PAIN RELIEF FOR INFANTS UNDERGOING ABDOMINAL SURGERY: COMPARISON OF INFUSIONS OF I.V. MORPHINE AND EXTRADURAL BUPIVACAINE

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SUMMARY
We have undertaken a prospective, randomized double-blind study to compare extradural bupivacaine infusions with i.v. morphine infusions for postoperative analgesia in 32 infants younger than 4 yr undergoing abdominal surgery. "Sham" extradural or i.v. catheters were used to maintain the blinded nature of the study. Both techniques provided adequate analgesia for most of the 36-h postoperative period; differences in the pattern or quality of the analgesia were not detected. Patients in the i.v. morphine group were significantly more sedated; this was accompanied by slower ventilatory frequencies (26.7 (SD 1.8) b.p.m.) compared with the extradural group (33.6 (1.3) b.p.m.). Similarly, oxygen saturation was significantly less (P < 0.01) in patients receiving morphine (medians and quartiles of 94.0 (93-96)% compared with 96.0 (93-96)%). Mean systolic arterial pressure was similar in the two groups and there were no life-threatening complications. The lack of sedation was troublesome in three patients in the extradural group. (Br. J. Anaesth. 1993; 70: 10-16)

KEY WORDS

The current debate on management of pain in neonates [1] has encouraged renewed interest in the use of regional analgesia for infants undergoing surgery. Extradural anaesthesia with bupivacaine has been shown to modify the haemodynamic [2], hormonal [3] and metabolic [4] responses to surgery in children, and provides effective postoperative analgesia [5]. However, insertion of a lumbar or thoracic extradural block in a small infant requires a high level of technical expertise, and identification of the extradural space becomes progressively more difficult with decreasing age of the subject [2]. A technique of inserting an extradural catheter up to a thoracic level via the easier caudal route has been described for postoperative analgesia [7]. Variable rate i.v. opioid infusions are used even in young infants for postoperative analgesia, but may have serious side effects such as impaired consciousness or ventilatory depression [8]. Extradural infusions of bupivacaine offer an alternative which avoids opioids, but also has the potential to produce hypotension and complications from extensive local block [9] or systemic absorption of local anaesthetic [10]. We are not aware of any study in this age group comparing analgesia, recovery and side effects of these two techniques. We therefore designed a randomized double-blind study to evaluate the use of i.v. morphine infusions and extradural infusions of bupivacaine after abdominal surgery in infants and small children.

PATIENTS AND METHODS
After obtaining approval by the local Ethics Committee and informed parental consent, we studied 32 healthy patients (ASA status I and II) aged less than 4 yr undergoing elective abdominal, renal or bladder surgery. Infants older than 4 months received oral trimeprazine 1.5 mg kg⁻¹ and topical EMLA (eutectic mixture of local anaesthetic) 90 min before the estimated time of surgery, while those younger than 4 months were not premedicated. Thiopentone and alcuronium were given i.v. at induction of anaesthesia. After tracheal intubation, the lungs were ventilated to normocapnia with 70% nitrous oxide and enflurane up to 1% in oxygen. During operation, an infusion of 5% glucose and 0.225% sodium chloride was given for fluid maintenance, and other fluid losses were replaced with Hartmann's solution, blood or blood products. In addition to this standardized general anaesthetic, patients were allocated randomly to receive either i.v. morphine or extradural bupivacaine during and after surgery. The 16 patients assigned to the i.v. morphine group had a second i.v. cannula inserted before the start of surgery, specifically for the morphine infusion. After a loading dose of morphine 0.15 mg kg⁻¹, an infusion of morphine in 50 ml of 0.9% saline was started. Solutions were made at different concentrations to take into account the increased sensitivity of younger infants.
children to opioids: a 50-μg ml⁻¹ solution for children weighing less than 10 kg and a 100-μg ml⁻¹ solution for those heavier than 10 kg. Initial infusion rates were 0.1 ml kg⁻¹ h⁻¹ (5 μg kg⁻¹ h⁻¹ for < 10 kg and 10 μg kg⁻¹ h⁻¹ for > 10 kg) and corresponded to the usual starting dosage for morphine infusions in infants at the Bristol Royal Hospital for Sick Children. The 16 patients allocated to the extradural group were turned on their left side before starting surgery, and under sterile conditions an 18- or 19-gauge Tuohy needle from a Portex minipack system 1 (Ref: 100/391/118 or 100/391/019) was inserted through the sacrococcygeal hiatus. After the absence of blood or CSF was confirmed, the catheter (0.9 mm or 0.63 mm o.d.) was inserted rostrally to a distance calculated to leave the tip between the first and second lumbar vertebrae. An initial dose of 0.25 % plain bupivacaine was injected according to the formula by Takasaki [11] relating the volumes of injectate to the required number of spinal segments to be blocked (0.05 ml kg⁻¹ per segment). An infusion of 0.25 % bupivacaine was commenced immediately after the initial dose and infused throughout surgery at a rate of 0.1 ml kg⁻¹ h⁻¹. Intraoperative heart rate and arterial pressure were measured at 5-min intervals and were maintained within 20 % of the preoperative values using additional doses of either morphine 40 μg kg⁻¹ or 0.25 % bupivacaine up to a maximum of 1 ml kg⁻¹, depending on the group.

