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Abstract

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Combination of a reduced dose of an intrathecal local anesthetic with a small dose of an opioid: A meta-analysis of randomized trials

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ABSTRACT

We tested whether the combination of a reduced dose of a local anesthetic (LA) with an opioid compared with a standard dose of the same LA alone guaranteed adequate intraoperative anesthesia and postoperative analgesia and decreased LA-related adverse effects. We systematically searched (to November 2012) for randomized comparisons of combinations of a reduced dose of an LA with a concomitant opioid (experimental) with a standard dose of the LA alone (control) in adults undergoing surgery with single-injection intrathecal anesthesia without general anesthesia. We included 28 trials (1393 patients). In experimental groups, the median decrease in LA doses was 40% (range, 12%–70%). There was no difference between experimental and control groups in the need for intraoperative opioids or general anesthesia for failed block or in the duration of postoperative analgesia. With experimental interventions, there was evidence of a reduction in the duration of motor blockade postoperatively (average, 50 minutes), time to discharge from hospital or PACU (33 minutes), time to ambulation (28 minutes), and time to urination (14 minutes). There was also evidence of a decrease in the risk of shivering (risk ratio [RR]: 0.26; 95% confidence interval [CI]: 0.12–0.56), nausea (RR: 0.45; 95% CI: 0.31–0.66), and arterial hypotension (RR: 0.52; 95% CI: 0.35–0.78). The risk of pruritus was increased (RR: 11.7; 95% CI: 6.2–21.9). Adding an opioid to a reduced dose of an intrathecal LA can decrease LA-related adverse effects and improve recovery from the spinal block without compromising intraoperative anesthesia or duration of postoperative analgesia.

1. Introduction

Intrathecal anesthesia with a local anesthetic (LA) is frequently used for ambulatory surgery [28]. Advantages include short recovery time, reduced postoperative pain scores, and less need for analgesics in the recovery room [33]. However, intrathecal anesthesia has also important limitations (eg, prolonged motor block, arterial hypotension, disturbed proprioception, urinary retention). These adverse effects may interfere with early mobilization of patients and increase the risk of a prolonged stay in the postanesthetic care unit (PACU) or even of unplanned admission after ambulatory surgery.

Motor block, arterial hypotension, and urinary retention are all due to the intrathecal LA and are likely to be dose dependent [2]. There is, therefore, an argument to decrease the dose of the LA and to administer minimal effective doses only. However, there may then be an increased risk of inappropriately short analgesia, or even block failure, with the subsequent need for general anesthesia.

Opioids are often used as adjuvants for intrathecal LA. As long as the dose of the LA is not reduced, it may be expected that with the addition of a small dose of an opioid, postoperative analgesia will be prolonged by several hours, depending on the opioid used, and also that postoperative analgesic consumption and pain intensity will be reduced [19,40]. However, it remains unclear to what extent the dose of the intrathecal LA may be reduced when a opioid is added and whether that reduction eventually leads to a decrease in the incidence of the typical, LA-related adverse effects (eg, arterial hypotension, muscle weakness) without jeopardizing the success of the spinal anesthesia. Our meta-analysis was designed to address these questions.
2. Methods

We followed the PRISMA recommendations for the reporting of this systematic review [36]. Our working hypothesis was that the combination of a small dose of an opioid with a reduced dose of an intrathecal LA was useful only if, compared with a standard dose of the same LA alone, three criteria were fulfilled. First, intraoperative analgesia was still adequate to perform surgery (ie, no increase in the risk of failures). Second, postoperative analgesia was not jeopardized (ie, no shortening of the duration of analgesia). Third, LA-related effects that prevented early postoperative mobilization (eg, motor block, arterial hypotension, urinary retention) were significantly reduced.

2.1. Protocol and registration

The protocol for this meta-analysis is not registered but is available on request from the authors.

2.2. Eligibility criteria

We included full reports of randomized, controlled trials comparing a combination of a reduced dose of a LA with a concomitantly administered opioid (experimental intervention) with a standard dose of the same intrathecal LA (control intervention). Only studies in adults (18 years of age and older) undergoing surgical procedures with single-injection intrathecal anesthesia without a general anesthetic or an additional regional anesthesia were included. For eligibility, studies had to report on any outcome that enabled us to test our working hypothesis. Continuous intrathecal or combined spinal-epidural anesthesia techniques were not considered. If additional drugs were given intrathecally (eg, epinephrine), a trial was considered for analysis only if both experimental and control groups received the same dose of the adjuvant (ie, the trial was strictly controlled).

