Premedication of Nalbuphine Benefits Children Gastrointestinal Endoscopy Screening Under Sedation: A Randomized, Controlled, Double-Blinded Clinical Trial

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Research article

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Abstract

Background: Nalbuphine may be a useful opioid for postoperative use in children, but exact efficacy of premedication of nalbuphine in gastrointestinal endoscopy has not been determined yet. This study aims to compare the benefits between premedication with nalbuphine or fentanyl on children undergoing gastrointestinal endoscopy screening under sedation with propofol.

Methods: A total of 460 children with age 3-10 years old, undergoing elective gastrointestinal endoscopy screening with ASA I -II were randomly assigned to fentanyl group(premedication with 1ug/kg fentanyl) or nalbuphine group (premedication with 0.1mg/kg nalbuphine), and then they were all subsequently administrated propofol through target-controlled infusion (TCI) with an effect-site concentration of 3.5 ug/ml, before and during the procedure. We compared postoperative pain acquired according to FLACC, the total consumption of propofol, the cardiovascular parameters, satisfaction scores of patients' parents, adverse events (respiratory depression, bradycardic, pruritus, nausea and vomiting and so on) in patients, injection pain scores and recovery time.

Results: The postoperative pain at time of entering PACU and 10min later in nalbuphine group were lower than that in fentanyl group, but the injection pain of propofol and the recovery time is approximate. The consumption of propofol was higher in fentanyl group than nalbuphine group. The incidence of bucking/hiccupping was lower than in the nalbuphine group than that in the fentanyl group. The incidence of body movement was also lower in the nalbuphine group than the fentanyl group. The satisfaction scores by patients 'parents were higher in the nalbuphine group. The incidence of pruritus is lower in the nalbuphine group.

Conclusion: The analgesic effect of nalbuphine is superior to that of fentanyl in premedication for children endoscopy screening sedation.

Trial registration:

The study was registered with the Chinese Clinical Trial Registry (registration number: ChiCTR1900023082) on May 10, 2019.

Background

Propofol is often used as a sedative agent in children and adults gastrointestinal endoscopy screening, but its adverse effects including hypotension, bradycardia, and respiratory depression, injection pain has also been reported [1, 2]. In addition, pediatric patients undergo invasive examination the same as adult patients, but generally because of excessive concerns about the side effects of analgesics, lower doses of analgesics per body weight are prescribed compared with those for adult patients, which results in inadequate management of perioperative pain. And several surveys in recent years demonstrated that perioperative pain in children is still a relevant problem[3, 4].

Nalbuphine is an opioid analgesic agent widely used for control of mild-to-severe pain. And the analgesic potency were already reported in adults[5] and in children[6]. Its analgesic potency is equivalent to that of morphine on a milligram basis in adults. Nalbuphine hydrochloride is a synthetic narcotic agonist–antagonist analgesic of the phenanthrene series with a duration of analgesia of 2–6 h[5, 7]. As nalbuphine is a kappa-receptor agonist and μ-receptor antagonist, it can releive μ receptor -related adverse reactions respiratory depression and opioid -induced adverse events such as pruritus, nausea and vomiting in theory. Compared with morphine, nalbuphine could induce less respiratory depression at high doses because of its ceiling effect[8]. What's more, it had less effect on arterial pressure[9] and it could reduce the incidence of vomiting[10]and pruritus.[11, 12]

This study was performed to evaluate whether premedication with nalbuphine can bring much benefits for children gastrointestinal endoscopy screening under sedation with TCI of propofol.

Methods

The study adheres to the applicable CONSORT2010 guidelines. This prospective, randomized, double-blind, placebo-controlled, single-center clinical trial was done at The Ningbo City First Hospital (Ningbo, Zhejiang Province, China). The study was registered with the Chinese Clinical Trial Registry (ChiCTR1900023082). The trial was approved by Ethics Committee of Ningbo City First Hospital (2018-R16). The parents or legal guardians of each patient were supplied with comprehensive information by one of the investigators, regarding the study's risk, benefits, objectives, and procedures. The parents/legal guardians signed informed consent before the patient's inclusion in the study.

Study design

It's a prospective, randomized, double-blinded, and placebo-controlled clinical trial and the allocation ratio is 1:1 in the project.

