World Journal of Pediatric Surgery

Impact of intravenous administration of nalbuphine at different time points for postoperative analgesia and sedation in adenotonsillectomized children: a prospective, randomized controlled trial

Hongmin Cao,[1] Chunying Bao,[1] Haiya Tu,[1] Jing Gao,[1] Jinjin Huang,[1] Qixing Chen [2]

To cite: Cao H, Bao C, Tu H, *et al*. Impact of intravenous administration of nalbuphine at different time points for postoperative analgesia and sedation in adenotonsillectomized children: a prospective, randomized controlled trial. *World J Pediatr Surg* 2023;**6**:e000662. doi:10.1136/wjps-2023-000662

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/wjps-2023-000662).

Received 10 July 2023
Accepted 8 October 2023

[1]Department of Anesthesiology, Zhejiang University School of Medicine, National Clinical Research Center for Child Health, Hangzhou, Zhejiang, China
[2]Department of Clinical Research Center, Zhejiang University School of Medicine, National Clinical Research Center for Child Health, Hangzhou, Zhejiang, China

Correspondence to
Dr Qixing Chen; qixingchen@zju.edu.cn

ABSTRACT

Objective To compare the efficacy of intravenous administration of nalbuphine at different time points for postoperative analgesia and sedation in adenotonsillectomized children.

Methods Patients with obstructive sleep apnea syndrome scheduled for adenotonsillectomy were randomly divided into group A (patients received intravenous nalbuphine 0.2 mg/kg before anesthesia induction), group B (patients received intravenous nalbuphine 0.2 mg/kg 10 min before the end of surgery), and group C (patients did not receive nalbuphine injection). The time points for measuring outcomes were before anesthesia induction (T0), extubation (T1), and 0, 15, 30, or 45 min in the postanesthesia care unit (PACU) (T2–T5, respectively).

Results There were 40 patients in group A, 41 patients in group B and 39 patients in group C. Patients in group B had significantly lower FLACC (Face, Legs, Activity, Cry, Consolability) pain scores at T2–T5 than those in group C (all $p<0.05$). Patients in group B had higher Ramsay Sedation Score at T2–T4 than those in group C (all $p<0.05$). The proportion of patients who received remedial analgesia in the PACU in group A (17.5%, $p=0.008$) and group B (9.8%, $p<0.001$) was significantly lower than that in group C (46.2%).

Conclusion Intravenous administration of nalbuphine 10 min before the end of adenotonsillectomy in children could decrease pain intensity and increase sedation levels during the recovery period with the reduction of remedial analgesia in the PACU.

Trial registration number ChiCTR2200060118.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Adenotonsillectomy under general anesthesia is the first-line treatment for obstructive sleep apnea syndrome.
⇒ Postadenotonsillectomy pain is the most common reason why patients contact their surgeon postoperatively.
⇒ Nalbuphine, a κ receptor agonist and μ receptor antagonist, can be used as a long-standing opioid for systemic use in children for mild to moderate pain.

WHAT THIS STUDY ADDS

⇒ Previous studies have only observed the use of nalbuphine at one time point and lacked a longitudinal time comparison of the use of nalbuphine for pain control in pediatric patients with a single disease.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Intravenous administration of nalbuphine 10 min before the end of surgery is effective in the control of postadenotonsillectomy pain.
⇒ The optimal time for administration of nalbuphine in adenotonsillectomized children who underwent general anesthesia needs to be further investigated in a large sample size.

INTRODUCTION

Obstructive sleep apnea syndrome (OSAS), a kind of respiratory sleep disorder in children (more common in boys than in girls) with a prevalence of 2%–4%,[1] is characterized by episodes of partial or complete upper airway obstruction during sleep, resulting in abnormal ventilation and atypical sleep patterns.[2] OSAS is associated with an increased incidence of cardiovascular and metabolic disease[3] and has been reported to be associated with neurocognitive, behavioral, and mood abnormalities and growth retardation in children without adequate diagnosis and/or treatment.[4 5] To date, adenotonsillectomy under general anesthesia has been the first-line treatment for OSAS.[6] However, adenotonsillectomy can cause several risks, ranging from minimal to life-threatening, mostly related to postoperative factors and events.[7] As the most common reason why patients contact their surgeon postoperatively, postadenotonsillectomy pain may lead to dehydration, insufficient oral intake,

nausea, respiratory problems, and bleeding, thus causing rehospitalization, parental anxiety, or repeated visits to the emergency department.[8 9]

