs all belong to the same pharmacological group, they may well differ in their clinical efficacy. They were also administered at different time points relative to surgery making it more difficult to judge their overall effect as a group. Furthermore, there were not enough data to separate out their efficacy based on the timing of their administration relative to surgery.

The pooling of gabapentin and pregabalin provided an estimate for the efficacy of two very similar GABA-like (gamma-aminobutyric acid) drugs, that while they share a similar mechanism of action, they have several pharmacokinetic and pharmacodynamic differences which may affect their efficacy. Several of the effect estimates were also limited by significant unexplained important heterogeneity.

Quality of the evidence

Acute postoperative pain intensity

For the primary outcome of acute postoperative pain intensity, the quality of the evidence varied across interventions.

For NSAIDs, the overall quality of the evidence was judged to be high (Summary of findings for the main comparison).

For dexmedetomidine, the evidence was also judged to be of moderate quality for the pooled estimate of effect for acute postoperative pain intensity in the first six hours after surgery, after having been being downgraded one level due to a small pooled sample size. For postoperative pain intensity at 12 hours and at 24 hours, the quality of the evidence was judged to be low, due to a small pooled sample size in addition to unexplained important heterogeneity and imprecision respectively (Summary of findings 2).

For pregabalin or gabapentin, the evidence was judged to be of low quality at all time points due to small pooled sample sizes and possible indirectness of effect due to difference in pharmacological properties between the two drugs (Summary of findings 3).

For acetaminophen, the quality of the evidence for acute postoperative pain intensity in the first 6 hours and at 12 hours was judged to be moderate, being downgraded one level due to a small pooled sample size. The quality of the evidence for pain intensity at 24 hours was judged to be high (Summary of findings 4).

For scalp infiltration, the overall quality of the evidence was judged to be moderate for the pooled estimates of effect for acute postoperative pain intensity in the first 6, 24 and 48 hours after surgery after having been being downgraded one level due to unexplained important heterogeneity or small sample sizes. For acute postoperative pain intensity at 12 hours, the quality of the evidence was judged to be low due to a small pooled sample size and loss of significance of results on sensitivity analysis (Summary of findings 5).

For scalp block, the overall quality of the evidence was judged to be low for the pooled estimates of effect for acute postoperative pain intensity in the first 6 hours, at 12 hours and at 24 hours after surgery, after having been downgraded two levels due to unexplained important heterogeneity and failure to retain significance of results on sensitivity analysis. For acute postoperative pain intensity at 48 hours, the quality of the evidence was judged to be very low, due to unexplained important heterogeneity, small pooled sample size and failure to retain the initial beneficial effect with sensitivity analysis (Summary of findings 6).

Additional analgesia requirement

For the outcome of additional analgesia requirement in the first 24 hours postoperatively, a low quality rating was assigned to the pooled estimates of effect for NSAIDs (due to a small pooled sample size and a wide 95% CI), dexmedetomidine and scalp block (due to a small pooled sample size and unexplained important heterogeneity) (Summary of findings for the main comparison; Summary of findings 2; Summary of findings 6), and gabapentin and pregabalin due to a small pooled sample size and indirectness of effect (Summary of findings 3). A high quality rating was assigned

to the pooled estimate of effect for acetaminophen (Summary of findings 4).

A very low-quality rating was also assigned to the effect estimate for scalp infiltration due to a small pooled sample size, a wide 95% CI and unexplained important heterogeneity (Summary of findings 5).

A high-quality rating was assigned to the effect estimate for acetaminophen (Summary of findings 4).

Length of hospital stay (hours)

For the one intervention (acetaminophen) that measured this outcome, the quality of the evidence was judged to be moderate, being downgraded one level due to a small pooled sample size (Summary of findings 4).

Adverse event: nausea and vomiting

The quality of the evidence for this outcome was judged to low for NSAIDs, dexmedetomidine and scalp infiltration, being downgraded two levels due to a small number of total events and wide 95% CIs (Summary of findings for the main comparison; Summary of findings 2; Summary of findings 5). The quality of the evidence for this outcome for gabapentin or pregabalin was also judged to be low due to a small number of total events and indirectness, as the two drugs differ somewhat in their pharmacological properties (Summary of findings 3). The quality of the evidence for this outcome for scalp blocks was judged to be very low on the basis of a small number of total events, unexplained important heterogeneity and a wide 95% CI (Summary of findings 6).

Potential biases in the review process

Differences between the protocol and review

Due to the way in which data were reported in the included studies, it was necessary to make several deviations from the protocol in an effort to make the best use of available data (see Differences between protocol and review). The change from the intended measure of pain intensity over time periods to the actual measure of pain intensity at discrete times compromises the accuracy of any inference regarding the analgesic efficacy of included interventions at time points other than those analysed. Similarly, the change in the measure of additional analgesia consumption over the intended four time periods to the single 0 to 24-hour period (which was again made to reflect the way in which studies reported this outcome), means that inferences about time periods outside 0 to 24 hours postoperatively are subject to inaccuracy.

We chose to exclude studies that investigated the use of agents with analgesic potential for non-analgesic purposes. The rationale for this decision was based on a high likelihood of important differences in inclusion and exclusion criteria, dosages, timing, ancillary analgesic usage, and attributable side effects between studies that investigated these agents for their analgesic efficacy and studies that investigated them for their non-analgesic effects. While this approach meant that potential outcomes of interest were not captured when these agents were investigated for their other non-analgesic effects, it provided a more accurate estimate of the effects and side effects of those agents, when used with analgesic intent.

Approach to overall risk of bias judgements

To determine whether a study had an overall high risk of bias, we choose the following definition: a high risk of bias in four or more of the seven domains of bias, or a high risk of bias in three or more of the seven domains of bias with an unclear risk of bias in one or more domain. This approach is more liberal than the Cochrane guidance (Higgins 2011), which recommends classifying a study at an overall high risk of bias if it is deemed to be at high risk of bias in one or more domains or raises concerns across multiple domains. We choose a more liberal definition on the basis of the following considerations.

Firstly, our review examined a discrete population with higher short-term morbidity and mortality than many other study populations. Clinical studies in this population often have to be conducted with smaller sample sizes and are subject to early losses to follow-up due to a higher incidence of postoperative complications, need for advanced life support and relatively high postoperative mortality. Classifying studies as having an overall high risk of bias on the basis of high loss to follow-up alone would have incurred the risk of undervaluing a sizeable amount of data, and limiting external validity by giving greater credence to studies that may have included participants with lower perioperative mortality and morbidity than the average patient undergoing brain surgery. While small sample sizes are common in clinical studies of discrete populations, and while we chose not to use this criterion in isolation to judge a study as being at high risk of bias, we did downgrade the quality of evidence for effect estimates where the pooled sample size was small.

Secondly, many of our included studies were deemed to be at high of bias due to lack of allocation concealment. While allocation concealment is an important measure to prevent selection bias, classifying studies that did not report it as having an overall high risk of bias would likely overestimate the true occurrence and impact of selection bias for trials that were conducted in a discrete group of patients with similar baseline characteristics who were undergoing similar surgery and whose postoperative outcomes would be assessed over similar time periods. While allocation concealment would be the ideal measure to ensure minimization of selection bias, its absence does not necessarily imply that research personal would have either the inclination or opportunity to preselect patients from an already predefined cohort to achieve a particular result or that the probability of achieving that result would be significantly altered by their actions. The complex reality of pain physiology with psychosocial, genetic, biochemical and, as yet, unknown mechanisms all feeding into individual pain perception and pain reporting make predicting individual postoperative pain outcomes among otherwise similar groups of patients very difficult and not likely to be easily predicted or influenced by research personnel.

Thirdly, although blinding is important for validity, for patient-reported pain outcomes, the impact of lack of blinding on study validity is likely to be greater when the study participants are not blinded then when the study personnel are not blinded. A lack of blinding of study personnel would be much more likely to compromise validity where study participants are not blinded either. All three studies that we deemed to have a high risk of bias due to lack of blinding of study participants, (Choi 2009; Kiskira 2006; Zhang 2003), were also at high risk of bias due to lack of

blinding of study personnel and all three studies were deemed to have an overall high risk of bias based on our criteria.

Our more liberal definition seemed a sensible approach to estimating the overall risk of bias for studies of the efficacy of different interventions for preventing patient-reported pain in those undergoing brain surgery. However, it may have underestimated the overall risk of bias for studies where a high risk or unclear risk of bias in any particular domain may have had a particular influence on study validity. What effect these factors have in isolation on overall study validity are difficult to estimate but it is probably fair to say they are more likely to compromise it significantly if other efforts to reduce risk of bias are not robust.

Scope of the review

Another important limitation of this review is that it addressed only pharmacological interventions aimed at preventing postoperative pain and did not address other approaches to pain prevention, including acupuncture, hypnosis or psychological techniques, some of which have been shown to be effective in other surgical populations (Powell 2016).

Agreements and disagreements with other studies or reviews

We found three other systematic reviews of pain relief after craniotomy.

The study by Hansen and colleagues, (Hansen 2011), included only double-blind trials in which the results were published in English. Four interventions were included: scalp block, scalp infiltration, morphine and parecoxib, but no pooled estimates of effect were calculated. They concluded that scalp block may provide analgesia up to six hours postoperatively, scalp infiltration may provide analgesia adequate analgesia for the first few hours after surgery, morphine may reduce additional analgesia consumption, with little evidence to support the use of parecoxib.

A systematic review and meta-analysis of regional scalp block after craniotomy including seven RCTs (Gilfoyle 2012), found a pooled mean reduction in pain score (measured on a scale of 0 to 10) at one hour postoperatively of −1.61 (95% CI −2.06 to −1.15; P < 0.001). Subgroup analysis showed that preoperative scalp block reduced pain significantly in the first four hours after surgery while postoperative scalp block reduced pain significantly up to 12 hours postoperatively. There was also an overall reduction in the opioid requirements over the first 24 hours postoperatively. The authors concluded scalp block had a role in the reduction of pain after craniotomy.

A recently published review of 19 RCTs showed that opioids provided superior pain relief over other analgesics (Tsaousi 2016), however there were some important limitations to their findings: four of the five included studies examining the role of opioids for pain relief after craniotomy used an active comparator rather than a control with the comparison being between different opioid regimens rather than an evaluation of the efficacy of opioids alone; no pooled estimate of effect was calculated; and no studies published in a language other than English or published prior to 2011 were included. The same study evaluated scalp infiltration and scalp blocks together and only three RCTs were included. The results of these studies were presented separately with no overall assessment of effect, making it difficult to draw any conclusion regarding overall effectiveness. The authors found some evidence to support the use of diclofenac and dexmedetomidine with the caveat that the number of included studies for each intervention was small (three RCTs each).

When comparing our results to these three published reviews, it is important to note these comparisons are limited by the methodologic differences between our review and these published studies. Overall, our review captures a broader view of the available evidence as it is neither language-restricted or intervention-specific. It also differs from the study by Tsaosi in that only interventions evaluated against a control or placebo were included.

Both Hansen and colleagues (Hansen 2011), and Gilfoyle and colleagues (Gilfoyle 2012) reported beneficial effects of scalp blocks in reducing early postoperative pain. When we excluded studies with a high risk of bias, we did not find benefit in the very early postoperative period but did find that scalp block reduced pain at 12 hours. Interestingly, our subgroup analysis results differed from those of Gilfoyle, in that we found that scalp blocks performed before surgical incision reduced pain at 12 and 24 hours postoperatively, while those performed after the surgical incision, reduced pain in the first 6 hours. These effects were only seen when we excluded studies with a high risk of bias which may in part explain why our findings differed from those of Gilfoyle. When we did not exclude studies with a high risk of bias, we found the post-incision scalp block produced significant pain relief at all time points up to and including 24 hours.

Unlike the study by Hansen (Hansen 2011), we did not find that scalp infiltration reduced early postoperative pain but we did find that it reduced pain at 48 hours.

Similar to the study by Tsaousi (Tsaousi 2016), we found that both NSAIDs and dexmedetomidine may have a role in the reduction of post-craniotomy pain.

Regarding the role of opioids, we did not find an adequate number of eligible studies to calculate a pooled estimate of effect for their effect on postoperative pain intensity or additional analgesia consumption, and so can neither refute nor confirm their role in either regard.

Comparing our results to systematic reviews of postoperative analgesia in wider surgical populations, there are some commonalities.

Doleman and colleagues (Doleman 2018), addressed the role of pre versus post-incision opioids in adults undergoing all types of surgery and did not find any significant difference in analgesic efficacy with the important caveat that their findings were severely limited by both the quantity and quality of evidence. We encountered a lack of evidence to guide intervention timing, with scalp block being the only intervention with enough high-quality studies to provide robust information regarding the efficacy of pre- versus post-incision blocks.

Jessen Lundoff and colleagues (Jessen Lundorf 2016,) examined the role of dexmedetomidine in pain reduction after abdominal surgery and found that it seemed to have an opioid-sparing effect but did not, in general, reduce acute postoperative abdominal pain. Their results contrast with our findings of a reduction in pain in the first 12 hours after brain surgery in patients receiving

dexmedetomidine, but are concordant with our findings of reduced additional analgesia requirements in those who received dexmedetomidine. However, it is important to note that the quality of the evidence that we found for the postoperative analgesic effect of dexmedetomidine was generally low. The only moderate-quality evidence available was for its analgesic potential in the first six hours after surgery.

It makes physiological sense for a reduction in additional analgesia requirement to be related to analgesic benefit and so it is reasonable to assume that an effective analgesic would lessen the need for other analgesics. However, like Lundoff, our review did not find the two effects were consistently linked. We found, for instance, that NSAIDs provided effective pain relief for up to 24 hours after brain surgery, but did significantly result in reduced additional analgesia requirements in the same time period. The reason for this dichotomy is uncertain, with the quality and quantity of the evidence being a confounding factor when determining whether it is a true finding or not.

AUTHORS' CONCLUSIONS

Implications for practice

There is high-quality evidence that NSAIDs reduce pain up to 24 hours postoperatively. The evidence for reductions in pain with dexmedetomidine, pregabalin or gabapentin, scalp blocks, and scalp infiltration is less certain and of generally low quality. There is low-quality evidence that scalp blocks and dexmedetomidine may reduce additional analgesics requirements. There is evidence that gabapentin or pregabalin may decrease nausea and vomiting, with the caveat that the total number of events for this comparison was low.

Implications for research

Future studies addressing this research question would benefit from focusing on some of the limitations we encountered with current evidence.

Specifically:

1. Most existing data arise from studies of pain measured at discrete time points, making the assessment of pain as a true continuous outcome very difficult. To get an accurate picture of postoperative pain, future studies would benefit from measuring it over time periods rather than at discrete time points.
2. We found most eligible studies did not address pain or additional analgesia requirements beyond the first 24 hours postoperatively; in order to get a more complete picture of the effect of any pain-reducing intervention, future studies should consider addressing pain outcomes beyond the first 24 hours.
3. There is currently a paucity of data regarding chronic headache after craniotomy and the role of pain-reducing interventions in its incidence.
4. Aside from nausea and vomiting, other adverse events were not generally widely studied or well defined; future studies should ensure that clearly defined adverse events are included in their outcomes.
5. Some of our findings were limited by the methodologic quality of the included studies; as with all research questions, methodologic rigour should be a priority to provide an accurate answer to the question being addressed.

Given the limitations we encountered, our study did provide some potentially interesting information that may inform future research in this area:

1. NSAIDs showed significant analgesic efficacy up to 24 hours postoperatively. However, one should bear in mind their potential side effects which are particularly relevant in this population;
2. We found it somewhat surprising that while NSAIDs produced a reduction in pain intensity; this did not translate into a significant reduction in additional analgesia requirements and this would be worth investigating further;
3. Gabapentin or pregabalin reduced pain up to six hours postoperatively, with the limitation of this finding being based on low-quality evidence;
4. Dexmedetomidine is a relative newcomer to the postoperative analgesia scene and may have a role in the reduction of early postoperative pain after craniotomy. Further studies addressing its effects in this population would help establish whether the benefit we observed is real or not. The generally low quality of the evidence we found for its postoperative analgesic potential in this population underscores the uncertainty regarding its effectiveness;
5. Similar to previous reviews, we found scalp block to be beneficial for acute postoperative pain but, in contrast to previous reviews, we found that scalp blocks performed before surgery might provide more prolonged pain relief while those performed after surgery might provide more prompt pain relief;
6. While scalp infiltration reduced pain 48 hours after surgery, we did not find that it was effective in the reduction of pain at any time prior to this.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Akcil 2017

Methods	Study design: randomized, placebo controlled study (3 arms) Study duration: May 2014 to December 2016 Study setting: hospital, single centre, Turkey
Participants	Adults undergoing elective infratentorial craniotomy (n = 45) **Inclusion criteria** 1. ASA I to ASA III **Exclusion criteria** 1. Allergy to bupivacaine or opioids 2. Chronic hypertension 3. Coronary artery disease, arrhythmia 4. Coagulopathy, cerebrovascular disease 5. Raised intracranial pressure 6. Trigeminal neuralgia 7. Previous craniotomy **Mean age, range (years)** 1. 39 (18 to 70) **Numbers allocated to each arm** 1. Group S (scalp block) (n = 15) 2. Group I (local anaesthetic infiltration) (n = 15) 3. Group C (control) (n = 15) **Male gender** 1. Group S (scalp block) = 7/15 2. Group I (local anaesthetic infiltration) = 4/15 3. Group C (control) = 4/15
Interventions	**Technique and timing** 1. **Scalp block:** performed 10 minutes before pinning. The supraorbital and supratrochlear nerves were blocked bilaterally with 6 mL bupivacaine 0.5% injected above the midline of the eyebrow, perpendicular to the skin. The auriculotemporal nerves were blocked bilaterally with 4 mL bupivacaine 0.5% injected to 1.5 cm anterior of the ear at the level of tragus, the needle was introduced perpendicular to the skin and injection was performed deeply to fascia and superficially as the needle was withdrawn. The postauricular branches of the greater auricular nerves were blocked bilaterally with 2 mL bupivacaine 0.5% injected to 1 cm posterior to the ear at the level of tragus, between bone and skin. The greater, lesser and third occipital nerves were blocked bilaterally with 8 mL bupivacaine 0.5% injected along the superior nuchal line, approximately halfway between the occipital protuberance and mastoid process. 2. **Local anaesthetic infiltration:** performed 10 minutes before pinning. The pinning points and the surgical incision sites were infiltrated with 20 mL of bupivacaine 0.5%. 3. **Control group:** IV bolus 50 µg remifentanil was administered 10 minutes before pinning.
Outcomes	**Primary**

Akcil 2017 *(Continued)*

	1. Haemodynamic response to pin head holder application and to skin incision in infratentorial craniotomies **Secondary** 1. Pain scores in the first 24 hours after surgery 2. Morphine consumption in the first 24 hours after surgery
Notes	**Funding** None

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote ''Patients were randomized to one of three groups using a closed envelope technique.'' The authors describe the study as randomized, providing details about how allocations were concealed. However, they do not describe how random assignment was ensured
Allocation concealment (selection bias)	Low risk	Sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: ''The patient and the anesthesiologist who recorded postoperative pain scores were blinded in every case. But the anesthesiologist who applied the scalp block and followed the haemodynamic response to pin fixation and skin incision were sometimes same person''. This implies that study personnel blinding was not consistent for their primary outcome of intraoperative haemodynamic response to pin insertion but was consistent for the their secondary postoperative pain outcomes.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: ''the patient and the anesthesiologist who recorded postoperative pain scores were blinded''.
Incomplete outcome data (attrition bias) All outcomes	Low risk	2/45 patients were excluded, 1 due to intraoperative blood loss and 1 due to a low level of consciousness at the end of surgery.
Selective reporting (reporting bias)	Low risk	Outcomes were reported as specified
Other bias	Unclear risk	Small study

Ali 2010

Methods	Study design: randomized controlled trial (2 arms) Study duration: Febuary 2007 to September 2008 Study setting: hospital, single centre, Egypt
Participants	Adults undergoing elective trans-nasal resection of pituitary tumours **Inclusion criteria**

Ali 2010 *(Continued)*

	1. ASA I to ASA II **Exclusion criteria** 1. Decreased level of consciousness 2. Bleeding disorder 3. Raised ICP 4. Liver, renal, cardiac or pulmonary dysfunction 5. Receiving drugs that affect coagulation or cardiovascular medications **Mean age, range (years)** 1. 40 (20 to 60) **Numbers allocated to each arm** 1. Group intervention (n = 15) 2. Group control (n = 15) **Male gender** 1. Group intervention: 9/15 2. Group control: 10/15
Interventions	**Technique and timing** 1. Bilateral sphenopalatine ganglia blocks with 1.5 mL of 0.5% bupivacaine versus 1.5 mL of saline, administered after induction of anaesthesia (n = 30) **Dosage** 1.5 mL
Outcomes	**Primary** 1. Intraoperative sevoflurane requirement **Secondary** 1. Intraoperative nitroglycerine requirement 2. Pain as measured by the visual analogue scale (VAS) measured at 30-minute intervals up to 180 minutes after surgery 3. Postoperative recovery time as measured by an Alderet Score of less than or equal to 9 4. Adverse events - nausea and vomiting, sedation, headache, nose bleed, visual disturbance, agitation
Notes	**Funding** None

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Reported as randomized but method not reported
Allocation concealment (selection bias)	Low risk	Sealed envelopes

Ali 2010 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Study solutions were prepared by an investigator who was not otherwise involved in the study.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Study solutions were prepared by an investigator who was not otherwise involved in the study.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants were included in the final analysis.
Selective reporting (reporting bias)	Low risk	Outcomes reported as specified
Other bias	Unclear risk	Small study

Artime 2018

Methods	Study design: randomized controlled trial (2 arms) Study duration: 2013 to 2016 Study setting: hospital, single centre, USA
Participants	**Inclusion criteria** 1. Adults undergoing scheduled supratentorial craniotomy for mass resection **Exclusion criteria**. 1. Chronic opioid therapy 2. Liver or renal dysfunction 3. Any pain medication received in the 12 hours before surgery 4. Weight < 50 kg or more than 120 kg 5. Allergy to study medications 6. Neurological conditions rendered them unable to be evaluated reliably after surgery **Mean age (years)** 1. 50 **Numbers allocated to each arm** 1. Group intervention (n = 50) 2. Group control (n = 50) **Male gender** 1. Group intervention: 26/50 2. Group control: 19/50
Interventions	**Technique and timing** 1. Patients randomized to the intervention group received 1000 mg of IV acetaminophen in the operating room after induction of general anaesthesia but before skin incision. This dose was to be repeated

Artime 2018 *(Continued)*

	every 6 hours for a total of 24 hours after the conclusion of surgery. Patients randomized to the placebo group received the same volume (100 mL) of 0.9% saline instead at similar times. **Dosage** As above
Outcomes	**Primary** 1. Total amount of opioid consumed in the 24 hours after surgery, calculated in morphine equivalents **Secondary** 1. Pain as measured by the visual analogue score 2. Patient satisfaction 3. Nausea and vomiting 4. Pruitis 5. Drowsiness 6. Time to extubation 7. Time to discharge from the postoperative recovery unit
Notes	**Funding** The study was sponsored by Mallinckrodt Pharmaceuticals.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: ''Randomization was performed by the hospital investigational pharmacy based on computer based random list generator''.
Allocation concealment (selection bias)	Low risk	Quote: ''Patients and all study personnel including research assistants, anaesthesiologists, neurosurgeons, and intensivists were blinded to group allocation''.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: ''Patients and all study personnel including research assistants, anaesthesiologists, neurosurgeons, and intensives were blinded to group allocation''.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote ''This blind remained closed until after collection of data and analysis by the biostatistician''.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	5 patients in the intervention group were not included in the analysis (2 had mental status changes that precluded assessment, 2 had redo procedures and 1 had a different procedure). 9 patients in th control group were not included in the analysis (1 had a missing data sheet, 5 had complications, 3 withdrew from the study).
Selective reporting (reporting bias)	Unclear risk	The title focused on a positive secondary outcome while the primary outcome itself was not statistically significant.
Other bias	Unclear risk	Funded by a pharmaceutical company After losses to follow-up the study was underpowered for its primary outcome.

Bala 2006

Methods	Study design: randomized controlled trial (2 arms) Study duration: not reported Study setting: hospital, single centre, India
Participants	Adult patients undergoing elective supratentorial craniotomy for brain tumours (n = 40) **Inclusion criteria** 1. ASA I to ASA II **Exclusion criteria** 1. Decreased level of consciousness 2. Allergy to bupivacaine 3. Undergoing emergency surgery **Mean age, range (years)** 1. 34 (18 to 50) **Numbers allocated to each arm** 1. Group intervention (n = 20) 2. Group control (n = 20) **Male gender** 1. Group intervention: 10/20 2. Group control: 15/20
Interventions	**Technique and timing** Scalp block of the following nerves with 0.5% bupivacaine and adrenaline 1:400,000 adrenaline 1. Supraorbital and supratrochlear 2. Zygomaticotemporal 3. Auriculotemporal 4. Postauricular branches of the greater auricular 5. Greater, lesser, and third occipital nerves versus scalp block, with saline and adrenaline 1:400,000, at the end of surgery **Dosage** 20 mL
Outcomes	**Primary** 1. Pain as measured by the NRS (numerical pain rating scale) in the first 12 hours postoperatively (measured at 30 minutes, 1, 2, 4, 6, 8 and 12 hours) **Secondary** 1. Total amount of rescue analgesia required 2. Time to requirement of rescue analgesia 3. Blood pressure, heart rate and respiratory rate 4. Sedation Score using a 4-point scale

Bala 2006 *(Continued)*

	5. GCS (Glasgow Coma Scale)
Notes	**Funding** No funding source reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: ''patients were randomly divided into two groups using a computer generated random number chart''.
Allocation concealment (selection bias)	High risk	Authors did not provide any details regarding how the allocation sequence was concealed.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: ''the neurosurgeon, the anaesthetist performing the scalp block and the patients were blinded to the drug being administered''.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: ''the anaesthetist performing the block did not participate in the post-operative pain assessment''.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All enrolled participants were followed up for outcomes.
Selective reporting (reporting bias)	Low risk	Outcomes reported as specified
Other bias	Unclear risk	Small study

Batoz 2009

Methods	Study design: randomized controlled trial (2 arms) Study duration: June 2006 to April 2007 Study setting: hospital, single centre, France
Participants	Adults undergoing elective craniotomy for tumour resection (n = 53) **Inclusion criteria** 1. ASA I to ASA III **Exclusion criteria** 1. Pre- or postoperative aphasia 2. Neurological disorders preventing a good understanding of the protocol and the visual analogue scale (VAS) and use of narcotic analgesics 3. Chronic pain 4. Alcohol or drug misuse 5. Stroke or neurosurgery 6. Suspicion of high intracranial pressure

Batoz 2009 *(Continued)*

	7. Glasgow coma scale < (GCS) 15 8. Pregnant 9. Age < 18 years or > 80 years **Mean age, range (years)** 1. 61 (50 to 70) **Numbers allocated to each arm** 1. Group intervention (n = 25) 2. Group control (n = 27) **Male gender** 1. Group intervention: 12/25 2. Group control: 12/27
Interventions	**Technique and timing** 1. Scalp infiltration with 0.75% ropivacaine versus no scalp infiltration, at the end of surgery before wound closure **Dosage** Not reported
Outcomes	**Primary** 1. Nalbuprine consumption in the first 24 hours postoperatively **Secondary** 1. Pain as measured by the visual analogue scores during the first 24 hours postoperatively 2. Incidence of postoperative nausea and vomiting 3. Persistent pain at 2 months postoperatively 4. Persistent neuropathic pain at 2 months postoperatively
Notes	**Funding** None reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Authors reported that a computer-generated randomization method was used.
Allocation concealment (selection bias)	High risk	Authors did not provide any details regarding how the allocation sequence was concealed.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The participants were blinded but the method and its adequacy was not described and no mention was made of blinding those who administered the intervention.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Those assessing outcomes were blinded to treatment received but again the method and its adequacy were not described.