After surgery, patients were taken to a recovery area where the route of analgesia was disguised to prevent observer bias on pain observations. The analgesic solution (containing either morphine or bupivacaine) passed from the syringe pump labelled with the trial number to a bacterial filter wrapped in gauze and strapped to the chest. Two tubes emerged from the gauze wrapping. In the morphine group, the bacterial filter was connected to the i.v. cannula via covered infusion tubing, while a “sham” extradural cannula was strapped down the back to make it indistinguishable from a true extradural. In the extradural group, the bacterial filter was connected to the extradural cannula, while a sham i.v. infusion catheter and cannula were strapped to the arm under opaque tape to make them indistinguishable, by direct observation, from an i.v. cannula. Additional doses of i.v. morphine or extradural bupivacaine were given as necessary by one of the investigators to ensure that all patients were free from pain before returning to the ward and commencing pain observations.

On arrival of the patient in the ward, arterial pressure, oxygen saturation and ventilatory frequency were recorded. Sedation and analgesia were assessed after 1 h by a trained nurse observer who was unaware of the type of analgesia given. Further assessments were made hourly for the first 6 h, then 3-hourly up to 30 h and finally at 36 h according to observed behaviour during the preceding period. Sedation was assessed with a four-point scale: 0 = appropriately asleep; 1 = awake and alert; 2 = drowsy but responds to stimulation; 3 = very sedated. Pain measurement was based on a scoring system described by Hannallah and colleagues [12], which obtains a summed value of between 0 and 10 from observations of arterial pressure, crying, movement, agitation and localization of pain. If pain scores increased to greater than 4, the nursing staff were permitted to increase the infusion rate incrementally by 1 ml h⁻¹ after informing one of the investigators. The maximum infusion rate permitted was 4 ml h⁻¹. The nurse observers were instructed to decrease the infusion rate and inform one of the investigators if systolic arterial pressure decreased to less than 20 % of the baseline value, if ventilatory frequency decreased to less than 15 b.p.m. or if the patient became sedated or difficult to rouse (sedation score 3). Infusion rates could also be reduced incrementally according to usual ward practice if patients appeared to have little or no pain. Other recordings included major side effects or complications and the time to first bowel action after surgery. Oxygen saturation was monitored continuously during the infusions and set to alarm at oxygen saturations less than 85 %. If parenteral analgesia was still required after 36 h, the patient continued with the same method of pain relief but in an unblinded fashion. Paracetamol was not prescribed routinely in the first 36 h, but could be given if the patient became pyrexial. While the nurse observers remained “blinded”, it was necessary for the anaesthetic team to be aware of which infusion was being used. Any procedure that could result in unblinding the trial was carried out by another member of the ward staff or an anaesthetist. This included daily inspections of the i.v. and extradural sites to ensure that they remained clean and were functioning normally, but every effort was made to limit the interaction between the anaesthesia team and the nurse observers.

Statistical significance for parametric data was determined using analysis of variance and Student’s t test. Ordinal data and nominal data were analysed by the Mann–Whitney U test and chi-square analysis with Yates’ correction.

