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INTRAVESICAL MORPHINE ANALGESIA IS NOT EFFECTIVE AFTER BLADDER SURGERY IN CHILDREN: RESULTS OF A RANDOMIZED DOUBLE-BLIND STUDY

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ABSTRACT

Purpose: Intravesical morphine was recently recommended to reduce postoperative pain after reimplantation surgery for vesicoureteral reflux in children. The efficacy of such treatment, so far solely evaluated by open study, needed to be confirmed.

Materials and Methods: After parental informed consent was obtained, 80 children requiring Cohen cross-trigonal reimplantation were considered for inclusion in a double-blind study. On the day of surgery patients were randomly assigned to receive either 0.04 mg./kg. morphine per hour or placebo (normal saline) at a constant intravesical infusion rate of 0.08 ml./kg. per hour. Postoperative pain was assessed every 3 hours using a pain score adapted to patient age. If the score was above a predefined limit, patients received intravenous acetaminophen and nalbuphine alternately every 3 hours. Bladder infusion was discontinued after 48 hours.

Results: Mean and maximum pain scores as well as the number of scores above the limit were not statistically different when comparing the morphine and placebo groups. There was no difference in the number of doses of analgesics administered. Urine output, voiding frequency and the number of painful voiding episodes were not significantly different between the 2 groups. Plasma morphine concentrations were 3.0 ± 2.7 and 1.9 ± 1.9 ng./ml. at 24 and 48 hours in the morphine group and undetectable in the placebo group.

Conclusions: Intravesical administration of morphine is not effective for relieving postoperative pain during the first 48 hours after intravesical ureteral reimplantation. This study emphasizes the importance of controlled studies in evaluating the effectiveness of a new drug or procedure before recommending its use for all patients.

KEY WORDS: analgesia, morphine, bladder, surgery, child

Vesicoureteral reflux affects 1% to 2% of apparently healthy children and is present in 30% to 40% of children suffering from urinary tract infection. The nephropathy frequently associated with vesicoureteral reflux can result in end stage renal failure and hypertension. Optimal management of vesicoureteral reflux, either medically or surgically, is still under evaluation.[1]

When surgery is performed management of postoperative pain is often the limiting factor that extends the hospital stay. Indeed, intensity of pain after transvesical bladder surgery was the main reason for renewing the extravesical technique to avoid bladder spasms and dysuria.[2] Postoperative pain is usually managed either by parenteral opioids or regional analgesics by caudal or epidural infusion. Although continuous epidural infusion provides satisfactory pain control after ureteroneocystostomy in children and does not delay hospital discharge, it is associated with a significant increase in the incidence of postoperative fever and overall cost compared to standard methods of postoperative pain management.[3] Continuous intravenous morphine infusions for acute postoperative pain are also used regularly but there are many adverse effects. Esmail et al studied the adverse effects in 110 pediatric patients receiving continuous intravenous morphine for postoperative pain.[4] Nausea and/or vomiting was commonly reported (42.5%). Other side effects included urinary retention, pruritus, dysphoria, hypoxemia and difficulty in arousal. Moreover, inadequate analgesia occurred in 65.5% of patients during the initial 24 hours of therapy.

A method for administering local analgesia to the bladder urothelium is needed to soothe postoperative voiding discomfort, avoid systemic side effects and shorten hospital stay. It has been shown that intravesical morphine controlled postoperative pain in children efficiently and the authors recommended its use after bladder surgery.[5,6] However, these open studies only evaluated treated patients and did not include a control group, which we believe is mandatory for the evaluation of postoperative pain and efficiency of local morphine administration before extending its use to all patients and to more extensive bladder surgery.

We assessed whether morphine administered in the bladder could lower pain scores and reduce the need for systemic analgesics in the first 2 postoperative days. In a randomized double-blind study we compared children treated with morphine to those receiving a placebo after transvesical ureterovesical reimplantation procedures.

METHODS

This study was approved by the Ethics Committee of Paris-Bichat Claude Bernard. After parental informed consent was obtained, 80 children with primary reflux requiring Cohen cross-trigonal reimplantation were considered for study during the preoperative visit, when the decision was made to

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operate. On the day of surgery parents were asked to sign an informed consent form for final study inclusion. Patients were then randomly assigned to receive either morphine or placebo and infusions were prepared by the pharmacist.

Cohen cross-trigonal reimplantation was performed in all cases with general anesthesia. Epidural and caudal anesthesia were not used and no tapering was performed. A single suction drainage tube was placed in the prevesical space for 48 hours. A small (4Fr) catheter was placed in the bladder through a separate puncture site and anchored to the skin. After skin closure, the catheter was connected to the infusion pump and administration of either 0.04 mg./kg. morphine or 0.08 ml./kg. saline per hour was started. All patients received simultaneously 15 mg./kg. acetaminophen intravenously.

