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Continuous Infusion of Bupivacaine *Via* Intrapleural Catheter for Analgesia after Thoracotomy in Children

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Reiestad *et al.*[1,2]¶ have reported the successful use of intrapleural analgesia in adults after mastectomy, cholecystectomy, and renal surgery. Seltzer *et al.*[3] and Kambam *et al.*[4] have also reported plasma levels of bupivacaine after intrapleural bolus injection in adults. The use of this technique in children has not been reported previously.

MATERIALS AND METHODS

With institutional review board approval and informed consent/assent from the parent/patient, we studied 14 consecutive patients presenting for thoracotomy. An anesthetic technique was designed to ensure tracheal extubation and a warm, awake patient at the end of surgery. Before chest closure, the surgeon percutaneously inserted a 20-G epidural catheter into the intrapleural space by passing an 18-G Tuohy-Schliff epidural needle through the intercostal space immediately below the incision. The internal end of the catheter was loosely sutured at the postero-medial aspect of the incision. A sterile plastic dressing was applied at the skin entry site and the catheter was connected with a filter to a computer-controlled syringe pump. An intra-arterial catheter and a central venous catheter were inserted in all patients as required for intraoperative and postoperative management. A tube thoracostomy was positioned anteriorly in the pleural space and attached to low suction.

When the patient was alert in the Post-anesthesia Care Unit, a pre-infusion pain score (table 1) was determined and an arterial blood sample drawn. A 24-h continuous infusion of 0.25% bupivacaine with 1:200,000 epinephrine was begun *via* the intrapleural catheter at 0.5 $ml \cdot kg^{-1} \cdot h^{-1}$. Patients were nursed while supine or with the operated side elevated approximately 30–45°. The following data were recorded hourly for 32 h: systolic/diastolic blood pressure, heart rate, respiratory rate, temperature (rectal or axillary), drug infusion rate, and pain score as assessed by an observer and the nurse caring for the patient. Rectal chloral hydrate and intravenous diazepam were given for sedation with rectal acetaminophen as needed for fever. To treat inadequate analgesia, the nurse was allowed to increase the infusion rate of bupivacaine incrementally from the starting rate of 0.5 $ml \cdot kg^{-1} \cdot h^{-1}$ to a maximum of 1 $ml \cdot kg^{-1} \cdot h^{-1}$. Narcotic analgesics could be given if an-

TABLE 1. Pain Scale Used to Evaluate Patients during Study

Observation	Criteria	Points
Blood pressure	±10% preop	0
	>20% preop	1
	>30% preop	2
Crying	Not crying	0
	Crying, responds to TLC	1
	Crying, doesn't respond	2
Movement	None	0
	Restless	1
	Thrashing	2
Agitation	Patient asleep or calm	0
	Mild	1
	Hysterical	2
Verbalizes	Asleep, or states no pain	0
	Cannot localize	1
	Localizes	2
Total		10

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¶ Reiestad F, Stromskag KE: Intrapleural catheter in the management of postoperative pain. Regional Anesthesia 11:89–91, 1986

TABLE 2. Age, Weight, and Sex of Patients Studied According to Surgical Procedure (Mean ± SEM)

Patient Group	Age (Months)	Weight (kg)	Sex (M/F)
Anterior fusion	180.1 ± 41.3	54.2 ± 8.4	2/5
Coarctation	79.5 ± 59.2	23.50 ± 5.2	5/2
All patients	129.9 ± 71.6	38.73 ± 23.9	7/7

algesia at the maximum infusion rate was inadequate. Failure to control pain within 30 min of a rate increase was sufficient to terminate the study. Intravenous morphine was used for analgesia after the termination of the infusion at 24 h when the intrapleural catheter was withdrawn. Total number of doses of acetaminophen, chloral hydrate, diazepam, and morphine were recorded for each patient.

Arterial blood samples, drawn every 4 h, were refrigerated until centrifugation at 3000 RPM for 10 min. The supernatant was decanted and frozen at −20° C until analysis. Bupivacaine analysis, following the method of Mather and Tucker,[5] was performed with gas chromatography and a nitrogen specific detector, using mepivacaine as an internal standard. Assay sensitivity was 2 $ng \cdot ml^{-1}$ with a coefficient of variation of 3%.

For the purposes of data analysis, the one patient undergoing a tumor resection was included in the coarctation group. Wilcoxon signed rank test for paired data was used to compare pre-infusion vital signs and pain scores with those at each hourly measurement interval. Paired Student's *t* test and Wilcoxon signed rank test were used to compare the paired nurse and observer pain scores for all intervals and patients. *P* values of less than 0.05 were considered significant.

