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Perioperative Dextromethorphan as an Adjunct for Postoperative Pain: a Meta-Analysis of Randomized Controlled Trials

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Abstract

Background—N-methyl-D-aspartate (NMDA) receptor antagonists have been shown to reduce perioperative pain and opioid use. We performed a meta-analysis to determine whether the use of perioperative dextromethorphan lowers opioid consumption or pain scores.

Methods—PubMed, Web of Science, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, pubget, and Embase were searched. Studies were included if they were randomized, double-blinded, placebo controlled trials written in English, performed on patients ≥12 years. For comparison of opioid use, included studies tracked total consumption of intravenous or intramuscular opioids over 24 to 48 hours. Pain score comparisons were performed at 1 hour, 4 to 6 hours, and 24 hours postoperatively. Difference in means (MD) was used for effect size.

Results—Forty studies were identified and 21 were eligible for one or more comparisons. In 848 patients from 14 trials, opioid consumption favored dextromethorphan (MD -10.51 mg intravenous morphine equivalents; 95% confidence interval [CI]: -16.48 mg to -4.53 mg; $p = 0.0006$). In 884 patients from 13 trials, pain at 1 hour favored dextromethorphan (MD -1.60; 95% CI: -1.89 to -1.31; $p < 0.00001$). In 950 patients from 13 trials, pain at 4-6 hours favored dextromethorphan (MD -0.89; 95% CI: -1.11 to -0.66; $p < 0.00001$). In 797 patients from 12 trials, pain at 24 hours favored dextromethorphan (MD -0.92; 95% CI: -1.24 to -0.60; $p < 0.00001$).

Conclusions—This meta-analysis suggests dextromethorphan use perioperatively reduces postoperative opioid consumption at 24-48 hours and pain scores at 1, 4-6, and 24 hours.

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Introduction

N-methyl-D-aspartate (NMDA) receptor antagonists have become widely used adjuncts for postoperative analgesia.[1-2] Ketamine, a well-studied NMDA antagonist, has been shown to decrease postoperative pain when administered preemptively,[3-4] intraoperatively,[5] and postoperatively,[6-7] without causing an increase in sedation but with a notable increase in hallucinations and nightmares.[8] Dextromethorphan, an NMDA antagonist that is most routinely used as an oral antitussive, has also been extensively studied for its use as a perioperative analgesic adjunct.[9-29] Dextromethorphan has previously undergone systematic review without quantitative meta-analysis in which the authors determined that the drug was a potentially useful analgesic adjunct, but there still remained significant questions about the consistency of findings between studies.[30] Since that systematic review was accepted for publication in 2005 there have been more than ten additional studies[9-14,31-34] on dextromethorphan for postoperative pain control. A meta-analysis of the results of studies that investigate DM for its effect on postoperative pain and opioid reduction has not yet been published. We therefore performed a meta-analysis on the use of preoperative dextromethorphan and its effects on opioid consumption and postoperative pain scores.

Materials and Methods

This study is a meta-analysis of existing literature, did not involve the collection of new human or animal data, and is exempt from institutional review board review. The Cochrane specifications for systematic reviews was used to guide the construction of this meta-analysis.[35] A systematic search was performed in PubMed, Web of Science, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, Pubget, and EMBASE on August 4th, 2014. The following search terms were used: (dextromethorphan) AND acute pain; (dextromethorphan) AND postoperative pain; (dextromethorphan) AND pain. Trials were only included if they were randomized, double-blinded, placebo-controlled, and published in English. Unpublished abstracts and reports were excluded. Pediatric trials on patients less than twelve years of age were also excluded. Authors of the trials were not contacted for original data.

To ensure the quality of included trials, each was scored based on a modified validated scale previously used for meta-analysis.[36] The scale was designed to evaluate the quality of placebo-controlled, randomized trials and includes the following parameters:

1. Randomization: a point was given for stating the trial was randomized. An additional point was given if randomization was described and appropriate, such as the use of a random number generator.

2. Blinding: a point was given if the trial was stated to be double-blind. If blinding method was described and appropriate, such as the use of identical placebo pills, an additional point was given.

3. Withdrawals: a point was given if patient withdrawals and the reasons for withdrawals were reported.

4. **Pain intensity**: to ensure that the trial evaluated clinically significant pain, a point was given if mean visual analog pain scores were greater than 30 mm or greater than 3 out of 10 on a numeric rating scale.
5. **Power analysis**: a point was given if sample size was determined through the use of a power analysis.

Thus, the minimum requirements for inclusion would be a score of 2 points and the maximum score would be 7 points.

To be included in the meta-analyses, we required all trials to have a treatment arm in which intravenous, intramuscular, or per os dextromethorphan was administered prior to surgery – if treatment groups also received intraoperative or postoperative doses of dextromethorphan (table 1) they were included as well. Only test groups from studies in which dextromethorphan was administered preoperatively were included for analysis. If test groups were administered dextromethorphan only intraoperative or postoperatively, they were not included for analysis. If multiple dextromethorphan dosages were administered in an included study, the highest dose group was used for the comparison. However, as a sensitivity analysis, all comparisons were recalculated, where possible, using the lowest dose groups.

