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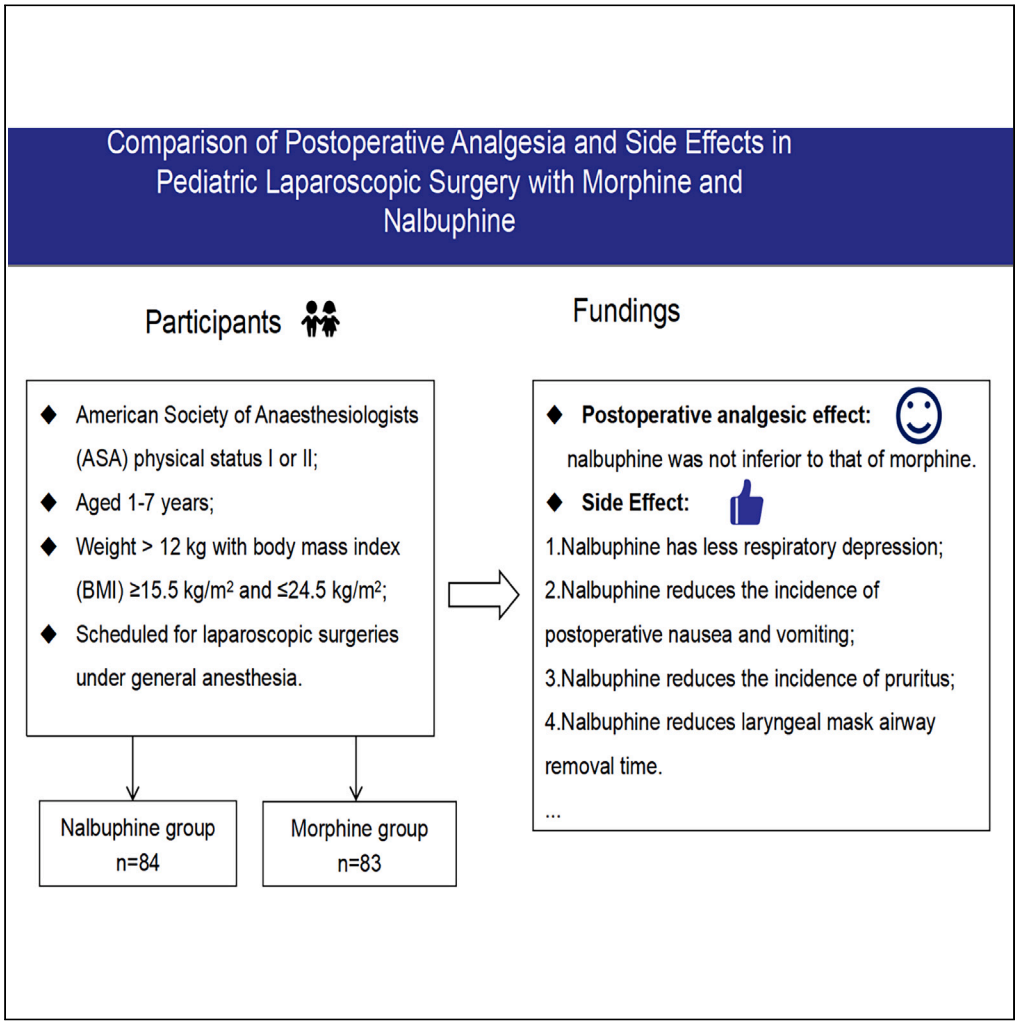

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Highlights

Nalbuphine provides an equipotent analgesic effect to morphine in children

Nalbuphine exhibits a lower incidence of side effects than morphine

Nalbuphine provides a shorter laryngeal mask airway removal time than morphine

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Comparison of postoperative analgesia and side effects in pediatric laparoscopic surgery with morphine and nalbuphine

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SUMMARY

There is currently no consensus on the optimal perioperative pain management strategy involving specific opioids. This study aims to compare the postoperative analgesia, the associated side effects between nalbuphine and morphine in children undergoing laparoscopic surgery. One hundred ninety children were randomly assigned to nalbuphine (0.2 mg/kg) or morphine (0.2 mg/kg). Nalbuphine's analgesic effect was non-inferior to morphine, with similar total rescue analgesic consumption during PACU stay (0.03 $\pm$ 0.05mg vs. 0.04 $\pm$ 0.06 mg, p > 0.05). Nalbuphine group had a lower incidence of respiratory depression (RR $\leq$ 10/min) (4.8% vs. 38.6%, p < 0.001), PONV (2.4% vs. 18.1%, p = 0.002), and pruritus (0% vs. 16.9%, p < 0.001) than morphine. Additionally, nalbuphine showed a shorter laryngeal mask airway removal time (13.9 [12.7, 15.1]) compared with morphine (17.0 [15.1, 18.9], p = 0.011). Nalbuphine provides equipotent analgesia with significantly lower incidences of respiratory depression, PONV, and pruritus compared with morphine in pediatric laparoscopic surgery.

