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ORIGINAL ARTICLE

Efficacy of epidural dexamethasone versus fentanyl on postoperative analgesia

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Abstract
Purpose Dexamethasone has analgesic, anti-inflammatory, and antiemetic effects. This prospective, randomized, double-blind, controlled study was designed to evaluate the efficacy of adding dexamethasone versus fentanyl to epidural bupivacaine on postoperative analgesia.
Methods Ninety patients ASA I–II scheduled for lower abdominal surgeries were randomly allocated into three groups to receive a total of 10 mL epidural plain bupivacaine 0.25% in the control group (group B), with either 50 μg fentanyl in group BF or 4 mg dexamethasone in group BD. Patients then received general anesthesia. Sedation, satisfaction, and visual analogue pain scores (VAS) were measured postoperatively. Meperidine was administered when VAS ≥4. Intraoperative fentanyl dose, postoperative meperidine consumption, and the time to first analgesic requirement were recorded.
Results Intraoperative fentanyl requirements were comparable among groups. Time to first analgesic requirement was significantly prolonged (5.2 times) in the BF group and (4.8 times) in the BD group compared with group B ($p < 0.01$). There was significant reduction in postoperative meperidine consumption during the first 24 h in the BF and BD groups (65, 62.5% respectively) in comparison with group B ($p < 0.01$). VAS scores were significantly lower and patient satisfaction score was significantly higher in the BF and BD groups compared with group B ($p < 0.01$). Postoperative nausea was significantly lower in the BD group versus the B and BF groups ($p < 0.05$).
Conclusions This study revealed that epidural bupivacaine–dexamethasone admixture had almost the same analgesic potency as bupivacaine–fentanyl with opioid-sparing and antiemetic effects. Further studies are required to evaluate the optimum dose of epidural dexamethasone for postoperative analgesia.

Keywords Epidural · Dexamethasone · Fentanyl · Bupivacaine · Analgesia

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Introduction

Inadequate postoperative pain relief can delay recovery, increase health care costs, and reduce patient satisfaction [1]. Various adjuvants are used in regional anesthesia to enhance and prolong local anesthetic analgesia, and reduce opioid requirements and their side effects. The combination epidural opioid–local anesthetic provides good pain control during the first postoperative day, but is associated with nausea, vomiting, sedation, pruritus, urinary retention, and respiratory depression [2].

Dexamethasone is a high-potency, long-acting glucocorticoid with little mineralocorticoid effect that has been used for prophylaxis of postoperative nausea [3]. Single doses of dexamethasone and other glucocorticoids have also been reported to improve analgesia after various operations [4–8], whether by oral [8] or intravenous [6] routes. Although epidural steroids were effective in the treatment of low back pain [9], their potential postoperative analgesic benefits have not been efficiently evaluated. The safety of epidural steroid injections has been demonstrated [10]. Corticosteroids are known to inhibit phospholipase A_2

and expression of cyclo-oxygenase-2 during inflammation, thus reducing prostaglandin synthesis. This suppresses hyperalgesia associated with acute nociception during surgery [11]. The extraordinary range of effects of glucocorticoids upon target tissues have been focused on the molecular cell biology action through glucocorticoid receptors [12].

Thus preoperative epidural dexamethasone administration is assumed to provide analgesic, opioid-sparing, and antiemetic effects. Accordingly, this prospective, randomized, double-blind, controlled study was designed to evaluate the efficacy of adding dexamethasone versus fentanyl to epidural bupivacaine on postoperative analgesia.

Materials and methods

This study was conducted after the approval of the institutional ethical committee and after obtaining an informed written consent from every patient. The study involved 90 adult patients aged 25–65 years of either sex, ASA I–II, scheduled for various lower abdominal/urological surgeries, for example bladder stone, varicocelectomy, orchiectomy, and herniorrhaphies. Patients were excluded if they had a history of peptic ulcer diseases, had contraindication to epidural anesthesia (back fusion, coagulopathy, local infection), or failure to achieve epidural analgesia. Patients were also excluded if they were obese, diabetic, had received corticosteroids or immunosuppressive drugs in the last 6 months, or if they had contraindication to corticosteroids. Two patients were excluded from the study after randomization because of epidural analgesia failure. The study protocol and the epidural procedure were explained to each patient during the preoperative visit.

