Original Article

Efficacy of epidural local anesthetic and dexamethasone in providing postoperative analgesia: A meta-analysis

ABSTRACT

Background: Dexamethasone is a potent anti-inflammatory, analgesic, and antiemetic drug. Individual randomized controlled trials found a possible benefit of epidural dexamethasone. The purpose of this meta-analysis is to estimate the benefit of epidural dexamethasone on postoperative pain and opioid consumption and to formulate a recommendation for evidence-based practice.

Materials and Methods: Prospective, randomized controlled trials comparing the analgesic efficacy of epidural local anesthetic and dexamethasone combination, with local anesthetic alone for postoperative pain management after abdominal surgery, were planned to be included in this meta-analysis. PubMed, PubMed Central, Scopus, and Central Register of Clinical Trials of the Cochrane Collaboration (CENTRAL) databases were searched for eligible controlled trials using the following search words: "Epidural," "dexamethasone," and "postoperative pain," until February 20, 2015.

Results: Data from five randomized control trials have been included in this meta-analysis. Epidural dexamethasone significantly decreased postoperative morphine consumption (mean difference −7.89 mg; 95% confidence interval [CI]: −11.66 to −3.71) and number of patients required postoperative rescue analgesic boluses (risk ratio: 0.51; 95% CI: 0.41–0.63).

Conclusion: The present data shows that the addition of dexamethasone to local anesthetic in epidural is beneficial for postoperative pain management.

Key words: Dexamethasone; epidural; opioid consumption; postoperative pain

Introduction

Since its discovery in the 1940s, dexamethasone, a selective glucocorticoid agonist with strong anti-inflammatory properties, has been used in the treatment of variety of conditions such as rheumatoid arthritis, allergic disorders, bronchial asthma, inflammatory bowel disease, autoimmune disorders, and certain malignancies.[1] Its role as a drug for postoperative nausea and vomiting (PONV) prophylaxis is well-established in literature.[2-4] Apart from PONV prophylaxis, dexamethasone is being used in the perioperative settings to reduce the cerebral[5] and airway edema.[6] Recently, the analgesic efficacy of this drug has been the topic of intense scientific research. Epidural injection of steroids remains one of the most effective treatments for chronic pain conditions such as lumbosacral radiculopathy, sciatic, and femoral neuralgias.[7] Administration of dexamethasone preoperatively by oral[8,9] or intravenous route[10,11] has been shown to provide postoperative analgesia. Several studies have analyzed the analgesic efficacy of epidural

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dexamethasone. However, randomized control trials (RCTs) are not unanimous in reporting the postoperative analgesic efficacy of epidural dexamethasone. This meta-analysis was done to assess whether epidural dexamethasone is a good adjunct to local anesthetic for postoperative analgesia.

Materials and Methods

The reporting of this systematic review and meta-analysis follows the PRISMA recommendations.[12]

Protocol and registration

A protocol for this systematic review and meta-analysis has not been registered.

Eligibility criteria

Prospective, randomized controlled trials comparing the analgesic efficacy of epidural local anesthetic and dexamethasone combination, with local anesthetic alone for postoperative pain management after abdominal surgery, were planned to be included in this meta-analysis. RCTs reporting at least postoperative opioid consumption was included in this analysis. We did not impose any language restriction and seek for unpublished trials or data those are not reported in published studies.

Information sources and search method

Two authors (BJS and SM) independently searched PubMed, PubMed Central, Scopus, Central Register of Clinical Trials of the Cochrane Collaboration (CENTRAL), and Google Scholar for eligible controlled trials using following search words: "Epidural," "dexamethasone," and "postoperative pain," until February 20, 2015. The detailed search strategy in PubMed is described in Appendix 1. No non-English database was searched. A manual search was done in the reference lists of the resulting list of publications for any relevant trials.

Study selection

Two authors (BJS and PK) independently searched for the potentially eligible trials and selected the trials to be included. It was decided that, if any disagreement arises between these two authors, would be settled by a third author (DKB).

Exclusion criteria

Prospective observational studies, retrospective analysis, trials conducted in pediatric populations, case reports, case series, animal studies, and studies not reporting on any one of the predefined outcome were excluded from the analysis. However, in any study that fulfills our inclusion criteria, if any possibilities of biases are found, a sensitivity analysis was planned to be done for each outcome excluding that study.