The outcome variables we sought were postoperative opioid consumption, pain scores, and incidence of side effects. The investigation of published studies led to the *a posteriori* selection for analysis of total opioid consumption for 24-48 hours postoperatively, numeric pain scores at 1, 4-6, and 24 hours, and the incidence of opioid- and dextromethorphan-related side effects. For comparison of postoperative opioid use, studies were included if they tracked total use of opioids over a 24 or 48 hour period. If an opioid other than intravenous morphine was used, such as meperidine, the reported values were converted into IV morphine equivalents using an online calculator.[37] Inclusion required sole use of opioids as a PRN analgesic. Comparisons between groups that received the same non-opioid intervention (such as a single dose of a non-steroidal anti-inflammatory agent in both control and dextromethorphan groups) were also included.

Studies were eligible for pain score comparisons if they reported pain scores on a standardized 0 to 10 numeric rating scale, such as the visual analog scale. Numeric pain score comparisons were performed at three time points: 1, 4-6, and 24 hours post-operatively. For the 1 hour group, studies were included if they reported pain scores within 1 hour post-operatively. Thus, studies were also included in this group if they did not report pain scores at 1 hour but did report in the first hour in the post-anesthetic care unit. For the 4 to 6 hour group, studies were included if they reported pain scores at 4 or 6 hours. If a study reported pain scores at both times, the score at 4 hours was used.

We intended to compare the incidence of opioid-related side effects, such as nausea and itching, as well as dextromethorphan-related side effects, such as nausea and euphoria, but this was not feasible due to the small number of events reported. Thus, rather than report meta-analysis of side effects, we systematically reviewed the included trials for reported side effects.

Statistical analyses were performed with Review Manager version 5.3 (The Nordic Cochrane Centre, Copanhagen, Denmark). All calculations required knowledge of the mean and standard deviation for the compared parameters. Some studies represented mean and standard deviation graphically – in these cases the computer program Plot Digitalizer[38] was used to estimate values at the set time points. As mean and standard deviation were used for comparison calculation, the effect size is expressed as difference in means (MD). By convention, MDs favoring dextromethorphan were considered negative and those favoring control considered positive. To account for anticipated heterogeneity, a random-effects model[39] was used for all calculations. We also utilized the I^2 statistic to assess the degree to which differences between trials were due to heterogeneity.[40] Alpha was set at 0.05 and, after performing a Bonferroni correction accounting for four total comparisons, the significance criterion set at 0.0125. All comparisons are presented graphically in this manuscript using forest plots.[41]

Results

Study selection

The selection process is summarized in figure 1. Table 1 lists all studies used in the comparisons including pertinent aspects of their design and subgroups. A total of 40 studies were identified and a total of 19 were excluded, leaving 21 studies which were used in at least one comparison. The median quality score of these studies was 5 out of 7 with an interquartile range of 2.

Total opioid consumption

A total of 14 trials reported mean and standard deviation of opioid consumption for the first 24 or 48 hours post-operatively and a total of 848 patients were included in the comparison. MD favored dextromethorphan (MD: -10.51 milligrams [mg] of intravenous morphine equivalents; 95% confidence interval [CI]: -16.48 mg to -4.53 mg; p = 0.0006; Figure 2). Three studies in particular, Weinbroum *et al.* 2002a,[19] Helmy *et al.* 2001,[22] and Wu *et al.* 2000,[25] were statistical outliers with a MD of less than -20. To ensure that these three studies alone had not resulted in the comparison's significance, a sensitivity analysis was performed with them excluded. The overall effect was lessened but the comparison remained significant (MD: -4.45 mg intravenous morphine equivalents; 95% CI, -7.47 mg to -1.43 mg; p = 0.004) and I^2, although still high, was reduced from 97% to 88%.

Pain scores at 1, 4-6, and 24 hours

Pain scores at 1 hour were reported as mean and standard deviation in 13 studies with a total of 884 included patients. MD favored dextromethorphan (-1.60; 95% CI, -1.89 to -1.31; $p < 0.00001$; Figure 3). Weinbroum et al. 2002a[19] was an outlier with a MD of less than -4. After exclusion, the overall effect was lessened but the comparison remained significant (-1.50; 95% CI, -1.78 to -1.22; $p < 0.00001$) and I^2 decreased from 91 to 90%.

Pain scores at 4 to 6 hours were reported in 13 studies with a total of 950 included patients. Three subgroups in two studies (Suski *et al.* 2010[10]; Weinbroum 2002b[20]) reported pain scores at both 4 and 6 hours and the values recorded at the 4 hours were used in the comparison. MD favored dextromethorphan (-0.89; 95% CI, -1.11 to -0.66; p < 0.00001; Figure 4) with an I^2 of 88%.

Pain scores at 24 hours were reported in 12 studies with 797 included patients. Dextromethorphan was also favored at this time point (MD: -0.92; 95% CI, -1.24 to -0.60; p < 0.00001; Figure 5) with an I^2 of 92%.

Comparisons using lower dose dextromethorphan groups

A total of 3 studies in the opioid consumption, 24 hour pain score, and 1 hour pain score comparisons and 2 studies in the 4-6 hour pain score comparison included multiple dosing regimens of dextromethorphan. Of note, two of these studies (Wu *et al.* 2000[25] and Weinbroum *et al.* 2001[21]) were completed by groups that only used their highest dose in subsequent studies – thus their highest dosing groups best approximated the most common dextromethorphan doses in the study and were used for the initial comparisons. When comparisons were recalculated using the low dose instead of high dose groups for comparison, all results remained significant although with a lower magnitude of effect (opioid consumption MD -10.05 mg of intravenous morphine equivalents; 95% CI: -15.79 mg to -4.31 mg, p = 0.0006; pain at 1 hour MD -1.50; 95% CI: -1.79 to -1.21, p < 0.00001; pain at 4-6 hours MD -0.87; 95% CI: -1.11 to -0.64, p < 0.00001; pain at 24 hours MD -0.65; 95% CI: -0.95 to -0.35, p < 0.0001).

