Randomized Trial

Epidural Dexamethasone Influences Postoperative Analgesia after Major Abdominal Surgery

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Disclaimer: There was no external funding in the preparation of this manuscript. Conflict of interest: Each author certifies that he or she, or a member of his or her immediate family, has no commercial association (i.e., consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted manuscript.

Manuscript received: 06-24-2016 Revised manuscript received: 11-10-2016 Accepted for publication: 12-30-2016

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Background: Epidurally administered dexamethasone might reduce postoperative pain. However, the effect of epidural administration of dexamethasone on postoperative epidural analgesia in major abdominal surgery has been doubtful.

Objectives: To investigate the effects and optimal dose of epidural dexamethasone on pain after major abdominal surgery.

Study Design: A prospective randomized, double-blind study.

Setting: University hospital.

Methods: One hundred twenty ASA physical status I and II men, scheduled for gastrectomy, were enrolled. Patients were randomly assigned to receive one of 3 treatment regimens (n = 40 in each group): dexamethasone 5 mg (1 mL) with normal saline (1 mL) (group D) or dexamethasone 10 mg (2 mL) (group E) or 2 mL of normal saline (group C) mixed with 8 mL of 0.375% ropivacaine as a loading dose. After the surgery, 0.2% ropivacaine - fentanyl 4 μg/mL was epidurally administered for analgesia. The infusion was set to deliver 4 mL/hr of the PCEA solution, with a bolus of 2 mL per demand and 15 minutes lockout time. The infused volume of PCEA, intensity of postoperative pain using visual analogue scale (VAS) during rest and coughing, incidence of postoperative nausea and vomiting (PONV), usage of rescue analgesia and rescue antiemetic, and side effects such as respiratory depression, urinary retention, and pruritus were recorded at 2, 6, 12, 24, and 48 hours after the end of surgery.

Results: The resting and effort VAS was significantly lower in group E compared to group C at every time point through the study period. On the contrary, only the resting VAS in group D was lower at 2 hours and 6 hours after surgery. Total fentanyl consumption of group E was significantly lower compared to other groups. There was no difference in adverse effect such as hypotension, bradycardia, PONV, pruritis, and urinary retention among groups.

Limitations: Use of epidural PCA with basal rate might interrupt an accurate comparison of dexamethasone effect. Hyperglycemia and adrenal suppression were not evaluated.

Conclusions: Epidural dexamethasone was effective for reducing postoperative pain. Especially, an epidural dexamethasone dose of 10 mg was more effective than a lower dose in patients undergoing gastrectomy which was associated with moderate to severe postoperative pain.

IRB approval: D-1507-019-042

Clinical trials registration: KCT0001754

Key words: Patient controlled epidural analgesia, opioid, fentanyl, local anesthetic, ropivacaine, dexamethasone

Pain Physician 2017; 20:261-269

Thoracic epidural analgesia is a common modality for pain control after major abdominal surgery (1). Combined usage of local anesthetics with an opioid alleviates postoperative pain. However, epidural administration of an opioid is commonly associated with nausea, vomiting, sedation, pruritus, urinary retention, and respiratory depression (2,3). As most analgesics, including opioids, have various side effects, multimodal analgesic strategies are commonly adopted for postoperative analgesia. Several adjuvants including midazolam, tramadol, and steroids have been investigated to maximize the efficacy of epidural analgesia. Epidural steroids have been known to be effective not only in postoperative pain control but in the treatment of low back pain.

Although the Federal Drug Administration (FDA) announced a safety label warning that epidural use of triamcinolone acetonide, a particulate steroid, is not recommended due to adverse outcomes such as loss of vision, stroke, paralysis, and death (4), these FDA announcements have met with some criticisms.

Dexamethasone, a non-particulate steroid with a soluble nature, is a long-acting steroid and has a high potency which has been known as a safer option, despite some uncertainties on the duration of action due to its solubility. Previous studies suggested that epidural dexamethasone can reduce pain intensity in several types of surgical patients (5,6). However, the effect of epidural administration of dexamethasone on postoperative epidural analgesia in a different surgery has not been fully investigated. Additionally, the optimal dose of dexamethasone in a different surgery needs to be investigated.