Participants

We enrolled 460 children (age 3–10 years old) whose American Society of Anesthesiologists physical status was I or II and who were scheduled for elective gastrointestinal endoscopy (esophagogastroduodenoscopy followed by colonoscopy) in endoscopy center of The Ningbo City First Hospital during the period from May 10 to December 5, 2019. Exclusion criteria:(1) be allergic to nalbuphine, its components and opioid medicine;(2)preoperative using analgesic, sedatives, antiemetics or antipruritic in 24 h; (3) preoperative body temperature was higher than 38℃ or suffering from upper respiratory infection in 24 h;(4)suffered from bronchial asthma;(5) suffering from severe obstructive sleep apnea syndrome and arrhythmia;(6)had abnormal surgery; (7) intracranial hypertension;(8)suffering from mental disease or can't express their mind exactly.(9) BMI ≥ 27.5 kg/m2 or ≤ 13.0 kg/m2 or body weight□12 kg.

Interventions

Anesthesia induction: the subjects weren't administration any other sedatives or analgesics as premedication except fentanyl or nalbuphine. The baseline of vital signs (HR, RR) were acquired at the calm state of subjects entering into operating room. An intravenous cannula was placed in the peripheral vein of right hand for fluid infusion and medicine administration. Oxygen at a rate of 3L/min was delivered via Venturi mask when patients entered the endoscopy unit. Monitors included blood pressure (NIBP), electrocardiogram (ECG), peripheral oxygen saturation (SpO2), CO2 exhalation and respiratory rate (the Intelli Vue MP50; Philips, Shanghai, China). Vital signs were recorded every three minutes. Vital signs 10-minutes after patients lying down on the mobile operating table and administrated with clinical trial medicine were defined as the baselines.

Either nalbuphine(0.1 mg/kg) or fentanyl(1ug/kg) were administered through peripheral vein access which was established preoperatively with a intravenous cannula by the same supervising nurse. Five minutes later, Propofol infusion is initiated via a TCI system with pediatric model (CONCERT-CL, Guangxi Veryark Technology Co. Ltd, Nanning, Guangxi, China). Before the TCI system was started, the pediatric age, weight, height and the effect-site concentration were needed to be set in the TCI system machine. The effect-site concentration was set as 3.5ug/ml. During the procedure, various standard interventions were employed depending on the clinical situation including (i) administration of a 0.5 mg/kg bolus of propofol if the patient moved; (ii) use of a jaw-thrust to open the airway and/or mask ventilation if the patients develop respiratory depression as determined by the anesthesiologist; and (iii) administration of 0.01 mg/mg atropine if the HR was reduced to lower than 20% of baseline.

Once anesthesia induction was achieved, which was confirmed by the loss of eyelid reflex, the same senior endoscopist executed the gastrointestinal endoscopy, starting with esophagogastroduodenoscopy, then colonoscopy. When the colonoscope is at the ileocecal valve and prepared to be removed, the infusion of propofol by TCI system was terminated. Both the endoscopist and the anesthesiologist were blinded to the grouping information.

Outcomes

The primary indicator was pain scores of patients' awaking time point(t1) and 10 minutes later of recovery time(t2). The secondary indicators included the total consumption of propofol, injection pain scores of propofol, satisfaction scores of patients, recovery time and adverse events such as bucking/hiccupping, body movement. The satisfaction scores of patients 'parents were acquired by a survey[13] (1–5 points, representing Not Satisfied At All to Highly Satisfied) when the endoscopy was completed. Patients were fully oriented as determined by if patient could tell who is his or her parents. RR, HR at 6 different time-points were recorded. The six different time-points were, T1, the time-point after induction; T2, the time-point of insertion of gastroscope into oropharynx. T3, the time-point of the gastroscope removal from the mouth; T4, the time-point of colonoscope entry into the anus; and T5, the time point of the colonoscope reaching the ileocecal valve; T6, the recovery time-point. Besides, the vital signs (HR, RR) at the station of inhaling air in the PACU and the satisfactory degree of parents of children were also as secondary indicators. The general analgesic satisfaction of patients and discomfort was acquired through the questionnaire as Table 1.

