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Review Article

The impact of neuraxial clonidine on postoperative analgesia and perioperative adverse effects in women having elective Caesarean section—a systematic review and meta-analysis

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Abstract

Neuraxial clonidine improves postoperative analgesia in the general surgical population. The efficacy and safety of neuraxial clonidine as a postoperative analgesic adjunct in the Caesarean section population still remains unclear. This systematic review and meta-analysis aims to evaluate the effect of perioperative neuraxial clonidine on postoperative analgesia in women having Caesarean section under neuraxial anaesthesia. We included randomized controlled trials comparing the analgesic efficacy of the perioperative administration of neuraxial clonidine alone or in combination with a local anaesthetic and/or opioids in women having elective Caesarean section under neuraxial anaesthesia when compared with placebo. PubMed, the Cochrane Central Register of Controlled Trials, and EMBASE were searched until February 2017. Eighteen studies were included in the meta-analysis. Neuraxial clonidine reduced 24 h morphine consumption [mean difference (MD): −7.2 mg; 95% confidence interval (CI): −11.4, −3.0 mg; seven studies] and prolonged time to first analgesic request (MD: 135 min; 95% CI: 102, 168 min; 16 studies) when compared with the control group. Neuraxial clonidine increased intraoperative hypotension [odds ratio (OR): 2.849; 95% CI: 1.363, 5.957], intraoperative sedation (OR: 2.355; 95% CI: 1.016, 5.459), but reduced the need for intraoperative analgesic supplementation (OR: 0.224; 95% CI: 0.076, 0.663). The effect of clonidine on intraoperative bradycardia, intraoperative and postoperative nausea and vomiting, postoperative sedation, and pruritus were inconclusive. Neuraxial clonidine did not negatively impact neonatal umbilical artery pH or Apgar scores. This review demonstrates that neuraxial clonidine enhances postoperative analgesia in women having Caesarean section with neuraxial anaesthesia, but this has to be balanced against increased maternal adverse effects.

Keywords: adrenergic alpha-2 receptor agonist; caesarean section; clonidine

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Caesarean section is one of the most common surgical procedures performed in the obstetric patient population.[1] Pregnant women rate pain during and after Caesarean delivery as their primary concern.[2] The postoperative management of pain after Caesarean section still remains a challenge. Poorly controlled acute postoperative pain can affect a new mother's mobility, mood, and ultimately her ability to care for her newborn baby.[3] Poorly controlled acute postoperative pain also increases the risk for persistent pain for up to 8 weeks postpartum.[3] Current strategies for the management of postoperative pain mainly involve the use of neuraxial opioids when neuraxial anaesthetic techniques are used. Even though neuraxial opioids have improved the quality of postoperative analgesia, they are associated with opioid related side effects such as nausea, vomiting, and pruritus.[4] Additionally, in an increasing number of opioid tolerant patients, opioids may be less effective.[5] Furthermore, in some countries long-acting opioids such as preservative-free morphine or diamorphine may not be readily available. As a result, there is renewed interest in the use of non-opioid analgesic adjuncts administered via the neuraxial route, such as clonidine, for the optimisation of postoperative pain after Caesarean section.

Clonidine is an α_2 agonist that mediates its analgesic effect via the α_2 receptor located post-synaptically on the dorsal horn of the spinal cord. Stimulation of the α_2 receptor reduces afferent transmission of pain producing analgesia.[6] In the general surgical population, the administration of i.v. clonidine to patients receiving general anaesthesia reduced morphine consumption and pain scores at 24 h after surgery, when compared with placebo.[7] Similarly, the administration of clonidine intrathecally enhanced the effect of local anaesthetics and opioids resulting in a longer time to first request for analgesia and a reduction in 24 h morphine consumption.[8,9] The analgesic effect of neuraxial clonidine for post-Caesarean analgesia still remains unclear, with studies investigating its analgesic effect yielding conflicting results. Recent evidence also suggests that clonidine may reduce acute hyperalgesia and possibly the development of chronic persistent pain after Caesarean section.[10] However, while clonidine may improve post-Caesarean delivery analgesia, it has been associated with an increased incidence of maternal hypotension, sedation, and foetal acidosis, limiting its clinical use.[8,11]

To address these concerns we performed a systematic review and meta-analysis to evaluate the effect of perioperative neuraxial clonidine administration on postoperative analgesia in women having Caesarean section under neuraxial anaesthesia. Our hypothesis was that in women having Caesarean section under neuraxial anaesthesia, the administration of neuraxial clonidine would improve postoperative analgesia. This improvement would be determined by a reduction in morphine consumption and/or an increase in the time to first analgesic request, our primary outcomes of interest. We also investigated whether the administration of clonidine would be associated with a reduction in maternal opioid-related side effects. Finally, we investigated whether the administration of clonidine would be associated with an increase in maternal or foetal adverse effects.

Methods

This systematic review and meta-analysis was reported in accordance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement.[12]

Eligibility criteria

We performed a search of the published literature for randomised controlled trials comparing the analgesic efficacy of the perioperative administration of single or multiple doses of neuraxial clonidine alone or in combination with a local anaesthetic and/or opioid in women having elective Caesarean section under neuraxial anaesthesia when compared with placebo. Specifically, these trials needed to report 24 h opioid analgesic consumption (or the closest time point) and/or time to first analgesic request in both experimental arms. When studies reported multiple treatment arms using additional non-narcotic adjuncts, only data from the groups utilizing an amide local anaesthetic (with/without opioid) and clonidine (with/without opioid) were extracted. We included studies where neuraxial clonidine was administered in addition to short and long acting neuraxial opioids for surgical anaesthesia and/or postoperative analgesia. However, we excluded studies where clonidine was co-administered with differing doses of opioids for determining synergism or relative potency. We also excluded studies where the dose of local anaesthetic was different in the control and treatment arms of the study and where neuraxial clonidine was administered in patients who received general anaesthesia. Data from abstracts and unpublished trials were excluded. Eligibility was assessed independently by two individuals (T.K.A. and B.M.M.). Disagreements were reconciled by discussion and then by a 3rd member of the study team (A.S.H.) when necessary.

