Perioperative pain management based on enhanced recovery after surgery in children undergoing adenotonsillectomy: A prospective, randomized controlled trial

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Funding information
Major Scientific and Technological Innovation Project of Shandong Province, Grant/Award Number: 2020CXGC011302; National Natural Science Foundation of China, Grant/Award Number: 82071021

Abstract

Background: Pain management, as a key component of enhanced recovery after surgery (ERAS), can effectively relieve perioperative pain and anxiety. However, there are few studies on the application of pain management based on ERAS in pediatric surgery patients. We aimed to examine the effect of ERAS-based perioperative pain management in children with obstructive sleep apnea (OSA) undergoing adenotonsillectomy.

Methods: From March 2021 to July 2021, a randomized controlled single-blind study was conducted on children with OSA and scheduled to undergo adenotonsillectomy. The children were randomly assigned to either control group (n = 60) or ERAS group (n = 60). Traditional analgesia measures were provided to children in the control group, whereas ERAS-based optimized analgesia measures were provided to children in the ERAS group. The pain scores, anxiety scores and diet quality scores were compared between the two groups.

Results: The pain scores after surgery in the ERAS group were significantly lower than those in the control group at 6 h, 1 day, 3 days, and 5 days after surgery. Furthermore, the diet quality scores in the ERAS group were significantly higher than those in the control group at 6 h, 1 day, 3 days, and 5 days after surgery. The anxiety scores after surgery in the ERAS group were significantly lower than those in the control group.

Conclusions: Perioperative pain management based on ERAS can significantly alleviate postoperative pain, improve quality of life, and promote the accelerated rehabilitation of children with OSA undergoing adenotonsillectomy.

Level of evidence: 1.
1 | INTRODUCTION

Tonsils and adenoid hypertrophy are the main causes of OSA in children. Adenotonsillectomy can effectively relieve upper airway obstruction, and thereby reduce the adverse effects of OSA on a child’s growth and development. The children with OSA undergoing adenotonsillectomy suffer severe oropharyngeal pain, resulting in decreased oral intake, dehydration, dysphagia, sleep disturbance, behavioral changes, or readmission to the hospital. While single-dose analgesia and on-demand analgesia have both been used for controlling postoperative pain in children, neither method produces sustainable relief. Instead, the level of pain usually increases, resulting in increasing parental anxiety, an adverse effect on the nutritional status of the operated child, and a possible delay in discharge from the hospital.

Enhanced recovery after surgery (ERAS) was first proposed by the Danish scholar Kehlet. ERAS attempts to apply a series of perioperative optimization measures supported by evidence-based medicine, and thereby reduce patient’s complications, hospitalization time, the risk for re-admission and death, and medical expenses. Pain management, as a key component of ERAS, has been widely used in various professional fields, which can effectively relieve their tension and anxiety, improve their compliance with early intake and activities, and accelerate the recovery of bodily functions. Few studies focus on the application of pain management in pediatric surgery patients. In this study, we aimed to establish a pain management process consisting of a series of ERAS-based optimization measures and evaluate its effect on perioperative pain control for children with OSA undergoing adenotonsillectomy.

2 | MATERIALS AND METHODS

2.1 | Study design

From March 2021 to July 2021, 243 children with OSA who were scheduled to undergo adenotonsillectomy were randomly assigned to control group or ERAS group. Patients or their parents who were unwilling to accept the program were excluded. Inclusion criteria included a parental report of snoring, polysomnography (PSG) showing an obstructive apnea-hypopnea index (AHI) ≥ 2 events per hour of sleep, and an otolaryngology evaluation showing that the child was a candidate for adenotonsillectomy. The study physicians evaluated the need for adenotonsillectomy in children with OSA based on the degrees of obstruction and tonsillar/adenoid hypertrophy. An a priori sample size calculation was performed. Using the pain scores as primary outcomes, with an α of .05 and β of .2, we calculated a sample size of 17 patients in each group. Eventually, 120 children were enrolled in the study (Figure 1). All patients underwent adenoidal ablation and total bilateral tonsillectomy using coblation by surgeons with the same level of professional title.
### TABLE 1 Comparison of perioperative pain management measures and procedures used in the control and ERAS groups