Table 1
Questionnaire table

The satisfaction survey of patients' parents
1.On a scale of 1–5`how satisfied are you with this process of postoperative analgesic.
Circle your answer below
1 2 3 4 5
(Not satisfied at all) (Highly satisfied)
The discomfort survey of patients
1.Are you feel pruritus in the process of postoperative analgesic? Circle yes or no.
Yes No 2.Are you feel nausea and vomiting in the process of postoperative analgesic? Circle yes or no Yes No
3.Do you feel any other discomfort in the process of postoperative analgesic? Circle yes or no Yes No

Adverse effects such as delayed recovery, respiratory depression (That respiratory rate is lower than 10 per minute or SPO2 is lower than 92% and interval time is longer than 10 s is characteristic as respiratory depression), low blood pressure(20% and more lower than baseline of BP), bradycardic, nausea and vomiting, pruritus were needed to be noted in detail.

Samples size calculation

Because this study was a non-inferiority clinical trial, the sample size was calculated with PASS according to the reference literature in which the non-inferiority value is 1 and standard deviation is 3.189 samples for each group met the requirement of α = 0.05 and power = 0.9.But with the consideration of 20% dropping-out of samples, 230 samples were decided to be enrolled into each group. Totally, 460 samples were collected. With the drop-out or other reasons ,425 samples statistics were useful to make analysis at last.

Statistical analysis

The measurement data with normal distribution was analyzed with independent 2-sample t-test and the measurement data with abnormal distribution was analyzed with nonparametric test. The count data expressed as frequency or rate was compared using Chi-Square test or Fisher's exact test .The recording P value was 2-sided,with P 0.05 considered statistically significant. All the data was analyzed with SPSS23.

Random and double-blind

A total of 460 subjects were randomly distributed in the nalbuphine or fentanyl group according to the random number table generated by Dr Yong Li by using SPSS23. One stable nurse prepared the clinical trial medicine according to the random number table.10 mg nalbuphine hydrochloride injection and 0.1 mg fentanyl citrate injection were diluted into 10 ml with saline respectively. Nalbuphine hydrochloride injection and fentanyl citrate injection were similar in appearance, extrinsic feature, color and weight. In addition, the preparing process of clinical trial medicine is unknown to researcher and patient.

Results

A total of 460 patients were enrolled, with 35 following up loss or violating the protocol, 209 patients were recruited to analyze in fentanyl group and 216 in nalbuphine group finally, the patient flowchart is presented in Fig. 1. None of the patients involving had severe complications. All the measurement data was recorded as Mean ± SD. The characteristic of the patients is presented in Table 2. There is no difference in these parameters including the proportion of genders, the mean age, BMI, weight and height in two groups (all $P > 0.05$).

Table 2
the characteristic parameter

	Nalbuphine group	Fentanyl group
Age(year)	5.81 ± 1.86	5.55 ± 1.85
Body weight(kg)	23 ± 7.9	22.5 ± 7.3
Height(cm)	115.6 ± 14.5	113.8 ± 16.1
BMI(kg/㎡)	16.9 ± 2.6	16.8 ± 2.3
Gender(Girl/Boy)	106/110	100/109

The postoperative pain score in accordance with FLACC is lower in nalbuphine group compared with fentanyl group presented in Table 3. No statistically significant difference was noted in injection pain of propofol according to the scoring standard as Table 4, respiratory depression rate, nausea and vomiting rate, but the incidence of bucking/hiccupping, body movement and pruritus were lower in the nalbuphine group compared to fentanyl group, presented in Table 5 and Table 6. In addition, there were also no significant difference for vital signs including heart rate, respiratory rate presented in Fig. 2. The consumption of propofol is higher in fentanyl group than that in nalbuphine group and satisfaction scores is lower in fentanyl group compared with nalbuphine group.

Table 3
Postoperative pain score in accordance with FLACC

	Nalbuphine group	Fentanyl group
t1	1.8 ± 1.9*	2.3 ± 2.2
t2	1.7 ± 1.8*	2.1 ± 2.0
nalbuphine group vs fentanyl group *$P < 0.05$		

Table 4
Pain scale for evaluation of propofol-induced injection pain

Verbalisation scale	Response to propofol injection Pain score
0	No vocalisation
1	Purposeless moaning
2	Explicit protest
3	Screams, cries

Table 5
The incidence of respiratory depression, pruritus, nausea and vomiting of the patients.

