Peritonsillar infiltration with levobupivacaine for posttonsillectomy pain relief: does concentration have any effect? A double-blind randomized controlled clinical study

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Abstract. – **OBJECTIVE:** Post-tonsillectomy pain is believed to be mediated by noxious stimulation of C-fiber afferents located in the peritonsillary space, and local anesthetic infiltration to this area may decrease pain by blocking the sensory pathways and thus preventing the nociceptive impulses. We aimed to compare the effects of different concentrations of preincisional peritonsillar levobupivacaine (0.25% and 0.5%) infiltration on postoperative pain and bleeding in a placebo-controlled design.

PATIENTS AND METHODS: After obtaining Institutional Ethics Committee approval, 72 ASA I-II patients between 3 and 12 years of age, scheduled to undergo tonsillectomy were enrolled and randomly assigned to one of the three groups using the sealed envelope technique, as Group I (Control group), Group II, and Group III receiving preincisional bilateral peritonsillar infiltration with saline, 0.25% levobupivacaine and 0.5% levobupivacaine, respectively (3 mL to each tonsil). Pain, fever, dysphagia; nausea-vomiting and hemorrhage were evaluated at postoperative 0, 30, and 60 minutes and 2, 6, 12, and 24 hours. Oral paracetamol was administered at a dose of 15 mg/kg when FLACC score was > 4. The number of paracetamol administrations within the first 24 hours were recorded.

RESULTS: The patients in Groups I, II and III defined pain (FLACC > 4) at a rate of 87%, 60.9%, and 54.2% within the postoperative first 24 hours, respectively. The total number of additional analgesic requirements was significantly low in Group II and III when compared with Group I. There was no difference between groups in terms of fever, dysphagia, nausea-vomiting, hemorrhage.

CONCLUSIONS: Both concentrations (0.50% and 0.25%) of levobupivacaine were found to be equally safe and effective during preincisional peritonsillar infiltration in children. NCT number: 02322346.

Key Words:
   Levobupivacaine, Infiltration, Tonsillectomy.

Introduction

Tonsillectomy is the most commonly performed procedure in children and a high risk procedure in terms of complications and malpractice claims. It is associated with severe morbidity and mortality due to pain, opioid related respiratory depression, postoperative bleeding, and anesthesia or surgery related risks[1-3].

It is already known that a moderate-severe persistent pain develops in the tonsillar bed and surrounding tissues following tonsillectomy as a result of compression caused by the retractor, venous congestion, edema, injury in sensorial fibers and contact of the wound with fluid and food. Posttonsillectomy pain (PTP) might cause unwanted events such as anxiety, nausea-vomiting, dysphagia, delayed oral intake, loss of weight, sleep disturbance, constipation, prolonged hospital stay, and behavioral disturbances[2,4-6].

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In recent years, with new developments in pain management, different PTP treatment strategies have been used such as preoperative topical application of local anesthetics, nerve blockade, the use of dexamethasone, opioids, acetaminophen, NSAIDs, perioperative hydration, family education, and different surgical approaches. However, there is still no consensus about relieving pain related to the tonsillar fossa and surrounding structures in children undergoing tonsillectomy[1,4,7-13].

It has been demonstrated that incisional local anesthetic infiltration modulates peripheral pain transduction by inhibiting transmission of noxious impulses from the site of injury. Although, there have previously been controversial results related to local anesthetic infiltration to tonsillar bed, recent reports have demonstrated favorable effects of local anesthetic infiltration on PTP[14-17].

Levobupivacaine is an S-enantiomer of bupivacaine with lesser cardiovascular and central nervous system side effects. It is preferred in procedures where high dose local anesthetics are required and also in pediatric patients[18,19].

Although the efficacy of bupivacaine and levobupivacaine (0.5%-0.25%) and addition of different adjuvants to these local anesthetics have been investigated in several studies, there are no studies that compare the different concentrations of levobupivacaine in the literature[20-24].

