ORIGINAL ARTICLE

Interpleural bupivacaine and intravenous oxycodone for pain treatment after thoracotomy in children

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ABSTRACT

Introduction: *The results of studies exploring the efficacy of interpleural analgesia in children post-thoracotomy have frequently been inconclusive. In this pilot study, we have evaluated the efficacy and safety of interpleural bupivacaine and intravenous (IV) oxycodone in pain treatment after thoracotomy in 10 generally healthy children, aged 10 months to 12 years, with patent ductus arteriosus who underwent thoracotomy.*

Methods: *After surgery, all 10 children were given ibuprofen 10 mg/kg rectally every six hours. The first dose of interpleural bupivacaine (2 mg/kg) was given with epinephrine at the end of surgery, and thereafter plain bupivacaine (1 mg/kg) was given every two hours if the pain score was 4 or higher on an 11-point numeric rating scale (0 = no pain, 10 = worst possible pain). For rescue analgesia, children were provided oxycodone 0.1 mg/kg IV if pain was not relieved sufficiently with ibuprofen and bupivacaine. Vital signs, pain scores, and all adverse effects were monitored continuously for 24 hours.*

Results: *All 10 children needed both interpleural bupivacaine and IV oxycodone. The number of bupivacaine doses ranged between three and 10 (mean = 6.1, SD = 2.3), and the number of oxycodone doses ranged between one and 12 (mean = 6.0, SD = 3.6). No cases of low respiratory rate or low peripheral oxygen saturation or any serious adverse events were recorded.*

Conclusion: *Scheduled nonopioid analgesic (ibuprofen) with interpleural bupivacaine did not provide sufficient analgesia for post-thoracotomy pain in young children. IV oxycodone was found to be an effective and safe opioid supplement to the pain regimen.*

Key words: oxycodone, intravenous, bupivacaine, interpleural, ibuprofen, rectal, thoracotomy, pain, child

INTRODUCTION

Patients undergoing thoracotomy experience significant postoperative pain. Studies in adults indicate that severe early postoperative pain predicts long-term pain after thoracotomy.[1-3] This may also be the case in children, and therefore effective pain management is essential not only to avoid unnecessary suffering immediately after surgery but also in order to prevent chronic pain.

Several methods may be used to prevent and treat established pain after thoracotomy, but no ideal method has been developed.[3] Regional anesthesia techniques are commonly used for the treatment of severe postoperative pain. Reiestad and Stromskag[4] described the technique of interpleural analgesia in adults in 1986, and two years later McIlvaine and co-workers[5] used this technique in children undergoing thoracotomy. Reiestad and Stromskag[4] used bolus injections of bupivacaine-epinephrine, while McIlvaine and co-workers[5] used a continuous infusion. Their preliminary results with this technique were encouraging, but in some later trials the technique has not performed sufficiently well.[6]

Oxycodone is the most commonly used analgesic for the management of moderate and severe postoperative pain in adults in Finland,[7] and a potent pain-relieving effect has also been confirmed in children.[8] Oxycodone induces the same adverse effects that occur commonly with any opioid, but it does not release histamine, and it may cause less nausea, vomiting, and sedation and fewer excitatory central nervous system effects than morphine.[9,10] In our institution, we have used oxycodone for postoperative pain management in children for the last two decades, and our experiences have been promising.[11,12] However, we are unaware of any published data about how repeated doses of oxycodone perform in young children undergoing thoracic surgery.

In order to improve pain treatment and to gather necessary background information in the target population, we designed this clinical trial to evaluate the efficacy and safety of intravenous (IV) oxycodone in adjunct to scheduled ibuprofen, a traditional nonsteroidal anti-inflammatory analgesic (NSAID), and interpleural bupivacaine, a long-acting local anesthetic, in children undergoing thoracotomy. Post-thoracotomy pain consists of incisional pain and pleural pain originating from the indwelling chest tube.[3] Local anesthesia in combination with a topical anesthetic applied directly to the pleura is expected to reduce post-thoracotomy pain. NSAIDs may be sufficient to

treat incisional pain if pleural pain is not present. For these reasons, it was hypothesized that interpleural bupivacaine in conjunction with an NSAID would provide sufficient analgesia to obviate the need for opioids.

