Epidural dexamethasone for post-operative analgesia in patients undergoing abdominal hysterectomy: A dose ranging and safety evaluation study

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ABSTRACT

Aim: Number of studies revealed that epidural bupivacaine-dexamethasone has the same analgesic potency as bupivacaine-fentanyl with opioid sparing and antiemetic effects. Different doses of dexamethasone were used in different studies. This study was designed to evaluate the optimum dose of epidural dexamethasone for post-operative analgesia. Materials and Methods: In this double-blinded randomized controlled study, we evaluated the efficiency and safety of different doses of epidural dexamethasone for post-operative analgesia in 160 patients aged 45-60 years scheduled for total abdominal hysterectomy. Patient were randomly allocated into four groups to receive a total volume of 10 ml epidural plain bupivacaine 0.25% in the control group (Group D0) with either 4 mg dexamethasone in (Group D4) or 6 mg dexamethasone in (Group D6) or 8 mg dexamethasone in (Group D8). Patients then received general anesthesia. Sedation, satisfaction and visual analog pain scores (VAS) at rest and with effort were measured post-operatively. Meperidine was administered when VAS \( \geq 4 \). Intra-operative fentanyl dose, post-operative meperidine consumption and the time to first analgesic requirement were recorded by a blinded observer. Blood glucose was measured pre-operatively and at 4 h and 8 h after study drug administration. Wound healing and infection were assessed after 1 week.

Results: Intraoperative fentanyl requirements were comparable among groups. The time to first analgesic requirement was significantly prolonged 5.5 times in D8 Group but only 1.5 times in D6 and D4 Groups more than the analgesic duration in the control Group D0, with a \( P < 0.01 \). There was a significant reduction in post-operative meperidine consumption during the first 24 h in the D8 (75%) in comparison with D6 and D4 Groups (50%), respectively, \( (P < 0.01) \) and the control Group D0 (0%) \( (P < 0.01) \). VAS scores were significantly lower and patient satisfaction score was significantly higher in the D8 and compared with Groups D6 and D4 \( (P < 0.01) \) and the control Group D0 \( (P < 0.01) \). Post-operative nausea was significantly lower in the D8, D6 and D4 Groups versus the D0 Group \( (P < 0.05) \). Conclusion: Epidural dexamethasone in a dose of 8 mg is probably more effective than lower doses to control moderate to severe post-operative pain. This dose is not associated with increased glucose level or delayed wound healing.

Key words: Abdominal hysterectomy, bupivacaine, dexamethasone, epidural, pain

INTRODUCTION

Inadequate post-operative pain relief can delay recovery, increase health-care costs and reduce patient satisfaction. 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 post-operative day, but is associated with nausea, vomiting, sedation, pruritus, urinary
retention and respiratory depression.\[9\] Dexamethasone is a high-potency, long-acting glucocorticoid with little mineralocorticoid effect that has been used for prophylaxis of post-operative nausea.\[9\] Single doses of dexamethasone and other glucocorticoids have also been reported to improve analgesia after various operations,\[4-8\] whether by oral\[10\] or intravenous (I.V.)\[9\] routes. Some studies revealed that epidural bupivacaine-dexamethasone admixture had almost the same analgesic potency as bupivacaine-fentanyl with opioid sparing and antiemetic effects.\[9\] The optimum dose of epidural dexamethasone for post-operative analgesia has not been yet evaluated. This randomized, double-blind, controlled study was designed to evaluate the effect of different doses of epidural dexamethasone for post-operative analgesia in patients undergoing abdominal hysterectomy.

**MATERIALS AND METHODS**

This study was conducted after the approval of the hospital ethical committee and after obtaining an informed written consent from every patient. The study involved 164 adult female patients aged 45-60 years, American Society of Anesthesiologists (ASA) II-III, scheduled for total abdominal hysterectomy (TAH) for perimenopausal bleeding. 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. Other two patients were lost to follow-up. The study protocol and the epidural procedure were explained to each patient during the pre-operative visit. Patients were pre-medicated with I.V. administration of 0.05 mg/kg midazolam. In the operating room, routine monitoring included five leads electrocardiography, non-invasive blood pressure, arterial oxygen saturation (SpO₂), 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), SpO₂ and end tidal carbon dioxide (EtCO₂). A total volume of 500 ml lactated Ringer’s solution was infused as a preload then at a rate 6 ml/kg/h I.V. throughout the operation.