2.3. Information sources and search

Databases (MEDLINE, CENTRAL, EMBASE, BIOSIS, CINAHL) were searched using high-sensitivity and low-specificity search strategies. Key words (eg, spinal, intrathecal, analgesia) were combined using the Boolean meanings of “and” and “or” (Appendix A, Supplemental Data 1). The last electronic search was in November 2012. Bibliographies of retrieved articles were searched for additional references. No language restriction was used.

2.4. Study selection

Retrieved articles were reviewed for inclusion by one author (D.M.P.). Criteria for inclusion were checked by another author (M.W.). Queries were resolved through discussion with two additional authors (N.E., M.R.T.).

2.5. Data collection process

One author (D.M.P.) extracted all relevant information from original reports. Another author checked all extracted data (M.W.). Discrepancies were resolved through discussion with two additional authors (N.E., M.R.T.).

When continuous data were not reported as means with SDs, we contacted the authors of the original trials and asked them to provide the necessary data. If this was unsuccessful, we computed the data whenever feasible, as previously proposed [10,23].

2.6. Data items

We extracted information on study characteristics (year of publication, type and duration of surgery, regimens of LA and opioids, number of randomized patients). We extracted any continuous or dichotomous data that enabled us to test our working hypothesis. We also extracted data on the length of stay in the PACU or the hospital. Finally, we extracted data on adverse effects that were potentially related to the opioids (nausea, vomiting, pruritus, respiratory depression).

2.7. Risk of bias in individual studies

Quality of data reporting was assessed by one author (D.M.P.) and was checked by another author (M.W.), using a modified 4-item, 7-point Oxford scale taking into account the method of randomization, concealment of treatment allocation, degree of blinding, and reporting of dropouts, as previously described [17]. To overcome random play of chance on the estimation of treatment effects, we excluded studies with <10 participants per group [31,37]. Subgroup analyses comparing low-quality studies (quality score below the median of all scores of all trials) and high-quality studies (quality score equal to or above the median) were performed for all outcomes.

2.8. Analyses

As with previous similar analyses, there was an arbitrary decision that meta-analyses would be performed only when data could be combined from at least 5 trials or at least 100 patients [16,40].

For dichotomous data, we calculated the risk ratios (RR) with 95% confidence interval (CI). When the 95% CI around the RR did not include 1, results were considered statistically significant. To estimate the clinical relevance of beneficial or harmful effects, we additionally computed, for results that were statistically significant, the number needed to treat/harm (NNT/NNH) with 95% CI. For continuous data, weighted mean difference (WMD) with 95% CI was calculated.

Because the impact of adding an opioid to a reduced dose of an intrathecal LA may differ according to different surgical settings, we used a random-effects model throughout.

Analyses were performed using the computer program RevMan version 5.0.25 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark); Microsoft Excel version 14.1.0 for Mac (Microsoft, Redmond, WA, USA); and STATA version 11 (StataCorp, College Station, TX, USA).

3. Results

3.1. Selection of trials

We retrieved 247 potentially relevant trials (Fig. 1). Of those, 28 randomized, controlled trials met all inclusion criteria and underwent further analyses.

3.2. Trial characteristics

Trials were published between 1992 and 2012 and included data on 1393 patients, 733 of whom received intrathecal opioids (Table 1) [1,3–8,11–14,22,24–27,29,30,32,34,35,38,39,42–46]. The median group size was 20 patients (range, 10–60 patients).

We contacted 9 authors and asked for additional data; 2 responded and their data could be included in our analysis [4,30]. The local anesthetics used were bupivacaine 4 to 20 mg (19 trials), lidocaine 50 and 75 mg (3 trials), ropivacaine 10 and 15 mg (2 trials), and tetracaine 8 mg, mepivacaine 45 mg, and...
levobupivacaine 13 mg (1 trial each). The added opioids were fentanyl 10 to 25 μg (23 trials), sufentanil 2.5 to 10 μg (3 trials), and meperidine 22 to 30 mg (2 trials) (Table 1).

