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The effects of levobupivacaine versus levobupivacaine plus magnesium infiltration on postoperative analgesia and laryngospasm in pediatric tonsillectomy patients

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Summary

Background: The aim of this study was to evaluate whether the addition of magnesium to levobupivacaine will decrease the postoperative analgesic requirement or not, and to investigate the possible preventive effects on laryngospasm.
Methods: Seventy-five children undergoing elective tonsillectomy and/or adenoidectomy surgery. The drug was prepared as only NaCl 0.9% for the first group (Group S, $n = 25$), levobupivacaine 0.25% for the second group (Group L, $n = 25$), and levobupivacaine 0.25% plus magnesium sulphate 2 mg/kg for the third group (Group M, $n = 25$). Pain was recorded at 15th minute, 1st, 4th, 8th, 16th, and 24th hour postoperatively. Pain was evaluated using a modified Children's Hospital of Eastern Ontario pain scale (mCHEOPS). Incidence of postoperative nausea and vomiting (PONV) was assessed at various time intervals (0–2, 2–6, 6–24 h) by numeric rank score. Patients were followed for laryngospasm for 1 h in recovery room after extubation. Other complications appeared within 24 h postoperatively were recorded.
Results: All postoperative CHEOPS values were lower than control in both groups. Analgesic requirement was decreased significantly in both groups in comparison with control patients, but this requirement was significantly lower in Group M ($p < 0.05$). Although laryngospasm was not observed in Group M, the difference between groups was not statistically significant. PONV was similar in both groups.

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Conclusions: Levobupivacaine and Levobupivacaine plus magnesium infiltration decrease the post-tonsillectomy analgesic requirement. Insignificant preventive effect of low doses of magnesium infiltration on laryngospasm observed in this study needs to be clarified by larger series.

1. Introduction

Postoperative pain is an important problem, and still continues to be undertreated in pediatric population [1]. The pain after tonsillectomy cumulates within first 3 days, and decreases gradually following 4 days in pediatric patients [2]. About 1% of patients operated were reported to be readmitted to the hospital because of odynophagia and dehydration [3]. Different methods including intraoperative arrangements of anesthetic regimens [4], corticosteroids [5,6], adjustment of surgical technique [7], intraoperative local anesthetic [5,8—10] and ketamine injection [11] have been studied to reduce the pain after tonsillectomy operations. Epinephrine and clonidine were reported to be added to local anesthetics to increase analgesic efficacy after tonsillectomy in some studies [1,5,12].

The number of studies was increased during last few years about the local or systemic use of *N*-methyl-D-aspartate (NMDA) receptor antagonists, ketamine and magnesium (Mg), after understanding the role of this receptor on postoperative pain pathophysiology. It was proved that sole magnesium has analgesic effect when used intra-articularly, increases the efficacy of prilocaine in axillary block and of fentanyl in spinal anesthesia. We could not find any study about levobupivacaine or magnesium injection alone or in combination used for post-tonsillectomy pain in the literature. Mg was also reported to decrease the incidence of laryngospasm in pediatric patients when used intravenously after tonsillectomy operations.

In this study we aimed to evaluate the effects of peritonsillary infiltration of levobupivacaine on the cessation of post-tonsillectomy pain and the prevention of laryngospasm, and to compare them with the infiltration of levobupivacaine plus magnesium.

2. Methods

After obtaining approval from the institutional ethics committee and parental consent, 75 American Society of Anesthesiologist (ASA) class I children between 3 and 12 years of age, who were scheduled for tonsillectomy or/and adenoidectomy, were enrolled for the study between 1 May 2006 and 1 August 2007, in a double-blind, randomized, prospective manner. Exclusion criteria were psychiatric illness, kidney failure, hypotension, atrioventricular block, myasthenia gravis, known hypersensitivity to levobupivacaine or magnesium, and regular use of analgesic medication.

All patients received a standard anesthetic protocol including premedication with oral midazolam 0.5 mg/kg 30 min preoperatively. In the operating room, heart rate, blood pressure, SpO_2 and temperature were monitored. Induction of anesthesia was achieved with 1.5% incremental doses of sevoflurane up to 7%. The intravenous catheter was inserted and 1/3 isodeks (Eczacıbaşı/Baxter, İstanbul, Türkiye) solution 3—5 ml/(kg h) was given intravenously during surgery. Lidocaine 1 mg/kg and fentanyl 0.5 μg/kg were administered. Neuromuscular block achieved with 0.1 mg/kg vecuronium and the trachea was intubated. Anesthesia was maintained with sevoflurane 2% and 60% nitrous oxide in oxygen.

