Dexamethasone as an adjuvant to thoracic epidural provided more prolonged analgesia for post-thoracotomy pain than clonidine and fentanyl

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Objectives
To evaluate the analgesic yield of thoracic epidural (TE) analgesia using bupivacaine in combination with dexamethasone, clonidine versus fentanyl for thoracotomy patients.
Patients and methods
Sixty patients were divided into four equal groups, which received TE analgesia immediately at end of surgery during skin closure using bupivacaine either alone (C group) or in combination with dexamethasone (S1 group), clonidine (S2 group), or fentanyl (S3 group). Postoperative (PO) pain was measured using a visual analogue scale (VAS); rescue analgesia (50 mg mepridine) was given when a patient had a VAS score of 40, and the duration of analgesia and the total mepridine doses consumed were determined during 24-h postoperatively. Verbal rating scores were used for the evaluation of PO sedation and nausea and vomiting (PONV).
Results
The mean duration of analgesia was significantly longer in the study groups compared with group C, with a significantly longer duration in the S1 group compared with the S3 group. The mean 24-h cumulative pain VAS score and the total PO rescue analgesia consumed were significantly lower in the S1 group compared with the other groups and in the S2 group compared with group C. Both S2 and S3 groups showed significantly higher frequency of higher sedation scores compared with the C and S1 groups. The frequency of patients who had a PONV zero score was significantly higher in the S1 group compared with the other groups, with a nonsignificant difference among the other groups.
Conclusion
TE analgesia using bupivacaine with clonidine or dexamethasone is an efficient therapeutic modality for post-thoracotomy pain. Dexamethasone as an adjuvant provided more prolonged PO analgesia, with a reduction of rescue analgesia consumption without PO sedation, and spares the use of antiemetics for PONV that was minimized in frequency and severity.

Keywords:
clonidine, dexamethasone, fentanyl, post-thoracotomy pain, thoracic epidural

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Introduction

Perioperative pain management is crucial, especially for patients undergoing major surgeries. Postoperative (PO) pain after chest surgery is multifactorial; first, surgery and tissue trauma with concomitant nerve sparing or scarification may be the most dominant nociceptive mechanism, second, acute inflammation induced by tissue injury with the concomitant release of nociceptive cytokines and inflammatory mediators plays a role in induction and/or aggravation of pain, and third, a characteristic feature for chest surgery conducted through intercostal incision is pain during respiration. In addition, thoracotomy results in severe PO pain potentially leading to chronic pain [1,2].

Pain relief after thoracic surgery is of particular significance for the reduction of PO pulmonary and cardiac complications; however, because of the difficulty in pain control, many approaches have been suggested, but a multimodal therapeutic strategy that provides a central or a peripheral block associated with nonsteroidal anti-inflammatory and adjuvant drugs is now the cornerstone of treatment [3,4].

Epidural analgesia has multiple inherent advantages including the ability of stress response suppression, hemodynamic stability, and proper pain control in addition to reduction in the consumption of PO analgesia. Thoracic epidural has certain additional advantages as it allows early extubation, better ventilatory mechanisms and gas exchange, and decreased incidence of atelectasis, pneumonia, and chronic PO pain [5–7].

Multiple studies have attempted to use an adjuvant for thoracic epidural analgesia for alleviation of pain after

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thoracotomy; however, the results have been disappointing as Allen *et al.* [8] reported that an infusion of local anesthetic into the subcutaneous area and around the rib fracture site did not improve the outcome of epidural analgesia. Chandra *et al.* [9] found that addition of transcutaneous electric nerve stimulation to epidural analgesia led to a significant reduction in pain with no sequelae, but the effects are short lasting.

Considering the advantages of thoracic epidural analgesia for post-thoracotomy pain relief, the current study aimed to evaluate the analgesic yield of using bupivacaine in combination with dexamethasone, clonidine, or fentanyl in patients undergoing thoracotomy.