This randomized, double-blind study was designed to evaluate the effect of different doses of epidural dexamethasone for postoperative analgesia in patients undergoing gastrectomy.

Methods

This prospective, randomized, and controlled study was approved by the institutional ethics committee. We enrolled 120 ASA physical status I and II men who were diagnosed with gastric cancer, undergoing elective gastrectomy. Written informed consent was obtained from all patients. Patients with a history of drug abuse, allergies to any of the drugs, patients with Parkinsonism or psychiatric problems, patients who received any steroid or analgesia medication, and patients who had respiratory impairment or liver or renal dysfunction were excluded. All patients accepted the use of patient-controlled epidural analgesia (PCEA) for perioperative pain control. On the day before surgery, patients were instructed on effort and resting visual analogue scale (VAS; 0, no pain; 10, worst pain imaginable) and how to use the PCEA (Pain Management Provider, Abbott, USA) device. On the day of surgery, no premedication was administered. The anesthetic regimen and postoperative pain management were standardized in all patients. In the operating room patients were placed in the lateral decubitus position and an epidural catheter was inserted via an 18-gauge Tuohy needle at the T8/9 interspace and was advanced 3 cm into the epidural space toward the cephalad direction. A standard test dose of lidocaine 2% with epinephrine 5 μg/mL was injected to rule out an intrathecal or intravascular position of the catheter. According to a computer-generated random number table, patients were randomly chosen to receive dexamethasone 5 mg (1 mL) with normal saline (1 mL) (group D) or dexamethasone 10 mg (2 mL) (group E) or 2 mL of normal saline (group C) epidurally mixed with 8 mL of 0.375% ropivacaine as a loading dose. The final concentration of ropivacaine used was 0.3%. The study solutions were prepared as 10 mL of 0.375% ropivacaine by one of the investigators not taking further part in data collection and patient care.

Then, anesthesia was induced with propofol (1.5 mg/kg) and rocuronium (0.6 mg/kg) and maintained with 1:1 mixture of oxygen and air with a small concentration (1.0 – 1.5%) of sevoflurane. Mechanical ventilation was adjusted to maintain an end-tidal carbon dioxide concentration of 30 – 35 mm Hg throughout the surgery using an anesthetic/respiratory gas analyzer. Neuromuscular block was maintained via intermittent intravenous injection of rocuronium 0.2 mg/kg. The bispectral index scale (BIS) value was used to guide administration of sevoflurane and the target range of BIS during maintenance was 40 – 50. An infusion of Ringer's solution (10 mL/kg/h) was given intravenously (i.v.) together with 10 mg boluses of ephedrine to maintain mean arterial pressure within 20% of baseline values throughout the surgery.

Before the end of an operation, an infusion device (Abbott Ambulatory Infusion Manager® plus, Abbott Laboratories, North Chicago, USA) prefilled with 0.2% ropivacaine and 1,000 μg of fentanyl with a total volume of 250 mL was connected to the epidural catheter. The PCEA solution for postoperative analgesia was composed of 4 μg/mL of fentanyl in 0.2% ropivacaine. The PCEA pump was programmed with a basal infusion rate

4 mL/hr of the study solution with a bolus of 2 mL per demand and a 15 minute lockout time. No other opioids were administered during the surgery. At the end of the surgery, glycopyrrolate 7 μg/kg and pyridostigmine 30 μg/kg were administered i.v. for antagonism of residual neuromuscular blockade. In the postanesthetic care unit (PACU), patients were supplied with oxygen and cautiously monitored with an electrocardiogram, pulse oximetry, and non-invasive blood pressure.

The patients were transferred to the ward when they were alert and the vital signs were stable. Data were collected 2, 6, 12, 24, and 48 hours after the end of the surgery by a study-blinded anesthesiologist.

Pain intensity scores were measured with a VAS from 0 (no pain) to 10 (the worst possible pain) at rest and with effort (coughing at 30 degree sitting). If analgesia was inadequate (VAS on coughing > 5) or patients asked for more analgesia, ketorolac 50 mg i.v. as a rescue analgesic was administered, and the epidural catheter was checked to ensure correct placement. Motor blockade was assessed according to a modified Bromage score with 0 = no motor block, 1 = inability to raise the extended leg, 2 = inability to flex the knee, and 3 = inability to move the lower limb.