The aim of the present study is to compare the effects of different concentrations of preincisional peritonsillar levobupivacaine (0.25% and 0.5%) infiltration on postoperative pain and bleeding in a placebo-controlled design.

Patients and Methods

After obtaining Institutional Ethics Committee approval and written informed parental consent, 72 ASA I-II patients between 3 and 12 years of age, who were scheduled to undergo tonsillectomy were enrolled in this randomized, prospective and placebo-controlled study. The indications for tonsillectomy were recurrent infections and tonsillar hypertrophy leading to obstructive symptoms.

The exclusion criteria were hypersensitivity to sevoflurane, benzodiazepine, fentanyl analogues, propofol and components, paracetamol, levobupivacaine, the presence of coagulation disorders and chronic diseases, regular use of analgesics, presence of analgesic use within 24 hours prior to surgery, presence of upper respiratory system infection, and the inability to understand the pain scales, being unable to communicate.

All children were premedicated with midazolam hydrochloride 0.5 mg/kg orally (with maximum 25 mL of fruit juice) or intravenous (IV) midazolam 0.05 mg/kg, 20 minutes prior to surgery. Patient monitorization included electrocardiography (ECG), noninvasive blood pressure (NIBP), and pulse oximetry (SpO$_2$). Anesthesia was induced with 8% sevoflurane and after inserting the IV cannula, 2-3 mg/kg propofol and 0.5-1 µg/kg remifentanil were administered. Oral endotracheal intubation was performed without muscle relaxants and ventilation was arranged to maintain the ETCO$_2$ concentration at 30-40 mmHg. Anesthesia was maintained by sevoflurane 2-3% in O$_2$ 50% and N$_2$O 50% mixture. Intravenous fluids were given as 1/3 isodex solution (Eczacibasi/Baxter, Istanbul, Turkey) at a rate of 3-5 mL/kg/hour during surgery. Before surgery, 0.5 mg/kg dexamethasone, IV and 4 mg ondansetron were given to all patients for postoperative nausea and vomiting, and 1 mg/kg tramadol HCL was also administered for postoperative analgesia.

The study medications were prepared by an anesthesiologist who was not involved in anesthesia management and postoperative follow-up. The anesthesiologist who was involved in anesthesia management and the postoperative follow-up, the surgeon, and the parents were all blinded to the treatment groups. The patients were randomly assigned to one of the three groups as Group I (Control group), Group II, and Group III receiving preincisional bilateral peritonsillar infiltration with a total of 6 mL of saline, 0.25% levobupivacaine and 0.5% levobupivacaine, respectively (3 mL to each tonsil). Randomization was provided by sealed, opaque, numbered envelopes. The randomization schema of the study is shown in Figure 1. The solutions were given to the upper and lateral poles of each tonsil at the same volume, by the same surgeon with a 25 G needle. No peritonsillar infiltration of adrenaline and/or ephedrine was administered.