INTRODUCTION

Pediatric laparoscopic surgery is recognized for its advantages of minimal trauma, swift recovery, and reduced hospitalization time.[1] However, these benefits come with heightened requirements for anesthesia drugs, particularly opioids. The choice of different opioids used for perioperative pain control would play the essential role for the fast-track process.

Reports showed that opioid usage for the care of postoperative pain in children has not been addressed appropriately,[2,3] and those drugs remain confusing among clinicians due to their unequal analgesic efficacy and associated side effects.[4,5] With the diverse receptor-activation mechanisms, individual opioid may offer different levels of analgesia, so as the degrees of side effects. Morphine, a mu-receptor agonist, is the standard opioid analgesic for pain controls, and if used appropriately, about 80% of patients will achieve adequate pain relief.[6] However, the side effects associated with morphine's application cannot be neglected, especially in children. Nalbuphine, an opioid agonist-antagonist, also provides effective analgesia with minor adverse effects.[7] Therefore, the decision to choose which opioid for postoperative pain control might bring forth significantly different outcomes.[7] Comparative studies have shown that nalbuphine and morphine have provided the equal analgesia during variety of surgical procedures, and patients who received nalbuphine in perioperative periods had significantly lower incidence of severe side effects, such as respiratory depression and nausea and vomiting.[7,8]

However, no similar studies were conducted to look into the details of nalbuphine and morphine in children undergoing laparoscopic surgeries. This study aims to compare the postoperative analgesia, the associated side effects between nalbuphine and morphine in children undergoing laparoscopic surgery.

RESULTS

Initially, 220 children were screened for eligibility and 30 children were excluded due to meeting the exclusion criteria. Then, a total of 190 children were randomly assigned into nalbuphine (n = 95) and morphine group (n = 95). Twenty-three children were excluded from the final

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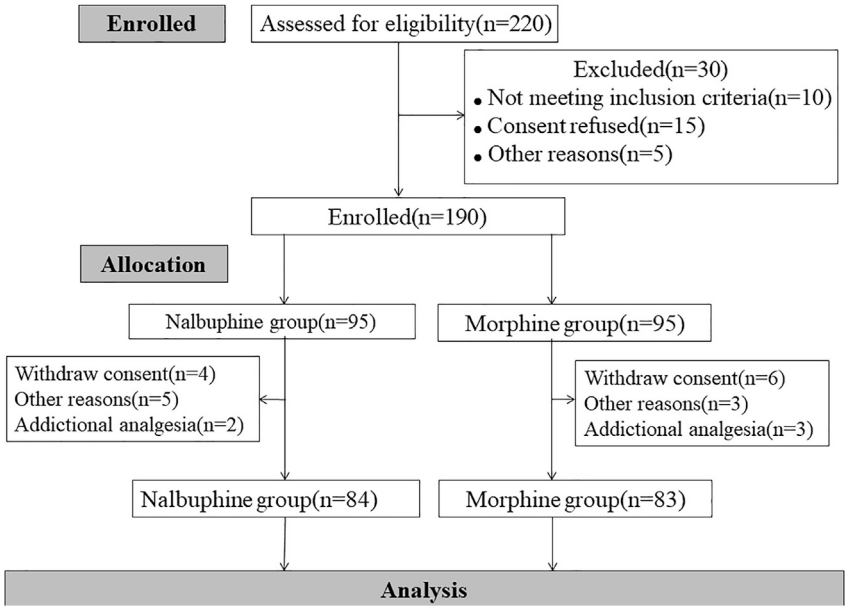

Figure 1. Patient disposition

analysis for incomplete data collection (11 in nalbuphine group and 12 in morphine group) (Figure 1) and that left 167 children who finished the study. All children underwent laparoscopic inguinal hernia repair. Demographic data and clinical profiles of patients were summarized in Table 1. There were no significant differences in terms of gender, age, weight, and BMI for children between nalbuphine and morphine group.

FLACC pain scores and Ramsay sedation scores

The analgesic effect of nalbuphine is not inferior to that of morphine (Figure 2; Table 2). Stratified analysis showed that the analgesic effect of nalbuphine was not inferior to that of morphine from 2 h to 24 h in the infant cohort and that the analgesic effect of nalbuphine was not inferior to that of morphine at all follow-up times except 15 min in the preschool cohort (Table 3). Meanwhile, there was no significant difference between two groups regarding the total numbers of patients whose FLACC was $\geq$4 in PACU (Table 4). Five children in the morphine group and six in the nalbuphine group required more than two doses of rescue pain drugs and other supplemental analgesics. There was no difference found between two groups concerning Ramsay sedation scores over the PACU course (Figure 2).

