Clinical Trial/Experimental Study

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Dexamethasone and post-adenotonsillectomy pain in children

Double-blind, randomized controlled trial

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Abstract

Objective: To assess the impact of intraoperative intravenous dexamethasone on the reduction of postoperative morbidity in children undergoing adenotonsillectomy.

Methods: A double blind randomized controlled trial conducted among children undergoing adenotonsillectomy at a tertiary hospital in Korea from November 2018 to June 2019. Children were randomly assigned to receive dexamethasone (0.5 mg/kg, maximum dose 24 mg) or placebo intravenously after induction of anesthesia. The primary endpoint was the reduction of postoperative pain and postoperative nausea and vomiting (PONV); secondary endpoints were adverse effects like postoperative hemorrhage.

Results: The study included 105 children, and 67 were male. Their mean age was 6.2 ± 2.1 years. There was no significant difference between the groups in terms of demographic data or the operation time. The pain scores of the dexamethasone group were lower than those of the control group, but no significant difference was found (all $P > .05$). The average pain visual analog scale (VAS) during the study period (day 0–7) was 3.67 ± 1.59 and 4.40 ± 2.01 in the dexamethasone group and control group, respectively (P-value = .107). When we compared early pain VAS (day 0–2) and late pain VAS (day 5–7), the dexamethasone group showed significantly lower early mean VAS compared to the control group (4.55 ± 1.78 vs 5.40 ± 2.05, P-value = .046). The mean VAS for PONV was significantly lower in the dexamethasone group than in the control group (1.89 ± 2.22 vs 3.00 ± 2.37, P value = .044).

Conclusion: In children undergoing adenotonsillectomy, dexamethasone decreased the early postoperative pain and PONV without increasing postoperative hemorrhage.

Abbreviations: PONV = postoperative nausea and vomiting, VAS = visual analog scale.

Keywords: dexamethasone, postoperative hemorrhage, postoperative nausea and vomiting, postoperative pain, tonsillectomy

1. Introduction

Adenotonsillectomy is routinely performed for children with sleep-disordered breathing or recurrent infectious tonsillitis.[1] Currently, it is 1 of the most common surgical procedures in children, and the incidence appears to be increasing.[2] Nevertheless, post-adenotonsillectomy pain, as well as postoperative nausea and vomiting (PONV), remains a significant clinical problem.[3] Recent survey identified that pain associated with adenotonsillectomy was a top concern for over 90% of surveyed parents.[3] Although several strategies were attempted to reduce postoperative pain and enhance recovery after operation, a prospective cohort study has shown that tonsillectomy remains 1 of the most painful surgical procedures, even when compared to major surgery procedures.[4–6]

Here, we focused on the effect of dexamethasone on post-adenotonsillectomy pain and PONV. The Clinical Practice Guideline for tonsillectomy in children strongly recommends administering a single, intraoperative dose of intravenous dexamethasone for children.[7] In addition, a Cochrane meta-analysis of randomized controlled trials concluded that a single dose of dexamethasone is 'virtually without harmful effect.'[8] However, despite a large body of evidence regarding dexamethasone for tonsillectomy, many Korean ENT surgeons are reluctant to use intravenous dexamethasone for children in real-clinical settings. Because of ideas of whether dexamethasone may be associated with increase in bleeding risk and endocrine disorder, as well as immune system suppression.

The aim of this prospective double-blind, randomized controlled study was to evaluate the effect of intravenous dexamethasone administration on post-adenotonsillectomy pain, as well as PONV in children.

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YK and EJK equally equally contributed to the work.

The authors have no conflicts of interest to disclose.

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

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2. Materials and methods

2.1. Ethical considerations

This prospective, double-blind, randomized controlled study was performed at Chungbuk National University Hospital, Korea in accordance with the Declaration of Helsinki. It was approved by the institutional review board of Chungbuk National University Hospital (IRB no. 2018-11-011). Written informed consent was obtained from the parents and also from children if they were able to read and sign a specifically designed information sheet.

