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A prospective, randomized comparison of preoperative and continuous balanced epidural or paravertebral bupivacaine on post-thoracotomy pain, pulmonary function and stress responses

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Both epidural and paravertebral blocks are effective in controlling post-thoracotomy pain, but comparison of preoperative and balanced techniques, measuring pulmonary function and stress responses, has not been undertaken previously. We studied 100 adult patients, premedicated with morphine and diclofenac, allocated randomly to receive thoracic epidural bupivacaine or thoracic paravertebral bupivacaine as preoperative bolus doses followed by continuous infusions. All patients also received diclofenac and patient-controlled morphine. Significantly lower visual analogue pain scores at rest and on coughing were found in the paravertebral group and patient-controlled morphine requirements were less. Pulmonary function was significantly better preserved in the paravertebral group who had higher oxygen saturations and less postoperative respiratory morbidity. There was a significant increase in plasma concentrations of cortisol from baseline in both the epidural and paravertebral groups and in plasma glucose concentrations in the epidural group, but no significant change from baseline in plasma glucose in the paravertebral group. Areas under the plasma concentration *vs* time curves for cortisol and glucose were significantly lower in the paravertebral groups. Side effects, especially nausea, vomiting and hypotension, were troublesome only in the epidural group. We conclude that with these regimens, paravertebral block was superior to epidural bupivacaine.

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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 immobilized to control this pain, it must remain in constant motion, indeed vigorous motion, if secretions are to be cleared. Additional challenges are that many patients are elderly, they may be malnourished and they frequently have co-existing cardiac and respiratory diseases.

Many strategies to control this pain have been described, but when the factors influencing its generation are considered, regional analgesia is the most logical approach. This is because 'neurogenic' pain, which occurs with intercostal nerve damage resulting from chest wall trauma, in addition to central nervous system hyperexcitability, are both known to be poorly sensitive to opioids,[1 3 4] and reliance on these drugs has many detrimental effects, especially on respiration and oxygenation.[1 2] For the optimal effect it is logical to start the regional analgesic regimen in the preoperative period[5] and to maintain it after operation for several days until wound healing is established. At the same time the use of a multimodal or 'balanced' approach to premedication and postoperative analgesia should also be considered.[1 6] Combination regimens consisting of an effective afferent block, an opioid and a non-steroidal anti-inflammatory drug (NSAID), starting in the preoperative period and continued into the postoperative period, may be expected to produce optimal results.[7]

Both epidural and paravertebral local anaesthetic blocks have been shown to be highly effective in controlling this pain. Three prospective, randomized comparisons have been made,[8–10] but the use of preoperative and continuous balanced techniques and investigation of their effects on pulmonary function (our primary research question) and stress responses do not appear to have been undertaken previously.

Patients and methods

We studied 100 consecutive patients, aged 17–80 yr, undergoing elective posterolateral thoracotomy after obtaining approval from the Local Ethics Committee and informed patient consent. Exclusion criteria were: lack of patient consent; sepsis over the thoracic vertebrae, empyema or systemic sepsis; allergy to amide-type local anaesthetics, diclofenac or morphine; contraindications to NSAID; psychiatric disease; inability to comprehend pain scoring, use of the hand-held spirometer or patient-controlled analgesia; poor command of the English language; need for an additional incision (e.g. laparotomy); endocrine disease, including diabetes mellitus; and coagulopathy.

Before operation, the use of the hand-held spirometer (Respiradyne Cheeseborough Ponds, USA)[11] was explained and preoperative baseline peak expiratory flow rate (PEFR) was obtained. Linear visual analogue pain scores were also explained, as was the use of a patient-controlled analgesia machine (PCA) (Baxter UK). Premedication consisted of morphine 10 mg and prochlorperazine 12.5 mg i.m., 1 h before operation with rectal diclofenac 50 mg.

Randomization in the anaesthetic room was by sequential allocation of eligible patients to computer-generated random numbers. In the epidural group, preoperative catheterization of 5 cm of catheter, directed cephalad at T7–10 under local anaesthesia, was followed by a test dose of 0.5% bupivacaine 3 ml and then 0.25% bupivacaine 10–15 ml. In the paravertebral group at T6–8, ipsilateral to the thoracotomy, a standard space location technique was used[12] and this was followed by injection of 0.5% bupivacaine up to 20 ml. At least 20 min were allowed to elapse before the start of surgery.