Batoz 2009 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	There were relatively few losses to follow-up and clear reasons were provided for these: 52 of the 53 enrolled participants were followed up for the primary outcome, 1 participant being lost to follow-up as their data were mislaid. 48 participants were followed up for pain outcomes at 2 months, 3 had died and 1 participant had moved away.
Selective reporting (reporting bias)	Low risk	All outcomes were reported in the priority in which they were specified.
Other bias	Unclear risk	Small study

Bekker 2008

Methods	Study design: randomized controlled trial (2 arms) Study duration: not reported Study setting: hospital, single centre, USA
Participants	Adults undergoing elective craniotomy (n = 72) **Inclusion criteria** 1. Adults undergoing elective craniotomy **Exclusion criteria** 1. Significant laboratory abnormalities 2. Advanced heart block 3. Allergy to study drugs **Mean age, range (years)** 1. 42 (18 to 65) **Numbers allocated to each arm** 1. Group intervention: not reported but 28 included in analysis 2. Group control: not reported but 28 included in analysis **Male gender** 1. Group intervention: 17/28 2. Group control: 20/28
Interventions	**Technique and timing** 1. Dexmedetomidine by intravenous infusion as an initial bolus of 10 mcg/kg/hr for 10 minutes and then 5 mcg/kg/hr, commenced after intubation and continued until 20 minutes before the end of surgery versus saline infusion **Dosage** 1. Bolus of 10 mcg/kg/hr for 10 minutes and then 5 mcg/kg/hr
Outcomes	**Primary** 1. Haemodynamic response to surgery

Bekker 2008 *(Continued)*

	Secondary 1. Analgesic requirement in the postoperative recovery unit 2. Anti-emetic requirement in the postoperative recovery unit 3. Antihypertensive requirement in the postoperative recovery unit 4. Adverse events - hypertension (systolic blood pressure > 130 mmHg), hypotension (systolic blood pressure < 90 mmHg), tachycardia (heart rate < 50), bradycardia (heart rate > 90)
Notes	**Funding** None

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: ''patients scheduled for elective craniotomy were randomly assigned to receive either sevoflurane–opioid or sevoflurane–opioid–DEX anaesthesia''. However, the method of randomization was not described.
Allocation concealment (selection bias)	High risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: ''the anaesthetic was managed by experienced neuroanaesthesiologists blinded to DEX or placebo regimen''. There was no mention of blinding participants, however as the infusion was started after the participants were anaesthetized and stopped before they were woken up, the lack of patient blinding is very unlikely to have had a significant impact on the results.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: ''anesthesiologist and nurses who were unaware of anaesthetic technique managed postoperative recovery of the study patients''.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	16 participants were recruited but not included in the final analysis. Of these, 1 from each of the study groups was removed from analysis, 1 because of bleeding and the other because they remained intubated after surgery. The remaining 14 recruited participants were not included in the final analysis as technical problems precluded recovery of their data.
Selective reporting (reporting bias)	Low risk	Outcomes reported as specified
Other bias	Unclear risk	Small study

Biswaz 2003

Methods	Study design: randomized controlled trial (2 arms) Study duration: not reported Study setting: hospital, single centre, India
Participants	Adults undergoing elective supratentorial craniotomy for tumour resection (n = 50) **Inclusion criteria** 1. ASA I to ASA II

Biswaz 2003 *(Continued)*

2. Fully conscious
3. No signs of raised intracranial pressure

Exclusion criteria

1. Chronic narcotic use
2. Diabetes mellitus
3. Cerebrovascular disease
4. Coronary artery disease, hypertension
5. Allergy to local anaesthetics
6. Previous scalp incision
7. Those who required skull pin fixation
8. Surgery planned for sitting position
9. Inability to understand the visual analogue scale
10. Documented or suspected hypersensitivity to NSAIDS
11. Following termination of anaesthesia, patients who were drowsy (Glasgow Coma Score < 14) after extubation and patients who could not be extubated were also excluded from the study.

Mean age, range (years)

1. 39 (32 to 45)

Numbers allocated to each arm

1. Group intervention (n = 25)
2. Group control (n = 25)

Male gender

1. Group intervention: 14/21
2. Group control: 10/20

Interventions	**Technique and timing** 1. Scalp infiltration with 0.25% bupivacaine versus scalp infiltration with saline, pre surgical incision **Dosage** 25 mL
Outcomes	**Primary** 1. Pain as measured by VAS at the following times 1, 6, 12, 24, 36, and 48 hours postoperatively **Secondary** 1. Time to requirement of rescue analgesia 2. Total amount of rescue analgesia required
Notes	**Funding** No funding source reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Authors reported that a computer-generated randomization method was used.

Biswaz 2003 *(Continued)*

Allocation concealment (selection bias)	High risk	Authors did not provide any details regarding how the allocation sequence was concealed.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: ''one investigator prepared 25 mL of bupivacaine (0.25%) without adrenaline for the treatment group and a 25-mL solution of normal saline for the control group and handed it to the assisting nursing staff for scalp infiltration by the neurosurgeon. All solutions were prepared in identical syringes, and everyone was blinded to the assignment except the second author''.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: '' each patient was coded by the second author. The code was broken only after all the data were collected and analysed by the first author''.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Nine participants were excluded from the analysis as they required postoperative ventilation: 5 from the intervention group: 4 from control group. The subsequent lack of an intention-to-treat analysis makes the effects of their exclusion on the measured outcomes difficult to determine.
Selective reporting (reporting bias)	Low risk	All outcomes were reported in the priority in which they were specified.
Other bias	High risk	Small study and no sample size calculation provided

Bloomfield 1998

Methods	Study design: randomized controlled trial (2 arms) Study duration: not reported Study setting: hospital, single centre, USA
Participants	Adults undergoing elective craniotomy (n = 36) **Inclusion criteria** 1. ASA II and ASA III participants undergoing elective supratentorial craniotomy for brain tumours, clipping of an unruptured cerebral aneurysm, or removal of an epileptic focus **Exclusion criteria** 1. Previous scalp incision 2. Previous history of hypertension 3. Local anaesthetic allergy 4. Surgery in the sitting position **Mean age, range (years)** 1. 43 (18 to 68) **Numbers allocated to each arm** 1. Group intervention (n = 18) 2. Group control (n = 18)

Bloomfield 1998 *(Continued)*

	Male gender 1. Group intervention: 14/18 2. Group control: 6/18
Interventions	**Technique and timing** 1. Scalp infiltration with 0.25% bupivacaine with epinephrine 1:200,000 versus scalp infiltration with saline with epinephrine 1:200,000, presurgical incision and again at the end of surgery. Pin sites were injected before skeletal fixation. The site of incision was infiltrated subcutaneously using a sterile syringe and 22-gauge needle. At the end of surgery and before final closure of the scalp, the surgeon again infiltrated the wound margins with the same solution that was used at the beginning of the procedure. **Dosage** Max 2 mg/kg
Outcomes	**Primary** 1. Haemodynamic parameters (heart rate, blood pressure) intra and postoperatively **Secondary** 1. Pain as measured by the VAS in the first 60 minutes after arrival in the postoperative recovery unit
Notes	**Funding** No funding source reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Reported as randomized but no details were provided regarding the method used
Allocation concealment (selection bias)	High risk	Authors did not provide any details regarding how the allocation sequence was concealed.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: ''the anaesthesiologist, surgeon, and patient were blinded to the solution''. However no details were provided regarding the method used or how or if its adequacy was assessed.
Blinding of outcome assessment (detection bias) All outcomes	High risk	No details were provided as to whether or not those assessing outcomes were blinded to treatments received.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No participants were lost to follow-up and all 36 participants were included in the final analysis.
Selective reporting (reporting bias)	Low risk	Outcomes were reported as specified.
Other bias	High risk	Small study and no sample size calculation provided

Can 2017

Methods	Study design: randomized, placebo controlled study (3 arms) Study duration: March 2008 to April 2009 Study setting: hospital, single centre, Turkey
Participants	Adults undergoing elective craniotomy (n = 90) **Inclusion criteria** 1. ASA II and ASA II participants undergoing elective craniotomy **Exclusion criteria** 1. Arrhythmia 2. Uncontrolled hypertension 3. Diabetes 4. Coronary artery disease 5. Coagulopathy 6. Local anaesthetic allergy **Mean age, range (years)** 1. 48 (18 to 85) **Numbers allocated to each arm** 1. Group B (n = 30) 2. Group L (n = 30) 3. Group C (n = 30) **Male gender** 1. Group B = 11/30 2. Group L = 11/30 3. Group C = 15/30
Interventions	**Technique and timing** Scalp block of the following nerves: 1. Supraorbital and supratrochlear 2. Zygomaticotemporal 3. Auriculotemporal 4. Postauricular branches of the greater auricular 5. Greater, lesser, and third occipital nerves 5 minutes prior to pinning, using either 20 mL of 0.5% bupivacaine, 20 mL of 0.5% levo-bupivacaine or saline
Outcomes	**Primary** 1. Mean arterial blood pressure **Secondary** 1. Heart rate 2. Pain as measured by the VAS in the first 24 hours after surgery 3. Additional drug requirement intraoperatively 4. Numbers of participants requiring additional analgesia in the first 24 hours postoperatively

Can 2017 *(Continued)*

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote 'The patients were randomly divided into three groups using a sealed-enveloped technique'' The authors describe allocation concealment but do not provide details regarding how random allocation was ensured
Allocation concealment (selection bias)	Low risk	Sealed envelope
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Block solutions were prepared and numbered by a blinded assistant.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Those assessing outcomes were unaware of the treatment allocations.
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were no losses to follow-up.
Selective reporting (reporting bias)	Low risk	Outcomes were reported as specified.
Other bias	High risk	Long time between study conduct and publication and small study

Choi 2009

Methods	Study design: randomized controlled trial (2 arms) Study duration: not reported Study setting: hospital, single centre, China
Participants	Adults undergoing elective craniotomy (n = 32) **Inclusion criteria** 1. Adults undergoing elective craniotomy **Exclusion criteria** 1. Inability to understand the pain scoring system 2. Allergy to study drugs **Mean age, range (years)** 1. 44 (18 to 70) **Numbers allocated to each arm** 1. Group intervention (n = 16) 2. Group control (n = 16)

Choi 2009 *(Continued)*

	Male gender 1. Group intervention: 5/16 2. Group control: 4/16
Interventions	**Technique and timing** Scalp block of the following nerves: 1. Supraorbital and supratrochlear 2. Zygomaticotemporal 3. Auriculotemporal 4. Postauricular branches of the greater auricular 5. Greater, lesser, and third occipital nerves with 0.75% ropivacaine versus scalp block with saline, at the end of surgery **Dosage** 2 to 3 mL per nerve
Outcomes	**Primary** 1. Pain as measured by the VAS (0 to 100 mm) during the first 48 hours postoperatively (at 30 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 12 hours, 24 hours and 48 hours) **Secondary** 1. Time to requirement of rescue analgesia 2. Total amount of rescue analgesia required 3. Heart rate and blood pressure
Notes	**Published in Chinese only** 1. Paper published in Chinese only, translator used but translation errors possible **Funding** None

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A computer-generated randomization table was used.
Allocation concealment (selection bias)	High risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not reported
Incomplete outcome data (attrition bias)	Low risk	No losses to follow-up. All participants were included in the final analysis.

Choi 2009 *(Continued)*

All outcomes

Selective reporting (reporting bias)	Low risk	Outcomes reported as specified
Other bias	Unclear risk	Small study

Cokay 2013

Methods	Study design: randomized controlled trial (2 arms) Study duration: not reported Study setting: hospital, single centre, Turkey
Participants	Adults undergoing elective craniotomy (n = 60) **Inclusion criteria** 1. ASA I to ASA III participants **Exclusion criteria** 1. Not specified **Mean age, range (years)** 1. 49 (18 to 80) **Numbers allocated to each arm** 1. Not reported **Male gender** 1. Not reported
Interventions	**Technique and timing** 1. Scalp block with 2.5% bupivacaine versus scalp block with saline before surgery, specific nerves blocked were not reported **Dosage** 20 mL
Outcomes	**Primary** 1. Haemodynamic parameters (no specific details provided) **Secondary** 1. Pain as measured by the visual analogue score 2. Time to requirement of rescue analgesia 3. Total amount of rescue analgesia required
Notes	**Published in abstract format only** 1. Paper published in abstract format only so many details not reported **Funding**

Cokay 2013 *(Continued)*

	None

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Reported as randomized but method used was not reported
Allocation concealment (selection bias)	High risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Reported as double-blinded but method or adequacy not reported
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	Not reported
Selective reporting (reporting bias)	Low risk	Outcomes were reported as specified.
Other bias	High risk	A lot of data missing so difficult to determine overall methodologic rigour

Dilmen 2016

Methods	Study design: randomized controlled trial (4 arms) Study duration: June 2013 to January 2015 Study setting: hospital, single centre, Turkey
Participants	Adults undergoing elective supratentorial craniotomy (n = 83) **Inclusion criteria** 1. ASA I to III participants **Exclusion criteria** 1. Neurological disorders compromising communication 2. Aphasia 3. Drug or alcohol addiction 4. Chronic pain 5. Raised intracranial pressure 6. Allergy to any study drug 7. Liver or kidney dysfunction 8. Dementia 9. Peptic ulcer disease 10. Glasgow coma score < 15

Dilmen 2016 *(Continued)*

	Mean age, range (years) 1. 44 (18 to 70) **Numbers allocated to each arm** 1. Group 1: dexketoprofen: 18 2. Group 2: paracetamol :20 3. Group 3: metamizole: 19 4. Group 4: saline control: 18 **Male gender** 1. Group 1: 9/18 2. Group 2: 11/20 3. Group 3: 8/19 4. Group 4: 11/18
Interventions	**Technique and timing** 1. Bolus intravenous injections of dexketoprofen, paracetamol, metamizole or 0.9% saline were given at skin closure and repeated every 8 hours in the dexketoprofen and every 6 hours in the paracetamol, metamizole and control groups. **Dosage** 1. Group 1: dexketoprofen 50 mg 2. Group 2: paracetamol 1 gram 3. Group 3: metamizole 1 gram 4. Group 4: saline control: not reported
Outcomes	**Primary** 1. Pain in the first 24 hours postoperatively as measured by the visual analogue score (measured at 1, 2, 6, 12 and 24 hours) **Secondary** 1. Postoperative morphine consumption 2. Adverse events: nausea and vomiting, pruritis, rash
Notes	**Funding** None

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: ''patients were randomised to one of four groups using opaque envelopes.'' However, it was not clear how the envelopes were selected to ensure random allocation.
Allocation concealment (selection bias)	High risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: ''the study drugs that were dissolved in 100 mL 0.9% saline solution were prepared by a nurse and administered by another nurse whereas postoperative data were collected by a blinded anaesthesiologist''.

Dilmen 2016 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Postoperative data was collected by a blinded anaesthesiologist.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	8 participants were excluded from the analysis. 1 participant: could not be extubated at the end of surgery (did not state which group he or she was in) 2 participants: did not regain consciousness at the end of surgery (both in the metamizol group) 3 participants: suffered seizures (1 in the dexketoprofen group and 2 in the paracetamol group) 2 participants: required merperidine for postoperative shivering (both in the saline control group)
Selective reporting (reporting bias)	Low risk	Outcomes reported as specified
Other bias	Unclear risk	Small study

El-Dawlatly 2007

Methods	Study design: randomized controlled trial (2 arms) Study duration: not reported Study setting: hospital, single centre, Saudi Arabia
Participants	Adults undergoing elective supratentorial craniotomy for tumour resection (n = 60) **Inclusion criteria** 1. ASA I to ASA II participants **Exclusion criteria** 1. GCS < 15 2. Raised intracranial pressure 3. Allergy to local anaesthetics or NSAIDS **Mean age, range (years)** 1. 44 (18 to 70) **Numbers allocated to each arm** 1. Group intervention (n = 30) 2. Group control (n = 30) **Male gender** Not reported
Interventions	**Technique and timing** 1. Scalp infiltration with 0.25% bupivacaine versus scalp infiltration with saline, before insertion of skull pins

El-Dawlatly 2007 *(Continued)*

	Dosage 10 mL
Outcomes	**Primary** 1. Pain as measured by the visual analogue score during the first 48 hours postoperatively (measured at 2, 4 ,6, 8, 10, 12, 18, 24, 36 and 48 hours) **Secondary** 1. Adverse events: nausea, vomiting, shivering
Notes	**Funding** No funding source reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: ''randomisation was performed by a computer generated form''.
Allocation concealment (selection bias)	High risk	Authors did not provide any details regarding how the allocation sequence was concealed.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: ''bupivacaine 0.25% without adrenaline or saline was prepared in a 10 mL identical syringe, by the second author. It was then given to the surgeon to infiltrate in a sterilized manner. Everyone was blind about the study drug except the second author. The code was broken only after all the data were collected and analysed by the first author''.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: '' the code was broken only after all the data were collected and analysed by the first author''.
Incomplete outcome data (attrition bias) All outcomes	High risk	The numbers who received each treatment as intended, the numbers lost to follow-up and the numbers included in the final analysis were not reported.
Selective reporting (reporting bias)	Low risk	All outcomes were reported in the priority in which they were specified.
Other bias	High risk	Small study and no sample size calculation was reported making it difficult to determine if the study was adequately powered for the primary outcome.

Ganzoni 2008

Methods	Study design: randomized controlled trial (2 arms) Study duration: not reported Study setting: hospital, single centre, USA
Participants	Adults undergoing elective supratentorial craniotomy for tumours (n = 30) **Inclusion criteria**

Ganzoni 2008 *(Continued)*

1. Adults undergoing elective supratentorial craniotomy for tumours

Exclusion criteria

1. Pregnancy
2. Pre-existing intracranial defect
3. Allergy to study drugs

Mean age, range (years)

1. Not reported

Numbers allocated to each arm

1. Group intervention (n = 14)
2. Group control (n = 16)

Male gender

1. Not reported

Interventions	**Technique and timing** Scalp block of the following nerves: 1. Supraorbital and supratrochlear 2. Zygomaticotemporal 3. Auriculotemporal 4. Postauricular branches of the greater auricular 5. Greater, lesser, and third occipital nerves with 0.5% ropivacaine versus no scalp block, after induction of anaesthesia **Dosage** Maximum of 30 mL
Outcomes	**Primary** 1. Haemodynamic response to skull pin placement **Secondary** 1. Haemodynamic variability 2. Intraoperative anaesthetic requirement 3. Postoperative pain as measured by the visual analogue score (measured in the first 4 hours after surgery) 4. Postoperative narcotic consumption 5. Postoperative nausea and vomiting
Notes	**Funding** None

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Reported as a randomized study but method of randomization not described

Ganzoni 2008 *(Continued)*

Allocation concealment (selection bias)	High risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Reported as blinded but method used not reported
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	All enrolled participants were followed up for outcomes.
Selective reporting (reporting bias)	Low risk	Outcomes were reported as specified.
Other bias	Unclear risk	Small study

Greenberg 2017

Methods	Study design: randomized controlled trial (2 arms) Study duration: Febuary 2012 to September 2015 Study setting: hospital, single centre, USA
Participants	Adults undergoing craniotomy of > 2 hours duration (n = 140) **Inclusion criteria** 1. Adults undergoing craniotomy of > 2 hours duration **Exclusion criteria** 1. Opioid or tramadol use daily for > 7 days before study medication administration 2. Chronic pain 3. Hypersensitiviy to opioids or acetaminophen 4. Known or suspected history of alcohol or drug misuse in the 2 years before the proposed surgery 5. Impaired liver function (aspartate aminotransferase/alanine aminotransferase/bilirubin abnormality, 6. Clinically significant liver disease or any other disease suggestive of increased susceptibility to hepatotoxicity with acetaminophen) 7. Taking NSAIDs 8. Taking certain herbal supplements within 14 days of surgery 9. Significant medical disease or laboratory abnormality that in the investigator's judgment could compromise the subject's welfare **Mean age, range (years)** 1. 58 (18 to 90) **Numbers allocated to each arm** 1. Group intervention (n = 66) 2. Group control (n = 65)

Greenberg 2017 *(Continued)*

	Male gender 1. Group intervention = 26/66 2. Group control = 29/65
Interventions	**Technique and timing** Immediately upon the beginning of closure (time 0), 1000 mg of IV acetaminophen (in 100 mL) or 100 mL of IV placebo (normal saline) was administered. The study drug or placebo was then administered every 6 hours thereafter (for a total of 3 additional doses, at 6, 12, and 18 hours). **Dosage** 1000 mg
Outcomes	**Primary** 1. Number of participants requiring no hydromorphone equivalents in the first 24 hours **Secondary** 1. Time to rescue analgesia 2. Total hydromorphone equivalents in the first 24 hours 3. Patient satisfaction 4. Intensive care unit length of stay 5. Hospital length of stay 6. Pain intensity in the first 24 hours (measured at 8, 16 and 24 hours) 7. Delirium 8. Sedation 9. Successful neurological examination 10.Temperature
Notes	**Funding** Funding in the amount of USD 9000 was provided by Mallinckrodt Pharmaceuticals.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The participants were randomized to receive either placebo (saline) or acetaminophen using a computer-generated randomization code.
Allocation concealment (selection bias)	Low risk	Quote: ''individual group assignments were concealed in opaque envelopes''.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: ''the clinical providers administering placebo or IV acetaminophen were blinded to the group to which patients were assigned''.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Those assessing outcomes were not aware of treatment received.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	4 participants in the acetaminophen group and 5 participants in the control group did not receive the intervention as intended and were excluded from the final analysis.

Greenberg 2017 *(Continued)*

Selective reporting (reporting bias)	Low risk	Outcomes were reported as specified.
Other bias	High risk	Study likely not adequately powered, long study duration and multiple outcomes

Hernández Palazón 2007

Methods	Study design: randomized controlled trial (2 arms) Study duration: not reported Study setting: hospital, single centre, Spain
Participants	Adults undergoing elective supratentorial craniotomy for resection of brain tumours (n = 30) **Inclusion criteria** 1. ASA I to III participants **Exclusion criteria** 1. Inability to understand the pain scoring system 2. Allergy to study drugs 3. Long-term opioid treatment **Mean age, range (years)** 1. 44 (18 to 69) **Numbers allocated to each arm** 1. Group intervention (n = 15) 2. Group control (n = 15) **Male gender** 1. Group intervention: 9/15 2. Group control: 8/15
Interventions	**Technique and timing** Scalp block of the following nerves: 1. Supraorbital and supratrochlear 2. Zygomaticotemporal 3. Auriculotemporal 4. Postauricular branches of the greater auricular 5. Greater, lesser, and third occipital nerves with 0.25% bupivacaine with adrenaline 1:200,000 versus scalp block with saline, at the end of surgery **Dosage** 20 mL
Outcomes	**Primary** 1. Morphine consumption in the first 24 hours postoperatively

Hernández Palazón 2007 *(Continued)*

	Secondary 1. Time to requirement of rescue analgesia 2. Pain as measured by the visual analogue score during the first 24 hours postoperatively (measured at 2, 4, 8, 12,16 and 24 hours) 3. Sedation score 4. Adverse events – nausea and vomiting, pruritis, respiratory depression
Notes	**Paper published in Spanish only** Paper published in Spanish only, translation software used but translation errors possible **Funding** No funding source reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Reported as randomized but method not reported
Allocation concealment (selection bias)	High risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Reported as double-blinded but method or adequacy not reported
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Anaesthesiologist performing postoperative pain assessment did not participate in scalp block.
Incomplete outcome data (attrition bias) All outcomes	High risk	Losses to follow-up and numbers included in final analysis were not reported.
Selective reporting (reporting bias)	Low risk	Outcomes reported as specified
Other bias	Unclear risk	Small study

Hwang 2015

Methods	Study design: randomized controlled trial (2 arms) Study duration: not reported Study setting: hospital, single centre, Korea
Participants	Adults undergoing elective supratentorial craniotomy for clipping of an unruptured cerebral aneurysm (n = 52) **Inclusion criteria** 1. ASA I to II participants

Hwang 2015 *(Continued)*

	Exclusion criteria 1. Ruptured cerebral aneurysm 2. Allergy to local anaesthetics 3. Chronic opioid usage 4. Previous craniotomy incision 5. Undergoing emergency surgery 6. Unable to understand the numerical pain rating scale 7. Glasgow Coma Score (GCS) < 14 8. Active psychiatric disease **Mean age, range (years)** 1. 47 (19 to 75) **Numbers allocated to each arm** 1. Group intervention: not reported but 23 were included in the analysis 2. Group control: not reported but 23 were included in the analysis **Male gender** 1. Group intervention: 6/23 2. Group control: 7/23
Interventions	**Technique and timing** Scalp block of the following nerves 1. Supraorbital and supratrochlear 2. Zygomaticotemporal 3. Auriculotemporal 4. Postauricular branches of the greater auricular 5. Greater, lesser, and third occipital nerves with 0.75% bupivacaine with adrenaline 1:200,000 versus scalp block with saline, at the end of surgery **Dosage** 7 mL
Outcomes	**Primary** 1. Pain as measured by the numerical rating score during the first 72 hours postoperatively (measured at 1, 2, 4, 6, 8, 12, 16, 24, 48 and 72 hours) **Secondary** 1. PCA (patient-controlled analgesia) consumption 2. Adverse events – haemodynamic instability, seizures, nausea and vomiting, fever (axillary temperature > 37.8 degrees celsius), dizziness, respiratory depression (respirator rate < 8 or SaO_2 < 90%), sleepiness, delirium
Notes	**Funding** None

Risk of bias

Bias	Authors' judgement	Support for judgement

Hwang 2015 *(Continued)*

Random sequence generation (selection bias)	Low risk	A computer-generated random number chart was used for randomization.
Allocation concealment (selection bias)	Low risk	An independent anaesthesiologist was responsible for patient allocation.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: ''syringes containing the same volume (7 mL) of normal saline (group C) or 0.75% levo bupivacaine with epinephrine (group L) were prepared by an anaesthetic nurse not involved in the study. The anaesthesiologist performing the scalp block, patients, and investigators were blinded to group assignments''.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: ''the anaesthesiologist performing the scalp block, patients, and investigators were blinded to group assignments."
Incomplete outcome data (attrition bias) All outcomes	Low risk	46 of the original 52 participants were included in the final analysis. 3 participants from the intervention group were too sedated to assess outcomes. 3 participants from the control group were not included due to delayed extubation. As the losses were equal in both groups and the reasons for the losses were clinically similar, their omission was unlikely to have had a significant impact on the results.
Selective reporting (reporting bias)	Low risk	All outcomes were reported in the priority in which they were specified.
Other bias	Unclear risk	Small study

Jellish 2006

Methods	Study design: randomized controlled trial (3 arms) Study duration: not reported Study setting: hospital, single centre, USA
Participants	Adults undergoing elective skull base surgery (n = 120) **Inclusion criteria** 1. ASA I to ASA III participants undergoing middle and posterior fossa tumour resection **Exclusion criteria** 1. Pregnant 2. Neurovascular, trigeminal nerve pain procedures 3. Undergoing emergency surgery 4. Unable to give consent **Mean age, range (years)** 1. 51 (range: not reported) **Numbers allocated to each arm**

Jellish 2006 *(Continued)*

1. Group 1: placebo (n = 30)
2. Group 2: morphine 5 mg/mL (n = 40)
3. Group 3: morphine 5 mg/mL with ondansetron 10 mg/mL (n = 40)

Male gender

1. Group 1: 15/30
2. Group 2: 17/40
3. Group 3: 25/40

Interventions	**Technique and timing** 1. Intravenous morphine patient-controlled analgesia (PCA) plus or minus added ondansetron, for the first 24 hours postoperatively **Dosage** 1. Group 1: placebo: dosage not specified 2. Group 2: morphine 5 mg/mL 3. Group 3: morphine 5 mg/mL with ondansetron 10 mg/mL
Outcomes	**Primary** 1. Incidence of nausea and vomiting **Secondary** 1. Incidence of pain using the verbal numerical score 2. PCA consumption 3. Severity of nausea and vomiting 4. Rescue analgesia consumption
Notes	**Funding** No funding source reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A computer-generated randomization table was used.
Allocation concealment (selection bias)	High risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: ''all study drugs were prepared in the pharmacy", implying investigators were blinded. Not clear if patients were blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: ''all study drugs were prepared in the pharmacy. The PCA container held the same volume of solution and was blinded to all individuals who collected the data''.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants were followed up and included in the analysis.

