Original article

A pilot study of nalbuphine versus tramadol administered through continuous intravenous infusion for postoperative pain control in children

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Abstract. Nalbuphine and tramadol are potent analgesic drugs. Our aim was to preliminarily assess and compare the efficacy and safety of nalbuphine and tramadol for postoperative analgesia in children. In a double-blind design, 24 ASA 1-3 children aged 1 to 10 years undergoing a scheduled surgical procedure were randomly allocated to receive either an intravenous bolus dose of nalbuphine 100 μg/kg immediately before the end of surgery followed by an infusion of 0.2 μg/kg/min for 72 hrs., or an intravenous bolus dose of tramadol 1,000 μg/kg followed by an infusion of 2.0 μg/kg/min for 72 hrs. Postoperative pain control and drug-related adverse events were recorded. Three children who received nalbuphine required an extra bolus dose within the 12 hrs. of post-surgery versus one child in the tramadol group. A similar number of patients in both groups required an increment in the infusion rate within the 72 post-surgery hours. Sedation was observed in 2 children in the nalbuphine group and in 1 child in the tramadol group. Four children presented vomiting with tramadol and two with nalbuphine. Cardiovascular parameters remained within the normal ranges in both groups. In conclusion, the bolus/infusion regimen of tramadol evaluated in this study appears to have better postoperative analgesic efficacy than the bolus/infusion regimen of nalbuphine. These preliminary results require further confirmation by studies with a sample size enough to clearly identify differences in their efficacy as well as in the rate of adverse events secondary to the administration of each of them.
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Key words: Analgesics, opioid analgesics, postoperative pain, randomized controlled trials

Introduction

Nalbuphine is a semi-synthetic opioid with potent analgesic effects due to its agonist actions on the κ opioid receptors in the central nervous system (CNS). However, due to its agonist actions on the μ_2 opioid receptors, its administration is often associated with sedation, disphory, and urinary retention (1). Its half-life is relatively short, approximately from 3 to 6 hours (2). In children, nalbuphine has been used at bolus doses of 100-150 μg/kg to control moderate to severe pain without significant secondary effects (3). Its onset of action is 5-10 min after its intravenous injection and its duration of action is 3-6 hours (4).

Tramadol, a derivate of aminocyclohexanol, is a potent analgesic drug which moderately bounds to μ_1 and μ_2 opioid receptors, inhibits the reuptake of noradrenaline, serotonine and 5-hydroxytryptamine, and enhances the inhibitory actions of descent pain pathways (5). In contrast with other opioids such as nal-

buphine, buprenorphine and morphine, tramadol does not induce tolerance in rodents (6). In pediatric surgical patients, it has been used as an intra-operative analgesic agent as well as in the prevention of postoperative pain at intravenous doses of 1,000-3,000 μg/kg (7). In comparison with morphine, its administration shows lower rates of nausea and vomiting. For the control of post-operative pain, an intravenous bolus dose of tramadol 750 μg/kg has the same effects as morphine (100-200 μg/kg) and nalbuphine (100 μg/kg) (7). Intravenous infusion of tramadol may decrease the adverse effects while preserving or improving its analgesic efficacy (6). Under this perspective, we designed this pilot study in order to compare nalbuphine versus tramadol administered through continuous intravenous infusions for postoperative analgesia and to preliminarily evaluate the incidence of adverse events.

Methods

The study was approved by the Institutional Review Board and was performed at the Department of Anesthesia, Hospital Infantil de México 'Federico Gómez'. Written parental informed consent was obtained from every patient.

We included 24 children, aged from 1.6 to 10 years and weighting from 10 to 35 kg, American Society of Anesthesiologists class 1-3, undergoing a scheduled surgical procedure with expected moderate to severe postoperative pain (as judged by the anesthesiologist according to the surgical procedure). The children did not present morbid obesity, psycho-motor delay or esophageal reflux, and had not received opioids at least one month before the surgical procedure.