A standard surgical technique (sharp dissection with cautery for hemostasis) was used. After tonsillectomy; study drug was superficially infiltrated into the peritonsillary fossa at the lower pole, the upper pole, and between these two (3 ml per tonsil) with the use of an aspiration-injection technique. A straight 23-G needle was used for infiltration. The infiltrate was free of adrenaline and the adenoid bed was not injected. Tonsillectomies and infiltrations were performed by the same surgeon (FY).

Cases were divided into three groups with closed envelope technique. The study drug was prepared into the injector making totally 6 ml by the anesthesiologist who was not included in postoperative evaluation. The drug was prepared as only NaCl 0.9% for the first group (Group S, $n = 25$), levobupivacaine 0.25% for the second group (Group L, $n = 25$), and levobupivacaine 0.25% plus magnesium sulphate 2 mg/kg for the third group (Group M, $n = 25$).

Residual neuromuscular block was reversed with atropine 0.02 mg/kg and neostigmine 0.05 mg/kg at the end of surgery after the discontinuation of anesthetic gases, and the patient was extubated. Oxygen was administered to the patient after extubation until emergence from anesthesia, and patient was observed for laryngospasm until the time of discharge from the postanesthesia care unit.

Laryngospasm was defined as the complete airway obstruction associated with SpO_2 85%, unrelieved by maneuvers. The treatment of laryngospasm was standardized according to the following protocol: (i) positive pressure ventilation with 100% O_2 with face mask, if symptoms persist; (ii) administration of lidocaine 1 mg/kg, if symptoms still persist; (iii) administration of succinylcholine 1 mg/kg and tracheal intubation [13].

The patients' pain scores were assessed using a modified Children's Hospital of Eastern Ontario pain scale (mCHEOPS) [14] at 15th minute after arrival to postanesthesia care unit (PACU) and 1st, 4th, 8th, 16th, and 24th hour postoperatively. The pain scoring is shown in Table 1. All measurements were done by an attending anesthesiologist blinded to the study groups.

Oral intake was stopped for the first 4 h postoperatively. If the CHEOPS score was greater than 5, a rescue medication including for <10 years 0.5 g, for >10 years 1 g metamizol i.v. was administered in the first 4 h postoperative period, and when patients tolerated fluids, oral acetaminophen 15 mg/kg was given. The time to the first request for analgesia and additional analgesic requirements were recorded. All patients were discharged on postoperative day 1. All adverse effects, including postoperative nausea and vomiting (PONV), abdominal pain, constipation, arrhythmia, and allergic reactions were recorded. The incidence of PONV was assessed for the first 24 h, and at various time intervals (0—2, 2—6, 6—24 h) by using numeric rank score (NRS) (0: no nausea and no vomiting; 1: nausea but no vomiting; 2: one episode of vomiting; 3: 2 or ±2 episodes of vomiting) [15]. No prophylactic agents were given to any case for nausea—vomiting. 10 mg metachlopramide i.v. was given to cases with NRS values more than or equal to 1 in the postoperative period.

Table 1 Modified CHEOPS scoring

Item structure	Parameter	Points
Crying	None	0
	Crying, moaning	1
	Screaming	2
Facial expression	Smiling	0
	Neutral	1
	Grimacing	2
Verbal expression	Positive	0
	None or another complaint	1
	Complaining of pain	2
Torso	Neutral	0
	Squirming, tense, upright	1
	Restrained	2
Legs	Neutral	0
	Kicking, restless fetal position	1
	Restrained	2

Power analysis was performed using software package, Epi info 2002 (Centers for Disease Control and Prevention, Atlanta, GA, USA). Data were analyzed using SPSS software program, version 11.5, for Windows (SPSS Inc., Chicago, IL). Values were noted as average and standard deviation. Normalization test was done with Kolmogorov Smirnov *Z*-test. One-way variance analysis and Chi-square test were used for statistical analysis. Multiple comparisons were performed with Bonferroni test. p values <0.05 were considered as statistically significant.

3. Results

Demographic and surgical data (age, sex, body weight, operation times, and operation type) of all participants are shown in Table 2, and were similar in all groups.

All CHEOPS values at postoperative 4th, 8th, and 16th hour were significantly lower in Group L&M than control group ($p < 0.05$) (Table 3). Total analgesic requirement was significantly decreased in Group L&M at the end of postoperative 24th hour compared to Group S ($p < 0.05$) (Table 4).