Data collection

We collected the required data from the full-text of the trials. Initially, all data were tabulated in Microsoft Excel™ spreadsheet. One author (BJS) initially extracted data from the eligible trials, and these data were cross-checked independently by another author (PK). Statistical analyses were done by two authors (SM and BJS) independently and cross-validated.

Data items

The following data were collected from each of their studies: Name of the first author, year of publication, patient population, surgical procedure done, details of epidural anesthesia, postoperative epidural analgesic protocol, anesthetic technique and use of rescue analgesic postoperative opioid consumption, postoperative pain scores at different time points, postoperative opioid-related adverse effects, and any other reported complications. All opioid usage was converted into the equianalgesic doses of intravenous morphine for making the comparison easier.[13] If two or more studies reported the endpoint of interest, meta-analysis was done.

Risk of bias assessment

Quality of eligible trials was assessed using the tool of "risk of biases" according to Review Manager, version 5.2.3 software (RevMan; Cochrane Collaboration, Oxford, UK) and also by Jadad scoring system.[14] Random sequence generation, allocation concealment, blinding, incomplete data, and selective reporting were assessed independently by two authors (DKB and PK) based on the method of the trials, each was graded as "yes," "no," or "unclear," which reflected a high risk of bias, low risk of bias, and uncertain bias, respectively, as per Cochrane methodology. Publication bias was assessed by visual inspection of funnel plot.

Statistical analysis

Meta-analyses were performed using RevMan (version 5.3.5.

Appendix 1

Epidural (All Fields) AND ("dexamethasone" [MeSH Terms] OR "dexamethasone" [All Fields]).

Epidural (All Fields) AND ("dexamethasone" [MeSH Terms] OR "dexamethasone" [All Fields]) AND ("postoperative period" [MeSH Terms] OR ("postoperative" [All Fields] AND "period" [All Fields]) OR "postoperative period" [All Fields] OR "postoperative" [All Fields]).

Epidural (All Fields) AND ("dexamethasone" [MeSH Terms] OR "dexamethasone" [All Fields]) AND ("pain, postoperative" [MeSH Terms] OR ("pain" [All Fields] AND "postoperative" [All Fields]) OR "postoperative pain" [All Fields] OR ("postoperative" [All Fields] AND "pain"[All Fields])).

Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). For continuous outcomes, a pooled mean difference (MD) was calculated using the inverse variance statistical method, as all studies have used the same unit. For dichotomous variables, pooled risk ratio (RR) was calculated using the Mantel-Haenszel method, as the number of included studies was small. The I^2 was used to evaluate heterogeneity of included studies. In case of significant heterogeneity ($I^2 > 40\%$), random analysis model was used, and in other cases, fixed analysis model was used. All statistical variables were calculated with 95% confidence interval (95% CI). A two-sided $P < 0.05$ was considered significant.

Results

Five trials met the eligibility criteria after abstract perusal of 37 results obtained by the above-mentioned search strategy. Flow diagram of the study selection procedure has been depicted in Figure 1. Trial characteristics are shown in Table 1. Four out of five studies achieved a Jadad score of 5, and one study achieved a score of 4. All studies were done in patients undergoing abdominal surgery,[15-19] and one study included thoracic surgery also.[18] There was a significant variability in anesthetic regimens between trials.

Postoperative morphine consumption at 24 h was measured in all 5 trials, and it was found to be significantly lesser in epidural dexamethasone group (MD −7.89 mg; 95% CI: −11.66 to −3.71; $P = 0.0001$, Figure 2). Three trials[16,17,19] reported the number of patients required rescue analgesia, and it was found; it is significantly less in patients received epidural dexamethasone (RR 0.51; 95% CI: 0.41-0.63; $P < 0.00001$, Figure 3). Analysis of two trials[16,17] failed to show a statistically significant difference in the satisfaction score (MD 1.27; 95% CI: −0.12 to 2.66; $P = 0.07$).