Search strategy

We searched PubMed (1966–2017), the Cochrane Central Register of Controlled Trials, and EMBASE using the search strategies described in the supplementary file up to February 2017. We imposed no language restrictions. The bibliographies of retrieved trials were also used to identify other relevant articles. Where appropriate, authors were contacted for missing or additional data. The methodological quality of included studies was assessed by two persons (T.K.A. and R.Y.K.) using the Cochrane collaboration tool for assessing risk of bias. Included studies were assessed for selection bias, performance bias, detection bias, attrition bias, and reporting bias.[13] Studies were assessed as low risk of bias (low risk of bias for all key domains), unclear risk of bias (unclear risk of bias for any of the key domains), or high risk of bias (high risk of bias for one or more key domains).[13]

Data were extracted and entered in a Microsoft Excel® (Microsoft Corporation, WA, USA) spreadsheet independently by two authors (T.K.A. and B.M.M.) and checked for accuracy by a third author (R.Y.K.). We extracted data on the country where the study was performed, neuraxial anaesthetic technique, type and dose of local anaesthetic administered, type and dose of neuraxial opioid administered, timing of administration and route of administration (spinal *vs* epidural) of neuraxial clonidine, and postoperative analgesic regime. We also extracted data on:

1. Our primary outcomes: i.v. morphine consumption at 24 h (or closest reported time point) and the time to first analgesic request. When studies reported postoperative analgesic consumption using other opioids or anti-inflammatory agents, they were converted to i.v. morphine equivalents using the following conversion factors: i.v. ketorolac 30 mg was equivalent to 10 mg of i.v.

morphine and 100 mg of meperidine was equivalent to 10 mg of i.v. morphine.[14,15]
2. Other analgesic outcomes: intraoperative need for supplemental analgesia, postoperative pain scores on movement at 0–6 and 6–24 h.
3. Maternal adverse effects: intraoperative hypotension, intraoperative vasopressor dose requirements, intraoperative bradycardia, intra- and postoperative nausea and vomiting, intra- and postoperative sedation, pruritus, and respiratory depression. Vasopressor doses were converted to an equivalent dose of ephedrine when phenylephrine was the vasopressor used based on a potency ratio of 81.2 between phenylephrine and ephedrine.[16]
4. Neonatal outcomes: foetal umbilical artery pH and Apgar scores at 1 and 5 min.

Authors were contacted to provide additional data that were not reported in the manuscript or that were presented graphically. Alternately, we also extracted data on outcomes from graphical information using the software GraphClick (Version 3.0.3, Arizona Software, www.arizona-software.ch/graphclick) when the raw data were not available from authors.

Data analysis

Data from dichotomous outcomes were summarized using odds ratio (OR) and 95% confidence intervals (CI). The number needed to treat (NNT) and number needed to harm (NNH) were computed for statistically significant outcomes. Continuous outcomes extracted as mean and standard deviation were summarized as mean difference (MD) and 95% CI. Where appropriate, when data were expressed as median, interquartile range and range, they were converted to means and standard deviation.[17] In studies investigating multiple doses of clonidine, treatment groups were combined to allow a single pairwise comparison with the control group. A random effects statistical model was used as the default for the analysis. Forest plots were used to graphically represent and evaluate treatment effects. Statistical heterogeneity was formally assessed using the I^2 test (I^2>50% defined as significant heterogeneity). To test the validity of our results we performed a sensitivity analysis for the primary outcomes after excluding studies with a high risk of bias. To explore the causes of heterogeneity on our primary outcomes, we planned *a priori* to perform subgroup analyses using data from studies where clonidine was administered exclusively by the intrathecal route or epidural route. We also performed a subgroup analysis on studies where clonidine was co-administered without long acting neuraxial opioids such as morphine. Subgroup analyses were only performed when three or more studies met the criteria for inclusion. To determine the effect of dose on our primary outcomes, we compared studies and/or subgroups where clonidine was administered at a dose ≤75 μg (or 1 μg kg^{-1}) with those where clonidine was administered at a dose of >75 μg (or 1 μg kg^{-1}) using the Q-test for heterogeneity. Publication bias for the primary outcomes was initially assessed using funnel plots and the regression test described by Egger and colleagues.[18] When there was evidence of funnel plot asymmetry, we attempted to investigate the cause of this asymmetry by examining contour-enhanced funnel plots[19] and determining the location and significance of any missing studies using the trim and fill method.[20] Analyses were performed using Comprehensive Meta-Analysis (Version 2.2.050, Biostat™, Englewood, NJ, USA) and the metafor package in R version 3.1.1 (R Core Team (2013). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL http://www.R-project.org/). A P value <0.05 was considered to indicate statistical significance.

Results

Our search returned 394 articles initially. Of these, 31 studies were identified for full review (Fig. 1). We then excluded a further 13 studies, leaving 18 studies[10,21–37] for inclusion and analysis. Three authors provided additional data on request.[10,29,33] The characteristics of the included studies are shown in Table 1. The risk of bias summary for each study is summarized in Table 2. Clonidine was administered at doses ranging from 30 to 800 μg. Clonidine was administered via the intrathecal route in 12 studies[10,21,22,24,29–33,35–37] and via the epidural route in the six remaining studies.[23,25,28,34] In two of the epidural studies, clonidine was administered as a bolus followed by a continuous epidural infusion.[25,27] In the remaining four studies,[23,26,28,34] clonidine was administered as a bolus, with two studies administering repeated epidural boluses.[23,34] Clonidine was administered with bupivacaine in 14 studies,[10,21–24,28–33,35–37] with ropivacaine in one study[34] and without local anaesthetic or opioid in three studies.[25–27] Clonidine was administered as part of the neuraxial anaesthetic technique in 13 studies[10,21,22,24,28–33,35–37] but administered at the end of surgery in four studies.[23,25–27] In the study by Huntoon and colleagues,[25] clonidine was administered at the end of surgery after epidural anaesthesia with bupivacaine or 2-chlorprocaine. As prior administration of 2-chlorprocaine may inhibit the effects of subsequently administered epidural analgesic agents,[25,38] we extracted data from the patients receiving epidural bupivacaine only. In one study, clonidine was administered as part of the anaesthetic technique for Caesarean section at one dose and administered at the end of surgery at a different dose.[34] For this study, we only extracted data on intraoperative outcomes and time to first analgesic request.

24 h morphine consumption

Seven studies[10,25–27,29,30,33] reported 24 h analgesic consumption, with 194 patients in the control group *vs* 371 patients in the clonidine-treated groups. The postoperative analgesic regime is described in Table 1. Meperidine was administered as the postoperative analgesic in one study[30] and i.v. ketorolac was used in another study.[26] I.V. patient-controlled analgesia (PCA) with morphine was administered in the remaining five studies.[10,25,27,29,33] Overall, the administration of clonidine reduced 24 h morphine consumption by 7.2 mg (95% CI: −11.4, −3.0 mg, I^2: 61%) when compared with the placebo group (Fig. 2a). With a mean 24 h morphine consumption of 32.6 mg in the control group, this MD represents a 21% reduction in 24 h morphine consumption. When the studies with a high risk of bias were excluded,[26,27] the reduction in 24 h morphine consumption was still statistically significant [−6.19 mg (−11.12, −1.12 mg), I^2: 65%].