Epidural anesthesia with the 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 four groups (40 patients per group) using computer-generated random numbers. Patients received a single-shot of 10 ml epidural plain bupivacaine (0.25%) (Marcaine 0.5%; AstraZeneca, Sweden) (Group D0). The other three groups received 10 ml epidural plain bupivacaine (0.25%) containing either 4 mg dexamethasone (Group D4) or 6 mg dexamethasone (Group D6) or 8 mg dexamethasone (Group D8). All study drugs were prepared by the pharmacy and given in equal volumes of 10 ml so that the patient, anesthesiologist and observers collecting data were blinded to the drug and dose. General anesthesia was induced I.V. 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% O₂ in the air and isoflurane (0.7-1% end tidal concentration) to maintain normocarbia at end tidal CO₂ between 35 and 40 mmHg. All TAHs were performed through low transverse abdominal incision (bikini-line incision). A clinical response to intraoperative surgical stimulation was defined as an increase in HR and/or MAP of 30% of baseline values after induction and was treated with fentanyl 0.5 μg/kg I.V. boluses. Muscle relaxation was maintained by 0.02 mg/kg cisatracurium when the first twitch in the train-of-four (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%. Blood glucose levels were checked at induction, 4 h and 8 h after injection of study drug. In the post-anesthesia care unit, 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.\[10\] Quality of analgesia was measured by visual analog score (VAS) on a 0-10 cm scale, where a Score of 0 represents no pain and 10 is the worst pain imaginable.\[11\] VAS was measured every hour up to 6 h post-operatively and then at 6 h intervals for 24 h and either by an observing nurse in the recovery room or the trained ward nurse. Whenever, the VAS Score was 4 or the patient requested pain medication, analgesia was provided by meperidine 0.5 mg/kg I.V. ordered by the anesthesiologist concerned with post-operative pain control. Satisfaction score was measured on a linear numerical scale; ranging from 0 = complete dissatisfaction to 10 = complete satisfaction.\[12\] Any post-operative 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 SpO₂ <90%, were recorded. Metoclopramide 10 mg intramuscular was prescribed for
nausea/vomiting. The cumulative intraoperative fentanyl dose given by the I.V. route (including the induction dose and top-up dose), post-operative meperidine consumption in 24 h post-operatively, number of patients requiring analgesia and the time to first analgesic requirement were recorded. Patients were followed up in the obstetric-Gynecologist out-patient department at 1 week after surgery by a gynecologist for occurrence of possible side-effects accompanying dexamethasone usage such as wound infection or delayed wound healing. Hysterectomy scar healing and any inflammation or discharge from the wound was evaluated. The examining Gynecologist was not aware of the group to which the patient belonged.

**Statistical analysis**

Pre-study power analysis showed that 40 patients were required in each group to have a 95% chance ($\beta = 0.05$) of detecting a pain numerical scale more than four at 95% confidence interval limits ($\alpha = 0.05$). A series of one-way analysis of variance tests were conducted to examine differences in the mean values of the variables among the four groups. If a significant difference was found, $t$-test with Bonferroni correction was applied to detect the intergroup differences. Student’s $t$-test or Mann-Whitney rank sums test was used for continuous and ordinal variables, respectively. Nominal variables were analyzed using $\chi^2$ tests to detect differences among the four groups and intergroup differences.