Since we were not able to identify any previous studies comparing tramadol versus nalbuphine to allow us to estimate a sample size, we limited our study to 24 children divided into two equal groups of 12 subjects. In order to maintain balanced age groups across treatments, 6 children aged from 1 to < 6 years and 6 children aged from ≥6 to 10 years were included in each group (Figure 1).

Procedures

By means of a predesigned table of random numbers, children were allocated to receive either nalbuphine (Group 1) or tramadol (Group 2), as follows. Children in Group 1 received an i.v. bolus dose of 100 μg/kg of nalbuphine (Bufigen 10 mg/mL; Laboratorios Pisa, Mexico DF, Mexico) immediately before the closure of the surgical incision. Once the patient entered

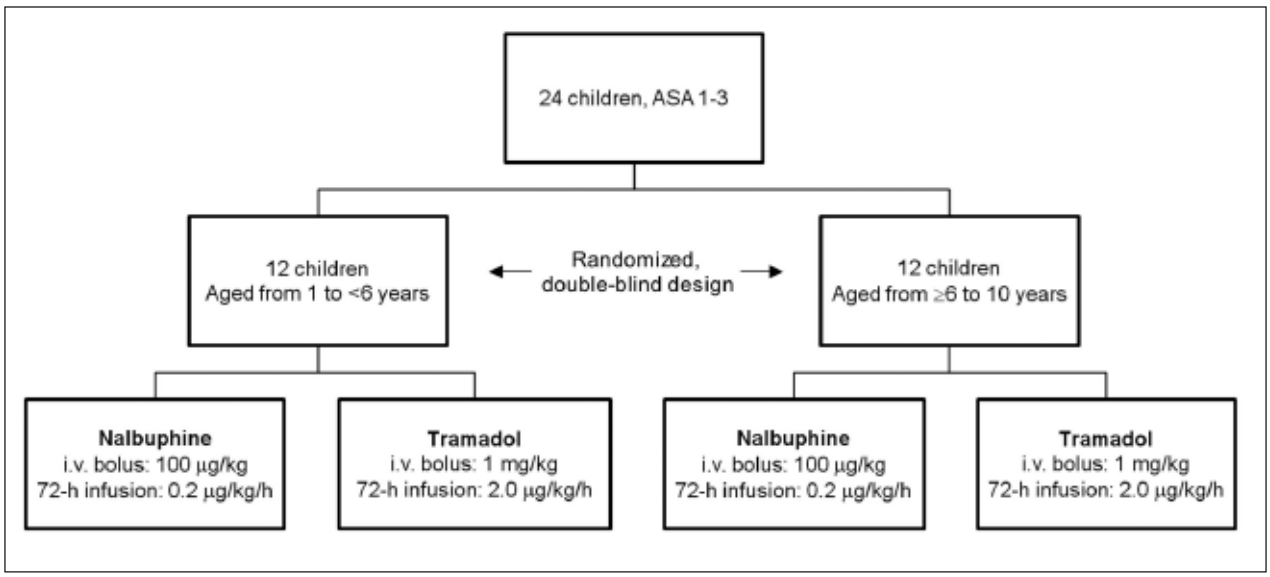

Figure 1. Flow-chart of the study

the recovery room, an i.v. infusion of nalbuphine (0.2 μg/kg/min) was started and maintained for the next 72 hours. In Group 2, children received an i.v. bolus dose of 1,000 μg/kg of racemic tramadol (Tradol 100 μg/2 ml; Laboratorios Grunenthal, Mexico DF, Mexico) followed by an i.v. infusion of tramadol 2.0 μg/kg/min under similar conditions than Group 1 (Figure 1).

Bolus doses of either nalbuphine or tramadol were prepared in 30 ml of NaCl 0.9% sterile solution and administered during a 10-min period. The infusions of nalbuphine and tramadol were prepared daily in a NaCl 0.9% solution that was administered at a rate of 1 ml/h by means of an automatically-controlled infusion pump. Administration of NaCl 0.9% was independent of the fluids administered to the patients as part as the post-surgical treatment.

