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Thoracic epidural for post-thoracotomy pain: a comparison of three concentrations of sufentanil in bupivacaine

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ABSTRACT

Background: The aim of this prospective, double blind, randomised trial was to compare the analgesic and adverse effects of three concentrations of the thoracic epidural sufentanil with bupivacaine in patients undergoing thoracotomy.

Methods: We studied 60 (randomised) patients who were to receive a 10 ml bolus dose of sufentanil, 1μg/ml, 2 μg/ml and 3 μg/ml, in bupivacaine 0.125%, via thoracic epidural. Postoperatively, pain at rest, on coughing and with ambulation was assessed using a visual analogue scale (VAS) and observer verbal ranking score (OVRS) at 2, 6, 12 and 24 hours. Adverse effects were simultaneously assessed.

Results: There was no significant difference in the baseline characteristics between the three groups. The number of patients with episodes of unsatisfactory pain, i.e. a VAS scores ≥ 40 and OVRS ≥ 2, at each of the four assessments postoperatively, was significantly higher with sufentanil 1 g/ml than with sufentanil 2 μg/ml or μ3 g/ml ($p < 0.05$). In the 3 μg/ml sufentanil group, four patients (20%) had a sedation score ≥ 3 compared with one (5%) and no (0%) patients in the 2 μg/ml and 1 μg/ml sufentanil groups, respectively ($p < 0.05$). In addition, 30% patients experienced pruritus in the 3 μg/ml sufentanil group compared with 10% and 5%, respectively, in the 2 μg/ml and 1 μg/ml sufentanil groups. In the sufentanil 3 μg/ml, 2 μg/ml and 1 μg/ml groups, 30%, 20% and 5% patients, respectively, had emetics symptoms ($p < 0.05$).

Conclusions: We conclude that a thoracic epidural bolus of 10 ml sufentanil 2 μg/ml with bupivacaine 0.125% provides the optimal balance between pain relief and side-effects following thoracotomy.

Introduction

Thoracotomy, with its associated pathophysiological abnormalities, produces one of the most damaging surgical insults which it is possible to inflict on patients.[1,2] Thoracotomy pain arises as a result of severe chest wall trauma including fractured ribs and damaged peripheral nerves, and central nervous system hypersensitivity.[1,2] The chest wall cannot be immobilised to control this pain; it must remain in constant motion, indeed vigorous motion, if secretions are to be cleaned. Additional challenges are that many patients are elderly, they may be malnourished, and frequently have co-existing cardiac and respiratory diseases.

Optimum pain relief after thoracotomy is essential if the incidence of atelectasis and postoperative pneumonia are to be reduced.[3,4] Patients must not only be pain free at rest but must also be able to breath deeply, cough effectively and comply with postoperative physiotherapy.

There have been a number of analgesic techniques used to achieve this end point. Thoracic epidural administration of bupivacaine, in high concentration, can produce excellent analgesia. However, the incidence of hypotension with 0.5% bupivacaine is high, and lower concentrations, when used unsupplemented, are likely to be less effective.[5] Epidural opioids have also been used after thoracotomy. Lipophilic drugs such as fentanyl are popular in this respect and probably have a lower incidence of side-effects than hydrophilic opioids such as morphine. The optimum concentration of fentanyl that balances efficacy against side-effects is thought to be 5 μg/ml. There has been much recent interest in attempts to improve the quality of epidural opioid analgesia by the addition of a low concentration of local anaesthetic in the hope of reducing the incidence of side-effects.[6,7]

Sufentanil is a short-acting opioid analgesic related to pethidine. Sufentanil is highly lipid soluble, with rapid onset and a short duration of action. A review of the available literature reveals that the standard dose of sufentanil in thoracic epidural has not been established yet. Therefore, this prospective, randomised, double blind study was designed to compare the analgesic and adverse effects of three concentrations of thoracic epidural sufentanil with 0.125% bupivacaine in patients undergoing thoracotomies.

Material and methods

After obtaining approval from the ethics committee of the medical university, written informed consent was obtained from the patients scheduled to undergo thoracotomies. Patients aged 18–60 years, of either sex, belonging to ASA physical status I, II and III, and with ± 25% ideal weight and height were included in the study. The exclusion criteria were: patients with pre-existing motor and sensory deficit, addicted to hypnosedative drugs, on chronic opioid or analgesic therapy, sensitive to local anaesthetic or study medication, or having contraindications to regional anaesthesia.