Patients were premedicated with intravenous (iv) administration of 0.05 mg/kg midazolam. In the operating room, routine monitoring included five leads ECG, noninvasive blood pressure, SpO_2, capnography, anesthetic gas analyzer, temperature, and a peripheral nerve stimulator (Infinity Kappa, Dräger, Lübeck, Germany) was attached to the patient. The following variables were measured at pre and post-induction, and every 15 min thereafter until the end of surgery: mean arterial pressure (MAP), heart rate (HR), arterial oxygen saturation (SpO_2), and end tidal carbon dioxide ($EtCO_2$). 500 mL lactated Ringer's solution was infused as a preload then at a rate 6 ml/kg/h intravenously throughout the operation. Epidural anesthesia with loss of resistance technique was employed at L2–3 level using an 18-gauge Tuohy epidural needle. A test dose of 3 mL lidocaine 2% with adrenaline 1:200,000 was used to exclude both subarachnoid and intravascular injection. Patients were randomly allocated on treatment analysis approach into one of three groups (30 patients per group) using computer-generated random numbers. Patients received a single-shot of 5 mL epidural plain bupivacaine (25 mg) (Marcaine 0.5%; AstraZenca, Sweden) + 5 mL normal saline in the control group (group B). The other two groups received 5 mL epidural plain bupivacaine 0.5% (25 mg) + 4 mL normal saline + 1 mL of either 50 μg fentanyl in group BF, or 4 mg dexamethasone in group BD. The final concentration of bupivacaine used was 0.25%. The patient, anesthesiologist, and observers collecting data were blinded to the patient's study group allocation.

General anesthesia was induced intravenously by fentanyl 1 μg/kg, propofol 2 mg/kg, and cisatracurium 0.15 mg/kg. The patient's lungs were then mechanically ventilated with 30% O_2 in air and isoflurane (0.7–1% end-tidal concentration) to maintain normocarbia at end tidal CO_2 between 35 and 40 mmHg. A clinical response to intraoperative surgical stimulation was defined as an increase in HR and/or MAP >30% of baseline values after induction and was treated with fentanyl 0.5 μg/kg iv boluses. Muscle relaxation was maintained by 0.02 mg/kg cisatracurium when the first twitch in the TOF (T1) is recovered to 25% of its baseline height. At the end of surgery, residual neuromuscular block was antagonized by 35 μg/kg neostigmine together with 20 μg/kg atropine when the T4/T1 ratio reached 75%.

In the postanesthesia care unit (PACU), sedation score was assessed on a four categorical scale as 0, alert and aware; 1, drowsy, not sleeping; 2, asleep, arousable by verbal contact; and 3, asleep not arousable by verbal contact [13]. Quality of analgesia was measured by visual analogue score (VAS) on a 0–10 cm scale, where a score of 0 represents no pain and 10 is the worst pain imaginable [14]. VAS was measured every hour up to 6 h postoperatively, and then at 6 h intervals for 24 h. Whenever the VAS score was ≥4 or the patient requested pain medication, analgesia was provided by meperidine 0.5 mg/kg iv. Satisfaction score was measured on a linear numerical scale; ranging from 0 = complete dissatisfaction to 10 = complete satisfaction [15]. Any postoperative side effects, for example nausea, vomiting, itching, bradycardia, hypotension, excessive sedation, inadequate analgesia, retention of urine, or respiratory depression defined as respiratory rate <10/min or SpO_2 <90%, were recorded. Diphenhydramine 25 mg im and metoclopramide 10 mg im were prescribed for itching and nausea/vomiting, respectively.

The cumulative intraoperative fentanyl dose given by the intravenous route (including the induction dose and top-up dose), postoperative meperidine consumption in 24 h postoperatively, number of patients requiring analgesia, and the time to first analgesic requirement were recorded.

Statistical analysis

On the basis of previous studies, sample size was calculated according to the variability of total meperidine consumption during the first 24 h postoperatively. Assuming $\alpha = 0.05\%$ and power of 80%, 30 patients per group were required to detect a difference of meperidine consumption within 20 mg (with 5% precision). Results are expressed as means ± standard deviation (SD) or number (%). Comparison between numerical data was performed using ANOVA with post hoc Bonferroni test. Comparison between categorical data was performed using the chi-squared test. Data were considered significant if p values were ≤ 0.05. Statistical analysis was performed with the aid of the SPSS computer program (version 12 windows) [16].