2.2. Participants

Children aged 3 to 12 years scheduled for elective adenotonsillectomy for sleep apnea were eligible to enter the study. Children were excluded if they had a history of allergy or hypersensitivity to dexamethasone, recent (<1 month) therapy with steroids or immunotherapy, mental retardation, if they had taken recent vaccination (<1 month). Children with anticipated difficult airway, history of peritonsillar abscess, and upper respiratory infections were excluded. Moreover, children with a suspected hemostasis disorder through patient or family history or those who were taking aspirin, non-steroidal anti-inflammatory drugs, or other drugs that interfere with coagulation were not considered for inclusion in the study.

2.3. Randomization and intervention

Children were randomly assigned to the dexamethasone group or control group. Randomization was performed by excel random number production. Dexamethasone (0.5 mg/kg, maximum dose 24 mg) for the dexamethasone group or an equivalent volume of 0.9% normal saline (placebo) for the control group was intravenously injected after induction by a clinician who had no relation with the operation and the study for blinding. The operation was completed with routine pediatric anesthesia. Classic complete tonsillectomy with dissection in the pericapsular plane was performed in all children using monopolar and bipolar forceps by three surgeons (SWS, LDW, and JHJ). Adenoidectomy was done with micro-debrider in the oscillating mode with saline irrigation using adenoidectomy blades.

Since the study was double-blind, neither the surgeon nor the anesthesiologist was aware of the injected solution content and were not involved in data collection. All participants received oral acetaminophen (15 mg/kg) every 8 hours postoperatively until the day after surgery. Patients were not given additional analgesics. Children were discharged home the day after surgery and were instructed to return to the emergency department in case of serious adverse events. They received written instructions to provide an exclusively cold or room temperature soft diet. When discharged, all participants were prescribed oral amoxicillin-clavulanic acid (25/3.6 mg/kg) twice daily and acetaminophen (15 mg/kg) three times daily for 1 week. The parents were instructed to follow the medication schedule diligently.

The parents who collected the data were also unaware of the patient's assigned group. Parents were given the questionnaires about postoperative pain scales to be answered daily. The questionnaires were obtained at the outpatient clinic at follow up, which was scheduled for all children after 7 days.

2.4. Outcomes

Primary outcome measures were to investigate the effect of dexamethasone for reducing postoperative pain and PONV at postoperative 24 hours. Pain intensity was assessed using pain scales: a 0- to 10-point visual analog scale (VAS). Generally, higher numbers indicate more pain (0 = no pain; 10 = most imaginable pain). The pain was measured from 6 hours post-surgery (day 0) and every morning from the day after surgery (day 1–7). Pain scoring was performed by patients and their parents together. The first 2 pain scoring checks were done during the hospitalization, therefore, they were instructed to put a mark on the point indicating the pain that they felt by a clinician who was blinded to the patient's group status. PONV was evaluated at 24 hours after surgery, before discharge. Vomiting was defined as the forcible ejection of the contents of the stomach through the mouth. Nausea was defined as the feeling of the urge to vomit. Vomiting and nausea were evaluated by counts and VAS (0- to 10-point), respectively. Nausea is difficult to assess in children since they are not able to verbalize their feelings. Therefore, a blind clinician instructed their parents on VAS scoring for nausea.

The secondary outcome was the postoperative hemorrhage episodes. The study stratified postoperative hemorrhage episodes into 1 of 3 categories based on severity:

(1) a history of bleeding leading to readmission but without evidence of bleeding at the medical examination;
(2) readmission due to bleeding with evidence of bleeding at the medical examination but no need for reoperation; and
(3) emergency reoperation due to bleeding.[9]

2.5. Statistical analysis

Data are presented as mean ± standard deviation. The dexamethasone group was compared with the control group. Continuous variables were analyzed using the 2-sided *t*-test, and categorical variables using the $\chi 2$ test (SPSS 12.0 software, Chicago, Illinois). A *P*-value of $< .05$ was considered to indicate statistical significance.