Incidence	nalbuphine group	fentanyl group
respiratory depression	5.90%	3.20%
pruritus	1.0%	4.8%*
degree of nausea and vomiting	fentanyl group	nalbuphine group
0	190	198
1	16	17
2	3	1
nalbuphine group vs fentanyl group *$P < 0.05$		

Table 6
the incidence of bucking/hiccupping, body movement and injection pain of propofol

subgroups	bucking /hiccupping	Body movement	injection pain
fentanyl group	14.3%	18.7%	0.76 ± 0.83
nalbuphine group	6%***	7.9%***	0.74 ± 0.85
nalbuphine group vs fentanyl group ***P < 0.005			

Table 7
Other outcomes

subgroups	satisfaction scores	consumption of propofol(mg)
fentanyl group	4.7 ± 0.5	78.3 ± 13.6
nalbuphine group	4.9 ± 0.3*	71.2 ± 13.9*
nalbuphine group vs fentanyl group *P < 0.05		

Discussion

The ideal perioperative pain relief for pediatric patients should be easy to administer and should have sufficient analgesic effects as well as enough safety[14]. Nalbuphine may be a suitable analgesic agent for children because of its ceiling effect, the dose of maximum analgesic action is 0.3–0.4 mg kg-1. Higher doses neither increase the analgesic effects nor substantially increase the risk of respiratory failure. A neonate mistakenly administered a dose ten-fold higher than required has been described and resulted in only a prolonged sedation without respiratory failure[15]. What's more, nalbuphine can reverse the opioid - induced respiratory depression[16].

The study outcome showed that the postoperative analgesia effect of premedication with nalbuphine is superior to the fentanyl, but the analgesia effect to relief the injection pain of propofol is similar to fentanyl. It may be because of the time of nalbuphine approaching to peak effect of analgesia effect and it has sedative effect[5]. The reason can also explain that the total consumption of propofol and incidence of adverse effect such as bucking /hiccupping and body movement is less in nalbuphine group compared to fentanyl group. The advantage of relief incidence respiratory depression is not obvious. Maybe because the usage dose of two groups is not enough. In addition, the study outcome showed that nalbuphine has less incidence of pruritus than fentanyl, which could be explained by its characteristic.[5]

Nalbuphine was proved to be a relative efficient agent. It can decrease the tourniquet pain when added to intravenous regional anesthesia [17]. And it can significantly prolong the duration of sensory blockade and postoperative analgesia without any side effect or complication when introduced intrathecally along with hyperbaric bupivacaine[18]. Furthermore, a single dose of nalbuphine (0.1 mg/kg) at the end of an anesthetic may dramatically reduce the incidence of emergence agitation and offers a favorable benefit-to-risk ratio[19]which is benefit to postoperative recovery for children. It could be demonstrated in this trial.

Compared with previous research[20],in which nalbuphine was proved to be less effective intraoperative analgesia than morphine and show the similar postoperative analgesia and side effects, our study outcomes show difference. Therefore, whether nalbuphine can bring much more benefits especially in gastrointestinal endoscopy screening need multicenter and abundant samples study.

There were few limitations in our study. Firstly, we used only a single low dose of nalbuphine and thus did not compare the effects of different doses. Secondly, we only considered the postoperative pain scored according to FLACC, when calculating the sample size, which may not be adequately powered for injection pain of propofol. Future studies should consider it, while calculating the sample size. Thirdly, we don't record the sedation degree which possibly made influence on pain score.

Conclusion

In conclusion, premedication of nalbuphine has some benefits to children gastrointestinal endoscopy screening under sedation,especially analgesic effect.

Abbreviations

ASA
American Society of Anesthesiologists; BP:Blood pressure;
ECG
Electrocardiogram; HR:Heart rate; PACU:Post-anesthesia care unit;
RR
respiratory rate; SpO2:Pulse oximetry; TCI:target-controlled infusion
BMI
body mass index

Declarations

Ethics declarations

Ethics approval and consent to participate

The protocol was approved by the Ethics Committee of Ningbo City First Hospital (2019-R16). Address: The Ningbo City First Hospital, NO. 59, Liu Ting Street, Ningbo, Zhejiang, China. The study was registered with the Chinese Clinical Trial Registry (registration number: ChiCTR1900023082) on May 10, 2019. Website: http:// http://www.chictr.org.cn/edit.aspx?pid=38882&htm=4. Written informed consent was obtained from the parents or legal guardians of all participants in the trial.