Jellish 2006 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	The secondary outcome of pain was given greater reporting priority than the primary outcome of nausea and vomiting.
Other bias	Low risk	No other significant biases were identified.

Jones 2009

Methods	Study design: randomized controlled trial (2 arms) Study duration: not reported Study setting: hospital, single centre, Australia
Participants	Adults undergoing elective craniotomy (n = 82) **Inclusion criteria** 1. Adults undergoing elective craniotomy **Exclusion criteria** 1. Confusion 2. Contraindications to NSAIDS 3. Chronic pain 4. Regular opioid usage **Mean age, range (years)** 1. 47 (18 to 75) **Numbers allocated to each arm** 1. Group intervention (n = 41) 2. Group control (n = 39) **Male gender** 1. Group intervention: 24/41 2. Group control : 17/39
Interventions	**Technique and timing** 1. Parecoxib versus saline, given intravenously at dural closure **Dosage** 40 mg
Outcomes	**Primary** 1. Morphine consumption in the postoperative recovery unit **Secondary** 1. Morphine consumption in the first 24 hours postoperatively 2. Pain as measured by the visual analogue score (measured at 1, 6, 12 and 24 hours) 3. Sedation score 4. Patient satisfaction 5. Adverse events - nausea and vomiting

Jones 2009 *(Continued)*

Notes	**Funding** Vincents research grant

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated permuted block
Allocation concealment (selection bias)	High risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Study drugs were prepared by a third party and labelled 'study drug'.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessors were blinded to treatment received.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	2 participants were excluded as surgery was cancelled. An intention-to-treat analysis was not performed and the groups to which these participants were initially assigned was not reported.
Selective reporting (reporting bias)	Low risk	Outcomes were reported as specified.
Other bias	Unclear risk	Small study

Kiskira 2006

Methods	Study design: randomized controlled trial (2 arms) Study duration: not reported Study setting: hospital, single centre, Greece
Participants	Adults undergoing elective supratentorial craniotomy (n = 40) **Inclusion criteria** 1. Adults undergoing elective supratentorial craniotomy **Exclusion criteria** 1. Not specified **Mean age, range (years)** 1. 46 (24 to 67) **Numbers allocated to each arm** 1. Not reported **Male gender**

Kiskira 2006 *(Continued)*

	1. Not reported
Interventions	**Technique and timing** 1. Scalp infiltration with 0.25% bupivacaine with adrenaline 5 mcg/mL versus scalp infiltration with saline, pre-surgical incision and again at the end of surgery **Dosage** 30 mL
Outcomes	**Primary** 1. Pain as measured by the visual analogue score during the first 24 hours postoperatively **Secondary** 1. Time to rescue analgesia requirement 2. Total paracetamol consumption 3. Total opioid consumption 4. Mean pain score in the first 24 hours postoperatively
Notes	**Published in abstract format only** 1. Paper published in abstract format only so many details not reported **Funding** No funding source reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Reported as randomized but method of randomization not reported
Allocation concealment (selection bias)	High risk	Authors did not provide any details regarding how the allocation sequence was concealed.
Blinding of participants and personnel (performance bias) All outcomes	High risk	No details provided as to whether or how the study was blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	No details provided as to whether or how the study was blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	No details provided regarding numbers allocated to each treatment arm, numbers who received each treatment, numbers followed up or numbers analysed
Selective reporting (reporting bias)	Low risk	Outcomes reported as specified
Other bias	High risk	A lot of unreported data, so difficult to determine how robust the methodology was

Law-Koune 2005

Methods	Study design: randomized controlled trial (3 arms) Study duration: not reported Study setting: hospital, single centre, France
Participants	Adults undergoing elective supratentorial craniotomy for tumour resection (n = 80) **Inclusion criteria** 1. ASA I to ASA III participants undergoing elective supratentorial craniotomy for tumour resection **Exclusion criteria** 1. Inability to understand the visual analogue scale 2. Previous scalp incision 3. Intracranial hypertension 4. Cerebrovascular disease 5. Allergy to any study drug 6. Regular opioid usage 7. Surgery scheduled to start after 2 pm **Mean age, range (years)** 1. 49 (18 to 80) **Numbers allocated to each arm** 1. Group 1: scalp infiltration with either 0.375% bupivacaine with 1:200,000 epinephrine (n = 20) 2. Group 2: scalp infiltration with 0.75% ropivacaine (n = 20) 3. Group 3: scalp infiltration with 20 mL of saline (n = 40) **Male gender** 1. Group 1: 8/20 (analysed patients) 2. Group 2: 8/19 (analysed patients) 3. Group 3: 16/37 (analysed patients)
Interventions	**Technique and timing** 1. Scalp infiltration with 0.375% bupivacaine with epinephrine 1:200,000 versus scalp infiltration with 0.75% ropivacaine versus scalp infiltration with saline with epinephrine 1:200,000, before scalp closure **Dosage** 20 mL
Outcomes	**Primary** 1. Total morphine requirement during the first 16 hours postoperatively **Secondary** 1. Pain as measured by the visual analogue scale 2. Sedation score: from 'alert' to 'roused only by shaking': 1 to 5 3. Adverse events: nausea, vomiting, pruritis, urinary retention, need for antihypertensive medication, haematoma
Notes	**Funding**

Law-Koune 2005 *(Continued)*

	No funding source reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A table of random numbers was used for randomization
Allocation concealment (selection bias)	High risk	Authors did not provide any details regarding how the allocation sequence was concealed.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: ''the anaesthesiologist, surgeon, and patient were blinded to the solution''. However no details were provided regaining the method used or how or if its adequacy was assessed.
Blinding of outcome assessment (detection bias) All outcomes	High risk	No details were provided as to whether or not those assessing outcomes were blinded to treatments received.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	4 participants were excluded from the final analysis due to postoperative complications: 3 in the control group (2 due to unspecified neurological complications and 1 due to excessive sedation) 1 in the ropivacaine group (due to an unspecified neurological complication) The lack of an intention-to-treat analysis made the effect of their exclusion difficult to determine.
Selective reporting (reporting bias)	Low risk	Outcomes were reported as specified.
Other bias	Unclear risk	Small study

Misra 2013

Methods	Study design: randomized controlled trial (2 arms) Study duration: not reported Study setting: hospital, single centre, India
Participants	Adults undergoing elective craniotomy for tumour resection who were receiving preoperative intravenous (IV) dexamethasone for at least 48 hours (n = 79) **Inclusion criteria** 1. Adults undergoing above surgery **Exclusion criteria** 1. Pregnancy 2. Breast feeding 3. Patients on preoperative anti-emetic, gabapentin or pregabalin 4. Patients with an allergy to any study drug

Misra 2013 *(Continued)*

5. Renal dysfunction
6. Significant nausea or vomiting preoperatively
7. Emergency craniotomy

Mean age, range (years)

1. 39 (18 to 60)

Numbers allocated to each arm

1. Group intervention (n = 39)
2. Group control (n = 40)

Male gender

1. Group intervention: 20/36 (participants analysed)
2. Group control: 20/37 (participants analysed)

Interventions	**Technique and timing** 1. Gabapentin 600 mg orally, given 2 hours before surgery versus vitamin B placebo given at the same time point **Dosage** 600 mg
Outcomes	**Primary** 1. Incidence of nausea and vomiting in the first 24 hours after surgery **Secondary** 1. Postoperative pain scores as measured on a scale of 0 to 3 2. Incidence of moderate/severe pain 3. Intraopertive anaesthetic requirement 4. Postoperative narcotic consumption 5. Postoperative nausea and vomiting
Notes	**Funding** None

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: ''randomisation was done by means of a computer-generated random number scheme.'' Patients were allocated to receive either placebo (vitamin B-complex capsule) (group D) or 600 mg of gabapentin (group GD), administered orally, 2 hours before the induction of anaesthesia by means of a sealed envelope.
Allocation concealment (selection bias)	Low risk	Quote: ''patients were allocated to receive either placebo (vitamin B-complex capsule) (group D) or 600 mg of gabapentin (group GD), administered orally, 2 hours before the induction of anaesthesia by means of a sealed envelope''.
Blinding of participants and personnel (performance bias)	Low risk	Placebo tablets were used to blind participants.

Misra 2013 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	6 participants were lost to follow-up: 3 in each group due to delayed extubation. An intention-to-treat analysis was not used.
Selective reporting (reporting bias)	Low risk	Outcomes reported as specified
Other bias	High risk	Small study and no sample size calculation provided

Molnár 2015

Methods	Study design: randomized controlled trial (2 arms) Study duration: not reported Study setting: hospital, single centre, Hungary
Participants	Adults undergoing elective craniotomy (n = 200) **Inclusion criteria** 1. Adults undergoing above surgery **Exclusion criteria** 1. Not alert postoperatively 2. Preoperative aphasia 3. On NSAIDS preoperatively **Mean age, range (years)** 1. 55 (45 to 65) **Numbers allocated to each arm** 1. Group intervention (n = 100) 2. Group control (n = 100) **Male gender** 1. Group intervention: 44/100 2. Group control: 44/100
Interventions	**Technique and timing** 1. Oral diclofenac 1 hour before surgery versus no diclofenac **Dosage** 100 mg
Outcomes	**Primary**

Molnár 2015 *(Continued)*

	1. Pain as measured by the visual analogue score (VAS) during the first 5 days postoperatively (measured on days 0, 1 and 5) **Secondary** 1. Morphine requirement in the postoperative recovery unit 2. Morphine requirement in the first 24 hours postoperatively 3. Moderate/severe postoperative pain i.e. VAS > / = 3 4. Morphine equivalent dosage to keep VAS
Notes	**Funding** 1. Hungarian Brain Research Program **Other methodologic issues** 1. No placebo used

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomization table
Allocation concealment (selection bias)	Low risk	Sequentially numbered opaque envelopes
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: ''neither the physician performing the anaesthesia, nor the physicians obtaining post-operative VAS scores were aware of patient assignments; the study was thus entirely double-blinded''. However, the blinding method or its adequacy was not described, a factor which is especially relevant since there was no placebo medication used.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: ''neither the physician performing the anaesthesia, nor the physicians obtaining post-operative VAS scores were aware of patient assignments; the study was thus entirely double-blinded''. However, the blinding method or its adequacy was not described, a factor which is especially relevant since there was no placebo medication used.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All enrolled participants were followed up and included in the final analysis.
Selective reporting (reporting bias)	Low risk	Outcomes reported as specified
Other bias	Unclear risk	Subgroup analysis was not prespecified.

Nguygen 2001

Methods	Study design: randomized controlled trial (2 arms) Study duration: not reported Study setting: hospital, single centre, Canada
Participants	Adults undergoing elective supratentorial craniotomy (n = 30)

Nguygen 2001 *(Continued)*

Inclusion criteria

1. ASA I to III participants

Exclusion criteria

1. Inability to understand the visual analogue scale
2. Incision extending beyond the field of the block
3. Allergy to local anaesthetics or codeine
4. Regular opioid use

Mean age, range (years)

1. 44 (18 to 70)

Numbers allocated to each arm

1. Group intervention (n = 15)
2. Group control (n = 15)

Male gender

1. Group intervention: 8/15
2. Group control: 5/15

Interventions

Technique and timing

Scalp block of the following nerves:

1. Supraorbital and supratrochlear
2. Zygomaticotemporal
3. Auriculotemporal
4. Postauricular branches of the greater auricular
5. Greater, lesser, and third occipital nerves

with 0.75% ropivacaine versus scalp block with saline, at the end of surgery

Dosage

20 mL

Outcomes

Primary

1. Pain as measured by the visual analogue score (VAS) during the first 48 hours postoperatively (measured at 4 ,8, 12, 16, 20, 24 and 48 hours)

Secondary

1. Total dosage of rescue analgesia required

Notes

Funding

1. None reported

Other methodologic issues

1. No sample size calculation was reported making it difficult to determine whether or not the study was adequately powered for the primary outcome.

Risk of bias

Bias	Authors' judgement	Support for judgement

Nguygen 2001 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Reported as randomized but method not reported
Allocation concealment (selection bias)	High risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not clear, the solution for the block was prepared by the attending anaesthesiologist and administered by the principal investigator but the authors did not provide information as to whether or how the solution was presented in a way to disguise its true contents.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	For primary outcome – the numbers followed up was not stated. Quote: ''only data obtained from patients who were oriented with regard to person, place, and time and with a Glasgow coma score of at least 14 (they would open their eyes to speech) were considered for statistical analysis'' suggesting that some participants were excluded. For the secondary outcome, from the numbers presented in the results, it appeared that all 30 participants were followed up.
Selective reporting (reporting bias)	Low risk	Outcomes reported as specified
Other bias	High risk	Small study and no sample size calculation provided

Peng 2015

Methods	Study design: randomized controlled trial (2 arms) Study duration: not reported Study setting: hospital, single centre, China
Participants	Adults undergoing elective supratentorial craniotomy (n = 80) **Inclusion criteria** 1. ASA I to III adults undergoing above surgery **Exclusion criteria** 1. Allergy to study medications 2. BMI < 15 or > 40 3. Significant cardiopulmonary disease, renal or liver disease 4. Long-term opioid usage 5. Long-term benzodiazepine usage 6. Alcohol misuse GCS < 15 7. Intracranial hypertension 8. Uncontrolled epilepsy 9. Chronic pain **Mean age, range (years)**

Peng 2015 *(Continued)*

1. 42 (18 to 65)

Numbers allocated to each arm

1. Group intervention (n = 40)
2. Group control (n = 40)

Male gender

1. Group intervention: 15/40
2. Group control: 18/40

Interventions	**Technique and timing** 1. Intravenous infusion of dexmedetomidine versus placebo, started after induction of anaesthesia and continued until the start of skin closure **Dosage** 0.5 mcg/kg/hr
Outcomes	**Primary** 1. Pain using the numerical rating scale (NRS) in the first 24 hours postoperatively (measured at 30 minutes, 1, 2 ,4, 8, 12, 18 and 24 hours) **Secondary** 1. Tramadol consumption 2. Sedation score 3. Adverse events - nausea and vomiting, hypotension, bradycardia
Notes	**Funding** 1. None **Other methodologic issues** 1. Study was powered for a secondary outcome rather than the primary outcome.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomization table was used.
Allocation concealment (selection bias)	Low risk	Randomization and study drug preparation were done by a research assistant who was not otherwise involved in the study.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: ''all patients, anaesthesiologists, surgeons, and postoperative observers were blinded to the group allocation''.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: ''all patients, anaesthesiologists, surgeons, and postoperative observers were blinded to the group allocation''.
Incomplete outcome data (attrition bias)	Low risk	4 participants, 2 from each group were excluded from the analysis as they required re-operation. As the numbers excluded and reasons for exclusion were

Peng 2015 *(Continued)*

All outcomes		the same in both groups, the impact on the effect estimate was likely not significant.
Selective reporting (reporting bias)	Low risk	Outcomes were reported as specified.
Other bias	High risk	The study was likely underpowered for the primary outcome.

Peng 2016

Methods	Study design: randomized controlled trial (2 arms) Study duration: 2009 to 2012 Study setting: hospital, single centre, China
Participants	Adults undergoing elective supratentorial craniotomy for tumour resection (n = 94) **Inclusion criteria** 1. ASA I to II adults undergoing above surgery **Exclusion criteria** 1. BMI > 30 2. Mini-mental state score < 24 3. History of other malignancy, diabetes, psychiatric disorder, drug or alcohol misuse 4. Inability to consent **Mean age, range (years)** 1. 42 (18 to 65) **Numbers allocated to each arm** 1. Group intervention (n = 46) 2. Group control (n = 48) **Male gender** 1. Group intervention: 19/40 (participants analysed) 2. Group control - 20/40 (participants analysed)
Interventions	**Technique and timing** 1. Lidocaine intravenous bolus of 1.5 mg/kg after induction of anaesthesia followed by an infusion of 2 mg/kg/hr for the duration of the operation versus saline bolus and infusion **Dosage** As above
Outcomes	**Not clear which outcomes were primary and which were secondary** The authors reported outcomes for: 1. Differences in mean arterial blood pressure 2. Heart rate 3. Bispectral index 4. Pain score in postoperative recovery unit

Peng 2016 *(Continued)*

	5. Incidence of hypertension 6. Incidence of tachycardia 7. Incidence of dysphoria 8. Nausea and vomiting
Notes	**Funding** None **Other methodologic issues** No sample size calculation reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomization table
Allocation concealment (selection bias)	Low risk	Coded vials
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: ''a research nurse gave the participants an equal volume of lidocaine or saline from a coded vial according to the randomised control table".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: ''the research team that collected and analysed the data was blinded to the treatment allocation''.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	14 participants were excluded from the analysis. Group intervention: 6 excluded (2 due to delayed extubation, 4 not alert enough to assess pain score) Group control: 8 excluded (3 due to delayed extubation, 4 not alert enough to assess pain score, 1 due to dysphoria)
Selective reporting (reporting bias)	Unclear risk	Unclear outcome priority
Other bias	High risk	No sample size calculation

Rahimi 2006

Methods	Study design: randomized controlled trial (2 arms) Study duration: not reported Study setting: hospital, single centre, USA
Participants	Adults undergoing elective supratentorial craniotomy (n = 27) **Inclusion criteria** 1. Adults undergoing above surgery

Rahimi 2006 *(Continued)*

Exclusion criteria

1. Pregnant
2. Age < 18 yrs
3. Ventilator dependant > 24 hours
4. Allergy to study medications
5. Emergency surgery
6. History of cardiovascular disease

Mean age, range (years)

1. 44 (range not reported)

Numbers allocated to each arm

1. Group intervention (n = 14)
2. Group control (n = 13)

Male gender

1. Group intervention - 9/14
2. Group control - 5/13

Interventions	**Technique and timing** 1. Oral COX 2 Inhibitor twice daily plus narcotic medication as needed versus narcotic medication as needed, timing relative to surgery unclear **Dosage** 25 mg per dose
Outcomes	**Primary** 1. Pain as measured by the visual analogue score (VAS) **Secondary** 1. Additional analgesia usage 2. Length of hospital stay 3. Anti-emetic usage 4. Cost
Notes	**Funding** None **Other methodologic issues** Lack of details regarding several aspects of study design and methodology including randomization, blinding methods, sample size and timing of outcome measurements

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Authors stated that it was randomized but no details were provided.
Allocation concealment (selection bias)	High risk	Not reported

Rahimi 2006 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Authors stated that it was single-blinded but did not report how or whom was blinded.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	2 participants from the intervention group were not included in the analysis for the primary outcome. No reason was provided by the authors.
Selective reporting (reporting bias)	Low risk	Outcomes reported as specified
Other bias	High risk	General lack of detail about study design, sample size, timing of outcome measures

Rahimi 2010

Methods	Study design: randomized controlled trial (2 arms) Study duration: not reported Study setting: hospital, single centre, USA
Participants	Adults undergoing elective craniotomy (n = 50) **Inclusion criteria** 1. Adults undergoing above surgery **Exclusion criteria** 1. Pregnant 2. Age < 18 yrs 3. Ventilator dependant > 24 hours 4. Allergy to study medications 5. Emergency surgery **Mean age, range (years)** 1. 44 (range not reported) **Numbers allocated to each arm** 1. Group intervention (n = 25) 2. Group control (n = 25) **Male gender** 1. Group intervention: 13/25 2. Group control: 10/25
Interventions	**Technique and timing**

Rahimi 2010 *(Continued)*

	1. Oral tramadol 100 mg twice daily plus narcotic medication as required (oxycodone/acetaminophen 5/325 mg every 4 hours as needed and 1 to 2 mg of IV morphine every 2 hours as needed) versus narcotic medication (as above) only **Dosage** As above
Outcomes	**Primary** 1. Pain as measured by the visual analogue score (VAS) **Secondary** 1. Length of hospital stay 2. Cost
Notes	**Funding** None **Other methodologic issues** Lack of details regarding several aspects of study design and methodology including randomization, blinding methods, sample size and timing of outcome measurements

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Reported as randomized but method not reported
Allocation concealment (selection bias)	High risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Reported as blinded but authors did not report who was blinded or how they were blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants were followed up and included in the analysis.
Selective reporting (reporting bias)	Low risk	Outcomes reported as specified
Other bias	High risk	Lack of details regarding several aspects of study design and methodology including randomization, blinding methods, sample size and timing of outcome measurements

Rigamonti 2013

Methods	Study design: randomized controlled trial (2 arms) Study duration: not reported Study setting: hospital, single centre,Canada
Participants	Adults undergoing elective supratentorial craniotomy (n = 89) **Inclusion criteria** 1. Adults undergoing above surgery **Exclusion criteria** 1. Not reported **Mean age, range (years)** 1. Not reported **Numbers allocated to each arm** 1. Group intervention (n = 44) 2. Group control (n = 45) **Male gender** 1. Not reported
Interventions	**Technique and timing** 1. Scalp block with 0.5% bupivacaine versus scalp block with saline pre-insertion of skull pins **Dosage** 20 mL
Outcomes	**Primary** 1. Pain as measured by the VAS (visual analogue score) during the first 24 hours postoperatively **Secondary** 1. Pain at days 5, 30 and 60 2. Total opioid consumption 3. Adverse events - nausea and vomiting
Notes	**Published in abstract format only** Paper published in abstract format only so many details not reported **Funding** None

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method not reported

Rigamonti 2013 *(Continued)*

Allocation concealment (selection bias)	High risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Reported as 'double-blinded' but method or adequacy not reported
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	Not reported
Selective reporting (reporting bias)	Low risk	Outcomes reported as specified
Other bias	High risk	Lots of unreported data, so difficult to determine overall methodologic rigour

Ryan 2005

Methods	Study design: randomized controlled trial (2 arms) Study duration: not reported Study setting: hospital, single centre, United Kingdom
Participants	Adults undergoing elective craniotomy (n = 42) **Inclusion criteria** 1. Adults undergoing above surgery **Exclusion criteria** 1. Not reported **Mean age, range (years)** 1. 45 (18 to 71) **Numbers allocated to each arm** 1. Group intervention: not reported 2. Group control: not reported **Male gender** 1. Not reported
Interventions	**Technique and timing** Oral rofecoxib verus placebo given 1 hr prior to surgery **Dosage** 50 mg

Ryan 2005 *(Continued)*

Outcomes	**Primary** 1. Pain as measured by the visual analogue score (VAS) **Secondary** 1. Morphine consumption postoperatively 2. Consciousness level 3. Sedation score
Notes	**Published in abstract format only** Paper published in abstract format only so many details not reported **Funding** No funding source reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Reported as randomized but no details reported
Allocation concealment (selection bias)	High risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Reported as 'double-blinded' but no details provided
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	8 participants were lost to follow-up. No reasons were provided.
Selective reporting (reporting bias)	Unclear risk	Absolute figures were only provided for 'morphine consumption', with no figures provided for the primary outcome.
Other bias	High risk	Lots of unreported data

Saringcarinkul 2015

Methods	Study design: randomized controlled trial (2 arms) Study duration: 2006 to 2009 Study setting: hospital, single centre, Thailand
Participants	Adults undergoing elective supratentorial craniotomy (n = 50) **Inclusion criteria**

Saringcarinkul 2015 *(Continued)*

1. ASA I to III adults undergoing above surgery

Exclusion criteria

1. Allergy to local anaesthetics
2. GCS < 15
3. Complication during surgery such as brain swelling, cranial nerve injury, massive bleeding, unstable vital signs
4. Difficulty in communicating
5. No plan to extubate

Mean age, range (years)

1. 42 (18 to 65)

Numbers allocated to each arm

1. Group intervention (n = 25)
2. Group control (n = 25)

Male gender

1. Group intervention: 13/25
2. Group control: 9/25

Interventions

Technique and timing

1. Scalp infiltration with 0.5% bupivacaine and adrenaline 1:400,000 versus scalp infiltration with saline with adrenaline 1:400,000, at the end of surgery before skin closure

Dosage

20 mL

Outcomes

Primary

1. Pain as measured by the numerical pain rating scale (NRS) during the first 12 hours postoperatively (measured at 30 minutes, 1, 2, 4, 6, 8 and 12 hours)

Secondary

1. Incidence of pain requiring rescue medication
2. Adverse events - nausea and vomiting
3. Sedation Score- from 'alert' to 'unresponsive': 1 to 4
4. Total dose of rescue analgesia required

Notes

Funding

Chiang Mai University

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A computer-generated random number chart was used.
Allocation concealment (selection bias)	High risk	Authors did not provide any details regarding how the allocation sequence was concealed.