The median of all mean reductions in the doses of the LAs in experimental groups compared with control groups was 40% (range, 12%–70%).

In 11 reports (39%), the principal aim of the study was to test whether equal analgesic efficacy but fewer adverse effects could be achieved with the combination of a small dose of an opioid with a reduced dose of an LA [4,5,7,12,24,34,38,39,42,43,46]. In the other 17 reports, there was a large variety of working hypotheses: different analgesic efficacy and different risks of adverse effects.
with experimental interventions [1,3,8,11,12,24,26,32,44]; improved analgesia and fewer adverse effects [13,25]; improved analgesia and equal risk of adverse effects [30]; equal analgesia and equal risk of adverse effects [22]; fewer adverse effects with no statement about analgesic efficacy [27,35]; and improved analgesia and potentially increased risk of adverse effects [22,35].

Selection of the LA dose in controls was based on literature findings in 6 reports [7,12,26,38,43,45], on previous personal findings in 2 [24,29], but unclear in the remaining 18 (64%).

The median quality score was 3 (range, 1–7); 8 trials (29%) had a score <3 and were considered low quality. Twenty-two trials (81%) had a double-blind design; randomization was adequately described in 12 (44%), and concealment of treatment allocation was reported in 10 (37%). None described transparently the follow-up of all randomized patients.

### 3.3. Challenge of working hypothesis

Five endpoints enabled us to test our working hypothesis: risk of block failure, duration of postoperative analgesia, and the risk of relevant LA-related adverse effects (arterial hypotension, motor block, urinary retention).

#### 3.3.1. Risk of block failure

Fourteen trials (662 patients) reported failed blocks defined as the need for supplementary intraoperative systemic opioids [5,6,11,12,22,24,25,29,30,34,39,43–45]. In controls, 8.2% of patients needed supplementary analgesia, with experimental interventions in 5.4%. That difference was not statistically significant (RR: 0.67; 95% CI: 0.37–1.22) (Fig. 2; Appendix A, Supplemental Data 2).

Eleven trials (550 patients) reported failed blocks defined as the need for a general anesthetic [6,11,13,22,24,29,34,42–44,46]. In controls, 2.2% of patients needed a general anesthetic, with experimental interventions in 2.5%. That difference was not statistically significant (RR: 1.07; 95% CI: 0.39–2.94) (Fig. 2; Appendix A, Supplemental Data 3).

#### 3.3.2. Duration of postoperative analgesia

Seven trials (274 patients) reported the duration of postoperative analgesia, defined as the time from the end of surgery until total recovery of motor function of the lower extremities (ie, Bromage scale score of 0) [3,4,8,11,12,14,24,26,30,43,46]. In controls, 81% had a double-blind design; randomization was adequately described in 12 (44%), and concealment of treatment allocation was reported in 10 (37%). None described transparently the follow-up of all randomized patients.

#### 3.3.3. Arterial hypotension

Twenty-three trials (1075 patients) reported the presence or absence of perioperative arterial hypotension defined as systolic blood pressure <90 to 100 mmHg or a 20% to 30% reduction in systolic blood pressure compared with baseline [1,3–8,11–14,23–27,29,30,32,34,39,43,46]. In controls, 33% of patients had at least 1 episode of hypotension, with experimental interventions in 16%. That reduction was statistically significant (RR: 0.52; 95% CI: 0.35–0.78; NNT = 7, 95% CI: 4.6–8.6) (Fig. 2; Appendix A, Supplemental Data 5).

#### 3.3.4. Duration of motor block

Eleven trials (470 patients) reported the duration of motor block postoperatively, defined as the time from the end of surgery until total recovery of motor function of the lower extremities (ie, Bromage scale score of 0) [3,4,8,11,12,14,24,26,30,43,46]. In controls, the median of mean durations of motor block was 136 minutes (range, 51–291 minutes). With experimental interventions, that duration was significantly reduced (WMD: −30 min; 95% CI: −62 to −38) (Fig. 3; Appendix A, Supplemental Data 6).

#### 3.3.5. Urinary retention

Four trials (231 patients) reported the risk of postoperative urinary retention [4,29,38,45]. In controls, 3.5% of patients had urinary retention, with experimental interventions in 4.2%. That difference was not statistically significant (RR: 1.00; 95% CI: 0.27–3.69) (Fig. 2; Appendix A, supplemental data 7).