Noninvasive arterial blood pressure, heart rate, oxygen saturation, and untoward events were measured. Occurrence of clinically relevant hemodynamic adverse events, including hypotension (systolic arterial blood pressure decrease < 90 mmHg) and bradycardia (heart rate decrease < 45 bpm), requiring treatment were recorded. Reduction in oxygen saturation < 90% was treated with supplemental oxygen by face mask, and need for oxygen therapy during the postoperative period was recorded as a minor respiratory complication. However, hypoxemia refractory to oxygen therapy or respiratory depression defined as bradypnea episodes (a ventilation frequency < 10/min) lasting over 10 minutes was regarded as unacceptable major respiratory complications in this context, and reported by any health care personnel with the patient then being switched to an alternate analgesic modality. Pruritus and urinary retention as well as any noted side effects were also evaluated.

An estimated sample size indicated that 35 patients per group would give a β risk of 80% at an α level of 0.05 for detecting a difference of fentanyl consumption within 100 μg of the population mean during the first 48 hours. To compensate for possible exclusions, we decided to randomize 40 patients in each group. Age, height, weight, intraoperative consumption of ropivacaine, and duration of anesthesia were compared with ANOVA. VAS (resting and coughing) scale and cumulative fentanyl consumption were analyzed by repeated measures of ANOVA for inter-group comparison to compare different response curves over time. At each time point, ANOVA with post hoc analysis was performed separately for direct comparison between the groups. The chi-square test was used to compare gender, type of surgery, and incidence of adverse effects. The level of statistical significance was set at $P < 0.05$.

Results

Five patients were excluded from the analysis, 2 from group C and 3 from group E because of protocol violations (Fig. 1). Therefore, 115 patients were analyzed. There were no significant differences among the 3 groups with respect to patient, surgical, and anesthetic characteristics (Table 1).

The resting and effort VAS was significantly lower in group E compared to group C at every time point throughout the study period. On the contrary, only the resting VAS in group D was lower at 2 hours and 6 hours after surgery (Figs. 2, 3). Total fentanyl consumption of group E was significantly lower compared to other groups (Fig. 4).

Postoperative rescue analgesic requirements and adverse effects are shown in Table 2. The total requirements of rescue ketorolac were significantly less in group E compared to groups C and D at postoperative 48 hours ($P = 0.0493$). Although there was no difference among the groups, motor weakness was reported. One patient in group D (2.5%) showed motor blockade (Bromage scale 1) up to 2 hours after the operation. In group E, 2 patients (5.4%) showed prolonged motor blockade (Bromage scale 1) up to 2 hours after the operation. Adverse effects such as hypotension and bradycardia commonly occurred; however, there was no significant difference among the groups and most of the patients who experienced those adverse effects are easily controlled with 10 mg of ephedrine. The number of patients required antiemetics were 3 in group C, one in group D, and 0 in group E. No patient reported bradypnea during the observation period. The incidence of pruritis and urinary retention was low and there was no significant difference among groups.

Discussion

This study revealed the analgesic efficacy of thoracic epidural dexamethasone in patients undergoing subtotal gastrectomy. The addition of dexamethasone