RESULTS

The ages, weights and duration of the surgical procedure did not differ significantly between the groups (table 1).

Pain scores were categorized into three groups

| TABLE 1. Patient data and duration of surgery (median (range)), with operation type by group allocation |
|-------------------------|-------------------------|
|                         | Extradural group | Morphine group |
| Age (months)            | 9 (3–46)           | 14 (3–42)      |
| Weight (kg)             | 9.8 (6.0–16.0)     | 11 (5.2–21.4) |
| Duration of op. (min)   | 125 (100–210)      | 120 (80–340)  |
| Operation               |                        |                |
| Renal transplantation   | 7                      | 3              |
| Nephrectomy             | 5                      | 4              |
| Partial nephrectomy     | 1                      | 2              |
| Bladder surgery         | 1                      | 1              |
| Pyeloplasty             | 1                      | 3              |
| Pyelolithotomy          | —                      | 2              |
| Laparotomy              | 1                      |                |
| Body wall sarcoma       | —                      | 1              |
| Total                   | 16                     | 16             |
FIG. 1. Comparison of the numbers of patients in the extradural bupivacaine (○) and morphine (●) groups with pain scores of 4 or more ("in pain") over the 36-h study period. *P < 0.05.

FIG. 2. Distribution of the total pain scores accumulated over 36 h (cumulative pain score) by each patient for the extradural bupivacaine (○) and morphine (●) groups. Cumulative pain scores are displayed in bins of 10 on the X axis and the number of patients in each bin are shown on the Y axis.

According to previous experience with this scoring system: 0-3 = minimal or no pain; 4-6 = mild pain; 6 or greater = moderate to severe pain. The majority of patients were in the "no pain" category during the study, regardless of the designated method of analgesia. Comparison of the numbers of patients judged to have pain (pain score greater than 3) did not show any significant differences between the groups except at the 21-h observation (fig. 1). All patients completed the study and none had to be withdrawn because of failure of analgesia. There was variation in the quality of analgesia between patients which was reflected in the range of cumulative pain scores for each patient (fig. 2), but there was no difference in the distribution of cumulative pain scores between the groups.

Most patients required increases in the infusion rates from the baseline settings: extradural infusion rates varied from 0.1 to 0.4 ml kg⁻¹ h⁻¹, while morphine delivery varied from 10 to 40 µg kg⁻¹ h⁻¹. In both groups, the mean infusion rates increased to a maximum at 15 h and then declined. Increasing the infusion rates for those patients in pain appeared to control analgesia, although pain scores did not always decrease in the first 1 h after the increase. Further stepwise increases in infusion rate were often needed before pain was controlled. No patient required reduction of infusion rates because of hypotension or ventilatory depression. One patient in the extradural group was inadvertently given paracetamol for pain, and another three patients in each group were given paracetamol during the study because of pyrexia.

Patients in the bupivacaine group were less sedated than those in the morphine group (fig. 3). Significant differences were observed during the first 1 h after operation and again at 27 and 30 h. The lack of sedation became troublesome in three of the patients having extradural infusions. The nurse observers noted agitation, fidgeting and restlessness as side effects in these patients. Although these patients could be settled without changing infusion rates, they needed regular attention to stop them from interfering with dressings and drains. It had been expected that sedation might interact with observed pain scores such that sedated patients would have lower pain scores than unsedated ones. However, while patients who were appropriately asleep (sedation 0) usually had a pain score of 3 or less for that observation period (96.6% in the extradural group and 98.2% in the morphine group), overall comparison of sedation scores and pain scores did not show a correlation in either of the groups.

Observed ventilatory frequencies were significantly less in the morphine group (fig. 4), and this was reflected in reduced oxygen saturation in the early postoperative period (fig. 5). Mean ventilatory frequencies over the 36-h study, calculated from an averaged value for each individual, were 33.6 (SD 1.3) b.p.m. in the extradural group and 26.7 (1.8) b.p.m in the morphine group. Median oxygen...
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Fig. 3. Comparison of the numbers of patients in the extradural and morphine groups observed as sedated (sedation score 2) or very sedated (sedation score 3) over the first 36 h after operation. [ ] = Bupivacaine group with sedation score 2; □ = morphine group with sedation score 2; △ = morphine group with sedation score 3. * P < 0.05.