Patients remained in the recovery room for the initial 3 postoperative hours and were then admitted to the Clinical Investigation Centre for 48 hours for pain evaluation and additional drug administration as necessary. The surgeon and anesthetist supervised the postoperative period. Bladder morphine catheters were removed 48 hours postoperatively, and patients were transferred to the standard inpatient surgery unit for an additional 24 hours before discharge home. None of the patients had a bladder or ureteral catheter postoperatively.

Postoperative pain was assessed by a specialized nurse every 3 hours using a pain score adapted to patient age. The Children's Hospital of Eastern Ontario Pain Scale (CHEOPS) was used for patients younger than 6 years.[7] It is based on evaluation of 5 items (cry, facial expression, verbalization, torso position, touch and leg position) with a maximum score of 13. When the CHEOPS score was greater than 6, the child was given analgesics intravenously. A 10 cm. Visual Analog Scale (VAS), graded from 0 to 100 (minimum to maximum individual pain estimation),[8] was used in children 6 years old or older. The lower limit for analgesic administration was 40. If the pain score was above the limit either with the CHEOPS or VAS, patients received 15 mg./kg. acetaminophen intravenously (limited to 60 mg./kg. daily) and 0.2 mg./kg. nalbuphine per dose alternately every 3 hours.

In addition to pain evaluation, cardiac rhythm and blood pressure, respiratory rhythm and oxygen saturation were monitored continuously. Voiding frequency and volume and number of voids associated with pain were also noted. A bolus of 10 mg./kg. sodium chloride was administered once if urinary output was less than 10 ml./kg. in a 6-hour interval during postoperative day 1. Blood samples to determine morphine concentration were drawn from a peripheral intravenous catheter 24 and 48 hours postoperatively and immediately centrifuged. Plasma was kept frozen at −20C. Morphine concentration was also assessed in the liquid collected through the drainage suction tube.

Morphine concentration was measured by high-performance liquid chromatography mass spectrometry assay. The high-performance liquid chromatography system consisted of a series 200 pump and autosampler equipped with a 20 μl. sample loop (PerkinElmer, Norwalk, Connecticut). A SCIEX API 150 EX (PerkinElmer) quadrupole mass spectrometer equipped with a turbo ion spray interface was used. Extraction was performed with 5 ml. of a mixture of dichloromethane/isopropyl alcohol (90/10, volume per volume). The mobile phase was acetonitrile/10 mM. ammonium acetate, adjusted at pH 3, and the column was a 5 μm. Satisfaction C8 Plus stationary phase (CIL Cluzeau, Sainte Foy La Grande, France) with a running time of 10 minutes. Mass spectrometry detection was performed using a single quadrupole operating in positive ion mode. Under these chromatographic conditions, retention times for morphine and nalorphine (internal standard) were 4.03 and 7.03 minutes, respectively. The percentage extraction recovery of morphine and nalorphine was 81.6% and 79.9%, respectively (data not shown). Calibration curves for morphine with naloxone as an internal standard ranged from 0.5 to 50 ng./ml. The limit of assay quantification was 0.5 ng./ml. with a detection limit of 0.25 ng./ml. Results are presented as mean and standard deviation (SD). Analysis of variance with $p < 0.05$ as the minimum level of significance was used for comparison between groups.

RESULTS

A total of 80 patients were considered for study but parents of 2 children refused final inclusion. Of the remaining 78 patients 6 (3 receiving morphine and 3 receiving placebo) were excluded from study on postoperative day 1 due to catheter dysfunction (4) or delayed voiding (1 in the morphine group and 1 in the placebo group). In addition, 1 patient in the placebo group who underwent circumcision in addition to the Cohen procedure and 1 in the morphine group who had an infusion rate constant of 0.07 instead of 0.08 ml./kg. per hour were analyzed separately. Therefore, analysis was performed on 72 patients, including 37 in the morphine group and 35 in the placebo group. Mean (SD) patient age was 4.8 (2.9) years (range 1.3 to 13) years, mean (SD) weight was 17.6 (7.4) kg. and female-to-male ratio was 56:16 with no difference between the 2 groups.

The CHEOPS score was used for 48 children (66%) younger than 6 years (23 in the morphine group and 25 in the placebo group) while the VAS score was used in the remaining 24 (33%) children 6 years old or older (14 in the morphine group and 10 in the placebo group). Mean value for the 2 scores calculated on days 1 and 2 is presented in table 1. The number of children with at least 1 score above the limit of analgesic administration was 58 (32 in the morphine group and 26 in the placebo group, 80%) on day 1 and 35 (20 in the morphine group and 15 in the placebo group, 48%) on day 2. There was no difference between the 2 groups in the number of patients who required additional analgesia.

