Efficacy of adding clonidine to intrathecal morphine in acute postoperative pain: meta-analysis

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Editor’s key points
- Clonidine may be given with morphine intrathecally for postoperative analgesia.
- Meta-analysis of seven studies shows some increase in the duration of analgesia and reduced morphine requirement.
- However, clonidine was associated with higher incidence of hypotension.
- Results strongly influenced by the study that included intrathecal fentanyl in addition to clonidine.

Background. Clonidine may be used along with intrathecal morphine for single-dose postoperative analgesia in adults. The efficacy of this is not clear.

Methods. A meta-analysis was performed for two endpoints of efficacy: the time to first postoperative analgesia request and the amount of systemic morphine used during the first 24 h after operation. A Bayesian inference supporting direct statements about the probability of the magnitude of an effect was also used. The frequency of the five adverse events (postoperative nausea or vomiting, sedation, respiratory depression, pruritus, and hypotension) was analysed.

Results. Clonidine increased the duration of analgesia by 1.63 h [95% confidence interval (CI): 0.93–2.33]. There is a 90% probability that clonidine increases the duration of postoperative analgesia by more than 75 min compared with morphine alone. Clonidine reduced the amount of postoperative morphine by a mean of 4.45 mg (95% CI: 1.40–7.49 mg). There is a probability of 90% to obtain a decrease >2.3 mg but only 35% to obtain a decrease >5 mg. The incidence of hypotension was the only adverse event increased by clonidine (odds ratio 1.78; 95% CI: 1.02–3.12).

Conclusions. The addition of clonidine to intrathecal morphine extends the time to first analgesia and decreases the amount of morphine used. However, as the effects are small, and the results heavily influenced by a study in which intrathecal fentanyl was also given, this must be balanced with the increased frequency of hypotension.

Keywords: anaesthesia; spinal; analysis; meta-analysis; intrathecal clonidine; intrathecal morphine; pain, postoperative

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Intrathecal injection of morphine to provide postoperative analgesia during the initial 24 h after operation is a widely used technique. A simple search on US ClinicalTrials.gov for ‘Intrathecal morphine’ lists 25 studies either ongoing or recently completed or planned, showing the ongoing interest about this topic. Two recent meta-analyses summarize the profile of its analgesic effect. Another meta-analysis reviewed the effects of intrathecal clonidine used in order to enhance analgesia during and after surgery. Several recent studies have compared the analgesic effects of intrathecal morphine alone compared with a combination of morphine and clonidine. This meta-analysis compares two effects, the time to first postoperative analgesia request and the amount of opioid given during the initial 24 h, as measures of postoperative analgesia. The adverse effects reported are also analysed.

Methods
This meta-analysis considers the efficacy of intrathecal clonidine added to intrathecal morphine used as a one-shot administration before surgery and adheres to the recommendations of the Preferred Reporting Items for Systematic reviews and Meta-Analyses statement (PRISMA). As there is a lack of evidence for a dose–response to intrathecal morphine in both meta-analyses on the subject, all doses of intrathecal morphine were initially grouped in a single analysis.

Embase, Medline, Pubmed, Biosis, CAB Abstracts, Derwent Drug File, Current Content Search, and the Cochrane database were searched by one of the authors (E.E.), for controlled trials using the following search criteria: ('clonidine' [MeSH Terms] OR ‘clonidine’[All Fields]) AND ('pain'[MeSH Terms] OR ‘pain’[All Fields]) AND (surgery)[Subheading] OR 'surgery'[All Fields] OR 'surgical procedures, operative'[MeSH Terms]) OR ('surgical'[All Fields] AND 'procedures'[All Fields] AND ‘operative’[All Fields]) OR (operative surgical procedures'[All Fields] OR ‘surgery'[All Fields] OR ‘general surgery'[MeSH Terms]) OR (general[All Fields] AND surgery'[All Fields] OR ‘general surgery'[All Fields]) AND (humans'[MeSH Terms] AND Randomized Controlled Trial[ptyp] AND ‘adult’[MeSH Terms]). The last search was conducted in January...
2012. This resulted in 253 articles which were then screened manually for studies of the analgesic effects of clonidine in the perioperative period (Supplementary Fig. S1). Further screening identified those in which clonidine was given intrathecally and then those in which this was combined with intrathecal morphine. The references in the retrieved articles and the studies included in the three existing meta-analyses\(^1\) - \(^5\) were searched in order to detect any other studies.

The inclusion criteria were parallel-group randomized controlled trials enrolling only adults undergoing surgery under general anaesthesia who also received single-shot spinal analgesia before the start of surgery. Spinal analgesia in the control group consisted of morphine and the intervention group received the same dose of morphine along with clonidine.