On arrival in the operating room a venous line was secured and Ringer's lactate solution was transfused at the rate of 10–15 ml/min. Patients were monitored with non-invasive blood pressure, pulse oximetry and continuous ECG. All patients were pre-medicated with midazolam 1 mg, glycopyrrolate 0.2 mg and fentanyl 2 μg/kg IV. After pre-oxygenation for 5 min, general anaesthesia was induced with propofol (2–3 mg/kg). Neuro-muscular block was achieved with succinylcholine and endotracheal intubation was performed using an appropriate sized cuffed double-lumen tube. Correct tube position was confirmed and anaesthesia was maintained with 50% N_2O in oxygen, halothane 0.5–1% and vecuronium bromide. In the left lateral decubitus position a mid-thoracic (T_{5-6} or T_{6-7} inter vertebral space) epidural catheter was placed using an 18 G Tuohy needle, and 4 cm of the catheter was left in the epidural space. A 3 ml test dose of 2% lidocaine with epinephrine (1:2,00,000) was then administered. Subsequently, the patients were randomly allocated to one of the three groups using a computer-generated table of random numbers.

Group I: Patients received 10 ml solution of 0.125% bupivacaine with 1 µg/ml of sufentanyl.
Group II: Patients received 10 ml solution of 0.125% bupivacaine with 2 µg/ml of sufentanyl.
Group III: Patients received 10 ml solution of 0.125% bupivacaine with 3 µg/ml of sufentanyl.

The epidural local anaesthetic solution was prepared by the anesthaesia technician (who otherwise did not participate in the study). The patients and anaesthetist/nurse were blind to the group allocation of the patients. Surgical incision was allowed after 10 min of epidural bolus. At any time during surgery, if the mean arterial pressure and heart rate increased to ≥ 25% of baseline, supplemental IV analgesic in the form of fentanyl 50 µg was given. Any episode of hypotension (systolic arterial pressure ≥ 90 mmHg), excluding surgical blood loss and bradycardia (heart rate < 50/min) was treated with ephedrine and atropine, respectively. On completion of surgery the patients were reversed with neostigmine and glycopyrrolate. Patients were then managed in a post-anaesthesia care unit (PACU) for 24 hours. Analgesia was assessed at 2, 4, 6, 12 and 24 hours using a visual analogue scale (VAS) (0 = no pain; 100 = worst pain imaginable) both at rest, and with cough and ambulation, after extubation. At the same time, pain was assessed using a four-point observer verbal ranking scale (OVRS) for pain[8] (Table I).

Table I: Observer verbal ranking scale for pain[8]

Pain score	Pain experience
0	No pain; pain not restricting any activity, e.g. cough, turning on the side
1	Mild pain, able to take maximal deep breath but movement and coughing slightly restricted by pain; physiotherapy effective
2	Moderate pain, needs help to move onto side; cough and deep breathing restricted by pain; physiotherapy ineffective
3	Severe pain; pain making turning onto side impossible and/or ineffective, or patient refuses to try

Sedation scores were also judged by the observer (1 = wide awake, 2 = drowsy, 3 = dozing intermittently, 4 = mostly sleeping but easily aroused, 5 = awakened only by shaking, 6 = unarousable).[8] At a VAS score of ≥ 40 and OVRS ≥ 2 supplemental analgesic was given in the form of epidural 5 ml bolus of bupivacaine 0.125%. Any episodes of nausea and/or vomiting, pruritis, urinary retention, sedation and respiratory depression were recorded at the same time as pain scores, and treated accordingly. Oxygen supplementation was given by Venturi mask if Spo2 fell below 92%.

Sample size estimation was based on an assumption to detect at least 20% difference in the number of patients with OVRS (≥ 2) at any time interval postoperatively among the groups to provide 95% power for two tail 't' tests at the level of 5% significance. A minimum sample size of 20 patients was determined for each group.

Data were collected by a blinded observer and are presented as mean ± SD or n (%). One-way ANOVA with reference correction for multiple comparisons was used to test normally distributed data for significance. Chi-square analysis or Fisher's exact test was used as appropriate for categorical data. The final analysis of the outcome of variables of pain scores was performed using a repeated measures analysis of variance. A p-value of < 0.05 was taken to be significant.