There was evidence of funnel plot asymmetry for 24 h morphine consumption [Intercept (95% CI) −3.816 (−5.209, −2.426), P=0.001]. Examination of the contour enhanced funnel plot indicated that the missing studies were in the area of statistical significance 0.05>P>0.01 and P<0.01 (Fig. 3a). This suggests that the funnel plot asymmetry may be as a result of other factors apart from publication bias, such as

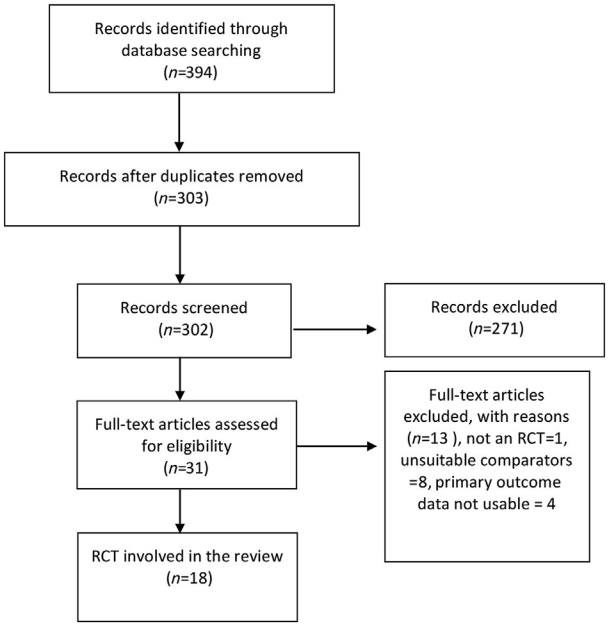

Fig 1. Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram. RCT = Randomised Controlled Trial.

the variable study quality of the studies included in the analysis.

The effect of intrathecal and epidural clonidine

When the analysis was restricted to studies where clonidine was administered only via the intrathecal route,[10,29,30,33] clonidine reduced 24 h morphine consumption by 4.3 mg (95% CI: −7.0, −1.5 mg, I^2: 0%). Only in one study[29] was clonidine co-administered via the intrathecal route with morphine and when this study was excluded from this subgroup analysis, the reduction in morphine consumption was still statistically significant [−3.9 mg (95% CI: −7.0, −0.9 mg, I^2: 0%)]. When administered by the epidural route, clonidine significantly reduced morphine consumption by 18.9 mg (95% CI: −34.8, −3.0 mg, I^2: 79%) when compared with placebo.[25–27]

Exclusion of studies where clonidine was co-administered with morphine

Overall when the two studies[26,29] where neuraxial clonidine was co-administered with morphine were excluded, clonidine still reduced morphine consumption by 8.7 mg (95% CI: −15.3, −2.0 mg, I^2: 73%) when compared with the control group.

The effect of clonidine dose

There was no difference in the 24 h morphine consumption when we compared subgroups investigating doses of clonidine ≤75μg [MD (95% CI) −4.8mg (−10.1, 0.5 mg)] with those investigating doses >75 μg [MD (95% CI) −8.0 mg (−12.3, −3.7 mg)] (P=0.36).

Time to first analgesic request

Sixteen studies[10,21–24,26,28–37] reported the time to first analgesic request with 432 patients in the placebo group *vs* 664 patients receiving clonidine. Overall, the administration of clonidine increased the time to first analgesic request by 135 min (95% CI: 102, 168 min, I^2: 96%) (Fig. 2b). When the studies with a high risk of bias were excluded,[21,26,28] the administration of clonidine increased the time to first analgesic request by 150 min (95%CI: 110, 190 min, I^2: 97%). There was evidence of funnel plot asymmetry for the time to first analgesic request [Intercept (95% CI) 6.166 (1.998, 10.334), P=0.007]. Examination of the contour-enhanced funnel plot indicated that the missing studies were in the area of statistical non-significance (Fig. 3b). This suggests that the funnel plot asymmetry may in fact be because of publication bias.

The effect of intrathecal and epidural clonidine

When the analysis was restricted to studies where clonidine was administered via the intrathecal route,[10,21,22,24,29–33,35–37] clonidine still prolonged the time to first analgesia request by 124 min (95% CI: 89, 160 min, I^2: 96%). Exclusion of the study by Paech and colleagues[29] where clonidine was co-administered with morphine via the intrathecal route still resulted in a significant increase in time to first request for analgesia by 126 min (95% CI 88, 164 min, I^2: 97%). When clonidine was administered by the epidural route,[23,26,28,34] the time to first request for analgesia was prolonged by 218 min (95% CI: 111, 325 min, I^2: 97%) when compared with the control group.

Exclusion of studies where clonidine was co-administered with morphine

When the three studies[23,26,29] where clonidine was administered with morphine were excluded, clonidine administration

Table 1 Study characteristics of studies included in the review. CSE, combined spinal epidural; MAP, mean arterial pressure; PCA, patient controlled analgesia; SBP, systolic blood pressure; VAS, visual analogue pain scores.