| Pain management measures                  | Control group | ERAS group | Implementation schedule |
|-------------------------------------------|---------------|------------|-------------------------|
| Pain education                            | None          | 1. Inform the children's patients and family members about the harm produced by pain and necessity of analgesia. 2. Describe the chosen strategy for perioperative analgesia. |
| Anti-anxiety                              | None          | 1. The nurse in the ward gives lidocaine cream to infiltrate the venous puncture site prior to receiving the child. 2. Parents accompany the pediatric patient into the pre-anesthesia room. Under the guidance and supervision of the anesthesiologist and the assistance of parents, the child will inhale sevoflurane through a fruity face mask of their choosing. When the child falls asleep, an itinerant nurse carries the child into the operating room. |
| Fasting and water prohibition             | Fasting for 12 h before surgery, and no water consumption for 4 h before surgery. | 1. Fasting 6–8 h before surgery, and no water intake for 2 h before surgery. 2. Drinking 10% glucose is allowed within 2 h before anesthesia (5 ml/kg, total volume ≤300 ml). |
| Anesthesia method                         | Intravenous inhalational general anesthesia | Intravenous inhalational general anesthesia + local incision infiltration with 0.375% ropivacaine prior to incision. |
| Prevention of nausea and vomiting        | Intravenous dexamethasone 3–5 mg | Intravenous dexamethasone 3–5 mg |
| Postoperative analgesia                   | On-demand analgesia: Acetaminophen should be administered to patient when necessary according to the degree of pain (15 mg/kg) | On-time analgesia: Acetaminophen suspension drops (15 mg/kg) should be administered orally starting at 6 h after surgery, and subsequently once every 6 h. The dose and be decreased according to the level of pain after 3 consecutive days of administration. |

### TABLE 2 Clinical characteristics of patients in the control and ERAS groups

|                     | Control group (n = 60) | ERAS group (n = 60) | χ²/t/Z Value | p value |
|---------------------|------------------------|---------------------|--------------|---------|
| Age                 | 4.89 ± 1.36            | 4.94 ± 1.38         | −0.34        | .74     |
| Gender (Male)       | 42/60                  | 34/60               | 2.30         | .13     |
| Body mass index     | 15.51 ± 1.50           | 15.92 ± 1.91        | 1.31         | .19     |
| Previous operative history | 0/60                  | 0/60               | −            | −       |
| Apnea–hypopnea index | 3.27 (2.78, 5.35)    | 3.53 (3.06, 5.71)   | −0.50        | .61     |

### TABLE 3 Descriptive statistics for pain scores and diet scores over time after surgery

|                     | 6 h         | 1 day       | 3 days      | 5 days      | 7 days      |
|---------------------|-------------|-------------|-------------|-------------|-------------|
| Pain scores         |             |             |             |             |             |
| Control group       | 4.20 ± 0.66 | 4.07 ± 0.78 | 3.10 ± 0.60 | 2.37 ± 0.66 | 1.93 ± 0.73 |
| ERAS group          | 2.87 ± 0.68 | 2.57 ± 0.72 | 2.20 ± 0.71 | 1.93 ± 0.73 | 1.80 ± 0.48 |

### Note
Data are presented as mean ± standard deviation.
2.2 | Ethical issues

The study was conducted in accordance with the Declaration of Helsinki and its amendments and was registered at the Chinese Clinical Trial Registry (No. ChiCTR2100044771) on March 27, 2021. The final protocol was approved by the ethics committee of Yantai Yuhuangding Hospital of Qingdao University (Approval No. 2020-298). The parents of all patients provided their signed informed consent.

2.3 | Randomization and blinding

A clinical research coordinator randomly assigned each child to ERAS group or control group at admission using a table of random digits to generate the allocation sequence. Allocation cards were sealed in opaque and sequentially numbered envelopes. The attending doctors and the nurses in charge provided the designated interventions for each group of patients. Postoperative follow-up was provided by phone and scores after surgery were recorded by another investigator. This allowed the researchers to remain single-blinded in terms of intervention methods.