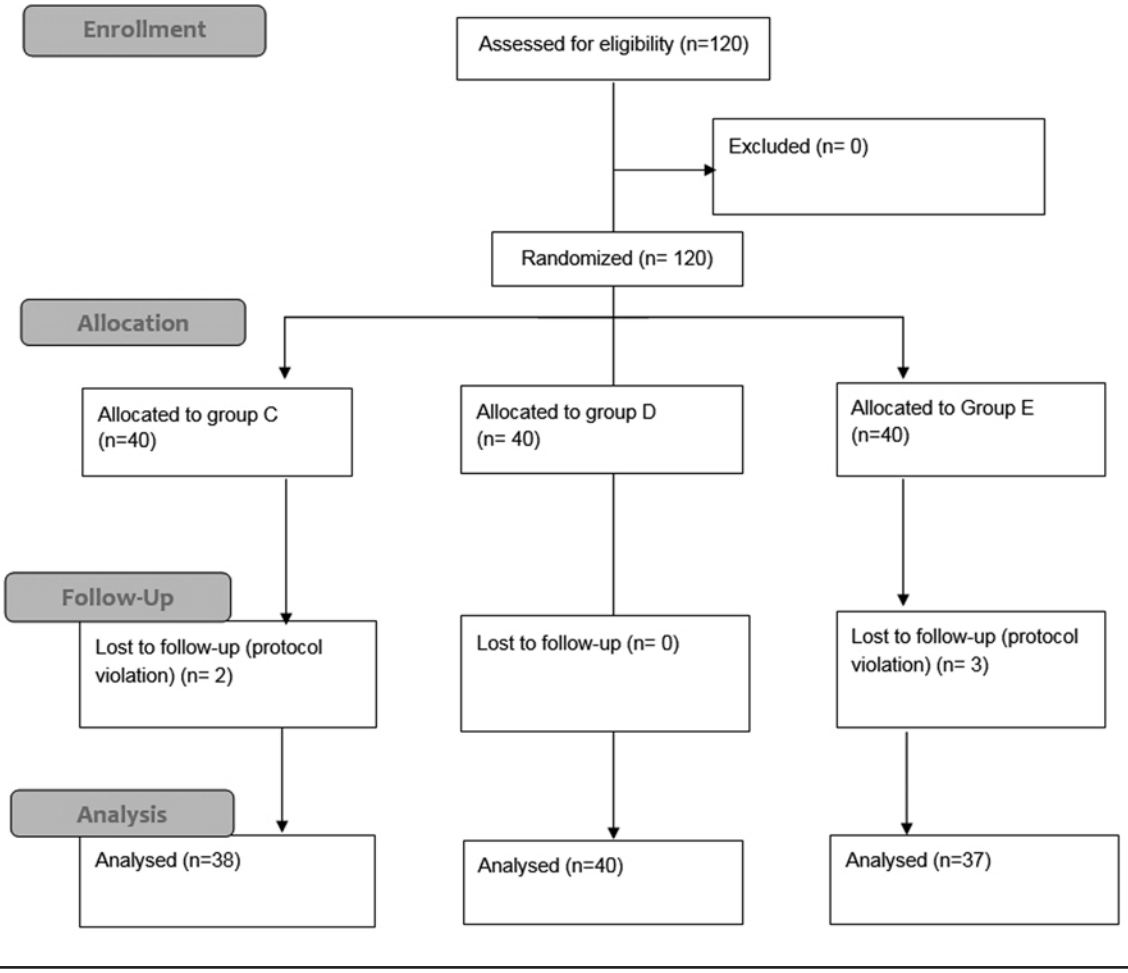

Fig. 1. *Consort flow diagram.*

Table 1. *Demographic data, intraoperative usages of ropivacaine, and duration of anesthesia.*

	Group C (n = 38)	Group D (n = 40)	Group E (n = 37)	*P*-value
Age (yr)	57.9 (10.5)	60.2 (10.5)	59.3 (12.4)	0.6525
Height (cm)	164.4 (8.2)	163.7 (7.2)	163.9 (7.9)	0.9159
Weight (kg)	60.6 (7.4)	60.3 (8.8)	62.4 (8.7)	0.4941
Gender (M/F)	28/10	28/12	27/10	0.9282
Operation				0.2370
LADG	14	13	18	
Subtotal gastrectomy	18	18	13	
Total gastrectomy	16	9	6	
Duration of anesthesia (min)	235.1 (74.0)	267.2 (95.3)	238.3 (46.6)	0.1154

Note: Values expressed are means (SD) or numbers of patients. There were no significant differences among the groups. Group C: ropivacaine + 2 mL normal saline; Group D: ropivacaine + 5 mg Dexamethasone + 1 mL normal saline; Group E: ropivacaine + Dexamethasone 10 mg.

reduced pain intensity and opioid consumption. The addition of 10 mg dexamethasone to epidural ropivacaine preoperatively reduced pain intensity and cumulative fentanyl consumption compared to the control group by 48 hours after the end of the operation. On the contrary, the addition of 5 mg dexamethasone reduced pain only until 6 hours after surgery.