Recent advances have been made with the use of various anesthetic drugs to reduce postoperative pain effects.[10] Several studies have reported postadenotonsillectomy pain management in children, which includes application of xylocaine[9] and dexamethasone.[11] To date, nalbuphine, which demonstrated a similar efficacy to morphine, has gained increasing interest as an agent for procedural sedation and analgesia. Nalbuphine, as a type of κ receptor agonist and μ receptor antagonist, can be used as a long-standing opioid for systemic use in children for mild to moderate pain.[12] Leister *et al*[13] found nalbuphine to have a sufficient analgesic effect for pain therapy with decreased emergence delirium/agitation in children undergoing general anesthesia for ophthalmic surgery. Moreover, more studies reported postoperative pain control in children by intravenous administration of nalbuphine before the induction of anesthesia,[14] during the anesthesia induction period,[15] before the end of the surgery,[16] and after arrival at the recovery room.[17] However, these studies only observed the use of nalbuphine at one time point and lacked a longitudinal time comparison of the use of nalbuphine for pain control in pediatric patients with a single disease.

Therefore, we designed this prospective, randomized controlled study to compare the efficacy of intravenous administration of nalbuphine at different time points for analgesia and sedation in adenotonsillectomized children during the recovery period from general anesthesia and to explore a more appropriate time point for nalbuphine treatment.

MATERIALS AND METHODS

Subjects and data collection

Children with OSAS aged 4–10 years who were scheduled for adenotonsillectomy under general anesthesia at the Children's Hospital of Zhejiang University School of Medicine were recruited between May 2022 and January 2023 in the study. Eligible participants met the following criteria: a low American Society of Anesthesiologists physical status I/II[18] and undergoing normal weight and physical examinations. Children were excluded if they (1) had any drug allergy to either trial medication or preoperative medication; (2) received analgesics, sedatives, antiemetics, or antipruritics 24 hours before adenotonsillectomy; (3) had immunological, neurological, hematological, or vascular disorders; (4) had a temperature >38°C or had signs and symptoms of an acute upper respiratory tract infection 24 hours before adenotonsillectomy; (5) had abnormal liver and renal functions; and (6) showed any contraindications to any drug used. Ultimately, 120 patients were included. Clinical data, including gender, age (in months), height (in centimeters), weight (in kilograms), and body mass index (BMI) (in kg/m^2), were obtained from hospital records.

The patients were divided into three groups by random assignment:

- Group A included children who were intravenously injected with 0.2 mg/kg nalbuphine (H20130127; Humanwell Pharmaceutical, Yichang, China) diluted in 5 mL of normal saline before anesthesia induction.
- Group B included children who were intravenously injected with 0.2 mg/kg nalbuphine diluted in 5 mL of normal saline 10 min before the end of adenotonsillectomy.
- Group C included children who did not receive nalbuphine injection.

Anesthetic management

All patients fasted for an appropriate period (8 hours for food and 2 hours for water). After monitoring, all children received preoxygenation and intravenous injections of anesthetic drugs for induction with standard anesthetics, including 0.1 mg/kg dose of midazolam, 2–3 mg/kg dose of propofol, 4 μg/kg dose of fentanyl, 0.6 mg/kg dose of rocuronium, 0.01 mg/kg dose of atropine, and 0.1 mg/kg dose of dexamethasone. Approximately 3–5 min later, tracheal intubation was performed to provide mechanical ventilation. Anesthesia was maintained with infusion of propofol at 50–100 μg/kg/min and remifentanil at 0.3–0.5 μg/kg/min. The patients were not intraoperatively given local anesthesia, rocuronium, or any other sedative/anesthetic drug. The patients were brought directly to the postanesthesia care unit (PACU) after recovery with spontaneous breathing (tidal volume: 6 mL/kg; respiratory rate: 18 breaths/min; oxygen saturation of inhaled air: >92%).