In order to preserve the double-blind design of the study, drugs were prepared on a case-by-case basis, according to the predesigned table of random numbers, by one of the investigators of the study (JCR-M) who did not participate in the evaluation of patients' eligibility or study outcomes. Evaluation of patients' eligibility, pain score in younger children, application of the visual analogue scale (VAS) in older children, and evaluation of adverse events during the study period were performed by an investigator (JCH-P) who was unaware of the patients' allocation group. Adherence to the protocol was also monitored by another investigator (DM-G).

Pain assessment

In patients <6 years, pain intensity was measured according to two different scales: the facial pain intensity scale consisting of six scores ranging from zero (without pain) to five (severe pain) (8), and the Children Hospital of Eastern Ontario behavioral scale (CHEOPS) (9).

A VAS consisting of a 100-mm line drawn horizontally on paper with right angle stops placed at both ends and verbal anchors of "no pain" and "pain as bad as it could be" written respectively on the left and right sides (10), was used to evaluate pain intensity in children ≥6 years. The scale was explained to children twice, before surgery and once the patients recovered their alert state. We did not observe any difficulty in explaining the scale and children did not express any problem in understanding the scale itself nor in scoring their pain.

The first assessment of postoperative analgesia was performed when children arrived at the recovery room and thereafter every 1 h for the first 24 hrs. followed by evaluations every 4 hrs. until the end of the 72-hr. study period. If the pain intensity score was ≥40 mm in children ≥6 years old, the infusion rate was increased to 2 ml/h (nalbuphine 0.4 mg/kg/min or tramadol 4 μg/kg/min) and remained at this rate level for 72 hrs. unless sedation occurred. Thirty minutes after the infusion rate was increased, children were requested to evaluate the pain intensity. If it remained at ≥40 mm, an i.v. bolus of either nalbuphine (100 μg/kg) or tramadol (1,000 μg/kg) was administered. If required, a bolus dose was repeated 1 hour later. The maximum number of rescue bolus was limited to three doses.

In children <6 years old, if a score ≥3 was obtained in the six-grade faces scale together with a CHEOPS score ≥ 7, increments in dose and administration of additional i.v. bolus doses were similar to those above described for older children. The maximum total daily dose was limited to 6,000 μg/kg of tramadol or 600 μg/kg of nalbuphine (5).

Study outcomes

As a parameter of efficacy, the number of patients requiring dose increments was recorded for purpose of the study. Several parameters of safety were assessed. Sedation was assessed according to whether the patient was awake and alert, sleeping and easy to arouse, difficult to arouse, responded with shaking, or did not respond [11]; the scale varied from 1 (awake and alert) to 5 (patient does not respond). Heart and respiratory rates, diastolic and systolic blood pressure, and SaO_2 (%) were monitored at the same times as the evaluation of pain scales. Finally, the number of patients vomiting as well as the times of vomiting within the 72-hour evaluation period were also recorded.

Data analysis

Groups were masked with codes and data analysis was performed by other of the investigators who

was did not know the patients' allocation and did not participate in the evaluation of the study outcomes (AAN-O). Demographic characteristics (age, weight and height) were compared between groups by means of a Student t test for unpaired data. Sex distribution was compared between groups by means of a Fisher's exact test, and a $P \leq 0.05$ was considered as the statistical limit. The study outcomes were not compared between groups due to the small number of patients; results were presented in a descriptive way.