3. Results

3.1. Patients and enrollment

Between November 2018 and June 2019, 140 children were initially screened. Seventeen children were excluded because they underwent ventilation tube insertion or turbinoplasty concurrently with adenotonsillectomy. Children (n = 123) were randomly assigned to receive dexamethasone (n = 60), or control group (n = 63). All children received their assigned study treatment. We further excluded 18 children (9 children from each the dexamethasone group and the control group) who did not reply to the pain intensity assessment questionnaires at one week after surgery. Finally, 51 children of the dexamethasone group and 54 children of the control group were analyzed (Fig. 1). The mean age of the study participants was 6.2 ± 2.1 years. A total of 63.8% (67 out of 105) of the participants were male. Patient characteristics, including sex, age, tonsil size, and frequent tonsillitis history, were not statistically different between both groups (all $P > .05$). There was also no statistically significant difference in the operation time between the 2 groups (*P*-value = .763) (Table 1).

3.2. Primary outcomes

In both groups, postoperative pain was recorded from the operation day (day 0) until seven days after the operation. The pain continuously decreased in both groups from day 0 to the

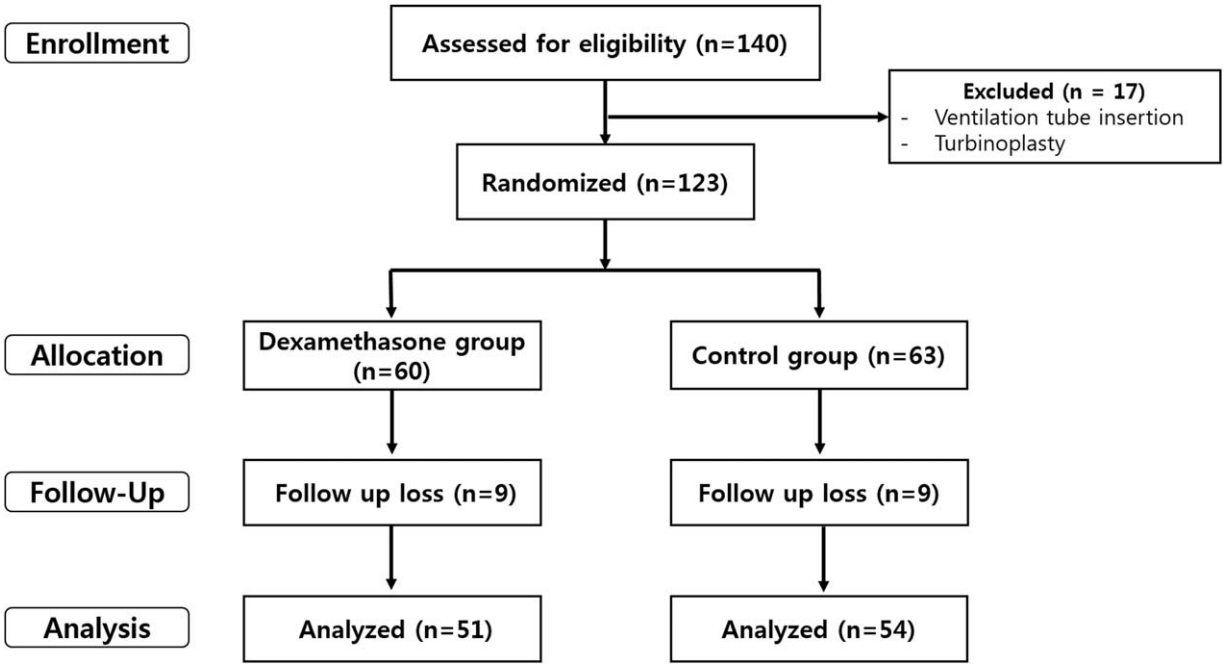

Figure 1. Flowchart of patient enrollment.