Six trials (387 patients) reported the time to first postoperative urination defined as the time from intrathecal injection until first urination [6,8,22,24,29,38]. In controls, the median of mean times to urination was 207 minutes (range, 154–318 minutes). With experimental interventions, the time to urination was borderline significantly reduced (WMD: −13 minutes; 95% CI: −27 to 1) (Fig. 3; Appendix A, Supplemental Data 8).

### 3.4. Further dichotomous endpoints

With experimental interventions, there was a statistically significant reduction in the risk of shivering (NNT = 6; 95% CI: 3.8–8.3) (Fig. 2; Appendix A, Supplemental Data 9) [3,11,12,14,25,26,30,32] and nausea (NNT = 9; 95% CI: 5.6–15) (Fig. 2; Appendix A, Supplemental Data 10).
There was no significant difference between groups in the risk of bradycardia (defined as a heart rate <45–50 min⁻¹ or the need for atropine) (Fig. 2; Appendix A, Supplemental Data 11) [4,7,8,13,14,24,26,29,30,38] and vomiting (Fig. 2; Appendix A, Supplemental Data 12) [3–5,11,12,14,22,24–27,29,30,32,34,38,43,45].

With experimental interventions, there was a statistically significant increase in the risk of pruritus (NNH = 3; 95% CI: 2.8–3.8) [Figs. 2 and 4] [1,3,4,7,13,14,22,24–27,29,30,32,34,38,43–45].

In 7 trials (270 patients), the authors searched for symptoms of respiratory depression defined as a respiratory rate <8 min⁻¹ or an Sao₂ <85%–90% [1,7,13,14,26,30,34]. No case of respiratory depression was reported.

Several trials reported on the incidence of post–dural puncture headache [6,8,11,22,29,30,38,43,45,46], or transient neurological symptoms [6,29,30,38]. There was no evidence of any difference in these outcomes between control and experimental interventions.

Sedation and backache were reported in <5 trials or 100 patients and were not further analyzed.

### 3.5. Further continuous endpoints

With experimental interventions, there was a statistically significant shortening of the duration of PACU or hospital stay (defined as the time from the end of surgery until transfer to the ward or discharge home) (Figs. 3 and 5) [6,22,29,30,38,43,45,46], time to first ambulation (defined as the time from end of surgery until first walk) (Fig. 3; Appendix A, Supplemental Data 13) [8,22,24,29,38,45,46], and duration of sensory block measured by pin prick (Fig. 3; Appendix A, Supplemental Data 14) [6,8,11,12,14,22,25,26,30,35,38,43,46].

Additional continuous endpoints were onset of motor block, onset of sensory block, duration of sensory block, time to maximal motor block, time to maximal sensory block, and time to 2-segment regression. We regarded none of these as important for clinical decision making and therefore did not analyze them further.

### 4. Discussion

#### 4.1. Main results

Adding a small dose of an opioid to a reduced dose of an intrathecal LA significantly reduces the risk of LA-related adverse effects and simultaneously allows analgesic efficacy to be maintained compared with a standard dose of the same LA. Thus, we were able to confirm our working hypothesis. With the combination regimens, the duration of postoperative motor blockade was shortened by 50 minutes. Time to ambulation, to discharge from the PACU or from the hospital, and duration of sensory block was reduced by ~30 minutes, and time to urination by ~15 minutes. Additionally, the risk of shivering, arterial hypotension, and nausea was significantly reduced. Conversely, there was no evidence of an increased risk of analgesic failure; the number of patients who needed systemic analgesia or a general anesthetic intraoperatively, and the time to first analgesic request postoperatively were not different between interventions. Finally, there was a lack of evidence of an increase in the risk of respiratory depression, transient neurological symptoms, or post–dural puncture headache with combination regimens.

The only disadvantage of the combination regimens was the increased risk of pruritus. This outcome was not unexpected, and it is well established that the risk of pruritus depends on the opioid administered intrathecally [40]. In these trials, the most frequently used opioid was fentanyl.