Study ID	Country of origin	Anaesthetic technique	Local anaesthetic used for anaesthesia	Neuraxial route of clonidine administration	Dose of clonidine	Control group (*n*)	Intervention group (*n*)	Timing of clonidine administration	Postoperative analgesic regime	Definition of intraoperative hypotension
Lavand'homme and colleagues[10]	Belgium	Spinal	Hyperbaric bupivacaine dose was adjusted based on patient height: 9 mg when <160 cm, 10 mg for height between 160 and 175 cm, and 11 mg for >175 cm	Intrathecal	75,150 μg	Hyperbaric bupivacaine + sufentanil 2 μg (*n* = 32)	Group 1: hyperbaric bupivacaine + sufentanil 2 μg + clonidine 75 μg (*n*=32) Group 2: hyperbaric bupivacaine + clonidine 150 μg (*n*=32)	At spinal anaesthesia	IV morphine PCA analgesia All the parturients received i.v. postoperative diclofenac 150 mg daily (started in the recovery room) + i.v. acetaminophen 1 g 6 h^{-1} as needed	20% Reduction from the pre-anaesthetic baseline SBP
van Tuijl and colleagues[33]	The Netherlands	Spinal	Hyperbaric bupivacaine 11 mg	Intrathecal	75 μg	Hyper baric bupivacaine 0.5% (2.2 ml) + 0.5 ml saline 0.9% (total 2.7 ml) (*n*=53)	Hyperbaric bupivacaine 0.5 (2.2 ml) + clonidine 75 μg in 0.5 ml saline 0.9% (total 2.7 ml) (*n*=53)	At spinal anaesthesia	IV PCA morphine + i.v. bolus morphine (5 mg) if VAS >4 and repeated once if VAS did not decrease below 4 within 20 min	20% Reduction from the baseline MAP
Paech and colleagues[29]	Australia	Spinal	Hyperbaric bupivacaine 12.5 mg	Intrathecal	30, 60, 90, 150 μg	Hyperbaric 0.5% bupivacaine 2.5 ml + morphine 100 μg (*n*=39)	Hyperbaric 0.5% bupivacaine 2.5 ml + morphine 100 μg in all groups plus Group1: clonidine 30 μg (*n*=41) Group 2: clonidine 60 μg (*n*=38) Group 3: clonidine 90 μg (*n*=38) Group 4: clonidine 150 μg (*n*=37).	At spinal anaesthesia	IV PCA morphine, naproxen 500 mg (rectally) at end of surgery and then 500 mg orally twice per day	20% reduction in baseline SBP
Benhamou and colleagues[21]	France	Spinal	Hyperbaric bupivacaine 0.6 mg/cm of body height	Intrathecal	75 μg	Hyperbaric bupivacaine and 1 ml of saline (*n*=26)	Group 1: hyperbaric bupivacaine + clonidine 75 μg + saline (*n*=26) Group 2: hyperbaric bupivacaine + fentanyl 12.5 μg + clonidine 75 μg (*n*=26)	At spinal anaesthesia		SBP<100 mm Hg
Pan and colleagues[30]	Taiwan	Spinal	Hyperbaric bupivacaine 10 mg	Intrathecal	150 μg	Hyperbaric bupivacaine (*n*=20)	Hyperbaric bupivacaine + clonidine 150 μg (*n*=20)	At spinal anaesthesia	Meperidine – regime not described	SBP below 100 mmHg
Braga and colleagues[22]	Brazil	CSE	Hyperbaric bupivacaine 10 mg	Intrathecal	75 μg	Hyperbaric bupivacaine (*n*=24)	Hyperbaric bupivacaine + clonidine 75 μg (*n*=24)	At spinal anaesthesia	Tenoxicam 40 mg, dipyrone 30 mg kg^{-1} VAS>3 in PACU	SBP<20% of baseline or SBP< 100 mm Hg
Singh and colleagues[32]	India	Spinal	Hyperbaric bupivacaine 10 mg	Intrathecal	50, 75 μg	Hyperbaric bupivacaine + fentanyl 25 μg (*n*=35)	Group 1: hyperbaric bupivacaine + clonidine 50 μg (*n*=35) Group2: hyperbaric bupivacaine + clonidine 75 μg (*n*=35)	At spinal anaesthesia	Intramuscular diclofenac 1.5 mg kg^{-1}	20% decrease from baseline SBP
Khezri and colleagues[36]	Iran	Spinal	Bupivacaine 10 mg	Intrathecal	75 μg	Bupivacaine + 0.5 ml sterile water (*n*=30)	Bupivacaine + 75 μg clonidine (*n*=30)	At spinal anaesthesia	Diclofenac sodium 100 mg rectally every 8 h Pethidine 25 mg i.v. prn	SBP<20% below baseline, SBP<90 mm Hg
Cho and colleagues 2003[24]	Korea	Spinal	Hyperbaric bupivacaine 8 mg	Intrathecal	75 μg	Hyperbaric bupivacaine + 0.55 ml 0.9% saline (*n*=20)	Hyperbaric bupivacaine + clonidine 75 μg (*n*=20)	At spinal anaesthesia	Not described	SBP<100 mm Hg

Continued

Table 1 Continued

Study ID	Country of origin	Anaesthetic technique	Local anaesthetic used for anaesthesia	Neuraxial route of clonidine administration	Dose of clonidine	Control group (*n*)	Intervention group (*n*)	Timing of clonidine administration	Postoperative analgesic regime	Definition of intraoperative hypotension
Shidhaye and colleagues[31]	India	Spinal	Hyperbaric bupivacaine 10 mg	Intrathecal	60 μg	Hyperbaric bupivacaine + fentanyl 25 μg (*n*=20)	Hyperbaric bupivacaine + clonidine 60 μg (*n*=20)	At spinal anaesthesia	Intramuscular diclofenac 75 mg (administered when VAS>7)	>20% reduction in baseline blood pressure
Li and colleagues[35]	China	CSE	Hyperbaric bupivacaine 10 mg	Intrathecal	75 μg	Hyperbaric bupivacaine + 0.9% saline (*n*=21)	Hyperbaric bupivacaine + clonidine 75 μg (*n*=21)	At spinal anaesthesia	Not described	20% fall in pre-induction SBP
Bhattacharjee and colleagues[37]	India	Spinal	Hyperbaric Bupivacaine 10 mg	Intrathecal	75 μg	Hyperbaric bupivacaine + 0.9% saline (*n*=30)	Hyperbaric bupivacaine + clonidine 75 μg (*n*=30)	At spinal anaesthesia	Not described	Not described
Capogna and colleagues[23]	Italy	Epidural	Epidural 2% lidocaine with epinephrine 1:800 000	Epidural	75,150 μg	10 ml solution containing 2 mg morphine diluted with 0.125% bupivacaine + 1:800 000 epinephrine (*n*=20)	Group 1: 10 ml solution containing 2 mg morphine diluted with 0.125% bupivacaine + 1:800 000 epinephrine + clonidine 75 μg (*n*=20) Group 2: 10 ml solution containing 2 mg morphine diluted with 0.125% bupivacaine + 1:80 000 epinephrine + clonidine150 μg (*n*=20)	End of surgery	10 ml solution containing 2 mg morphine diluted with 0.125% bupivacaine + 1:800 000 epinephrine + 0, 75, 150 μg clonidine was repeated on patient's request up to 36 h postoperatively	
Onat and colleagues[28]	Turkey	Epidural	Epidural bupivacaine 0.5% (16 mL)	Epidural	150 μg	Epidural bupivacaine 0.5% + fentanyl 50 μg (*n*=20)	Epidural bupivacaine 0.5% + clonidine 150 μg (*n*=20)	At placement of epidural catheter	Not described	SBP<30% of baseline
Bajwa and colleagues[34]	India	Epidural	Epidural 0.75% ropivacaine (20 ml)	Epidural	75 μg	Epidural 0.75% ropivacaine (*n*=24)	Epidural 0.75% ropivacaine + clonidine 75 μg (*n*=27)	At placement of epidural catheter	At the onset of postoperative pain epidural 8 mL of 0.175% ropivacaine was administered in the control group vs 0.175% + clonidine 50 μg in the intervention group	20% reduction in SBP
Massone and colleagues[26]	Italy	CSE	Spinal isobaric bupivacaine 0.5% 2.7 −3 mL + 250 μg preservative free morphine	Epidural	150 μg	Epidural saline (*n*=20)	Epidural clonidine 150 μg (*n*=20)	At the end of surgery after sensory block regression	IV ketorolac 30 mg as requested	
Mendez and colleagues[27]	USA	Epidural	Bupivacaine 0.5%	Epidural bolus followed by infusion	400 μg bolus + 10 μg/h, 800 μg bolus + 20 μg/h	Epidural saline 10ml bolus + 2 mL/h for 24 h	Group 1: Epidural clonidine 400 μg bolus + 10 μg/h for 24 h (*n*=20) Group 2: Epidural clonidine 800 μg bolus + 20 μg/h for 24 h (*n*=20)	On admission to recovery room	PCA morphine	
Huntoon and colleagues[25]	USA	Epidural	Either 3% 2-chloroprocaine or 0.5% bupivacaine	Epidural bolus followed by infusion	400 μg bolus + 40 μg h^{-1}, 800 μg bolus + 40 μg h^{-1}	Epidural saline 10 ml bolus + 2 ml h^{-1} for 24 h (*n*=10)	Group 1: epidural clonidine 400 μg bolus + 40 μg h^{-1} for 24 h (*n*=10) Group 2: epidural clonidine 800 μg bolus + 40 μg h^{-1} for 24 h (*n*=10)	On first request for analgesia in the recovery room	PCA morphine initiated 15 min after epidural bolus injection	

Table 2 Summary of risk of bias assessments for the included studies.