Fig. 4. Ventilatory frequencies (f) for patients receiving extradural bupivacaine (■) or morphine (▲) analgesia (mean, sd). * P < 0.05; ** P < 0.01.

saturations and quartiles were 96 (95.2–97) % in the bupivacaine group and 94 (94–94.7) % in the morphine group.

The decreased ventilatory frequencies and oxygenation did not appear to have any clinical consequences in this study and, although the oxygen saturation monitor alarmed occasionally because of disconnection, there were no episodes of major ventilatory depression or apnoea causing desaturation to less than 85 %.

One patient in the extradural group had a dural tap at the time of insertion of the Tuohy needle. After removing the needle, the procedure was repeated without a problem and the caudal catheter inserted. CSF could not be aspirated through the threaded catheter and the patient remained in the study without further complication. The averaged systolic arterial pressure for each patient was significantly less (P < 0.01) in the bupivacaine group (97.4 (sd2.7) mm Hg) than in the morphine group (101.1 (3.6) mm Hg) during surgery, but this difference did not continue in the postoperative period. Mean systolic arterial pressures during the postoperative period were 109.3 (3.7) mm Hg for the extradural group and 110.3 (5.3) mm Hg for the morphine group, and there were no individual problems with hypotension. None of the patients in either group had distressing or persistent vomiting. There was wide variability in the time to first bowel action after surgery, but no difference between treatment groups could be detected: 62.9 (44.8) h for the extradural group and 65.6 (36.3) h in the morphine group. No other major complications or side effects were noted by the nursing staff, except for the comments on
restlessness discussed above. The incidence of urinary retention could not be evaluated because 30 of the patients had indwelling urinary catheters.

**DISCUSSION**

Postoperative analgesia with nurse-administered i.m. opioids still remains the most common method of pain relief after surgery [13], despite the availability of more effective techniques. i.v. morphine infusions have been used in children for some years [8, 14] and are feasible even in infants younger than 6 months [15]. However, the technique is not used commonly outside an intensive care unit in younger age groups because of the risks of ventilatory depression and the requirements for close monitoring. Infusions of extradural bupivacaine [2, 5] can also provide postoperative analgesia in children, but have never been compared with morphine.

A prospective double-blind study comparing extradural bupivacaine with i.v. morphine would not be possible in adults because of the obvious changes in sensation from the local anaesthesia. However, it was achieved in a younger age group because of their limited verbal communication, the lack of motor block from a 0.25% bupivacaine infusion [2], and by elaborately disguising the technique. In this study, most patients had good analgesia, irrespective of the method used. The distributions of pain scores with time (fig. 1) or by patient (fig. 2) were similar. While the null hypothesis cannot be proven from this study of 32 patients, the results show no major clinical difference in analgesia between the two techniques. It could be argued that the pain scoring system was not sensitive enough to discern differences between the two groups. However, significant differences in pain scores have been recorded in previous studies on the same ward using identical methods [16, 17]. There was no correlation between levels of sedation and pain scores in this study, which was surprising. The unsedated patient can become agitated and rate high pain scores without being in pain. Analgesic techniques, such as i.v. morphine, that produce sedation in addition to pain relief may appear more effective than a non-sedating technique such as extradural bupivacaine because of the reduction in conscious level.

The difference in sedation scores between the two groups was marked. Infants in the extradural group were active much of the time and this was beneficial from the aspect of nursing supervision for ventilatory depression. However, while the lack of sedation made little difference in the infants younger than 6 months, it was more noticeable and occasionally troublesome in the older children (three patients). Overactivity and restlessness have not been reported previously as side effects of extradural analgesia, although they should be expected, particularly in the older and more mobile infants who have little or no pain. This can become a problem for the nursing staff in a busy ward if a child needs supervision to stop it investigating newly placed dressings and drains. Sedation with morphine or diazepam may occasionally be required, to supplement an extradural technique.