Anaesthesia, sufficient to obtund cardiovascular responses, was provided using propofol, fentanyl and isoflurane in air or oxygen. Double-lumen, endobronchial intubation and ventilation were facilitated with rocuronium or vecuronium. Perioperative use of glucose-containing i.v. fluids was avoided. Standard posterolateral thoracotomy was carried out in all patients, the intercostal level of which generally depended on whether lung surgery (T5–6) or oesophageal surgery (T7–8) was being carried out. The planned level of thoracotomy was known to the anaesthetist and the level of regional nerve block corresponded with this level. Single rib excision was carried out in all patients.

In the paravertebral group, before chest closure, an epidural-type catheter was inserted by the surgeon into the paravertebral space under direct vision using a standard technique.[13] During chest closure, a second bolus dose of 0.25% bupivacaine up to 20 ml was injected into the paravertebral space or up to 10 ml in the epidural space. In both groups this was followed by continuous postoperative infusion of bupivacaine; 0.25% in the epidural group and 0.5% in the paravertebral group, at a rate of 0.1 ml kg^{-1} h^{-1}. After operation, all patients also received diclofenac 50 mg 8-hourly, orally or rectally, and patient-controlled morphine using a 1-mg bolus, 5-min lockout period and no background infusion. Buccal prochlorperazine 3 mg 6-hourly was given on demand for nausea and/or vomiting.

All patients were subjected to the same postoperative active nursing and physiotherapy regimen.[1 2] Briefly, all patients were returned to the thoracic ward where they were nursed upright in bed for the rest of the day of operation, they were seated out of bed on day 1 and were expected to be walking, mobile and self-caring by day 2. Continuous 40% oxygen was given for the first 3 nights after operation. The continuous regional analgesic technique with regular NSAID was continued for 5 days.

The postoperative data collection period lasted for 48 h and this was carried out, non-blinded, by the nursing staff and physiotherapists: the difference in concentration of bupivacaine between the two groups was immediately obvious to the nurses who changed the infusion syringes. The aims of the study were deliberately not discussed with the ward staff to minimize bias. Four-hourly pain scores at rest and on maximal coughing were recorded. A visual linear analogue scale (VAS) was used with patients making a mark on a 10-cm line (0=no pain; 10=worst pain imaginable). Morphine requirements were transcribed from the PCA machine memory. Hourly sedation scores, nausea and vomiting episodes for the first 24 h, and then 4-hourly scores were collected. A four-point scale was used for sedation, but only patients who were difficult to rouse (grade 4) are presented. Four-hourly oximetry was recorded. The sitting position, in bed or in a chair, was adopted for 12-hourly spirometry, and maximal effort was encouraged by the nursing staff. Blood for measurement of glucose and cortisol concentrations was obtained before operation in the anaesthetic room, 15 min after skin incision, and 4, 12, 24 and 48 h after operation. Untoward effects such as hypotension, defined as a decrease in preoperative systolic or diastolic arterial pressure of 20% or more, and urinary retention, defined as requirement for catheterization, were noted. Postoperative respiratory morbidity was defined as three or more of the following: sputum changes, abnormalities in auscultation, chest radiological changes, fever greater than 38°C, leucocytosis greater than a total white cell count of 14×10^9 $litre^{-1}$ and oxygen saturation less than 90% of air. Serious complications such as these were included if they occurred at any time during the hospital stay, the duration of which was also recorded. The number of patients complaining of pain at the 6-month outpatient follow-up was also recorded.