Saringcarinkul 2015 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: ''both solutions were prepared by the scrub nurse, who did not participate in the postoperative pain assessment. The neuro-surgeon performing the infiltration, anaesthesiologist and patient were blinded to the drug being administered''.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The nurse performing the outcome assessments was blinded to treatment received.
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 participant was excluded from the final analysis due to decreased level of consciousness. Although an intention-to-treat analysis was not performed, the omission of 1 participant only is unlikely to have had a significant impact on the results.
Selective reporting (reporting bias)	Low risk	Outcomes were reported as specified.
Other bias	Unclear risk	Small study

Shepherd 2018

Methods	Study design: randomized controlled trial (2 arms) Study duration: 2015 to 2016 Study setting: hospital, single centre, USA
Participants	Adults participants undergoing transsphenoidal surgery for resection of pituitary tumours **Exclusion criteria** 1. Allergy or intolerance to acetaminophen, ibuprofen, or opioids 2. Preoperative opioid tolerance, dependence, or abuse 3. Anaphylaxis to opioids 4. History of peptic ulcer disease or recent gastrointestinal bleed requiring surgery 5. Cirrhosis, hepatitis, liver transplant, or abnormal liver function studies 6. Subject unwilling or unable to sign informed consent for the study 7. Pregnancy 8. Incarcerated patients 9. Non-English speaking and literate or unable to understand the use of a pain scale 10. Body Mass Index < 19 and > 40 kg/m^2 11. Renal failure **Mean age (years)** 1. 55 **Numbers allocated to each arm** 1. Group intervention - scheduled IV ibuprofen, scheduled oral acetaminophen, and rescue opioids 2. Group control - scheduled IV placebo, scheduled oral acetaminophen, and rescue opioids **Male gender** 1. Group intervention: 15/28 2. Group control: 18/34

Shepherd 2018 *(Continued)*

Interventions	**Technique and timing** 1. Intravenous ibuprofen versus placebo **Dosage** 800 mg every 8 hours with the first dose given intraoperatively
Outcomes	**Primary** 1. Postoperative pain as measured by the VAS score measured every 4 hours to a max of 48 hours **Secondary** 1. Breakthrough narcotic requirement 2. Total number of doses and type of any anti-emetic required postoperatively in both groups 3. The number of patients who did not have a bowel movement during hospitalization in both groups 4. The number of patients in both groups with opioid-associated adverse events, such as respiratory depression or sedation, using Pasero Opioid-Induced Sedation Scale 5. Total cost of hospital charges compared between 2 arms 6. Other adverse events 7. Cost of pharmacy charges compared between 2 arms 8. Length of stay in hospital compared between 2 arms 9. Adverse events
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote:''Patients were randomised in a 1:1 ratio with blinded treatment assignment. The patients were randomised using a computer-generated list of random numbers from www.random.org.''
Allocation concealment (selection bias)	High risk	Quotes: ''The randomised list was placed with an ordered list of numbers from 1 to 100. Odd numbers were assigned to Group 1 and even numbers to Group 2.'' ''The research nurse generated the random number sequence and performed the blinded assignment''. This implied that treatment allocation was predictable to the research nurse before the moment of allocation.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: ''Patients, family members, bedside nurses, and providers were blinded to treatment assignment. The treatment assignment was known by the research nurse and a research pharmacist''. Blinding was neither well described nor complete.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned in the report who exactly assessed outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomized patients were included in the analysis.

Shepherd 2018 *(Continued)*

Selective reporting (reporting bias)	Low risk	Outcomes were reported as specified.
Other bias	High risk	The study was substantially underpowered for its primary outcome. Quote:''Fifty treated patients in each group were required to detect a 2-point MD on the 11-point (0–10) VAS, with a standard deviation of 3.2 for the placebo group and 3.5 for the treatment group, with α set at 0.05 and 90% power.''

Shimony 2016

Methods	Study design: randomized controlled trial (2 arms) Study duration: not reported Study setting: hospital, single centre, Israel
Participants	Adults undergoing elective craniotomy for tumour resection (n = 100) **Inclusion criteria** 1. ASA I to III adults undergoing above surgery **Exclusion criteria** 1. Allergy to propofol, pregabalin, opioids, NSAIDS, dipyrone 2. Chronic pain 3. Psychiatric disorder 4. Chronic usage of sedatives, antidepressants, antipsychotics or antiepileptic drugs 5. Receiving anti-emetic or anticonvulsant drugs 6. Age < 18 or > 80 7. In military service 8. Emergency surgery 9. Pregnant 10.Planning to undergo deep brain stimulation 11.Inability to consent 12.Severe liver or renal failure 13.Those expected to require a prolonged hospital stay after surgery **Mean age, range (years)** 1. 39 (18 to 60) **Numbers allocated to each arm** 1. Group intervention (n = 50) 2. Group control (n = 50) **Male gender** 1. Group intervention: 42% (denominator not clear) 2. Group control: 55% (denominator not clear)
Interventions	**Technique and timing** 1. Pregablin, given orally, the evening before surgery, 90 minutes before surgery, 2 hours after surgery and every 12 hours thereafter for a total of 72 hours versus starch placebo given at the same time points

Shimony 2016 *(Continued)*

	Dosage 150 mg per dose
Outcomes	**Primary** 1. Pain score day 0 to 3 after surgery as rated by numerical rating scale (NRS) (measured at days 0, 1, 2 and 3) **Secondary** 1. Analgesic consumption day 0 to 3 after surgery 2. Late pain scores (up to 3 months) 3. Use of analgesics after hospital discharge 4. Length of stay 5. Patient satisfaction 6. Anxiety levels 7. Sleep quality 8. Anti-emetic usage
Notes	**Funding** None

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomization list
Allocation concealment (selection bias)	High risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	It was clear how participants were blinded. Quote: ''patients in the placebo group were given identical capsules containing 500 mg of starch at the same time points''.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The trial was reported as 'double-blinded' but it was not clear how investigations were blinded.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	12 participants were lost to follow-up, 5 in the intervention group and 7 in the control group. The reasons were not clearly explained in the report with the CONSORT flowchart mentioning these as having (quote): ''dropped out''. However, the authors did perform an intention-to-treat analysis.
Selective reporting (reporting bias)	Low risk	Outcomes reported as specified
Other bias	Unclear risk	Massive number of comparisons were made with no statistical adjustment for multiple testing.

Sivakumar 2018

Methods	Study design: randomized controlled trial (2 arms)

Sivakumar 2018 *(Continued)*

	Study duration: 2013 to 2015 Study setting: hospital, single centre, USA
Participants	Adults undergoing elective craniotomy (n = 212) **Inclusion criteria** 1. Adults undergoing above surgery **Exclusion criteria** 1. Age < 18 years 2. Weight < 50 kg 3. Not admitted to neuro-critical care unit after surgery 4. Posterior fossa surgery 5. Allergy to acetaminophen 6. Severe liver or renal impairment 7. Pregnant 8. Breast feeding 9. Not able to consent 10. No substitute decision maker **Mean age, range (years)** 1. 50 **Numbers allocated to each arm** 1. Group intervention -106 2. Group control -106 **Male gender** 1. Group intervention - 31 2. Group control - 48
Interventions	**Technique and timing** 1. Acetominophen intravenously versus saline, every 8 hours for a total of 48 hours with the first dose given intraoperatively after surgery was complete **Dosage** 1000 mg
Outcomes	**Primary** 1. Narcotic consumption **Secondary** 1. Pain scores using the visual analogue scale 2. Adverse events - nausea and vomiting, urinary retention, constipation 3. Length of stay in neuro-critical care 4. Length of stay in hospital
Notes	**Funding** Hospital

Sivakumar 2018 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: ''Randomization was performed with the use of a block-of-4 randomisation scheme. Randomization was performed by the investigational drug service at the university hospital, thereby maintaining the double-blind aspect of the study (patients and study personnel/investigators). Patient study identification numbers were recorded in an Excel database, randomized permuted blocks of 4 were created, and patients were allotted to either the acetaminophen or placebo group by the pharmacy.''
Allocation concealment (selection bias)	Low risk	Drugs were prepared by pharmacy.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Method not well described
Incomplete outcome data (attrition bias) All outcomes	Low risk	8 participants (4 in each group) were excluded after randomization due to untimely administration of the study drug or patient transfer . As equal numbers were lost from both groups, it was unlikely to have a significant impact on the results.
Selective reporting (reporting bias)	Low risk	Outcomes reported as specified
Other bias	Unclear risk	The study was slightly underpowered with the power calculation being based on a total of 210 patients.

Song 2016

Methods	Study design: randomized controlled trial (2 arms) Study duration: 2006 to 2009 Study setting: hospital, single centre, China
Participants	Adults undergoing elective supratentorial craniotomy (n = 60) **Inclusion criteria** 1. ASA I to III adults undergoing above surgery **Exclusion criteria** 1. History of ischaemic heart disease or conduction defects 2. Pulmonary disease 3. Hepatic disease 4. Renal impairment 5. Cognitive defect

Song 2016 *(Continued)*

6. Long-tern use of beta blockers, angiotension-converting enzyme inhibitors, analgesics, sedatives or antidepressants
7. Allergy to study drugs

Mean age, range (years)

1. 39 (18 to 60)

Numbers allocated to each arm

1. Group intervention (n = 30)
2. Group control (n = 30)

Male gender

1. Group intervention: 17/25 (participants analysed)
2. Group control: 15/27 (participants analysed)

Interventions	**Technique and timing** Intravenous infusion of dexmedetomidine 0.5 mcg/kg/hr for 10 minutes before induction of anaesthesia, then 0.2 to 0.5 mcg/kg/hr until skin closure versus placebo **Dosage** As above
Outcomes	**Not clear from the report, which outcomes were primary and which were secondary** 1. Postoperative pain using the NRS – numerical rating scale (measured at 1, 2 ,4, 6, 8, 12 and 24 hours) 2. Sedation – Ramsey Scale – up to 24 hours postoperatively 3. Morphine consumption – up to 23 hours postoperatively 4. Respiratory depression 5. Hypotension 6. Bradycardia
Notes	**Funding** None

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random number table
Allocation concealment (selection bias)	Low risk	Quote: ''an anaesthesia nurse prepared the syringe according to the computer-generated random number and was the only person who knew whether the active drug or placebo was administered''.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: ''an anaesthesia nurse prepared the syringe according to the computer-generated random number and was the only person who knew whether the active drug or placebo was administered''.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not clear if the anaesthesia nurse who prepared the study drugs was involved in assessing outcomes or not

Song 2016 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	3 participants (1 in the intervention group and 2 in the control group) did not receive their allocated treatments as their surgery was cancelled. 5 participants were lost to follow-up after receiving their allocated treatments as they were not extubated after surgery (4 in the invention group and 1 in the control group). An intention-to-treat analysis was not performed.
Selective reporting (reporting bias)	Unclear risk	The lack of clarity regarding outcome priorities makes it difficult to exclude reporting bias.
Other bias	Unclear risk	Small study

Tucinda 2010

Methods	Study design: randomized controlled trial (3 arms) Study duration: 2006 to 2007 Study setting: hospital, single centre, Thailand
Participants	Patients undergoing elective supratentorial craniotomy (n = 60) **Inclusion criteria** 1. ASA I to ASA II participants undergoing elective supratentorial craniotomy **Exclusion criteria** 1. Allergy to local anaesthetics 2. Hypertension 3. Coagulopathy 4. Opioid dependency 5. Scalp infection 6. Previous craniotomy 7. Not able to assess pain **Mean age, range (years)** 1. 41 (16 to 65) but youngest included participant was 21 **Numbers allocated to each arm** 1. Group 1: scalp block with 0.5% bupivacaine with 1:200,000 adrenaline (n = 20) 2. Group 2: scalp block with 0.25% bupivacaine with 1:200,000 adrenaline (n = 20) 3. Group 3: scalp block with saline with 1:200,000 adrenaline (n = 20) **Male gender** 1. Group 1: 10/20 (analysed participants) 2. Group 2: 8/19 (analysed participants) 3. Group 3: 4/20 (analysed participants)
Interventions	**Technique and timing** Scalp block of the following nerves: 1. Supraorbital and supratrochlear

Tucinda 2010 *(Continued)*

	2. Zygomaticotemporal 3. Auriculotemporal 4. Postauricular branches of the greater auricular 5. Greater, lesser, and third occipital nerves with 0.5% bupivacaine with 1:200,000 adrenaline (Group 1) versus 0.25% bupivacaine with 1:200,000 adrenaline (Group 2) versus saline with 1:200,000 adrenaline (Group 3), before surgery **Dosage** Max 3 mg/kg
Outcomes	**Primary** 1. Mean arterial blood pressure on skin incision **Secondary** 1. Postoperative pain as measured by the mean verbal numerical pain (VAS) rating scale (measured at 0.5, 1, 2, 6, 12 and 24 hours) 2. Sedation scores at the same time points (4-point scale: 1 to 4, awake, response to speech, response to pain, unresponsive) 3. Nausea and vomiting scores at the same time points (0 to 3: none, mild nausea, severe nausea, vomiting) 4. Total amount of morphine required during the first 24 hours
Notes	**Funding** Chulalongkorn University

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method not reported
Allocation concealment (selection bias)	High risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Anaesthesiologist performing the block was blinded but the method or its adequacy were not reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 participant from group 2 was excluded after he/she developed a postoperative intracranial haematoma; 59/60 participants were included in the final analysis.
Selective reporting (reporting bias)	Low risk	Outcomes reported as specified
Other bias	Unclear risk	Small study

Willams 2011

Methods	Study design: randomized controlled trial (2 arms) Study duration: not reported Study setting: hospital, single centre, Australia
Participants	Adults undergoing elective supratentorial craniotomy (n = 100) **Inclusion criteria** 1. ASA I to III adults undergoing above surgery **Exclusion criteria** 1. Ischaemic heart disease 2. Cerebrovascular disease 3. Asthma 4. Renal impairment 5. Allergy to any study drug 6. Chronic pain 7. Regular opioid usage 8. Heavy alcohol usage 9. Chronic benzodiazepine usage 10.Angiotensin-converting enzyme inhibitor or diuretic usage 11.Administration of paracetamol within 8 hours of anaesthesia induction 12.GCS < 15 13.Cognitive defect 14.Language barrier 15.Intellectual disability **Mean age, range (years)** 1. 42 (18 to 65) **Numbers allocated to each arm** 1. Group intervention (n = 50) 2. Group control (n = 50) **Male gender** 1. Group intervention: 23/49 (participants analysed) 2. Group control: 22/47 (participants analysed)
Interventions	**Technique and timing** 1. Parecoxib versus saline, given intravenously at dural closure **Dosage** 40 mg
Outcomes	**Primary** 1. Morphine consumption in the first 24 hours postoperatively **Secondary** 1. Postoperative pain using the visual analogue score (VAS), measured at 1, 6, 12 and 24 hours

Willams 2011 *(Continued)*

2. Sedation score: scored from 'alert' to 'roused only by pain' - 1 to 4
3. Nausea and vomiting – score – 'none', 'nausea not requiring treatment', 'nausea requiring treatment', 'vomiting' - 0, 1, 2, 3
4. Systolic blood pressure
5. Heart rate
6. Respiratory rate

Notes	**Funding** None

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A computer-generated randomization list was used.
Allocation concealment (selection bias)	Low risk	Quote: ''computer-generated randomisation results were concealed in opaque envelopes until consent had been obtained. The randomisation was stratified by gender''.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: ''the study medication was prepared by an anaesthetist who was not involved with the case. The patients, attending anaesthetists, surgeons, and postoperative observers were blind to group allocation''.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors were blinded.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	4 participants were lost to follow-up after enrolment. 1 was excluded as surgery was cancelled and 2 participants in the intervention group and 1 in the control group withdrew consent after surgery. These were not included in the final analysis. The lack of an intention-to-treat analysis makes it difficult to accurately estimate the impact of these losses on the effect estimate.
Selective reporting (reporting bias)	Low risk	Outcomes were reported as specified.
Other bias	Low risk	No other significant biases were identified.

Yardav 2014

Methods	Study design: randomized controlled trial (3 arms) Study duration: 2010 to 2013 Study setting: hospital, single centre, India
Participants	Adults undergoing elective craniotomy (n = 390) **Inclusion criteria** 1. ASA I to ASA II participants undergoing elective craniotomy

Yardav 2014 *(Continued)*

Exclusion criteria

1. BMI < 19 or > 35
2. Allergy to study drugs
3. Inability to tolerate oral medication
4. Inability to understand the pain score
5. History of peptic ulcer
6. Renal, hepatic, cardiac or respiratory disease
7. Pregnancy
8. Semi or unconscious
9. Disoriented
10. Haemodymanically unstable

Mean age, range (years)

1. 44 (18 to 70)

Numbers allocated to each arm

1. Group 1: placebo (rantidine 150 mg + Vit B capsule) (n = 124)
2. Group 2: diclofenac 50 mg + Vit B capsule (n = 125)
3. Group 3: flupirtine 100 mg + rantidine 150 mg (n = 122)

Male gender

1. Group 1: 67/124
2. Group 2: 61/125
3. Group 3: 67/122

Interventions	**Technique and timing** 1. Group 1: placebo (rantidine 150 mg + Vit B capsule) 2. Group 2: diclofenac 50mg + Vit B capsule 3. Group 3: flupirtine 100 mg + rantidine 150 mg given orally every 8 hours, beginning on the second postoperative day and continued for a total of 48 hours **Dosages** As above
Outcomes	**Primary** 1. Pain as measured by the visual analogue score (VAS) during the first 48 hours postoperatively (measured at 6, 12, 18, 24, 36 and 48 hours) **Secondary** 1. Additional analgesia requirement: morphine equivalent 2. Sedation: Ramsey sedation scale 3. Adverse events/side effects: nausea and vomiting, bleeding, diarrhoea, constipation and depression
Notes	**Funding** 1. None

Risk of bias

Bias	Authors' judgement	Support for judgement

Yardav 2014 *(Continued)*

Random sequence generation (selection bias)	Low risk	Computer-generated randomization table
Allocation concealment (selection bias)	High risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: ''a nurse, who was not part of the study, administered 1 tablet and 1 capsule of similar shape to all the patients 8 hourly, on second postoperative day for 48 hours. Neither patients nor the observer was aware of the type of medications''.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: ''a nurse, who was not part of the study, administered 1 tablet and 1 capsule of similar shape to all the patients 8 hourly, on second postoperative day for 48 hours. Neither patients nor the observer was aware of the type of medications''.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	6 participants were excluded from the analysis (6 in group 1, 5 in group 2 and 8 in group 3); the authors did not provide details of the reasons or the stage in the study at which these patients were excluded.
Selective reporting (reporting bias)	Low risk	Outcomes reported as specified
Other bias	Low risk	No other significant biases were identified.

Yun 2016

Methods	Study design: randomized controlled trial (3 arms) Study duration: not reported Study setting: hospital, single centre, China
Participants	Adults undergoing elective supratentorial craniotomy (n = 150) **Inclusion criteria** 1. ASA I to ASA II participants undergoing above surgery **Exclusion criteria** 1. GCS < 15 2. Bradycardia: HR < 50 3. Hypertension: systolic blood pressure > = 180 mmHg or diastolic > / = 110 mmHg 4. History of lung, liver or kidney disease 5. Allergy to study drugs 6. Body weight 15% above or below normal: Brocas index **Mean age, range (years)** 1. 50 (35 to 65) **Numbers allocated to each arm** 1. Group 1: dexmedetomidine infusion 0.4 mcg/kg (n = 50) 2. Group 2: dexmedetomidine infusion 0.8 mcg/kg (n = 50) 3. Group 3: control, saline infusion (n = 50)

Yun 2016 *(Continued)*

	Male gender 1. Group 1: 13/45 (patients analysed) 2. Group 2: 15/43 (patients analysed) 3. Group 3: 20/46 (patients analysed)
Interventions	**Technique and timing** 1. Different dosages of dexmedetomidine by intravenous infusion given or a total of 10 minutes, 1 hour before the end of surgery Group 1: dexmedetomidine infusion 0.4 mcg/kg Group 2: dexmedetomidine infusion 0.8 mcg/kg Group 3: control,saline infusion **Dosages** As above
Outcomes	**Primary** 1. Hypertension on emergence **Secondary** 1. Tachycardia on emergence 2. Incidience of significant postoperative pain –NRS – numerical rating score > / = 4 3. Cough after extubation 4. Adverse event - nausea and vomiting
Notes	**Funding** None

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote. ''using computer-generated random numbers and a sealed-envelop technique, patients were allocated randomly into 1 of 3 groups: small-dose DEX (0.4 mg/kg), median-dose DEX (0.8 mg/kg), or vehicle control (an equivalent volume of normal saline)."
Allocation concealment (selection bias)	Low risk	Sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote. "the attending anaesthesiologists were unaware of the grouping'', implying that those administering the infusion were unaware of the contents of the syringe''.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: ''the attending anaesthesiologists were unaware of the grouping, and the measurements were recorded by 1 nurse, who was also blinded''.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	17 participants were excluded from the final analysis as follows: 8 participants did not receive the allocated intervention.

Yun 2016 *(Continued)*

		Group 1: 3 excluded (1 had prolonged surgery and 2 had blood loss > 1400 mL) Group 2: 2 excluded (1 had a seizure and 1 had blood loss > 1400 mL) Group 3: 2 excluded (1 had a prolonged surgery and 1 had blood loss > 1400 mL) 9 participants were lost to follow-up after receiving their allocated intervention. Group 1: 2 excluded (1 had an intracranial bleed and 1 had a seizure requiring sedation) Group 2: 5 excluded (1 had a weight < 45 kg, 1 had an intracranial bleed, 1 had prolonged surgery, 1 had delayed recovery and I had an unclear reason) Group 3: 2 excluded (1 had an intracranial bleed and 1 had a low level of consciousness) The relatively large numbers excluded and the inequality of both numbers and reasons across groups together with the lack of an intention-to-treat analysis, made it difficult to measure the true effect estimate accurately.
Selective reporting (reporting bias)	Low risk	Outcomes reported as specified
Other bias	Unclear risk	Small study

Zeng 2019

Methods	Study design: randomized controlled trial (2 arms) Study duration: not reported Study setting: hospital, single centre, China
Participants	Adults undergoing elective subtemporal or suboccipital craniotomy (n = 150) **Inclusion criteria** 1. ASA I to ASA II participants undergoing above surgery **Exclusion criteria** 1. History of psychiatric disorder 2. Pregnant or lactating 3. Alcohol addiction 4. Paticipitation within another study within the last 30 days 5. Body mass index > 30 6. Allergy to study drugs **Mean age, range (years)** 1. 43.5 (18 to 65) **Numbers allocated to each arm** 1. Group 1: Placebo Vitamin B (n = 61) 2. Group 2: Gabapentin 600 mg orally twice before surgery (n = 61) **Male gender**

Zeng 2019 *(Continued)*

1. Group 1: 22/50
2. Group 2: 24/52

Interventions	**Technique and timing** 1. Gabapentin or placebo orally the night before surgery and again at 2 hours before induction of anaesthesia Group 1: Placebo Vitamin B capsules Group 2: Gabapentin 600 mg orally the night before surgery and again 2 hours before induction of anaesthesia **Dosages** As above
Outcomes	**Primary** 1. Postoperative pain on head movement, as measured by the visual analogue score at 24 hours **Secondary** 1. Postoperative pain on head movement, as measured by the visual analogue score at 1, 2 and 48 hours 2. Postoperative pain at rest, as measured by the visual analogue score at 1, 2 and 48 hours 3. Postoperative opioid consumption 4. Postoperative sedation levels 5. Incidence of postoperative nausea and vomiting
Notes	**Funding** Youth Programme Funding of Beijing Tiantan Hospital, Capital Medical University (number: YQN201210)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: ''A computer-generated randomisation table prepared by an investigator with no involvement in the trial was used.''
Allocation concealment (selection bias)	Low risk	Quote: ''An individual not involved in the enrolment handled the randomisation list to guarantee allocation concealment''.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: ''The nurse, anesthesiologists, patients, and outcome assessors were all blinded to the grouping.''
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: ''The nurse, anesthesiologists, patients, and outcome assessors were all blinded to the grouping.''
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	11 patients in the placebo group and 9 patients in the treatment group were lost to follow-up.
Selective reporting (reporting bias)	Low risk	Outcomes were reported as specified.

Zeng 2019 *(Continued)*

Other bias	Unclear risk	Analysis was not intention-to-treat.

Zhang 2003

Methods	Randomized controlled trial (4 arms)
Participants	Adults undergoing elective craniotomy (n = 60) **Inclusion criteria** 1. ASA I to III participants undergoing elective supratentorial craniotomy **Exclusion criteria** 1. None reported **Mean age, range (years)** 1. 44 (18 to 70) **Numbers allocated to each arm** 1. Group 1: control: 10 2. Group 2: scalp block: 17 3. Group 3: wound infiltration: 17 4. Group 4: superficial cervical plexus block: 16 **Male gender** 1. Not reported
Interventions	**Technique and timing** 1. Regional infiltration or block 0.75% ropivacaine at the end of surgery **Dosages** 1. Unclear from report
Outcomes	**Primary** 1. Pain as measured by the visual analogue score (VAS) during the first 48 hours after surgery **Secondary** None
Notes	Paper only available in Chinese so some translation errors possible **Funding** None

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method not reported

Zhang 2003 *(Continued)*

Allocation concealment (selection bias)	High risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	Not reported
Selective reporting (reporting bias)	Low risk	Outcomes reported as specified
Other bias	High risk	Small study and analysis method not completely described

Zhou 2016

Methods	Study design: randomized controlled trial (2 arms) Study duration: not reported Study setting: hospital, single centre, China
Participants	Adults undergoing elective craniotomy (n = 154) **Inclusion criteria** 1. ASA I to III adults undergoing above surgery **Exclusion criteria** 1. Unable to understand visual analogue scale 2. Spinal or epidural analgesia 3. Patient-controlled or postoperative intravenous analgesia 4. GCS < 15 5. Allergy to study medications 6. Previous scalp incision 7. Chronic pain i.e. treated with opioids for > / = 14 days or non opioid medications > 5 times a week **Mean age, range (years)** 1. 44 (18 to 70) **Numbers allocated to each arm** 1. Group intervention (n = 53) 2. Group control (n = 53) **Male gender** 1. Group intervention: 30/53

Zhou 2016 *(Continued)*

	2. Group control: 27/53
Interventions	**Technique and timing** Scalp infiltration with 0.5% ropivacaine versus scalp infiltration with saline before surgery **Dosage** 10 mL
Outcomes	**Primary** 1. Morphine consumption during the first 24 hours postoperatively **Secondary** 1. Time to requirement for rescue analgesia 2. Postoperative pain as measured by the visual analogue score (VAS) 3. Sedation score 4. Adverse events
Notes	**Funding** Study was funded by a pharmaceutical company Astra Zeneca.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A computer-generated random number chart was used.
Allocation concealment (selection bias)	Low risk	Opaque sealed envelopes were used to conceal the allocation sequence.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: ''on the day of surgery, according to the random code of the patient, an anaesthetic nurse prepared the solution of normal saline or ropivacaine. All solutions were prepared in identical syringes. The random code, patient's information and group name were enclosed in the sealed opaque envelope. The anaesthetists who performed the anaesthesia and recorded the intraoperative data, the neurosurgeons who performed the scalp infiltration, and patients were all blinded to the group assignment. The envelope was opened only if emergency un blinding was required''.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: ''all the follow-up procedures were conducted by another nurse who was also blind to the treatment group assignment."
Incomplete outcome data (attrition bias) All outcomes	High risk	48 participants were lost to primary outcome follow-up, after randomization: 7 due to cancelled surgery 3 due to requiring admission to intensive care 16 due to inability to communicate 12 due to requiring analgesia other than morphine 5 more participants were lost to follow-up for outcomes measured at 3 months.

Zhou 2016 *(Continued)*

		These participants were excluded from the analysis.
Selective reporting (reporting bias)	Low risk	Outcomes were reported as specified.
Other bias	Unclear risk	Study was funded by a pharmaceutical company Astra Zeneca.