Results

Sixty patients were enrolled into the study and randomised into one of the three groups of 20 patients in each group. The three groups were comparable in age, weight, height, sex, ASA classification, duration of surgery and other variables recorded before operation (Table II). In the 1 µg/ml and 2 µg/ml sufentanil groups 80% and 30% patients, respectively, required supplementary fentanyl in the intraoperative period while none of the patients in the 3 µg/ml sufentanil group required such.

The dose of fentanyl required was also significantly higher in the 1 ≥g/ml group than in the 2 µg/ml sufentanil group (p < 0.05) (Table III). At some point during the study period 80%, 30% and 25% of patients, respectively, showed VAS for pain ≥ 30 (Figure 1).

Table II: Demographic characteristics and pre-operative variables of the three study groups

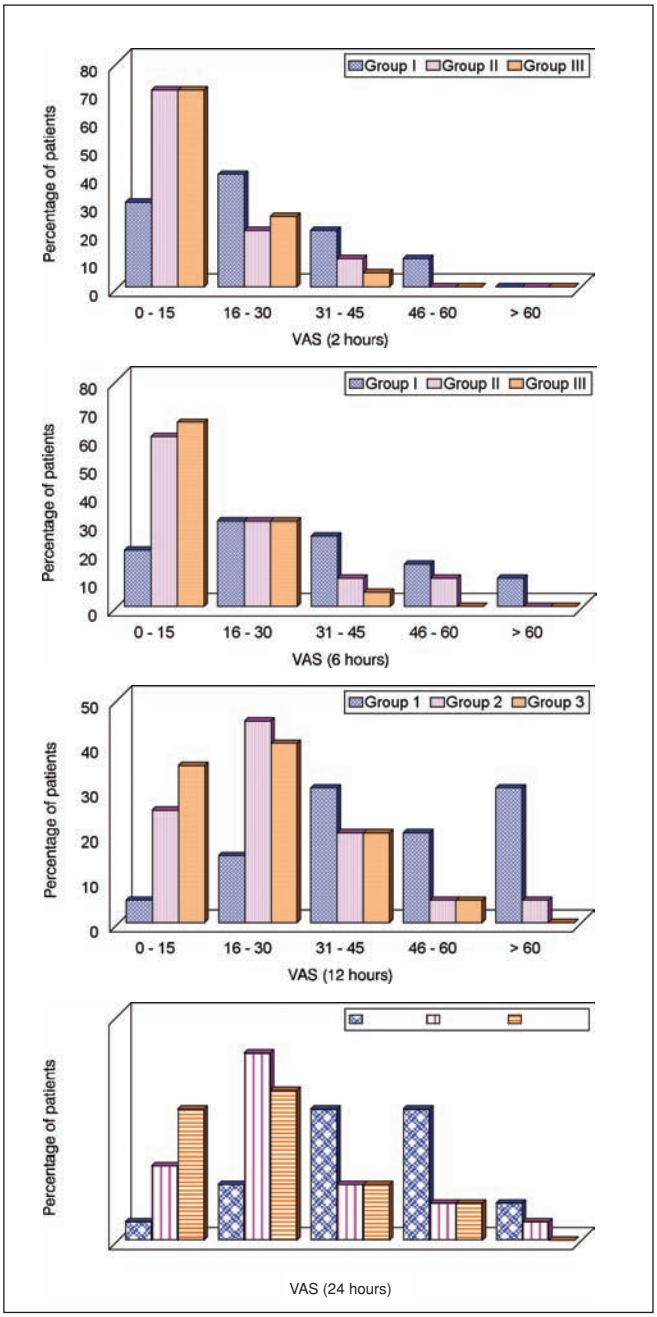
	Group I	Group II	Group III
Age (years)	45 ± 8	42 ± 18	43 ± 16
Sex (M:F)	11:9	9:11	10:10
Height (cm)	165 ± 15	170 ± 15	168 ± 18
Weight (kg)	68 ± 12	65 ± 14	70 ± 16
Duration of surgery (min)	145 ± 35	150 ± 30	148 ± 36
ASA (I:II:III)	4:10:6	3:10:7	5:9:6
RR (per min)	22 ± 4	23 ± 4	22 ± 3
HR (per min)	82 ± 12	86 ± 14	80 ± 12
SAP (mmHg)	150 ± 28	142 ± 32	146 ± 30
FEV_1 (forced expiratory volume in one second) (litre)	1.9 ± 0.3	2.0 ± 0.4	1.9 ± 0.2
FVC (forced vital capacity) (litre)	2.4 ± 0.6	2.5 ± 0.3	2.4 ± 0.4
PEFR (peak expiratory flow rate) (litre/min)	390 ± 110	380 ± 120	395 ± 115