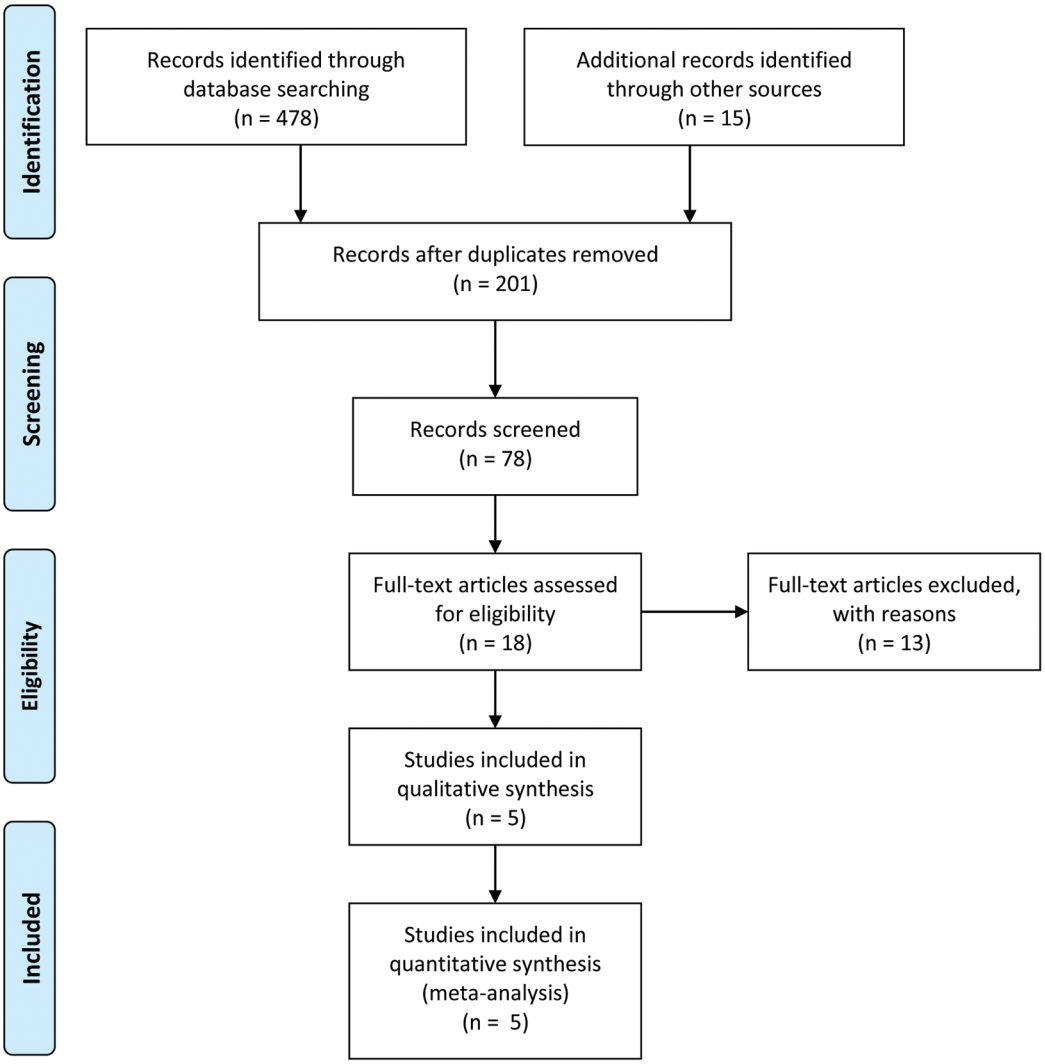

Figure 1: PRISMA flow diagram of study selection

Table 1: Characteristics of the included studies

Study	Jadad score	Number of patients	Surgery	Sex	Anaesthesia strategy	Neuraxial drugs other than dexamethasone	Dose of epidural dexamethasone bolus	Epidural infusion	Total dexamethasone dose in 24 H	Postoperative analgesia	Metho data sources
Thomas S *et al*. [17]	5	30/30	Laparoscopic cholecystectomy	Both	Epidural + GA	Epidural Bupivacaine 20 mg	5 mg	-	5 mg	IV Morphine 2 - 4 mg boluses	Text/Tables
Khafagy HF *et al*. [18]	5	30/30	Lower abdominal and urological surgery	Both	Epidural + GA	Epidural Bupivacaine 25 mg	4 mg	-	4 mg	IV Meperidine 0.5 mg/ kg	Text/Tables
Hefni AF *et al*. [19]	5	40/40	Abdominal hysterectomy	Females	Epidural + GA	Epidural Bupivacaine - Dose not specified	4 mg	-	4 mg	IV Meperidine 0.5 mg/kg	Text
Naghipour B *et al*. [20]	5	35/35	Abdominal and thoracic surgeries	Both	Epidural + GA	Epidural Bupivacaine 60 mg [abdominal surgery]/40 mg [thoracic surgery] + Fentanyl 50 mcg	8 mg	-	8 mg	IV Pentazocine 10 mg bolus	Text/Tables
Jo YY *et al*. [21]	4	30/30	Radical subtotal fast rectory	Both	Epidural + GA	Epidural Ropivacaine 50 mg	5 mg	Ropivacaine 7.5 mg/h + 1000 mcg fentanyl in 25 ml NS for 24 hrs	Total dose not specified	IV Fentanyl 50 mcg bolus [in PACU] & IV Meperidine 25 mg bolus [in ward]	Text/Tables

There was no difference in sedation score between epidural dexamethasone and placebo group (MD 0.02; 95% CI: −0.15-0.19; $P = 0.81$). No incidence of hypotension, bradycardia, and respiratory depression was reported in any of the trials.

Discussion

Principal finding of our meta-analysis is that the postoperative opioid consumption and the number of patients, who requested analgesia, were significantly lesser in patients, who received epidural dexamethasone.