All surgical procedures were started five minutes after the peritonsillar infiltration and the surgeries were again performed by the same surgeon. The tonsils and capsules were dissected from extra-capsular surrounding tissues and removed by using scissors and dissectors. The hemorrhages were controlled with bipolar cauterization. The amount of intraoperative bleeding
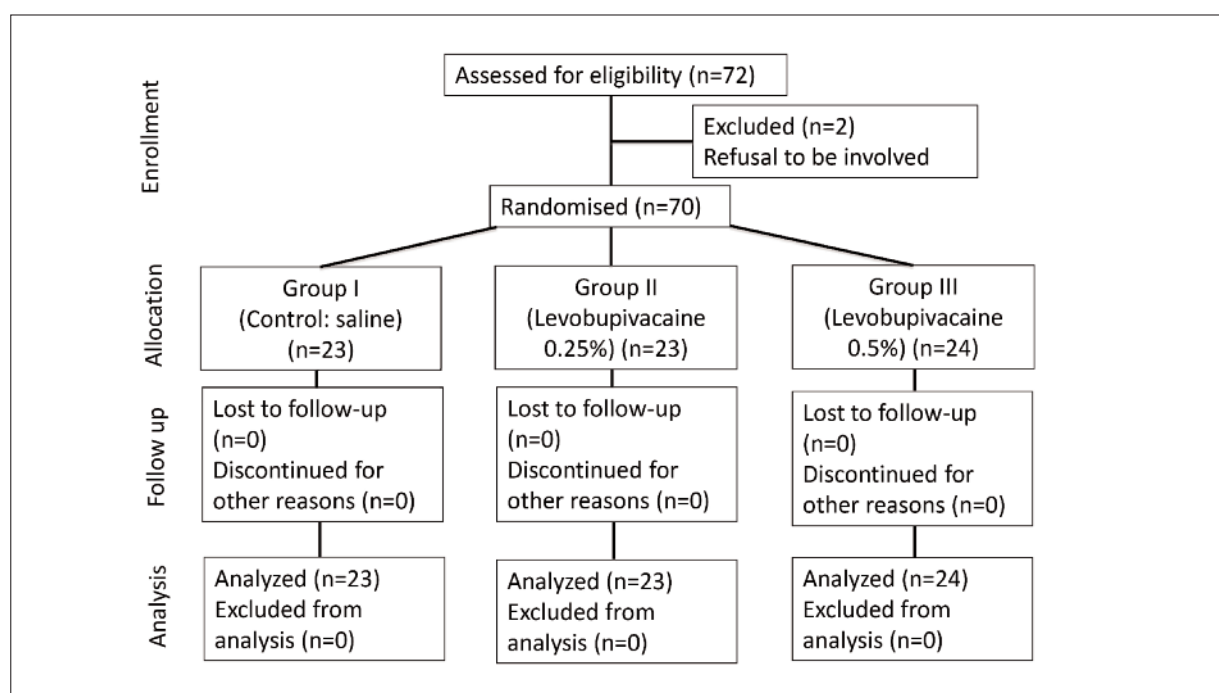
Figure 1. Randomization schema.

was defined by the surgeon in a 3-point scale (0=no bleeding, 1=mild bleeding, 2=moderate bleeding, 3=severe bleeding).

The mean arterial pressures (MAP) and heart rates (HR) of all patients were recorded during the duration of anesthesia and surgical procedures. The duration of anesthesia and surgery were also recorded. Additionally 1 µg kg^{-1} remifentanil IV was administered to the patients if HR was increased by 25 % of the basal value.

Symptoms such as pain, fever and dysphagia; and adverse affects such as nausea and vomiting and hemorrhage were all evaluated at postoperative 0, 30, and 60 minutes and 2, 6, 12, and 24 hours.

Pain was evaluated by the FLACC (faces, leg, activity, cry, consolability) scale. The evaluation criteria for FLACC (0-10) is demonstrated in Table I (0=relaxed and comfortable, 1-3=mild discomfort, 4-6=moderate pain, 7-10=severe discomfort or pain or both)[25]. The FLACC scale is shown in Table I.

Table I. FLACC (faces, leg, activity, cry, consolability) Behavioral Pain Assessment Scale[25].

Categories	0	1	2
Face	No particular expression or smile	Occasional grimace or frown; Frequent to constant frown, clenched jaw, withdrawn, disinterested	Frequent to constant frown, clenched jaw,
Legs	Normal position or relaxed	Uneasy, restless, tense	Kicking or legs drawn up
Activity	Lying quietly, normal position, moves easily	Squirming, shifting back and forth, tense	Arched, rigid, or jerking
Cry	No crying (awake or asleep)	Moans or whimpers, occasional complaints	Crying steadily, screams or sobs; frequent complaints
Consolability	Content, relaxed	Reassured by occasional touching, hugging, or being talked to; distractable	Difficult to console or comfort

In the current study, a score of > 4 on the FLACC scale was defined as pain requiring analgesia. Oral paracetamol was administered at a dose of 15 mg/kg in the presence of pain or fever ($\geq$ 38º). The number of paracetamol administrations in the presence of pain were recorded within the first 24 hours. The oral intake of the patients was started with water and cold milk at the postoperative third hour and ice cream at the sixth hour. If the patients had no complications, they were discharged at the postoperative 24th hour.