Results

All randomized patients completed the study in their corresponding group and were evaluated as planned by the protocol. Demographic characteristics were similar between the nalbuphine and tramadol groups (Table 1). Children aged between 1 and < 6 years who received nabuphine underwent the following surgical procedures: perineal fistula and bladder neck closure (n=1), bilateral elongation of Achilles tendon (n=1), iliac crest grafting and closure of nasoalveolar fistula (n=1), bilateral oblique pelvic osteotomy (n=1), rib grafting and auricular plasty (n=1), and laparoscopic cholecystectomy (n=1). Children aged from 1 to < 6 years who received tramadol underwent exploratory laparotomy (n=1), bilateral oblique pelvic osteotomy (n=2), thoracotomy and exploratory laparotomy (n= 1), ileostomy closure (n=1), and plasty for hypospadias (n=1). Children aged between ≥ 6 and 10 years who received nalbuphine underwent the following surgical procedures: resection of dermoid cyst (n=1), exploratory laparotomy and intestinal biopsy (n=1), right thoracotomy and lobectomy (n=1), right nephrectomy (n=1), plasty for hypospadias (n=1), and bilateral release of the Achilles tendon. Finally, children aged from ≥ 6 to 10 years who received tramadol underwent resection of choledochous cyst (n=1), right thigh grafting and scar release on right hand (n= 1), bilateral plasty of cuadriceps (n=1), anatomical bladder amplification (n=1), resection of an extra left rib (n=1), and resection of hard palate and left upper maxillary (n=1).

Table 1. Demographic characteristics

	Nalbuphine (n= 12)	Tramadol (n= 12)
Sex (M:F)	7:5	7:5
Age (years)	6.2 (2.5-10.0)	4.4 (1.6-10.0)
Weight (kg)	18 (10-30)	16.5 (10-35)
Height	112.5 (90-135)	102.5 (80-133)

M: male; F: female.
No differences (P > 0.10) were observed between groups in any of the parameters

Table 2. Outcomes of the study in the postoperative period

	Nalbuphine (n= 12)	Tramadol (n= 12)
Additional bolus dose within 12 hrs. post-surgery	3	1
Increments in the IR in the 72-hrs. study period	8	7
Children with sedation	2	1
Patients with vomiting	2	4

IR: Infusion rate
Due to the small sample sizes, no statistical analysis was performed.

In the nalbuphine group we observed more patients who required rescue bolus doses within the first post-surgical 12 hours (Table 2). However, in a similar number of patients the infusion rate was increased within the 72 post-surgery hours in the two study groups. More patients were sedated in the nalbuphine group whereas there were more patients vomiting in the tramadol group. In both groups, sedated patients were easily aroused by verbal commands except in one child receiving 2xIR of tramadol who required movements to be aroused but responded satisfactory when tramadol infusion was decreased to 1xIR. Vomiting was successfully controlled with metochlopramide in all cases. Vomiting in the tramadol group was associated with dose increments. Because of the limited sample size, we did not sub-analyze the results of efficacy and tolerability by age group.

Although cardiovascular parameters showed limited variations throughout the study period, a large intragroup variability was observed. However, these variations were within the normal ranges and no significant differences were observed between nalbuphine and tramadol groups (Figure 2). Similar results were observed in relationship with respiratory rate and SaO_2 (Figure 3).