seventh postoperative day (Fig. 2). The average pain VAS during the study period (day 0–7) was 3.67 ± 1.59 and 4.40 ± 2.01 in the dexamethasone group and control group, respectively. However, no significant difference was seen between the groups (*P*-value = .107) (Fig. 3). On the operation day, the mean VAS value for pain in the dexamethasone group tended to be lower compared to the control group (5.21 ± 2.6, 6.39 ± 2.59, respectively), but there was no significant difference between the groups (*p*-value = 0.056) (Fig. 4A). When we compared early pain VAS (0–2 days after surgery) and late pain VAS (5–7 days after surgery), the dexamethasone group showed significantly lower early mean VAS compared to the control group (4.55 ± 1.78 vs. 5.40 ± 2.05, *p*-value = 0.046) (Fig. 4B). In the late mean VAS, there was no significant difference between groups (2.63 ± 1.58, 3.17 ± 2.52, respectively, *P*-value = .243) (Fig. 4C).

There was no vomiting event after surgery in both groups. During the first 24 hours after surgery, the mean VAS for PONV was significantly lower in the dexamethasone group (1.89 ± 2.22) than in the control group (3.00 ± 2.37) (*P*-value = .044) (Fig. 5).

3.3. Secondary outcomes

None of our patients had postoperative hemorrhage, which may require intervention and surgical bleeding control. A total of 2 patients (2 for category 2) revisited the hospital for minor postoperative hemorrhage from the control group on 8th and 10th postoperative days, respectively. No postoperative hemorrhage events from the dexamethasone group. However, there was no statistically significant difference between the groups (*P*-value = .159).

Table 1

Baseline characteristics of the study population.

	Dexamethasone group	Control group	*P*-value
Gender (Male: Female)	31: 20	36: 18	.598
Age, yr	5.7 ± 1.9	6.5 ± 2.1	.087
BMI, kg/m^2	17.45 ± 3.27	17.96 ± 3.39	.509
Tonsil size	grade III: 27, IV: 24	grade III: 34, IV: 20	.614
Frequent tonsillitis history	12 (23.5%)	20 (37.0%)	.135
Operation time, min	38.9 ± 10.5	38.1 ± 11.3	.763

4. Discussion

This prospective, double-blind, randomized controlled study evaluated whether intraoperative intravenous administration of dexamethasone for adenotonsillectomy in children can reduce postoperative pain as well as PONV. Overall postoperative pain tended to decrease in the dexamethasone group; in particular, early postoperative pain showed a statistically significant decrease. PONV was significantly reduced in the first 24 hours after surgery, and there was no increase in postoperative hemorrhage.

Adenotonsillectomy is currently one of the most common surgical procedures performed in children.[10] However, postoperative pain and PONV, followed by poor oral intake, dehydration, prolonged hospitalization, and postoperative hemorrhage still remain problems.[11–14] In addition, these problems lead to poor patient satisfaction, impair recovery, and increase health care costs.[15,16] Therefore, effective management of pain and PONV in this population is important.

The mechanism for post-adenotonsillectomy pain has yet to be clearly defined. However, the factors causing pain include inflammation, pharyngeal muscle spasm, venous congestion, edema, damage to the sensory fibers, compression of the mouth opener, and contact of the wound site with food.[17–19] This pain lasts until the peritonsillar muscles become covered with mucosa, 14 to 21 days after surgery.[20] Considering these possible mechanisms, dexamethasone is expected to reduce postoperative pain after adenotonsillectomy.[21–23] Its role as an adjuvant for