Table III: Intra-operative supplementary fentanyl requirement

	Group I (n = 20)	Group II (n = 20)	Group III (n = 20)
Number of patients requiring supplementary fentanyl n (%)	16 (80%)	6 (30%)*	0 (0%)*+
Dose of fentanyl (Mn SD) (in µg)	76 22	42 18*	0 0*+

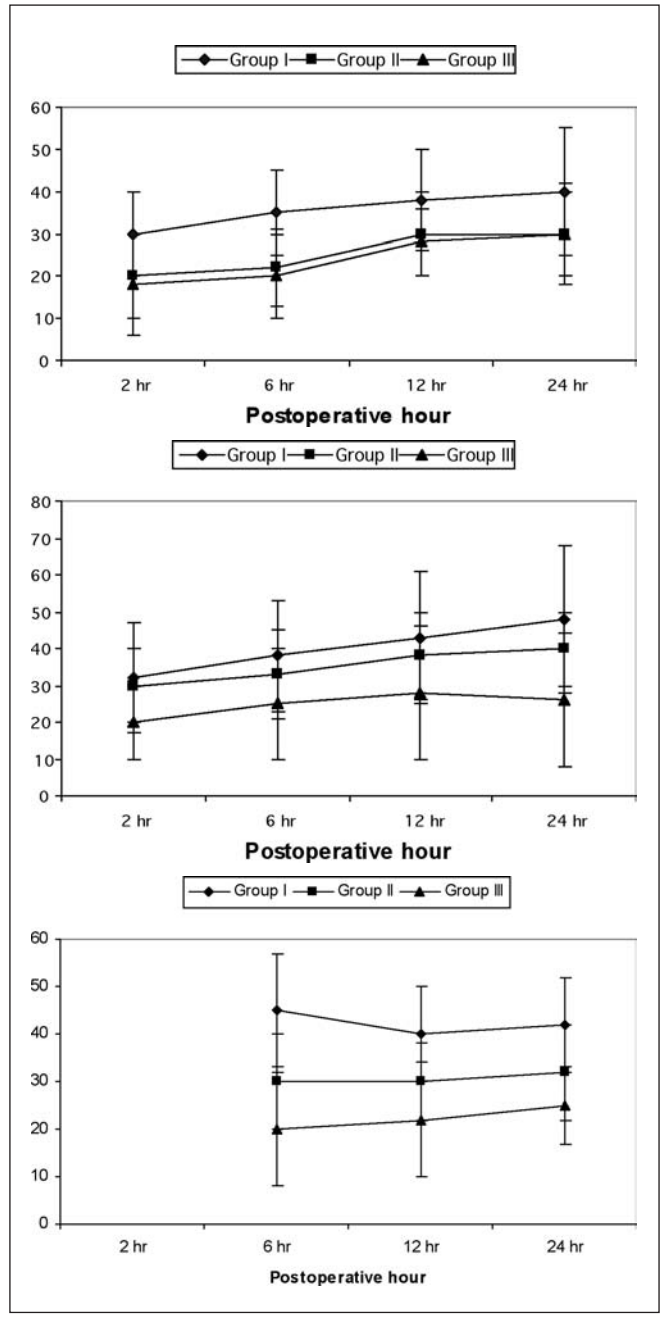
* p < 0.05 (I vs II and I vs III)
+ p < 0.05 (II vs III)