Two endpoints for the efficacy of adding clonidine were considered, the time to first postoperative analgesic drug request (h), and the total morphine usage (mg) during the first 24 h after operation. Studies had to report at least one of the two endpoints for inclusion in the present meta-analysis. It was also pre-planned to analyse five specific adverse events: postoperative nausea or vomiting (PONV), postoperative sedation, respiratory depression, pruritus, and hypotensive events. We used the definition of these events as used by the authors of the included studies.

Five sensitivity analyses were performed. First, the effect of the dose of intrathecal morphine. Secondly, the effect of the local anaesthetic in the injected mixture. Thirdly, the influence of the studies in which statistically identical values of visual analogue scale (VAS) for pain were observed or not 24 h after surgery. This analysis stems from the analgesic requirement outcome measure only being valid when the active treatment and control groups achieved similar pain scores.\(^7\) \(^8\) The fourth sensitivity analysis was added as it became apparent that other analgesic drugs were given on the first 24 h after surgery. This analysis stems from the analgesic requirement outcome measure only being valid when the active treatment and control groups achieved similar pain scores.\(^7\) \(^8\) The effect sizes for efficacy for those receiving morphine only were compared with those receiving an additional analgesic drug. A fifth sensitivity analysis was added as all patients in one of the studies,\(^1\) with four study arms, received also 15 \(\mu\)g of intrathecal fentanyl. This study was compared with all the other studies to detect any influence of intrathecal fentanyl.

### Statistical analysis

The time to first postoperative analgesic drug was evaluated using the mean value and standard deviation (SD) of the time (h) for the active treatment and control groups. If the values were reported as median and an interquartile range or total range of values, the mean value was estimated using the median and the low and high end of the range for samples smaller than 25; for samples greater than 25, the median itself was used.\(^1\)\(^3\) The SD was estimated from the mean and the low and high end of the range for samples smaller than 15, as range/6 for samples from 15 to 70, and as range/4 for samples from 15 to 70, and as range/6 for samples more than 70.\(^1\)\(^3\) If only an inter-quartile range was available, SD was estimated as inter-quartile range/1.35.

The same methods were applied to the amount of morphine (mg) used during the first 24 h.

The incidence of adverse effects was expressed as the number of patients.

All meta-analysis computations, using Review Manager version 5.1.6 (The Cochrane Collaboration, 2011, The Nordic Cochrane Centre, Copenhagen), were performed using the inverse variance method and a random-effects model. A Forest plot was produced for each endpoint, showing a subgroup analysis for each different dose of clonidine, an overall result, and a comparison between the doses. The results for the adverse events were expressed as an odds ratio. Heterogeneity in the meta-analysis was assessed by the \(I^2\) and \(I^2\) statistics.

For all tests, statistical significance was defined as a two-sided \(P\)-value of < 0.05. The role of publication and selection bias was estimated by visual inspection of the funnel plot for asymmetry. In addition, the data were formally tested for publication bias using Egger’s regression approach.\(^1\)\(^4\) An Egger’s \(P\)-value of < 0.10 was considered to indicate significant asymmetry and therefore possible publication bias.

In order to express a direct statement about the probability of the magnitude of an effect, we used a Bayesian inference. This allows expressing the results as a probability distribution for the parameter of interest.\(^1\)\(^5\) For the time to first analgesia and the total morphine, the overall result of the classical meta-analysis was used to compute a posterior distribution that was then used to determine probabilities of specified effects.\(^1\)\(^5\) We used a non-informative prior distribution expressed as a normal distribution with a mean zero and an SD of 10 on the natural log scale. The posterior distribution was used to determine probabilities relating to specific effects after computation of the area under the curve of the normal distribution. To calculate these values, we used the @NORMAL function in Lotus 1-2-3 97 Edition for 3 min increments of time. This function approximates the cumulative distribution function to within \(\pm 7.5 \times 10^{-8}\). The results are presented as a probability graph.