**RESULTS**

From 164 patients were enrolled in the study, one patient each in Groups D0 and D4 was lost to follow-up, also epidural procedure cannot be established in one patient each in Groups D6 and D8. So finally 160 patients were involved and divided into four groups, 40 each in Group D0, D4, D6 and D8. Among the 160 patients randomized for the study, there were no significant differences between groups in patient characteristics such as age, weight, ASA physical status and duration of surgery [Table 1]. The cumulative intraoperative fentanyl requirements given by the I.V. route were comparable among the four groups [Table 2]. The time to first analgesic requirement was significantly prolonged 5.5 times in D8 Group but only 1.5 times in D6 and D4 Groups more than the analgesic duration in the control Group D0, with a $P < 0.01$. There was a significant reduction of meperidine consumption in the D8 Group (75%), in the D6 Group (50%) and in the D4 (50%) Group during the first 24 h compared with Group D0, with a $P < 0.01$. All patients of Group D0 required analgesia, but only 10% in Group D8, 50% in Group D6 and Group D4 were in need [Table 2]. While VAS scores were comparable between patients in the D8, D6, D4 and D0 Groups during the immediate post-operative period, but at 3-4 h post-operative, score of patients in the D8 was significantly lower than those of Group D6, D4 and Group D0 with a $P < 0.01$ [Figure 1]. The intraoperative SpO$_2$, EtCO$_2$, HR and MAP values and post-operative sedation score were comparable among the four groups [Table 3]. Patient satisfaction score was significantly higher for patients of the D8 more than those in D6, D4 and D0 Groups, with a $P < 0.01$. The incidence of post-operative nausea during the 24 h observation period was lower in D8, D6 and D4 Groups than in the D0 Group, with a $P < 0.05$ [Table 4]. No patients experienced wound infection or delayed wound healing at follow-up after 1 week. Pre-operative blood glucose was similar in all groups [Table 5]. There was no significant increase in blood glucose levels recorded at the end of 4 h or 8 h.
The pathophysiological mechanisms for epidural steroid effects may be related to the anti-inflammatory action, edema reduction, or shrinkage of connective tissue.\[9\] Local steroid application was found to suppress transmission in thin unmyelinated C-fibers but not in myelinated A-beta fibers.\[14\] 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 through gene transcription.\[15\] Last, epidural dexamethasone may affect intraspinal prostaglandin formation. Acute noxious stimulation of peripheral tissues during surgical stimulation leads to activation of phospholipase A2 and up-regulation of the expression of cyclo-oxygenase-2 in the spinal cord, leading to prostaglandin synthesis and a resultant hyperalgesic state.\[16\] Inflammatory, metabolic, hormonal and immune responses to surgery are activated immediately after the surgical incision, so pre-operative administration of steroids may reduce these responses, by virtue of their anti-inflammatory and immunosuppressive effects, by inhibiting both phospholipase A2 and cyclo-oxygenase-2 enzymes.\[17\] This was obvious with the reduction of C-reactive protein levels, pain and fatigue scores in patients who received pre-operative dexamethasone.\[16\] Different doses of pre-operative epidural dexamethasone have been used in different clinical trials.\[9,13,18\]

Thomas and Beevi\[13\] used epidural dexamethasone 5 mg pre-operatively in combination with bupivacaine in patients that undergo laparoscopic cholecystectomy. It found to reduce post-operative pain and decrease post-operative morphine consumption in these patients. Khafagy et al.\[9\] used epidural dexamethasone 4 mg pre-operatively in combination with bupivacaine in patients that undergo lower abdominal surgery (e.g., varicocelectomy, herniorrhaphy), it was found to have the same analgesic potency as bupivacaine-fentanyl combination. Jo et al.\[18\] used epidural dexamethasone 5 mg in combination with ropivacaine administrated either pre- or post-operatively in patients undergoing radical subtotal gastrectomy. It was found to reduce post-operative pain and analgesic requirements.

This study revealed that addition of 8 mg dexamethasone to epidural bupivacaine pre-operatively to patients undergo TAH is more efficient than adding either 4 mg or 6 mg dexamethasone as to reduce post-operative pain score significantly (Max VAS 2.0 Group D8, Max VAS 4.5 Groups D6, D4), reduce analgesic requirements (by 75% Group D8, by 50% Groups D6 and D4) and also reduce the number of patient requiring analgesia post-operatively (only 10% Group D8, 50% in Groups D6 and D4), together with prolonged post-operative analgesic duration up to 24 h and better patient satisfaction (9.3 ± 0.7 Group D8, 7.42 ± 0.55 Group D6, 7.3 ± 0.48 Group D4). All the three dexamethasone groups achieve better results than the