Incidence of side effects

Eighteen out of 21 trials included in our meta-analyses tracked the incidence of side effects, which for both opioids and dextromethorphan primarily consist of nausea, vomiting, dizziness, and lightheadedness. Ten studies reported either no side effects or a non-significant difference between groups.[9-10,13-14,16,19-20,22,24,27,29] Five studies did, however, did report a decrease in side effects in groups receiving dextromethorphan.[15,17-18,25-26] One study[23] found a higher incidence of nausea in the dextromethorphan group, with rating mild to moderate nausea reported by patients at 31 time points in the dextromethorphan group compared to 20 time points in the control group, although no patients reported severe nausea at any time. Weinbroum *et al.* 2001[21] tracked sedation using a standardized scale and found an increase in sedation in the placebo group.

Discussion

A variety of study designs in multiple hospital settings and countries have attempted to elucidate the value of perioperative dextromethorphan as an adjunctive analgesic. In a prior report, these efforts were synthesized in a qualitative systematic review of NMDA receptor antagonists' role in decreasing postoperative pain and opioid consumption, which demonstrated a significant benefit from dextromethorphan in 67% of included studies.[2] Additionally, a separate qualitative systematic review of dextromethorphan only that shared in common fifteen of the studies used in this analysis suggested that dextromethorphan had potential as an adjunct to postoperative opioid analgesics, but did note variability among the analyzed studies.[30] Here we have systematically searched the published literature on the preoperative use of dextromethorphan to decrease postoperative pain and opioid use.

Ultimately, we identified 21 trials published between 1998 and 2013 that addressed these metrics and were suitable for quantitative meta-analysis. The results of our meta-analyses suggest that, when used preoperatively, dextromethorphan significantly decreases pain and opioid use in the postoperative period.

To objectively index included trials by design quality, we scored each trial based on a quality index. The majority of studies in our meta-analyses scored in the 5 to 7 range. These studies demonstrated a high degree of transparency in their study designs and sampling processes. A minority of studies scored in the 2-4 range, with a score of 2 representing the minimum requirements of being a randomized, blinded trial. Although we did not weigh trials based on their scores, the average scores of the trials do reflect the on average high quality of the studies from which we draw our conclusions.

As an NMDA receptor antagonist,[42] dextromethorphan has been proposed to exert its effects as a preemptive analgesic by preventing NMDA-mediated calcium current and subsequent modulation of nociception in spinal pain fibers and the central nervous system. This in turn prevents a pain phenomenon known as “windup” that results in amplified subsequent responses to painful stimuli and poorer responses to opioids.[43-46] In previous trials, dextromethorphan has shown benefit in various chronic pain conditions including diabetic neuropathy, postherpetic neuralgia,[47] and phantom limb pain.[48-49] Effects on cancer pain have also been investigated in at least two trials with mixed results.[50-51]

Multimodal preemptive analgesic adjuncts including NMDA receptor antagonists, local anesthetic infiltration, non-steroidal anti-inflammatory agents (NSAIDs), epidural analgesia, and preemptive opioids and have been the subject of a prior meta-analysis.[36] This study found benefit with preemptive NSAIDs, epidural analgesia, and local anesthetic infiltration, but its comparisons for both ketamine and dextromethorphan were equivocal. In contrast, the same year a meta-analysis of perioperative intravenous ketamine use reported a mean of 15.7 mg less morphine consumption at 24 hours and mean pain score improvements of 0.89 at 6 hours, 0.42 at 12 hours, 0.35 at 24 hours, and 0.27 at 48 hours.[52] These results are remarkably similar to our own. A more recent meta-analysis of perioperative intravenous ketamine found benefits for opioid consumption and time to first analgesic, but did note increased hallucinations and nightmares.[8] The statistic used for this analysis was the standardized mean difference rather than mean difference, making direct comparison to effect observed in our own study difficult.

However, while ketamine is widely used as a multimodal adjunct worldwide, our anecdotal experience from multiple institutions is that dextromethorphan does not appear to share the same level of popularity and is very rarely used as an adjunct for postoperative analgesia. Based on our findings, the use of dextromethorphan perioperatively could potentially provide similar benefits to preemptive ketamine therapy in a simple oral, IM, or IV formulation. Further investigation, particularly a head to head randomized trial alongside placebo, may help clarify whether the different NMDA antagonists provide similar levels of relief with a similar incidence of dysphoric or other side effects, or not. Additional research may also explore if there is benefit from the simultaneous use of more than one NMDA receptor antagonist as it is unclear if this would result in an additive, synergistic, or antagonistic effect.

Well-documented dextromethorphan side effects and concerns include dose-related tachycardia, respiratory depression, and gastrointestinal symptoms, as well as abuse potential.[53] Although its recreational abuse potential is clear, dextromethorphan dependence has only been rarely described[54-55] and its abuse is best described in adolescents.[56-57] Recent work has described dose-dependent hallucinogenic properties of dextromethorphan as well as acute changes in memory and cognition,[58-59] although these effects typically occurred at doses well in excess of those used in the included studies. Thus, it seems reasonable to avoid doses above 2 mg/kg PO, which has been described as a dose above which dissociative effects are typically seen,[60] in order to prevent neurologic disturbances before surgery. However, there exists to our knowledge no evidence that a single dose of dextromethorphan for preemptive analgesia would increase potential for postoperative abuse, and indeed review of the included trials revealed a minimal incidence of dextromethorphan-related adverse effects.