ASA: American Anesthesiology Society Classification
BMI: body mass index
COX: cyclo-oxygenase
DEX: dexmedetomidine
GCS: Glasgow coma score
Hr: hour
HR: heart rate
Hrs: hours
ICP: intra cranial pressure
IV: intravenous
kg: kilograms
mcg: micrograms
mg: milligrams
mL: millilitres
mmHg: millimetres of mercury
n: number
NRS: numerical pain score
NSAID: non steroidal anti inflammatories
PCA: patient controlled analgesia
VAS: visual analogue pain score
Vit: vitamin

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Ackil 2018	No control group - morphine v dexketoprofen
Ayoub 2006	No control group: morphine v scalp block
Bajaj 2017	Outcomes of Interest not addressed This study was conducted to establish the efficacy and safety of clonidine in reducing intraoperative oozing and improving operating conditions in pituitary adenoma surgery. The purpose of the study was not to establish its analgesic potential efficacy or safety in the context of use for as an analgesic.
Bishnoi 2016	Outcomes of Interest not addressed This study was conducted to establish it dexmedetomidine reduced unwanted intraoperative patient movement and patient and surgical satisfaction. The purpose of the study was not to establish its analgesic potential efficacy or safety in the context of use as an analgesia.
Citerio 2012	No control group: all 3 groups received opioid medication.
Dolmatova 2009	No control group: scheduled v as-needed lornoxicam
Domenech 2006	No control group: parecoxib v paracetamol

Study	Reason for exclusion
Doumiri 2015	No postoperative pain outcomes. The aim of this study was to establish the intraoperative haemodynamic stability profile of a lidocaine scalp block. It was not conducted to address either its analgesic potential or side effect profile in the context of use for analgesic purposes.
Dudko 2014	No control group: bupivacaine v paracetamol and ketoprofen
El Dahab 2009	No control group: skull block v fentanyl
Ferber 2000	No control group: 2 different doses of tramadol
Girard 2010	No control group: morphine v codeine
Goldsack 1996	No control group: superficial cervical plexus block v morphine
Graham 1999	No control group: tramadol v codeine phosphate
Hassani 2015	No control group – sufentanil v paracetamol v morphine
Honnma 2002	No control group and no randomization
Imaev 2008	No control group: lornoxicam v ropivacaine v fentanyl
Imaev 2010	No control group: xefocam v ropivacaine v durogesic
Jayaram 2016	No control group: maxillary block v scalp block
Jeffrey 1999	No control group: codeine v tramadol
Jose 2017	No control group: local anaesthetic with added steroid v local anaesthetic alone
Lu 2009	Different patient population: participants already had established postoperative pain No control group: morphine/acetaminophen v rotunidine
Luo 2014	No control group: lidocaine v procaine
Mohamed 2018	No control group - scalp block v scalp block with hyaluronidase
Morad 2009	No control group: fentanyl as required v fentanyl PCA
Na 2011	No control group: fentanyl and ketorolac as required v fentanyl and ketorolac PCA
Palazón 2006	No control group – sevoflurane v propofol
Rajan 2016	No control group: dexmedetomidine infusion versus remifentanil infusion
Reddy 2018	No control group - scalp block v local anaesthetic infiltration
Simon 2012	No true control group – intervention group were enrolled prospectively and the historical controls were randomly selected from a database
Soliman 2011	No distinction between intraoperative and postoperative pain outcomes
Stone 2018	Cross-over study of acetaminophen versus placebo in patients undergoing bilateral craniotomies for Moyamoya disease. Excluded due to the high potential for carry-over effects and period effects

Study	Reason for exclusion
Stoneham 1996	No control group – morphine v codeine phosphate
Sudheer 2007	No control group – morphine v tramadol v codeine phosphate
Tanskanen 1999	No control group – paracetamol v ketoprofen
Theerth 2018	Bo control group - scalp block v local anaesthetic infiltration
Ture 2009	No control group – gabapentin v phenytoin
Vallapu 2018	No control group - scalp infiltration v scalp block
Venkatraghavan 2016	Different patient population – patients already had established postoperative pain.
Verchere 2002	No control group – paracetamol v tramadol v nalbuphine
Wu 2014	Ongoing study. Different patient population: participants admitted to ICU with delayed extubation after craniotomy
Zhao 2013	Different patient population: participants admitted to ICU with delayed extubation after craniotomy

ICU: intensive care unit
PCA: patient controlled analgesia
V: versus

Characteristics of ongoing studies *[ordered by study ID]*

KCT0000274

Trial name or title	Scalp blocks with levo-bupivacaine reduced postoperative pain and the requirement of anti-hypertensive agent after craniotomy for aneurysmal clipping
Methods	Randomized controlled double-blinded trial, target sample size 52, single centre, South Korea
Participants	Adult patients undergoing craniotomy for elective cerebral aneurysm clipping Exclusion criteria: 1. Inability to understand the pain score 2. Previous craniotomy 3. Allergy to local anaesthetic medications 4. Treatment with narcotics for more than 2 weeks
Interventions	Scalp block with levo-bupivacaine versus scalp block with saline
Outcomes	Primary 1. Requirement for antihypertensive medications 2. Postoperative pain as measured by the VAS at 1, 2, 4 ,8, 12, 16, 24, 48, 72 hours 3. Fentanyl consumption Secondary 1. Arterial blood pressure and heart rate at the same time points 2. Time to first dose of rescue analgesia

KCT0000274 *(Continued)*	3. Use of vasopressors 4. Nausea and vomiting 5. Respiratory depression 6. Use of rescue analgesics 7. Time to discontinuation of PCA
Starting date	Registered Nov 2011, anticipated completion date was May 2012 but no further details available regarding progress
Contact information	Junghee Ryu, Seoul National University Bundang Hospital
Notes	1. Long interval between registration and completion 2. No progress update since 2012 3. 3 primary outcomes 4. Declarative title in advance of study results

PCA: patient controlled analgesia
VAS: visual analogue pain score

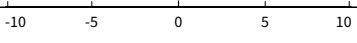
DATA AND ANALYSES

Comparison 1. NSAIDs versus control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Acute pain 0 to 6 hours	6	742	Mean Difference (IV, Random, 95% CI)	-1.11 [-1.64, -0.58]
2 Acute pain at 12 hours	6	742	Mean Difference (IV, Random, 95% CI)	-0.74 [-1.22, -0.26]
3 Acute pain at 24 hours	6	742	Mean Difference (IV, Random, 95% CI)	-0.70 [-1.26, -0.14]
4 Additional analgesia requirements 0 to 24 hours	4	265	Mean Difference (IV, Random, 95% CI)	-1.07 [-4.85, 2.72]
5 Nausea and vomiting	2	345	Risk Ratio (M-H, Random, 95% CI)	1.34 [0.30, 5.94]

Analysis 1.1. Comparison 1 NSAIDs versus control, Outcome 1 Acute pain 0 to 6 hours.

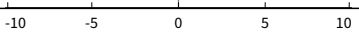
Study or subgroup	NSAIDS N	NSAIDS Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Dilmen 2016	19	1.5 (2)	9	1.5 (1.8)		9.03%	0.02[-1.46,1.5]
Dilmen 2016	18	1.9 (2.1)	9	1.5 (1.8)		8.65%	0.38[-1.15,1.91]
Jones 2009	41	2.5 (2.2)	39	3.8 (2.2)		15.35%	-1.3[-2.26,-0.34]
Molnár 2015	100	2.5 (3.6)	100	4.4 (3.5)		15.04%	-1.9[-2.88,-0.92]
Shepherd 2018	28	1.6 (2.1)	34	3.7 (2.4)		12.99%	-2.1[-3.22,-0.98]



Study or subgroup	NSAIDS N	NSAIDS Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Willams 2011	47	2 (2.6)	49	3 (2.6)		14.16%	-1[-2.04,0.04]
Yardav 2014	125	2 (2)	124	3 (2)		24.77%	-1[-1.49,-0.51]
Total ***	**378**		**364**			**100%**	**-1.11[-1.64,-0.58]**

Heterogeneity: Tau²=0.23; Chi²=11.72, df=6(P=0.07); I²=48.83%

Test for overall effect: Z=4.13(P<0.0001)

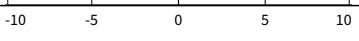


Analysis 1.2. Comparison 1 NSAIDs versus control, Outcome 2 Acute pain at 12 hours.

Study or subgroup	NSAIDS N	NSAIDS Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Dilmen 2016	19	1.1 (1.3)	9	1.5 (1.4)		12.92%	-0.45[-1.55,0.65]
Dilmen 2016	18	1.2 (1.9)	9	1.5 (1.4)		10.51%	-0.28[-1.55,0.99]
Jones 2009	41	2.5 (4.2)	39	2.7 (4.2)		5.94%	-0.2[-2.02,1.62]
Molnár 2015	100	2.5 (3.5)	100	4.4 (3.5)		15.09%	-1.9[-2.88,-0.92]
Shepherd 2018	28	2.7 (2.3)	34	3.3 (2.2)		12.2%	-0.6[-1.75,0.55]
Willams 2011	47	2 (2.5)	49	2 (2.5)		15.05%	0[-0.98,0.98]
Yardav 2014	125	2 (2)	124	3 (2)		28.3%	-1[-1.49,-0.51]
Total ***	**378**		**364**			**100%**	**-0.74[-1.22,-0.26]**

Heterogeneity: Tau²=0.15; Chi²=9.59, df=6(P=0.14); I²=37.42%

Test for overall effect: Z=3.03(P=0)



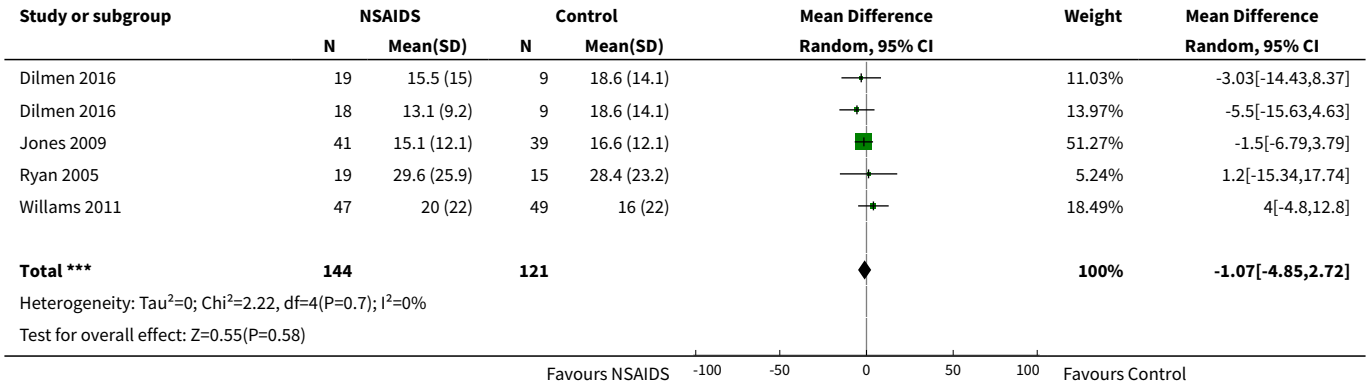
Analysis 1.3. Comparison 1 NSAIDs versus control, Outcome 3 Acute pain at 24 hours.

Study or subgroup	NSAIDS N	NSAIDS Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Dilmen 2016	19	1 (1.5)	9	1.2 (1.6)		12.26%	-0.16[-1.38,1.06]
Dilmen 2016	18	2.1 (2)	9	1.2 (1.6)		10.5%	0.95[-0.44,2.34]
Jones 2009	41	2.5 (2.2)	39	2.8 (2.2)		15.89%	-0.3[-1.25,0.65]
Molnár 2015	100	4 (3)	100	5.6 (3.5)		16.52%	-1.6[-2.51,-0.69]
Shepherd 2018	28	1.6 (2.5)	34	2.8 (2.6)		11.62%	-1.2[-2.48,0.08]
Willams 2011	47	1 (2.5)	49	2 (2.5)		15.15%	-1[-2,0]
Yardav 2014	125	2 (3.3)	124	3 (3.3)		18.05%	-1[-1.82,-0.18]
Total ***	**378**		**364**			**100%**	**-0.7[-1.26,-0.14]**

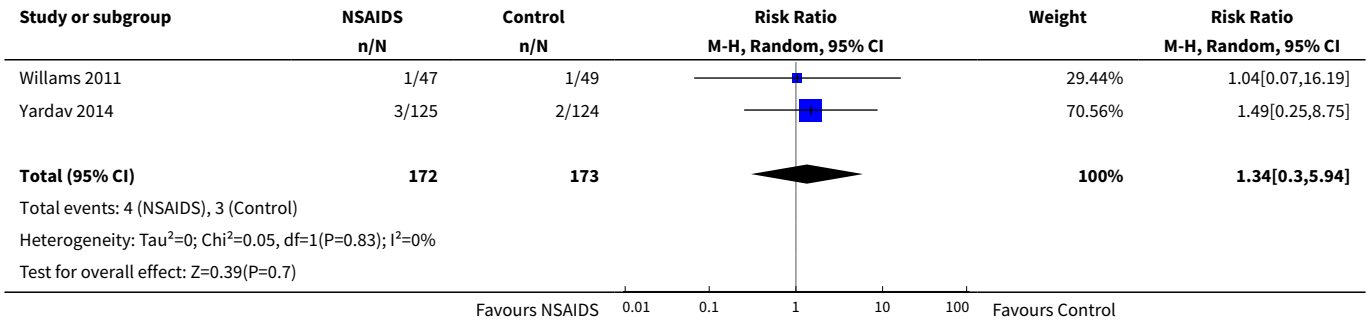
Heterogeneity: Tau²=0.28; Chi²=11.95, df=6(P=0.06); I²=49.8%

Test for overall effect: Z=2.46(P=0.01)

Analysis 1.4. Comparison 1 NSAIDs versus control, Outcome 4 Additional analgesia requirements 0 to 24 hours.



Analysis 1.5. Comparison 1 NSAIDs versus control, Outcome 5 Nausea and vomiting.



Comparison 2. Dexmedetomidine versus control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Acute pain 0 to 6 hours	2	128	Mean Difference (IV, Random, 95% CI)	-0.89 [-1.27, -0.51]
2 Acute pain at 12 hours	2	128	Mean Difference (IV, Random, 95% CI)	-0.81 [-1.21, -0.42]
3 Acute pain at 24 hours	2	128	Mean Difference (IV, Random, 95% CI)	-0.08 [-0.32, 0.16]
4 Additional analgesia requirements 0 to 24 hours	2	128	Mean Difference (IV, Random, 95% CI)	-21.36 [-34.63, -8.09]
5 Nausea and vomiting	4	323	Risk Ratio (M-H, Random, 95% CI)	0.43 [0.06, 3.08]
6 Hypotension	3	184	Risk Ratio (M-H, Random, 95% CI)	0.5 [0.05, 5.28]

Analysis 2.1. Comparison 2 Dexmedetomidine versus control, Outcome 1 Acute pain 0 to 6 hours.

Study or subgroup	Dexmedetomidine N	Dexmedetomidine Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Peng 2015	38	3 (7)	38	3 (7)		1.44%	0[-3.15,3.15]
Song 2016	25	2.7 (0.7)	27	3.6 (0.7)		98.56%	-0.9[-1.28,-0.52]
Total ***	**63**		**65**			**100%**	**-0.89[-1.27,-0.51]**

Heterogeneity: Tau^2=0; Chi^2=0.31, df=1(P=0.58); I^2=0%

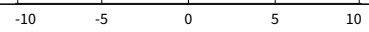
Test for overall effect: Z=4.6(P<0.0001)

Analysis 2.2. Comparison 2 Dexmedetomidine versus control, Outcome 2 Acute pain at 12 hours.

Study or subgroup	Dexmedetomidine N	Dexmedetomidine Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Peng 2015	38	2 (0.7)	38	3 (0.7)		53.74%	-1[-1.31,-0.69]
Song 2016	25	2.5 (0.7)	27	3.1 (0.7)		46.26%	-0.6[-0.98,-0.22]
Total ***	**63**		**65**			**100%**	**-0.81[-1.21,-0.42]**

Heterogeneity: Tau^2=0.05; Chi^2=2.52, df=1(P=0.11); I^2=60.29%

Test for overall effect: Z=4.09(P<0.0001)

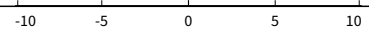


Analysis 2.3. Comparison 2 Dexmedetomidine versus control, Outcome 3 Acute pain at 24 hours.

Study or subgroup	Dexmedetomidine N	Dexmedetomidine Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Peng 2015	38	2 (0.7)	38	2 (0.7)		59.64%	0[-0.31,0.31]
Song 2016	25	2.5 (0.6)	27	2.7 (0.8)		40.36%	-0.2[-0.58,0.18]
Total ***	**63**		**65**			**100%**	**-0.08[-0.32,0.16]**

Heterogeneity: Tau^2=0; Chi^2=0.63, df=1(P=0.43); I^2=0%

Test for overall effect: Z=0.65(P=0.52)



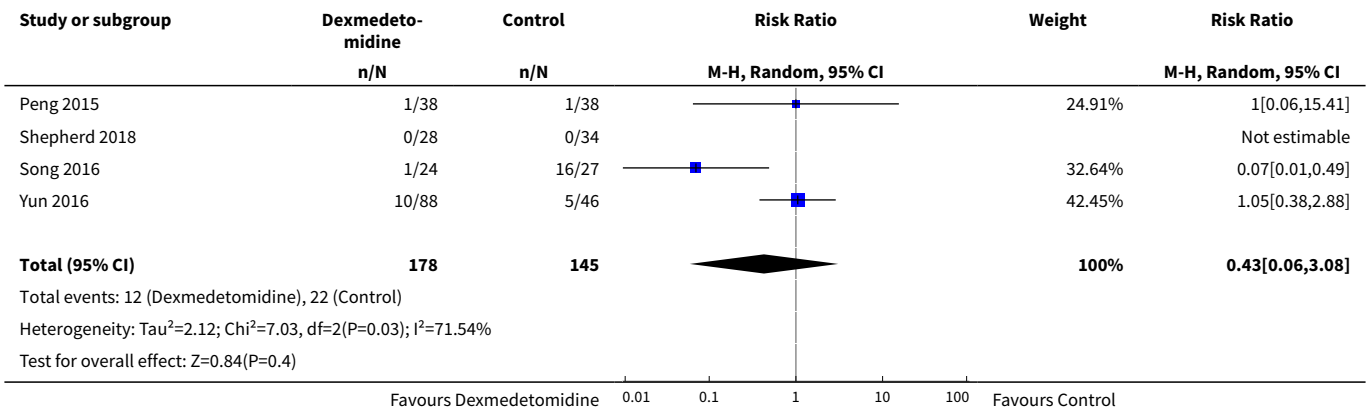
Analysis 2.4. Comparison 2 Dexmedetomidine versus control, Outcome 4 Additional analgesia requirements 0 to 24 hours.

Study or subgroup	Dexmedetomidine N	Dexmedetomidine Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Peng 2015	38	139 (28.9)	38	169.6 (39.9)		34.93%	-30.6[-46.26,-14.94]
Song 2016	25	35.6 (6.9)	27	52 (5.7)		65.07%	-16.4[-19.86,-12.94]
Total ***	**63**		**65**			**100%**	**-21.36[-34.63,-8.09]**

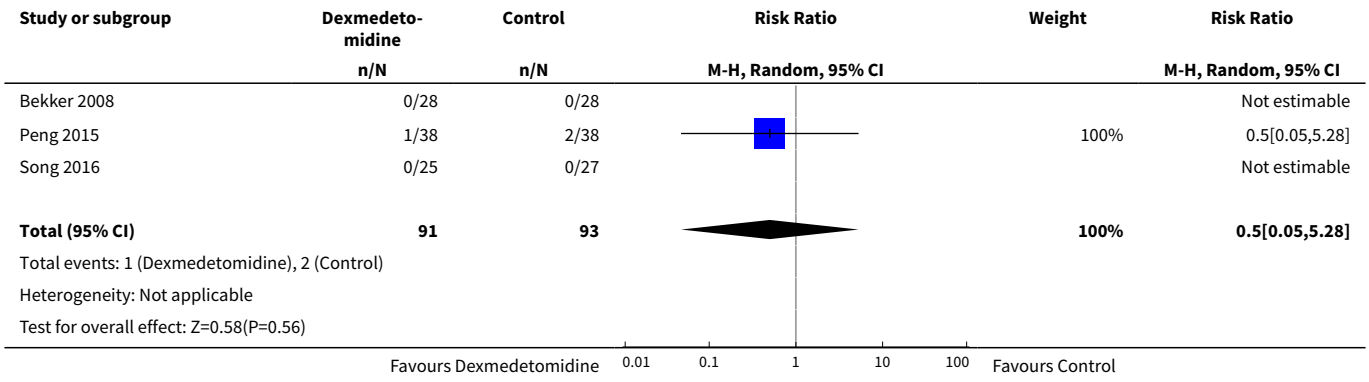
Heterogeneity: Tau^2=67.33; Chi^2=3.01, df=1(P=0.08); I^2=66.78%

Test for overall effect: Z=3.16(P=0)

Analysis 2.5. Comparison 2 Dexmedetomidine versus control, Outcome 5 Nausea and vomiting.



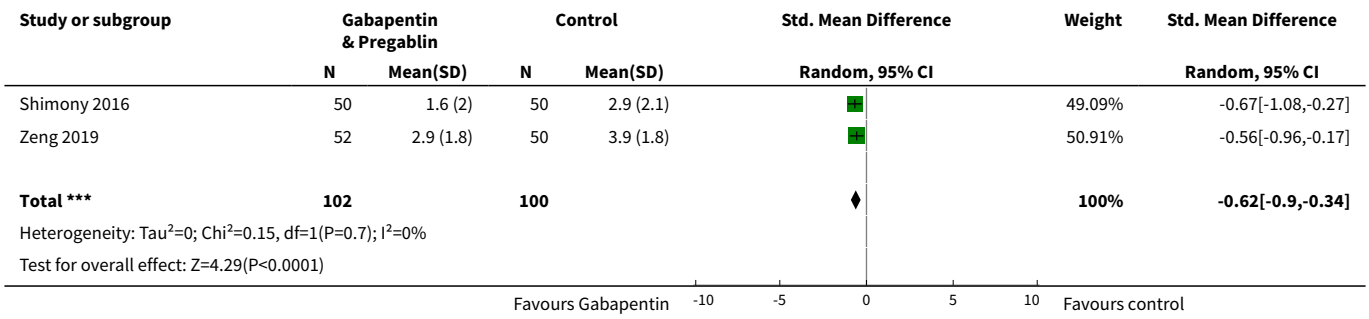
Analysis 2.6. Comparison 2 Dexmedetomidine versus control, Outcome 6 Hypotension.



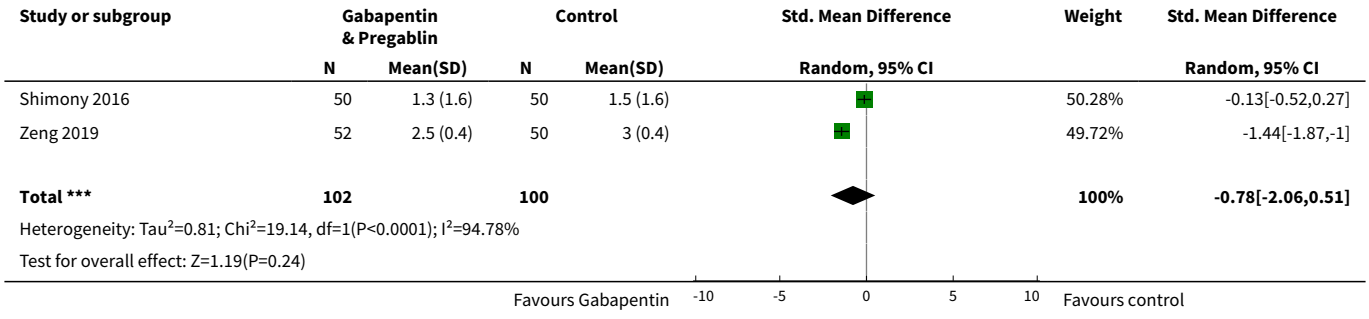
Comparison 3. Gabapentin and pregabalin versus control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Acute pain 0 to 6 hours	2	202	Std. Mean Difference (IV, Random, 95% CI)	-0.62 [-0.90, -0.34]
2 Acute pain at 24 hours	2	202	Std. Mean Difference (IV, Random, 95% CI)	-0.78 [-2.06, 0.51]
3 Acute pain at 48 hours	2	202	Std. Mean Difference (IV, Random, 95% CI)	-0.02 [-0.29, 0.26]
4 Additional analgesia requirement 0 to 24 hours	3	235	Std. Mean Difference (IV, Random, 95% CI)	-0.37 [-1.10, 0.35]
5 Nausea and vomiting	3	275	Risk Ratio (M-H, Random, 95% CI)	0.51 [0.29, 0.89]

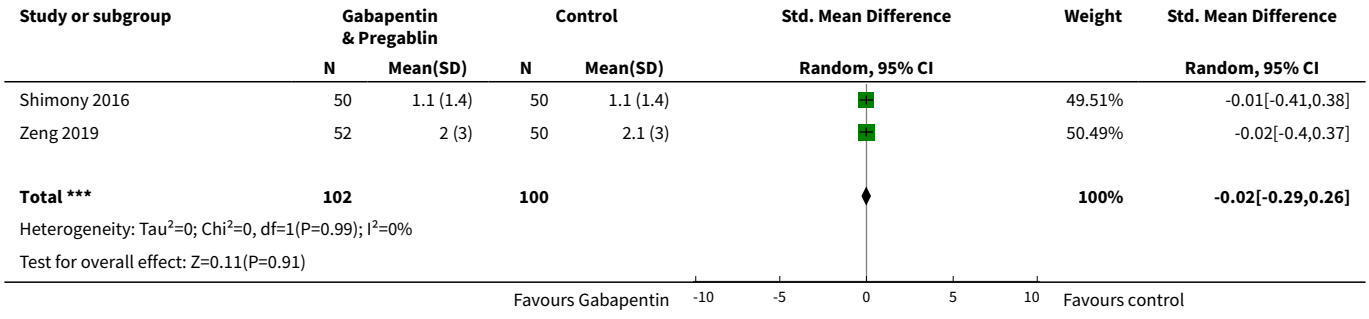
Analysis 3.1. Comparison 3 Gabapentin and pregabalin versus control, Outcome 1 Acute pain 0 to 6 hours.



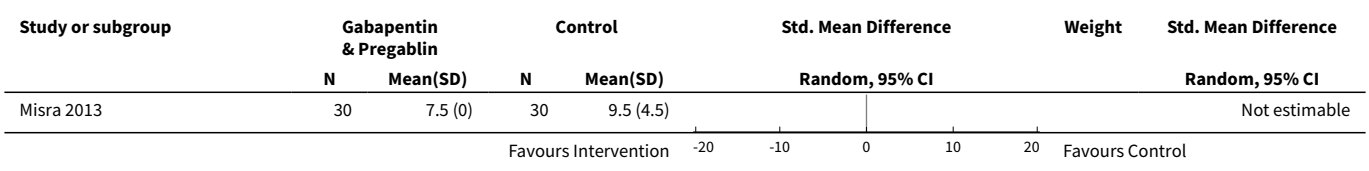
Analysis 3.2. Comparison 3 Gabapentin and pregabalin versus control, Outcome 2 Acute pain at 24 hours.