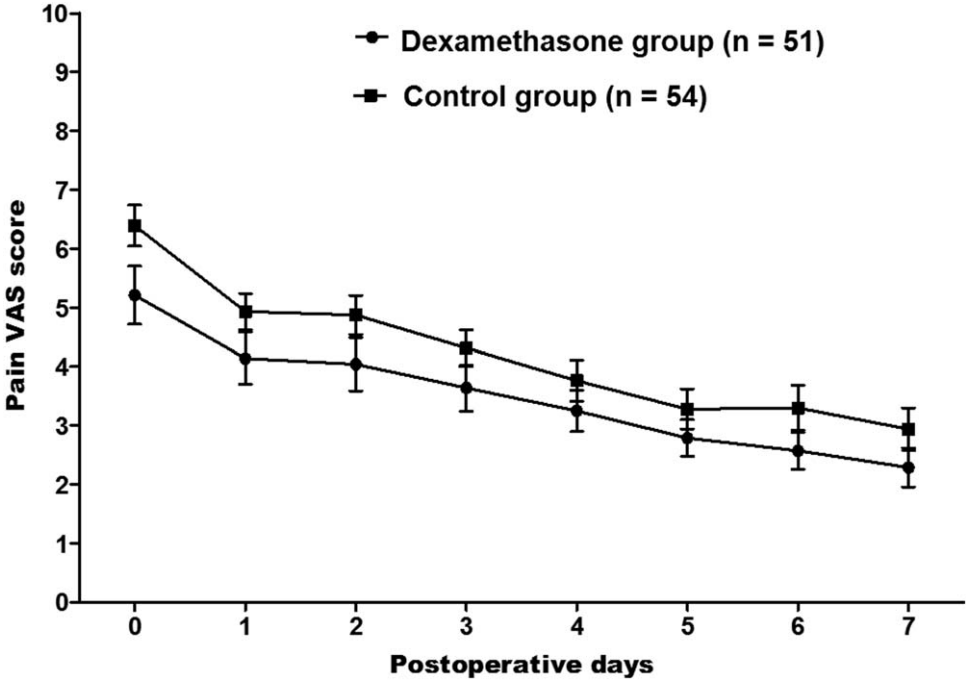

Figure 2. Postoperative VAS pain scores in dexamethasone group versus control group.

postoperative pain management is mainly mediated by inhibiting the production of inflammatory cell factors, resulting in decreased extravasation of leucocytes, decreased lysosomal enzyme release, and decreased vascular permeability in areas of injury.[24] These effects reduce edema and sensitization on pain nerve terminals at the operation site. In addition, oropharyngeal pain and irritation of gastric mucosa caused by swallowed blood are the main contributors to the high incidence of PONV following adenotonsillectomy.[25] As well as decreasing pain, dexamethasone exerts antiemetic activity through prostaglandin antagonism, the release of endorphins, and tryptophan depletion.[26] A meta-analysis for the use of steroids following tonsillectomy in pediatric patients shows that it reduces PONV.[8]

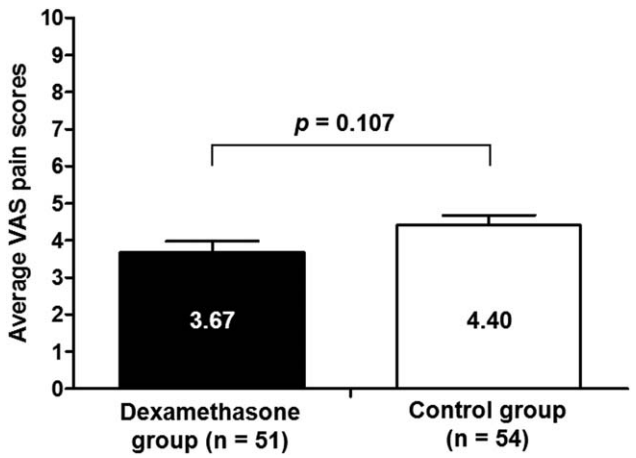

Figure 3. Average VAS pain scores.