Hemodynamics, respiratory rate, and SpO_2

Figure S3 demonstrated the perioperative hemodynamic changes during the study, and there were no differences in HR and mean BP between two groups. No hypotension or bradycardia was recorded in both groups (Table S2). Intraoperative respiratory metrics were similar between two groups because all patients were ventilated mechanically. Overall, there was no significant difference in postoperative RR during 1-h PACU stay between two groups (Figure S3). Although, the average SpO_2 level was trending relatively lower in morphine group than in nalbuphine group within 30 min after PACU admission (Figure S3), no statistical difference was detected. In nalbuphine group, significantly fewer patients developed respiratory depression while compared with morphine group at the time of PACU admission (4 vs. 15) and at 15 min after PACU admission (0 vs. 13) (Table 5). Also, at 15 min after PACU admission, six children, all from the morphine group, displayed an RR $\leq$ 8 breath/min accompanied with hypoxemia (SpO_2 <90 lasted for $\geq$5 s). Five of those patients received supplemental oxygen via face mask and one required assisted positive pressure ventilation with 100% oxygen to reverse the hypoxemia (Table S2). None of the children in nalbuphine group developed RR $\leq$ 8 and hypoxemia.

Other clinical profiles and side effects

There were no differences in surgical times, surgical bleedings, and time of hospitalization. Both groups had similar anesthesia profiles regarding total IV fluids, the intraoperative dosages of fentanyl and propofol, waking time from anesthesia, and PACU discharge times (Table 6). Patients in nalbuphine group had reached time to remove the laryngeal mask airway criteria significantly faster than those in morphine group (13.9 vs. 17.0 min) ($p = 0.011$). Also, lower incidence of PONV and pruritus was observed in nalbuphine group ($p < 0.01$) (Table S2) than that in morphine group.

Table 1. Demographic data of patients

	Overall (n = 167)	Morphine (n = 83)	Nalbuphine (n = 84)	p value
Sex (male/female)	129/38	64/19	65/19	0.887
Age (years)	3 (2.8, 3.2)	3 (2.7, 3.3)	3 (2.7, 3.3)	0.911
Weight (kg)	15.6 (15.0, 16.2)	15.6 (14.7, 16.5)	15.5 (14.7, 16.3)	0.877
Height (cm)	94.8 (94.5, 95.5)	97.6 (93.4, 101.5)	96.3 (93.2, 99.4)	0.859
BMI (kg/m^2)	16.7 (16.3, 17.1)	16.7 (16.3, 17.1)	16.7 (16.1, 17.3)	0.496
ASA				0.190
I	87 (52.1)	48 (57.1)	39 (47.0)	
II	80 (47.9)	36 (42.9)	44 (53.0)	
Surgery duration (min)	23.0 (20.9, 25.1)	22.7 (20.2, 25.2)	23.4 (20.0, 26.8)	0.758
Anesthesia time (min)	33.3 (30.8, 35.8)	33.8 (30.7, 36.9)	32.8 (28.9, 36.7)	0.242
Time of hospital stay (days)	3.19 (3.11, 3.27)	3.24 (3.12, 3.36)	3.19 (3.08, 3.30)	0.579

ASA, American Society of Anesthesiologists; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); values are number (percentage, %) for number of ASA and other values are mean (95% confidence interval [CI]).

DISCUSSION

This study aims to compare the postoperative analgesia, the associated side effects between nalbuphine and morphine in children undergoing laparoscopic surgery. The results showed that both opioids had compatible postoperative analgesic efficacy, whereas nalbuphine resulted in fewer side effects, such as hypoxemia, PONV, and pruritus in PACU after laparoscopic surgeries.

Laparoscopic surgery is getting popular these days for its advantages of no large and wide-open wounds or incisions, reduced blood loss, pain, and discomfort, and it causes fewer untoward consequences from surgical trauma and anesthesia.[9] If pain and other side effects are controlled appropriately, early discharge to surgical ward or home can be expected. Obviously, this fast-track process is greatly affected by the choice of opioid analgesics because of the unequal potency for pain control, the duration, and the side effects carried by those drugs.

Opioids remain the most commonly used perioperative analgesics, and morphine is the standard drug in this category for pain control.[10] Morphine is a pure μ-receptor agonist, and it induces effective pain relief in surgical patients, but often with concerning undesired effects, such as respiratory depression, pruritus, and PONV etc.[11] Nalbuphine, a semi-synthesized partial μ-receptor antagonist and kappa receptor agonist opioid, is considered having equianalgesic efficacy of morphine but with less side effects associated with morphine.[12] A few studies in adult patients have suggested that nalbuphine provides better hemodynamic stability and analgesia, postoperative pain relief with less incidence of PONV compared with morphine in variety of surgical procedures.[12–15] However, the comparative results of efficacy and safety between these two drugs are not always consistent among reports,[5,16] as one study showed nalbuphine was not as effective as morphine for intraoperative pain management.[13] In our study, we found that both groups had similar FLACC scores, and the total doses of rescue analgesics given postoperatively were 34 in nalbuphine group vs. 30 in morphine group. We concluded that nalbuphine and morphine had provided the equianalgesic potency for postoperative pain control in children who underwent laparoscopic surgeries. Krishnan et al. compared the analgesic effects of morphine and nalbuphine in children who underwent tonsillectomy and found that these two drugs provided equal analgesic efficacy, which was significantly better than the placebo group.[17] This argument is widely believed to be true because morphine is standardized for all other opioids to be compared regarding their potency of pain relief, whereas the analgesic efficacy of nalbuphine is approximately 0.8–0.9 times of morphine. So, in clinical practice, nalbuphine is considered equianalgesic to morphine when administered in equal doses.[18] Analgesia induced by opioids is often closely associated with sedation caused by those