Statistical Analysis

Data were described with the use of mean±standard deviation [median (minimum-maximum)] for metric variables and frequency (percent) for categorical variables. To compare more than two independent groups in terms of metric variables, one-way analysis of variance (ANOVA) or Kruskal-Wallis variance analysis were performed. The chi-square test was used to compare groups for categorical variables. $p < 0.05$ was considered statistically significant.

Results

Seventy-two patients scheduled for elective tonsillectomy surgery due to recurrent infections and tonsillar hypertrophy leading to obstructive symptoms were eligible. Two patients were excluded because of their refusal, and 70 were randomly assigned to one of the three groups. Among 70 patients who completed the study, 23 patients assigned to Group I (Control), 23 to Group II, and 24 to Group III (Figure 1). Demographic variables of the patients as age, height, weight, and gender were similar in all groups. The duration of surgery and anesthesia were also similar (Table II).

There was no significant difference between groups in terms of intraoperative HR and MAP ($p > 0.05$). The remifentanil requirement during the operation was similar in all study groups (Table II) ($p > 0.05$). There was no significant difference between groups in terms of intraoperative bleeding scores (Table III).

Pain that necessitate paracetamol administration developed in 87%, 60.9%, and 54.2% of the patients at any time during the postoperative first 24 hours, in Groups I, II and III (FLACC > 4) respectively (Table III). The number of patients experiencing postoperative pain in Group II and III were significantly lower than Group I (control group) ($p < 0.05$) but there was no significant difference between Group II and III.

When the severity of posttonsillectomy pain between groups were compared using the FLACC scores, FLACC score at T0 was significantly low in Group III when compared to Group I and Group II; however, the difference between Group I and Group II was not significant. The FLACC score at T30 in Group III was significantly lower than Group II and FLACC score at T30 in Group II was significantly lower than Group I. The FLACC score at T60 and T120 were significantly higher in Group I when compared with Group II and Group III, but no significant difference was observed between Group II and III. There was no significant difference in the FLACC scores at other time intervals. The FLACC score within the time is demonstrated in Figure 2. The total number of additional paracetamol requirements was significantly low in Group II and III when compared with Group I, however, the difference between Group II and Group III was not statistically significant (Table III).

There was no difference between groups in terms of fever and dysphagia ($p > 0.05$) (Table III). Nausea and vomiting wasn't observed in any of the patients. No patient had overt complications of anesthetic and surgical intervention.

Table II. Demographical variables of all patients of all groups.

	Group I (n = 23)	Group II (n = 23)	Group III (n = 24)	*p*
Age (year)	7.57 ± 2.62	7.26 ± 2.66	7.38 ± 2.78	> 0.05
Height (cm)	124 ± 11.5	123.7 ± 12	124.3 ± 12.4	> 0.05
Weight (kg)	26.6 ± 8	26.7 ± 9.3	26.6 ± 8.6	> 0.05
Gender (F/M)	12/11	12/11	14/10	> 0.05
Duration of surgery (min)	49.2 ± 13.6	48.5 ± 12	48.6 ± 12.9	> 0.05
Duration of anesthesia (min)	64.7 ± 15	63.1 ± 13.6	62.1 ± 14.2	> 0.05
Remifentanil use (µg)	12 ± 3.6	12.8 ± 4.2	13.1 ± 4.3	> 0.05

Table III. Comparison of pain, fever, dysphagia, and a number of additional analgesic requirements during the postoperative first 24 hours.