Patients and methods

The current double-blind prospective comparative study was carried out at Departments of Anesthesia and Chest surgery, Benha University Hospital, from July 2011 to February 2012. After approval of the study protocol by the Local Ethical Committee and patient consent was obtained, the study was designed to include 60 patients assigned for thoracotomy for one-segment lobectomy. Patients with an infection at the puncture site or those with coagulation disorders or vertebral anomalies were excluded from the study. The demographic and clinical data of all the patients enrolled were obtained. Patients were randomly divided into four equal groups ($n = 15$), using sealed envelopes, according to the medication used for thoracic epidural analgesia: the control group (group C) was assigned to receive plain bupivacaine 0.3 mg/kg at a 0.25% concentration (2.5 mg/ml) [10]. There were three study groups (groups S): the S1 group included patients assigned to receive a combination of bupivacaine 0.3 mg/kg at a 0.25% concentration (2.5 mg/ml) and dexamethasone 8 mg [11], and the mixture was diluted with saline to a total volume of 10 ml, the S2 group included patients assigned to receive a combination of bupivacaine 0.3 mg/kg at a 0.25% concentration (2.5 mg/ml) and clonidine 1 μg/kg [12], and the mixture was diluted with saline to a total volume of 10 ml, and the S3 group included patients assigned to receive a combination of bupivacaine 0.3 mg/kg at a 0.25% concentration (2.5 mg/ml) and fentanyl at a dose of 1 μg/kg [13], and the mixture was diluted with saline to a total volume of 10 ml.

All patients were taken into the operating room unpremedicated and after standard monitoring of noninvasive blood pressure, ECG, and peripheral oxygen saturation (SpO_2), the administration of Lactated Ringer's solution was started. Patients were positioned in the optimal sitting position, and after the identification of the epidural space using the loss of resistance technique, a 20-G epidural catheter was inserted through an 18-G Touhy needle that was placed at the T_{6-7} interspace and advanced 3–5 cm into the epidural space. After an injection of 3 ml of 2% xylocaine through the epidural catheter as a test dose, the catheter was fixed and the patient was repositioned in a supine position. All epidural study medications were injected at the end of the operation during skin closure.

The same anesthetic regimen was applied for all the study groups; general anesthesia was induced with thiopental (3–5 mg/kg), fentanyl (1–2 μg/kg), and rocuronium (0.5 mg/kg), and then controlled mask ventilation for 1.5 min was continued with isosflurane 1.5% until complete muscle relaxation. Then the patient was intubated with a suitable size endotracheal tube. Anesthesia was maintained by isoflurane 1% and controlled ventilation using a closed circuit system with 100% O_2. Ventilation parameters were a tidal volume of 6–8 ml/kg, ventilatory rate adjusted to maintain end tidal CO_2 between 35 and 40 mmHg, and an inspiratory to expiratory ratio (I : E) of 1 : 2.

During the intraoperative period, standard monitoring was carried out including systolic blood pressure (SAP), heart rate (HR), and partial arterial SpO_2. To avoid hypothermia during the operative period, the patients received prewarmed fluids at the end of the surgery; residual neuromuscular block was reversed with neostgmine (0.04 mg/kg) and atropine (0.01 mg/kg), and the patients were extubated when they fulfilled the criteria of extubation. Vital signs including SAP, HR, respiratory rate (RR), and SpO_2 were assessed, after transfer to the postanesthetic care unit, every 30 min for 2 h and then 2 hourly for 12 h and 4 hourly thereafter, and were expressed as the mean of cumulative measures throughout the first 24 PO hours.

The intensity of PO pain was measured using the visual analogue scale (VAS) (a 100 mm scale, with '0' indicating no pain and '100' indicating worst pain ever) [14] every 30 min until the first request of rescue analgesia. Rescue analgesia was provided when the patient had a VAS score of 40 and the duration of analgesia, defined as the time lapsed since the epidural injection till the first request of rescue analgesia, was determined during 24 h postoperatively. PO rescue analgesia was provided in the form of meperidine hydrochloride (pethidine) at a dose of 50 mg to be repeated according to the need and the total dose consumed.