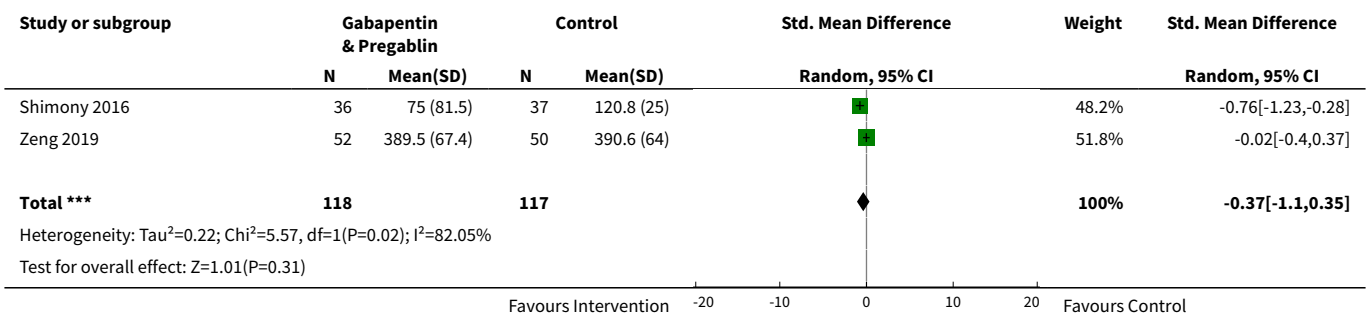


Analysis 3.3. Comparison 3 Gabapentin and pregabalin versus control, Outcome 3 Acute pain at 48 hours.

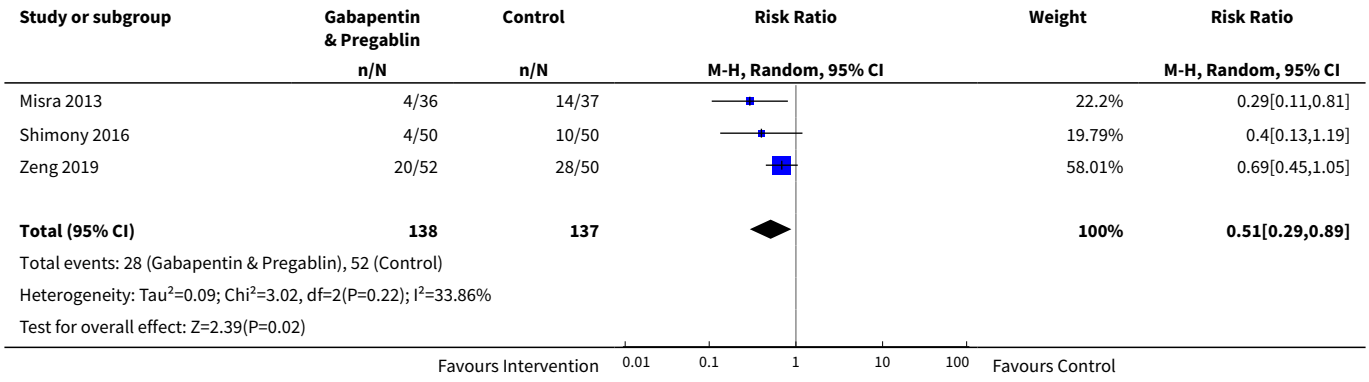


Analysis 3.4. Comparison 3 Gabapentin and pregabalin versus control, Outcome 4 Additional analgesia requirement 0 to 24 hours.





Analysis 3.5. Comparison 3 Gabapentin and pregabalin versus control, Outcome 5 Nausea and vomiting.



Comparison 4. Acetaminophen versus control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Acute pain 0 to 6 hours	3	332	Mean Difference (IV, Random, 95% CI)	-0.35 [-1.00, 0.30]
2 Acute pain at 12 hours	3	332	Mean Difference (IV, Random, 95% CI)	-0.51 [-1.04, 0.03]
3 Acute pain at 24 hours	4	439	Mean Difference (IV, Random, 95% CI)	-0.34 [-1.20, 0.52]
4 Additional analgesia requirement 0 to 24 hours	4	459	Mean Difference (IV, Random, 95% CI)	0.07 [-0.86, 0.99]
5 Length of stay in hospital (hours)	2	335	Mean Difference (IV, Random, 95% CI)	-3.71 [-14.12, 6.70]

Analysis 4.1. Comparison 4 Acetaminophen versus control, Outcome 1 Acute pain 0 to 6 hours.

Study or subgroup	Acetominophen N	Mean(SD)	Control N	Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Artime 2018	45	2 (2.2)	41	3 (1.8)		32.38%	-1[-1.84,-0.16]
Dilmen 2016	22	1.8 (2.2)	20	1.5 (1.8)		20.7%	0.32[-0.88,1.52]
Sivakumar 2018	102	5.4 (2.2)	102	5.6 (1.8)		46.93%	-0.2[-0.75,0.35]
Total ***	**169**		**163**			**100%**	**-0.35[-1,0.3]**
Heterogeneity: Tau^2=0.16; Chi^2=3.78, df=2(P=0.15); I^2=47.08%							
Test for overall effect: Z=1.06(P=0.29)							

Analysis 4.2. Comparison 4 Acetaminophen versus control, Outcome 2 Acute pain at 12 hours.

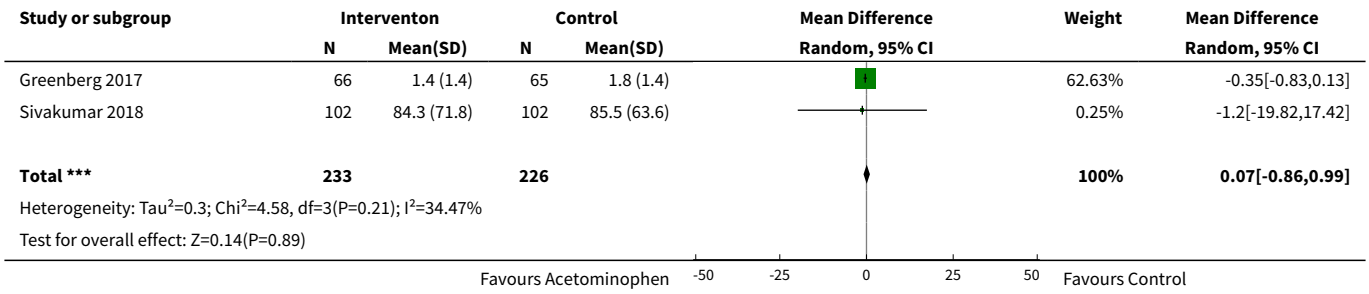
Study or subgroup	Acetominophen N	Mean(SD)	Control N	Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Artime 2018	45	2 (1.1)	41	2 (1.4)		33.53%	0[-0.53,0.53]
Dilmen 2016	22	0.8 (1.1)	20	1.5 (1.4)		24.91%	-0.7[-1.46,0.06]
Sivakumar 2018	102	5 (1.1)	102	5.8 (1.4)		41.56%	-0.8[-1.14,-0.46]
Total ***	**169**		**163**			**100%**	**-0.51[-1.04,0.03]**
Heterogeneity: Tau^2=0.15; Chi^2=6.24, df=2(P=0.04); I^2=67.97%							
Test for overall effect: Z=1.85(P=0.06)							

Analysis 4.3. Comparison 4 Acetaminophen versus control, Outcome 3 Acute pain at 24 hours.

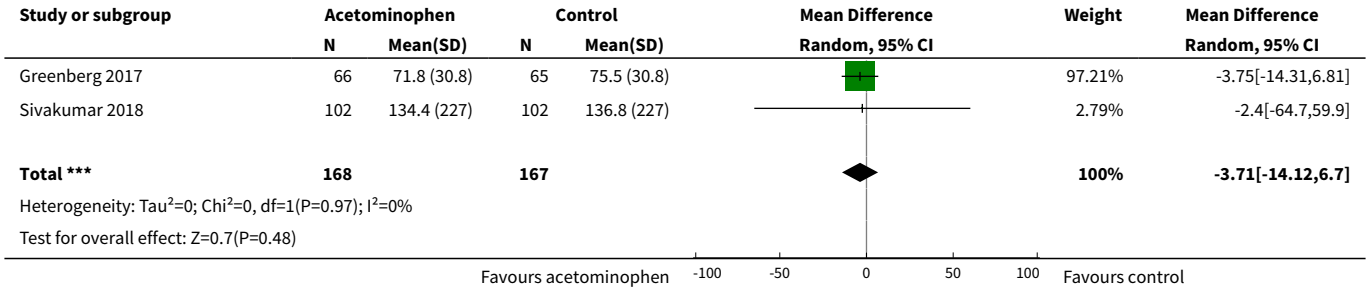
Study or subgroup	Experimental N	Mean(SD)	Control N	Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Artime 2018	45	2 (3.6)	41	2 (3.7)		20.34%	0[-1.54,1.54]
Dilmen 2016	20	1.1 (1.4)	18	1.2 (1.6)		34.46%	-0.11[-1.05,0.83]
Greenberg 2017	59	3 (5.8)	52	2 (5.8)		12.44%	1[-1.16,3.16]
Sivakumar 2018	102	4.1 (3.6)	102	5.4 (3.7)		32.76%	-1.3[-2.3,-0.3]
Total ***	**226**		**213**			**100%**	**-0.34[-1.2,0.52]**
Heterogeneity: Tau^2=0.33; Chi^2=5.35, df=3(P=0.15); I^2=43.92%							
Test for overall effect: Z=0.77(P=0.44)							

Analysis 4.4. Comparison 4 Acetaminophen versus control, Outcome 4 Additional analgesia requirement 0 to 24 hours.

Study or subgroup	Interventon N	Mean(SD)	Control N	Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Artime 2018	45	11 (2.6)	41	10.1 (2.6)		36.02%	0.9[-0.21,2.01]
Dilmen 2016	20	15.3 (13.4)	18	18.6 (14.1)		1.1%	-3.25[-12.01,5.51]



Analysis 4.5. Comparison 4 Acetaminophen versus control, Outcome 5 Length of stay in hospital (hours).



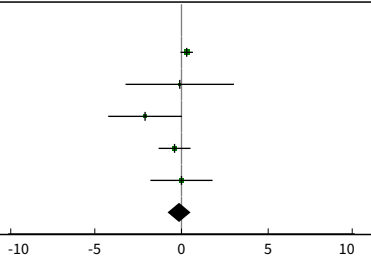
Comparison 5. Scalp infiltration versus control

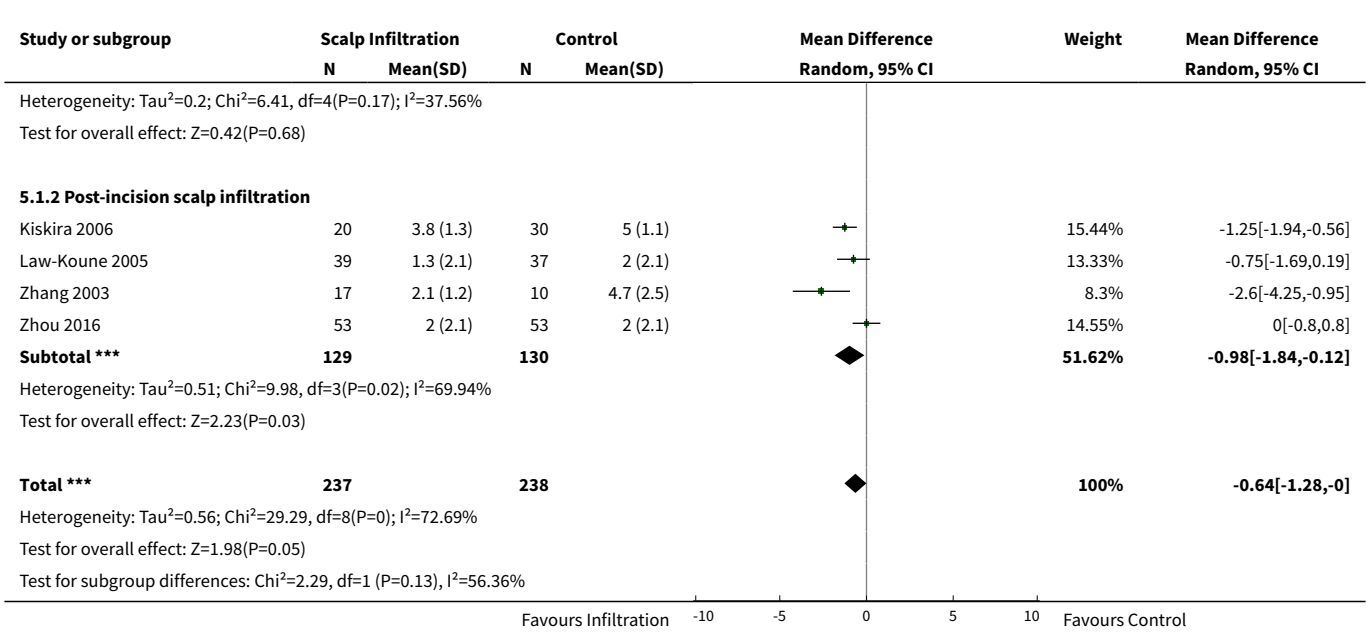
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Acute pain 0 to 6 hours	9	475	Mean Difference (IV, Random, 95% CI)	-0.64 [-1.28, -0.00]
1.1 Pre-incision scalp infiltration	5	216	Mean Difference (IV, Random, 95% CI)	-0.14 [-0.80, 0.52]
1.2 Post-incision scalp infiltration	4	259	Mean Difference (IV, Random, 95% CI)	-0.98 [-1.84, -0.12]
2 Acute pain 0 to 6 hours (excluding studies with a high risk of bias)	6	362	Mean Difference (IV, Random, 95% CI)	-0.04 [-0.43, 0.35]
2.1 Pre-incision scalp infiltration	4	180	Mean Difference (IV, Random, 95% CI)	0.20 [-0.13, 0.52]
2.2 Post-incision scalp infitration	2	182	Mean Difference (IV, Random, 95% CI)	-0.39 [-1.22, 0.44]
3 Acute pain at 12 hours	7	309	Mean Difference (IV, Random, 95% CI)	-0.71 [-1.34, -0.08]
3.1 Pre-incision scalp infiltration	4	180	Mean Difference (IV, Random, 95% CI)	-0.52 [-1.46, 0.41]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.2 Post-incision scalp infiltration	3	129	Mean Difference (IV, Random, 95% CI)	-1.14 [-1.77, -0.50]
4 Acute pain at 12 hours (excluding studies with a high risk of bias)	5	232	Mean Difference (IV, Random, 95% CI)	-0.35 [-1.31, 0.61]
5 Acute pain at 24 hours	6	260	Mean Difference (IV, Random, 95% CI)	-0.39 [-1.06, 0.27]
5.1 Pre-incision scalp infiltration	3	131	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.84, 0.81]
5.2 Post-incision scalp infiltration	3	129	Mean Difference (IV, Random, 95% CI)	-0.78 [-1.72, 0.17]
6 Acute pain at 24 hours (excluding studies with a high risk of bias)	4	183	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.73, 0.72]
7 Acute pain at 48 hours	3	128	Mean Difference (IV, Random, 95% CI)	-1.09 [-2.13, -0.06]
8 Acute pain at 48 hours (excluding studies with a high risk of bias)	2	100	Mean Difference (IV, Random, 95% CI)	-0.76 [-1.20, -0.32]
9 Nausea and vomiting	4	318	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.48, 1.14]
10 Additional analgesia requirements (in milligrams) 0 to 24 hours	6	345	Mean Difference (IV, Random, 95% CI)	-9.56 [-15.64, -3.49]
10.1 Pre-incision scalp infiltration	4	217	Mean Difference (IV, Random, 95% CI)	-12.54 [-25.20, 0.13]
10.2 Post-incision scalp infiltration	2	128	Mean Difference (IV, Random, 95% CI)	-8.57 [-13.26, -3.87]
11 Additional analgesia requirements 0 to 24 hours (excluding studies with a high risk of bias)	4	229	Mean Difference (IV, Random, 95% CI)	-8.16 [-16.50, 0.18]

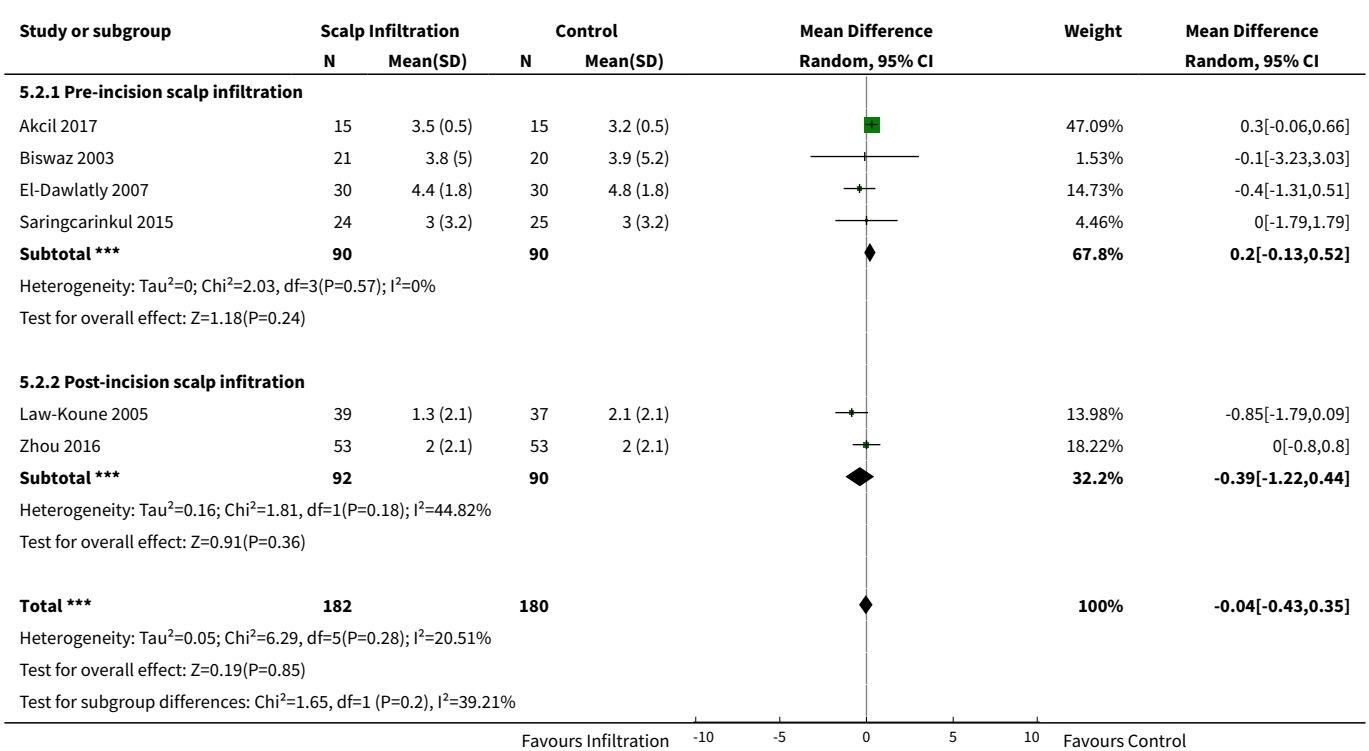
Analysis 5.1. Comparison 5 Scalp infiltration versus control, Outcome 1 Acute pain 0 to 6 hours.

Study or subgroup	Scalp Infiltration N	Scalp Infiltration Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
5.1.1 Pre-incision scalp infiltration							
Akcil 2017	15	3.5 (0.5)	15	3.2 (0.5)		17.83%	0.3[-0.06,0.66]
Biswaz 2003	21	3.8 (5)	20	3.9 (5.2)		3.39%	-0.1[-3.23,3.03]
Bloomfield 1998	18	3.3 (3.1)	18	5.4 (3.4)		6.07%	-2.1[-4.23,0.03]
El-Dawlatly 2007	30	4.4 (1.8)	30	4.8 (1.8)		13.55%	-0.4[-1.32,0.52]
Saringcarinkul 2015	24	3 (3.2)	25	3 (3.2)		7.55%	0[-1.79,1.79]
Subtotal * **	**108**		**108**			**48.38%**	**-0.14[-0.8,0.52]**



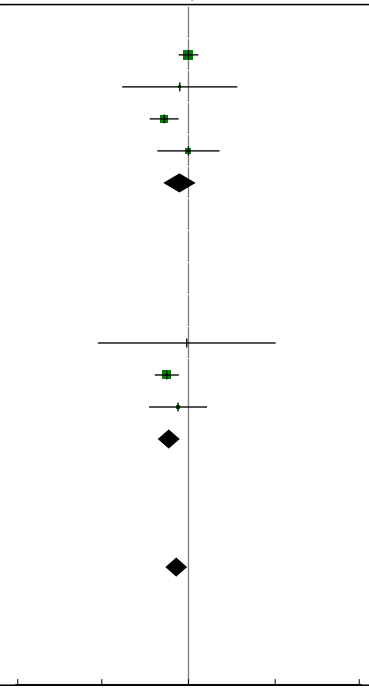


Analysis 5.2. Comparison 5 Scalp infiltration versus control, Outcome 2 Acute pain 0 to 6 hours (excluding studies with a high risk of bias).



Analysis 5.3. Comparison 5 Scalp infiltration versus control, Outcome 3 Acute pain at 12 hours.

Study or subgroup	Scalp Infiltration N	Mean(SD)	Control N	Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
5.3.1 Pre-incision scalp infiltration							
Akcil 2017	15	3 (1)	15	3 (0.5)		28.3%	0[-0.57,0.57]
Biswaz 2003	21	3.5 (5)	20	4 (5.8)		3.25%	-0.5[-3.82,2.82]
El-Dawlatly 2007	30	2 (1.7)	30	3.4 (1.7)		22.25%	-1.4[-2.24,-0.56]
Saringcarinkul 2015	24	3 (3.2)	25	3 (3.2)		9.19%	0[-1.79,1.79]
Subtotal ***	**90**		**90**			**63%**	**-0.52[-1.46,0.41]**
Heterogeneity: Tau^2=0.47; Chi^2=7.61, df=3(P=0.05); I^2=60.6%							
Test for overall effect: Z=1.09(P=0.27)							
5.3.2 Post-incision scalp infiltration							
Batoz 2009	25	1.5 (9.5)	27	1.6 (9.4)		1.44%	-0.1[-5.23,5.03]
Kiskira 2006	20	3.8 (1.3)	30	5 (1.1)		25.39%	-1.25[-1.94,-0.56]
Zhang 2003	17	3.9 (2.5)	10	4.5 (1.9)		10.17%	-0.6[-2.27,1.07]
Subtotal ***	**62**		**67**			**37%**	**-1.14[-1.77,-0.5]**
Heterogeneity: Tau^2=0; Chi^2=0.66, df=2(P=0.72); I^2=0%							
Test for overall effect: Z=3.52(P=0)							
Total ***	**152**		**157**			**100%**	**-0.71[-1.34,-0.08]**
Heterogeneity: Tau^2=0.28; Chi^2=11.61, df=6(P=0.07); I^2=48.32%							
Test for overall effect: Z=2.21(P=0.03)							
Test for subgroup differences: Chi^2=1.15, df=1 (P=0.28), I^2=12.89%							

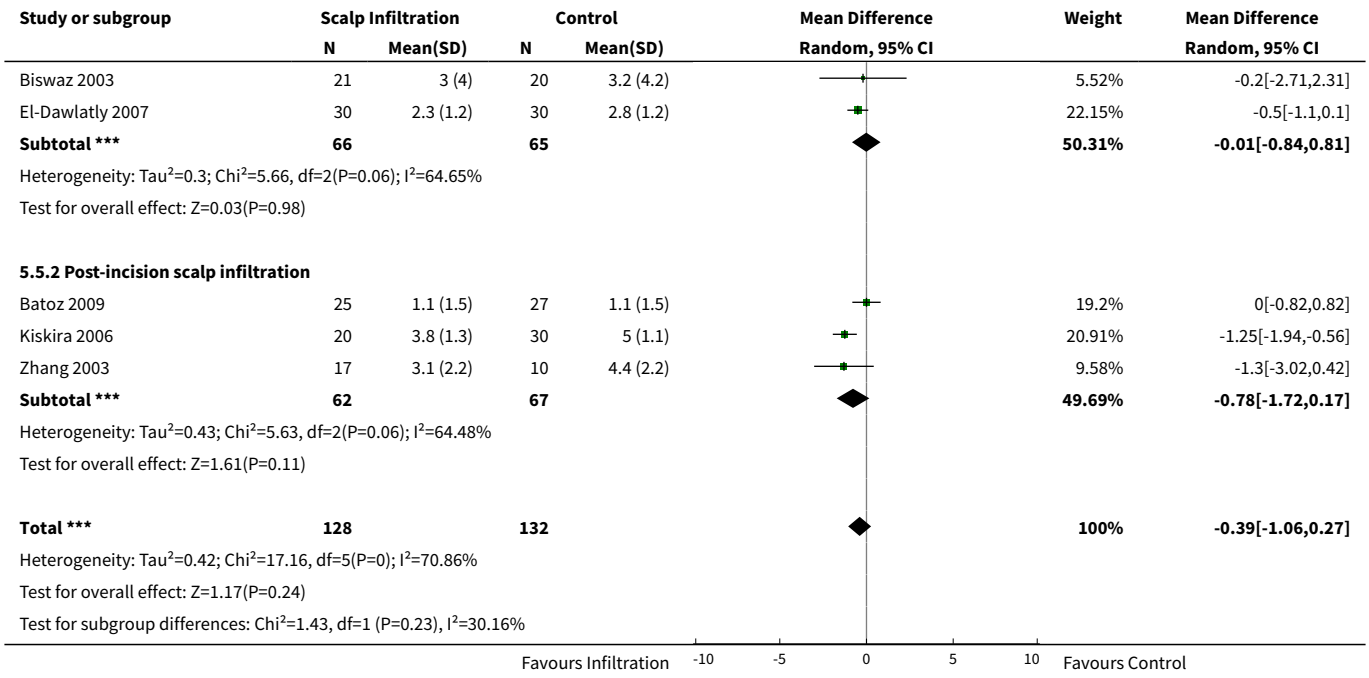


Analysis 5.4. Comparison 5 Scalp infiltration versus control, Outcome 4 Acute pain at 12 hours (excluding studies with a high risk of bias).

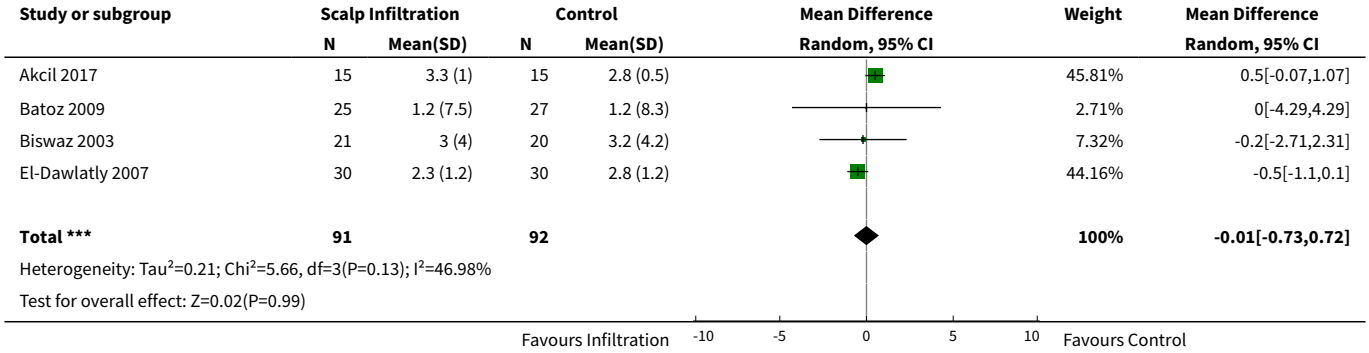
Study or subgroup	Scalp Infiltration N	Mean(SD)	Control N	Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Akcil 2017	15	3 (1)	15	3 (0.5)		38.7%	0[-0.57,0.57]
Batoz 2009	25	1.5 (9.5)	27	1.6 (9.4)		3.27%	-0.1[-5.23,5.03]
Biswaz 2003	21	3.5 (5)	20	4 (5.8)		7.07%	-0.5[-3.82,2.82]
El-Dawlatly 2007	30	2 (1.7)	30	3.4 (1.7)		33.43%	-1.4[-2.24,-0.56]
Saringcarinkul 2015	24	3.9 (3.2)	25	3 (3.2)		17.54%	0.9[-0.89,2.69]
Total ***	**115**		**117**			**100%**	**-0.35[-1.31,0.61]**
Heterogeneity: Tau^2=0.54; Chi^2=9.42, df=4(P=0.05); I^2=57.55%							
Test for overall effect: Z=0.71(P=0.48)							

Analysis 5.5. Comparison 5 Scalp infiltration versus control, Outcome 5 Acute pain at 24 hours.