Mean and maximum pain scores and number of scores above the limit of analgesic administration were calculated separately for CHEOPS and VAS and comparison was stratified according to the score used. The parameters were not statistically different between the morphine and placebo groups either on day 1 or 2, except for the maximum VAS

TABLE 1. *Evaluation of analgesia and administration of analgesics in 72 children after Cohen cross-trigonal reimplantation*

	Day 1 Mean (SD)		p Value	Day 2 Mean (SD)		p Value
	Morphine	Placebo		Morphine	Placebo	
Mean pain score:						
VAS	27 (12)	18 (14)	0.10	18 (13)	24 (19)	0.32
CHEOPS	1.3 (0.8)	1.4 (0.8)	0.56	1.7 (3.5)	0.8 (1.0)	0.23
Max. pain score						
VAS	79 (20)	38 (34)	0.001	50 (28)	47 (37)	0.85
CHEOPS	4.8 (2.1)	5.9 (2.5)	0.09	5.9 (15)	3.0 (2.7)	0.35
No. scores above limit (CHEOPS greater than 6, VAS greater than 40)	2.7 (2.1)	2.2 (1.8)	0.22	1.3 (2.1)	1.3 (1.9)	0.98
No. administration of nalbuphine	1.1 (1.1)	0.9 (0.9)	0.36	0.3 (0.8)	0.4 (1.0)	0.45
No. administration of acetaminophen	2.2 (1.0)	1.9 (0.9)	0.18	0.8 (1.0)	0.8 (1.1)	0.87

score, which was higher in the morphine than in the placebo group on day 1 (table 1). At least 1 analgesic was administered on day 1 (in addition to the initial acetaminophen dose) in 56 (77%) children and 32 on day 2 in (44%). Five patients did not receive any analgesic because pain resolved before drug administration. The requirement for acetaminophen and nalbuphine was similar in both groups on days 1 and 2 (table 1).

Urine output, voiding frequency and number of painful voids were also compared and none of these parameters was statistically different between the morphine and placebo groups (table 2). However, the bolus numbers for sodium chloride per patient were higher in the morphine than in the placebo group (0.6 versus 0.3, $p = 0.03$). In addition, cardiac rhythm, blood pressure, respiratory rhythm and oxygen saturation were in the physiological range and there was no significant difference between the groups (table 2). Mean plasma morphine concentrations plus or minus SD were 3.0 ± 2.7 and 1.9 ± 1.9 ng./ml. (mean and SD) at 24 and 48 hours in the morphine group and undetectable in the placebo group. Mean (SD) cumulative volume of drainage for 48 hours was 31.1 (22.9) ml. and morphine concentration in treated patients was 1.2 (6.2) μg./ml.

DISCUSSION

Peripheral effects of morphine on bladder function have been tested in rats and appeared biphasic with an initially weak excitatory effect followed by depression of detrusor activity.[9] The mechanisms of this depression effect are complex but may involve diminished acetylcholine release,[9] presynaptic inhibition of neuronal transmission[10] or direct smooth muscle effects.[11] Although the peripheral effects were weak, suggesting that the inhibitory effect of morphine on bladder motility was mainly mediated by central opioid receptors, they may allow a reduction in systemic administration of analgesic drugs during the immediate postoperative period, thus reducing the risk of side effects. Possible local effects of morphine at inflammatory sites during experimental studies on dogs provide additional arguments in favor of intravesical morphine after bladder surgery.[12,13] Indeed, opioids can produce potent antinociceptive effects by interacting with local opioid receptors in inflamed peripheral tissue. These results have been confirmed recently in a randomized study following knee surgery.[14]

In the study by Duckett et al 52 children undergoing intravesical ureteral reimplantation were randomized to receive 1 of 3 concentrations (0.05, 0.375 or 0.5 mg./ml. at the infusion rate of 0.04 ml./kg. per hour) of intravesical morphine.[5] Pain was significantly greater in 4 of 6, 8-hour nursing shifts on the first 2 days postoperatively for patients who received 0.05 mg./ml. morphine than for those who received 0.375 or 0.5 mg./ml. There was no difference between the 2 groups who received the higher doses (0.375 and 0.5 mg./ml.). Although the study was not controlled and pain management was variable and inconsistent between groups, the authors recommended the 0.5 mg./ml. dose for efficient postoperative analgesic effects. Encouraged by this report, Bertschy et al, following the same protocol, studied a group of 25 children undergoing ureterovesical reimplantation.[6] They also concluded that intravesical morphine was efficient in controlling postoperative pain and recommended its administration for the management of pain after bladder surgery in all children. However, again, the methodological approach was unsatisfactory since the study was open and there was no control group.