### Results

Seven studies,\(^9\)\(^1\)\(^2\)\(^1\)\(^6\) - \(^1\)\(^8\) including 10 study arms, met the inclusion criteria. A total of 187 patients received intrathecal morphine alone and 316 received a mixture of morphine and clonidine. The author of one study\(^1\)\(^1\) provided additional data allowing inclusion in the meta-analysis. The median Jadad score\(^1\)\(^9\) was 5 (range 2–5) (Table 1). In four studies,\(^1\)\(^0\) - \(^1\)\(^2\)\(^1\) the injectate also contained bupivacaine 12.5–15 mg. The type of surgery, the doses of intrathecal morphine and clonidine, the amounts of intraoperative opioids, and the postoperative analgesic treatments are described in Table 1. The dose of intrathecal morphine ranged from 100 to 500 \(\mu\)g. In two studies,\(^9\)\(^1\)\(^7\) a dose of 4 \(\mu\)g kg\(^{-1}\) was used and this was interpreted as a dose of
Table 1 Description of the studies included in the meta-analysis

<table>
<thead>
<tr>
<th>Study Authors</th>
<th>Jadad score</th>
<th>Surgery (number of patients)</th>
<th>Dose of intrathecal morphine (µg)</th>
<th>Dose of intrathecal clonidine (µg)</th>
<th>Dose of intrathecal bupivacaine (mg)</th>
<th>I.V. opioids during surgery. Control group, mean (so)</th>
<th>I.V. opioids during surgery. Study group, mean (so)</th>
<th>Postoperative analgesic treatment</th>
<th>PONV prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andrieu et al.</td>
<td>2</td>
<td>Radical prostatectomy (morphine alone: 17, morphine + clonidine: 17)</td>
<td>4 µg kg⁻¹</td>
<td>1 µg kg⁻¹</td>
<td>0</td>
<td>Sufentanil (µg); 55 (5.8)</td>
<td>Sufentanil (µg); 40 (8.1)</td>
<td>Acetaminophen 1 g i.v. every 6 h. Morphine PCA (1 mg bolus; lockout interval 7 min)</td>
<td>None</td>
</tr>
<tr>
<td>Gehling et al.</td>
<td>5</td>
<td>Hip or knee replacement (morphine alone: 15, morphine + clonidine: 15)</td>
<td>100</td>
<td>50</td>
<td>15</td>
<td>None</td>
<td>None</td>
<td>Metamizol 1 g oral or i.v. every 4 h. Piratramide 1.5 mg i.v. prn followed by 7.5 to 15 mg s.c. prn with a maximal dose of 60 mg/day</td>
<td>None</td>
</tr>
<tr>
<td>Grace et al.</td>
<td>5</td>
<td>Total hip replacement (morphine alone: 30, morphine + clonidine: 30)</td>
<td>500</td>
<td>75</td>
<td>13.25</td>
<td>None</td>
<td>None</td>
<td>Morphine PCA (1 mg bolus; lockout interval 5 min)</td>
<td>Prochlorperazine 12.5 mg i.m.</td>
</tr>
<tr>
<td>Lena et al.</td>
<td>5</td>
<td>Coronary artery bypass grafting (morphine alone: 15, morphine + clonidine: 15)</td>
<td>4 µg kg⁻¹</td>
<td>1 µg kg⁻¹</td>
<td>0</td>
<td>Sufentanil (µg kg⁻¹); 2.9 (0.4)</td>
<td>Sufentanil (µg kg⁻¹); 2.1 (0.4)</td>
<td>Morphine PCA (1 mg bolus; lockout interval 7 min; maximal dose 30 mg in 4 h)</td>
<td>None</td>
</tr>
<tr>
<td>Nader et al.</td>
<td>2</td>
<td>Coronary artery bypass grafting (morphine alone: 40, morphine + clonidine: 45)</td>
<td>500</td>
<td>100</td>
<td>0</td>
<td>Fentanyl (µg); 1069 (102)</td>
<td>Fentanyl (µg); 870 (135)</td>
<td>Morphine i.v. prn</td>
<td>None</td>
</tr>
<tr>
<td>Paech et al.</td>
<td>5</td>
<td>Elective Caesarean delivery (morphine alone: 39, morphine + clonidine 30 µg: 41, morphine + clonidine 60 µg: 38, morphine + clonidine 90 µg: 38, morphine + clonidine 150 µg: 37)</td>
<td>100</td>
<td>30</td>
<td>12.5</td>
<td>Intrathecal fentanyl; 15 µg all patients</td>
<td>Intrathecal fentanyl; 15 µg all patients</td>
<td>Naproxen 500 mg per rectum at end of surgery, and twice daily orally thereafter. Morphine PCA (1 mg bolus; lockout interval 5 min)</td>
<td>None</td>
</tr>
<tr>
<td>Sites et al.</td>
<td>4</td>
<td>Total knee arthroplasty (morphine alone: 20, morphine + clonidine: 20)</td>
<td>250</td>
<td>25</td>
<td>15</td>
<td>None</td>
<td>None</td>
<td>Ketorolac 30 mg i.v. (if &lt; 55 yr of age) or 15 mg i.v. (if &gt; 55 yr of age) every 6 h. Morphine PCA (1 mg bolus; lockout interval 6 min)</td>
<td>None</td>
</tr>
</tbody>
</table>
around 300 μg morphine. The dose of clonidine ranged from 30 to 150 μg. This range was allocated to three clusters: low dose 25–30 μg, medium dose 50–75 μg, and high dose 90–150 μg. The two studies using a 1 μg kg⁻¹ dose were put in the 50–75 μg cluster.