Outcomes measurement

The time points for measuring the outcomes were T0 (before anesthesia induction), T1 (extubation), T2 (0 min in the PACU), T3 (15 min in the PACU), T4 (30 min in the PACU), and T5 (45 min in the PACU). The outcomes included pain intensity, sedation level, operation time, dosage of propofol/remifentanil, time from the end of surgery to extubation, recovery time, heart rate, mean arterial pressure (MAP), postoperative side effects (including respiratory depression, edema, rash, or itching), and serum levels of tumor necrosis factor-α (TNF-α), interleukin 6 (IL-6), and cortisol.

The FLACC (Face, Legs, Activity, Cry, Consolability) pain score and the Ramsay Sedation Score[19] were recorded by an independent staff member to assess postoperative pain and sedation at T1–T5. The FLACC scale was scored between a range of 0 (no pain) and 10 (maximum pain). The Ramsay Sedation Score was determined using the following scale: 1: anxious, agitated, or restless; 2: cooperative, oriented, and tranquil; 3: responsive to commands; 4: asleep, but with a brisk response to a light glabellar tap or a loud auditory stimulus; 5: asleep, sluggish response to a glabellar tap or auditory stimulus; 6: asleep, no response.

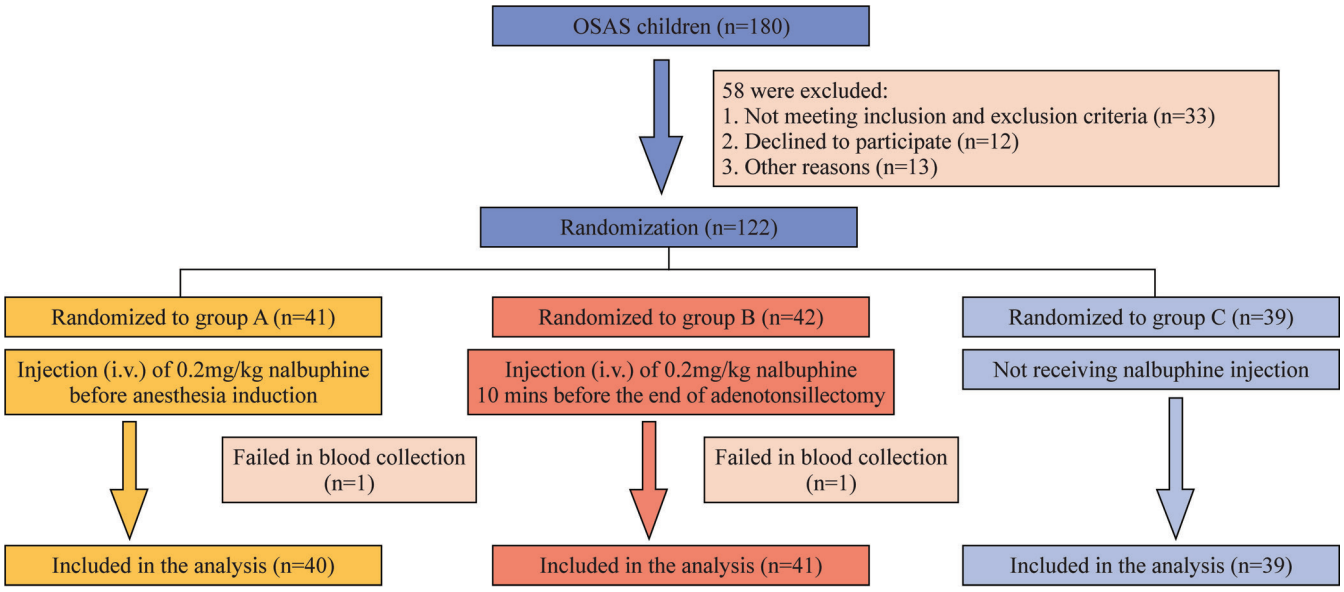

Figure 1 Flow chart of patient enrollment. i.v., intravenous. OSAS, obstructive sleep apnea syndrome.

The blood obtained at T0 and T4 was centrifuged at 3000 r/min for 5 min. The samples were immediately frozen at −80°C for detection of TNF-α, IL-6, and cortisol using commercially available ELISA kits (TNF-α and IL-6: Multi Sciences Biotech, Hangzhou, China; cortisol: R&D Systems, Minneapolis, Minnesota, USA) according to the manufacturer's instructions.