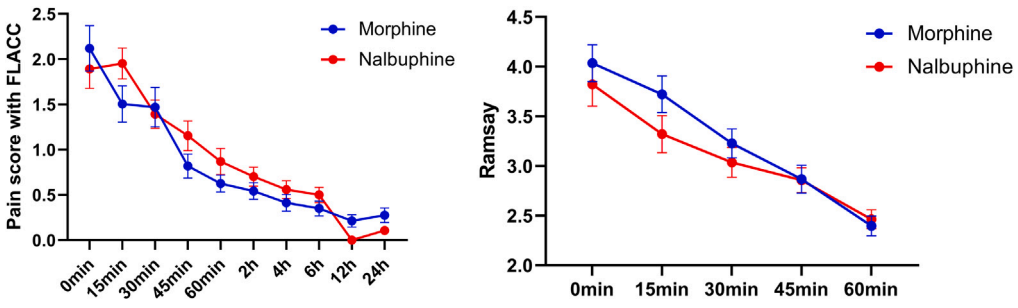

Figure 2. Postoperative FLACC score and Ramsay Sedation Scale (mean ± SD)

No differences were found for the assessment time points.

Table 2. Analgesic effect evaluation of different drugs

	FLACC				
Time	Morphine	Nalbuphine	Difference (95% CI)	p value	Significance criterion[a]
0 min	2.1 ± 2.3	1.9 ± 2.0	−0.2 (−0.9, 0.4)	0.001*	0.008
15 min	1.5 ± 1.8	2.0 ± 1.6	0.5 (−0.1, 1.0)	0.020*	0.025
30 min	1.5 ± 2.0	1.4 ± 1.4	−0.1 (−0.6, 0.5)	<0.001*	0.006
45 min	0.8 ± 1.2	1.2 ± 1.5	0.3 (−0.1, 0.8)	0.001*	0.013
60 min	0.6 ± 0.9	0.9 ± 1.3	0.3 (−0.1, 0.6)	<0.001*	0.005
2 h	0.5 ± 0.8	0.7 ± 1.0	0.2 (−0.1, 0.5)	<0.001*	0.004
4 h	0.4 ± 0.8	0.6 ± 0.9	0.2 (−0.1, 0.4)	<0.001*	0.004
6 h	0.3 ± 0.7	0.5 ± 0.8	0.2 (−0.1, 0.4)	<0.001*	0.003
12 h	0.2 ± 0.6	0.0 ± 0.0	−0.2 (−0.3, −0.1)	<0.001*	0.003
24 h	0.3 ± 0.7	0.1 ± 0.4	−0.2 (−0.3, 0.0)	<0.001*	0.003

[a]Holm–Bonferroni method: significance criterion for smallest p value = 0.025/k, where k = 10 tests; next smallest p value criterion is 0.025/(k-1).

drugs at the same time. Comparatively, we did not find any difference in Ramsay sedation scores over the PACU course between two groups as reported by Fragen and Caldwell.[19] It has been reported that kappa-receptor agonists have potent analgesic activity in a wide variety of visceral pain models, and so, nalbuphine might be more suitable for pain management in laparoscopic surgeries that are operated in contact to visceral organs and tissues.[20] People might have concerns that increased dosing of nalbuphine could result