Data were analysed using SPSS for Windows version 7.0 and Epidemiological Information for DOS version 5.0. The assumption of normality was checked using the Komolgorov–Smirnov test before applying *t* tests to parametric data. From each patient's serial measurements of PEFR, the lowest postoperative value was identified which was expressed as a fraction of the patient's preoperative control value. The distribution of these ratios was compared between the two groups using a two-tailed independent *t* test. The rate of recovery of PEFR at 48 h was assessed from the

Table 1 Patient characteristics and type of surgery in the paravertebral and epidural groups (mean (SD or range) or number)

	Epidural ($n=49$)	Paravertebral ($n=46$)
Age (yr)	61.7 (17–78)	62.5 (18–80)
Sex (M:F)	33:16	32:14
Weight (kg)	69.6 (13.8)	67.9 (13.9)
Oesophagastrectomy	6	5
Anti-reflux procedure	7	9
Lobectomy	27	23
Pneumonectomy	5	3
Pleurectomy	4	6

proportion of patients in each group achieving a PEFR within 95% of their own preoperative control and was compared using chi-square tests. The power of the study, based on PEFR as the main outcome measure, was 0.98 with a two-tailed alpha set at the conventional level of 0.05 and a difference in the means of 25%. For plasma cortisol and glucose measurements, the area under the curve for each patient was calculated using the trapezoid rule and independent two tailed *t* tests were used to analyse these distributions. Patients with an incomplete set of plasma cortisol and glucose measurements were excluded from analysis but not from graphical representation. Data were analysed using independent sample *t* tests, the Mann–Whitney *U* test, analysis of variance (ANOVA) and chi-square or Fisher's exact test, as appropriate. The null hypothesis was rejected at a level of α less than 0.05.

Results

There were no significant differences between the two groups in age, sex, weight or type of surgery (Table 1). An epidural catheter could not be sited in five patients and data from the remaining 95 patients were analysed. The presence of sensory loss to cold (ice), unilaterally in the paravertebral group and bilaterally in the epidural group, was confirmed in all patients in the early postoperative period although no formal assessment of this was made.

The distribution of visual analogue pain scores both at rest and on coughing were significantly different between groups (Mann–Whitney *U* test). Patients in the paravertebral group had significantly lower VAS pain scores both at rest and on coughing ($P=0.02$ and 0.0001, respectively) (Figs 1, 2). Cumulative morphine consumption in the first and second 24-h periods was significantly higher in the epidural group (mean 105.8 ($\pm$95% confidence intervals 20.4) mg and 262 (67) mg *vs* 85.5 (30) mg and 210.7 (63.8) mg; $P=0.008$ and 0.005, respectively). Pulmonary function, as assessed by PEFR, was significantly better preserved in the paravertebral group (Fig. 3). The lowest postoperative PEFR as a fraction of the preoperative control was 0.73 (SEM 0.06) in the paravertebral group in contrast with 0.54 (0.05) in the epidural group ($P<0.004$). These minima occurred at similar mean postoperative times of 19 (2.4) and 19.4 (3.2) h, respectively ($P=0.8$). Although PEFR rate recovered to within 95% of preoperative control values in 23 of 46 patients in the paravertebral group and in 18 of 49 in the epidural group, the difference was not statistically significant (chi-square, $P=0.19$). Oximetric recordings were significantly better in the paravertebral group throughout the 48-h

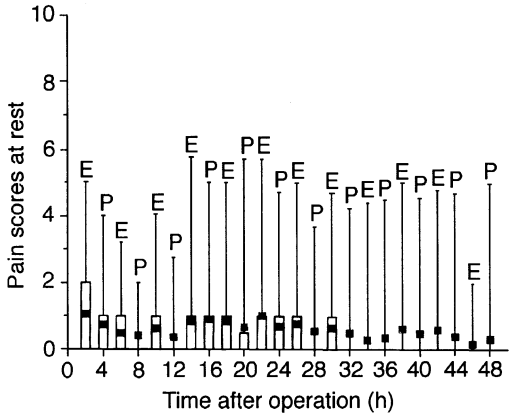

Fig 1 Mean pain scores at rest, represented by a 'box and whisker' plot; the range is shown by the single line, interquartile range by the box and the median by the shaded square. The paravertebral group (P) had significantly less pain than the epidural group (E) ($P=0.02$).