Study ID	Selection bias		Performance bias	Detection bias	Attrition bias	Reporting bias	summary of risk of bias
	Random sequence generation	Allocation concealment	Blinding of participants and researchers	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	
Lavand'homme and colleagues[10]	Low	Low	Low	Low	Low	Low	Low
van Tuijl and colleagues[33]	Low	Unclear	Unclear	Low	Unclear	Unclear	Unclear
Paech and colleagues[29]	Low	Low	Low	Low	Low	Low	Low
Benhamou and colleagues[21]	Low	Unclear	Low	Low	High	Unclear	High
Pan and colleagues 998[30]	Low	Unclear	Low	Low	Unclear	Unclear	Unclear
Braga and colleagues[22]	Unclear	Unclear	Low	Low	Low	Unclear	Unclear
Singh and colleagues[32]	Low	Low	Low	Low	Low	Unclear	Unclear
Khezri and colleagues[36]	Low	Low	Low	Low	Low	Low	Low
Cho and colleagues[24]	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Shidhaye and colleagues[31]	Low	Low	Low	Low	Unclear	Unclear	Unclear
Li and colleagues[35]	Unclear	Low	Low	Low	Unclear	Unclear	Unclear
Capogna and colleagues[23]	Unclear	Unclear	Low	Low	Unclear	Unclear	Unclear
Bhattacharjee and colleagues[37]	Low	Unclear	Low	Unclear	Low	Unclear	Unclear
Onat and colleagues[28]	Unclear	High	High	High	Unclear	Unclear	High
Bajwa and colleagues[34]	Low	Unclear	Low	Low	Low	Unclear	Unclear
Massone and colleagues[26]	Unclear	High	High	High	Low	Low	High
Mendez and colleagues[27]	Unclear	High	Low	Low	Unclear	Unclear	High
Huntoon and colleagues[25]	Unclear	Unclear	Low	Low	Unclear	Unclear	Unclear

still increased the time to first analgesic request by 114 min (95% CI: 82, 147 min, I^2: 97%).

The effect of clonidine dose

There was no significant difference between subgroups in time to first analgesic request if clonidine was administered at a dose ≤75 μg [MD (95% CI) 128 min (90, 166 min)] when compared with doses >75 μg [MD (95% CI) 195 min (131, 259 min)] (P=0.077).

Postoperative pain scores

Four studies[10,24,29,30] reported pain scores on movement at 0–6 h. There was no significant difference in pain scores on movement at 0–6 h between the clonidine-treated and placebo groups [MD (95% CI) 0.8 (−0.4, 2.0), I^2: 74%]. Five studies[10,24,29,30,33] reported pain scores on movement at 6–24 h. Clonidine was administered via the intrathecal route in all these studies. There was no significant difference in pain scores on movement at 24 h between the clonidine-treated and placebo groups [MD (95% CI) 0.2 (−0.2, 0.6), I^2: 0%]. Pain scores at rest were heavily skewed making data transformation and further quantitative analysis inappropriate.

Need for intraoperative analgesic supplementation/ intraoperative pain

Seven studies[10,21,22,29,30,32,33] reported the need for intraoperative analgesic supplementation. In all these studies, clonidine was administered by the intrathecal route. Clonidine was administered with local anaesthetic only in four studies.[22,30,32,33] It was co-administered with local anaesthetic and preservative-free morphine in one study,[29] sufentanil in one study,[10] and fentanyl in another study.[21] Intrathecal clonidine significantly reduced the need for intraoperative supplementation when compared with placebo with 17.1% (39/227) of patients in the control group *vs* 3.2% (15/475) patients in the clonidine-treated groups requiring supplementation [OR (95% CI)=0.224 (0.076, 0.663), I^2: 21%] with an NNT (95% CI) of 8 (5,11).

Hypotension

Twelve studies[10,22,24,28–33,35–37] reported the incidence of intraoperative hypotension after the administration of clonidine for anaesthesia for Caesarean section. Clonidine was administered via the intrathecal route in 11 studies[10,22,24,29–33,35–37] and via the epidural route in one study.[28] The definition of intraoperative hypotension for each study is described in Table 1. The administration of clonidine was associated with a significant increase in the incidence of intraoperative hypotension with an incidence in the control group of 33% (114/342) compared with 49% (260/525) in the clonidine-treated groups [OR (95%)=2.849 (1.363, 5.957), I^2: 76%] (Table 3).

Vasopressor dose requirements

Seven studies[10,21,24,29,30,33,36] reported vasopressor dose requirements intraoperatively. In all these studies, clonidine was administered via the intrathecal route. Ephedrine was used in six studies for treating established hypotension.[21,24,29,30,33,36] Paech and colleagues[29] administered a prophylactic infusion of ephedrine to maintain blood pressure within 20% of baseline. In one study, ephedrine was co-administered with phenylephrine and the phenylephrine dose was converted into the equivalent i.v. ephedrine dose and the total dose combined.[10] Overall there were no differences in the i.v. ephedrine dose equivalents between those patients receiving intrathecal clonidine and those receiving placebo [MD (95% CI) −0.6 mg (−4.5, 3.2 mg), I^2: 82%].