2.4 | Perioperative pain management measures based on the theory of ERAS

Patients in the ERAS group received optimized pain management measures and procedures throughout the perioperative period, including pain education, pain assessments, preoperative anti-anxiety measures, a shortened preoperative drinking prohibition time, and intraoperative and postoperative multi-code analgesia. The details were shown in Table 1.

2.5 | Data collection

Specialized doctors and nurses collected all relevant data for the two groups of patients in blinded manner during the patient’s hospitalization. Specialist nurses evaluated and monitored the treatments provided for their compliance with principles of pain management. The anxiety level was tested by modified Yale preoperative anxiety scale (mYPAS) at three-time points: after admission education (T1), before anesthetic induction (T2), and 24 h after operation (T3). The face rating scale (FRS) developed by Maunuksela et al. was used to monitor facial expressions in the range from happy, to sad, to crying (1–5, with 5 being the most intense pain) by the specialized doctors and nurses. A three-point visual analog scale was used to monitor dietary intake (0 points: liquid diet only; 1 point: soft food can be consumed; 2 points: limited normal diet; 3 points: normal diet). During hospitalization, specialist nurses taught parents how to assess pain, and diet scores after discharge were provided by the parents of each child by telephone.

2.6 | Statistical methods

All data were analyzed using IBM SPSS Statistics for Windows, 22.0 software (IBM Corp, Armonk, NY). Baseline descriptive statistics were compared using the Mann–Whitney U test or independent t-tests for continuous data and Chi-square analysis for categorical data. All analyses were based upon an intention-to-treat analysis approach. Continuous variables were revealed as normally distributed data using the Shapiro–Wilk test and repeated measures Analysis of Variance (ANOVA) statistical analysis were employed within subjects and between groups (groups X time). The main effect of intervention, the main effect of time as well as the interaction effect between intervention and time were investigated.

TABLE 4 Descriptive statistics for anxiety scores over time

| Anxiety scores | T1     | T2     | T3     |
|----------------|--------|--------|--------|
| Control group  | 32.47 ± 3.62 | 40.52 ± 3.58 | 35.65 ± 3.53 |
| ERAS group     | 29.97 ± 3.39 | 37.92 ± 3.40 | 32.77 ± 3.54 |

Note: Data are presented as mean ± standard deviation. T1: after admission education; T2: before anesthetic induction; T3: 24 h after operation.

FIGURE 2 Comparison of pain scores after adenotonsillectomy between the control group and ERAS group. **p < .01; ***p < .001

TABLE 5 Comparisons of pain scores, diet scores and anxiety scores within groups, between groups, or group–time interaction

|                    | Between groups | Within groups | Group-time interaction |
|--------------------|----------------|---------------|------------------------|
|                    | F    | p    | Effect size | F    | p    | Effect size | F    | p    | Effect size |
| Pain scores        | 143.77 | <.001 | 0.55    | 112.71 | <.001 | 0.80    | 17.61 | <.001 | 0.38    |
| Diet scores        | 43.18  | <.001 | 0.27    | 211.43 | <.001 | 0.88    | 32.95  | <.001 | 0.53    |
| Anxiety scores     | 17.87  | <.001 | 0.13    | 58886.71 | <.001 | 1.00    | 3.50   | .03   | 0.06    |
The repeated-measures data were checked for sphericity violation using Mauchly's test. Pairwise comparison and post-hoc analyses with LSD correction were conducted when significant group-time interaction arose. Effect sizes for significant interaction effects were reported as partial eta squared ($\eta^2$) with the following classification to define small ($\eta^2 = .01$), medium ($\eta^2 = .06$), and large ($\eta^2 = .14$) effect sizes.

3 | RESULTS

3.1 | Baseline characteristics

No significant differences were observed between both groups in terms of their baseline demographic and clinical details as shown in Table 2 ($p > .05$). Descriptive statistics for all the studied variables were presented in Tables 3 and 4. There were no missing data in the current study.