The spines were done before the start of surgery in all studies, at the L3–L4 or L4–L5 interspace in four studies, L2–L3 or L3–L4 in one study, L1–L2 in one study, and between L2 and L5 in one study. Six studies used morphine for postoperative analgesia, and piritramide was used in one study. We considered that 1 mg piritramide was equivalent to 1 mg morphine.

Endpoints for efficacy

Time to first postoperative analgesia

Clonidine delayed the first analgesic requirement by 1.63 h [95% confidence interval (CI): 0.93–2.33] (Fig. 1). There was no statistical difference between the three groups of clonidine doses.

Postoperative morphine requirement

There was a mean decrease of 4.45 mg i.v. or subcutaneous morphine (95% CI: 1.4–7.49) in patients who received intrathecal clonidine when compared with only morphine (Fig. 1). Although there was no statistical difference between the clonidine doses, only the highest dose (90–150 μg) reached statistical significance.

There was significant heterogeneity for both endpoints for efficacy in the 50–75 μg cluster of studies (Fig. 1). For the higher doses (90–150 μg), there was consistent efficacy without heterogeneity for the two endpoints, and for the lower dose (25–30 μg), there was a homogenous lack of efficacy for the decrease in morphine requirement (Fig. 1).

There was a probability of 90% of an increase of at least 75 min in the time to first analgesia, but after that the probability decreased abruptly (Fig. 2). For postoperative morphine, there was 90% probability of a decrease of >2.3 mg but only a 35% probability of a decrease of >5 mg (Fig. 2). There was a possible dose–effect for clonidine as the probability of a decrease with the small dose (25–30 μg) was <40%, but the probabilities for a decrease of at least 1.5 mg with the 50–75 μg dose and of at least 4 mg with the 90–150 μg dose were 90%. These results are consistent with the absence of heterogeneity for the clusters with highest and lowest doses of clonidine.

Adverse effects

Data were reported for PONV in four studies for oversedation in three studies, for respiratory depression in four studies, and for pruritus in five studies. There was no statistically significant difference in the odds ratios between patients with or without clonidine for any of these effects (Supplementary Fig. S2). However, there was a statistically significant increase in the frequency of patients with hypotension in four studies with an odds ratio of 1.78 (1.02–3.12) (Supplementary Fig. S2).

Sensitivity analysis

There was no statistical difference ($\chi^2$=2.31, $P=0.32$) in the morphine-sparing effect of clonidine between the different doses of intrathecal morphine; for 100 μg of morphine, the sparing effect was $-0.95 \text{ mg} (-9.86$ to 7.97 mg), for 250–300 μg of morphine, $-14.95 \text{ mg} (-30.68$ to 0.77 mg), and 500 μg of morphine $-4.45 \text{ mg} (-6.31$ to 4.26 mg).

There was no statistical difference (-standard error) in the morphine-sparing effect of clonidine between the four studies using another analgesic supplementing morphine without bupivacaine in the spinal mixture [sparing effect $-0.65$ to 3.44] and the three studies without bupivacaine [sparing effect $-8.93$ mg ($-17.85$ to 0.00)].

One study had a VAS for pain that was statistically significantly lower 24 h after surgery. There was no difference between the groups in the six other studies. Excluding this study, the effect of clonidine was a reduction of 5.10 mg of morphine (0.67–9.54), compared with 4.45 mg when this study is included.

Sensitivity analysis

There was no statistical difference ($\chi^2$=0.25, $P=0.61$) in the morphine-sparing effect of clonidine between the four studies using another analgesic supplementing morphine [$-3.05 \text{ mg} (-9.63$ to 3.52)] and the three studies using only morphine [$-5.33 \text{ mg} (-11.30$ to 0.64)].

Intrathecal fentanyl

In one study, fentanyl was used in combination with intrathecal morphine. This produced a statistically significant increase in time to first postoperative analgesia with intrathecal clonidine [1.84 h (1.05 to 2.62 h), $P<0.00001$] and a statistically significant decrease in postoperative morphine requirement [$-5.8 \text{ mg} (-11.0$ to 0.5 mg), $P=0.03$]. Combining all the other studies together showed no statistically significant increase in time to first postoperative analgesia by intrathecal clonidine [0.78 h (0.79 to 2.36), $P=0.33$] and no statistically significant decrease in morphine consumption [$-3.8 \text{ mg} (-8.3$ to 0.7 mg), $P=0.10$].