Verbal rating scores were used for the evaluation of PO sedation (0 = awake and alert, 1 = drowsy, 2 = mostly sleeping, and 3 = difficult or impossible to awaken), and PO nausea and vomiting (PONV) (0 = no nausea or vomiting, 1 = nausea, 2 = vomiting but not necessitating antiemetic, 3 = nausea and vomiting necessitating antiemetic) [15]. PO sedation was assessed half-hourly until 2 h postoperatively.

Statistical analysis

Data are presented as mean ± SD, ranges, numbers, and ratios. Data were analyzed using Wilcoxon's ranked test for unrelated data (Z-test) and the χ^2-test. Statistical analyses were carried out using SPSS (version 15, 2006) (APACHE software foundation, USA). A P value less than 0.05 was considered significant.

Results

The study included 60 patients, 48 men and 12 women, mean age 49.5 ± 8.3 years, range 36–66 years. Thirty-four patients (56.7%) were ASA grade I, 14 patients (23.3%)

Table 1 Patients' data and duration of surgery

Data	C group	S1 group	S2 group	S3 group
Age (years)	50 ± 8.6 (41–66)	49.6 ± 9.7 (36–65)	49.5 ± 7.1 (43–64)	49.1 ± 8.6 (39–65)
Sex (M:F)	11:4	12:3	12:3	13:2
ASA (I:II:III)	9:4:2	8:4:3	9:3:3	8:3:4
Weight (kg)	81.5 ± 5.7 (73–93)	85.1 ± 4.8 (76–95)	84.7 ± 8.1 (71–95)	83.1 ± 5.1 (75–92)
Height (cm)	165.7 ± 3.4 (161–175)	164.7 ± 4.3 (159–173)	163.9 ± 3.8 (159–171)	164.8 ± 4.6 (159–174)
BMI (kg/m^2)	29.7 ± 2.4 (24.8–34.2)	31.5 ± 2.7 (26.6–36.6)	31.6 ± 3.5 (24.6–34.9)	30.7 ± 3 (24.8–34.2)
Duration of surgery (min)	166.7 ± 18 (140–200)	169 ± 19.5 (130–200)	168.3 ± 17.6 (150–200)	164 ± 20.5 (135–200)

Data are presented as mean ± SD, ratio and ranges are in parentheses.
F, female; M, male.

were ASA grade II, and 12 patients (20%) were ASA grade III. All surgeries were completed uneventfully without intraoperative complications within a mean operative time of 167 ± 18.6, range 130–200 min. Patients' details and operative times are shown in Table 1. There was a nonsignificant ($P > 0.05$) difference between the patients studied in the age, sex, weight, height, BMI, ASA grade, and duration of surgery.

All PO baseline measures of SAP, HR, RR, and SpO_2 showed a nonsignificant ($P > 0.05$) difference between the groups studied. The mean SAP measures recorded at the end of the first 24 h postoperatively were significantly ($P < 0.05$) lower in patients who received epidural clonidine compared with their baseline measures, whereas the difference was nonsignificant ($P > 0.05$) in the other groups. Moreover, the mean PO SAP in the patients who received clonidine and fentanyl was significantly lower ($P < 0.05$) compared with those who received bupivacaine alone, whereas those who received epidural dexamethasone showed a nonsignificant ($P > 0.05$) difference compared with those who received bupivacaine alone. In contrast, the PO HR, RR, and SpO_2 measures showed a nonsignificant ($P > 0.05$) difference compared with their corresponding baseline data and the control group (Table 2).