Although opioids are a mainstay of effective perioperative analgesia, their use is nonetheless frequently associated with side effects that can increase hospital costs and length of stay.[61] Multimodal analgesia has been proposed as a way to improve pain control while reducing side effects,[62] but to date little evidence exists to link opioid-sparing analgesic regimens to reduced opioid-related adverse effects. The available studies were insufficient for meta-analysis on the incidence of side effects with dextromethorphan, but our qualitative review of the literature suggests that most studies saw minimal change in the incidence of side effects. Ketamine, in contrast, was shown in prior meta-analysis to increase the risk of hallucinations when administered in awake patients, although the incidence of opioid-related side effects was also unchanged.[52] This difference highlights the fact that different NMDA receptor antagonists are not necessarily interchangeable, and therefore continued exploration into other agents like dextromethorphan and memantine are still warranted. Larger studies may clarify if opioid-sparing doses of dextromethorphan are able to quantitatively decrease the incidence of opioid-related side effects without causing hallucinations at similar rates to ketamine.

Similar to Duedahl *et al.*'s 2006 systematic review[30] we observed a high degree of heterogeneity, with an I^2 greater than 80% in each comparison. This is likely a reflection of the variability between study designs, such as differences in type of surgery, dextromethorphan dosing regimens, dextromethorphan administration routes, and post-operative analgesic regimens. We had anticipated this and therefore used a random-effects model for all of our calculations. The high heterogeneity does, nonetheless, demonstrate the variability in findings among dextromethorphan studies and highlights the need for a larger study with a standardized protocol to clarify dextromethorphan's role in the perioperative setting. Important details to clarify include the optimal perioperative dextromethorphan dose and duration of use, the incidence of side effects, and whether or not the perioperative use of dextromethorphan improves outcomes such as hospital length of stay.

Our analysis is also limited by the fundamental reliance of meta-analyses on the existing data and the reporting mechanisms of the original studies. Many high quality studies needed to be excluded from the quantitative analyses due to reporting results in forms other than mean and standard deviation, tracking opioid use over periods less than 24 hours, or reporting pain scores in forms other than fixed intervals (such as only reporting the worst recorded). In a small number of studies with multiple dextromethorphan dosing arms, we also had to exclude groups in order to avoid duplicating control patients in our comparisons. As a result our quantitative analyses do not necessarily represent the full body of literature on the perioperative use of dextromethorphan. In addition, due to the heterogeneity of published studies, this is an *a posteriori* derived analysis of total opioid consumption for 24 to 48 hours postoperatively and pain scores at 0 to 1 hours, 4 to 6 hours, and 24 hours postoperatively.

Despite these limitations, our comparisons do nonetheless represent a cross-section of several hundred patients in the available randomized controlled trials on the effects of preoperative dextromethorphan on postoperative pain control with significantly favorable results. To date no large randomized controlled trial has been conducted on this topic. Our quantitative meta-analyses of the existing randomized controlled studies of dextromethorphan for postoperative pain control demonstrated a significant reduction in postoperative opioid use for 24 to 48 hours after surgery as well as pain represented by pain scores up to 24 hours after surgery. Due to high heterogeneity between the existing trials and the lack of a single large randomized study on this topic, further evidence is required to definitively determine a benefit.

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Final Box Summary Statement

What we already know

- Some NMDA receptor antagonists reduce postoperative pain and opioid requirements.
- Dextromethorphan, a low-affinity noncompetitive NMDA receptor antagonist, may be beneficial in the perioperative setting.

What this article tells us that is new

- This meta-analysis identified 21 studies describing the effects of dextromethorphan on postoperative pain and opioid consumption.
- Dextromethorphan was found to reduce pain from 1 to 24 hours postoperatively, and was found to reduce morphine requirements 24-48 hours after surgery.

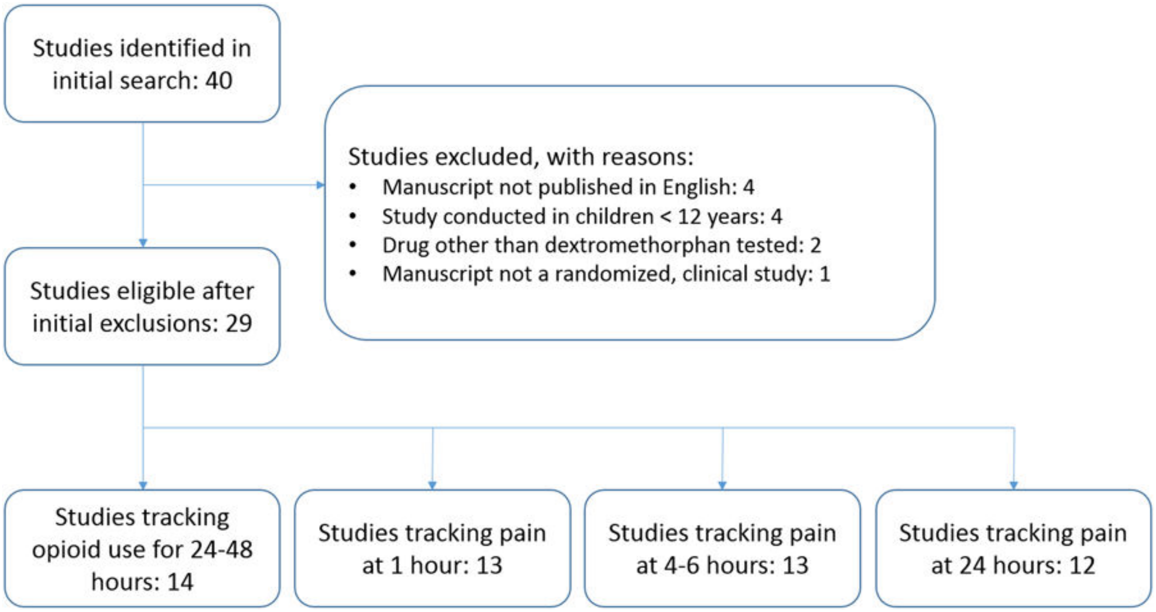


Figure 1.