#### 4.2. Clinical relevance

Intrathecal anesthesia with local anesthetics has become a popular technique for ambulatory surgery [15]. However, compared with patients undergoing surgery with a general anesthetic, duration of stay in the recovery room or total hospital stay is not necessarily decreased in patients receiving intrathecal anesthesia [18]. This is mainly due to prolonged motor and sensory blocks after the administration of an LA intrathecally. Therefore, our findings are of clinical relevance because they suggest that motor and sensory block can be effectively reduced by decreasing the LA dose. Currently, there is a lack of data on optimal intrathecal drug regimens [28]. This systematic review confirms this dilemma as, for example, the doses of bupivacaine varied from 4 to 20 mg, and the reason for this large variability remained unclear. Also, there is not one major endpoint that defines an optimal regimen in this context; it is more of a combination of favorable endpoints. Even some decrease in the risk of nausea may be important because this adverse effect remains a leading cause for unexpected hospital admissions after ambulatory surgery [21]. The higher incidence of nausea in controls receiving an intrathecal LA alone may be explained by the higher incidence of LA-related hypotension in this group. Our analyses suggest that several endpoints are favored by reducing the dose of...
the LA by adding an opioid; this further strengthens the clinical relevance of our findings. Only a limited number of adverse effects were reported in these trials. Respiratory depression was sought in some trials but was never reported. This potentially serious opioid-related adverse effect must not be ignored [40].

4.3. Limitations

First, although we performed exhaustive literature searches, we cannot exclude that we missed relevant trials. We did not search for unpublished data. Second, a large variety of intrathecal LA regimens were studied in patients undergoing different surgical interventions. The opioids were fentanyl, sufentanil, and meperidine. Others have added hydromorphone to intrathecal bupivacaine [20,32]. Nevertheless, the majority of the trials tested bupivacaine-fentanyl combinations. Also, bupivacaine, levo-bupivacaine, and ropivacaine have clinically similar effects [41]. Third, most of the trials were of limited size. Small trials may report on results by random chance, and, due to publication bias, the published trials are likely to overestimate the beneficial effects of an intervention, and this should be kept in mind when interpreting our findings. Fourth, the trials reported on a large variety of endpoints. Not all were clearly defined; this may cause problems when pooling data across studies. Also, the clinical relevance of some endpoints remained unclear (eg, onset of motor block, time to 2-segment regression). Finally, the rationale behind most studies was obscure. Often it remained unclear what the primary aim of the studies was.
and why and how the authors had chosen a dose of an intrathecal LA or an opioid. For instance, the large variability in the doses of intrathecal bupivacaine suggested that authors were choosing an intrathecal LA regimen according to the type of surgery. However, we were unable to establish a relationship between the dose of bupivacaine that was used in controls and, for example, the mean duration of surgery. It seemed that LA doses were chosen without any clear rationale. Also, mean reductions in the doses of the LA ranged from as little as 12% to as much as 70% and for no apparent reasons. It has been shown that sex may have a clinically relevant effect on the potency of intrathecal bupivacaine [9]. A systematic research program could not be identified; this is a major limitation of many investigator-driven studies.

4.4. Research agenda

Many questions remain unanswered; they may inform the research agenda. For instance, minimal effective doses of the LA and the opioids are still unknown. Also, even though the most frequently tested combination in these trials was bupivacaine with fentanyl, it remains unknown what the best drug combination actually is. Furthermore, adjuvants other than opioids may be used to try to decrease the dose of the LA (eg, agonists such as clonidine). Finally, the combination of several adjuvants (eg, fentanyl, clonidine) may allow the dose of the intrathecal LA to be further decreased.

4.5. Conclusions

The combination of a small dose of an opioid with a reduced dose of an intrathecal LA is useful in clinical practice because, compared with a standard dose of the same LA alone, intraoperative anesthesia is still adequate to perform surgery (ie, there is no increase in the risk of failures), postoperative analgesia is not compromised (ie, there is no shortening of the time to first rescue analgesia), and LA-related effects that prevent early postoperative mobilization (eg, motor block, arterial hypotension, urinary retention) are reduced. Perhaps most importantly, patients treated with an intrathecal combination regimen are staying for a shorter time in the PACU or the hospital. Thus, intrathecal regimens combining a reduced dose of an intrathecal LA with a small dose of an opioid should be routine practice in patients undergoing ambulatory surgery.

Conflict of interest statement

The authors declare that they have no conflict of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.pain.2013.04.023, and on the authors’ webpage, at http://anesthesiologe.hug.ge.ch/data.htm.

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