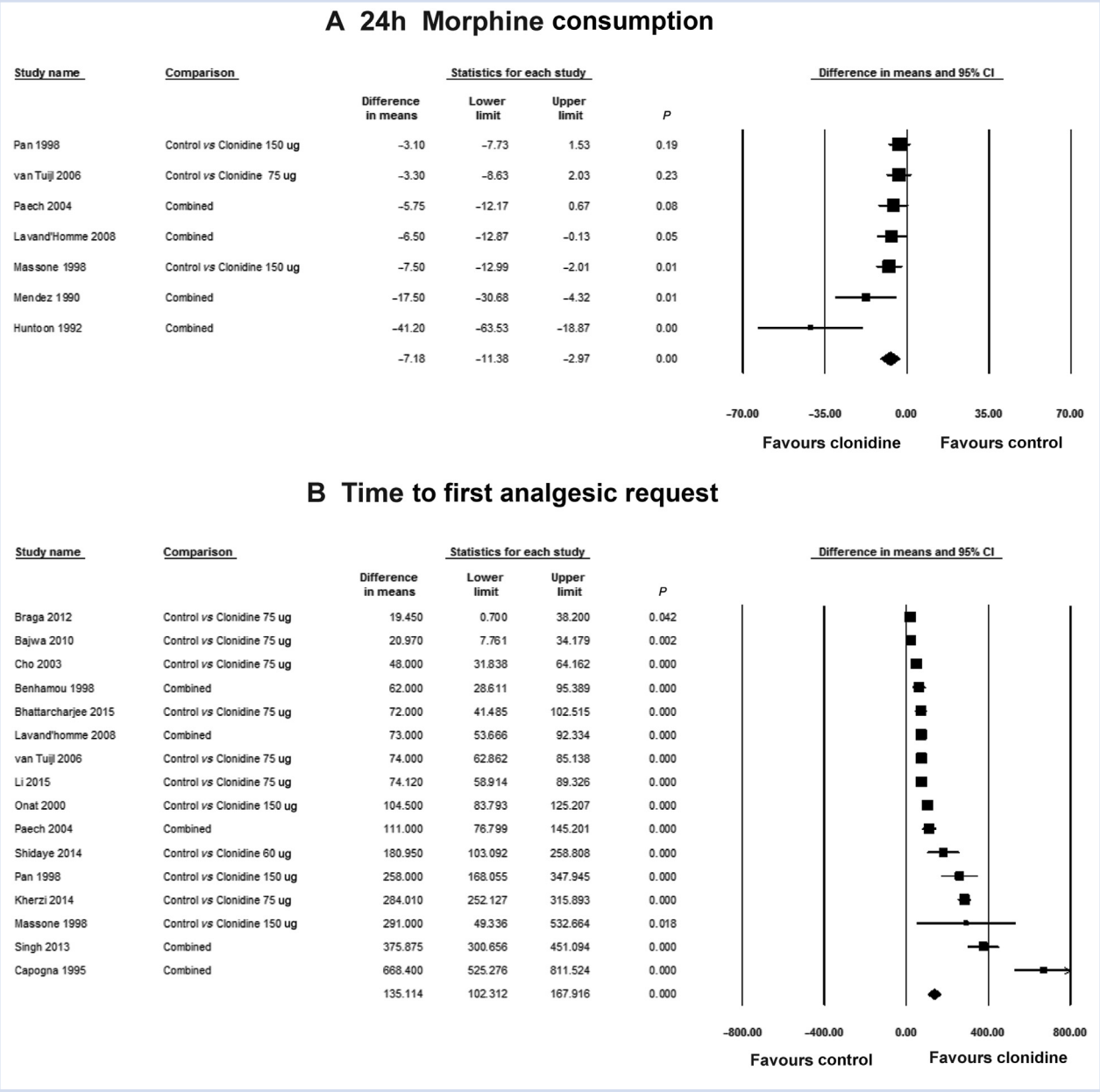

Fig 2. Pooled estimates of (a) 24 h morphine consumption and (b) time to first analgesic request in patients receiving neuraxial clonidine *vs* control. The combined comparisons represent studies in which multiple treatment arms were combined. CI, confidence interval.

Sedation

Five studies[10,21,28,32,34] reported the incidence of sedation intraoperatively. In three studies clonidine was administered via the intrathecal route,[10,21,32] and in two studies it was administered via the epidural route.[28,34] Clonidine significantly increased the incidence of sedation intraoperatively when compared with placebo [(OR (95%)=2.355 (1.016, 5.459), I^2: 23%] (Table 3). Four studies[23,25–27] reported the incidence of postoperative sedation. In all four studies, clonidine was administered via the epidural route at the end of surgery. The postoperative analgesic regimes are highlighted in Table 1. The effect of clonidine on postoperative sedation was inconclusive because of the wide 95% CI (Table 3).

Bradycardia

Seven studies[10,28,31,32,34,36,37] reported the incidence of bradycardia intraoperatively. In two studies, clonidine was administered via the epidural route.[28,34] Bradycardia was defined as a heart rate <45 beats min^{-1} in one study,[10] heart rate <50 beats min^{-1} in two studies,[32,36] heart rate <60 beats min^{-1} in one study,[31] heart rate <55 beats min^{-1} in one study,[34] and a heart rate <15 beats min^{-1} in another study.[28] We attempted to contact the authors of this latter study for clarification regarding their published definition of bradycardia, but did not receive a response. Bradycardia was not defined in one study.[37] The effect of clonidine on intraoperative bradycardia when compared with the placebo group was inconclusive because of the wide 95% CI (Table 3).

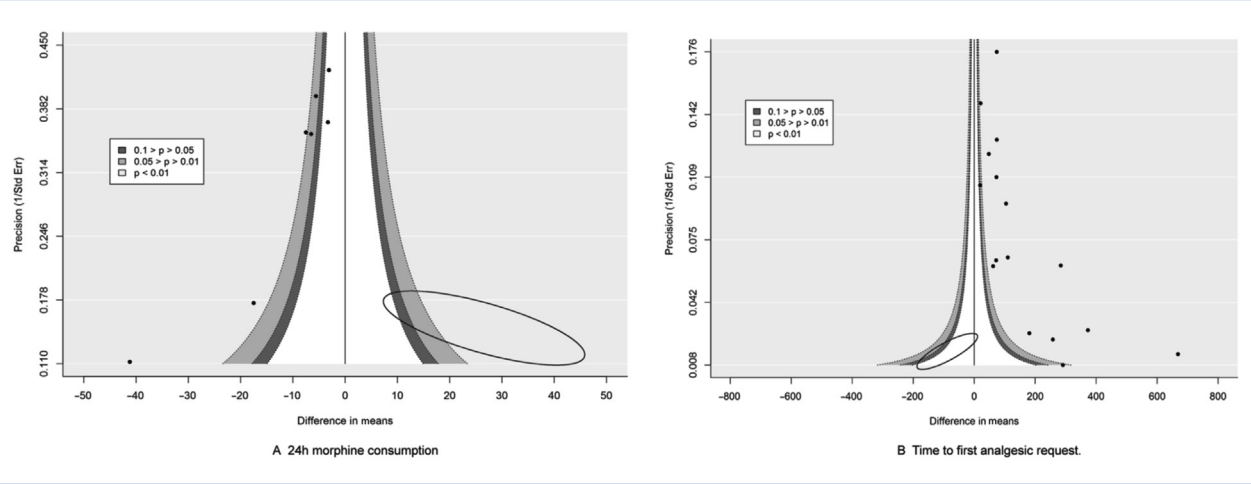

Fig 3. Contour enhanced funnel plot of (a) 24 h morphine consumption and (b) time to first analgesic request. The ellipse highlights areas where missing studies are expected.