Additional analgesic drug was needed 36 times by 19 different patients in Group S, 15 times by 11 cases in Group L, and 8 times by 8 cases in Group M. There is a decline in acetaminophen and metamizol requirement for Group L&M compared to Group S, however, the difference between control group and study groups was found to be statistically significant in only Group M (Table 5).

The number of cases having PONV during postoperative 24 h period was 5 (20%), 4 (16%) and 9 (36%) for Groups S, L and M, respectively. Although PONV occurrence was increased in magnesium group, this increase was not statistically significant. Laryngospasm was occurred in four cases in Group S, three cases in Group L, and was not observed in Group M. These differences between groups were not statistically significant ($p > 0.05$). In Group M, allergic reaction was seen in one case and arrhythmia has occurred in another case. Occurrence of adverse reactions is shown in Table 2.

Power analyses for CHEOPS; in one-way ANOVA study, sample sizes of 25, 25, and 25 are obtained from the three groups whose means are to be compared. The total sample of 75 subjects achieves 100% power to detect differences among the means

Table 2 Demographic characteristics, surgical procedure and adverse effects in groups (mean ± S.D.)

	Group S (n = 25)	Group L (n = 25)	Group M (n = 25)
Age (year)	7.44 ± 0.52	7.86 ± 0.49	7.00 ± 0.52
Gender (male/female)	8/17	11/14	14/11
Weight (kg)	22.80 ± 1.21	23.56 ± 1.47	21.88 ± 1.57
Anesthesia time (min)	36.36 ± 1.76	33.08 ± 1.48	33.12 ± 1.69
Adenotonsillectomy (n)	22	21	21
Tonsillectomy (n)	3	4	4
Abdominal pain (n)	2	1	1
Constipation (n)	3	2	2
Arrhythmia (n)	0	0	1
Allergic reaction (n)	0	0	1

versus the alternative of equal means using a F-test. A sample size of 75 achieves 92% power for Chi-square test for laryngospasm and PONV.

4. Discussion

The main finding we obtained in this study is that addition of magnesium to levobupivacaine infiltration has significantly decreased analgesic requirement postoperatively meaning a better analgesia than levobupivacaine infiltration alone. Post-tonsillectomy pain is believed to be mediated by noxious stimulation of C-fiber afferents located in the peritonsillary space [16], and injection of a local anesthetic agent may decrease pain by blocking the sensory pathways and thus preventing the nociceptive impulses [17]. Our results support the idea that a local anesthetic administered to the peritonsillary space is an attractive solution to the problem of post-tonsillectomy pain [5].

A lot of local agents were used as an infiltration up to now, and it was reported that peritonsillary infiltration of 0.5% bupivacaine caused analgesia better than bupivacaine spray or placebo [18]. Preoperative infiltrations of local anesthetics were compared with postoperative infiltration previously. Preoperative bupivacaine infiltration has been reported to have no analgesic or preemptive property in one study. On the other hand, Molliex et al. [17] noted that timing of bupivacaine infiltration had no clinical importance and did not affect the quality of postoperative analgesia. Nevertheless, it was concluded by many studies that post-tonsillectomy pain was decreased obviously by peritonsillary infiltration of bupivacaine [8,19,20]. Akoglu et al. [9] reported that ropivacaine and bupivacaine infiltration had equal efficacy in post-tonsillectomy pain relief. In another study ropivacaine with or without clonidine has been reported to have preemptive property and significantly decreased the postoperative opioid use [12].

Levobupivacaine is the S-enantiomer of bupivacaine [21,22], and is believed to have some benefits like less motor blockade and more prolonged postoperative analgesia [23—25] compared with bupivacaine [26—29] Levobupivacaine may be useful in pediatric practice. Because of the lack of enough data in the literature about its use in pediatric tonsillectomy cases for postoperative analgesia, we preferred levobupivacaine in our study.

Surgical trauma can cause central nervous system (CNS) changes resulting in provocation of pain and decrease in pain threshold, and these may cause postoperative hyperalgesia [30]. Activation of NMDA receptors found in dorsal horn of spinal cord accepted as the cause of changes in CNS. For this reason, blockade of the NMDA receptors has been

Table 3 CHEOPS scores for the study groups (mean ± S.E.M.)

Time of assessment postoperatively	Group S (n = 25)	Group L (n = 25)	Group M (n = 25)	p values
15 min	5.16 ± 0.49	3.88 ± 0.36	4.04 ± 0.34	0.06
1 h	3.12 ± 0.30	2.04 ± 0.38	2.72 ± 0.27	0.06
4 h	3.32 ± 0.39[a, b]	1.16 ± 0.29	1.92 ± 0.29	0.0001
8 h	2.08 ± 0.33[a, b]	0.60 ± 0.25	0.72 ± 0.15	0.0001
16 h	0.92 ± 0.17[a, b]	0.32 ± 0.21	0.40 ± 0.14	0.04
24 h	0.20 ± 0.08	0.08 ± 0.06	0.04 ± 0.04	0.16

[a] vs. Group L.
[b] vs. Group M.