3.2 | Pain scores after adenotonsillectomy in the control group and ERAS group

Repeated measure ANOVA revealed a significant group-time interaction effect on pain scores ($F = 17.61; p < .001$) with large effect sizes ($\eta^2 = .38$) as shown in Table 5, which indicated that there was a significant effect of ERAS-based pain management on pain scores. Meanwhile, statistically significant differences were found between groups in pain scores ($F = 143.77; p < .001$) with large effect size ($\eta^2 = .55$). Furthermore, statistically significant differences were observed in pain scores within groups over time ($p < .001$) as displayed in Table 5. As shown in Figure 2, pain scores progressively decreased over time in both the control and ERAS groups. Post-hoc analysis revealed the pain scores after surgery in the ERAS group were significantly lower than those in the control group at 6 h, 1 day, 3 days, 5 days after surgery ($p < .05$, all) and there were no statistically significant differences between groups ($p = .24$) at 7 days after surgery as displayed in Table 6.

3.3 | Food intake after adenotonsillectomy in the control group and ERAS group

Same as the pain scores, there was a significant group-time interaction effect on diet scores ($F = 32.95; p < .001$) with large effect sizes ($\eta^2 = .53$) as shown in Table 5. Statistically significant differences were also found between groups ($F = 43.18; p < .001$) with large effect size ($\eta^2 = .27$). Post-operation analysis showed that the diet quality scores in the ERAS group were significantly higher than those in the control group at 6 h, 1 day, 3 days, 5 days after surgery ($p < .05$, all) and there were no statistically significant differences between groups ($p = .35$) at 7 days after surgery (Table 6).
Statistically significant differences were observed within groups over time \((p < .001)\). Gradual improvements in food intake were observed over time in both control and ERAS groups as shown in Figure 3.

### 3.4 | Anxiety scores after adenotonsillectomy in the control group and ERAS group

Statistically significant differences were observed in anxiety scores within groups over time \((p < .001)\) as displayed in Table 5 and Figure 4. There was a significant effect of group-time interaction effect on anxiety scores \((F = 3.5; p = .03)\). As shown in Table 7, the anxiety scores after surgery in the ERAS group were significantly lower than those in the control group at T1, T2, and T3 (all \(p < .001\)).

### 4 | DISCUSSION

In recent years, the concept of ERAS and its implementation described in several randomized, controlled, evidence-based medicine clinical studies have led to improvements in pain management that play an important role in accelerating the postoperative recovery of patients who have undergone various types of surgery.\(^{12,13}\) Implementation of the ERAS programs results in major improvements in clinical outcomes and cost, and it has resulted in shorter length of hospital stay by 30%–50% and similar reductions in complications, whereas readmissions and costs are reduced.\(^{14}\) However, there are few reports on the research of perioperative pain management based on ERAS concept in children perioperative pain management, especially in children with OSA undergoing adenotonsillectomy. Our previous retrospective study found that the ERAS program can reduce physical and psychological trauma during the perioperative period of adenotonsillectomy performed for children with OSA.\(^{9}\) We further conducted a randomized controlled clinical trial based on the previous study and our study data showed that implementation of the ERAS pain management process significantly reduced the postoperative pain and anxiety scores and improved the quality of postoperative food intake after adenotonsillectomy.

The ERAS concept emphasizes that a proper strategy for postoperative pain management should cover the entire perioperative period, including pain education upon hospital admission, preoperative anti-anxiety measures, choice of anesthesia methods, intraoperative preventive analgesia, and postoperative continuous analgesia.\(^{15}\) The key of ERAS implementation is the combination of these optimization measures supported by evidence-based medical evidence. These measures have not been adopted by many institutes in clinical practice for some reasons, such as increased clinical burden, lack of recognition, and so on. We believe that the additional burden will be less when clinical staff become familiar with these practices and integrate them into their established workflow. We hope that the application of the pain management process can achieve the best analgesic effect as far as possible.