In the recent Clinical Practice Guideline report, the American Academy of Otorhinolaryngology-Head and Neck Surgery panel made a 'strong recommendation' that clinicians administer a single, intraoperative dose of intravenous dexamethasone to children undergoing tonsillectomy.[7] In addition, a recent Cochrane meta-analysis concluded that 'a single intravenous dose of dexamethasone is an effective, safe and inexpensive treatment for reducing morbidity from pediatric tonsillectomy'.[27] However, administrations of dexamethasone to pediatric adenotonsillectomy in real-clinical settings in Korea are relatively rare. The exact proportions have not been reported, but there are several reasons why physicians may not adhere to clinical practice guideline recommendations. There have been reports that intraoperative dexamethasone use may increase postoperative hemorrhage. Another possible cause is the concern about the adverse effects of dexamethasone that is immune suppression, endocrinologic problems like hyperglycemia.

In 2008, Czarnetzki et al. designed the randomized controlled trial to determine the dose-response relationship between perioperative dexamethasone and PONV, was terminated early due to data suggesting dexamethasone was associated with a dose-dependent increase in bleeding risk compared with placebo.[9] They suggested that glucocorticoids may inhibit the repair process of surgical wounds and contribute to postoperative bleeding. However, several methodological questions have been raised regarding this study, including non-standardization of diagnosis, administration of ibuprofen, and non-standard surgical technique.[28] Indeed, 4 of 8 patients requiring surgical re-intervention had bleeding on the day of surgery, an interval generally thought to be dependent on surgical technique.[29] This outcome was not significant when primary hemorrhage cases were excluded from the analysis, and bleeding was far outside the generally reported range of about 1%.[29] Jilma et al. reported that dexamethasone was expected to stabilize blood clots and

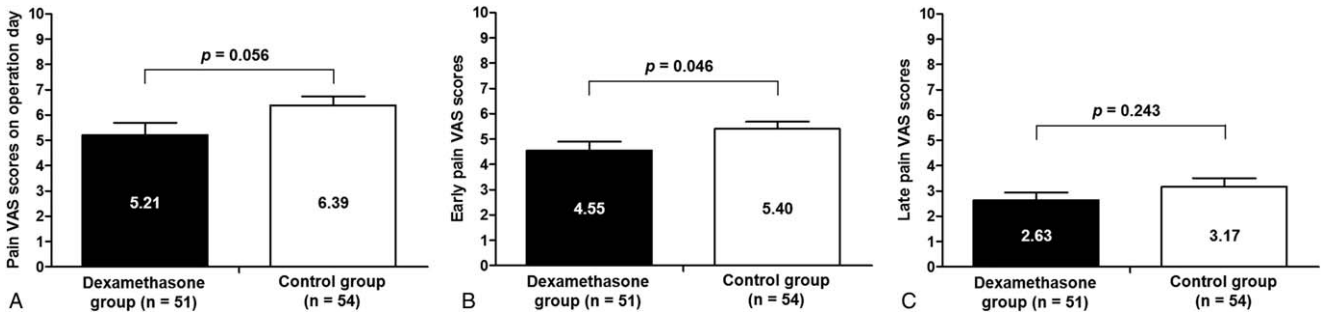

Figure 4. Pain VAS scores (A) On operation day, (B) Early, (C) Late.

theoretically decrease the rate of bleeding,[30] increased hemorrhage with dexamethasone has not occurred in any other pediatric published trials.[24] After these studies, several meta-analyses and a large observational study concluded that there is no clinically important risk of bleeding associated with dexamethasone use.[1,31–34] As regard to postoperative bleeding, in our study, the use of dexamethasone was not associated with increased risk of postoperative bleeding after operation.