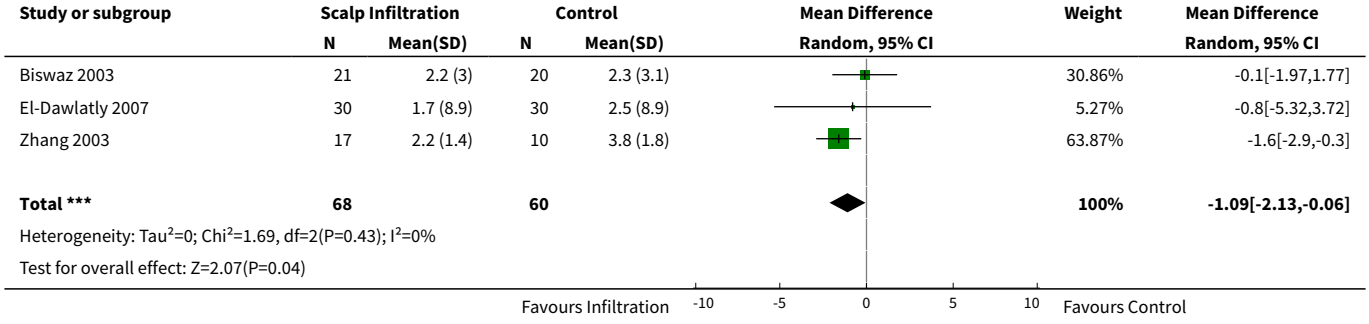
Study or subgroup	Scalp Infiltration N	Mean(SD)	Control N	Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
5.5.1 Pre-incision scalp infiltration							
Akcil 2017	15	3.3 (1)	15	2.8 (0.5)		22.64%	0.5[-0.07,1.07]



Analysis 5.6. Comparison 5 Scalp infiltration versus control, Outcome 6 Acute pain at 24 hours (excluding studies with a high risk of bias).

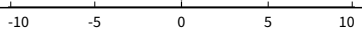


Analysis 5.7. Comparison 5 Scalp infiltration versus control, Outcome 7 Acute pain at 48 hours.



Analysis 5.8. Comparison 5 Scalp infiltration versus control, Outcome 8 Acute pain at 48 hours (excluding studies with a high risk of bias).

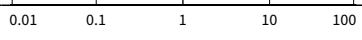
Study or subgroup	Scalp Infiltration N	Mean(SD)	Control N	Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Biswaz 2003	20	2.2 (3)	20	2.3 (3.1)		5.42%	-0.1[-1.99,1.79]
El-Dawlatly 2007	30	1.7 (0.9)	30	2.5 (0.9)		94.58%	-0.8[-1.25,-0.35]
Total ***	**50**		**50**			**100%**	**-0.76[-1.2,-0.32]**
Heterogeneity: Tau^2=0; Chi^2=0.5, df=1(P=0.48); I^2=0%							
Test for overall effect: Z=3.39(P=0)							



Favours Infiltration — Favours Control

Analysis 5.9. Comparison 5 Scalp infiltration versus control, Outcome 9 Nausea and vomiting.

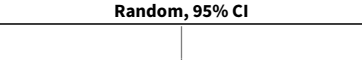
Study or subgroup	Scalp Infiltration n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
El-Dawlatly 2007	8/30	8/30		26.85%	1[0.43,2.31]
Law-Koune 2005	8/39	16/37		36.51%	0.47[0.23,0.97]
Saringcarinkul 2015	2/39	3/37		6.31%	0.63[0.11,3.57]
Zhou 2016	10/53	10/53		30.34%	1[0.45,2.2]
Total (95% CI)	**161**	**157**		**100%**	**0.74[0.48,1.14]**
Total events: 28 (Scalp Infiltration), 37 (Control)					
Heterogeneity: Tau^2=0; Chi^2=2.55, df=3(P=0.47); I^2=0%					
Test for overall effect: Z=1.36(P=0.17)					



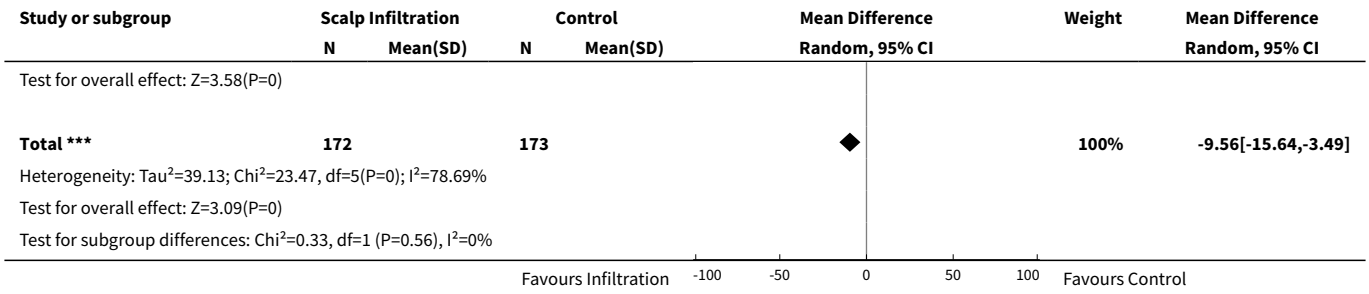
Favours Infiltration — Favours Control

Analysis 5.10. Comparison 5 Scalp infiltration versus control, Outcome 10 Additional analgesia requirements (in milligrams) 0 to 24 hours.

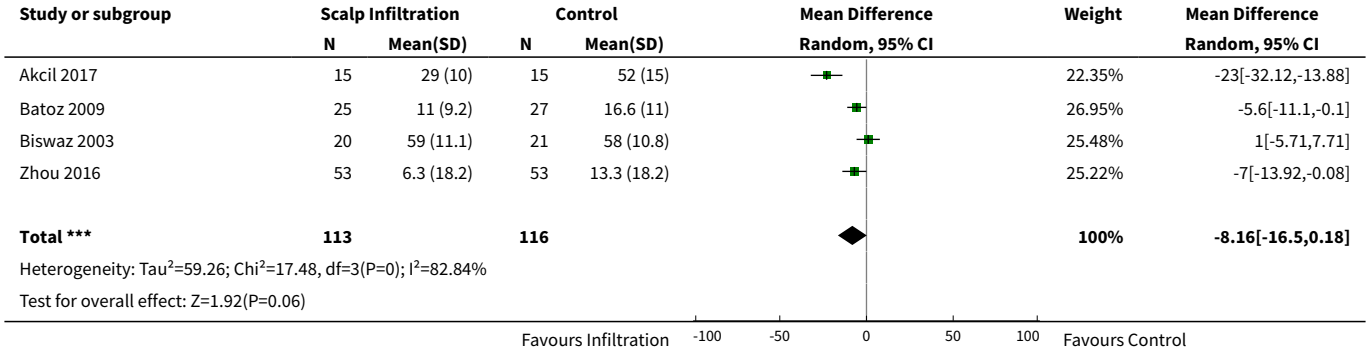
Study or subgroup	Scalp Infiltration N	Mean(SD)	Control N	Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
5.10.1 Pre-incision scalp infiltration							
Akcil 2017	15	29 (10)	15	52 (15)		15.79%	-23[-32.12,-13.88]
Biswaz 2003	20	59 (11.1)	21	58 (10.8)		18.88%	1[-5.71,7.71]
Kiskira 2006	20	7.5 (23)	20	45 (66)		3.39%	-37.5[-68.13,-6.87]
Zhou 2016	53	6.3 (18.2)	53	13.3 (18.2)		18.61%	-7[-13.92,-0.08]
Subtotal ***	**108**		**109**			**56.68%**	**-12.54[-25.2,0.13]**
Heterogeneity: Tau^2=126.02; Chi^2=20.94, df=3(P=0); I^2=85.67%							
Test for overall effect: Z=1.94(P=0.05)							
5.10.2 Post-incision scalp infiltration							
Batoz 2009	25	11 (9.2)	27	16.6 (11)		20.43%	-5.6[-11.1,-0.1]
Law-Koune 2005	39	11.5 (7.3)	37	22 (7.3)		22.89%	-10.5[-13.78,-7.22]
Subtotal ***	**64**		**64**			**43.32%**	**-8.57[-13.26,-3.87]**
Heterogeneity: Tau^2=6.67; Chi^2=2.25, df=1(P=0.13); I^2=55.54%							



Favours Infiltration — Favours Control



Analysis 5.11. Comparison 5 Scalp infiltration versus control, Outcome 11 Additional analgesia requirements 0 to 24 hours (excluding studies with a high risk of bias).



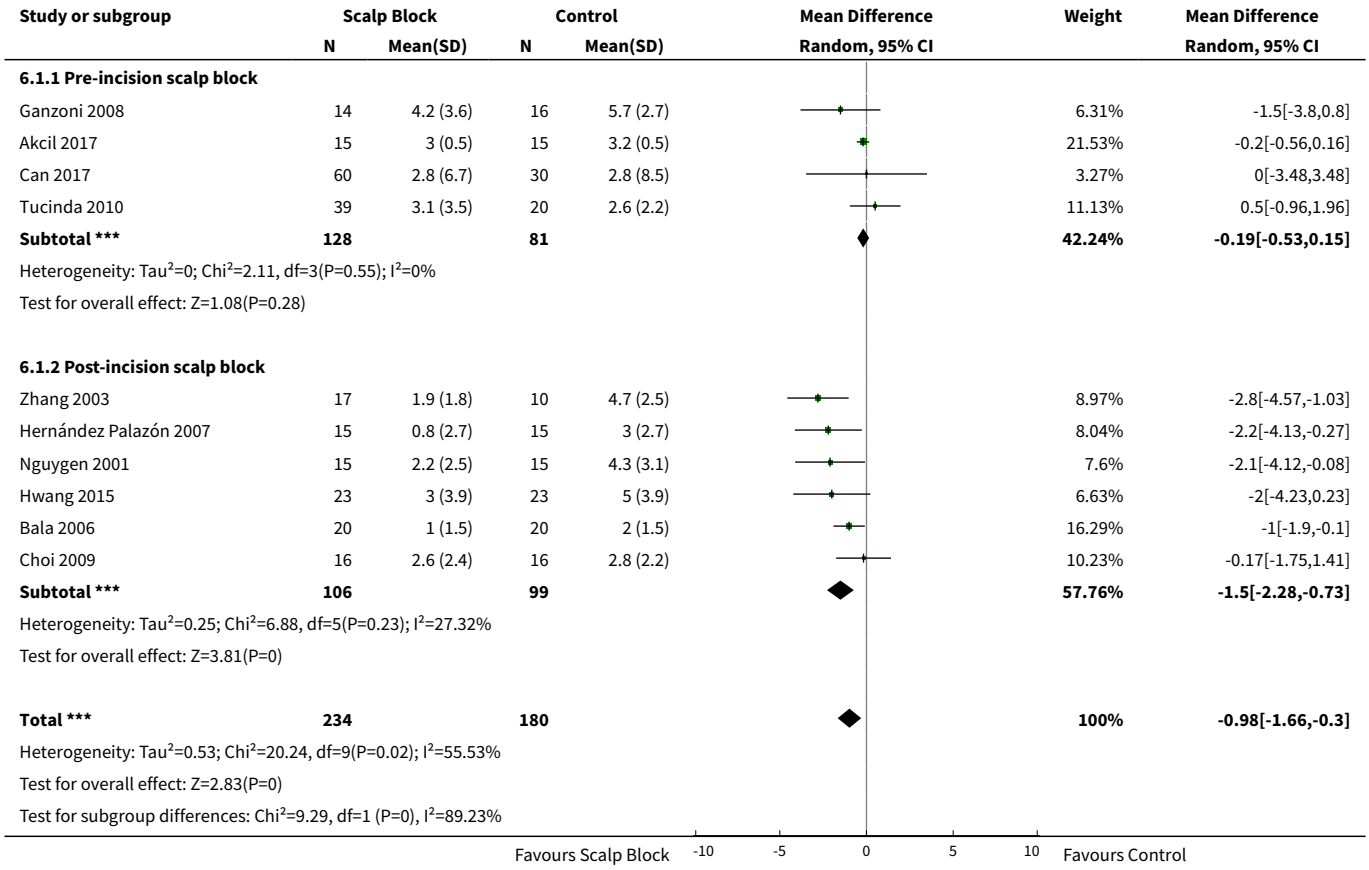
Comparison 6. Scalp block versus control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Acute pain 0 to 6 hours	10	414	Mean Difference (IV, Random, 95% CI)	-0.98 [-1.66, -0.30]
1.1 Pre-incision scalp block	4	209	Mean Difference (IV, Random, 95% CI)	-0.19 [-0.53, 0.15]
1.2 Post-incision scalp block	6	205	Mean Difference (IV, Random, 95% CI)	-1.50 [-2.28, -0.73]
2 Acute pain 0 to 6 hours (excluding studies with a high risk of bias)	7	325	Mean Difference (IV, Random, 95% CI)	-0.97 [-1.98, 0.05]
2.1 Pre-incision scalp block	4	209	Mean Difference (IV, Random, 95% CI)	-0.19 [-0.54, 0.15]
2.2 Post-incision scalp block	3	116	Mean Difference (IV, Random, 95% CI)	-1.71 [-2.44, -0.98]
3 Acute pain at 12 hours	8	294	Mean Difference (IV, Random, 95% CI)	-0.95 [-1.53, -0.37]

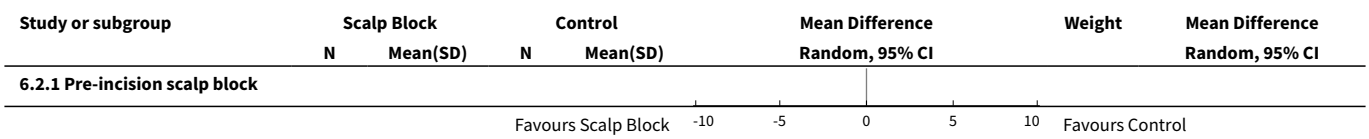
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Pre-incision scalp block	2	89	Mean Difference (IV, Random, 95% CI)	-0.46 [-0.80, -0.11]
3.2 Post-incision scalp block	6	205	Mean Difference (IV, Random, 95% CI)	-1.54 [-2.64, -0.44]
4 Acute pain at 12 hours (excluding studies with a high risk of bias)	5	205	Mean Difference (IV, Random, 95% CI)	-0.64 [-1.21, -0.07]
4.1 Pre-incision scalp block	2	89	Mean Difference (IV, Random, 95% CI)	-0.46 [-0.80, -0.11]
4.2 Post-incision scalp block	3	116	Mean Difference (IV, Random, 95% CI)	-1.54 [-3.33, 0.26]
5 Acute pain at 24 hours	9	433	Mean Difference (IV, Random, 95% CI)	-0.78 [-1.52, -0.05]
5.1 Pre-incision scalp block	4	268	Mean Difference (IV, Random, 95% CI)	0.02 [-0.76, 0.81]
5.2 Post-incision scalp block	5	165	Mean Difference (IV, Random, 95% CI)	-1.80 [-1.00, -0.59]
6 Acute pain at 24 hours (excluding studies with a high risk of bias)	5	255	Mean Difference (IV, Random, 95% CI)	-0.86 [-1.84, 0.12]
6.1 Pre-incision scalp block	3	179	Mean Difference (IV, Random, 95% CI)	-0.68 [-1.14, -0.22]
6.2 Post-incision scalp block	2	76	Mean Difference (IV, Random, 95% CI)	-1.61 [-4.35, 1.14]
7 Acute pain at 48 hours	4	135	Mean Difference (IV, Random, 95% CI)	-1.34 [-2.57, -0.11]
8 Acute pain at 48 hours (excluding studies with a high risk of bias)	2	78	Mean Difference (IV, Random, 95% CI)	-0.91 [-3.04, 1.23]
9 Additional analgesia requirement 0 to 24 hours	7	314	Std. Mean Difference (IV, Random, 95% CI)	-1.11 [-1.97, -0.25]
9.1 Pre-incision scalp block	4	208	Std. Mean Difference (IV, Random, 95% CI)	-0.62 [-1.52, 0.28]
9.2 Post-incision scalp block	3	106	Std. Mean Difference (IV, Random, 95% CI)	-2.12 [-4.27, 0.03]
10 Nausea and vomiting	4	165	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.33, 1.32]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
11 Additional analgesia requirement 0 to 24 hours (excluding studies with a high risk of bias)	5	195	Std. Mean Difference (IV, Random, 95% CI)	-1.71 [-2.95, -0.46]
11.1 Pre-incision scalp block	3	119	Std. Mean Difference (IV, Random, 95% CI)	-0.97 [-2.16, 0.23]
11.2 Post-incision scalp block	2	76	Std. Mean Difference (IV, Random, 95% CI)	-3.36 [-8.90, 2.19]

Analysis 6.1. Comparison 6 Scalp block versus control, Outcome 1 Acute pain 0 to 6 hours.



Analysis 6.2. Comparison 6 Scalp block versus control, Outcome 2 Acute pain 0 to 6 hours (excluding studies with a high risk of bias).

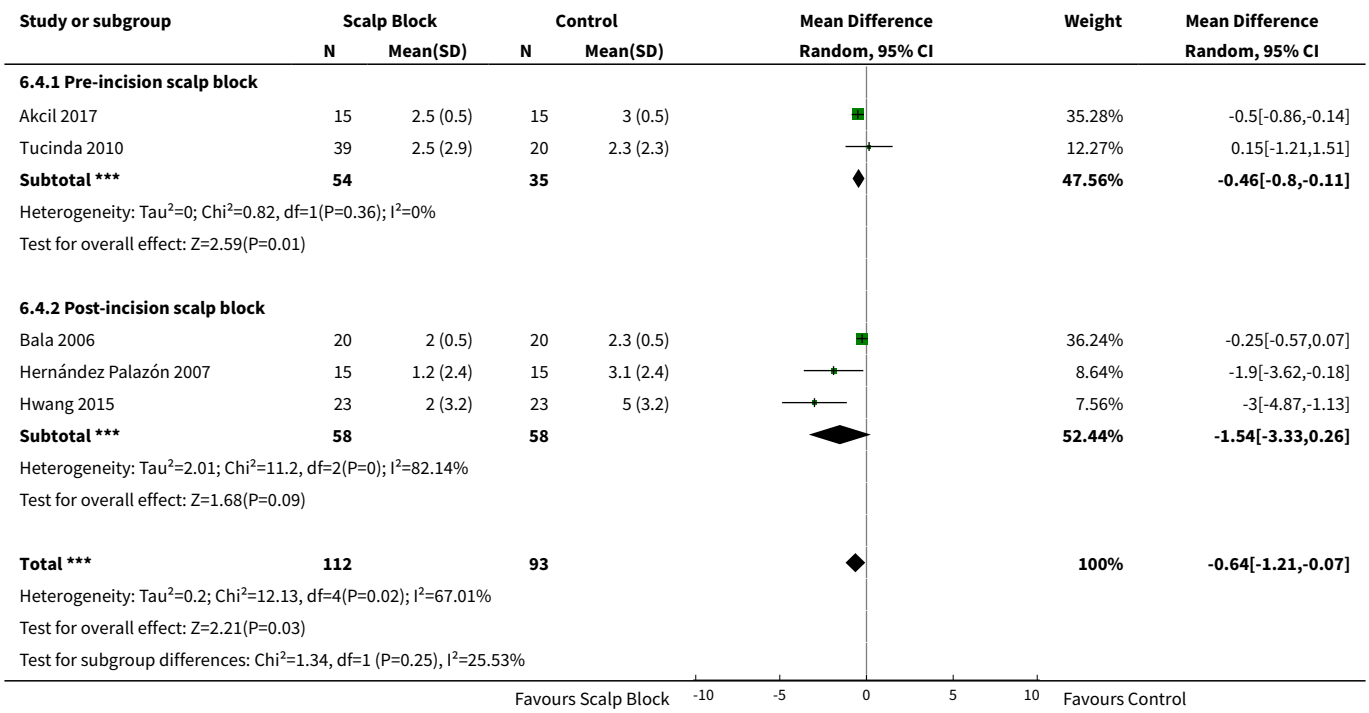


Study or subgroup	Scalp Block N	Scalp Block Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Akcil 2017	15	3 (0.5)	15	3.2 (0.5)		20.17%	-0.2[-0.56,0.16]
Can 2017	60	2.8 (6.7)	30	2.8 (8.5)		6.01%	0[-3.48,3.48]
Ganzoni 2008	14	4.2 (3.6)	16	5.7 (2.7)		10%	-1.5[-3.8,0.8]
Tucinda 2010	39	3.1 (3.5)	20	2.6 (2.6)		13.75%	0.5[-1.08,2.08]
Subtotal ***	**128**		**81**			**49.94%**	**-0.19[-0.54,0.15]**
Heterogeneity: Tau^2=0; Chi^2=1.99, df=3(P=0.58); I^2=0%							
Test for overall effect: Z=1.11(P=0.27)							
6.2.2 Post-incision scalp block							
Bala 2006	20	1 (1.5)	20	2 (1.5)		17.76%	-1[-1.9,-0.1]
Hernández Palazón 2007	15	0.8 (2.7)	15	3 (2.7)		11.81%	-2.2[-4.13,-0.27]
Hwang 2015	23	3 (0.4)	23	5 (0.4)		20.48%	-2[-2.22,-1.78]
Subtotal ***	**58**		**58**			**50.06%**	**-1.71[-2.44,-0.98]**
Heterogeneity: Tau^2=0.23; Chi^2=4.49, df=2(P=0.11); I^2=55.47%							
Test for overall effect: Z=4.58(P<0.0001)							
Total ***	**186**		**139**			**100%**	**-0.97[-1.98,0.05]**
Heterogeneity: Tau^2=1.29; Chi^2=78.37, df=6(P<0.0001); I^2=92.34%							
Test for overall effect: Z=1.87(P=0.06)							
Test for subgroup differences: Chi^2=13.51, df=1 (P=0), I^2=92.6%							

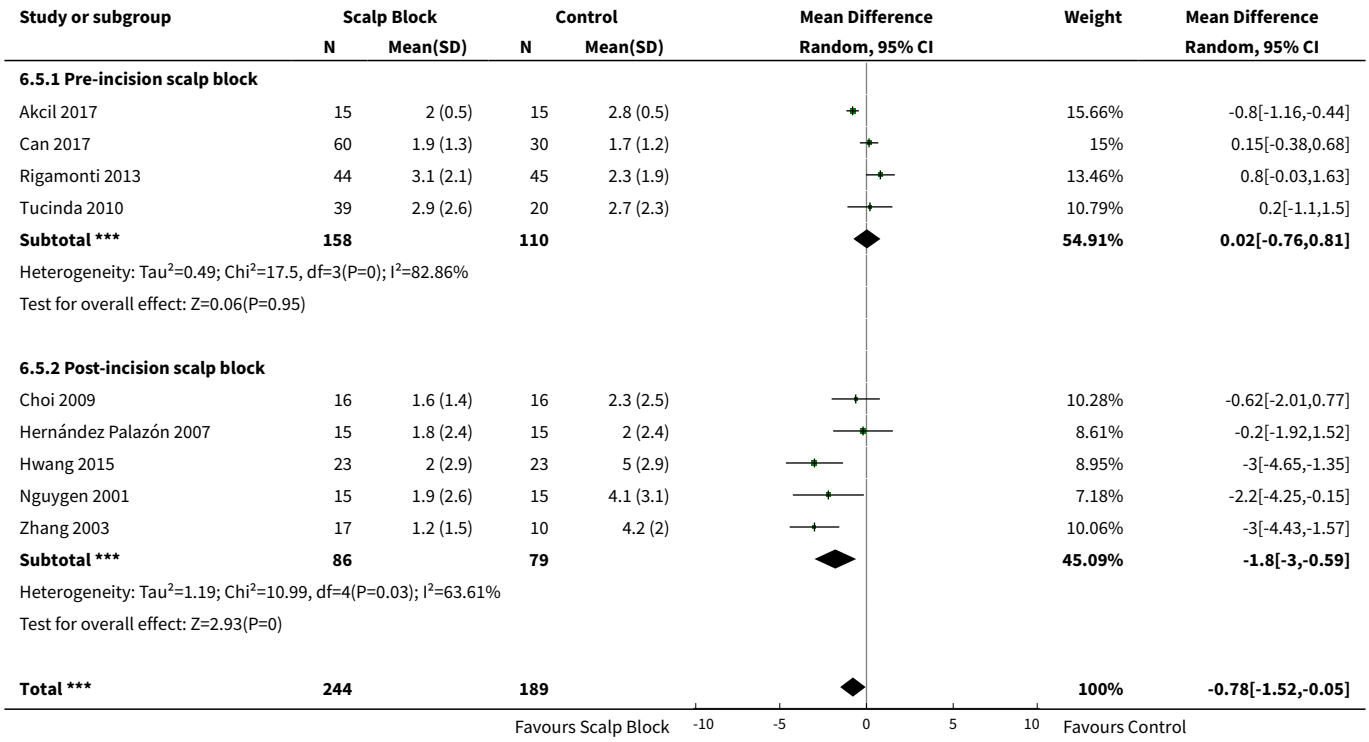
Analysis 6.3. Comparison 6 Scalp block versus control, Outcome 3 Acute pain at 12 hours.