Results

Ninety-five patients were approached to participate. Five were ineligible for the study because of chronic opioid use ($n = 3$) and recent steroid use ($n = 2$). Among the 90 patients randomized for the study, there were no significant differences between groups in demographic variables, or type and duration of surgery (Table 1).

The cumulative intraoperative fentanyl requirements given by the intravenous route were comparable among the three groups (Table 2). The time to first analgesic requirement was significantly prolonged 5.2 times in BF group and 4.8 times in BD group more than the analgesic duration in group B, with a p value <0.01. There was a significant reduction of meperidine consumption in the BF group (65%) and in the BD group (62.5%) during the first 24 h compared with group B, with a p value <0.01. All patients of group B required analgesia but only 50% in group BF and 60% in group BD were in need (Table 2). While VAS scores were comparable between patients in the BF and BD groups during the postoperative period, except at 12 h, their scores were significantly lower than those of group B with a p value <0.01 (Fig. 1). The intraoperative SpO_2, $EtCO_2$, HR, and MAP values and postoperative sedation score were comparable among the three groups (Tables 3, 4). Patient satisfaction score was significantly higher for patients of the BF and BD groups than for those of group B, with a p value <0.01. The incidence of postoperative nausea during the 24 h observation period was lower in the BD group than in the B and BF groups, with a p value <0.05 (Table 4). No patient in any group experienced itching, bradycardia, hypotension, headache, or respiratory depression.

Table 1 Demographic data, duration and type of surgery

	Group B ($n = 30$)	Group BF ($n = 30$)	Group BD ($n = 30$)
Age (years)	44 ± 9	42 ± 10	41 ± 7
Sex (F/M)	12 (40%)/18 (60%)	15 (50%)/15 (50%)	12 (40%)/18 (60%)
Weight (kg)	73 ± 4	73 ± 4	72 ± 4
Height (cm)	159 ± 4	160 ± 5	162 ± 5
ASA (I/II)	18 (60%)/12 (40%)	21 (70%)/9 (30%)	21 (70%)/9 (30%)
Duration of surgery (min)	100 ± 18	103 ± 14	100 ± 20
Type of surgery			
Bladder stone	15 (50%)	14 (46.7%)	12 (40%)
Varicocelectomy	3 (10%)	4 (13.3%)	6 (20%)
Orchiectomy	7 (23.3%)	6 (20%)	5 (16.7%)
Herniorrhaphy	5 (16.7%)	6 (20%)	7 (23.3%)

Group B, bupivacaine group; Group BF, bupivacaine + fentanyl group; Group BD, bupivacaine + dexamethasone group

Data are expressed as mean ± standard deviation or number (%)

Table 2 Intra and post-operative analgesia

	Group B ($n = 30$)	Group BF ($n = 30$)	Group BD ($n = 30$)
Time to 1st analgesia (h)	3.00 ± 0.56	15.60 ± 8.58*	14.40 ± 8.08*
Intraoperative fentanyl (μg)	102 ± 37	93 ± 29	91 ± 30
Postoperative meperidine (mg)	80 ± 25	28 ± 34*	30 ± 25*
Patients required analgesia [n (%)]	30 (100%)	15 (50%)*	18 (60%)*

Group B, bupivacaine group; Group BF, bupivacaine + fentanyl group; Group BD, bupivacaine + dexamethasone group

Data are expressed as mean ± standard deviation or number (%)