The reduced ventilatory frequency and oxygen saturation in those patients receiving morphine were not clinically obvious or important in this study, but may be relevant in the choice of postoperative analgesia for infants with immature ventilatory drive or pre-existing lung disease. Local techniques can eliminate the need for centrally acting drugs that depress ventilation and, used in place of general anaesthesia, may reduce postoperative apnoea in the “at risk” patient [18, 19]. Resting ventilation is reduced after extradural analgesia, but the ventilatory response to carbon dioxide is enhanced [20] and this may be protective, particularly in the early postoperative period. Extradural bupivacaine may, therefore, be a desirable alternative to opioid analgesia in the infant with ventilatory impairment.

The dose of morphine required to achieve an-
anesthesia in this study varied from 5 to 40 \( \mu g \) kg\(^{-1} \) h\(^{-1} \) and was similar to established treatment regimens for this age group [14]. The initial infusion rate of 5–10 \( \mu g \) kg\(^{-1} \) h\(^{-1} \) was adequate in the early postoperative period, but required adjustment as the effects of general anaesthesia and the initial loading dose of morphine decreased. Greater initial rates of infusion of i.v. morphine might have improved analgesia after 12 h, but would have increased sedation and ventilatory depression in the early postoperative period. In both groups, alteration of the infusion rates achieved pain control, but there was an inevitable lag between increasing the infusion rates and reduction in pain scores. Single additional doses of i.v. morphine or extradural morphine would have produced more immediate analgesia, but were not possible within the blinded study design.

Desparmet and colleagues [5] have used infusions of 0.25% bupivacaine via a lumbar extradural catheter in children undergoing urogenital or lower limb surgery and reported adequate analgesia with an infusion rate of 0.08 ml kg\(^{-1} \) h\(^{-1} \). In our study, an initial infusion rate of bupivacaine 0.1 ml kg\(^{-1} \) h\(^{-1} \) had to be increased in all but three patients to maintain adequate analgesia; a starting infusion rate of 0.15 ml kg\(^{-1} \) h\(^{-1} \) might have been more appropriate. The differences in our results may reflect that our patients were younger, that they underwent abdominal surgery and that a different technique was used for catheter insertion. Unlike local anaesthetic extradural infusions in adults [21], bupivacaine infusions in infants produce stable levels of analgesia [5] and can produce an ascending block [9]. Periodic pinch tests should be undertaken to ensure that the block is not extending too high a level. Infusions of extradural bupivacaine also have the potential to cause toxicity from systemic accumulation, but the risk appears to be low when appropriate infusion schemes are used [5].

Cannulation of the extradural space by the caudal route is technically less difficult than the lumbar route in small infants, but the risk of contamination and potential for infection may be greater because of close proximity to the perineum. A lumbar approach is generally preferable, but the choice of route depends on the size of the infant and expertise of the anaesthetist. In this study, all catheters were taped away from the perineum with waterproof dressings and removed within 3 days of insertion. We are not aware of any reported cases of infection caused by indwelling caudal catheters, but published experience with this technique remains limited. Long-term use of caudal catheters would be contraindicated unless they were tunnelled s.c.

Extradural morphine is used for postoperative analgesia in children, but can cause sudden and late onset and sometimes sudden ventilatory depression [22, 23]. Combining opioids and local anaesthetics in an extradural mixture may lessen the risks by reducing individual doses of the drugs and their side effects [16, 17], but younger infants still require intensive monitoring. Extraludal infusions of bupivacaine, combined if necessary with small incremental doses of i.v. morphine for additional analgesia and sedation, may be more appropriate in these patients and help avoid the need for a stay in the intensive care unit. Our current clinical practice is to give infants older than 6 months undergoing abdominal surgery an intrathecal dose of i.v. morphine 0.05–0.1 mg kg\(^{-1} \) or fentanyl 0.5–2 \( \mu g \) kg\(^{-1} \) in addition to extradural analgesia with 0.25% bupivacaine. The analgesia and sedation from the single dose of opioid helps to prevent restlessness in the early postoperative period.

In conclusion, extradural analgesia with bupivacaine given via a caudal catheter provided excellent postoperative analgesia in infants after abdominal surgery. It may be preferable to a morphine infusion in neonates and younger infants who are particularly sensitive to ventilatory depression and in whom sedation is neither necessary or desirable. Older children may require additional sedation or analgesia with this techniques to prevent restlessness in the postoperative period.

REFERENCES