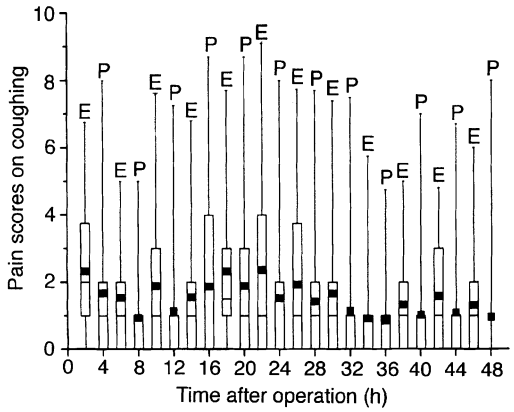

Fig 2 Mean pain scores on maximal coughing, represented by a 'box and whisker' plot; the range is shown by the single line, interquartile range by the box and the median by the shaded square. The paravertebral group (P) had significantly less pain than the epidural group (E) ($P=0.0001$).

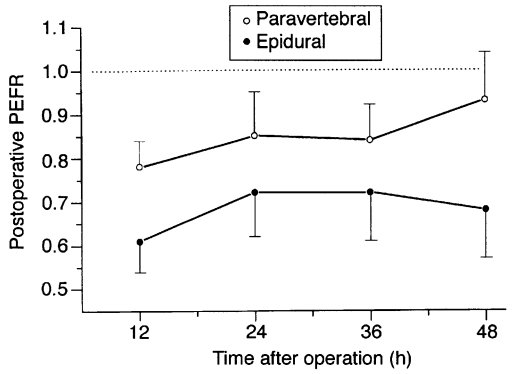

Fig 3 Postoperative mean peak expiratory flow rate (PEFR) as a fraction of preoperative control values. Error bars represent 95% confidence intervals. Pulmonary function in the paravertebral group was significantly better.

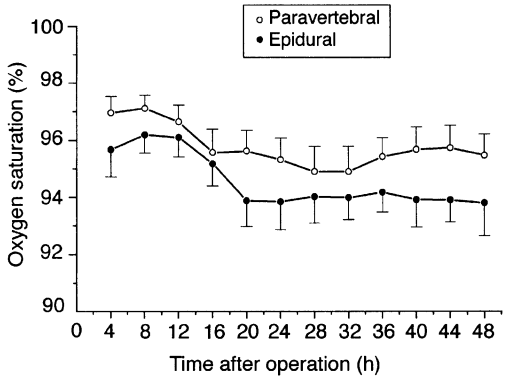

Fig 4 Mean oxygen saturation with 95% confidence intervals. The paravertebral group had significantly higher saturations after operation ($P=0.0001$).

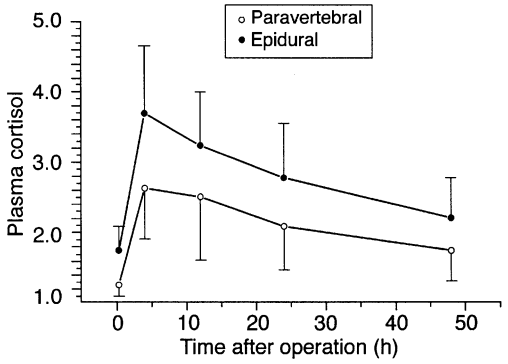

Fig 5 Mean plasma concentrations of cortisol as a fraction of preincisional control values, with 95% confidence intervals. The area under the curve was significantly lower in the paravertebral group ($P<0.004$).

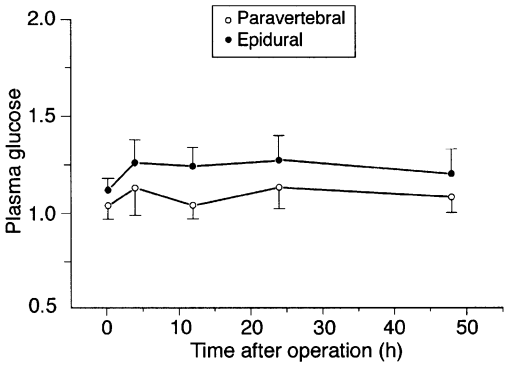

Fig 6 Mean plasma concentrations of glucose as a fraction of preincisional control values, with 95% confidence intervals. The area under the curve was significantly lower in the paravertebral group ($P=0.003$).

study (96 (0.2)%) compared with the epidural group (95 (0.2)%) ($P=0.0001$) (Fig. 4).