RESULTS

The ages, weights, and sexes of the patients studied are shown in table 2 according to surgical procedure. Figure 1 describes graphically the pain scores for the 14 patients as recorded by the nurse and the observer. All pain scores recorded show a statistically significant difference from control when analyzed with either Student's *t* test or the Wilcoxon signed rank sum test. Using the paired *t* test, we found that the nurse rated the patient's pain on average 0.20 points higher than the observer did ($P < 0.05$). Because these data result from 32 hourly observations in only 14 patients, caution must be used in interpreting the *P* value.

There are no statistically significant differences between any vital sign measurement and control at any time during the study. Figure 2 shows mean rate of drug infusion over time for all patients. Additional drugs required during the period of the infusion and after its discontinuation for the treatment of anxiety or fever are listed in table 3. Narcotics were not required in any patient during the infusion.

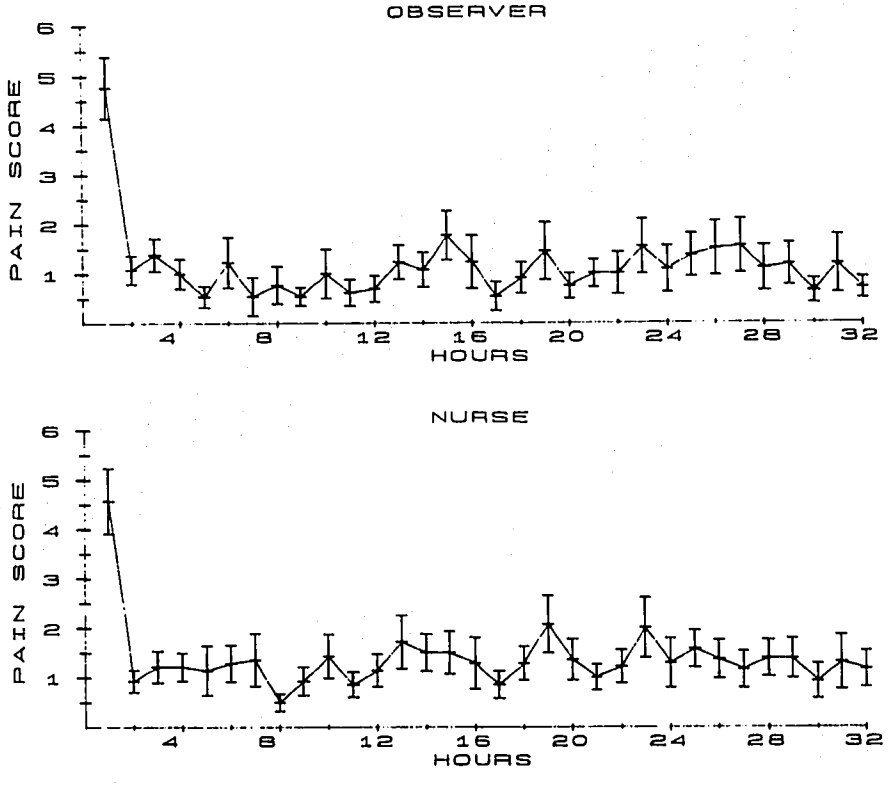

FIG. 1. Pain scores (mean ± SEM) over time in hours as determined by the nurse and the observer.

Mean arterial concentrations of bupivacaine are tabulated in table 4.

Discussion

The infusion of local anesthetics *via* intrapleural catheter in the postoperative period provides safe and effective analgesia in children as demonstrated by the lack of side effects or complications related to either the catheter or the local anesthetic. Because this is neither a truly blinded nor controlled study, we cannot compare the efficacy of the intrapleural technique to either thoracic epidural analgesia or patient-controlled analgesia. The technique appears to have very little effect on blood pressure or heart rate, which is surprising in view of the relatively large amounts of epinephrine administered with the local anesthetic solution.

Because subjective assessment and documentation of pain in children are difficult, we used a previously validated pain scale[6] and two observers. We did not perform specific assessment of the extent of analgesia along thoracic dermatomes with ice, alcohol, or pinprick. There is reasonable agreement between the pain score given by the nurse caring for the patient and the designated observer, although the nurse tended to give a score 0.20 points higher. The nurse also tended to give morphine for analgesia at lower pain scores after the infusion was discontinued.

A major concern raised in discussions with the ICU nursing staff was that the pain-free child still suffered emotional distress and anxiety by being in the intensive care unit. The provision of a sedative or anxiolytic helped the children sleep and reduced emotional distress. Analgesia alone is insufficient therapy for the pediatric patient during recovery in the ICU. Inadequate anxiolysis may be incorrectly identified as pain and, therefore, treated inappropriately. This facet of intensive care is especially important when dealing with the handicapped patient.