Table 4 Amount of total analgesic for groups (mean ± S.E.M.)

Variable	Group S (n = 25)	Group L (n = 25)	Group M (n = 25)	p values
Total analgesic number, children (criterions)	1.44 ± 0.24[a,b], 19 (36)	0.60 ± 0.16, 11 (15)	0.32 ± 0.10, 8 (8)	0.0001
Total metimazol number, children (criterions)	0.76 ± 0.14[b], 15 (19)	0.48 ± 0.12, 11 (12)	0.24 ± 0.09, 6 (6)	0.01
Total acetaminophen number, children (criterions)	0.76 ± 0.14[b], 13 (17)	0.48 ± 0.12, 2 (3)	0.24 ± 0.09, 2 (2)	0.0001

[a] vs. Group L.
[b] vs. Group M.

Table 5 PONV scores and laryngospasm incidence of the patients

	Group S	Group L	Group M
0—2 h NRS-1, -2 (%)	1, 0 (4, 0)	1, 2 (4, 8)	5, 0 (20, 0)
2—6 h NRS-1 (%)	4 (16)	1 (4)	4 (16)
6—24 h NRS-1 (%)	0	0	2 (8)
PONV 0—24 h, n (%)	5 (20)	4 (16)	9 (36)
Laryngospasm, n (%)	4 (16)	3 (12)	0

PONV, postoperative nausea and vomiting; NRS, numeric rank score.

suggested to inhibit central sensitization [31]. Magnesium is reported to have antinociceptive effects [32], which are primarily based on the regulation of calcium influx into the cell, and antagonism of the NMDA receptor [33].

Erhan et al. [11] reported that ketamine infiltration in pediatric tonsillectomy cases caused sufficient analgesia without any side effects. In a recent study, it was noted that i.v. ketamine and Mg alone or together had similar analgesic effects on tonsillectomy cases [34]. It was proved that Mg produced analgesia when used intra-articularly, and it increased the efficacy of primary drug when combined with prilocaine in axillary block, with lidocaine in regional intravenous anesthesia, and with fentanyl in spinal anesthesia. The dose of Mg used in the study about the addition of Mg to prilocaine in axillary block performed by Gunduz et al. [35] is 150 mg (approximately 2 mg/kg). We decided to use low doses of Mg in our study because of the lack of data about the use of Mg in combination with local anesthetic agents in peripheral blocks in pediatric cases. In spite of this low dose, PONV incidence increased insignificantly in Magnesium group. We thought that magnesium should be combined with different local anesthetics with different doses for pediatric cases to determine optimum doses in further studies.

Laryngospasm is particularly frequent in children after upper airway surgery; for example, after adenotonsillectomy, where the incidence is approximately 20% [36]. In our study, we did not observe laryngospasm in any patient in Group M. This finding supported by a report in which use of i.v. Mg (15 mg/kg) in pediatric tonsillectomy cases decreased the incidence laryngospasm significantly [37]. Intravenous magnesium has been used for the treatment of acute bronchospasm in pediatric age groups with doses of 10—25 mg/kg, or even up to doses of 100 mg/kg [38,39]. The paradoxical question of our study is the dose of Mg which was lower than that of previously used doses. It is unclear how this dose prevented the laryngospasm, however, we thought that it may be related with the smooth muscle relaxation achieved by local applications which may need to be clarified by further studies.

Most of the studies use visual analogue scale (VAS) or dynamic pain assessments (e.g., when drinking water or opening the jaw) to evaluate post-tonsillectomy pain in pediatric patients. It is generally accepted that evaluating pain in children is difficult, especially if the child is unwilling or unable to verbalize. In addition, VAS pain scale was reported by some authors to be confusing for children to use [12]. We preferred mCHEOPS, a valid and reliable method of assessing pain in children that has been used by some other investigators under different conditions [14].

As a result, levobupivacaine alone or with addition of magnesium causes lower CHEOPS values in pediatric patients after tonsillectomy operations, and addition of Mg to levobupivacaine provides significant decrease in additional analgesic consumption. More studies with larger number of participants are needed about the favorable effects of

peritonsillary magnesium infiltration on laryngospasm which we observed in this study.

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