Our study was conducted on patients following a Cohen procedure because the technique is standardized and most frequently performed on children with vesicoureteral reflux. The success rate is high (99.7%) while the complication rate is low.[15] In postoperative situations deficiencies in pain control for children were identified in the mid 1980s[16] and since then pain assessment devices have been developed with the aim of detecting the presence of pain, estimating its severity and ensuring appropriate treatment. In our study evaluation of pain was adapted to patient age. Self-reporting based on the use of visual analog scales is the reference method to evaluate pain in adults. As this method was reported to be generally satisfactory with children 5 years old or older,[17] we used it for that age group.[18] However, tests that rely on self reporting cannot be used on children who are too young to understand and verbalize. Therefore the evaluation of pain in children younger than 5 years was based on a validated observational pain score called CHEOPS and validated in the immediate postoperative period or for needle pain. The scale has proved to be sensitive to the administration of intravenous opioids and closely correlates with observations by nurses.[7]

Using these validated methods to evaluate pain, we demonstrated that patients experienced and expressed pain during the postoperative period, as 77% and 44% required analgesics at least once respectively on postoperative days 1 and 2. However, morphine administered as a continuous intravesical infusion for 48 hours did not reduce pain, as no difference in pain scores and systemic analgesia required were noted between the morphine and placebo groups. We also analyzed the number of painful voids, which usually last for short periods and may not correlate with the assessment of pain programmed at 3-hour intervals. Our data showed that morphine did not decrease voiding discomfort and that the number of painful voids was similar in both groups. The only unexplained difference observed between the morphine and placebo groups was that the mean pain score was significantly higher in the morphine group than in the placebo group during postoperative day 1 in patients older than 6 years. We also observed that the requirement for bolus doses of saline was significantly higher in the morphine than in the placebo group. As we did not catheterize our patients, it is difficult to differentiate between a delay in urine output or a delay in bladder emptying secondary to a local morphine effect.

In the previous study by Duckett et al morphine was undetectable in plasma after intravesical infusion.[5] In our study, using a sensitive high-performance liquid chromatography mass spectrometry method, morphine was detected in plasma but the concentrations were low and most likely associated with limited or no central analgesic effects and no

TABLE 2. *Comparison of urinary function and physiological parameters in 72 children after Cohen cross-trigonal reimplantation*

Parameters	Day 1 Mean (SD)		p Value	Day 2 Mean (SD)		p Value
	Morphine	Placebo		Morphine	Placebo	
Voiding frequency	17 (8)	17 (8)	0.68	20 (7)	16 (7)	0.06
No. voids associated with pain	6 (4)	8 (7)	0.18	6 (6)	5 (7)	0.58
Urinary vol. (ml./hr.)	52 (22)	56 (26)	0.51	67 (18)	68 (28)	0.83
Cardiac rhythm (beats/min.)	114 (13)	114 (18)	0.88	108 (15)	110 (20)	0.56
Systolic blood pressure (mm.Hg)	116 (10)	112 (10)	0.15	109 (8)	110 (8)	0.79
Oxygen saturation (%)	98 (1)	98 (1)	0.98	98 (1)	98 (1)	0.84
Respiratory rhythm (breaths/min.)	24 (4)	25 (5)	0.35	24 (4)	25 (4)	0.42

adverse effects.[19] Indeed, we did not observe any difference in respiratory rhythm, cardiac rhythm and blood pressure between the 2 groups.

Although pain after bladder surgery is considerable, as demonstrated by our study, we observed in both groups that the total amount of analgesics required for pain relief was lower at the Clinical Investigation Centre than the amount usually administered in our surgical department. Although speculative, this observation suggests that pain may be overestimated and/or over expressed in clinical settings compared to research situations. Indeed, differential analysis of pain, stress and anxiety is difficult in children and may lead to overestimation of pain. However, care in specialized units by trained nurses with more time to spend with the children may explain the low amount of analgesics required in the placebo and morphine groups.

CONCLUSIONS

In our study and in contrast to previously reported data morphine was not effective in reducing pain after bladder surgery in children. We emphasize the importance of randomized and controlled studies to evaluate the effectiveness of a new drug or procedure before making definitive conclusions and recommending it for all patients. In addition, as the requirement of postoperative analgesia was lower than currently reported, our study illustrates again that assessment and measurement of pain in children are difficult challenges and treatment procedures should include attentive nursing along with analgesic medications.

The nurses at the Clinical Investigation Centre assisted in the clinical management of our patients.

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