Table 3. Stratified analysis of drug analgesia effect

	FLACC				
Time	Morphine	Nalbuphine	Difference (95% CI)	p value	Significance criterion[a]
Infancy (1–3 years)					
0 min	2.1 ± 2.2	2.0 ± 2.0	0.0 (−0.8, 0.8)	0.010	0.005
15 min	1.6 ± 1.8	2.0 ± 1.7	0.4 (−0.3, 1.1)	0.045	0.013
30 min	1.4 ± 2.0	1.7 ± 1.5	0.3 (−0.4, 1.0)	0.019	0.008
45 min	0.8 ± 1.1	1.5 ± 1.7	0.8 (0.2, 1.3)	0.195	0.025
60 min	0.6 ± 0.9	1.1 ± 1.5	0.5 (−0.0, 1.0)	0.016	0.006
2 h	0.5 ± 0.7	0.8 ± 1.0	0.4 (0.0, 0.7)	0.001*	0.004
4 h	0.3 ± 0.6	0.7 ± 1.0	0.4 (0.1, 0.7)	<0.001*	0.004
6 h	0.3 ± 0.6	0.6 ± 0.9	0.3 (0.1, 0.6)	<0.001*	0.003
12 h	0.2 ± 0.6	0.0 ± 0.0	−0.2 (−0.4, 0.0)	<0.001*	0.003
24 h	0.3 ± 0.7	0.0 ± 0.2	−0.2 (−0.4, 0.0)	<0.001*	0.003
Preschool (4–7 years)					
0 min	2.2 ± 2.4	1.7 ± 1.9	−0.6 (−1.6, 0.5)	0.003*	0.013
15 min	1.4 ± 1.9	1.9 ± 1.4	0.4 (−0.4, 1.2)	0.082	0.025
30 min	1.5 ± 2.1	0.9 ± 1.2	−0.6 (−1.5, 0.3)	<0.001*	0.008
45 min	0.9 ± 1.3	0.7 ± 1.0	−0.3 (−0.9, 0.3)	<0.001*	0.006
60 min	0.6 ± 0.9	0. 6 ± 0.9	−0.1 (−0.5, 0.3)	<0.001*	0.004
2 h	0.6 ± 1.0	0.5 ± 1.0	−0.1 (−0.6, 0.4)	<0.001*	0.005
4 h	0.6 ± 1.1	0.4 ± 0.7	−0.2 (−0.7, 0.2)	<0.001*	0.004
6 h	0.5 ± 0.9	0.4 ± 0.6	−0.1 (−0.5, 0.3)	<0.001*	0.003
12 h	0.2 ± 0.5	0.0 ± 0.0	−0.2 (−0.4, 0.0)	<0.001*	0.003
24 h	0.3 ± 0.7	0.2 ± 0.6	−0.1 (−0.4, 0.2)	<0.001*	0.003

[a]Holm–Bonferroni method: significance criterion for smallest p value = 0.025/k, where k = 10 tests; next smallest p value criterion is 0.025/(k-1).

Table 4. Patients with FLACC ≥4 at each time point

	Overall (n = 167)	Morphine (n = 83)	Nalbuphine (n = 84)	p value
PACU	35 (21.0)	15 (18.1)	20 (23.8)	0.471
PACU + 15 min	29 (17.4)	13 (15.7)	16 (19.0)	0.709
PACU + 30 min	19 (11.4)	12 (14.5)	7 (8.3)	0.316
PACU + 45 min	5 (3.0)	2 (2.4)	3 (3.6)	0.989
PACU + 60 min	3 (1.8)	1 (1.2)	2 (2.4)	0.992
Postoperative 2 h	2 (1.1)	0 (0.0)	2 (2.3)	0.165
Postoperative 4 h	2 (1.1)	1 (1.2)	1 (1.2)	0.972
Postoperative 6 h	0 (0.0)	0 (0.0)	0 (0.0)	
Postoperative 12 h	0 (0.0)	0 (0.0)	0 (0.0)	
Postoperative 24 h	0 (0.0)	0 (0.0)	0 (0.0)	

PACU, post-anesthesia care unit. Value are numbers (percentages, %).

in a ceiling effect and thus less analgesia than expected.[12,21] Our results indicated that 0.2 mg/kg nalbuphine or morphine given during anesthesia induction were an appropriate loading dose to provide equal analgesia. Akshat et al.[13] found that with a loading dose of 0.1 mg/kg, nalbuphine provided less effective intraoperative analgesia than morphine in adult patients undergoing open gynecological surgery. We could not speculate the difference of conclusions because our study was to observe the postoperative analgesia in pediatric patients for laparoscopic procedures with a loading dose of 0.2 mg/kg.

Respiratory depression stands out as one of the most worrisome side effects induced by opioids.[11,12] Morphine, by activating opioid μ-receptors provides analgesia, but also accompanied with some side effects.[22] Nalbuphine can produce the same degree of respiratory depression as equianalgesic doses of morphine,[12] and however, it will not cause further respiratory depression beyond a therapeutic dosage.[23] One of the advantages for nalbuphine is that it is a partial μ-receptor antagonist and can be used to reverse respiratory depression caused by other opioids without loss of analgesia.[24] In our study, 32 patients in morphine group developed respiratory depression, and among them, six had RR ≤ 8 with subsequent hypoxemia, which required intervention. By contrast, only four patients in nalbuphine group had respiratory depression, and none of them had RR ≤ 8 and hypoxemia. Also, the overall SpO2 in morphine group was trending at low normal level in the first 30 min after PACU admission than in nalbuphine group. Similar results can be found in previous studies.[21]

Pruritus is another common side effect associated with morphine if given intravenously (infusion or patient-controlled analgesia) or via intrathecal routes (epidural and spinal).[25,26] It has been believed that opioid μ-receptors activation in the spinal nerve is involved, and peripherally, histamine release could be culpable for the development of pruritus. Nalbuphine, as a partial μ-receptors antagonist, could prevent the development of pruritus,[27] and also, it can be used effectively for the treatment of morphine-induced pruritus after cesarean delivery. In our study, 14 patients from morphine group, but none from nalbuphine group, developed postoperative pruritus, and our results would further support the previous study conclusions.