The Egger’s regression did not favour any publication bias for either of the two endpoints for efficacy as the regression line did not significantly differ from zero (Supplementary Fig. S3).

Discussion

This meta-analysis shows that adding clonidine to intrathecal morphine enhanced postoperative analgesia. However, it is clear that the effect, as measured by time to first postoperative analgesia and morphine sparing, is small may be of limited clinical significance, especially as the use of clonidine was associated with increased risk of hypotension.

The analgesic effects of intrathecal morphine in our group of studies, when compared with patients without spinal
analgesia, are similar to those reported previously.\textsuperscript{3,4} Five studies\textsuperscript{9} 10 12 16 17 included in our meta-analysis also had a study arm with patients receiving no spinal analgesia. Their mean sparing effect of intrathecal morphine was 15.7 mg, which is similar to previous meta-analyses which found 16.9 mg for all surgery combined\textsuperscript{3} and 12 mg (95% CI: 5–18 mg) for studies which excluded patients undergoing general anaesthesia or Caesarean section.\textsuperscript{4}

In the meta-analysis\textsuperscript{5} of studies of intrathecal clonidine supplementation of local anaesthetics, there was a linear dose-dependent prolongation of the time, but no dose relationship with the time to first postoperative analgesic.\textsuperscript{3} The
The principal limitation of our meta-analysis is the limited number of studies for each type of surgery and for the various doses of intrathecal clonidine and morphine. This could be a problem as it appears that the sparing effects of intrathecal morphine on postoperative i.v. morphine is greater in abdominal surgery than in cardiac and thoracic surgery.5

The effect of type of surgery with intrathecal clonidine has not been explored.5 However, in our meta-analysis, during the cardiac surgery studies,17 18 the morphine-sparing effect was –16.8 mg (–44.9 to 11.4), and in the abdominal surgery studies,9 11 the morphine-sparing effect was –6.0 (–10.6 to –1.9). This is not statistically significantly different ($\chi^2=0.55, P=0.46$), and the 95% CI did not include zero only in the abdominal surgery studies, which may indicate an influence of type of surgery. However, the same arguments that have been applied to intrathecal morphine could be applied to clonidine, that it is the site of injection (lumbar in all studies including cardiac surgery) rather than the type of surgery or the dose, that is important. However, it is also notable that there was no supplementary analgesic effect of intrathecal clonidine in the three studies10 12 16 after hip or knee surgery. The additional time to first analgesic was 0.23 h (–4.42 to 4.87 h) and the difference in postoperative morphine consumption was 0.19 mg (–3.26 to 3.63 mg). This limitation can also be applied to the sensitivity analyses and the adverse effects, as in all these analyses only a limited number of studies contributed data.

A potential problem in our analysis is that one study11 in which all patients also received 15 µg of fentanyl intrathecally had a significant influence on our meta-analysis. If this study is excluded, there is no statistically significant effect resulting from the addition of intrathecal clonidine. A recent-meta analysis5 showed that the addition of intrathecal fentanyl to bupivacaine did not reduce postoperative opioid requirement in the first 24 h. The use of combination of morphine, fentanyl, and clonidine does appear to have a different effect than the combination of morphine and clonidine.

Two studies22 23 have investigated the effect of 323 or 5 µg kg$^{-1}$.22 clonidine given orally before operation, as adjunct to intrathecal morphine and local anaesthetic. One study used i.v. morphine PCA23 and the other i.m. pentazocine22 as postoperative analgesic drug after radical prostatectomy23 or abdominal hysterectomy.22 In terms of morphine-sparing effect, the reduction is equal to –0.60 (–1.08 to –0.11) (95% CI) which overlaps with our results [–0.98 (–1.67 to –0.28)] when expressed in the same units. Although the oral doses of clonidine were higher than the intrathecal dose, there was no increased incidence of hypotension or amounts of ephedrine in the oral clonidine group.

In conclusion, it appears that the addition of intrathecal clonidine to intrathecal morphine provides only very small clinical benefits in addition to those provided by intrathecal morphine alone, especially when balanced with the increased frequency of hypotension. These small effects are not robust as they are heavily influenced by the presence
of a single study in which patients also received intrathecal fentanyl.

Supplementary material
Supplementary material is available at British Journal of Anaesthesia online.

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