METHODS

This study was approved by our ethics committee, and it was conducted in accordance with the latest revision of the Declaration of Helsinki. All parents and any children thought to be able to understand it were given information about the pain treatment protocol, and parents provided consent. Ten generally healthy children, aged 10 months to 12 years, scheduled for thoracotomy due to persistent patent ductus arteriosus were enrolled in the study. All the children were included after it was shown that they had no contraindications for the use of NSAIDs, opioids, or amide-type local anesthetics in their medical and surgical histories or in a physical examination (e.g., allergy to the drugs used, asthma, renal or hepatic diseases, snoring or sleep apnea).

All patients were premedicated with oral flunitrazepam 0.03 mg/kg 60 minutes before induction. A standardized general anesthesia, with IV induction with thiopental 5 mg/kg, fentanyl 10 µg/kg, and atracurium 0.5 mg/kg and maintenance with isoflurane and nitrous oxide in oxygen, was used in all children. The ligation of ductus arteriosus was performed from a left thoracotomy. At the end of surgery, before chest closure, the surgeon inserted a 20-gauge epidural catheter into the posterior interpleural space along the paravertebral column. A thoracostomy tube was positioned more anteriorly and attached to a 5 to 10 cm H_2O suction tube.

After surgery, the children were transferred to the postanesthesia care unit for continuous follow-up of vital signs and pain. The children were administered oxygen until they were able to keep their hemoglobin oxygen saturation (SpO_2), as measured by pulse oximetry, at 94 percent or higher when breathing room air. During the 24-hour study period, the following parameters were recorded on a follow-up chart every hour: systolic and diastolic blood pressure, pulse rate, respiratory rate, SpO_2, body temperature, and worst pain on an 11-point Maunuksela pain scale (0 = no pain, 10 = worst possible pain). The Maunuksela pain score is a validated observer assessment tool based on facial expression, vocalization, movement or rigidity of the limbs and body, response to handling, irritability, and measured cardiorespiratory variables.[13] All adverse effects were recorded. Prospective assessments defined desaturation as an SpO_2 of 90 or less; low respiratory rate was defined as fewer than 12 breaths/min in children older than seven years and fewer than 15 breaths/min in children younger than seven. Vomiting was defined as either retching or the forceful expulsion of liquid gastric contents, and nausea as an unpleasant sensation in the stomach, usually accompanied by the urge to vomit. Pruritus and urinary retention were recorded as present or not.

For prevention of postoperative pain, the children were given rectal ibuprofen 10 mg/kg (Burana, Orion-Pharma, Espoo, Finland), and bupivacaine (5 mg/ml at a dose of 2 mg/kg) with epinephrine (5 µg/ml) (Marcain-Adrenaline, AstraZeneca, Södertälje, Sweden) was introduced into the interpleural catheter at the end of surgery. The ibuprofen dose was repeated every six hours. If the child was in pain (observed pain score of 4 or higher on a 0 to 10 scale), bupivacaine 2.5 mg/ml (Marcain, AstraZeneca, Södertälje, Sweden), at a dose of 1 mg/kg, was given through the interpleural catheter. The thoracostomy tube was clamped for 10 to 15 minutes after bupivacaine administration. Interpleural bupivacaine was allowed to be given every two hours. If the pain was not diminished by bupivacaine within 15 minutes, IV oxycodone hydrochloride 0.1 mg/kg (Oxanest, Leiras, Turku, Finland) was provided every 15 minutes for rescue analgesia until the pain had diminished to "slight" (pain score of 3 or less). All doses and administration times for bupivacaine and oxycodone were recorded on the patients' follow-up sheets.

All patients were observed for 24 hours in the postoperative care unit. Following this, the interpleural catheters were removed and the patients were treated in a pediatric surgical ward. On the ward, the patients were provided ibuprofen 10 mg/kg every six hours, and IV oxycodone 0.1 mg/kg was allowed if the pain score was 4 or higher.

The sample size of 10 children was considered sufficient for this pilot study, as the study's aim was to provide necessary background information to see whether pain treatment with interpleural bupivacaine and ibuprofen would provide sufficient analgesia in this patient population. Because no control group was enrolled, no statistical tests were used. The results are presented as number of cases, minimum and maximum, and mean, with standard deviations as appropriate.