The development of opioids-induced PONV clearly has multifactorial mechanisms, in which the enhanced vestibular sensitivity by a direct stimulation of μ-receptors in the epithelium,[4] direct effects on chemoreceptor trigger zones, and delayed gastric emptying are suspected to be of major importance.[28] One report showed that morphine may cause more PONV (48%) than nalbuphine (36%),[29] and our study showed that the incidence of PONV in morphine group was 18.1% compared with only 2% in nalbuphine group, which indicated that nalbuphine has the advantage over the morphine with less occurrence of PONV.

Nalbuphine has similar onset and slightly longer duration compared with morphine.[30] But it seemed anesthesia recovery was not delayed in our study as both groups had similar PACU stay times. By contrast, our results showed that patients in nalbuphine group had met

Table 5. Patients with respiratory depression at each time point

	Overall (n = 167)	Morphine (n = 83)	Nalbuphine (n = 84)	p value
PACU	19 (11.4)	15 (18.1)	4 (4.8)	0.014
PACU + 15 min	13 (7.8)	13 (15.7)	0 (0.0)	<0.001
PACU + 30 min	2 (1.3)	2 (2.7)	0 (0.0)	0.221
PACU + 45 min	1 (0.7)	1 (1.4)	0 (0.0)	1
PACU + 60 min	1 (0.7)	1 (1.4)	0 (0.0)	1
Total	36	32	4	

Value is number (percentage, %). Respiratory depression was defined as RR was less than lower limit (1st percentile) for respiratory rate in 2-year-old is 18, 3-year-old is 17, and 4- to 5-year-old is 17.

Table 6. Time to remove the laryngeal mask airway, surgery duration, anesthesia time, hemorrhage, IV fluid, intraoperative doses of fentanyl and propofol, and pain control satisfaction

	Overall (n = 167)	Morphine (n = 83)	Nalbuphine (n = 84)	p value
Time to remove the laryngeal mask airway	15.4 (14.2, 16.6)	17.0 (15.1, 18.9)	13.9 (12.7, 15.1)	0.011
Hemorrhage (mL)	2.5 (2.2, 2.8)	2.5 (2.1, 2.9)	2.6 (2.2, 3.0)	0.876
IV fluid (mL)	106.2 (99.8, 112.6)	105.4 (95.4, 115.4)	107.0 (99.0, 115.0)	0.504
Intraoperative fentanyl (μg)	0.1 (0.06, 0.14)	0.1 (0.05, 0.15)	0.1 (0.03, 0.17)	0.965
Parent's satisfaction				0.330
1	81 (48.8)	45 (54.9)	36 (42.9)	
2	82 (49.4)	35 (42.7)	47 (56.0)	
3	3 (1.8)	2 (2.4)	1 (1.2)	
Propofol (mg)	49.8 (47.9, 51.7)	50.1 (47.1, 53.0)	49.5 (47.0, 52.0)	0.907

Pain control satisfaction: 1 point, highly satisfied; 2 points, satisfied; 3 points, dissatisfied; 4 points, not satisfied at all. Values are mean (95% CI) for time to remove the laryngeal mask airway, surgery duration, anesthesia time, hemorrhage, IV fluid, intraoperative fentanyl and propofol, or number (%) for pain control satisfaction.

airway-extubation criteria faster than those in morphine group. Our assumption was that nalbuphine has less negative impact on respiration, which may allow patients regain their normal regular breathing from anesthesia earlier than morphine does.

Limitations of the study

First, this study compared a single dose of morphine with a single dose of nalbuphine for laparoscopic surgery, which tends to be much less painful than many types of open surgery. Given the relative ceiling effect for nalbuphine's analgesic, it is unknown whether nalbuphine would perform equally well relative to morphine for more painful surgeries, e.g., open thoracotomies, open abdominal and pelvic surgeries, scoliosis surgery, and major hip surgery. Then, this study examined a specific age range. It is unknown whether results would be similar for older children and adolescents.

Conclusions

In children undergoing laparoscopic surgery, nalbuphine exhibited an equipotent analgesic effect to morphine, with significantly lower incidences of postoperative respiratory depression, pruritus, and PONV.

STAR★METHODS

Detailed methods are provided in the online version of this paper and include the following:

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SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.isci.2024.109287.

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AUTHOR CONTRIBUTIONS

Conceptualization, H.C.L., J.W.Z., and Z.W.; methodology, H.C.L. and J.W.; investigation, J.Z., F.W., M.Z., H.G., H.Y.M., and Y.H.C.; writing—original draft, J.C.; writing—review & editing, C.Y.W. and J.W.Z.; funding acquisition, H.C.L. and Y.H.C.; resources, H.C.L., J.Z., F.W., M.Z., and H.G.; supervision, H.C.L. and J.W.

DECLARATION OF INTERESTS

The authors declare that they have no conflict of interest.