Consent to publish

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors have no conflicts of interest.

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Authors' contributions

YL and CSH offered the clinical trial idea and make a protocol. YL and JGZ did the experiment and collected the experimental data. YL performed all statistical analyses. JGZ and YL were the major contributor in writing the manuscript and statistical analysis. All authors read and approved the final manuscript.

Acknowledge

Not Applicable

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Figures

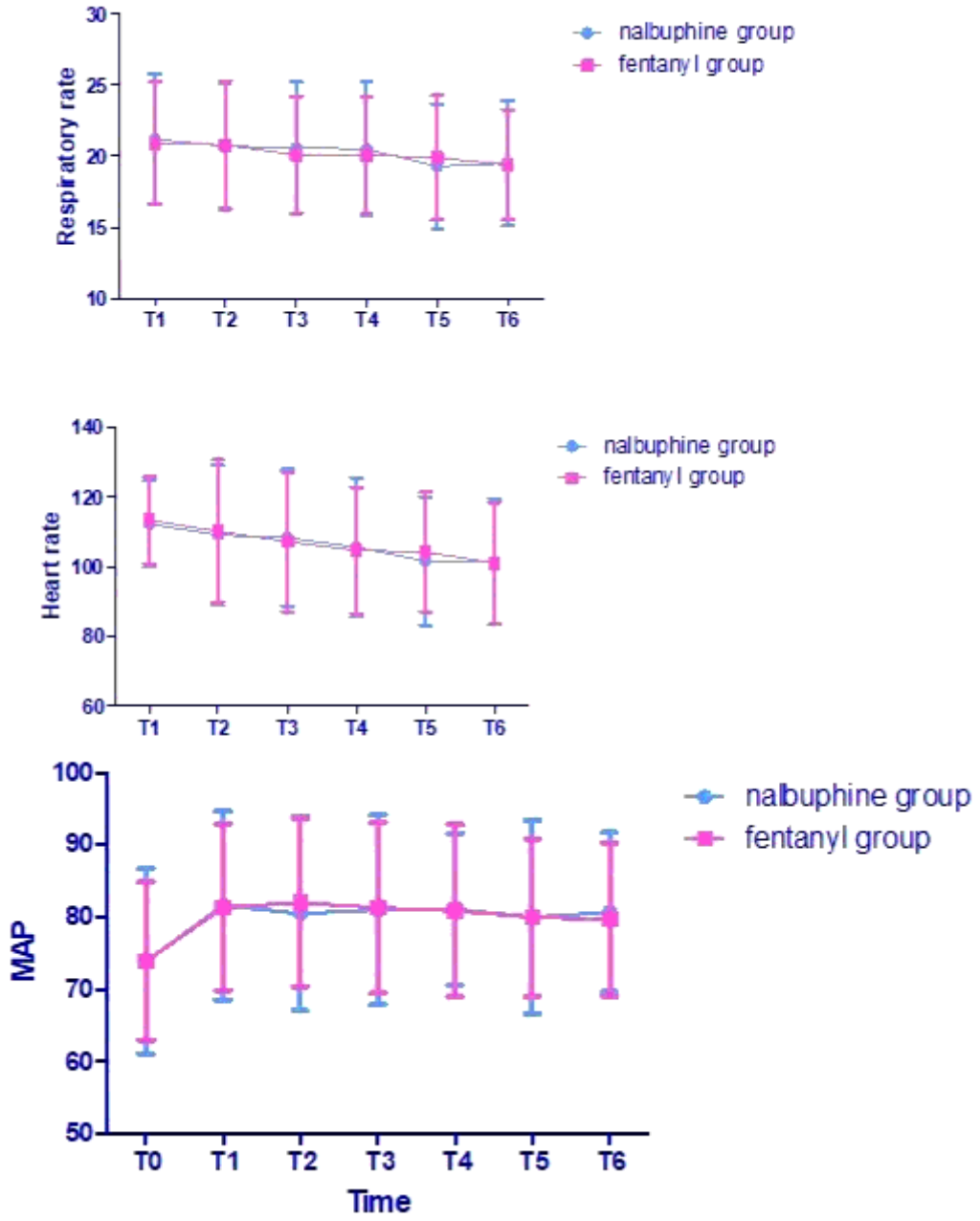
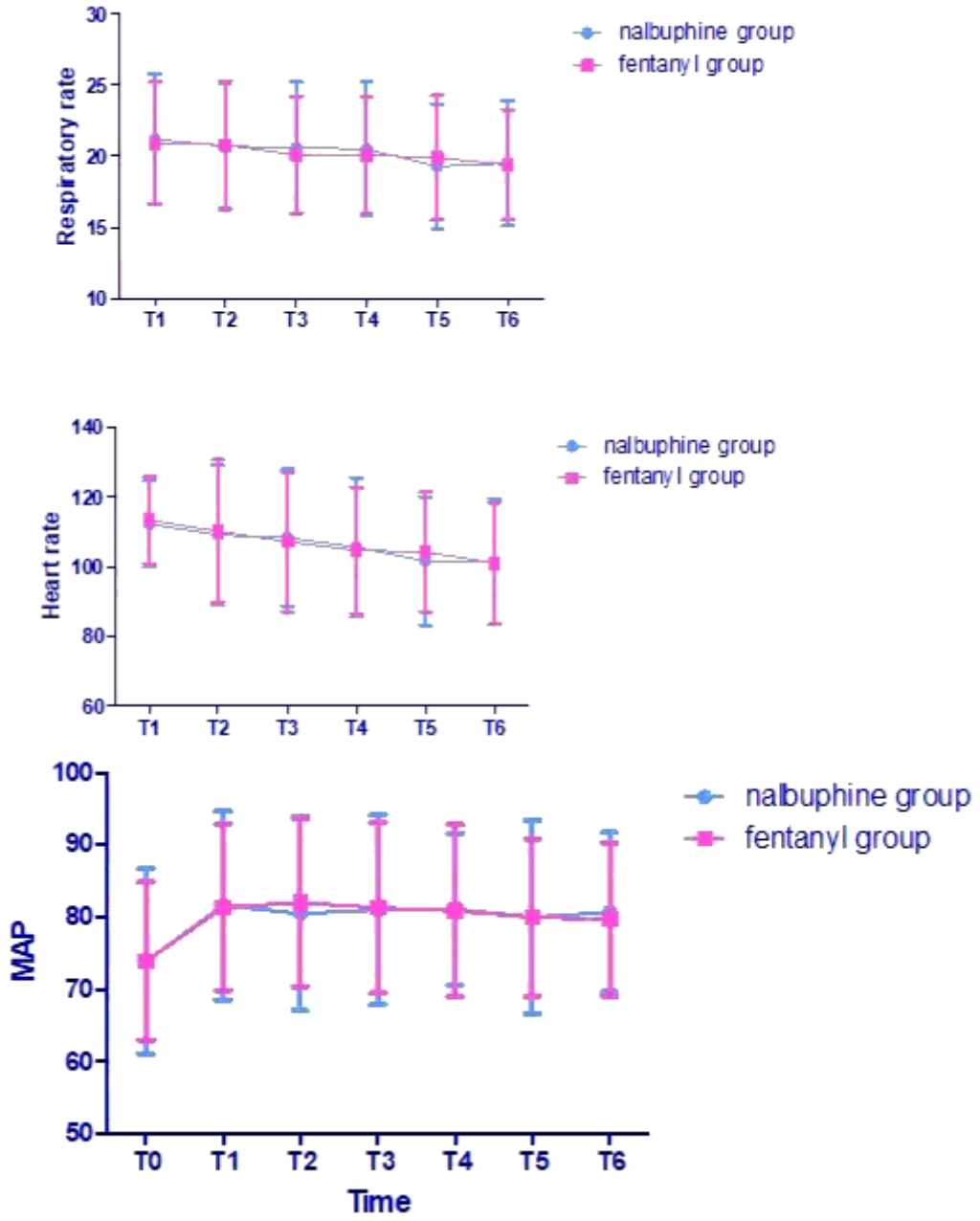