Education on all these topics is supplemented by quality control of the implementation process to increase the compliance of medical staff, patients, and parents with optimization measures employed at various times in the process. In this study, when compared to passive

| TABLE 7 | Pairwise comparison of anxiety scores between control \((n = 60)\) and ERAS \((n = 60)\) groups over time |
|---------|---------------------------------------------------------------|
|         | T1 | 95% CI | T2 | 95% CI | T3 | 95% CI |
|         | MD | SE  | Sig | LB  | UB  | MD  | SE  | Sig | LB  | UB  | MD  | SE  | Sig | LB  | UB  |
| Pain scores | 2.50 | 0.64 | <.001 | 1.23 | 3.77 | 2.60 | 0.64 | <.001 | 1.34 | 3.86 | 2.88 | 0.65 | <.001 | 1.61 | 4.16 |

Note: T1: after admission education, T2: before anesthetic induction; T3: 24 h after operation.
on-demand analgesia, we required medical staff to participate in pain education training to improve their understanding of the harm that pain produces to children and their parents before surgery. Clinicians should educate caregivers on how to manage and reassess pain. This is because caregivers have the most frequent contact with the child, and are often best suited to frequently monitor the child after a tonsillectomy. Pre-emptive analgesia administered during the operation had an important effect on postoperative pain relief among children in the ERAS group.\textsuperscript{16} We also explained the series of analgesic measures to be taken during the perioperative period, and encouraged parents to focus on non-drug analgesia to help alleviate postoperative pain in their children. Patient noncompliance is often a factor that contributes to poorly controlled postoperative pain. Some parents undertreat their child's pain in terms of the dosage and frequency of analgesics. Therefore, we provided pain education to the parents upon their child's admission, after surgery, before discharge, during discharge, and at follow-up visits, respectively, to improve their compliance with pain management.

Ropivacaine is less toxic to the central nervous and cardiovascular systems and can be administered with a high degree of safety, which makes it especially suitable for intraoperative analgesia in children.\textsuperscript{17} A local analgesic (ropivacaine) was injected into the tonsillar fossa to serve as an auxiliary form of general anesthesia, which had a synergistic effect with intravenous inhalational general anesthesia during adenotonsillectomy. At the same time, local infiltration analgesia with ropivacaine could provide continuous analgesia for 4–6 h, which also played an important role in postoperative analgesia. During surgery, blockade of pain impulses by preoperative analgesic drugs, infiltration, or topical administration of local anesthetic agents can reduce the hyperexcitability and has a preemptive analgesic effect.\textsuperscript{18} Some studies found that ropivacaine in local tonsillectomy was a safe and effective method for posttonsillectomy pain.\textsuperscript{17,19} Due to the short operation time of adenotonsillectomy, anesthesiologists often use short-term anesthesia, which produces less residual anesthetic effects and allows for a shorter rehabilitation time and reductions in postoperative respiratory depression and other complications. However, this can lead to a lack of analgesia after the child awakens from surgery, and result in complications such as postoperative restlessness and tachycardia.\textsuperscript{20} At the same time, intravenous dexamethasone, as an auxiliary drug, can not only reduce inflammation and pain, but also prevent postoperative nausea and vomiting, as well as possible complications such as wound bleeding and aspiration.\textsuperscript{21} Postoperatively, the metabolism of locally infiltrated general anesthetic drugs and pain in the incision wound can result in especially painful swallowing that seriously affects eating. A randomized clinical trial showed that acetaminophen could significantly reduce the average pain intensity score after surgery in children.\textsuperscript{22} For that reason, we began using acetaminophen to alleviate pain in the ERAS group starting at 6 h after the operation, and we then had those patients continue taking analgesic drugs after discharge. As the pain was gradually relieved over five days, the frequency of analgesic administration was reduced until the patient's eating pattern returned to normal. We found that the implementation of ERAS pain management procedures significantly reduced postoperative pain and improved the quality of postoperative food intake compared to the control group.