Diagram of study selection for each comparison. Note that exclusions on the comparison level, such as exclusion for not reporting mean and standard deviation for the specific comparison, are not shown.

Study or Subgroup	Dextromethorphan Mean	SD	Total	Control Mean	SD	Total	Difference in Means Random, 95% CI
Chau-In 2007 (12)	35.05	14.9	50	33.04	11.2	48	2.01 [-3.20, 7.22]
Entezary 2013 (9)	10.7	5.6	54	13.1	6.1	58	-2.40 [-4.57, -0.23]
Grace 1998 (28)	100.4	11.7	18	91.5	7.6	19	8.90 [2.51, 15.29]
Helmy 2001 (22)	18.7	8	20	76	9.3	20	-57.30 [-62.68, -51.92]
Liu 2000 (24)	8.47	8.61	30	18.7	8.25	30	-10.23 [-14.50, -5.96]
Mahmoodzadeh 2009 (11)	13.71	4.28	24	11.88	5.29	22	1.83 [-0.97, 4.63]
Suski 2010 (10)	30.2	12.44	30	32.6	11.64	30	-2.40 [-8.50, 3.70]
Wadhwa 2001 (23)	37.2	34.7	22	52.6	29.2	34	-15.40 [-32.91, 2.11]
Weinbroum 2002a (19)	18	11	23	38.5	10	24	-20.50 [-26.52, -14.48]
Wong 1999 (26)	0	1.3	30	10	6.7	30	-10.00 [-12.44, -7.56]
Wu 1999 (27)	2.7	3.21	30	12.1	8.69	30	-9.40 [-12.71, -6.09]
Wu 2000 (25)	9.3	3.9	15	33.5	6.6	15	-24.20 [-28.08, -20.32]
Wu 2005 (15)	4.21	5.11	25	11.6	6.36	25	-7.39 [-10.59, -4.19]
Wu 2005 - lidocaine groups (15)	1.25	2.93	25	6.72	6.63	25	-5.47 [-8.31, -2.63]
Yeh 2004 (16)	3.6	4.84	20	11.5	9.17	22	-7.90 [-12.28, -3.52]
Total (95% CI)			**416**			**432**	**-10.51 [-16.48, -4.53]**

Heterogeneity: Tau² = 131.16; Chi² = 532.16, df = 14 (P < 0.00001); I² = 97%

Test for overall effect: Z = 3.45 (P = 0.0006)

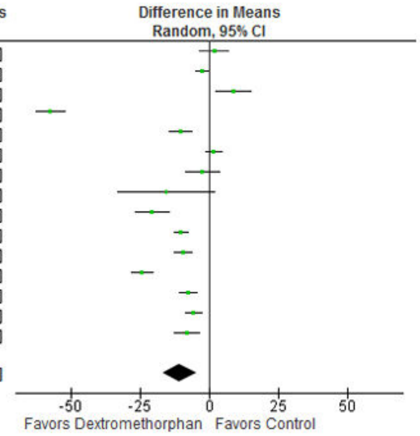


Figure 2.

Forest plot for total opioid use over 24 or 48 hours. The table displays the study with reference number in parenthesis, mean, standard deviation, sample size, difference in means in milligrams of intravenous morphine with 95% confidence interval, heterogeneity, overall effect, and p-value. The Forest plot displays point estimate and 95% confidence interval. CI = confidence interval, SD = standard deviation.

Study or Subgroup	Dextromethorphan Mean	SD	Total	Control Mean	SD	Total	Difference in Means Random, 95% CI
Chau-In 2007 (12)	6.26	0.54	50	7.57	0.5	48	-1.31 [-1.52, -1.10]
Entezary 2013 (9)	4.1	1.8	54	4.8	1.2	58	-0.70 [-1.27, -0.13]
Lu 2006 (13)	2.4	0.7	20	4.3	0.7	20	-1.90 [-2.33, -1.47]
Lu 2006 - ketorolac groups (13)	2.4	0.8	20	3	0.6	20	-0.60 [-1.04, -0.16]
Mahmoodzadeh 2009 (11)	5.28	2.81	24	5.55	1.38	22	-0.27 [-1.53, 0.99]
Suski 2010 (10)	1.6	2.37	30	4.6	2.27	30	-3.00 [-4.17, -1.83]
Weinbroum 2001 (21)	3.2	0.7	17	3.3	0.8	20	-0.10 [-0.58, 0.38]
Weinbroum 2002a (19)	1.2	1.9	23	5.4	2.2	24	-4.20 [-5.37, -3.03]
Weinbroum 2002b - PCA groups (20)	1.9	1.7	20	5.2	1.8	20	-3.30 [-4.39, -2.21]
Weinbroum 2002b - PCEA groups (20)	2.8	0.6	18	3.7	1.5	17	-0.90 [-1.67, -0.13]
Weinbroum 2003 (18)	2.1	1	29	5.6	1.4	27	-3.50 [-4.14, -2.86]
Wu 2000 (25)	6.3	1	15	8.6	0.8	15	-2.30 [-2.95, -1.65]
Wu 2005 (15)	4	0.2	25	5.7	0.3	25	-1.70 [-1.84, -1.56]
Wu 2005 - lidocaine groups (15)	3.3	0.1	25	4.6	0.2	25	-1.30 [-1.39, -1.21]
Yeh 2004 (16)	4	0.5	20	5.6	0.8	22	-1.60 [-2.00, -1.20]
Yeh 2004 - tenoxicam groups (16)	3.5	0.5	20	4.7	0.8	21	-1.20 [-1.61, -0.79]
Yeh 2005 (14)	3.5	4.7	30	5	5.2	30	-1.50 [-4.01, 1.01]
Total (95% CI)			**440**			**444**	**-1.60 [-1.89, -1.31]**