|	Group I (n = 23)	Group II (n = 23)	Group III (n = 24)	p
Postoperative pain % (+/-)	87% (20/3)	60.9 % (14/9)	54.2% (13/11)	< 0.05
Intraoperative bleeding score median (min-max)	0 (0-1)	0 (0-1)	0 (0-0)	> 0.05
Fever % (+/-)	8.7% (2/21)	17.4% (4/19)	8.3% (2/22)	> 0.05
Dysphagia % (+/-)	39.1% (9/14)	17.4% (4/19)	12.5% (3/21)	> 0.05
Nausea-vomiting % (+/-)	0% (0/23)	0% (0/23)	0% (0/23)	> 0.05
Number of analgesic requirements median (min-max)	2 (0-3)	1(0-3)	1 (0-3)	> 0.05

Discussion

The present study aimed to evaluate the effects of different concentrations of preincisional peritonsillar levobupivacaine infiltration (0.25% and 0.5%) on postoperative pain and bleeding and the main finding is that both concentrations have similar analgesic efficacy and could be reliably used for postoperative pain relief.

It has been reported that posttonsillectomy pain (PTP) is most severe on the postoperative first day, then it gradually decreases and it transiently increases at postoperative third and fourth days with development of scar tissue[4]. The patients included in the current study were hospitalized for 24 hours so PTP could only be evaluated during this period in which the pain is most severe.

Today, there is no consensus on treatment of PTP, especially in the pediatric age group. The reason for this is that the treatment of PTP in children is difficult because there is generally communication difficulties and anxiety related to the medication in this age group and also the procedures are generally day case surgeries; the peritonsillar region is rich in nerve innervation and the blockade of nociceptive pathway is difficult. The individual pain response (differs according to black or white race) in patients, surgical technique, the anxiety and education status of the family and children, and the previous experiences related to pain also complicate standardization of pain therapy for tonsillectomy procedures[4].

In the recent decade, the outpatient tonsillectomy procedures have almost increased two-fold and only < 3% of tonsillectomies have become to be performed in an inpatient setting. As tonsillectomies are generally performed in an outpatient setting, an effective, simple, and reliable analgesic method with minimal side effects is necessary for postoperative pain relief[2].
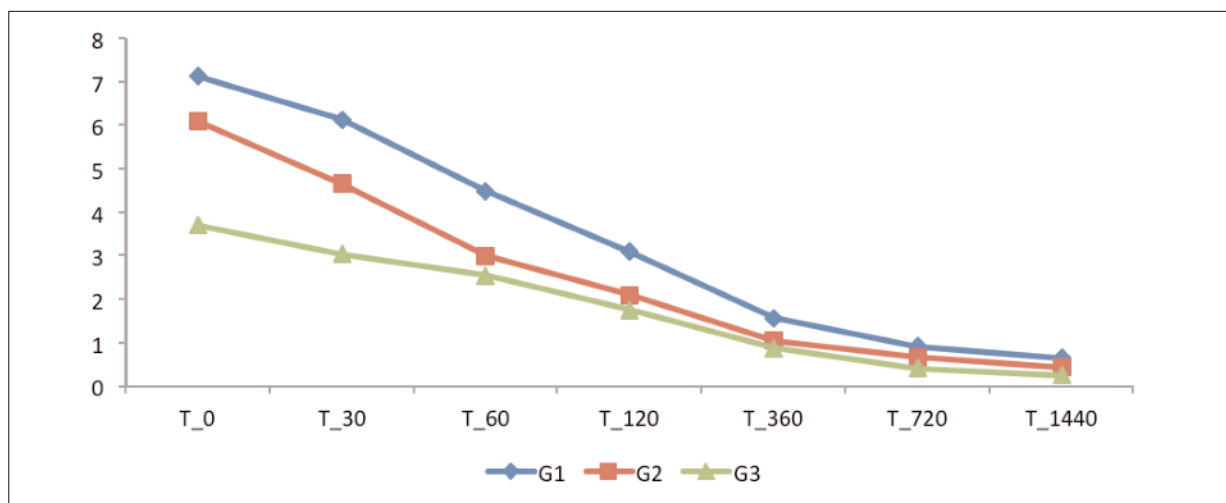
Figure 2. The comparison of FLACC value of the groups.