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STAR★METHODS

KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Chemicals, peptides, and recombinant proteins		
Nalbuphine	Yichang Human well Pharmaceutical CO	81J06021
Morphine	Yichang Human well Pharmaceutical CO	191113-2,190419-1
Deposited data		
Raw and analyzed data	Hua-Cheng Liu	huachengliu@163.com
Software and algorithms		
SAS	SAS	https://www.sas.com/zh_cn/home.html
GraphPad Prism	GraphPad	https://www.graphpad.com/

RESOURCE AVAILABILITY

Lead contact

Further information and requests for resources and reagents should be directed to and will be fulfilled by the lead contact, Hua-Cheng Liu (huachengliu@163.com).

Materials availability

This study did not generate new unique reagents.

Data and code availability

- Data reported in this paper will be shared by the lead contact upon request listed in the key resources table.
- This paper does not report original code.
- Any additional information required to reanalyze the data reported in this paper is available from the lead contact upon request.
- Data Sharing Statement: Data can be directed to the corresponding author/s.

EXPERIMENTAL MODEL AND STUDY PARTICIPANT DETAILS

Study design

This prospective, randomized, double-blind, and non-inferiority multicenter clinical trial was approved by the University's Institutional Review Board (IRB: the Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University of China, Reference No. LCKY2018-66) and written informed consent was obtained from all subjects participating in the trial. The trial was registered prior to patient enrollment at www.chictr.org.cn on June 30, 2019 (ChiCTR1900024202, Principal investigator: Huacheng Liu, Date of registration: June 30, 2019) and conducted between July 2019 to July 2020 by three medical facilities by the Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University of China, Beijing Children's Hospital of Capital Medical University, China and Shanghai Children's Medical Center, China. The study has been reported in line with CONSORT Guidelines.

Inclusion criteria

Male and female Chinese children with American Society of Anaesthesiologists (ASA) physical status I or II, aged 1-7 years, weight > 12 kg with body mass index (BMI) $\geq$15.5 kg/m^2 and $\leq$24.5 kg/m^2, and scheduled for laparoscopic surgeries under general anesthesia were eligible in this clinical trial.

Exclusion criteria

Children who had expected surgical time longer than 2 hours; allergic to either nalbuphine or morphine, or their derivatives; recent use of those analgesics or any other sedatives, antiemetic and anti-pruritic; history of severe obstructive sleep apnea and cardiovascular diseases, and displaying acute upper respiratory tract infection symptoms such as cough or/and fever or wheezing etc. in the past two weeks.

METHOD DETAILS

Randomization and blindness

Eligible recruits were randomly assigned into either nalbuphine or morphine group in a 1:1 ratio by a computer-generated digit number program (SAS PLAN; SAS Institute Inc.) in each individual participating medical center (The ratio of patients per center is 1:1). The assignment number was sealed in an envelope and revealed just before the drug's administration. The medications were prepared prior to the start of procedure according to the group allocation. For drugs given during anesthesia induction, Nalbuphine (10mg) or morphine (10mg) (Yichang Human well Pharmaceutical CO) was diluted to 10 ml in a syringe with isotonic saline. For the rescue analgesics given postoperatively in PACU, nalbuphine (50 $\mu g \cdot kg^{-1}$) or morphine (50 $\mu g \cdot kg^{-1}$) was prepared in a 5ml syringe with isotonic saline. The syringes were labeled with an individual assignment numbers, which matched the ones in pre-sealed envelopes. The anesthesiologist who administered the drugs, the outcomes evaluator, the parents or guardian and the children were all blinded to the drug's assignment. The trial Principal Investigators is Huacheng Liu.

Clinical protocol

The CONSORT diagram is shown in Figure 1. A written informed consent was obtained from participant's parent or legal guardian. The patient's preoperative fasting status in compliance with ASA guidelines was confirmed. No premedication was used. Peripheral venous access was established prior to the surgery according to the study protocol. The noninvasive blood pressure (NIBP), heart rate (HR), and oxygen saturation (SpO_2) were continuously monitored. Anesthesia was induced with 3.0 mg/kg intravenous propofol, and then, with the injection of either 0.2 mg/kg nalbuphine or morphine. 0.2mg/kg of cisatracurium was given to facilitate the insertion of Laryngeal Mask Airway. Mechanical ventilation was initiated with a 1:1 mixture of air and oxygen at a total flow of 2L/min.

Anesthesia was maintained with sevoflurane and anesthesia was adjusted to keep minimal alveolar concentration (MAC) value at 1.3-1.5, and the HR and mean arterial BP within 80–120% of baseline. The end-expiratory carbon dioxide partial pressure ($P_{ET}CO_2$) was maintained at around 35∼45mmHg by regulating the respiratory rate and tidal volume. 0.5μg/kg of fentanyl was given intraoperatively as supplemental analgesic and it could be repeated if necessary. Sevoflurane was discontinued and the oxygen flow was increased to 3.0-8.0 L/min at the closure of peritoneum. At the same time, 0.05 mg/kg nalbuphine or morphine was administered as postoperative pain management. Local anesthetic infiltration (0.15% ropivacaine+0.8% lidocaine) around the surgical incision was performed by surgeon as analgesic supplement. 0.1mg/kg of ondansetron were routinely used as prophylactic measure of postoperative nausea and vomiting (PONV). At the end of the procedure, the paralytic effect from cisatracurium was reversed with 0.02 mg/kg neostigmine and 0.01 mg/kg atropine, and the laryngeal mask airway was removed once the extubation criteria were met (regular breathing, normal SpO2, tidal volume ≥6ml/kg and purposeful movement). Then, patient was sent to post-anesthetic care unit (PACU) and allowed for spontaneous wakeup. All children were observed for at least 1h in PACU and the postoperative pain was scored with FLACC (Table S1).[31] Patient was transferred to the surgical ward when meeting discharge criteria (9 over a modified Aldrete score).[32]

