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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.

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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 anesthesia 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