

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

E. Engelman* and C. Marsala

Department of Anaesthesia, CUB Hopital Erasme, Route de Lennik 808, 1070 Brussels, Belgium

* Corresponding author. E-mail: eengelma@ulb.ac.be, edgard.engelman@skynet.be

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

Accepted for publication: 29 July 2012

Intrathecal injection of morphine to provide postoperative analgesia during the initial 24 h after operation is a widely used technique.^{1–2} 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^{3–4} summarize the profile of its analgesic effect. Another meta-analysis⁵ 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 statement⁶ (PRISMA). As there is a lack of evidence for a dose–response to intrathecal morphine in both meta-analyses on the subject,^{3–4} 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^{3–5} 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 analgesia 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 a scheduled base, in one study each for paracetamol,⁹ metamizol,¹⁰ naproxen,¹¹ and ketorolac.¹² 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,¹¹ with four study arms, received also 15 µg 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 inter-quartile 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.¹³ The SD was estimated from the median and the low and high end of the range for samples smaller than 15, as range/4 for samples from 15 to 70, and as

range/6 for samples more than 70.¹³ 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 τ^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.¹⁴ 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.¹⁵ 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.¹⁵ 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,^{9–12 16–18} 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 study¹¹ provided additional data allowing inclusion in the meta-analysis. The median Jadad score¹⁹ was 5 (range 2–5) (Table 1). In four studies,^{10–12 16} 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 µg. In two studies,^{9 17} a dose of 4 µg kg⁻¹ was used and this was interpreted as a dose of

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