Figure 1

The flowchart is the process from recruitment to statistical analysis of the trial



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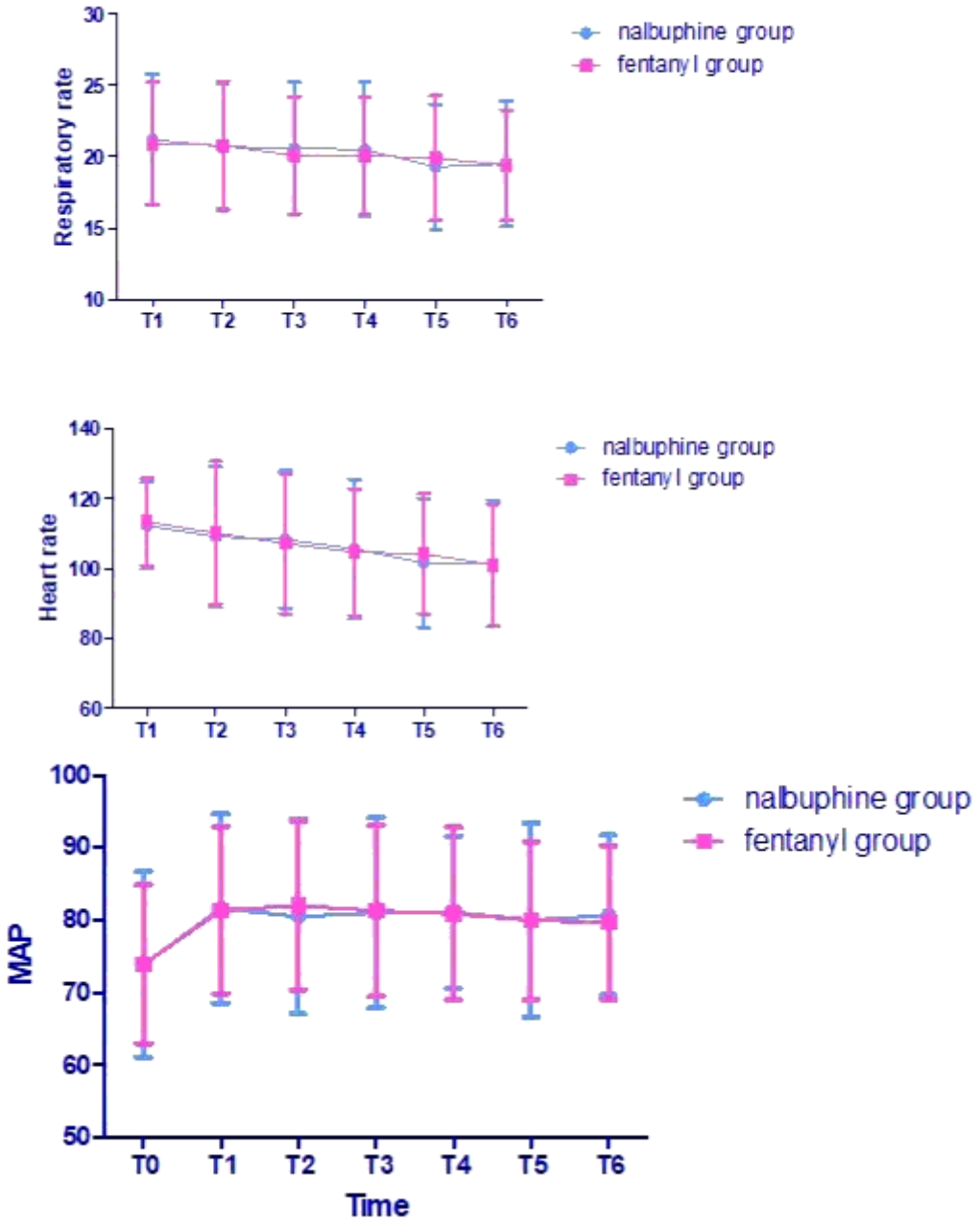

Figure 2

The important vital signs of children at six time points in this trial were presented in the figure. Compared with fentanyl, nalbuphine have no advantage of the influence of RR and HR in the trial.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- CONSORT2010Checklist2.doc
- supplementalfile.docx