In a report of Stevenson et al[26], investigating 233 malpractice claims related to tonsillectomy, they reported 96 deaths (41%) and 137 perioperative injuries (59%). The most common causes of death were reported as surgery (48%) and opioid toxicity (18%) and the most common causes of death related to surgery was bleeding (40%)[26].

In several previous studies, it has been demonstrated that acetaminophen/codeine combination is effective for postoperative pain relief and this combination therapy have been commonly used for PTP in children[27]. However, prolonged hospital stay and increased costs and genetic polymorphism of the liver CYP2D6 enzyme in children has lead to decreased use of codeine in children[4]. After the deaths reported in 2012, the FDA has forbidden codeine use in children following tonsillectomy-adenoidectomy surgeries in 2013[28]. In our medical center, not only codeine but also other opioids are not preferred for posttonsillectomy pain relief.

The aforementioned low safety of opioid use in children has led to the increased use of non-opioid analgesics, such as acetaminophen and NSAIDs for PTP relief. In the past, NSAID use for PTP relief was limited, as it was known to lead to platelet inhibition and postsurgical bleeding. However, at the present time, the use of NSAIDs, either alone or in combination with acetaminophen, has progressively increased[29-31]. In an analysis of 13 studies that have been conducted in children, NSAIDs were not found to be associated with postoperative bleeding and it has been found that increasing COX-2 selectivity increases the quality of analgesia and decreases opioid requirements and causes less nausea and vomiting[31].

At the present time, the change in pain modalities has shifted the pain treatment from high doses of central acting agents to peripherally acting agents and multimodal analgesia methods, including peripheral nerve blocks, and wound infiltration with combined use of low dose opioids, and non-opioid agents, have been developed, in order to minimalize the side effects caused by high dose opioid use[32].

The simplest method in PTP therapy is the topical application of local anesthetics and for this purpose different local anesthetic solutions have been used and it has been reported that topical analgesia is an effective and reliable method[9,33].

In a meta-analysis in 2000, the efficacy of peritonsillar local anesthetic infiltration has not been clearly demonstrated[17]. In another meta-analysis in 2008, Grainger et al[11] mentioned that pain is the most important cause of postoperative morbidity following tonsillectomy and they reported that peritonsillar local anesthetic infiltration significantly decreases PTP and this effect could last longer than the action time of local anesthetic agent. In the current study, levobupivacaine infiltration to the tonsillar bed at both concentrations (0.5% and 0.25%) also provided effective analgesia and decreased postoperative analgesic requirements without producing any side effects.

Post-tonsillectomy pain is believed to be mediated by noxious stimulation of C-fiber afferents located in the peritonsillary space, and local anesthetic infiltration to this area may decrease pain by blocking the sensory pathways and thus preventing the nociceptive impulses. The most common agent used in peritonsillar local anesthetic infiltration is bupivacaine[12,20,21,34-37]. Although no difference was found between levobupivacaine and bupivacaine in terms of analgesic efficacy in previous studies, it has been reported that levobupivacaine could be preferred as it causes lesser systemic toxicity[20,21]. In the study of Dere et al[38], it was reported that levobupivacaine has positive effects on wound healing so it might be a more preferred agent in the future. In the current study, we also preferred levobupivacaine.

It has been demonstrated that the intensity of pain developing after tonsillectomy procedure is higher in extracapsullar removal when compared with intracapsullar removal and cauterization also causes more pain[4]. In the current study, the surgeries were performed by the same surgical team and the preference of the surgeon was extracapsullar removal, he also used cauterization during surgery. In this respect, we tried to standardize the pain in all study groups.

It was reported in the literature that the peak time for tonsillectomy procedures is 5-8 years old[2]. In the current study, the mean age of the patients was between 7 and 8 in all study groups and this was also in accordance with the peak time for tonsillectomy procedures. The procedures performed in the current study were only tonsillectomy procedures. The patients undergoing both tonsillectomy and adenoidectomy procedures were not included to the study. In this respect, the patient characteristics were also similar.