Tucker[7] estimates that the potential range for CNS toxicity of bupivacaine is 2–4 $\mu g \cdot ml^{-1}$. Scott[8] suggests that the absolute toxic plasma concentration (Cp) may be more dependent on the rate of increase of the Cp than on any exact concentration of bupivacaine. In this group of 14 patients, there were no signs of cardiovascular or CNS toxicity, although 11 patients attained Cp's greater than 2 $\mu g \cdot ml^{-1}$, and five patients reached levels over 4 $\mu g \cdot ml^{-1}$, with one patient having a concentration over 7 $\mu g \cdot ml^{-1}$ after 24 h of therapy. The average Cp in patients undergoing anterior fusion reached 2 $\mu g \cdot ml^{-1}$ at about 12 h, and 4 $\mu g \cdot ml^{-1}$ at 24 h. Within the group of patients having coarctation repaired, the average arterial (Cp) was 2 $\mu g \cdot ml^{-1}$ after 22 h, and 2.4 $\mu g \cdot ml^{-1}$ after 24 h of therapy.

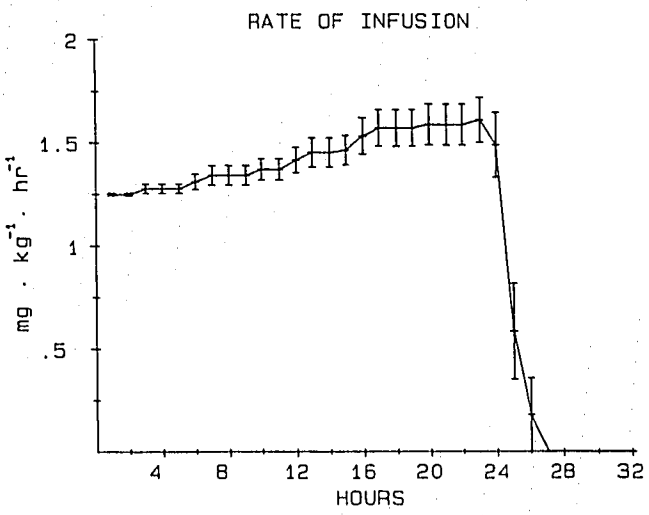

FIG. 2. Rate of bupivacaine infusion (mean ± SEM) in $mg \cdot kg^{-1} \cdot h^{-1}$ over time in hours.

The technique of Mather and Tucker[5] for the analysis of bupivacaine measures the total amount of drug present in serum. With this technique, we cannot assess the ratio of free to bound drug, the amount contained within the red blood cell, or the concentration of bupivacaine metabolites present after a 24-hour infusion. An important consideration is the concentration of alpha-1 acid glycoprotein (AAG or orosomucoid) in post-surgical patients as the amide type local anesthetics readily bind to this acute phase reactant. Without mea-

TABLE 3. Number of Doses of the Drugs Given for Fever, Sedation, or Analgesia during the Period of the Infusion and After its Termination

Drug	Period (Hours)	
	0–24	25–32
Acetaminophen	4	2
Chloral hydrate	14	1
Diazepam	4	1
Morphine	0	22

TABLE 4. Arterial Bupivacaine Concentrations (Mean ± SEM) in $\mu g \cdot ml^{-1}$, Measured every 4 h, for the Anterior Fusion Group, Coarctation Group, and All Patients

Time	Anterior Fusion (n = 7)	Coarctation (n = 7)	All
4	0.764 ± 0.248	0.77 ± 0.195	0.767 ± 0.152
8	1.388 ± 0.353	1.005 ± 0.186	1.196 ± 0.199
12	1.856 ± 0.387	1.243 ± 0.267	1.549 ± 0.241
16	2.727 ± 0.556	2.051 ± 0.381	2.389 ± 0.337
20	3.69 ± 0.561	2.281 ± 0.452	2.986 ± 0.397
24	4.246 ± 0.722	2.468 ± 0.521	3.357 ± 0.494
28	2.097 ± 0.359	1.039 ± 0.280	1.568 ± 0.263
32	1.486 ± 0.401	0.57 ± 0.185	1.028 ± 0.247

suring the level of AAG in the patient and determining the free *versus* bound ratio, it is impossible to comment on the significance of the arterial blood levels of bupivacaine in patients in this study. We do know that AAG levels change significantly with age and surgical trauma, among other factors.[9] We do not know precisely how plasma levels of bupivacaine affect binding of the drug to the various proteins present. Without a better understanding of the pharmacology of bupivacaine toxicity, we recommend the dosage schedule used in this study not be exceeded, and, further, that the efficacy of lower infusion rates be evaluated.