* $p < 0.01$ relative to group B

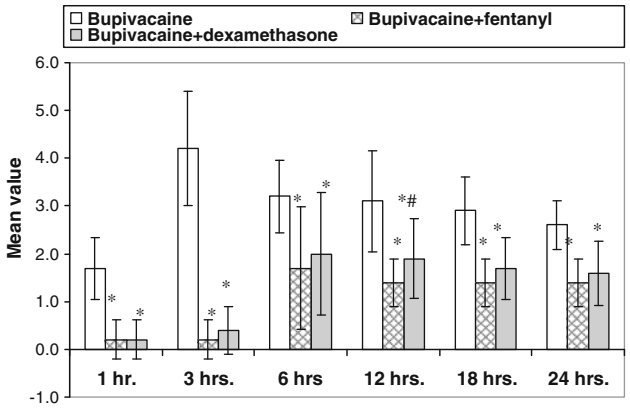

Fig. 1 Postoperative visual analogue score. Data are expressed as mean ± standard deviation. *$p < 0.01$ relative to bupivacaine group, #$p < 0.05$ relative to bupivacaine + fentanyl group

Discussion

This study revealed that addition of 4 mg dexamethasone to epidural bupivacaine reduced postoperative pain score, analgesic requirements, and the number of patients requiring analgesia, together with prolonged postoperative analgesic duration and better patient satisfaction than the control group. These results were comparable with those from bupivacaine–fentanyl admixture group with the advantage of opioid sparing and antiemetic effects of dexamethasone.

The results of this study are in agreement with the analgesic effects of preoperative administration of dexamethasone and other glucocorticoids given by oral, intravenous, or intramuscular routes in patients undergoing gynecological operations [17], dental extractions [8], laparoscopic cholecystectomy [6], foot [4] and spine [7] surgeries. Similarly, Thomas and Beevi [18] revealed that patients receiving epidural dexamethasone either alone or combined with bupivacaine had less postoperative VAS pain scores and analgesic consumption than observed in the control group who received iv dexamethasone and epidural bupivacaine. This indicates that dexamethasone had action at the spinal cord level, in addition to its action on the peripheral tissues, after systemic absorption from the epidural space. They found that postoperative analgesic duration was comparable among the three groups which may be because of administration of dexamethasone by either the intravenous or epidural route. Bisgaard et al. [6] concluded that preoperative iv dexamethasone improved surgical outcome in terms of significantly less pain, fatigue, nausea, vomiting, and analgesic opioid requirements; in addition, patients resumed recreational activity significantly faster compared with the placebo group. Moreover, Wang et al. [9] showed that epidural administration of 5 mg dexamethasone reduced the incidence and severity of post-epidural backache following hemorroidectomy, without adverse effects over a 3-day follow-up period.

The pathophysiological mechanisms for epidural steroid effects may be related to the anti-inflammatory action,

Table 3 Intraoperative hemodynamic data, SpO_2, and Et CO_2

	Group B ($n = 30$)	Group BF ($n = 30$)	Group BD ($n = 30$)
HR (beat/min)	76.90 ± 4.02	75.36 ± 3.72	75.97 ± 3.80
MBP (mmHg)	87.52 ± 3.18	86.04 ± 3.70	87.05 ± 3.32
SpO_2 (%)	99.3 ± 0.6	98.9 ± 0.7	99.5 ± 0.5
$EtCO_2$ (mmHg)	36.06 ± 0.81	36.22 ± 0.83	35.97 ± 0.63

Group B, bupivacaine group; Group BF, bupivacaine + fentanyl group; Group BD, bupivacaine + dexamethasone group

Data are expressed as mean ± standard deviation

Table 4 Postoperative satisfaction, sedation scores, and complications

	Group B ($n = 30$)	Group BF ($n = 30$)	Group BD ($n = 30$)
Satisfaction score	6.83 ± 0.76	8.60 ± 0.86*	8.82 ± 0.84*
Sedation score	0.45 ± 0.50	0.50 ± 0.49	0.47 ± 0.51
Nausea [n (%)]	6 (20%)	7 (23.3%)	1 (3%)$^{\$,\#}$
Urinary retention [(n (%)]	3 (10%)	3 (10%)	2 (6.7%)

Group B, bupivacaine group; Group BF, bupivacaine + fentanyl group; Group BD, bupivacaine + dexamethasone group

Data are expressed as mean ± standard deviation or number (%)