Both oral and intravenous dexamethasone has been found to provide perioperative analgesia. Epidural bupivacaine-dexamethasone combination has been found to provide similar quality analgesia to bupivacaine-fentanyl combination. Epidural dexamethasone might have an action at spinal cord level, and also Thomas and Beevi[15] have found that epidural dexamethasone is superior to intravenous dexamethasone. Apart from being an epidural adjunct, epidural dexamethasone may improve postoperative outcome in terms of fatigue, pain, and early return of recreational activity.[11] Gao *et al*.[20] found that local infiltration of dexamethasone at the site of epidural needle placement decrease a backache in patients undergoing gynecologic surgeries. Wang *et al*.[21] reported epidural dexamethasone also decreases the incidence of back pain after epidural anesthesia. A meta-analysis[22] also found that epidural steroids decrease pain in the short-term and shorten length of stay in adults undergoing lumbar spinal surgery for degenerative spinal disease.

Controversy exists about the optimum epidural dose of dexamethasone. The dose of dexamethasone required to provide significant opioid sparing effect seems to be around 4-8 mg. One study compared different doses of epidural dexamethasone.[17] They found that the dexamethasone at 8 mg dose provided superior analgesia than at 4 and 6 mg doses. None of the patients developed significant side effects such as bradycardia, hypotension, or respiratory depression; the sedation score was also not significant between the patients who received dexamethasone and those who did not. Only one of the included trials has actively sought for neurotoxic potential of dexamethasone.[15] There are sporadic vague reports in literature implicating accidental intrathecal steroid injections with arachnoiditis.[23] However, dexamethasone has not been cited as the cause in any of these reports. Although dexamethasone is particulate, its size is smaller than red blood cells, and it does not aggregate after injection. So for practical purposes, dexamethasone can be considered nonparticulate. In addition, the water-soluble nature of dexamethasone contributes for its safety profile