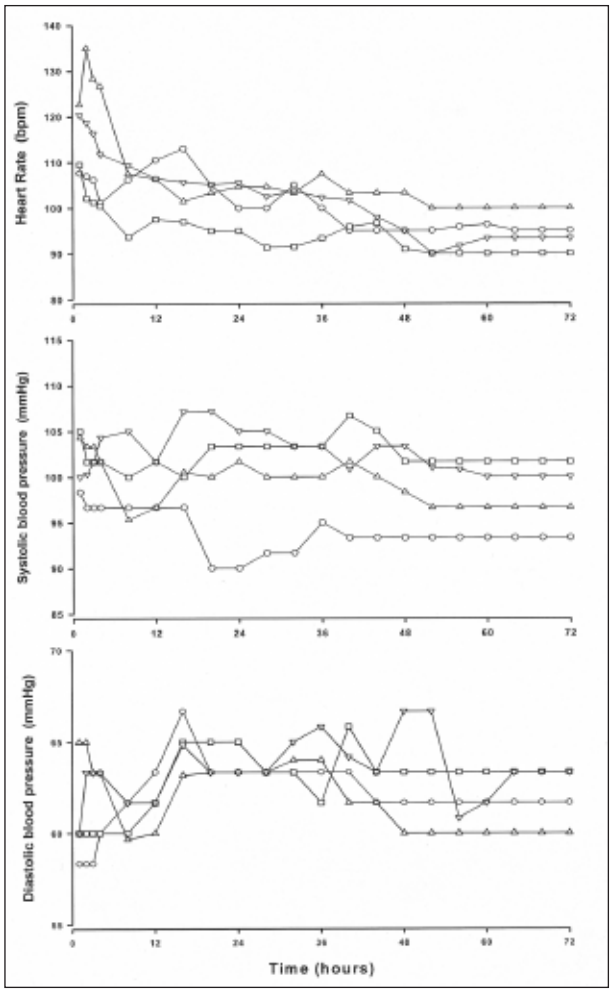

Figure 1. The cardiovascular response during the study period was similar among the two groups of nalbuphine and the two groups of tramadol. In order to simplify, only mean values were plotted.
Symbols: circles: nalbuphine in children aged from 1 to <6 years; squares: tramadol in children aged from 1 to <6 years; triangles: nalbuphine in children aged from ≥6 to 10 years; inverted triangles: tramadol in children aged from ≥6 to 10 years
Abbreviation: bpm: beats per minute

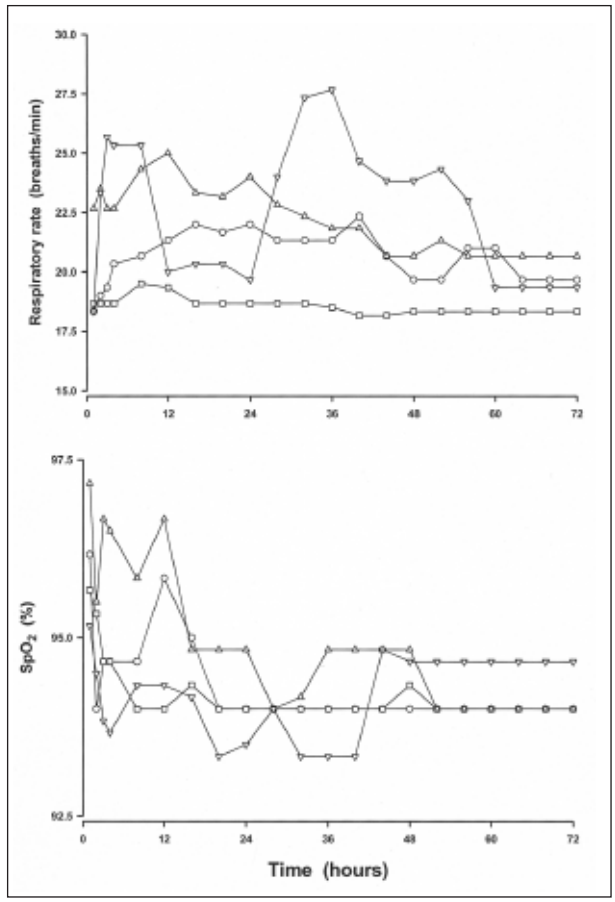

Figure 2. The respiratory changes during the study period were similar among the two groups of nalbuphine and the two groups of tramadol. In order to simplify, only mean values were plotted.
Symbols: circles: nalbuphine in children aged from 1 to <6 years; squares: tramadol in children aged from 1 to <6 years; triangles: nalbuphine in children aged from ≥6 to 10 years; inverted triangles: tramadol in children aged from ≥6 to 10 years

No patient required postoperative tracheal intubation, and all patients were discharged from the study at the end of the study period with no complications. A final clinical evaluation 8 hrs. after the end of the study showed no complications related to the study, and only three children reported mild pain that was controlled through acetaminophen administration.

Discussion

Since a wide range of possibilities for postoperative pain control are available (from loco-regional blocks with local anesthetics to systemic administration of opioid derivates), postoperative pain control in children is currently mandatory under an ethical and medical perspective. However, a proper balance between analgesic potency and safety is still a challenge when treating postoperative pain. For example, morphine is a potent analgesic drug that produces a high rate of respiratory depression and vomiting.