Table 3 Maternal adverse effects of neuraxial clonidine. CI, confidence intervals; I^2, heterogeneity; NNH, number needed to harm; OR, odds ratio.

Outcome	Number of studies	Control group *n/N* (%)	Clonidine group *n/N* (%)	OR	95% CI		I^2	NNH (95% CI)
					Lower limit	Upper limit		
Intraoperative hypotension	12	114/342 (33%)	260/525 (49%)	2.849	1.363	5.957	76%	7 (4, 10)
Intraoperative nausea	9	51/242 (21%)	79/422 (18%)	1.010	0.389	2.624	72%	
Intraoperative vomiting	9	26/242 (11%)	52/422 (12%)	0.935	0.499	1.751	3%	
Intraoperative sedation	5	25/135 (18%)	82/232 (35%)	2.355	1.016	5.459	23%	6 (4, 12)
Postoperative sedation	4	34/70 (46%)	84/120 (70%)	1.983	0.354	11.100	76%	
Intraoperative bradycardia	7	8/189 (4%)	16/260 (6%)	1.410	0.554	3.590	0%	
Postoperative nausea	5	33/134 (25%)	29/134 (22%)	0.806	0.436	1.487	0%	
Postoperative vomiting	6	21/154 (14%)	22/174 (13%)	1.040	0.510	2.123	0%	
Pruritus	12	77/322 (24%)	122/529 (24%)	0.657	0.265	1.628	54%	

Nausea and vomiting

Nine studies[21,24,28,29,31,32,34,36,37] reported the incidence of intraoperative nausea and intraoperative vomiting (Table 3). Five studies[24,26,30,33,35] reported the incidence of postoperative nausea and six studies[23,24,26,30,33,35] reported the incidence of postoperative vomiting (Table 3). The effect of clonidine on intraoperative nausea, intraoperative vomiting, postoperative nausea, and postoperative vomiting were inconclusive because of the wide 95% CI.

Pruritus

Twelve studies[21,23,25,26,28,29,31–33,35–37] reported the incidence of pruritus during the perioperative period. Neuraxial morphine was administered in three studies.[23,26,29] In the study by Paech and colleagues,[29] the patients receiving rescue antipruritics were considered as having pruritus. The effect of clonidine on the incidence of perioperative pruritus was inconclusive because of the wide 95% CI (Table 3).

Respiratory depression

Eight studies[22,25,27,28,30,31,35,36] reported the incidence of postoperative respiratory depression. These results are reported qualitatively. Respiratory depression was clearly defined in only three studies. However, in none of these studies was clonidine co-administered with neuraxial morphine. Only in one study investigating the analgesic efficacy of clonidine where clonidine was administered as a postoperative epidural infusion were there any reported cases of respiratory depression.[25] In this study, the authors reported a single case in the control group only. Overall, there were no cases of respiratory depression in the clonidine-treated groups (0/195) and only one patient had an episode of respiratory depression in the control group for an incidence of 0.01% (1/165).

Neonatal outcomes

Fetal umbilical artery cord pH was reported in four studies.[21,32,33,35] In these studies, clonidine was administered via the intrathecal route as part of the anaesthetic technique for Caesarean section. There was no difference in umbilical artery pH between the clonidine-treated and the placebo groups [MD (95% CI) 0.053 (−0.187, 0.293), I^2: 0%].

Apgar scores at 1 and 5 min were reported in six studies.[21,29,31–33,35] In all six studies, clonidine was administered via the intrathecal route as part of the anaesthetic technique for Caesarean section. There were no differences in Apgar

scores at 1 min [MD (95% CI) 0.113 (−0.016, 0.242), I^2: 0%] or 5 min [MD (95% CI) −0.007 (−0.045, 0.032), I^2: 0%] between the patients receiving intrathecal clonidine and those receiving placebo.

Discussion

The results of our meta-analysis highlight several key findings. The administration of neuraxial clonidine was associated with an improvement in postoperative analgesia as evidenced both by the modest reduction in i.v. morphine consumption at 24 h and the prolongation of time to first analgesic request. These outcomes were not influenced by the dose of clonidine administered. Despite this modest improvement in postoperative analgesia, there was no observed reduction in opioid related side effects. The administration of clonidine also reduced the need for intraoperative analgesic supplementation but increased the incidence of intraoperative hypotension and sedation. Finally, the administration of neuraxial clonidine did not adversely affect neonatal outcomes.

In the general surgical population, clonidine is known to exert analgesic effects when administered neuraxially.[8,9] In fact, two previous meta-analyses have investigated this effect, but one included studies where clonidine was co-administered with morphine and the majority of studies included patients also having general anaesthesia.[8,9] In both meta-analyses, patients undergoing Caesarean section made up the minority of articles included (two studies in one review, one study in the other). Despite this difference in the patient population, our results were comparable to both meta-analyses and provide evidence that clonidine enhances postoperative analgesia in women after Caesarean section. It is important to highlight that the reductions in opioid consumption and the prolongation of postoperative analgesia were modest and may not be clinically relevant. The limited clinical effect of neuraxial clonidine on postoperative analgesia is further highlighted by the fact that neuraxial clonidine administration did not significantly reduce pain scores on movement. This inability to demonstrate a reduction in the pain scores may also reflect differences in the postoperative analgesic regimes, as there was significant variation in how postoperative pain was managed in the included studies. We also observed that neuraxial clonidine reduced opioid consumption and prolonged postoperative analgesia even in the absence of long acting opioids such as intrathecal morphine. Neuraxial morphine is widely used in developed countries, but it is still unclear whether the addition of clonidine to neuraxial morphine will further enhance its analgesic efficacy after Caesarean section. The studies included tested a range of doses, but interestingly we were unable to demonstrate any significant differences between the clonidine doses $\leq$75 μg and doses >75 μg for both 24 h morphine consumption and time to first analgesic request. The ideal dose for clonidine that improves analgesia has not been established. However, in the absence of any clear evidence that higher doses are more efficacious at improving analgesia than lower doses, the minimal effective dose for analgesia would be appropriate.