Figure 1: Patients distribution according to VAS scores at different times



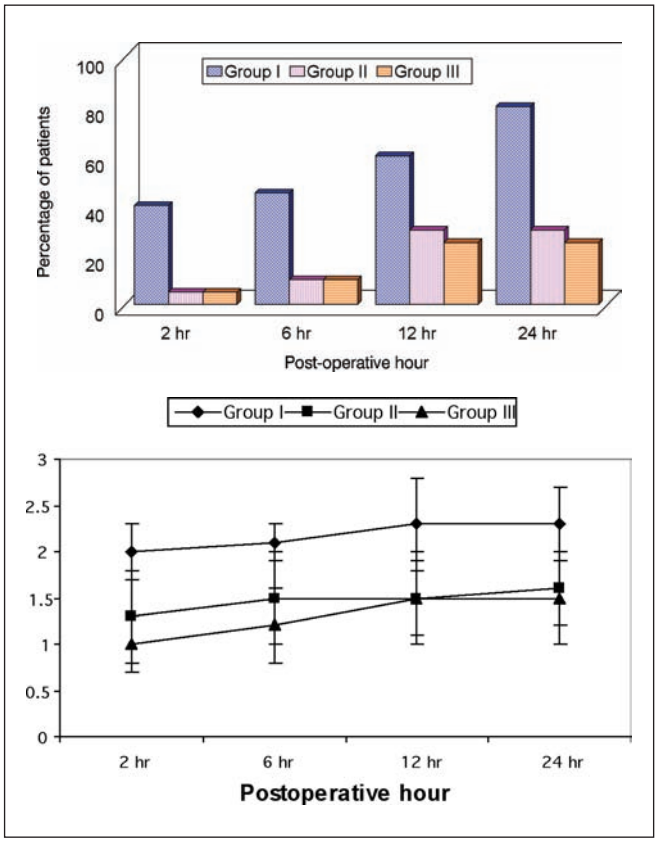
Mean pain scores were significantly greater in the 1 µg/ml sufentanil group at rest, with cough and with ambulation (p < 0.05) (Figure 2).

Figure 2: Visual analogue scores of patients for pain at rest, with cough and during ambulation, at different intervals postoperative



Patients with OVRS 2 during the study period were also comparable with VAS in different groups and similarly scores were also comparable (p < 0.05) (Figure 3).

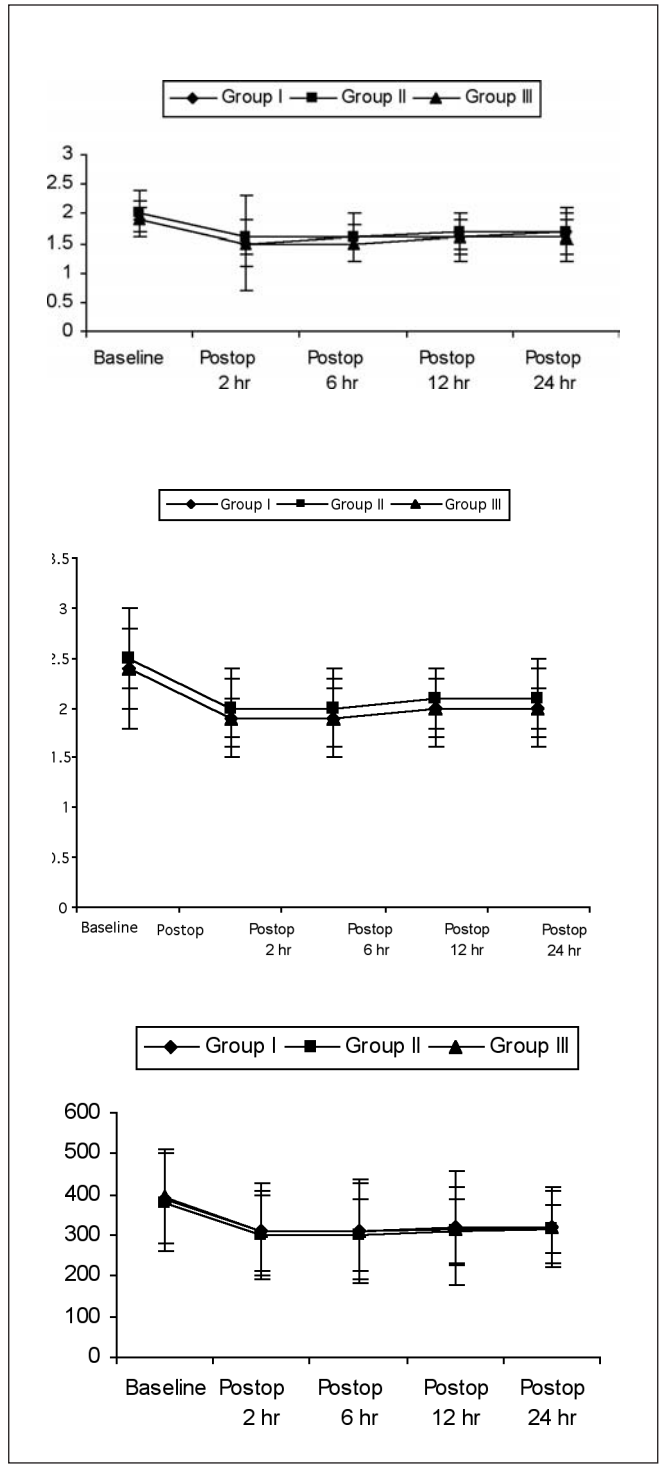
Figure 3: Comparison of OVRS and patient distribution according to OVRS 2 at different time intervals postoperative