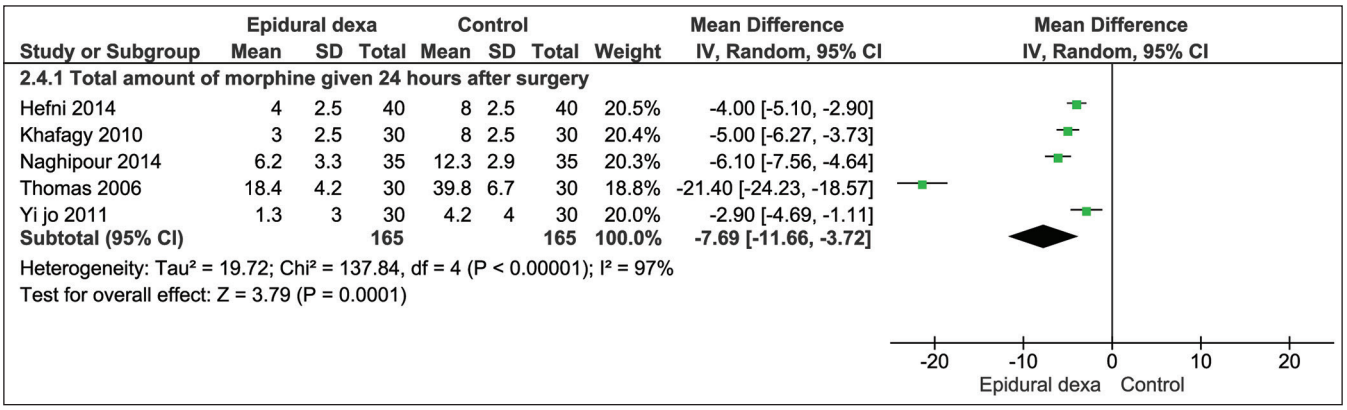

Figure 2: Forest plot for mean difference of postoperative morphine consumption

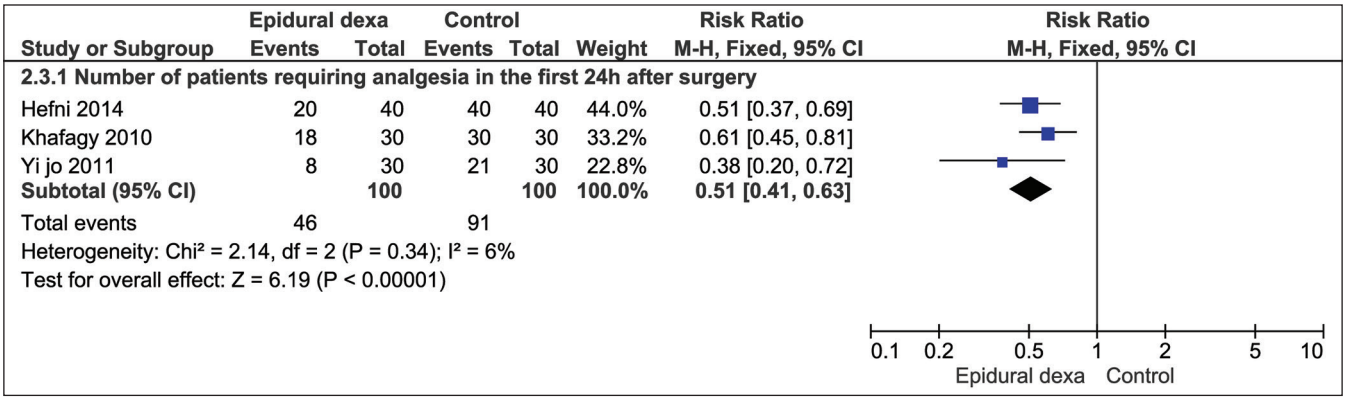

Figure 3: Forest plot for risk ration of number of patients required postoperative rescue analgesic

in neuraxial administration.[24] Further studies with better methods of assessing neurotoxic potential are needed before declaring the safety of neuraxial dexamethasone.

Limitations

Our meta-analysis is not free from limitations. First, the number of studies included in this analysis is small. Hence, a single study has a large influence in the ultimate outcome, which may lead to biases. Second, we have found significant heterogeneity in our primary outcome. Heterogeneity may be due to difference in the patient population, dose of epidural dexamethasone, type of surgery, volume of drug given, and dose of opioid added. However, as the number of included trials is small, a meta-regression analysis was not possible to identify source of heterogeneity. Third, there are inconsistencies in the data of acute pain-related endpoints. Because of all these reasons, we cannot apply and generalize the findings of this analysis to a general population.

Conclusion

The present data shows a potential role of dexamethasone as an adjuvant to local anesthetic for postoperative analgesia. However, these results should be interpreted with caution. There is no clear assessment of neurological complications with epidural dexamethasone in most clinical trials. Additional studies are needed to support the findings of this meta-analysis, before adopting this technique in routine clinical practice.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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