For children suffering from moderate or severe pain (FALCC ≥4 points) in PACU, intravenous rescue analgesia, either nalbuphine or morphine in accordance with the intraoperative group allocation, was administered. Those narcotics could be given repeatedly every 10-15 minutes for the maximum of three doses if FLACC score remained ≥4 points. The additional analgesics beyond study protocol, NSAIDS (acetaminophen, intravenous administration of 10 mg/kg) or other opioids, could be given at the discretion of the investigator (Figure S1).

Outcomes

The primary outcome was the postoperative pain score at 1 hour after surgery. The secondary outcomes were: postoperative pain scores at other time points (0, 15, 30, 45min after PACU admission, and postoperative 2h, 4h, 6h, 12h, 24h); the number of patients whose FLACC score were ≥4 points; the total doses of rescue pain medication administered in PACU and surgical ward; the scores on Ramsay sedation scale were collected at the same time when FLACC were assessed; Time to remove the laryngeal mask airway time (from the discontinuation of sevoflurane until the removal of laryngeal mask airway); waking-up time (from the discontinuation of anesthetics to the time of being fully conscious in PACU); recovery time (from arrival to PACU to discharge from PACU); vital signs (mean BP, HR, RR, oxygen saturation) in PACU; parent's satisfaction with analgesia over 24 h postoperatively and time of hospital stay. The incidence of pruritus and PONV were also recorded. Respiratory depression was defined as RR was less than lower limit (1st percentile) for respiratory rate in 2yo is 18, 3yo is 17, 4-5yo is 17.

Data collection

A case report form (CRF) was designed for the filing of the clinical data and study results, which were stored in a password protected computer to ensure the patients' confidentiality. During the study, the guideline of Good Clinical Practice (GCP) was strictly followed and an investigator was designated for the data collection, transfer and verification.

QUANTIFICATION AND STATISTICAL ANALYSIS

Based on data from a pilot study in 20 children, we expected a mean postoperative pain score at 1 hour after completion of surgery of 0.6 with a standard deviation of 0.8. Defining a non-inferiority margin of was 1. 90% power at a two-sided α of 0.05 to detect the difference between

two groups was provided by a sample size of 148 children (74 children per group). A minimum of 180 recruits at start of study (90 per group) was required to allow potential fallout of patients up to 20%.

Evaluate data consistency across centers using SSD (Standardized Site Difference). The SSD was between ± 1 for all centers at each follow-up time, and the inter-center variation was small enough to allow for combined analysis of the data across centers (Figure S1). Those with missing follow-up FLACC data were filled using the LOCF (Last Observation Carried Forward) method and then the data analysis set was generated. The mean (SD) of the normal distribution of continuous variables and the median (interquartile range [IQR]) of non-normal distribution of variables were calculated with one-sample Kolmogorov-Smirnov test. The means of two continuous normal distributed variables was analyzed with independent samples student's test. The Mann-Whitney U test and Kruskal-Wallis test were used to compare two groups of non-normally distributed variables respectively, while data were expressed in the number and percentage of categorical variables. The frequencies of categorical variables was compared with Pearson $\chi 2$ or Fisher's exact test whenever it was appropriate. ANOVA test was used to compare the perioperative data with continuous measurements.

Based on a non-inferiority design, we tested whether the analgesic effect of Nalbuphine was not inferior to that of morphine, the difference between FLACC scores of study subjects in group nalbuphine and group morphine did not exceed 1 (i.e., FLACCB-FLACCA < 1). Considering the non-independence of repeated measures data, a linear mixed-effects model was used to fit the change in FLACC score, and the interaction of time*drug group was estimated with time as the categorical variable, adjusting for gender, age, BMI, ASA classification, propofol dose, intraoperative fentanyl dose and remediation to explore the characteristics of the change in FLACC score in the study subjects and compare the analgesic effect of drugs. The study population was divided into early childhood and preschool age to investigate the effect of age on the analgesic effect of drugs. If ANOVA test was significant, the student's test with Bonferroni correction was used to calculate p value for pairwise comparisons. All tests were two-sided, and $p < 0.05$ was considered statistically significant. R version 4.0 was used for statistics analysis.

ADDITIONAL RESOURCES

Description: www.chictr.org.cn, identifier: ChiCTR1900024202. URL, https://www.chictr.org.cn/showproj.html?proj=40578.