**Table 4: Post-operative satisfaction, sedation scores, and complications**

| Score-complication | Group D0 (n=40) | Group D4 (n=40) | Group D6 (n=40) | Group D8 (n=40) |
|-------------------|--------------|--------------|--------------|--------------|
| Satisfaction score | 6.73±0.75 | 7.30±0.48 | 7.42±0.55 | 9.3±0.70 |
| Sedation score | 0.46±0.50 | 0.48±0.49 | 0.48±0.51 | 0.48±0.52 |
| Nausea (% | 8 (20) | 1 (2.5)* | 1 (2.5)* | 1 (2.5)* |
| Urinary (%) | 4 (10) | 1 (2.5) | 1 (2.5) | 1 (2.5) |

Data are expressed as mean±standard deviation or number (%). *P<0.05 relative to Group D0; **P<0.01 relative to Group D0.

**Table 5: Blood glucose levels**

| Outcome measure | Group D0 (n=40) | Group D4 (n=40) | Group D6 (n=40) | Group D8 (n=40) |
|-----------------|----------------|----------------|----------------|----------------|
| Pre-operative blood glucose | 88.3±14.8 | 93.7±10.3 | 85.8±12.5 | 84.3±16.5 |
| Post-operative blood glucose at 4 h | 104.4±16.8 | 105.6±19.5 | 105.6±25.8 | 109.4±20.3 |
| Post-operative blood glucose at 8 h | 110.3±10.5 | 112±14.2 | 111±16.6 | 115±17.4 |

Blood glucose is expressed as mean (SD) in mg/dl. No significant differences among the groups were found. SD: Standard deviation.

**Figure 1: Post-operative visual analog score. Data are expressed as mean ± standard deviation**

after baseline levels in any of the groups and there were no significant differences among the four groups.

**DISCUSSION**

Single dose of dexamethasone and other glucocorticoids have been reported to improve analgesia after various operations,\[4-8\] whether by oral\[8\] or I.V.\[5\] routes. Thomas and Beevi\[13\] found that epidural dexamethasone is significantly more effective than I.V. dexamethasone to reduce post-operative pain and morphine consumption following laparoscopic cholecystectomy. Some studies revealed that epidural bupivacaine-dexamethasone admixture had almost the same analgesic potency as bupivacaine-fentanyl with opioid sparing and antiemetic effects.\[9\]
control Group D0 (Max VAS 6, 0% decrease in analgesic requirements, all patients required post-operative analgesia, low patient satisfaction Score 6.7 ± 0.75). No difference in post-operative glucose levels between the control group and all dexamethasone groups. No patients experienced wound infection or delayed wound healing at follow-up. The efficiency of smaller doses of epidural dexamethasone in the previous trials may be related to the difference in the severity of post-operative pain. In Thomas and Beevi\[9\] trail the surgical procedure was laparoscopic which is known to be associated with less post-operative pain than open surgery. In Khafagy et al.\[9\] trail the surgical procedures were of that type associated with mild to moderate pain so smaller doses of dexamethasone could still be enough. In Jo et al.,\[18\] trail the dexamethasone administrated post-operatively in 5 mg dose was more effective to decrease post-operative pain at T3 (24 h post-operative) and T4 (48 h post-operative) than the same dose administrated pre-operatively. It seems that late administration allows more effective tissue concentration and so more effective post-operative pain control. A well-known principle in drug pharmacokinetics.\[19\] Although using patient controlled analgesia will achieve ideal post-operative pain control, it may not allow the observer precisely to pick-up the accurate maximum VAS scores in relation to time. So nearly all clinical trials in this issue used either intermittent pethidine or morphine boluses.\[9\,13,18,20\]

**CONCLUSION**

Epidural dexamethasone in a dose of 8 mg was more effective for post-operative analgesia in patients undergoing TAH than lower doses. There were no side-effects of dexamethasone usage such as increase of blood glucose, delayed wound healing and wound infection. We recommend further clinical trials in patients undergoing different types of surgical procedures associated with different levels of post-operative pain for further confirmations and comparisons.

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