Ergil et al[22] compared vasoconstrictive effects of levobupivacaine 0.25% with solutions containing adrenaline and they have demonstrated vaso-

constrictive effects with levobupivacaine 0.25%. In the current study, levobupivacaine 0.5% and 0.25% were used for infiltration and no additional vasoconstrictive agents were used concomitantly and no significant difference was observed between two groups in terms of intraoperative and postoperative bleeding. Although there was no significant difference between groups in terms of bleeding, the vasoconstrictive effect of levobupivacaine 0.25% which had been demonstrated by Ergil et al[22], could be a reason for its preference.

In previous studies[24,34,36,39-43], local anesthetic, ketamine, and tramadol infiltration have been performed either before incision or after tonsillectomy. In the present study, we preferred to administer different concentrations of levobupivacaine infiltration to each tonsillar bed before incision.

In adults, it is easier to evaluate the pain symptoms with a self-report measure but in children, a self-report measure is not sufficient and the age, cognitive level and the situation causing the pain should also be considered while choosing the appropriate pain assessment method. It is better to evaluate the behavioural factors such as vocalization, motor responses, facial expressions and crying for pain assessment in children[44]. In the current study, the FLACC scoring system was used for pain evaluation. Although the VAS scoring system is generally used in evaluation of pain in adults, we considered that it might be difficult to evaluate pain in children with a verbal scale so we preferred the FLACC scoring system, the validity of which has been demonstrated in studies that were performed on children[25].

In previous studies[20,24] related to levobupivacaine infiltration in pediatric tonsillectomies, levobupivacaine, either as 0.5% or 0.25%, have been administered as 3 mL. However, in the literature, there are no studies that compare the different concentrations of levobupivacaine in tonsillectomy procedures. The children are more sensitive to the toxic effects of local anesthetics, therefore, in the current study, we compared different concentrations of levobupivacaine and we attempted to find whether effective analgesia could be achieved with smaller concentrations of levobupivacaine or not. In the current study, high concentrations of levobupivacaine was found to be more effective for pain relief in the immediate postoperative period (first one hour), but evaluating the severity of pain in the immediate postoperative period could be misleading be-

cause children undergoing surgery are anxious especially after surgery and their behaviours immediately following surgery could be exaggerated. However the severity of pain in the late postoperative period (after first postoperative hour) was found to be similar in both groups so we could suggest that low concentrations of levobupivacaine could provide similar analgesic efficacy in long-term and by using smaller local anesthetic concentrations, possible toxic reactions caused by high concentrations could be prevented. The number of analgesic consumption was significantly low with both concentrations (0.5% and 0.25%) of levobupivacaine. But in the current study, the total number of analgesic consumption within 24 hours was evaluated and it is necessary to evaluate the number of analgesic consumptions in each measurement interval individually. This is one of the criticism of the current study.

In previous studies[45-47], complications such as facial nerve paralysis, upper airway obstruction and vocal cord paralysis have been reported related to local anesthetic infiltration to tonsillar bed for PTP relief. In the current study, none of the patients developed complications related to local anesthetic infiltration.

It has been demonstrated that perioperative hydration of patients causes less PTP[1]. It has been previously thought that family education increases anxiety and anxiety increases the level of pain perception; however, currently it is thought that education of family and child has positive effects on anxiety and level of pain[1,2]. In the current study, the perioperative hydration status and the anxiety of the family was not evaluated. This is another criticism of the current study.

Conclusions

In the current study, it has been demonstrated that both concentrations (0.50% and 0.25%) of levobupivacaine were equally safe during preincisional peritonsillar infiltration in children and their long-term efficacy were also similar. Therefore, to avoid local anesthetic toxicity in children, lower concentrations could be effectively and reliably used in peritonsillar infiltration but further studies are warranted.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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