RESULTS

Patient characteristics and main outcome data are summarized in Table 1.

All children needed rescue analgesic in addition to the baseline analgesics (rectal ibuprofen and interpleural bupivacaine). The number of rescue oxycodone doses ranged between one and 12 (mean = 6.0, SD = 3.6) doses. The multimodal pain treatment with ibuprofen, interpleural bupivacaine, and IV oxycodone was deemed to have performed sufficiently because the mean pain scores were low in all 10 children.

The time to first dose of oxycodone after surgery ranged between 50 minutes and 21 hours (mean = 7.1,

Table 1. Patients' characteristics and outcome data

Patient number	Gender	Age (months)	Weight (kg)	Height (cm)	Pain scores (0 to 10)*	Number of bupivacaine doses	Number of oxycodone doses	Lowest respiratory rate	Lowest SpO_2	Adverse reactions
1	Female	10	9	70	0 – 5 1.3 [1.7]	8	1	20	95	No
2	Male	13	8	76	0 – 4 0.7 [1.3]	7	12	14	94	Apnea (15 sec)
3	Female	38	13	95	0 – 5 1.2 [1.6]	8	5	19	91	Vomiting
4	Male	153	43	159	0 – 5 1.2 [1.6]	7	8	12	93	Nausea
5	Female	68	20	114	0 – 8 1.9 [2.2]	6	7	20	95	No
6	Male	41	12	89	Not available	3	3	24	92	No
7	Male	11	7	69	0 – 6 2.4 [2.2]	10	11	28	94	No
8	Female	13	11	78	0 – 4 0.4 [1.3]	3	4	24	97	No
9	Female	29	12	89	0 – 3 1.3 [1.3]	4	6	23	94	No
10	Female	27	12	92	0 – 4 1.2 [1.7]	5	3	24	96	Urinary retention
Mean (SD) min-max		40 (44) 10 – 153	15 (11) 7 – 43	93 (27) 69 – 159	1.3 (0.6) 0 – 8	6.1 (2.3) 3 – 10	6.0 (3.6) 1 – 12	20.8 (4.9) 12 – 28	94 (1.8) 91 – 97	

Bupivacaine was administered interpleurally at a dose of 1 mg/kg, and oxycodone hydrochloride IV at a dose of 0.1 mg/kg.
* Data are minimum-maximum and mean [SD] of 24-hourly recording.

SD = 6.2 hours). On most occasions (49 out of 60 administrations) a single 0.1 mg/kg dose of IV oxycodone provided sufficient pain relief for at least an hour. In nine children, the duration of the analgesic action of oxycodone doses ranged between 0.5 and 10 (mean = 2.7, SD = 2.1) hours. Patient 3 was an exception; she required three doses of oxycodone within 30 minutes at three hours after surgery, and two doses within 15 minutes at 17 hours, before her pain was diminished to "mild" (pain score < 3).

The pain treatment in this patient population was judged to be safe because no serious adverse events were recorded. Four nonserious adverse reactions were recorded. One child, a 13-month-old boy, developed brief apnea (duration of 15 seconds) two minutes after his tenth oxycodone injection (total dose of 1 mg/kg in 12 hours). His SpO_2 was 96 percent before and 94 percent immediately after the incident. His respiratory rate was 23 breaths/min before the incident, 14 breaths/min after the tenth oxycodone dose, and 15 to 20 breaths/min during the rest of the observation period. One three-year-old girl vomited twice, and one 12-year-old boy developed nausea. One two-year-old girl was catheterized due to urinary retention.

CONCLUSION

In the present study, interpleural analgesia with bupivacaine did not perform sufficiently after thoracotomy, as evidenced by the fact that all children needed IV oxycodone to achieve appropriate pain relief. Our data are consistent with the increasing evidence seen in studies of adult populations that interpleural analgesia may not be effective for post-thoracotomy pain. Scheinin et al.[14]

and Silomon et al.,[15] among others, found no opioid-sparing effect with repeated interpleural injections of bupivacaine in adults.