None of the patients in the 1μg/ml sufentanil group had sedation (score ≥ 3) while in the 2 μg/ml and 3 μg/ml groups 50% and 20% patients, respectively, had sedation ($p < 0.05$). Pruritus and emetic symptoms ranged from 5 to 30% among the groups. None of the patients in any of the groups complained of numbness or limb weakness. In the 3 μμg/ml sufentanil group 10% patients had hypotension while in each of the other two groups 5% had hypotension. One patient in each group had bradycardia that required treatment (Table IV).

FEV_1, FVC and PEFR were all reduced to 40–50% of their preoperative values throughout the study period in all three treatment groups. Oxygenation was satisfactory in all patients during the study period. There was no statistical difference between the groups (Figure 4).

Figure 4: Comparison of FEV_1, FVC and PEFR at different time intervals



Discussion

Epidural local anaesthetic agents have an established role in analgesia during thoracic surgery. Opioids administered via the epidural route have been found to be superior in terms of analgesia, side-effects, length of stay and postoperative complications after thoracotomy.[9] Morphine is the most commonly used opioid for this application, but it may produce delayed respiratory depression and have a slow onset of action. In contrast to morphine, sufentanil is highly lipophilic, and the high affinity of sufentanil for opioid receptors results in a rapid onset of analgesia when it is administered epidurally. Hypotension was the most common side-effect with the use of the above and bupivacaine 0.25% in thoracic epidural, occurring in 80% of cases of patients in whom satisfactory analgesia was achieved.[5] The high incidence of hypotension with bupivacaine can be attributed to sympathetic block.[10] Although epidural administration of opioids does not result in sympathetic block[11] hypotension has been observed with an epidural of 50 μg sufentanil,[12] which could be related to systemic uptake from epidural space. In view of these findings and to avoid hypotension associated with either a high concentration of bupivacaine or a high dose of sufentanil, we used a low dose of sufentanil (1 μg/ml to 3 μg/ml) in a lower concentration of bupivacaine (0.125%).

Patients who are listed for thoracotomy may have underlying lung pathology such as chronic obstructive pulmonary disease and pleural disease. Their surgery may involve lung collapse and re-expression, as well as lung resection. In the postoperative

Table IV: Adverse effects

	I (n-20)	II (n-20)	III (n-20)
	n (%)	n (%)	n (%)
Sedation (≥ 3) score	0 (0)	1 (5)	4 (20)*
Pruritus	1 (5)	2 (10)	6 (30)*
Emetic symptoms	1 (5)	4 (20)	6 (30)*
Numbness	0 (0)	0 (0)	0 (0)
Limb weakness	0 (0)	0 (0)	0 (0)
Hypotension	1 (5)	1 (5)	2 (10)
Bradycardia	1 (5)	1 (5)	1 (5)
Shoulder pain	0 (0)	0 (0)	0 (0)

* $p < 0.05$ (I vs III)

period there is a high risk of sputum retention, pneumonia and pulmonary oedema.[13] Consequently, provision of high quality analgesia following thoracotomy is essential. Demand-only patient-controlled epidural analgesia after thoracotomy and upper abdominal surgery using sufentanil with or without bupivacaine has been assessed in a previous study.[14] Sufentanil 1 μg/ml with bupivacaine 0.125% did not significantly reduce the amount of sufentanil required, the pain scores or the side-effects. Taking this into consideration we chose to use three different concentrations of sufentanil (1 μg/ml to 3 μg/ml) in 0.125% bupivacaine in our study.