Several glucocorticoids are available for commercial use and dexamethasone is a commonly used glucocorticoid. Dexamethasone is a long-acting glucocorticoid and has a high potency. Relative to naturally occurring cortisol (1.0), the anti-inflammatory potency of dexamethasone is 25. The duration of dexamethasone is 72 hours compared with 8 hours of cortisol's biologic action, which is much longer than 24 hours for prednisolone and 36 hours for methylprednisolone (7).

Although the potential mechanism of the analgesic effect of epidural steroids is still not clearly understood, it seems to be associated with the anti-inflammatory action, edema reduction, and shrinkage of connective tissue (5). In addition, it has been reported that local corticosteroid application blocks transmission in nociceptive C-fibers (8). Thus corticosteroids might have a local anesthetic effect on nerves due to direct membrane action. Another possible mechanism involves the effect of epidural steroids on intraspinal prostaglandin formation. Acute noxious stimulation at peripheral tissues during surgery leads to activation of phospholipase A2

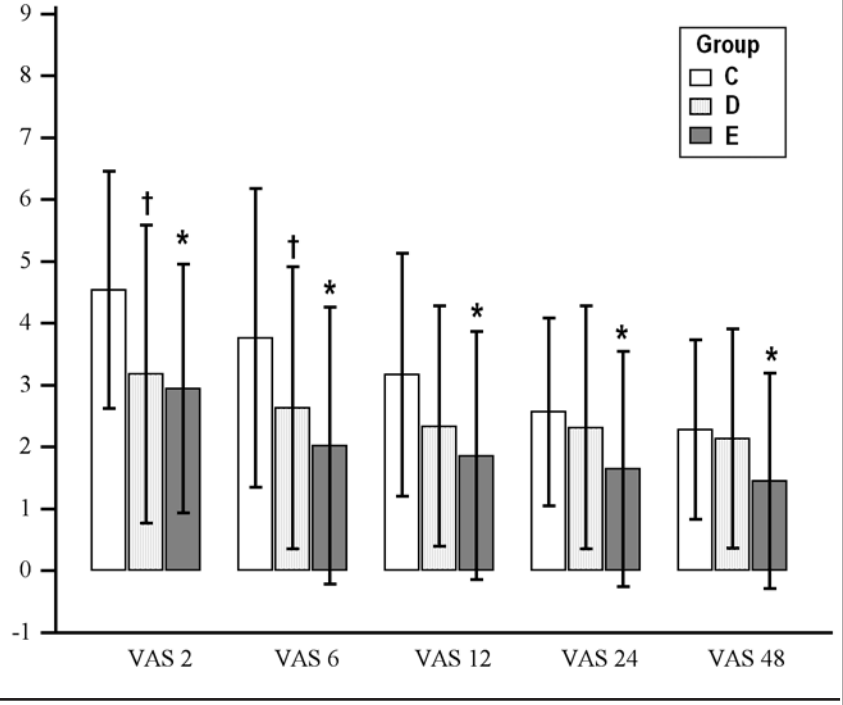

Fig. 2. *VAS on resting.*

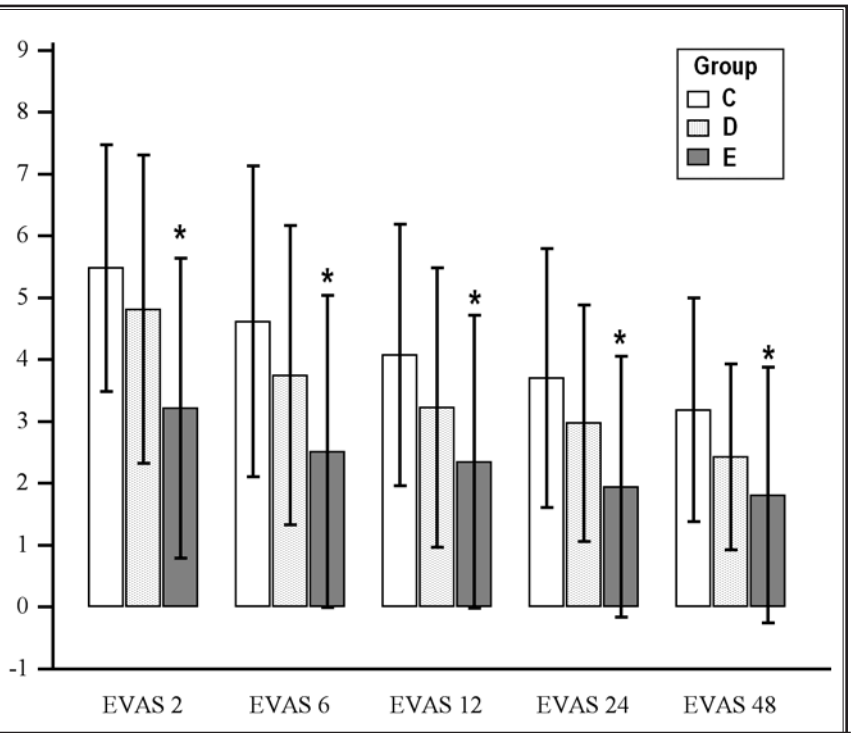

Fig. 3. *VAS on coughing.*

and up-regulation of the expression of cyclo-oxygenase-2 in the spinal cord, causing prostaglandin synthesis resulting in a hyperalgesic state (9). Preoperative steroids may reduce these responses and suppress the hyperalgesia by inhibiting both phospholipase A2 and cyclo-oxygenase-2 enzymes (10).

Dexamethasone has several beneficial effects on the management of not only surgical pain but postoperative nausea and vomiting (PONV). A single administration of dexamethasone by an oral or intravenous route has been reported to reduce PONV and postoperative pain (11-13).

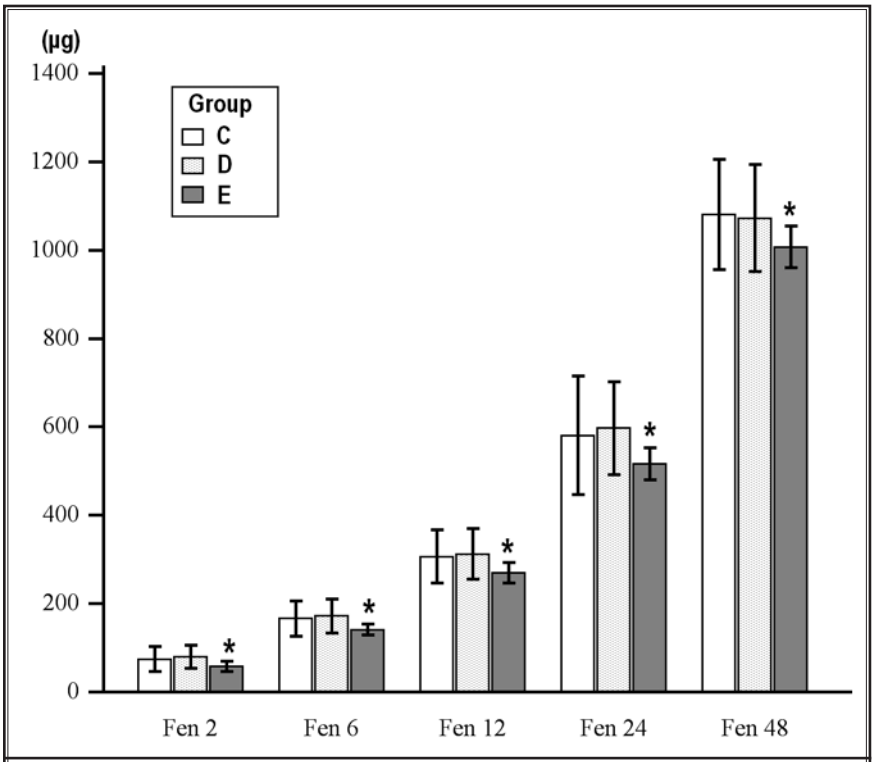

Fig. 4. *Consumption of PCEA.*

Table 2. *Adverse effects, consumption of rescue antiemetics and analgesics, and infused volume of PCEA analgesic solution.*