In some trials in children, interpleural bupivacaine has performed sufficiently, and children have not required supplementary opioids for pain relief.[5,16-18] However, many children in these studies also received sedatives to provide additional anxiolysis. In the Semsroth et al.[18] study, eight out of 11 children were administered midazolam, and in the McIlvaine et al.[16] investigation most children received diazepam and chloral hydrate. In young children, it is often difficult to separate pain from anxiety. After thoracotomy there is pleural pain from the therapeutic thoracostomy tube and incisional pain that is associated with breathing. Some of the children in previous studies who were treated with sedatives may actually have had pain and perhaps should have been provided analgesic rather than sedatives. Moreover, it should be noted that several children in the Semsroth et al.[18] study had SpO_2 values below 90 percent, with some of them even below 80 percent, although the children did not receive any postoperative opioids. Therefore, it can be assumed that during the postoperative period close monitoring of children is necessary not only when opioids are used but also after administration of sedatives and anxiolytics.

Extremely high infusion rates of interpleural bupivacaine have been required to achieve satisfactory analgesia after thoracotomy in children. In the McIlvaine et al.[5,16] and Semsroth et al.[18] studies, the mean rate of bupivacaine infusion was higher than 1 mg/kg/hr, and in some patients it went up to 2.5 mg/kg/hr. These doses may be considered unsafe because high plasma levels of bupivacaine are known to be toxic to the cardiovascular and central nervous systems.[19] McIlvaine et al.[5,16] measured high bupivacaine concentrations (> 2 μg/ml) in 75 percent of the patients, and the highest plasma concentration determined was 7 μg/ml, which is well above the potential central nervous toxicity level of 2 to 4 μg/ml.[20] Although none of the children was reported to develop central nervous system toxicity, it should be noted that the hypnotic-sedative drugs given to most of the children increase the threshold for convulsions. Moreover, the symptoms of anxiety and early signs of local anesthetic toxicity may be difficult to separate. Therefore, the infusion rates of bupivacaine used in these trials[5,16-18] may not be considered safe. Although the presence of chest tubes may remove large quantities of local anesthetic from the pleural cavity, as previously recommended with infusion in other sites,[19] we advise not exceeding a bupivacaine infusion rate of 0.4 mg/kg/hr in any continuous infusion.

In the present trial, pain treatment with oxycodone performed well, and no serious adverse reactions were recorded. The mean duration of the analgesic action of oxycodone was 2.7 hours, which corresponds well to the drug's elimination half-life of two to three hours in children.[9,21] The duration of analgesic action is also similar to that reported by Olkkola et al.,[8] who worked with children who had undergone strabismus surgery. In children undergoing tonsillectomies, oxycodone needed during the first 24 hours after surgery averaged 5.1 doses,[22] and after open appendectomy children needed 5.2 doses,[23] compared to the six doses called for in the present trial. However, it should be noted that in the two studies mentioned above a dose of 0.05 mg/kg of IV oxycodone was used, compared to 0.1 mg/kg in the present study. Moreover, the interindividual variation in pain and need for analgesics is large, and therefore in acute pain treatment the opioid dose should be individually titrated against the pain to achieve the optimal clinical response.

In the present trial, oxycodone did not cause significant respiratory depression. However, when any opioids are administered to children, the respiratory effects should be borne in mind. Olkkola et al.[8] administered oxycodone 0.1 mg/kg IV in children after strabismus surgery and found a significant respiratory depressive effect in several patients. Their results may be explained by the fact that they gave oxycodone shortly after halothane anesthesia to sleeping children without known pain. It is known that low levels of halothane (0.1 to 0.2 minimum alveolar concentration) markedly depress the hypoxic respiratory response.[24] On the contrary, pain stimulates ventilation by an additive effect, and it does not alter the chemoreflex response depressed by opioids.[25]

In conclusion, pain after thoracotomy seems to be significant in children. Because severe acute pain is a significant factor predicting continuing pain after surgery[1,3] and negative behavioral changes after discharge,[26] it is obvious that pain treatment after thoracotomy needs to be effective. The performance of new analgesic techniques should be evaluated before they are adopted into clinical use. In the present trial, interpleural bupivacaine did not perform sufficiently. However, IV oxycodone performed well, and no serious adverse reactions were observed in this small patient population.

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