The mean duration until the first request of rescue analgesia was significantly ($P = 0.001$) longer in the three study groups (7.5 ± 1.9, 6.8 ± 1.9, and 5.7 ± 1.7 h, respectively) compared with the control group (2.8 ± 0.9 h). Moreover, the mean duration until the first request of rescue analgesia was significantly ($P = 0.01$) longer in the S1 group compared with the S3 group, whereas the S2 group showed a nonsignificant ($P > 0.05$) difference compared with both the S1 and the S3 group (Fig. 1).

The mean cumulative pain VAS score, recorded throughout the first 24 h after surgery, was significantly lower in the S1 group (19.8 ± 5.3) compared with the control group ($P = 0.001$), the S2 group ($P = 0.007$), and the S3 group ($P = 0.003$), whereas the 24-h cumulative pain score recorded in the S2 group (26.1 ± 5.9) was significantly ($P = 0.029$) lower compared with the control group (34.2 ± 9.7), but nonsignificantly ($P > 0.05$) compared with the S3 group (30.7 ± 7.1), which had a nonsignificantly ($P > 0.05$) lower 24-h cumulative pain score compared with the control group (Fig. 2).

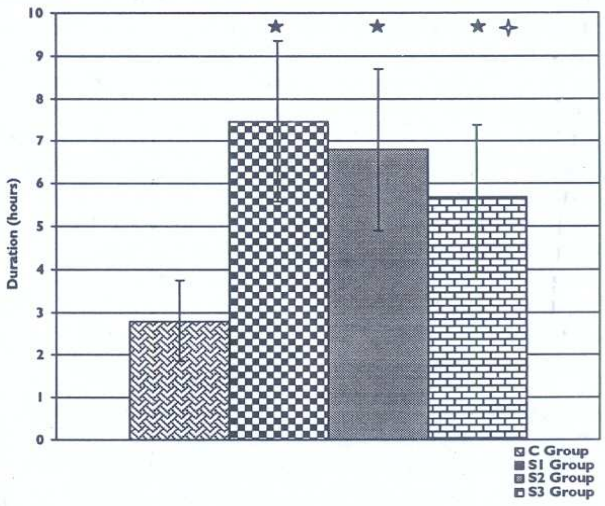
Throughout the first 24 h postoperatively, all patients requested rescue analgesia; 17 patients (28.3%) requested it once, 24 patients (40%) requested it twice,

Table 2 Patients' vital data recorded at the end of first 24 h after surgery compared with their baseline data

Data	C group	S1 group	S2 group	S3 group
SAP (mmHg)				
Baseline	123.5 ± 5.5	120.8 ± 4.1	121.7 ± 4	122.3 ± 4.5
End of PO 24 h	120.7 ± 4	118.6 ± 4.7	115.6 ± 8.2[a,b]	117.1 ± 6.9[b]
Heart rate (beats/min)				
Baseline	84.3 ± 2.4	82.7 ± 2.1	83.1 ± 2.8	82.9 ± 2.8
End of PO 24 h	82.5 ± 2.8	80.9 ± 3.2	80.4 ± 5.5	79.8 ± 4.7
Respiratory rate (breaths/min)				
Baseline	19.4 ± 1.5	19.8 ± 1.2	19.6 ± 1.3	19.6 ± 2
End of PO 24 h	19.3 ± 2.1	19.6 ± 2.2	19.4 ± 2.4	19.5 ± 2.2
SpO_2 (%)				
Baseline	98.5 ± 1.1	98.1 ± 1.1	98.3 ± 0.9	98.2 ± 1.2
End of PO 24 h	98.1 ± 1.7	97.3 ± 2.5	97.1 ± 3.4	97.4 ± 2.5

Data are presented as mean ± SD.
PO, postoperative; SAP, systolic arterial blood pressure; SpO_2, partial arterial oxygen saturation.
[a]Significant versus baseline.
[b]Significant versus C group.

