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Review Article

REVIEW ARTICLE

Co-administration of dexamethasone with peripheral nerve block: intravenous *vs* perineural application: systematic review, meta-analysis, meta-regression and trial-sequential analysis

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Abstract

Background: I.V. and perineural dexamethasone have both been found to prolong loco-regional analgesia compared with controls without dexamethasone. It is unclear whether perineural administration offers advantages when compared with i.v. dexamethasone.

Methods: A systematic literature search was performed to identify randomized controlled double-blind trials that compared i.v. with perineural dexamethasone in patients undergoing surgery. Using the random effects model, risk ratio (for binary variables), weighted mean difference (for continuous variables) and 95% confidence intervals were calculated. We applied trial sequential analysis to assess the risks of type I and II error, meta-regression for the study of the dose-responsive relationship, and the Grading of Recommendations Assessment, Development, and Evaluation system.

Results: We identified 10 randomized controlled double-blind trials (783 patients). When using conventional meta-analysis of nine low risk of bias trials, we found a statistically significantly longer duration of analgesia, our primary outcome with perineural dexamethasone (241 min, 95%CI, 87, 394 min). When trial sequential analysis was applied, this result was confirmed. Meta-regression did not show a dose-response relationship. Despite the precision in the results, using the Grading of Recommendations Assessment, Development, and Evaluation system (GRADE), we assessed the quality of the evidence for our primary outcome as low.

Conclusions: There is evidence that perineural dexamethasone prolongs the duration of analgesia compared with i.v. dexamethasone. Using GRADE, this evidence is low quality.

Key words: anaesthesia; dexamethasone; meta-analysis; review; systematic

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There is on-going research to improve strategies of analgesia after surgery. Postoperative pain, in addition to being an unpleasant experience, negatively affects postoperative recovery, can prevent early hospital discharge, and can increase the risk of postoperative complications and the development of chronic pain.[1] Despite progress in pain management, a recent study including more than 115,000 patients showed that the prevalence of severe postoperative pain on the first day after surgery is still high, even after minor surgery.[2] Regional anaesthesia can provide effective pain relief and methods that prolong its effect have obvious appeal.

Dexamethasone has been evaluated as an adjunct to regional anaesthesia compared with placebo.[3] Authors of one meta-analysis concluded that perineurally administered dexamethasone does prolong analgesia[4] and authors of another[5] suggested it is associated with a faster onset of analgesia, sensory and motor block. In studies focusing on brachial plexus blocks, it has been suggested that perineural dexamethasone can prolong the duration of analgesia and of motor block.[6]

I.V. dexamethasone has also been shown to reduce pain at rest and with movement and opioid consumption after surgery[7] when compared with placebo. To date, it is unclear whether the perineural administration confers advantages over the i.v. administration of this drug. One study found a longer duration of analgesia with i.v. dexamethasone compared with the perineural route[8] while another study[9] came to the opposite conclusion. With the present systematic review, we sought to integrate all the data assessing i.v. compared with perineural dexamethasone administration and its effect on postoperative pain outcomes in patients undergoing surgery under regional or combined regional and general anaesthesia. As there were several studies addressing this question in the public domain, with heterogeneous results, we aimed to conduct a systematic review with a meta-analysis and interpretation that included a thorough assessment of the certainty of the results. We added to the existing knowledge by using a conservative approach to meta-analysis, using a random effects model to account for between-studies heterogeneity and focusing on trials with low risk of bias. By including trial sequential analysis, we include consideration of the required information size for the clinical question that we pose and a more accurate estimate of the risk of random error in the current evidence.

Methods

Our systematic review was registered with PROSPERO, the international prospective register of systematic reviews of the National Institute for Health Research (www.crd.york.ac.uk/PROSPERO/#index.php, registration number CRD42016036798). The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[10] were followed.

Literature search

We performed a systematic electronic literature search in the databases Medline, Epub, Embase.com (Embase plus Medline), Cochrane Central, Web of Science, and Google Scholar on August 4, 2016 in order to identify trials that compared perineural with i.v. dexamethasone in patients receiving regional anaesthesia. The exact search strategies for the different databases are in Appendix 1.

The program endnote was used to manage the studies identified by the search. After removing duplicate citations, two authors (M.H., M.K.) independently screened the search results for eligible trials. In addition, we searched a clinical trials registry, www.clinicaltrials.gov.

Inclusion and exclusion criteria

We defined inclusion and exclusion criteria *a* priori.

For inclusion, studies had to have the following characteristics (specified according to the PICO acronym):

Patients: adults undergoing surgery under regional anaesthesia alone or combined with a general anaesthesia;

Intervention: addition of dexamethasone to local anaesthetic for perioperative analgesia (perineural dexamethasone group);

Comparator: i.v. dexamethasone (i.v. dexamethasone group);

Outcomes: Primary outcome - duration of analgesia.

Secondary outcomes - duration of sensory block, duration of motor block, onset time of block, pain after surgery, use of peripheral analgesics, opioid consumption, patient satisfaction, all adverse events reported in the trials.

Exclusion criteria were: patient age under 18 yr, studies without randomization.

Data extraction and data collection

Data were extracted by two authors (M.H., M.K.) from the reports that were considered eligible.

We report the primary outcome of each study included into our meta-analysis. The primary outcome was the outcome explicitly mentioned as primary in the text or the variable for which a sample size calculation was done or the variable that was first reported in the results section of the study.

If two or more groups using perineural dexamethasone were studied, these data were combined for meta-analysis. The same was planned for studies applying more than one i.v. dexamethasone dose. Combining dichotomous data was by simple addition; for the combination of continuous data we used the formula published in the Cochrane handbook.[11] We contacted authors of eligible studies to obtain missing original data.

Postoperative consumption of morphine equivalents was calculated from other opioids using the website: http://opioidcalculator.practicalpainmanagement.com/conversion.php. This site does not include piritramide and in case of this opioid, we assumed a relative potency of 0.7 compared with morphine.[12]

Assessment of risks of bias

We used the Cochrane Risk of Bias tool[13] to analyse the methodological quality of the studies; this analysis was done by two authors independently (M.H., M.K.). This tool allows for an assessment of the risks of selection bias (random sequence generation, allocation concealment), performance bias (blinding of participant and personnel), detection bias (blinding of assessor), and attrition bias. When it was unclear if a domain was satisfactory, we contacted the first author of the trial to try to clarify the methodology. In case of disagreement between the two authors (M.H., M.K.), we planned to consult a third author (S.H.) to resolve the disagreement. We considered a trial to be at low risk of bias when there was adequate random sequence generation, adequate allocation concealment and outcome assessment was adequately blinded.