Statistical analysis

The statistical analyses were performed using GraphPad Prism V.8.0 (GraphPad Software, San Diego, California, USA), with a probability value less than 0.05 considered statistically significant. After performing the Shapiro-Wilk test to assess data normality, an analysis of variance was used to compare continuous data with a normal distribution, with the data presented as mean±SD across the groups. For variables that did not conform to a normal distribution, the Kruskal-Wallis test was applied, and these data were presented as median with IQR. Subsequently, Tukey's multiple comparisons test was conducted to examine differences between specific group pairs and to compute multiplicity adjusted p values.[20 21] Categorical data such as sex were compared by χ^2 test.

RESULTS

Sociodemographic characteristics of patients among three groups

Totally, 180 chidren with OSAS who underwent adenotonsillectomy were included. After excluding 58 patients who did not meet the inclusion and exclusion criteria, 122 patients were finally divided into three groups for later analyses, including 40 in group A, 41 in group B and 39 in group C (figure 1). There was no significant difference in demographic data among these three groups with regard to gender (p=0.375), age (p=0.202), height (p=0.111), weight (p=0.114), and BMI (p=0.581) (table 1).

Comparison of pain intensity and sedation level among three groups

The FLACC score for pain intensity and the Ramsay Sedation Score for sedation level were measured

Table 1 Demographics of patients undergoing adenotonsillectomy

Variables	Group A (n=40)	Group B (n=41)	Group C (n=39)	P value
Gender				0.375
Male	23	28	28	
Female	17	13	11	
Age (months)	69.33±17.15	73.93±17.48	67.31±15.97	0.202
Height (cm)	116.08±10.05	118.85±11.28	113.97±9.63	0.111
Weight (kg)	20.20±5.07	21.96±6.49	19.40±5.05	0.114
BMI (kg/m^2)	14.85±2.14	15.27±2.42	14.78±2.34	0.581

Statistical significance for continuous data with a normal distribution (data presented as mean±SD) was analyzed using ANOVA for the three groups, followed by Tukey's correction for multiple subgroup comparisons, while categorical data were compared using χ^2 test.
ANOVA, analysis of variance; BMI, body mass index.