Plasma concentrations of cortisol increased significantly from baseline in the epidural and paravertebral groups (ANOVA, $P<0.004$ for both groups). Plasma concentrations of glucose increased significantly from baseline in the epidural group but not in the paravertebral group (ANOVA, $P=0.003$) (Figs 5, 6). When the areas under the plasma concentration *vs* time curves were compared (Mann–Whitney *U* test), the increases in both plasma cortisol and glucose concentrations were significantly less in the paravertebral group ($P=0.003$ and 0.006, respectively).

Table 2 Outcome in the epidural and paravertebral groups (number of patients)

	Epidural ($n=49$)	**Paravertebral ($n=46$)**
Urinary retention	11	5
Nausea	10	2
Vomiting	7	2
Chest infection	8	1
Ventilatory frequency <8 bpm	3	1
Hypotension	7	0
Wound infection	2	0
Myocardial infarction	0	1
Arrhythmia	3	1
Confusion	1	3
Somnolence	1	1
Cerebrovascular accident	1	0
Bleeding ulcer	1	0
Numb/heavy legs	3	0
Emergency intensive care unit admission	3	3
Hospital stay (days) (mean (range))	6.7 (3–16)	6.7 (4–11)
Deaths	2	5
Post-thoracotomy neuralgia	10	3

There were no neurological complications in either group as a result of epidural or paravertebral catheterization. The distribution of complications between the groups was significantly different (Mann–Whitney *U* test, $P=0.008$), with a greater incidence of nausea, vomiting and postoperative respiratory morbidity in the epidural group ($n=8$ *vs* 1) (Table 2). Postoperative hypotension, requiring temporary cessation of infusion, occurred in the epidural group only ($n=7$). All patients who underwent an oesophagectomy or pneumonectomy were catheterized as part of their monitoring; excluding these, there were 11 patients in the epidural group compared with five in the paravertebral group who required catheterization for retention of urine.

Mean hospital stay was 6.7 (range 4–11) days for the paravertebral group and 6.7 (range 3–16) days for the epidural group. Three patients in each group were admitted as emergencies to the intensive care unit and there were seven deaths in total. Two deaths occurred in the epidural group: one 10 days after operation as a result of an anastomotic leak and coeliac artery thrombosis and one at 7 days caused by post-pneumonectomy cardiac failure. There were five deaths in the paravertebral group (the difference was not significant): one 16 days after operation as a result of an anastomotic leak and multi-systems failure; two at 4 days as a result of cardiac causes, one a cardiac arrest in a post-lobectomy patient and the other after myocardial infarction in a post-pneumonectomy patient; and two at 4 days as a result of respiratory causes, one respiratory failure in a surgically inoperable patient and one respiratory failure in a post-lobectomy patient. At the follow-up outpatient clinic at 6 months, 10 patients in the epidural group had persistent chest pain (of a burning or dysaesthetic quality, not related to tumour recurrence or infection) compared with three in the paravertebral group (ns).

Discussion

We found that paravertebral nerve block provided significantly better pain scores at rest and on coughing and was accompanied by lower morphine requirements. These patients had superior pulmonary function, less postoperative respiratory morbidity and better oxygenation compared with those receiving epidural nerve block. The neuroendocrine axis, as assessed by plasma concentrations of cortisol and glucose, was less stressed in the paravertebral group. These advantages were accompanied by fewer opioid-related side effects and less hypotension than in the epidural group.

Many different drug regimens have been described for epidural analgesia. We used plain bupivacaine and tried to maximize its effect using substantial doses, especially before operation, balanced against maintenance of cardiovascular stability, especially in the postoperative period during our very active mobilization regimen. Despite good postoperative hydration, hypotension occurred in seven patients (compared with none in the paravertebral group). We believe that we had approached the cardiovascular limit of analgesic efficacy which it is possible to obtain with epidural bupivacaine. Addition of an epidural opioid may have been beneficial in terms of pain scores, but many studies in abdominal surgery have cast doubt over the probability of improved results with regard to pulmonary function and stress responses.[14] In the only prospective, randomized study of thoracotomy pain which we could find, spirometry was not improved by addition of a neuraxial opioid to the local anaesthetic.[15] An important practical factor mitigating against consideration of a local anaesthetic–opioid combination regimen was that all patients had to be returned to the general thoracic ward as our hospital (during the study) had no high dependency unit. Because of this we were unsure how to safely provide additional rescue opioid analgesia, as a combination of neuraxial and systemic opioids (for example) is known to be a major risk factor of respiratory depression.[16] Despite this potential study design drawback, most patients in the epidural group had pain scores and post-thoracotomy pulmonary function which were favourably comparable with other published prospective, randomized studies using epidural local anaesthetics,[9 17] combinations of epidural local anaesthetics and opioids,[15 18 19] or epidural opioids.[10 15 17 18 20–30]