Heterogeneity: Tau² = 0.25; Chi² = 170.46, df = 16 (P < 0.00001); I² = 91%
Test for overall effect: Z = 10.92 (P < 0.00001)

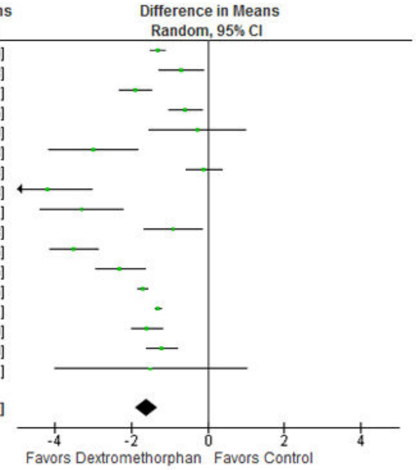


Figure 3.

Forest plot for comparison of pain scores at 1 hour post-op. The table displays the study with reference number in parenthesis, mean, standard deviation, sample size, difference in means of visual analog scale with 95% confidence interval, heterogeneity, overall effect, and p-value. The Forest plot displays point estimate and 95% confidence interval. CI = confidence interval, PCA = patient-controlled analgesia, PCEA = patient-controlled epidural analgesia, SD = standard deviation.

Study or Subgroup	Dextromethorphan Mean	SD	Total	Control Mean	SD	Total	Difference in Means Random, 95% CI
Chau-In 2007 (12)	5.62	0.25	50	5.84	0.39	48	-0.22 [-0.35, -0.09]
Entezary 2013 (9)	2.9	0.9	54	3.8	1.1	58	-0.90 [-1.27, -0.53]
Lu 2006 (13)	2.8	0.4	20	2.9	0.3	20	-0.10 [-0.32, 0.12]
Lu 2006 - ketorolac groups (13)	2.7	0.4	20	2.7	0.4	20	0.00 [-0.25, 0.25]
Mahmoodzadeh 2009 (11)	4.12	2.8	24	4.83	2.9	22	-0.71 [-2.36, 0.94]
Suski 2010 (10)	2.33	2.6	30	4.7	2.14	30	-2.37 [-3.57, -1.17]
Weinbroum 2001 (21)	1.5	0.3	17	2.5	0.7	20	-1.00 [-1.34, -0.66]
Weinbroum 2002b - PCA groups (20)	1.9	0.5	20	3.8	0.7	20	-1.90 [-2.28, -1.52]
Weinbroum 2002b - PCEA groups (20)	1.1	0.8	18	2.1	0.6	17	-1.00 [-1.47, -0.53]
Weinbroum 2003 (18)	1.5	0.5	29	3.2	1.2	27	-1.70 [-2.19, -1.21]
Weinbroum 2004 - PCA groups (17)	2.9	1.6	29	4.1	1.4	27	-1.20 [-1.99, -0.41]
Weinbroum 2004 - PCEA groups (17)	1.3	0.7	28	2.7	0.9	29	-1.40 [-1.82, -0.98]
Wu 2000 (25)	6.3	0.8	15	6.8	0.8	15	-0.50 [-1.07, 0.07]
Wu 2005 (15)	3.8	0.1	25	4.6	0.3	25	-0.80 [-0.92, -0.68]
Wu 2005 - lidocaine groups (15)	3.3	0.1	25	4.1	0.2	25	-0.80 [-0.89, -0.71]
Yeh 2004 (16)	3.7	0.5	20	4.5	0.5	22	-0.80 [-1.10, -0.50]
Yeh 2004 - tenoxicam groups (16)	3.5	0.6	20	4.4	0.5	21	-0.90 [-1.24, -0.56]
Yeh 2005 (14)	3.7	3.6	30	5	4.1	30	-1.30 [-3.25, 0.65]
Total (95% CI)			**474**			**476**	**-0.89 [-1.11, -0.66]**

Heterogeneity: $Tau^2 = 0.17$; $Chi^2 = 201.74$, df = 17 (P < 0.00001); $I^2 = 92\%$

Test for overall effect: Z = 7.77 (P < 0.00001)

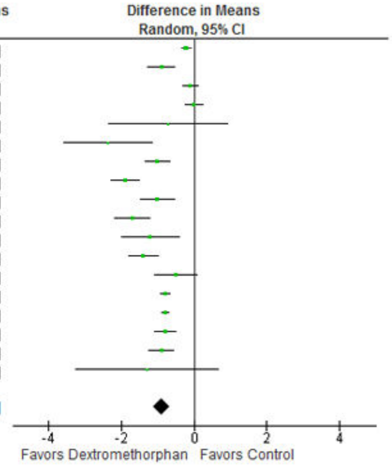
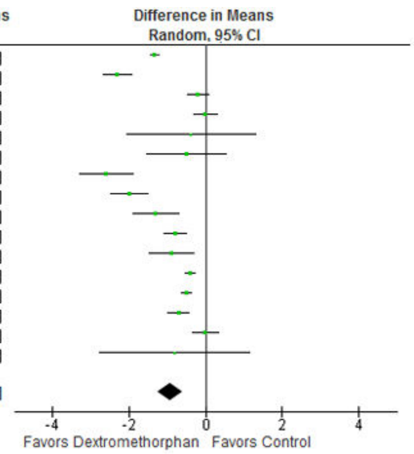


Figure 4.