Figure 1



Mean (± SD) duration until the first request of PO rescue analgesia. Black asterisk: significant difference versus C group. Four-point asterisk: significant difference versus S1 group. PO, postoperative.

13 patients (21.7%) requested it thrice, and six patients (10%) requested it more than three times. There was a significant ($P < 0.05$) difference in favor of group S1 in the frequency of lower number of rescue analgesia requests versus all of the other groups, with a significantly

($P<0.05$) lower frequency of requests in group S2 compared with groups C and S3 and a significantly ($P<0.05$) lower frequency of requests in favor of group S3 compared with group C (Fig. 3).

The mean consumed PO rescue analgesia was significantly reduced in group S1 (86.7 ± 44.2 mg) versus groups C ($P=0.001$), S2 ($P=0.007$), and S3 ($P=0.004$), whereas that of group S2 (100 ± 46.3 mg) was significantly ($P=0.004$) lower compared with group C, but nonsignificantly ($P>0.05$) versus group S3 (113.3 ± 39.8 mg), with nonsignificantly ($P>0.05$) lower consumption in group S3 compared with group C (133.3 ± 55.6 mg). In comparison with epidural plain bupivacaine, epidural dexamethasone reduced the consumption of PO rescue analgesia by $33.8 \pm 19\%$, epidural clonidine reduced it by $23.3 \pm 20.8\%$, and epidural fentanyl reduced it by $12.2 \pm 21.3\%$, with a significantly ($P<0.05$) higher percentage of reduction with dexamethasone compared with clonidine and fentanyl, which showed a nonsignificant ($P>0.05$) difference (Fig. 4).

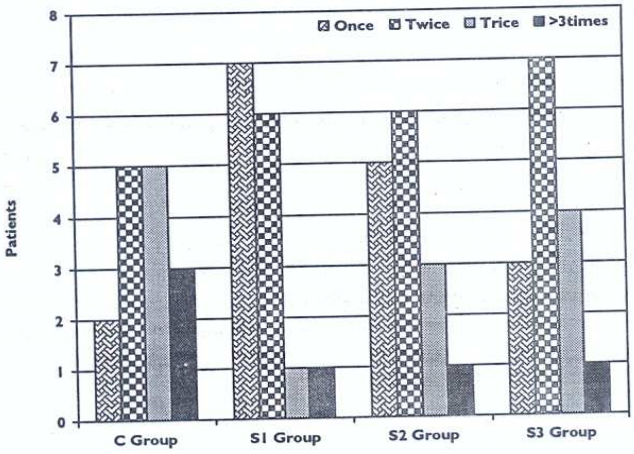
Only eight patients, three in S2 and five in S3 groups, had a sedation score of 3 immediately after surgery and four of them, one in S2 and three in S3 groups, remained sedated until half an hour after surgery. In contrast, no patient in C and S1 groups had sedation score 3 and 11 patients, seven in C and four in S1 groups, were aware and alert immediately after surgery and 17 patients, eight in C and nine in S1 groups, were aware and alert half an hour after surgery. Both S2 and S3 groups showed a significantly ($P<0.05$) higher frequency of higher sedation scores compared with the C and S1 groups (Table 3).

In terms of PONV scoring, 19 patients (31.7%) had a score of 0, 19 patients (31.7%) had a score of 1, 14 patients (23.3%) had a score of 2, and only eight patients (13.3%) had a score of 3; the frequency of patients with a 0 score was significantly ($P<0.05$) higher in the S1 group compared with the other groups, with a nonsignificant ($P>0.05$) difference among groups C, S2, and S3, but in favor of group S3 (Fig. 5).