Study or subgroup	Scalp Block N	Scalp Block Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
6.3.1 Pre-incision scalp block							
Akcil 2017	15	2.5 (0.5)	15	3 (0.5)		23.71%	-0.5[-0.86,-0.14]
Tucinda 2010	39	2.5 (2.9)	20	2.3 (2.3)		10.8%	0.15[-1.21,1.51]
Subtotal ***	**54**		**35**			**34.5%**	**-0.46[-0.8,-0.11]**
Heterogeneity: Tau^2=0; Chi^2=0.82, df=1(P=0.36); I^2=0%							
Test for overall effect: Z=2.59(P=0.01)							
6.3.2 Post-incision scalp block							
Bala 2006	20	2 (0.5)	20	2.3 (0.5)		24.11%	-0.25[-0.57,0.07]
Choi 2009	16	2.1 (1.7)	16	2.5 (2.3)		10.19%	-0.44[-1.87,0.99]
Hernández Palazón 2007	15	1.2 (2.4)	15	3.1 (2.4)		7.99%	-1.9[-3.62,-0.18]
Hwang 2015	23	2 (3.2)	23	5 (3.2)		7.08%	-3[-4.87,-1.13]
Nguygen 2001	15	2.1 (2)	15	3.9 (3.4)		6.43%	-1.8[-3.8,0.2]
Zhang 2003	17	1.8 (1.9)	10	4.5 (1.9)		9.69%	-2.7[-4.18,-1.22]
Subtotal ***	**106**		**99**			**65.5%**	**-1.54[-2.64,-0.44]**
Heterogeneity: Tau^2=1.33; Chi^2=21.81, df=5(P=0); I^2=77.07%							
Test for overall effect: Z=2.73(P=0.01)							
Total ***	**160**		**134**			**100%**	**-0.95[-1.53,-0.37]**
Heterogeneity: Tau^2=0.34; Chi^2=22.67, df=7(P=0); I^2=69.13%							
Test for overall effect: Z=3.19(P=0)							
Test for subgroup differences: Chi^2=3.36, df=1 (P=0.07), I^2=70.21%							

Analysis 6.4. Comparison 6 Scalp block versus control, Outcome 4 Acute pain at 12 hours (excluding studies with a high risk of bias).



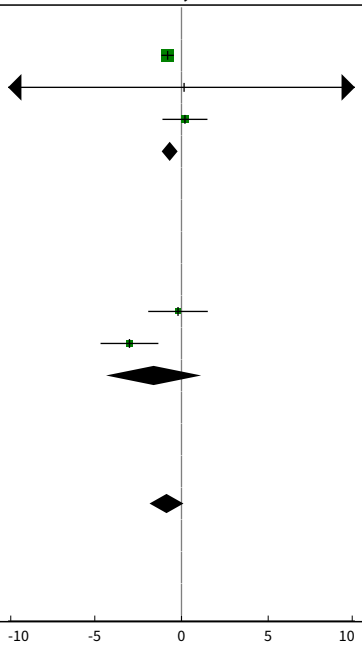
Analysis 6.5. Comparison 6 Scalp block versus control, Outcome 5 Acute pain at 24 hours.



Study or subgroup	Scalp Block N	Scalp Block Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Heterogeneity: Tau²=0.86; Chi²=42.34, df=8(P<0.0001); I²=81.1%							
Test for overall effect: Z=2.09(P=0.04)							
Test for subgroup differences: Chi²=6.18, df=1 (P=0.01), I²=83.81%							

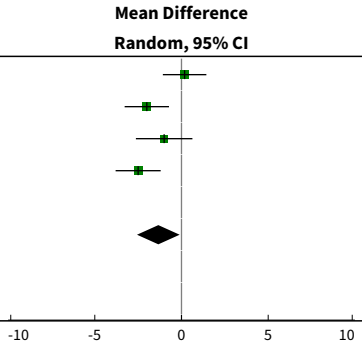
Analysis 6.6. Comparison 6 Scalp block versus control, Outcome 6 Acute pain at 24 hours (excluding studies with a high risk of bias).

Study or subgroup	Scalp Block N	Scalp Block Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
6.6.1 Pre-incision scalp block							
Akcil 2017	15	2 (0.5)	15	2.8 (0.5)		39.06%	-0.8[-1.16,-0.44]
Can 2017	60	1.9 (1.3)	30	1.7 (116)		0.06%	0.15[-41.36,41.66]
Tucinda 2010	39	2.9 (2.6)	20	2.7 (2.3)		23.92%	0.2[-1.1,1.5]
Subtotal ***	**114**		**65**			**63.04%**	**-0.68[-1.14,-0.22]**
Heterogeneity: Tau²=0.03; Chi²=2.12, df=2(P=0.35); I²=5.84%							
Test for overall effect: Z=2.9(P=0)							
6.6.2 Post-incision scalp block							
Hernández Palazón 2007	15	1.8 (2.4)	15	2 (2.4)		18.18%	-0.2[-1.92,1.52]
Hwang 2015	23	2 (2.9)	23	5 (2.9)		18.78%	-3[-4.67,-1.33]
Subtotal ***	**38**		**38**			**36.96%**	**-1.61[-4.35,1.14]**
Heterogeneity: Tau²=3.17; Chi²=5.26, df=1(P=0.02); I²=80.97%							
Test for overall effect: Z=1.15(P=0.25)							
Total ***	**152**		**103**			**100%**	**-0.86[-1.84,0.12]**
Heterogeneity: Tau²=0.61; Chi²=9.44, df=4(P=0.05); I²=57.64%							
Test for overall effect: Z=1.73(P=0.08)							
Test for subgroup differences: Chi²=0.43, df=1 (P=0.51), I²=0%							



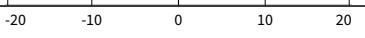
Analysis 6.7. Comparison 6 Scalp block versus control, Outcome 7 Acute pain at 48 hours.

Study or subgroup	Scalp Block N	Scalp Block Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Choi 2009	16	1.8 (1.6)	16	1.6 (2)		26.23%	0.18[-1.07,1.43]
Hwang 2015	23	2 (2.2)	23	4 (2.2)		25.96%	-2[-3.28,-0.72]
Nguygen 2001	15	1.6 (1.9)	15	2.6 (2.6)		22.09%	-1[-2.63,0.63]
Zhang 2003	17	1.3 (1.4)	10	3.8 (1.8)		25.72%	-2.5[-3.8,-1.2]
Total ***	**71**		**64**			**100%**	**-1.34[-2.57,-0.11]**
Heterogeneity: Tau²=1.09; Chi²=9.89, df=3(P=0.02); I²=69.68%							
Test for overall effect: Z=2.13(P=0.03)							



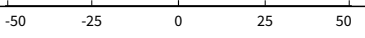
Analysis 6.8. Comparison 6 Scalp block versus control, Outcome 8 Acute pain at 48 hours (excluding studies with a high risk of bias).

Study or subgroup	Scalp Block N	Scalp Block Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Choi 2009	16	1.8 (1.6)	16	1.6 (2)		50.17%	0.18[-1.07,1.43]
Hwang 2015	23	2 (2.2)	23	4 (2.2)		49.83%	-2[-3.28,-0.72]
Total ***	**39**		**39**			**100%**	**-0.91[-3.04,1.23]**
Heterogeneity: Tau²=1.96; Chi²=5.69, df=1(P=0.02); I²=82.43%							
Test for overall effect: Z=0.83(P=0.41)							



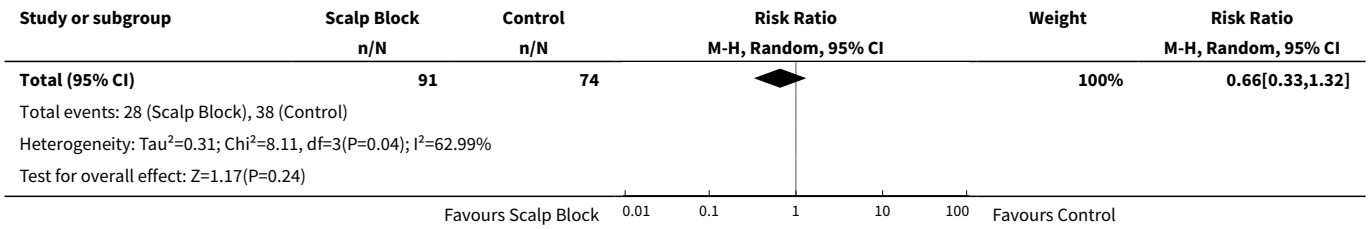
Analysis 6.9. Comparison 6 Scalp block versus control, Outcome 9 Additional analgesia requirement 0 to 24 hours.

Study or subgroup	Scalp Block N	Scalp Block Mean(SD)	Control N	Control Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
6.9.1 Pre-incision scalp block							
Akcil 2017	15	20 (10)	15	52 (15)		13.71%	-2.44[-3.42,-1.47]
Ganzoni 2008	14	25.5 (28.7)	16	41.3 (38.5)		14.88%	-0.45[-1.18,0.28]
Rigamonti 2013	44	4 (3.5)	45	3.2 (2.7)		16.03%	0.25[-0.16,0.67]
Tucinda 2010	39	13 (11)	20	15 (10)		15.63%	-0.18[-0.72,0.36]
Subtotal ***	**112**		**96**			**60.24%**	**-0.62[-1.52,0.28]**
Heterogeneity: Tau²=0.72; Chi²=25.28, df=3(P<0.0001); I²=88.13%							
Test for overall effect: Z=1.35(P=0.18)							
6.9.2 Post-incision scalp block							
Hernández Palazón 2007	15	3.7 (1.6)	15	17.2 (2.5)		9.42%	-6.26[-8.1,-4.41]
Hwang 2015	23	300 (49.4)	23	330 (49.4)		15.43%	-0.6[-1.19,-0.01]
Nguygen 2001	15	133 (82)	15	164 (135)		14.91%	-0.27[-0.99,0.45]
Subtotal ***	**53**		**53**			**39.76%**	**-2.12[-4.27,0.03]**
Heterogeneity: Tau²=3.27; Chi²=36.21, df=2(P<0.0001); I²=94.48%							
Test for overall effect: Z=1.93(P=0.05)							
Total ***	**165**		**149**			**100%**	**-1.11[-1.97,-0.25]**
Heterogeneity: Tau²=1.15; Chi²=66.23, df=6(P<0.0001); I²=90.94%							
Test for overall effect: Z=2.54(P=0.01)							
Test for subgroup differences: Chi²=1.59, df=1 (P=0.21), I²=37.3%							

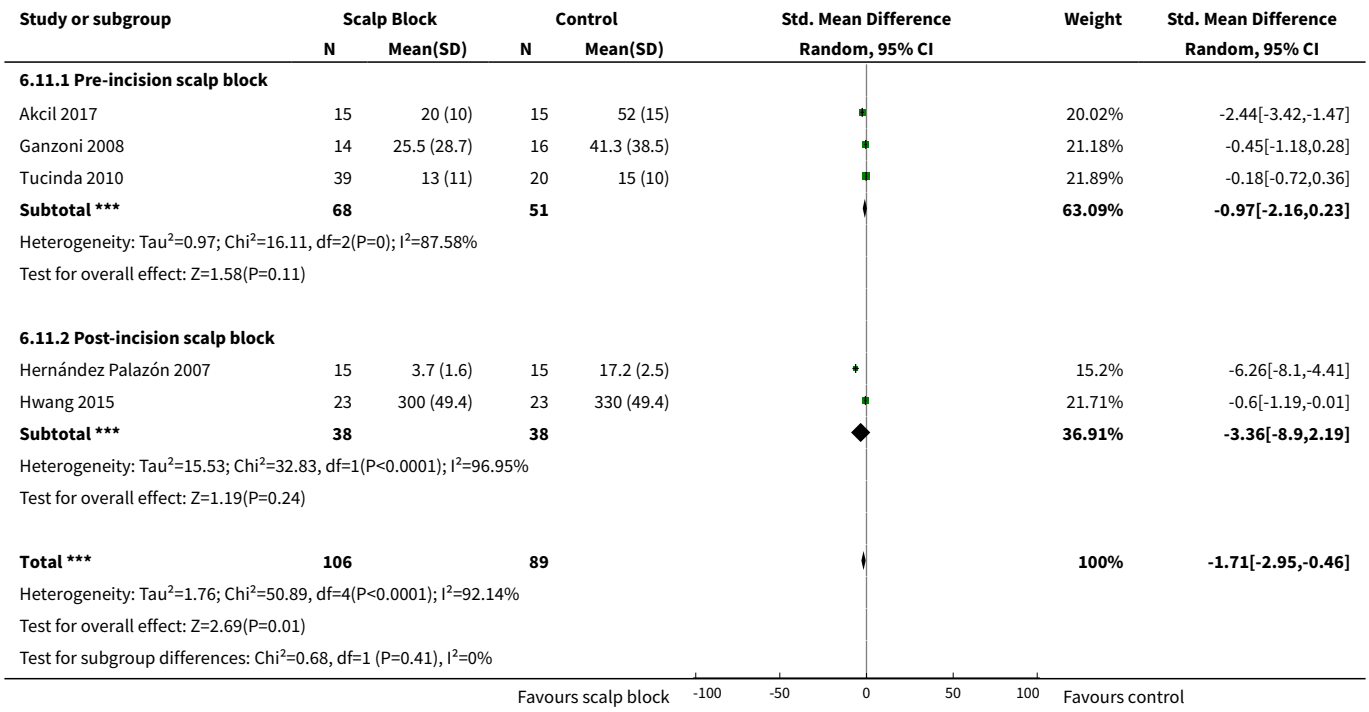


Analysis 6.10. Comparison 6 Scalp block versus control, Outcome 10 Nausea and vomiting.

Study or subgroup	Scalp Block n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Ganzoni 2008	8/14	8/16		29.9%	1.14[0.59,2.23]
Hernández Palazón 2007	2/15	10/15		16.4%	0.2[0.05,0.76]
Hwang 2015	7/23	15/23		29.45%	0.47[0.23,0.93]
Tucinda 2010	11/39	5/20		24.25%	1.13[0.45,2.8]



Analysis 6.11. Comparison 6 Scalp block versus control, Outcome 11 Additional analgesia requirement 0 to 24 hours (excluding studies with a high risk of bias).



APPENDICES

Appendix 1. Search Strategy

MEDLINE (R) ALL Ovid

1 Craniotomy/

2 Decompressive Craniectomy/

3 Trephining/

4 craniotomy.ab,ti.

5 craniectomy.ab,ti.

6 (brain adj3 (surg* or operat*)).ab,ti.

7 (post?craniotom* or post craniotom*).ab,ti.

8 (post?craniectom* or post craniectom*).ab,ti.

9 exp Brain Neoplasms/su [Surgery]

10 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9

11 exp Narcotics/

12 exp Analgesics/

13 exp Anesthetics, Local/

14 exp Aminopyridines/

15 flupirtine.ab,ti.

16 acetominophen.ab,ti.

17 acetaminophen.ab,ti.

18 morphine.ab,ti.

19 tramadol.ab,ti.

20 codeine.ab,ti.

21 paracetemol.ab,ti.

22 paracetamol.ab,ti.

23 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22

24 Pain, Postoperative/

25 exp Pain/ or pain.ti,ab.

26 Acute Pain/

27 headache/ or slit ventricle syndrome/

28 24 or 25 or 26 or 27

29 10 and 28

30 randomised controlled trial.pt.

31 controlled clinical trial.pt.

32 randomi?ed.ab.

33 placebo.ab.

34 drug therapy.fs.

35 randomly.ab.

36 trial.ab.

37 groups.ab.

38 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37

39 exp animals/ not humans.sh.

40 38 not 39

41 10 and 40

42 23 or 28

43 41 and 42

44 limit 43 to "all adult (19 plus years)"

45 limit 43 to "all child (0 to 18 years)"

46 43 not 45

47 44 or 46

Embase Ovid

1 craniotomy/

2 skull surgery/

3 cranioplasty/

4 craniectomy/

5 decompressive craniectomy/

6 exp brain surgery/

7 exp brain tumor/su

8 craniotomy.ab,ti.

9 craniectomy.ab,ti.

10 (post?craniotom* or post craniotom*).ab,ti.

11 (post?craniectom* or post craniectom*).ab,ti.

12 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11

13 exp narcotic agent/

14 exp analgesic agent/

15 exp local anesthetic agent/

16 aminopyridine derivative/

17 flupirtine/

18 paracetamol/

19 exp morphine/

20 tramadol/

21 exp codeine/

22 flupirtine.ab,ti.

23 acetominophen.ab,ti.

24 acetaminophen.ab,ti.

25 morphine.ab,ti.

26 tramadol.ab,ti.

27 codeine.ab,ti.

28 paracetemol.ab,ti.

29 paracetamol.ab,ti.

30 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29

31 postoperative pain/

32 pain/

33 exp "headache and facial pain"/

34 pain.ab,ti.

35 31 or 32 or 33 or 34

36 12 and 30 and 35

37 crossover procedure/

38 double blind procedure/

39 randomised controlled trial/

40 single blind procedure/

41 random$.mp.

42 factorial$.mp.

43 crossover$.mp.

44 cross-over$.mp.

45 cross over$.mp.

46 placebo$.mp.

47 (doubl$ adj blind$).mp.

48 (singl$ adj blind$).mp.

49 assign$.mp.

50 allocat$.mp.

51 volunteer$.mp.

52 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51

53 36 and 52

54 12 and 35 and 52

55 exp animal/ not exp human/

56 exp child/ not exp adult/

57 54 not 55

58 57 not 56

Central

#1 Craniotomy or craniectomy or trephining

#2 Pain, Postoperative or Pain or Acute Pain or headache or “slit ventricle syndrome”

#3 #1 and #2

Web of Science

#1 TS=(Craniotomy OR Craniectomy OR Trephining OR “brain surg*” OR postcraniotomy OR postcraniectomy) AND TS=(Pain OR “postoperative pain” OR headache* OR “acute pain” OR “slit ventricle syndrome”)

#2 TS=(“randomised controlled trial” or “controlled clinical trial” or placebo” or “drug therapy” or random* or trial or groups)

#3 #2 AND #1

CINAHL

S1 (MH "Craniotomy") OR (MH "Decompressive Craniectomy") OR (MH "Brain Surgery")

S2 "Trephining" Expanders - Apply related words

S3 (MH "Brain Neoplasms/SU")

S4 AB craniotomy Expanders - Apply related words

S5 TI craniotomy Expanders - Apply related words

S6 AB craniectomy Expanders - Apply related words

S7 TI craniectomy Expanders - Apply related words

S8 AB post?craniotomy Expanders - Apply related words

S9 AB postcraniotomy Expanders - Apply related words

S10 AB post-craniotomy Expanders - Apply related words

S11 TI postcraniotomy Expanders - Apply related words

S12 TI post-craniotomy Expanders - Apply related words

S13 AN postcraniectomy Expanders - Apply related words

S14 AN postcraniectomy Expanders - Apply related words

S15 AB postcraniectomy Expanders - Apply related words

S16 AB post-craniectomy Expanders - Apply related words

S17 TI postcraniectomy Expanders - Apply related words

S18 TI post-craniectomy Expanders - Apply related words

S19 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18

S20 (MH "Pain+") Expanders - Apply related words

S21 (MH "Postoperative Pain") Expanders - Apply related words

S22 (MH "Headache+") Expanders - Apply related words

S23 TI pain Expanders - Apply related words

S24 AB pain Expanders - Apply related words

S25 S20 OR S21 OR S22 OR S23 OR S24

S26 S19 AND S25

Appendix 2. Study selection form

STUDY TITLE:

(Continued)

AUTHORS:		
SOURCE:		
STUDY CHARACTERISTICS	**YES (*Please tick as appropriate*)**	**NO (*Please tick as appropriate*)**
Section 1. Design		
Prospective study		
Controlled trial		
Randomized		
Control		
YES to all – complete section 2.		
NO to 1 or more – exclude		
Section 2. Participants		
Participants ≥ 18 yrs		
Craniotomy or craniectomy		
YES to all – complete section 3.		
NO to 1 or more – exclude		
Section 3. Interventions		
Pharmacological intervention		
For prevention as opposed to relief of established pain after craniotomy		
Compared against placebo control		
YES to all – complete section 4.		
NO to 1 or more – exclude		
Section 4. Outcomes		
Validated measure of pain intensity in the first 4 days postoperatively		
Additional analgesia consumption in the first 4 days postoperatively		
Validated measure of depth of sedation in the same time period		
Any adverse event in the first 4 days postoperatively		
YES to any - include		
NO to all - exclude		

Appendix 3. Data extraction form

Review ID	**CARG 308** **Interventions for the prevention of acute postoperative pain in adults following brain surgery**
Review Author ID	
Study	
Study ID	
Citation	
Source	
Methods	
Study design	
Study start date	
Study end date	
Study duration	
Randomization method	
Sequence generation	
Allocation concealment method	
Blinded	Yes / No
Blinding method	
Blinding adequacy	
Participants	
Number	
Mean age	
No. of male participants	
Setting	
Surgical procedure type 1. Craniotomy or craniectomy 2. Infra or supratentorial 3. Elective or emergency	

(Continued)

4. Perioperative steroids

Anaesthetic type

1. Inhalation or TIVA

Inclusion criteria

Exclusion criteria

Interventions

No of arms

Intervention type

Intervention timing

Pre-, intra-, postoperatively

Route of administration

Dosage

Duration

Intervention Integrity

Ancillary treatment

Adjunctive therapy

Outcomes

Primary

Secondary

Adverse events

Reported events

Definitions used for each event

Severity

Seriousness

Association with intervention

Results

No. of participants allocated to each treatment arm

No. who received each treatment arm

No. who did not receive intended treatment and why

(Continued)

Number followed up
Number lost to follow-up and why
Number included in the final analysis
Analysis
Method
Sample size details
Reported effect size
Authors conclusions
Funding source
Reviewer comments

CONTRIBUTIONS OF AUTHORS

Imelda M Galvin (IMG), Ron Levy (RL), Andrew G Day (AGD), Ian Gilron (IG)

Conceiving the review: IMG, IG, RL

Co-ordinating the review: IMG

Undertaking manual searches: IMG, RL

Screening search results: IMG, RL

Organizing retrieval of papers: IMG, RL

Screening retrieved papers against inclusion criteria: IMG, RL

Appraising quality of papers: IMG, RL

Abstracting data from papers: IMG, RL

Writing to authors of papers for additional information: IMG

Providing additional data about papers: IMG, RL

Obtaining and screening data on unpublished studies: IMG, RL

Data management for the review: IMG, RL

Entering data into Review Manager 2014: IMG RL

RevMan statistical data: IMG, AGD

Other statistical analysis not using Review Manager 2014: IMG, AGD

Interpretation of data: IMG, RL, IG, AGD

Statistical inferences: IMG, AGD

Writing the review: IMG, RL, IG, AGD

Guarantor for the review (one author): IMG

Person responsible for reading and checking review before submission: IMG

DECLARATIONS OF INTEREST

Imelda M Galvin: none known

Ron Levy: none known

Andrew G Day: none known

Ian Gilron: in the past five years (2012 to 2017), IG has received consulting fees or honorarium (advisory board: Eli Lilly, Astra Zeneca; Johnson & Johnson, Pfizer); board membership: (Chair, Data Safety & Monitoring Board: Wex pharmaceuticals; Data Safety & Monitoring Board: Taris, Adynxx); consulted for various pharmaceutical companies (Johnson & Johnson, Astra Zeneca, Pfizer, Eli Lilly); received lecture fees from pharmaceutical companies that market analgesics and other healthcare interventions; received research support from government (Canadian Institutes of Health Research) and industry sources (Adynxx, Taris Biomedical, Wex Pharmaceuticals); grants/grants pending (research support 'in-kind' in the form of clinical trial study drug provision: Apotex, Ethypharm, Novopharm and Pfizer; industry-partnered research salary award (together with Canadian Institutes of Health Research): Pfizer) but no such support was received for this work.

SOURCES OF SUPPORT

Internal sources

- None, Canada.

External sources

- None, Canada.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We made the following changes to the published protocol (Galvin 2015).

1. Title

The protocol title was 'Interventions for the prevention of acute postoperative pain in adults following brain surgery' with the objectives of determining the effectiveness of pharmacological interventions for the prevention of acute postoperative pain in this population. On the recommendations of the CEU screening criteria and editors' plan of action to harmonise the pharmacological focus of the review throughout the review, the title was amended to 'Pharmacological interventions for the prevention of acute postoperative pain in adults following brain surgery'.

2. Background section. How the intervention might work

We added information regarding two other interventions, 'dexmedetomidine' and 'gabapentin and pregabalin'. We did this as both of these interventions were found on literature search to have studies that were eligible for inclusion in the review.

3. Exclusion Criteria

As specified a priori in our protocol, we excluded review articles, observational studies, case reports, case series, non-randomized studies and studies that had no control groups. We also excluded studies that investigated the use of agents with analgesic potential for non-analgesic purposes. The rationale for this decision was based on a high likelihood of important differences in inclusion and exclusion criteria, dosages, timing, ancillary analgesic usage and attributable side effects between studies that investigated these agents for their analgesic efficacy and studies that investigated them for their non-analgesic effects. While this approach meant that potential outcomes of interest were not captured when these agents were investigated for their other non-analgesic effects, it provided a more accurate estimate of the effects and side effects of those agents, when used with analgesic intent. A total of three studies were excluded on this basis (Bajaj 2017; Bishnoi 2016; Doumiri 2015); These studies used agents that have analgesia potential i.e. clonidine, dexmedetomidine and lidocaine; however, the focus of these studies was on their efficacy in a non-analgesic context and including them would have run the risk of .misrepresenting these agents efficacy and side effect profile when used with analgesic intent.

4. Outcomes

Primary outcome: pain intensity

Initially, we planned to produce pooled estimates of effect for the following outcomes:

Mean difference in validated measures of pain intensity in the following acute postoperative periods:

1. total (0 to four days);
2. early (0 to 12 hours);
3. intermediate (13 to 24 hours);
4. late (25 hours to four days).

We changed this to:

Mean differences in validated measures of pain intensity at:

1. Anytime in the first six hours postoperatively;
2. 12 hours postoperatively;
3. 24 hours postoperatively;
4. 48 hours postoperatively.

We did this because:

a) The use of discrete time points rather than time periods best reflected the way in which the vast majority of included studies reported this outcome.

b) We wanted to ensure accuracy of reported and calculated standard deviations, having found no accurate method of calculating standard deviations over time periods when the data were not reported in this way.

Secondary outcome: analgesic requirement

We measured this at '0 to 24 hours' only rather than over the four time periods stated in the protocol. We chose this approach as this was the most common time period over which the included studies reported this outcome, allowing the most accurate pooled estimate for each intervention and the best comparison between interventions.

5. 'Summary of findings' tables

Originally we intended to produce a 'Summary of findings' table for each comparison, addressing the following outcomes:

1. mean differences in validated measures of pain intensity in the total (0 to 4 days) postoperative period;
2. mean differences in validated measures of sedation in the total (0 to 4 days) postoperative period;
3. mean difference in additional analgesia requirement in the total (0 to 4 days) postoperative period;
4. mean difference in analgesic success in the total (0 to 4 days) postoperative period;
5. mean difference in length of stay in the critical care unit;
6. mean difference in length of stay in hospital;
7. mean difference in the incidence of headache persisting three months or more after surgery.

Instead, we produced a main 'Summary of findings' table for each comparison addressing the following outcomes:

1. Acute pain Intensity during the first six hours postoperatively;
2. Acute pain Intensity at 12 hours postoperatively;
3. Acute pain Intensity at 24 hours postoperatively;
4. Additional analgesia requirement from 0 to24 hours postoperatively;
5. Adverse events.

We did this because:

a) For the primary outcome of pain intensity, it allowed a simple summary comparison of pooled differences in pain scores at different time points for each intervention.

b) For secondary outcomes, it made the best use of the available data given that several of our prespecified secondary outcomes were not reported.

INDEX TERMS

Medical Subject Headings (MeSH)

Acute Pain [drug therapy] [*prevention & control]; Analgesia [*methods]; Analgesics [*therapeutic use]; Brain [surgery]; Pain Measurement; Pain, Postoperative [drug therapy] [*prevention & control]; Randomized Controlled Trials as Topic

MeSH check words

Humans