There are several important points learned from our experience. First, we deliberately positioned the catheter in the posterior portion of the chest cavity as close as possible to the postero-medial aspect of the incision, because we felt that this would maximize the delivery of local anesthetic to the area of trauma. By using a single suture around the catheter near the tip, we were attempting to prevent migration of the catheter. This is most important when a chest tube with or without suction is present, as it is conceivable that the local anesthetic might be removed from the pleural cavity before having an opportunity to diffuse through to the target nerve fibers.

Second, we believe that gravity also affects the distribution of the local anesthetic and, thus, the extent of the block. In two patients allowed to sit up for an hour, the block wore off. To re-establish analgesia, we placed them in the supine position 15° head down. When placed in this position, each patient quickly developed an ipsilateral miosis and ptosis suggestive of a Horner's syndrome and blockade of the stellate ganglion, as well as return of analgesia. Third, we have also observed venodilatation of the arm and hand with a rapid increase in skin temperature, suggesting that this technique may provide a sympathetic block of the upper extremity. Fourth, prior to starting the infusion, we remarked that most patients demonstrated marked ipsilateral splinting of the chest wall. Within minutes of beginning the infusion, the splinting disappeared. The clinical significance of this observation remains to be determined. We found no clinical evidence of diaphragmatic paralysis, although we did not search for it with a chest radiograph. Blockade of the phrenic, vagus, or recurrent laryngeal nerves is theoretically possible because of their anatomical courses through the chest.

The failure of Rosenberg *et al.*[10] to show effective analgesia with intrapleural bupivacaine after thoracotomy may be explained by several key differences between our studies. We studied children, not adults; thus, differences in anatomy and pleural membrane thickness may be of importance. Rosenberg *et al.*[10] did not specifically position the pleural catheter above the postero-medial aspect of the incision, did not anchor the tip of the catheter with a suture to prevent migration, did not specify that the chest tube was positioned in the anterior portion of the chest cavity, and did not specify the position of the patient during the infusion. These factors may have led to inadequate delivery of bupivacaine to the target nerves near the costovertebral junction. Although the high concentration of bupivacaine in the chest tube drainage is suggestive of significant loss of local anesthetic from the chest in their patients, the loss of bupivacaine cannot be quantitated without a record of the volume of fluid removed during the study period. Finally, their infusion rate (0.23–0.33 $mg \cdot kg^{-1} \cdot h^{-1}$) was much lower than ours (1.25–2.5 $mg \cdot kg^{-1} \cdot h^{-1}$), and may fall below the lowest effective dose which has not yet been clearly defined.

We conclude that the use of the intrapleural catheter to provide analgesia with a continuous infusion of bupivacaine after thoracotomy in children appears to be safe and effective. Because plasma bupivacaine concentrations exceeded recommended peak concentrations for adults, and because the toxicity of bupivacaine in children is unknown, we suggest that the infusion rate not exceed 0.5 $ml \cdot kg^{-1} \cdot h$ of 0.25% bupivacaine with 1:200,000 epinephrine.

References

1. Kvalheim L, Reiestad F: Intrapleural catheter in the management of postoperative pain (abstract). ANESTHESIOLOGY 61:A231, 1984
2. Reiestad F, Stromskag KE, Holmqvist E: Intrapleural administration of bupivacaine in postoperative management of pain (abstract). ANESTHESIOLOGY 65:A204, 1986
3. Seltzer JL, Larijani GE, Goldberg ME, Marr AT: Intrapleural bupivacaine—A kinetic and dynamic evaluation. ANESTHESIOLOGY 67:798–800, 1987
4. Kambam JR, Handte RE, Flanagan J, Fisher K, Lupinetti M, Hammon J: Intrapleural anesthesia for post-thoracotomy pain relief (abstract). Anesth Analg 66:S90, 1987
5. Mather LE, Tucker GT. Meperidine and other base drugs: General method for their determination in plasma. J Pharm Sci 63:306–7, 1974
6. Hannallah RS, Broadman LM, Belman AB, Abramowitz MD, Epstein BS: Comparison of caudal and ilioinguinal/iliohypogastric nerve blocks for control of post-orchiopexy pain in pediatric ambulatory surgery. ANESTHESIOLOGY 66:832–834, 1987
7. Tucker GT: Pharmacokinetics of local anaesthetics. Br J Anaesth 58:717–731, 1986
8. Scott DB: Evaluation of clinical tolerance of local anesthetic agents. Br J Anaesth 47:328, 1975
9. Wood M: Plasma drug binding: Implications for anesthesiologists. Anesth Analg 65:786–804, 1986
10. Rosenberg PH, Scheinin B M-A, Lepantalo MJA, Lindfors O: Continuous intrapleural infusion of bupivacaine for analgesia after thoracotomy. ANESTHESIOLOGY 67:811–813, 1987