It has been demonstrated that epidural sufentanil contributes significantly to the analgesia component of balanced anaesthetic during lung surgery.[12] It has also been reported that, when compared with IV sufentanil, epidural sufentanil decreases the need for supplementary IV sufentanil, and postoperative analgesia is better and longer lasting.[15] Our results show that epidural sufentanil with bupivacaine produces analgesia, and is concentration dependent. The duration and intensity of pain relief were increased when a higher concentration of the drug was given, up to a maximum concentration of 3 μg/ml. More patients receiving epidural sufentanil 1 g/ml in bupivacaine 0.125% had pain (VAS ≥ 30 and OVRS ≥ 2) compared with those who received sufentanil 2 μg/ml or 3 μg/ml in bupivacaine 0.125%.

Epidural sufentanil infusion combined with bupivacaine is an optimal analgesia when tailored to the site of nociceptive input.[16] Preoperative and postoperative thoracic epidural analgesia techniques have been assessed on post-thoracotomy pain: preoperative epidural analgesia was found to be an appropriate method and was more effective in preventing acute post-thoracotomy pain.[17] Taking this into consideration, we administered preoperative thoracic epidural analgesia in our study.

Different epidural analgesics and their effects on pulmonary function have been compared in the past. Throughout the postoperative period, reductions of up to 70% of the preoperative values (FEV_1, FVC and PEFR) were noticed. With the different concentrations of sufentanil used in our study, no difference was found among the groups with regard to pulmonary functions.

Epidural opioids are associated with dose-dependent adverse effects of sedation, pruritis, nausea and respiratory depression.[18] In this regard, in our study a concentration of 2 μg/ml sufentanil was found to be optimum. On the other hand, lower concentrations of epidural sufentanil (1 μg/ml) do not provide high quality analgesia following thoracic surgery. In patients who receive insufficient analgesia, an alternative method of increasing the concentration of epidural opioids is to consider an additional drug, i.e. clonidine.[19,20] In our study there appeared to be an increased incidence of pruritus (30%) in patients receiving epidural sufentanil 3 μg/ml. Our findings are in accordance with those of the previous report.[21] Up to 41% of patients experienced generalised pruritus but none required, or requested, treatment for this. Our findings suggest that an increasing concentration of epidural opioids leads to a significant increase in the incidence of pruritus.[24]

When, in the past, different doses of sufentanil (up to 50 μg) were used for postoperative Caesarean analgesia, mild dizziness and drowsiness were noted.[21–23] In contrast to this, 20% of patients in the 3 μg/ml sufentanil group in our study had a sedation score ≥ 3, which seems to be due to the synergistic effect of midazolam used as premedication by us, with sufentanil. Our findings concur with those of several earlier studies involving the use of fentanyl, viz increasing concentrations of fentanyl lead to increased sedation scores.[24,25]

In our study a significant difference in nausea and vomiting was found between the three treatment groups. Of the patients in the 3 μg/ml sufentanil (30 μg) group, 30% experienced nausea and vomiting. This result differs from results obtained in an earlier study.[26] In yet another study, only 5% of patients experienced only nausea with up to 30 μg of epidural sufentanil.[22] This difference may be because our patients received general anaesthesia with epidural analgesia, while in the other studies mentioned the patients received only epidural anaesthesia.

In conclusion, our study has shown that thoracic epidural sufentanil 2 or 3 μg/ml is associated with superior analgesia after thoracotomy compared with sufentanil 1 μg/ml in bupivacaine 0.125% in the immediate postoperative period. However, the use of sufentanil 3 μg/ml does improve analgesia, compared to sufentanil 2 μg/ml, but may increase the tendency to excessive sedation and pruritus. Therefore, epidural sufentanil 2 μg/ml in bupivacaine 0.125% would appear to provide the optimal balance between pain relief and adverse effects following thoracic surgery.

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