Another consideration should include endocrine disorders that may occur after dexamethasone administration in children, as well as immune system suppression resulting in severe systemic infection and avascular joint necrosis. Long-term use of intranasal corticosteroids can cause immunosuppression, metabolic disorders, iatrogenic Cushing's syndrome, and secondary adrenal insufficiency.[35] However, in previous studies, the long-term use of corticosteroids was defined as periods of at least four weeks. Therefore, only a single dose of corticosteroid, even a large dosage, is regarded as safe and has been without harmful effects.[36,37] No adverse effects of steroid administration were observed in any of the studies.

Our study had some limitations. First, despite the strength of exactly following the protocol-based pain and PONV management, we only evaluated pain on a VAS scale. Other measurements used as proxies for pain – delay until the first oral intake, time to resume normal solid diet, time to return to normal life – were not evaluated. Second, medications used by anesthesiologists to induce anesthesia or to reduce airway reactivities were not included in the analysis. Third, methodological issues for pain measurement might be considered. The present study used a VAS scoring system ranging from 0 – 10 points for assessment of postoperative pain. When performing a pain questionnaire on children, the Faces Pain Rating Scale, FLACC (face, leg, activity, cry, consolability) can be used.[38] In addition, pain scores are influenced by the psychological characteristics of patients, such as preexisting anxiety, depression, social and cultural background, their previous pain experiences, the presence or absence of preoperative pain, and multiple other factors.[39] However, study participants and their parents were repeatedly instructed to put a mark on the point indicating the pain that they feel under monitoring by the trained physician. VAS scoring for pain severity is regarded as a simple, reliable method of assessing pain in children as young as 3 years.[40] In Cochrane meta-analysis, they also analyzed the studies using VAS scoring system for pain evaluation in children.[8,27] Fourth, we did not administer different concentrations of dexamethasone, but we used only one dose (0.5 mg/kg). Although the intraoperative use of dexamethasone is recommended as a common practice at many institutions recently, the dosages are not standardized. A dexamethasone dose of 0.5 mg/kg was commonly used in many previous studies; however, a systematic review of RCTs showed that doses have ranged from 0.15 to 1.00 mg/kg, with a maximum of 8 to 25 mg.[8] Further studies are needed to confirm the dose-dependent pain control relationships.

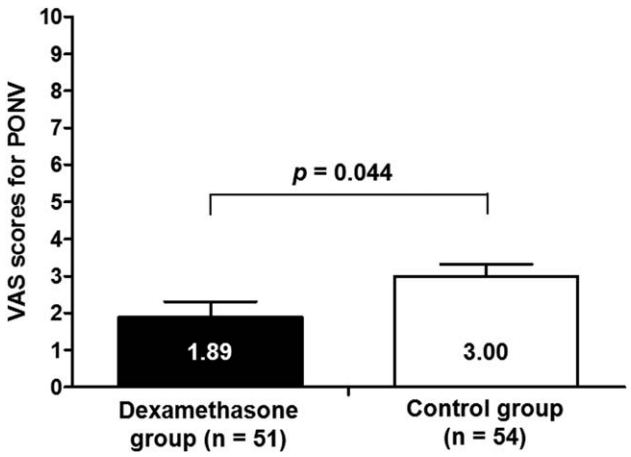

Figure 5. VAS scores for postoperative nausea and vomiting (PONV).

5. Conclusion

In conclusion, intravenous single-dose dexamethasone in children undergoing adenotonsillectomy can significantly reduce postoperative pain in early postoperative days. Moreover, it can reduce PONV significantly. This study suggests that intraoperative dexamethasone in children undergoing adenotonsillectomy could achieve adequate postoperative analgesia and antiemetic without side effects.

Author contributions

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Resources: Il Gu Jung.
Software: Il Gu Jung.

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Validation: Eu Jeong Ku, Young-Seok Choi, Hahn Jin Jung.
Visualization: Eu Jeong Ku.
Writing – original draft: Young Kang, Eu Jeong Ku, Il Gu Jung, Min Hyuck Kang.
Writing – review & editing: Young-Seok Choi, Hahn Jin Jung.

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