Forest plot for comparison of pain scores at 4 – 6 hours post-op. The table displays the study with reference number in parenthesis, mean, standard deviation, sample size, difference in means with 95% confidence interval, heterogeneity, overall effect, and p-value. The Forest plot displays point estimate and 95% confidence interval. CI = confidence interval, PCA = patient-controlled analgesia, PCEA = patient-controlled epidural analgesia, SD = standard deviation.



Study or Subgroup	Dextromethorphan Mean	SD	Total	Control Mean	SD	Total	Difference in Means Random, 95% CI
Chau-In 2007 (12)	2.57	0.285	50	3.9	0.325	48	-1.33 [-1.45, -1.21]
Kawamata 1998 (29)	3.1	0.3	12	5.4	0.6	12	-2.30 [-2.68, -1.92]
Lu 2006 (13)	2.5	0.5	20	2.7	0.4	20	-0.20 [-0.48, 0.08]
Lu 2006 - ketorolac groups (13)	2.5	0.5	20	2.5	0.5	20	0.00 [-0.31, 0.31]
Mahmoodzadeh 2009 (11)	3.24	2.95	24	3.62	2.92	22	-0.38 [-2.08, 1.32]
Suski 2010 (10)	4.3	1.92	30	4.8	2.21	30	-0.50 [-1.55, 0.55]
Weinbroum 2002a (19)	1.6	1	23	4.2	1.4	24	-2.60 [-3.29, -1.91]
Weinbroum 2003 (18)	1.3	0.4	29	3.3	1.2	27	-2.00 [-2.48, -1.52]
Weinbroum 2004 - PCA groups (17)	2.7	1	29	4	1.3	27	-1.30 [-1.91, -0.69]
Weinbroum 2004 - PCEA groups (17)	1.4	0.7	28	2.2	0.4	29	-0.80 [-1.10, -0.50]
Wu 2000 (25)	5.7	0.6	15	6.6	1	15	-0.90 [-1.49, -0.31]
Wu 2005 (15)	3.5	0.1	25	3.9	0.3	25	-0.40 [-0.52, -0.28]
Wu 2005 - lidocaine groups (15)	3	0.1	25	3.5	0.3	25	-0.50 [-0.62, -0.38]
Yeh 2004 (16)	3.6	0.5	20	4.3	0.4	22	-0.70 [-0.98, -0.42]
Yeh 2004 - tenoxicam groups (16)	3.6	0.5	20	3.6	0.6	21	0.00 [-0.34, 0.34]
Yeh 2005 (14)	3.4	3.3	30	4.2	4.4	30	-0.80 [-2.77, 1.17]
Total (95% CI)			**400**			**397**	**-0.92 [-1.24, -0.60]**

Heterogeneity: $Tau^2 = 0.34$; $Chi^2 = 312.39$, df = 15 (P < 0.00001); $I^2 = 95\%$
Test for overall effect: Z = 5.62 (P < 0.00001)

Figure 5.

Forest plot for comparison of pain scores at 24 hours post-op. The table displays the study with reference number in parenthesis, mean, standard deviation, sample size, difference in means with 95% confidence interval, heterogeneity, overall effect, and p-value. The Forest plot displays point estimate and 95% confidence interval, CI = confidence interval, PCA = patient-controlled analgesia, PCEA = patient-controlled epidural analgesia, SD = standard deviation.

Table 1

list of studies included in one or more of the comparisons in the meta-analysis. DM = dextromethorphan, GA = general anesthesia, IM = intramuscular, IV = intravenous, mg/kg = milligrams per kilogram, mg/ml = milligrams per milliliter, NCA = nurse controlled analgesia (doses dependent on patient request and nurse administration on a PRN schedule), PACU = post-anesthesia care unit,PCA = patient controlled analgesia, PCEA = patient controlled epidural analgesia, PO = per os, POD = postoperative day, PRN = pro re nata (as needed), pts = patients.