Clonidine's predominant analgesic effect is mediated through spinal α_2 adrenergic receptors and there is some evidence that this effect may be enhanced in pregnancy.[6,39,40] However, clonidine may also mediate some of its effects by increasing acetylcholine concentrations in cerebrospinal fluid.[41] Cholinergic activation of dorsal sensory neurons produces analgesic effects. Clonidine also provides analgesia for visceral pain and slows regression of the sensory block as reflected by the prolonged duration of analgesia in patients receiving a single dose of clonidine at the start of surgery.[8] This ability of clonidine to enhance the sensory block may explain not only its postoperative analgesic effect, but also the reduced need for intraoperative analgesic supplementation when it was administered as part of the neuraxial anaesthetic technique for Caesarean section. Importantly in the majority of studies investigating the need for intraoperative analgesic supplementation during Caesarean section, intrathecal clonidine was co-administered with local anaesthetic only, which is not standard practice in developed countries. In fact, the more common practice of co-administering short and intermediate acting lipophilic opioids with local anaesthetic intrathecally enhances intraoperative analgesia and reduces the need for intraoperative analgesic supplementation.[42,43] It is not clear if the addition of clonidine to a local anaesthetic and opioid mixture would confer any additional improvement in intraoperative analgesia.

The administration of neuraxial clonidine significantly increased the incidence of intraoperative sedation. The sedative effect of α_2 agonists may result from a supraspinal action inhibiting neuronal activity at the locus coeruleus in the medulla.[44,45] When administered neuraxially, this sedative effect may result from rostral spread of clonidine.[46] In the postoperative period, the non-significant increase in the incidence of sedation observed in patients receiving neuraxial clonidine could reflect an enhancement of the sedative effect of morphine co-administered i.v. or via the neuraxial route. In two of the studies, high doses of epidural clonidine as a bolus followed by continuous infusion were co-administered with PCA morphine after operation.[25,27] In one study, epidural clonidine was administered postoperatively in patients who had also received high dose intrathecal preservative morphine as a part of their anaesthetic technique,[26] and in another repeated boluses of clonidine and preservative free morphine were co-administered epidurally in the postoperative period for pain.[23] The administration of neuraxial clonidine as repeated boluses or as a high dose continuous infusion in conjunction with PCA morphine are not currently used postoperative analgesic regimes. Despite this, any increase in maternal sedation may be undesirable in the context of enhanced recovery protocols in current obstetric anaesthesia practice, as it could delay skin to skin contact, early initiation and continuation of breastfeeding, and prolong the length of stay in the post anaesthesia care unit.

Despite this sedative effect of clonidine, none of the studies reported an increase in the incidence of respiratory depression after operation. However, none of the studies reporting respiratory depression administered neuraxial morphine in conjunction with neuraxial clonidine. While neuraxial morphine may be associated with early onset and delayed respiratory depression and an increase in hypercapnia events, recent evidence suggests that the risk of clinically significant respiratory depression is extremely low in women receiving neuraxial morphine for post-caesarean analgesia.[47,48] It is also currently unclear whether clonidine would enhance the respiratory depression observed following neuraxial morphine administration. However, the increased sedation observed with neuraxial clonidine administration suggests that it could also enhance opioid-induced maternal respiratory depression and compromise maternal safety in the postoperative period.

Clonidine administration was associated with significant intraoperative hypotension, however there was no difference

in vasopressor requirements and neonatal outcomes, suggesting that these episodes of hypotension were not clinically relevant. The administration of intrathecal clonidine for labour analgesia has been associated with a reduction in umbilical artery pH and this was attributed to feto-placental hypoperfusion secondary to maternal hypotension.[11] In all the included studies that reported the incidence of intraoperative hypotension, vasopressors were administered to treat hypotension, but only in one study was a prophylactic ephedrine infusion administered.[29] While hypotension may be a concern with neuraxial clonidine administration, this adverse effect can be easily mitigated with the administration of prophylactic vasopressors to prevent maternal hypotension and reduce related side effects.[49–51]

Our systematic review has several limitations. Overall, several of the studies included were small clinical trials with unclear or high risk of bias limiting the validity of our findings. Limiting the analysis to studies with low risk of bias, however, did not alter our main findings. Despite clonidine being used as an analgesic adjunct, the majority of studies did not report on opioid consumption or pain scores, making it difficult to make robust recommendations on the analgesic effects of clonidine in the clinical setting. The studies also used different postoperative analgesic regimes, which may have contributed to the heterogeneity seen in our primary outcomes. We pooled studies administering epidural and intrathecal clonidine based on the fact that for the majority of the studies, the doses of clonidine used were comparable. However, there is little evidence to determine whether the pharmacokinetic and pharmacodynamic effects of clonidine administered by the epidural and intrathecal routes are comparable. Additionally, the epidural modes of delivery used were very heterogeneous, justifying a subgroup analysis. However, the analgesic effects of clonidine administered via the epidural route would be of clinical significance in obstetrics, as it is a frequently used anaesthetic technique for Caesarean section. Even though clonidine may enhance local anaesthetics with shorter acting opioids, its synergistic analgesic effects with neuraxial morphine and its effects on opioid-induced respiratory depression are less clear. Unfortunately, only in three included studies[23,26,29] was morphine used in conjunction with clonidine, and based on the small number of patients in the included trials, we could not specifically determine whether clonidine enhanced the analgesic effect of morphine or increased the risk of respiratory depression when compared with shorter acting opioids.

Given the widespread use of neuraxial morphine as an analgesic adjunct in Caesarean section, studies investigating the analgesic efficacy and safety of neuraxial morphine co-administered with clonidine are needed. The sedative effects of neuraxial clonidine co-administered with morphine on maternal bonding and initiation of breastfeeding also need to be addressed. Despite the modest analgesic effects seen with clonidine on postoperative analgesia, one area of emerging interest is its role in preventing wound hyperalgesia and resulting persistent pain after Caesarean section. Only one study included in this meta-analysis demonstrated that intrathecal clonidine at a dose of 150 μg reduced peri-incisional wound hyperalgesia, a surrogate marker for chronic incisional pain, at 48 h.[10] Further studies are needed to determine if clonidine may have a role in reducing persistent pain after Caesarean section, particularly in high risk women. Additionally, the fact that neuraxial clonidine produces its analgesic effects independent of opioid-dependent pain pathways suggests that it may be a useful adjunct in patients who are opioid-dependent or on opioid agonists for opioid addiction treatment. Studies investigating the role of neuraxial clonidine in the postoperative management regime of this challenging patient population would be a significant contribution to the field.

Conclusion

In summary, our findings demonstrate that neuraxial clonidine modestly enhances postoperative analgesia in women having Caesarean section with neuraxial anaesthesia. These beneficial effects have to be balanced against the increased incidence of intraoperative hypotension and sedation that may compromise maternal safety and no significant reduction in opioid-related side effects. Based on these findings, clonidine may be a useful analgesic adjunct in women having Caesarean section under neuraxial anaesthesia. Additionally, our findings demonstrate that α_2 agonists administered neuraxially may be an alternative mode of providing post-caesarean analgesia.

Authors' contributions

Study concept/design: all authors.
Data collection: T.K.A., B.M.M., R.Y.K.
Data analysis/interpretation, writing paper: T.K.A., A.S.H.
Revising paper: all authors.

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Declarations of interest

No conflicts of interest to declare.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.bja.2017.11.085.

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