Variables	Group C (n = 38)	Group D (n = 40)	Group E (n = 37)	P-value
Hypotension/ bradycardia	21	17	22	0.2963
Patients requiring ketorolac	6	4	0	0.0493
Patients requiring antiemetics	3	1	0	0.1608
Bradypnea	0	0	0	NS
Pruritus	0	0	2	0.1050
Urinary retention	1	0	1	0.5505

Note: Values expressed are means (SD) or numbers of patients. There were no significant differences among the groups. Group C: ropivacaine + 2 mL normal saline; Group D: ropivacaine + 5 mg Dexamethasone + 1 mL normal saline; Group E: ropivacaine + Dexamethasone 10 mg.

Through the literature, the effect of perioperative use of dexamethasone in surgical patients depends on the route of administration, dosage, timing of administration, and intensity of pain accompanying surgery. Although we did not compare the effect of dexamethasone based on the route of administration, there exists some debate. Some investigators suggested that intravenous and perineural dexamethasone are equivalent in increasing the analgesic duration in sciatic and interscalene block (14,15); however, other studies showed that the epidural route is more effective than the intravenous route to decrease postoperative pain and opioid consumption (6).

Dose-response studies indicated that between 2.5 and 5 mg of dexamethasone was the minimal dose required to obtain a major effect on PONV (16). However, the dose of epidural dexamethasone required for the prevention of postoperative pain following central sensitization is at the center of debate. Several studies reported that epidural steroids provided effective analgesia after various operations. And most of these studies showed that 5 mg of epidural dexamethasone was effective in reducing postoperative pain and analgesic requirement (5,6,17). However, in our study, although VAS was lower in the 5 mg dexamethasone group than the no dexamethasone group, it was not statistically significant after 6 hours postoperative in the resting state

and it was not significant in any period in the coughing state. Instead, 10 mg dexamethasone was significantly effective in reducing VAS and opioid consumption. This inconsistency may be related to difference in pain severity due to different surgical procedures, concentration, and combination of local anesthetics. Khafagy et al (5) demonstrated that epidural bupivacaine-4 mg of dexamethasone admixture had similar analgesic potency as bupivacaine-50 μg of fentanyl with opioid sparing and antiemetic effects in lower abdominal surgery. In Khafagy et al's study (5) enrolled groups were scheduled for lower abdominal surgeries which were associated with mild to moderate pain. Therefore 4 mg dexamethasone could be enough to control pain. And enrolled groups in the study of Thomas and Beevi (6) were scheduled for laparoscopic cholecystectomy which is associated with lesser pain than after open surgery, so 5 mg dexamethasone could be effective for reducing pain. In the study of Jo et al (18), enrolled groups were scheduled for radical subtotal gastrectomy which was similar to our groups and the efficacy of 5 mg dexamethasone was similar to our result from the 5 mg group. Hefni et al (19) also showed that 8 mg epidural dexamethasone was more effective than lower doses in total abdominal hysterectomy which was associated with moderate to severe pain. In our study, enrolled patients were scheduled for subtotal or total gastrectomy which was expected to cause moderate to severe pain. Hence, even though 5 mg dexamethasone was more effective than the control group, 10 mg dexamethasone, which is a higher dose, might be more effective than the lower dose and could be more suitable to control moderate to severe pain. Contrary to these studies, Blanloeil et al (20) showed that epidural steroids did not reduce pain after thoracotomy. A possible explanation for this difference may include the difference of steroid and severity of postoperative pain. In the study by Blanloeil et al (20) the used steroid was methylprednisolone which is a steroid less potent than dexamethasone. In addition, thoracotomy is associated with severe pain after operation. Therefore it seemed to be not enough to reduce pain after thoracotomy.