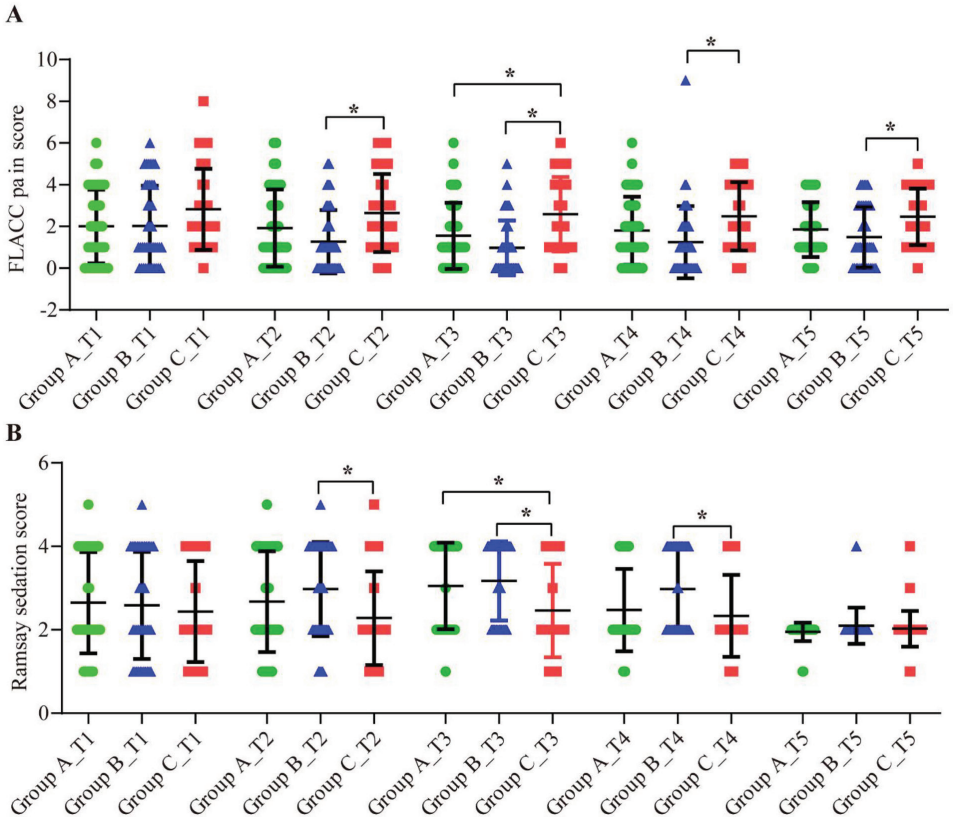

Figure 2 Comparison of pain intensity and sedation level for children undergoing adenotonsillectomy among the three groups: (A) Face, Legs, Activity, Cry, Consolability (FLACC) pain score; (B) Ramsay Sedation Score. Statistical significance for continuous data was analyzed using ANOVA for the three groups, followed by Tukey's correction for multiple subgroup comparisons. *P<0.05. T0, before anesthesia induction; T1, extubation; T2, 0 min in the PACU; T3, 15 min in the PACU; T4, 30 min in the PACU; T5, 45 min in the PACU. ANOVA, analysis of variance; PACU, postanesthesia care unit.

postoperatively. The patients in group B had significantly lower FLACC scores at T2–T5 compared with those in group C (all p<0.05). The patients in group A had significantly lower FLACC scores at T3 compared with those in group C (p<0.05). Regarding the sedation level, the patients in group B had significantly higher Ramsay Sedation Score at T2–T4 than those in group C (all p<0.05). The patients in group A had significantly higher Ramsay Sedation Score at T3 compared with those in group C (p<0.05). No case with excessive sedation (Ramsay Sedation Score ≥5) was observed. The details are shown in figure 2.

Comparison of other outcomes among three groups

For patient outcomes among the three groups, there was no significant difference in terms of operation time (p=0.963), dosage of propofol (p=0.460), dosage of remifentanil (p=0.523), time from the end of surgery to airway extubation (p=0.323), or recovery time (p=0.323) (table 2). Additionally, as shown in online supplemental

Table 2 Perioperative characteristics of patients undergoing adenotonsillectomy

	Group A (n=40)	Group B (n=41)	Group C (n=39)	P value
Operation time (min)	34.03±14.00	34.71±12.81	34.74±12.89	0.963
Dosage of propofol (mg)	91.38±48.08	92.93±49.84	80.77±42.85	0.460
Dosage of remifentanil (mg)	0.47±0.22	0.43±0.18	0.41±0.16	0.371
Time from the end of surgery to extubation (min)	9.63±5.00	8.78±3.34	10.23±4.14	0.304
Recovery time (min)	15.33±13.27	17.49±11.95	12.26±5.65	0.101
Proportion of remedial analgesia, n (%)	7 (17.5)	4 (9.8)	18 (46.2)*†	<0.001

Statistical significance for continuous data with a normal distribution (data presented as mean±SD) was evaluated using one-way ANOVA for the three groups, followed by Tukey's correction for multiple subgroup comparisons. Categorical data were compared using χ^2 test.
*Comparison with group A.
†Comparison with group B.
ANOVA, analysis of variance.

file, no significant difference was observed in heart rate or MAP among the three groups (all p>0.05). However, the proportions of patients in group A and group B who received remedial analgesia (ibuprofen) in the PACU were significantly lower, at 7 out of 40 (17.5%) and 4 out of 41 (9.8%), respectively, compared with that in group C, where 18 out of 39 (46.2%) patients received such analgesia (p=0.008 and p<0.001, respectively).

As shown in online supplemental file, the serum levels of proinflammatory cytokines (IL-6 and TNF-α) and cortisol at T0 and T4 showed no significant differences among the three groups (all p>0.05).

DISCUSSION

Nalbuphine administered intravenously can reduce the incidence of emergence agitation, defined as restlessness, disorientation, excitation, and/or inconsolable crying, during early recovery from general anesthesia in children undergoing adenotonsillectomy or ophthalmic surgery.[13 19 22] In the present study, we compared the use of nalbuphine at different time points after surgery in pediatric patients with adenotonsillectomy and found that intravenous administration of nalbuphine 10 min before the end of adenotonsillectomy in children was related to decreased pain intensity and increased sedation levels.