Discussion

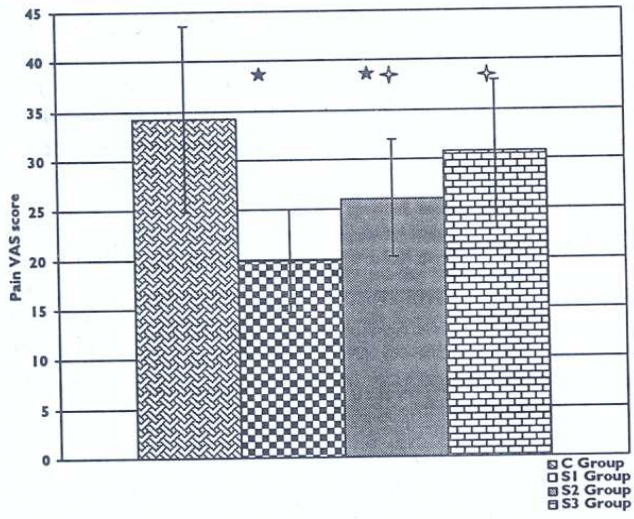
Thoracic epidural as a line for the management of PO pain, irrespective of the medication used, proved effective for the reduction of both the intensity of pain and the number of requests of rescue analgesia, with prolongation of duration until the first request of rescue analgesia. Such beneficial effects can be attributed to multiple factors: first, the epidural route of administration provided better and well-sustained analgesia compared

Figure 3



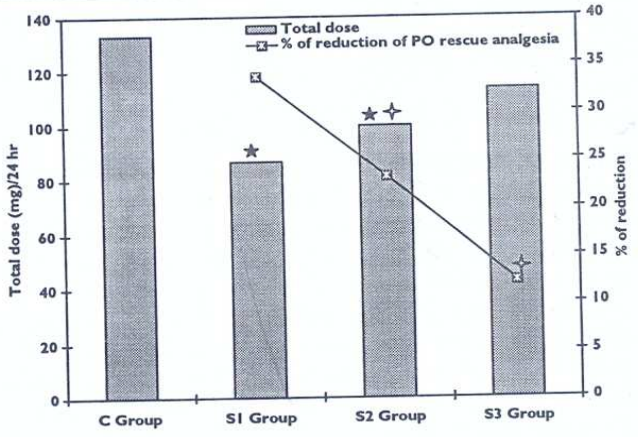
Patients' distribution according to the number of requests of rescue analgesia.

Figure 2



Mean (±SD) cumulative pain VAS score recorded during the first PO 24 h. Black asterisk: significant difference versus the C group. Four-point asterisk: significant difference versus the S1 group. PO, postoperative; VAS, visual analogue scale.

Figure 4



Mean total dose of mepridine consumed during the first 24 h postoperatively in relation to the percentage of reduction versus the control group. Black asterisk: significant difference versus the C group. Four-point asterisk: significant difference versus the S1 group. PO, postoperative.

Thomas and Beevi [11] found that preoperative epidural administration of dexamethasone 5 mg, with or without bupivacaine, reduced PO pain and morphine consumption following laparoscopic cholecystectomy. Also, Khafagy *et al.* [26] found that an epidural bupivacaine–dexamethasone admixture had almost the same analgesic potency as bupivacaine–fentanyl, with opioid-sparing and antiemetic effects.

Recently, Ayad and El-Masry [27] used a thoracic epidural injection of a mixture of 150 µg clonidine and 80 mg of methylprednisolone acetate diluted in 8 ml of 0.5% lidocaine as a therapeutic modality for chronic intractable post-thoracotomy pain and reported improvement in 12 of 13 patients, with greater than 50% reduction of pain, and allodynia, sleep disturbance, appetite changes, and daily activity improved in the injection group.

It can be concluded that thoracic epidural analgesia using bupivacaine with clonidine or dexamethasone is an efficient therapeutic modality for post-thoracotomy pain. Dexamethasone as an adjuvant provided more prolonged PO analgesia with a reduction in requests for rescue analgesia without PO sedation, and spares the use of antiemetics for PONV, which was minimized in frequency and severity. However, wider-scale studies are required before establishing dexamethasone as the adjuvant of choice for thoracic epidural analgesia.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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