$^{\$}$ $p < 0.05$

* $p < 0.01$ relative to group B

$^{\#}$ $p < 0.05$ relative to group BF

edema reduction, or shrinkage of connective tissue. Local steroid application was found to suppress transmission in thin unmyelinated C-fibers but not in myelinated A-beta fibers [19]. It has also been suggested that steroids may bind directly to the intracellular glucocorticoid receptor, and their effects are predominantly mediated through altered protein synthesis via gene transcription [20]. Last, epidural dexamethasone may affect intraspinal prostaglandin formation. Acute noxious stimulation of peripheral tissues during surgical stimulation leads to activation of phospholipase A_2 and up-regulation of the expression of cyclo-oxygenase-2 in the spinal cord, leading to prostaglandin synthesis and a resultant hyperalgesic state [11]. Inflammatory, metabolic, hormonal, and immune responses to surgery are activated immediately after the surgical incision, so preoperative administration of steroids may reduce these responses, by virtue of their anti-inflammatory and immunosuppressive effects, by inhibiting both phospholipase A_2 and cyclo-oxygenase-2 enzymes [21]. This was obvious with the reduction of C-reactive protein levels, pain, and fatigue scores in patients who received preoperative dexamethasone [6].

Only one patient in the dexamethasone group in this study experienced nausea. The mechanism by which glucocorticoids alleviate nausea and vomiting is not fully understood, but the effects are probably centrally mediated via inhibition of prostaglandin synthesis or inhibition of the release of endogenous opioids [22]. The lower incidence of postoperative nausea in the BD group in this study can also be explained by reduced postoperative narcotic requirements.

Corticosteroid toxicity is an iatrogenic illness associated with chronic inflammatory disease therapy which is proportional to the duration and intensity of this therapy. The most important potential risks in the postoperative period are gastrointestinal bleeding [23] or increased susceptibility to infection [24]. A gastroprotective regimen should be considered, particularly if a corticosteroid was given in large dose or in combination with non steroidal anti-inflammatory drugs [7]. Some surgeons have concerns about steroids masking the clinical signs of infection. However considering the biologic half-life of dexamethasone (36–58 h), it is customary for a postoperative wound to be re-dressed at 1 week, at which time the corticosteroid would have been totally eliminated from the body [25]. Maillefert et al. [26] found that a large dose of epidural dexamethasone (15 mg) may induce transient depression of the hypothalamic–pituitary–adrenal axis which was clinically benign and reversible. In an animal model, intrathecal infusion of low-dose dexamethasone was shown to be safe, whereas higher doses were associated with inflammation of subarachnoid space [27]. Arachnoiditis is a potential complication if deposteroids are accidentally injected intrathecally [28], but this risk was reduced in this study because dexamethasone is water soluble. Dexamethasone may increase sedation requirements through its central nervous system-stimulating side effects in the form of insomnia and agitation [29]. However, no signs of agitation were observed in this study, and there was no difference in sedation scores between the groups postoperatively. A meta-analysis [5] which included trials of major surgical procedures and used perioperative administration of high-dose methylprednisolone (30–35 mg/kg), a dose approximately 100 times the dose of dexamethasone used in this study (4 mg), found it was not associated with significant side effects. Therefore, there is evidence that single-dose preoperative treatment with a small dose of dexamethasone is safe in healthy patients, especially in minor procedures.

Contrary to the results of our study, Blanloeil et al. [30] reported that epidural steroids (methylprednisolone) do not reduce postoperative pain after posterolateral thoracotomy. Possible explanations for this contradiction include different sampling size, type of surgery, and use of steroids with different potencies.

Most previous studies [6–8, 17] used preoperative oral or intravenous dexamethasone and recommended a higher dose (ranging from 8 to 40 mg) than the small does (4 mg) used in this study and few studies were done on the effect of epidural dexamethasone on postoperative analgesia [9, 18]. This study tried to assess the analgesic effect of a single small dose of epidural dexamethasone and compared it with the standard analgesic fentanyl effect combined with bupivacaine.

Our study concluded that epidural 4 mg dexamethasone–bupivacaine admixture resulted in a lower postoperative pain score, lower analgesic requirements and number of patients requiring analgesia, and prolonged analgesic duration, together with better patient satisfaction score and fewer side effects compared with the control group. These effects were comparable with those with epidural 50 μg fentanyl–bupivacaine admixture but with less incidence of nausea in the dexamethasone group. Further studies are required to evaluate the optimum dose of epidural dexamethasone for simple and inexpensive postoperative analgesia.

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