Adenotonsillectomy-related pain has been reported in 20%–50% of children who underwent surgery.[23] Based on our results, the patients in group B had significantly lower FLACC scores at T2–T5 compared with those in group C. These findings suggest that nalbuphine injections (0.2 mg/kg intravenously) 10 min before the end of surgery could reduce postadenotonsillectomy pain. Similarly, a previous multicenter study by He *et al*[15] found that an intravenous injection of 0.1 mg/kg nalbuphine during general anesthesia induction reduced FLACC scores and the incidence of emergence agitation in children undergoing adenotonsillectomy. In addition, when compared with fentanyl, after the administration of nalbuphine during the maintenance of anesthesia in adenotonsillectomized children, a significantly lower FLACC score at 1 hour and 2 hours in the PACU was reported, with a longer time to first required rescue and fewer doses of rescue pain drugs and other analgesics.[16] Consistent with this report, our study also found that the proportion of patients in group B (9.8%) and group A (17.5%) who received remedial analgesia in the PACU was significantly lower than that in group C (46.2%). The administration of nalbuphine is associated with sedation due to its κ agonist action.[12]

Local trauma following adenotonsillectomy can trigger the release of inflammatory cytokines, which have been associated with nerve stimulation and pharyngeal muscle spasm, contributing to postoperative pain—an issue often encountered in pediatric surgery.[8] Our decision to monitor serum indicators at T4 (30 min in the PACU) was informed by previous research findings. Studies have suggested that the most suitable timeframe for evaluating the effects of painful procedures involving nalbuphine administration is typically within the first 30 min following intravenous administration of 0.1–0.2 mg/kg nalbuphine.[24 25] Additionally, in children undergoing adenotonsillectomy, nalbuphine's effects become evident immediately after intravenous injection, with peak effects occurring around 30 min postadministration.[15] Massive and continuous IL-6 release induces an acute phase response, but more importantly also accounts for the upregulation of major anti-inflammatory mediators, such as cortisol.[26] Several studies reported that the analgesic and anti-inflammatory effects of nalbuphine on patients after surgery were accompanied by reduced levels of TNF-α and IL-6.[27 28] However, no significant difference was found in the serum levels of TNF-α and IL-6 among the three groups at T0 and T4, suggesting that nalbuphine did not affect TNF-α and IL-6 in adenotonsillectomized children during the recovery period. Henley *et al*[29] reported a notable disruption in adrenocorticotropin activity, characterized by extended adrenocorticotropin and cortisol secretory episodes, along with increased pulsatile hormone release. The continuous release of IL-6, especially at high levels, triggers an acute phase response and concurrently upregulates key anti-inflammatory mediators, such as cortisol.[26] Cortisol is widely recognized for its potent immunosuppressive and anti-inflammatory properties.[30] Glucocorticoids, including cortisol, are primarily mediated through the glucocorticoid receptor (GR), which can function as a monomer or dimer.[31] It is crucial to note that high cortisol concentrations exhibit anti-inflammatory actions, while the presence of proinflammatory cytokines, such as IL-1α, can impede GR function.[32] In our study, we observed no significant differences in levels of cortisol among the three groups. The difference in our findings regarding inflammatory cytokines and cortisol may be attributed to the relatively short surgical duration and the short-term observation period of our study.

In summary, intravenous administration of nalbuphine 10 min before the end of surgery is effective in reducing pain intensity, increasing sedation level, and reducing postoperative analgesic requirements in adenotonsillectomized children during the recovery period after general anesthesia. These findings warrant further validation in multicenter studies with large sample sizes. Moreover, it is also worth investigating the optimal time for administration of nalbuphine during perioperation in adenotonsillectomized children who underwent general anesthesia.

Contributors HC contributed to study conception and design, data acquisition, analysis, and drafting of the manuscript. CB contributed to data acquisition and analysis. HT, JG and JH contributed to data curation and critical revision. QC contributed to study conception and design, critical revision, and supervision,and acted as guarantor.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

Ethics approval This study involves human participants and was approved by the Ethics Committee of Children's Hospital of Zhejiang University School of Medicine (approval number: 2021-IRB-072). The study was registered with the Chinese Clinical Trial Registry (ChiCTR2200060118). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request.

ORCID iD

Qixing Chen http://orcid.org/0000-0002-8435-6447

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