Study	Quality Score	Dextromethorphan pts	Control pts	Dextromethorphan dosing	Dextromethorphan dose timing	Surgery type	Anesthesia type	Comparisons tracked	PRN analgesic tracked	Tracked side effects	Comments
Entezary 2013 (9)	3	54	58	1 mg/kg PO	Night before surgery	Knee arthroscopy	Spinal	Pain 1, 4h Total opioid 24h	Morphine NCA	Yes	
Suski 2010 (10)	6	30	30	30 or 45 mg PO (weight based) ×4	1 hr pre-op and at 8, 20, and 32 hrs post-op	Scoliosis repair	General	Pain 1, 4/6, 24h Total opioid 24h	Morphine IV NCA	Yes	
Mahmoodzadeh 2009 (11)	6	23 (in 45 group) 24 (in 90 group)	22	45 or 90 mg PO	2 hrs pre-op	Open chole	General	Pain 1, 6, 24h Total opioid 24h	Morphine IV NCA	No	Used 90 mg group for comparison
Chau-In 2007 (12)	7	50	48	30 mg PO ×4	60 mins pre-op and 3 doses over first 24 hrs post-op	Total abdominal hysterectomy	General	Pain 1, 6, 24h Total opioid 24h	Morphine IV PCA	No	
Lu 2006 (13)	6	20 DM 20 DM + ketorolac	20 control 20 ketorolac	40 mg IM	30 mins pre-op	Vaginal hysterectomy	General	Pain 1, 4, 24h	Morphine IV PCA	Yes	Performed ketorolac and non-ketorolac comparisons
Yeh 2005 (14)	4	30 DM plus epidural	30 GA plus epidural; 30 GA only	40 mg IM	30 mins pre-op	Colon surgery	General + epidural	Pain 1, 4, 24h	0.2% ropivacaine and 0.1 mg/mL morphine PCEA	Yes	Excluded GA only group as no direct DM comparison
Wu 2005 (15)	5	25 DM 25 DM + lidocaine IV	25 control 25 lidocaine IV	40 mg IM	30 mins pre-op	Lap chole	General	Pain 1, 4, 24h Total opioid 48h	Meperidine IM NCA	Yes	Performed lidocaine and non-lidocaine comparisons
Yeh 2004 (16)	5	20 DM 20 DM + tenoxicam	22 control 21 tenoxicam	40 mg IM	30 mins pre-op	Lap chole	General	Pain 1,4, 24h Total opioid 48h	Meperidine IM NCA	Yes	Performed tenoxicam and non-tenoxicam comparisons
Weinbroum 2004 (17)	7	29 DM + PCA 28 DM + PCEA	27 PCA 29 PCEA	90 mg PO	90 mins pre-op	Bone tumor resection	General or general + epidural	Pain 6, 24h	PCEA (ropivacaine 3.2 mg plus fentanyl 8 mcg/dose) or PCA (morphine 2mg/dose) only in PACU, then diclofenac	Yes	PCA only used in PACU so no 24h opioid comparison
Weinbroum 2003 (18)	6	29	27	90 mg PO ×3	90 mins pre-op and on POD 1 and 2	Bone tumor resection	General + epidural	Pain 1, 6, 24h	PCEA (1.6 mg ropivacaine plus 4 mcg/mL fentanyl) continuous and by demand	Yes	
Weinbroum 2002a (19)	6	25 (in 60 group) 23 (in 90 group)	24	60 or 90 mg PO ×3	90 mins pre-op and on POD1 and 2	Bone tumor resection	General	Pain 1, 24h Total opioid 24h	Morphine IV PCA	Yes	Used 90mg group for comparison
Weinbroum 2002b (20)	6	18 DM + epidural 20 DM + GA	17 epidural 20 GA	90 mg PO	90 mins pre-op	Hernia repair or knee arthroscopy	General or epidural	Pain 1, 4/6h	Morphine IV PCA for 2 hours then diclofenac	Yes	Compared both epidural and GA groups
Weinbroum 2001 (21)	6	16 (in 60 group) 17 (in 90 group)	20	60 or 90 mg PO	90 mins pre-op	Hernia repair or knee arthroscopy	Epidural	Pain 1, 6h	Morphine IV PCA in PACU and diclofenac at home	Yes	Used 90 mg group for comparisons as this was used in all the group's further studies
Helmy 2001 (22)	5	20 (pre) 20 (post)	20	120 mg IM	30 mins before incision or 30 mins before end of surgery	Upper abdominal surgery	General	Total opioid 24h	Meperidine IV PCA	Yes	Excluded post group
Wadhwa 2001 (23)	7	22	34	200 mg PO ×3	120 mins pre-op and 8 and 16 hrs post-op	Knee replacement or reconstruction	General	Total opioid 24h	Morphine IV PCA	Yes	

Study	Quality Score	Dextromethorphan pts	Control pts	Dextromethorphan dosing	Dextromethorphan dose timing	Surgery type	Anesthesia type	Comparisons tracked	PRN analgesic tracked	Tracked side effects	Comments
Liu 2000 (24)	3	30	30	40 mg IM	30 mins pre-op	Hemorrhoidectomy	Local	Total opioid 48h	Meperidine IM NCA	Yes	
Wu 2000 (25)	3	15 (in 10 group) 15 (in 20 group) 15 (in 40 group)	15	10, 20, or 40 mg IM	30 mins pre-op	Upper abdominal surgery	General	Pain 1,4, 24h Total opioid 24h	Morphine IV PCA	Yes	Used 40 mg group for comparison as this was used in all the group's further studies
Wong 1999 (26)	3	30	30	40 mg IM	30 mins pre-op	Modified radical mastectomy	General	Total opioid 48h	Meperidine IM NCA	Yes	
Wu 1999 (27)	2	30 (given pre) 30 (given intra)	30	40 mg IM	Just prior to incision or intraoperative	Lap chole	General	Total opioid 48h	Meperidine IM NCA	Yes	Excluded intraoperative group
Grace 1998 (28)	5	18	19	60 mg PO ×2	Night before and 1 hour pre-op	Laparotomy	General	Total opioid 48h	Morphine IV PCA	No	
Kawamata 1998 (29)	5	12 (in 30 group) 12 (in 45 group)	12	30 or 45 mg PO	60 mins pre-op	Tonsillectomy	General	Pain 24h	Diclofenac PO at home	Yes	Used 45 mg group for comparison