Approximately twice as much bupivacaine was used in the paravertebral group compared with the epidural group and this probably influenced our results. We had considered and dismissed the idea of using equal doses of bupivacaine as we wished to optimize the use of each of these two local anaesthetic techniques. We were unable to use any more bupivacaine epidurally (see above), but lowering the dose of bupivacaine used paravertebrally would have disadvantaged this group of patients. One of the inherent advantages of paravertebral analgesia is that relatively large doses of local anaesthetic can be given safely (and are routinely in our unit),[31 32] although occasional episodes of temporary confusion can arise, probably caused by bupivacaine accumulation (three patients in this study) (Table 2). It is likely that this is one way in which a profound afferent block is effected with this technique (see below).[32 33]

Posterolateral thoracotomy has a detrimental effect on pulmonary mechanics. Although resection of pulmonary tissue contributes, the sudden deterioration in the early postoperative period is thought to be caused mainly by the respiratory effects of severe postoperative pain.[1 2] Within our heterogeneous surgical groupings, more patients in the epidural group underwent resection of pulmonary tissue (ns) and this may have had a minor mitigating effect on our results. However, we believe that in accordance with previous pathophysiological studies,[2] the different results in these two groups of patients was primarily a result of differences in postoperative pain and its management. Patients who are able to breathe deeply and cough effectively because their wound pain on movement is minimized ought to be expected to have a higher PEFR than patients who have pain on movement. The subsequent development of greater postoperative respiratory morbidity in the epidural group was probably likewise related to these qualitative differences in analgesia.

Differences in opioid use may have contributed to the observed differences in PEFR between the two groups. The epidural group used more morphine and it is known that opioids have undesirable effects on respiratory function resulting in progressive decreases in FRC.[2] Also, the higher incidences of nausea and vomiting in the epidural group (probably related to the greater use of morphine) may have had a negative effect on spirometric performance as forceful recruitment of the abdominal musculature may have been voluntarily inhibited.

Effort-related exhalation (PEFR) may have been inhibited by bilateral partial intercostal nerve block as weakness in the intercostal muscles is known to be induced by epidural local anaesthetic (although overall lung *volumes* are minimally affected).[34] There are no data for paravertebral block for comparison, but as its effects are unilateral,[32] contralateral chest wall function probably continued relatively unaffected in this group of patients.

Better oxygenation in the paravertebral group was probably related to better postoperative pulmonary function, less inhibition of clearance of secretions because of less pain on coughing and less opioid use. However, it is not possible to say if this significant finding has any clinical significance.

The increases in plasma concentrations of cortisol and glucose were significantly less in the paravertebral group compared with the epidural group (Figs 5, 6). Modification of neuroendocrine stress responses after upper abdominal[35] and thoracic surgery[7] has been demonstrated previously in studies using paravertebral nerve blocks but not epidural blocks.[14] We speculate that the reasons for this difference may be explained by qualitatively greater block of the somatic nerves (probably related to larger doses of bupivacaine) together with block of the sympathetic chain and

the rami communicantes when local anaesthetic is placed alongside the vertebral column rather than anatomically distant from it in the epidural space.[32 33]

We conclude that continuous paravertebral and epidural blocks, beginning before operation as part of a balanced analgesic regimen, were highly effective for post-thoracotomy pain. In this study, we found that paravertebral analgesia was superior in terms of analgesia, pulmonary function, neuroendocrine stress responses, side effects and postoperative respiratory morbidity.

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