We also found that the anxiety scores of patients in the ERAS group were significantly lower than those in the control group. Prolonged preoperative fasting and water deprivation result in hunger and thirst that significantly increase preoperative anxiety. Many children who are waiting for surgery experience anxiety prior to fasting, which can directly lead to longer hospital stays and exacerbation of postoperative pain.\textsuperscript{23,24} Increasing evidence suggests that oral sugar and adequate water intake before surgery can prevent intraoperative and early postoperative hypoglycemia, reduce the risk for insulin resistance, and improve the overall comfort of surgical patients. Fasting guidelines recommend consuming clear fluids and specific carbohydrate drinks until 2 h before anesthesia and it is not necessary to ban children from drinking water for >2 h before surgery.\textsuperscript{25,26} Magnetic resonance imaging showed that 7 ml/kg\textsuperscript{-1} of sugar water can be emptied from a child's stomach in <1 h.\textsuperscript{27} Studies have demonstrated that carbohydrate loading done within an acceptable timeframe prior to surgery does not increase the rate of complications.\textsuperscript{28} In this study, children in the ERAS group drank a 10% glucose solution (5 ml/kg) 2 h before surgery, which effectively relieved the discomfort and fear caused by starvation while waiting for surgery. Some parents are afraid to let their child drink water too close to the time of surgery because they believe it might affect the induction of anesthesia.\textsuperscript{29}

Therefore, we informed the children's parents about the hazards posed by a perioperative stress response in their children, and the various anti-anxiety measures that were employed to provide more humanistic care for their children. These methods improved the children's compliance with the subsequent pain management process.

4.1 | Strengths and limitations

The major strength of the present study is its high clinical relevance. The pain management process based on ERAS concept includes a series of analgesic optimization measures involving psychological and physiological intervention during the entire perioperative period, which can be easily applied in most children undergoing adenotonsillectomy in secondary and tertiary care. Further, our study was a randomized, controlled trial, reducing the risk of selection bias and allocation bias. However, this study was single-blinded for that the patients were informed about the details of the program. Therefore, there is a risk of attrition bias in this study. Another limitation of our study is that this is a single-center study and the number of patients enrolled is limited.

5 | CONCLUSION

Acute pain caused by adenotonsillectomy for the children with OSA can lead to a series of physical and mental complications, which should not be ignored. Establishment of a pain management program for children with OSA undergoing adenotonsillectomy can effectively
strengthens the compliance of medical staff and patients with optimized analgesic measures and alleviates postoperative pain continuously. Further high-quality multicentric clinical studies should be carried out to evaluate the effectiveness of the perioperative pain management program. At the same time, we should constantly add new pediatric analgesia measures based on evidence-based evidence into the program to evaluate the effectiveness of the program.

AUTHOR CONTRIBUTIONS
Yujuan Yang, Jiayu Cao, Yu Zhang, Xiumei Chen and Xicheng Song wrote the main manuscript text. Dawei Liu, Qiao Ying Lv, and Jiahai Ma contributed to data collection and analysis. All authors reviewed the manuscript.

ACKNOWLEDGMENT
The authors thank all the children and families who participated in this study, as well as staff members in the Departments of Otolaryngology, Head and Neck Surgery, and Anesthesiology.

FUNDING INFORMATION
The research was supported by the National Natural Science Foundation of China (82071021) and the Major Scientific and Technological Innovation Project of Shandong Province (2020CXGC011302).

CONFLICT OF INTEREST
The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT
All data generated or analyzed during this study are included in this published article.

ETHICS STATEMENT
The study protocol was approved by the Ethics Committee of Yantai Yuhuangding Hospital of Qingdao University (Approval No. 2020-298). Written informed consent was obtained from the patient’s parents. Parents of participants were informed that participation was optional and withdrawal was possible whenever they asked for. All methods were performed in accordance with the relevant guidelines and regulations.

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How to cite this article: Yang Y, Cao J, Chen X, et al. Perioperative pain management based on enhanced recovery after surgery in children undergoing adenotonsillectomy: A prospective, randomized controlled trial. Laryngoscope Investigative Otolaryngology. 2022;7(5):1634-1642. doi:10.1002/lio2.910