The addition of dexamethasone to local anesthetics not only potentiates analgesia but extends the duration of anesthesia and analgesia. The addition of 8 mg of dexamethasone induced a 1.58-fold prolongation of action during epidural block (372 minutes with 8 mg of dexamethasone and 234 minutes without dexamethasone with 0.5% bupivacaine) (21), and moreover, a 1.45-fold prolongation of action of local anesthetics during brachial plexus block (332 minutes with 8 mg of dexamethasone and 228 minutes without dexamethasone with 1.5% mepivacaine) (22). Although we did not accurately measure the action duration of local anesthetics with dexamethasone, the results showed better analgesic properties with 10 mg of dexamethasone for long duration up to 48 hours after the operation compared with other groups. Consequently, through our study, 2.5% of patients in the 5 mg group and 5.4% of patients in the 10 mg group showed prolonged motor blockade. Although, the intensity of the motor blockade was not profound in this study and might be masked after long surgery, the possibility of prolonged motor blockade should be considered for brief surgery and timely assessment of motor function should be needed.

Regarding the timing of administration, most researchers used dexamethasone at the preoperative period. Jo et al (18) demonstrated that the postoperative administration of dexamethasone was more effective than the preoperative dexamethasone in reducing VAS and opioid consumption. Nevertheless, we could not conclude that the postoperative administration was better, because we could not preclude the analgesic effect of local anesthetics as they administered the dexamethasone with 0.25% ropivacaine postoperatively.

In our study, the incidence of PONV was not significantly different among groups. This result may be associated with routine administration of antiemetics (ramosetron 0.3 mg) which probably masked the effect of dexamethasone. However other studies showed epidural dexamethasone reduced the incidence of postoperative nausea and vomiting (5,19). Although the mechanism is not clearly understood, it is probably associated with inhibition of prostaglandin synthesis or inhibition of the release of endogenous opioids (23). In addition, reduced opioid consumption could be partially associated with reduced postoperative nausea and vomiting.

Accidental intrathecal injection of particulate steroids may cause arachnoiditis, but this risk is low in dexamethasone which is water soluble (24). In animal models, although high dose intrathecal dexamethasone causes inflammation of the subarachnoid space, intrathecal infusion of low-dose dexamethasone was safe (25). In addition, Sauerland et al (26) reported high dose methylprednisolone (30 – 35 mg/kg), which is about 30 times the dose of dexamethasone 10 mg, was not associated with significant side effects. Williams et al (27) performed in vitro study in which the impact of

several adjuvants on ropivacaine-induced neuronal cell death was evaluated. They showed no significant cell death even at 667 μg/mL of dexamethasone alone; furthermore they showed that there was no additional cell death when combined with ropivacaine. Based on the pharmacokinetic study of single dose dexamethasone, the maximum plasma concentration occurred between 1.6 – 2.0 hours after doses of 0.5 – 3.0 mg (28). The plasma concentration reached 40 ηg/mL after intramuscular injection of 3.0 mg of dexamethasone (28). Another high single dose study reported plasma concentration would be 5 μg/mL after administration of 1.66 mg/kg of dexamethasone (29). Therefore, 10 mg of epidural dexamethasone might not induce neurotoxicity.

There were several limitations to our study. First, we used epidural PCA with basal rate and intermittent bolus for postoperative pain control unlike other studies to control moderate to severe postoperative pain after gastrectomy. This basal continuous epidural administration of ropivacaine with fentanyl could reduce the VAS score of all groups and prevent an accurate comparison of dexamethasone's effect. In spite of this confusing factor, our study demonstrated that the addition of epidural dexamethasone was effective for postoperative analgesia.

Secondly, we did not investigate side effects such as hyperglycemia and adrenal suppression. High dose dexamethasone has been reported to be able to cause side effects such as hyperglycemia, wound infection, and postoperative bleeding (17). However, no significant side effects of epidural dexamethasone have been reported through the study. Maillefert et al (30) reported that a large dose of epidural dexamethasone (15 mg) may be associated with transient adrenal suppression but it was clinically benign and reversible. In our study, we adopted 5 mg and 10 mg of dexamethasone which were lower than dose in the study by Maillerfert et al.

In our study, we found epidural dexamethasone was effective for reducing postoperative pain. Especially, an epidural dexamethasone dose of 10 mg was more effective than a lower dose in patients undergoing gastrectomy, which was associated with moderate to severe postoperative pain. Therefore we recommend an epidural dexamethasone dose of 10 mg as an effective pretreatment for postoperative analgesia in patients expected to experience severe pain after operation.

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