As judged by a high number of patients treated with rescue doses of nalbuphine in order to control pain, our study showed that a bolus dose of tramadol (1,000 μg/kg) followed by an infusion rate of 2.0 μg/kg/min may probably result in a better control of postoperative pain than a bolus dose of nalbuphine (100 μg/kg) followed by an infusion of nalbuphine (0.2 μg/kg/min). It may be argued that the dose of either nalbuphine or tramadol could be increased in order to enhance its analgesic efficacy. However, the number of cases with sedation secondary to nalbuphine might also increase. In adults, a bolus dose of 450 μg/kg of nalbuphine was associated with respiratory depression and deep sedation without improving its analgesic effects (5). In our study, we used a maximum daily dose of 600 μg/kg of nalbuphine. Depression may be present in a high number of children even if morphine is administered by caudal or epidural block (12). Nausea and vomiting are common adverse effects secondary to bolus doses of tramadol, as supported by our results. However, these complications were successfully controlled with the administration of metoclopramide.

Tramadol has been used in a dose ranging between 1,000-3,000 μg/kg q8hrs., which corresponds to 3,000-6,000 μg/kg/day (13); higher doses may induce severe nausea and vomiting. In our study, we limited the daily dose to a maximum of 6,000 μg/kg of tramadol. This drug has also shown to be effective for postoperative analgesia when administered to children through other ways including wound infiltration (14) or caudal administration concomitantly with bupivacaine 0.25% (15). A single intravenous bolus dose of tramadol (2,000 μg/kg) in children undergoing adeno-tonsillectomy for obstructive sleep apnea resulted in pain control that was very similar to morphine but with fewer episodes of oxygen desaturation (16); no cases of vomiting were observed. In addition, a recent review of the postoperative efficacy of tramadol in children properly summarized the different infusion regimens that are being used in children of different ages to maintain a target plasma concentration of 300 ng/mL (17); the maximum recommended dose for children of 1 to 3 years of age was 180 μg/kg/hrs. and for children to adults was 120 μg/kg/hrs. or 2 μg/kg/min. We used the latter dose for all the participants, from 1 to 10 years of age. Thus, we do not recommend intravenous doses of either tramadol or nalbuphine higher than those evaluated in our study.

The half-life of tramadol in children is approximately 5-6 hrs., its volume of distribution (Vd) is approximately 3.1 L/kg and total plasma clearance of 6.1 mL/kg/min (5, 18). Clearance of the (+)- and (-)-enantiomers of tramadol can be affected by patient's weight (19). Although we did not quantify plasma levels of tramadol, it is very unlikely that our patients may have reached toxic levels through accumulation since we did not observe time-dependent adverse effects. With reference to nalbuphine, its plasma half-life is approximately 2.5 hrs. and its Vd is of almost 4 L (16). Similar to tramadol, the adverse events observed in the nalbuphine group were not time dependent and were more likely dose dependent and therefore secondary to its action at different receptors.

The major limitation of our study was related to the small sample size that limited any type of subanalysis. However, our study may provide the basis for future trials in children. Tramadol caused nausea and vomiting in approximately 30% of patients and nalbuphine caused sedation in a similar number of patients (30%). Therefore, administration of e.g. metoclopramide to children receiving tramadol for postoperative pain control should be considered to prevent nausea and vomiting whereas a careful postoperative monitoring should be performed in patients under postoperative pain control with nalbuphine in order to prevent and identify potential ventilatory complications secondary to a deep sedation.

In conclusion, a single intravenous bolus dose of tramadol (1,000 μg/kg) before the closure of the surgical incision followed by an infusion of 2.0 μg/kg/min (120 μg/kg/h) for 72 h appears to produce better postoperative pain control than a single intravenous bolus dose of nalbuphine (100 μg/kg) before the closure of the surgical incision followed by an infusion of 0.2 μg/kg/min (12 μg/kg/h) for 72 h. Even at these infusion rates, tramadol caused vomiting whereas nalbuphine caused sedation.

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