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Effect of Postoperative Topical Administration of Magnesium Sulfate on Pain Relief in Paediatric Adenotonsillectomy: A Randomised Controlled Study

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Abstract This study aimed to investigate its topical effectiveness in post operative pain. One hundred and ten American Society of Anesthesiologist classes I and II patients aged 4 to 14 scheduled for adenotonsillectomy, were included in the study. In group M, the tonsillar fossa was packed for 3 minutes via 2.5×2.5 folded sterile gauzes saturated with 2 mg/kg of 20% magnesium sulfate (a NMDA antagonist) diluted with 10 cc normal saline, while for group S 10 cc of normal saline was used alone. The study showed a lower post operation pain score in group M in the 2 first hours after operation. Besides, analgesic consumption in the 1st and 2nd hours after the operation was significantly lower in group M, but it was not significant in the 3rd and 6th hours post surgery. Total analgesic consumption was lower in group M, while laryngospasm were not significantly different in the two groups and bleeding score was significantly higher in the first hour after operation. Topical magnesium sulfate in tonsillar fossa decreased post tonsillectomy pain in children.

Key words Adenotonsillectomy; Post tonsillectomy pain; Magnesium sulfate; NMDA antagonists

Introduction

Postoperative pain control, especially in paediatric population continues to be a big challenge while a definite ideal method of pain relief is not yet known.[1,2] Tonsillectomy is a frequent surgery in children and is often associated with moderate to severe pain.[3] Approximately 600 children per 100,000 undergo tonsillectomy annually in the United States and up to 50% of these children experience severe pain, defined as a pain score greater than or equal to 8, after surgery.[4] Tonsillectomy pain is higher in the first three days and gradually reduces after the fourth day.[5] Different ways of pain management are described including various methods of anesthesia, administration of corticosteroids, different surgical techniques, and use of topical anesthesia during surgery and ketamine or Magnesium sulfate injection.[6-10] During the past few years, after the discovery of the role of N-methyl-D-aspartate (NMDA) receptor on pathophysiology of postoperative pain, local and systemic use of NMDA receptor antagonists such as ketamine and magnesium has increased. Studies indicate that these receptors interact in the periphery[11,12] and their antagonists reduce chronic pain.[13] Magnesium is a calcium and NMDA receptor antagonist which can adjust pain and act as an opioidsparing especially if used in higher pain scores or with a larger dose.[14] However, the magnesium products, even if consumed in high doses are well tolerated.[15] On the other hand, many drugs are used in form of oral

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solutions to control oropharyngeal pain including the local anesthetics, antihistamines, anti-inflammatory agents and the opioids. Topical administration of drugs can locally control the pain with a few systemic complications and provide a good compliance for the patient as well.[16] In this study we investigated the beneficial effects of topical peritonsillar administration of Magnesium Sulfate in pain control in children.

Method

The study protocol was approved by the Institutional Ethics Committee of the Medical University of Lorestan and follows the Helsinki Declaration. After obtaining parental written informed consent, a prospective, randomised, double-blind clinical trial of 110 children undergoing adenotonsillectomy referred to Shohadaye Ashayer Medical Training Center, Khorramabad, Iran was performed. The selection criteria included any American Society of Anesthesiologist (ASA) classes I and II children aged 4 to 14 scheduled for adenotonsillectomy in year 2008 that did not have any of the characteristics for exclusion. Exclusion criteria included a present acute pharyngeal infection or a history of drug sensitivity or renal insufficiency. Patients were randomly assigned to two different groups (group M and group S) by the sequence of admission. Sample size was calculated using the following formula considering S = 1.5 and d = 0.8 according to our pilot study:

$$n = \frac{\left(z_{1-\alpha/2} + z_{1-\beta}\right)^2 \left(S_1^2 + S_2^2\right)}{d^2} \approx 55$$

As a result 55 patients were considered in each group. Demographic characteristics (age, sex, weight) were recorded. Patients did not receive solid foods from 8 hours before surgery. A peripheral vein access with blue angiocatheter number 27 was obtained and patients were premedicated with the standard protocol for anesthesia, including midazolam 0.01 mg/kg and alfantanil 2 µg/kg. Anesthesia was induced with sodium thiopental 5 mg/kg and atracurium 0.1 mg/kg until loss of consciousness. Tracheal intubation was facilitated with an appropriate size cuffed tracheal tube. The lungs were ventilated using a mixture of oxygen (40%) in N_2O (60%) and halothane 0-1.5%. Ringer solution was administered as maintenance hydration.

A standard surgical technique including blunt and sharp dissection associated with adenoid curettage was used by one surgeon. The study drug was prepared by the anesthesiologist who was not involved in the postoperative evaluation; group M received 2 mg/kg of magnesium sulfate 20% diluted in normal saline and group S received only 10 cc of normal saline, through a standard gauze of 10×10 cm in dimension folded 2 times to make a 2.5×2.5 cm one and put in the solution. Using the gauzes, each tonsillar fossa was packed by the surgeon who performed the tonsillectomy for 3 minutes; the surgeon was not involved in the postoperative evaluation. Residual neuromuscular block was antagonised with atropine (0.02 mg/kg IV) and neostigmin (0.05 mg/kg IV) after the discontinuation of anesthetic gases and the child was extubated at the end of the surgery. 100% saturated oxygen was administered via a face mask to the patient after extubation until emergence from anesthesia, and the patient was observed for laryngospasm until the time of discharge from the recovery room. Laryngospasm was defined as the airway obstruction associated with saturation of O_2 below 85%, unrelieved by appropriate maneuvers. The patients' pain scores were assessed using a modified Children's Hospital of Eastern Ontario Pain Scale (mCHEOPS) at fixed intervals after the surgery (1, 2, 3, 6 hours postoperatively) by an attending physician blinded to the study groups; the pain scoring is shown in (Table 1).

If the pain score was higher than 5, a rectal suppository acetaminophen 10 mg/kg was given. The amount of bleeding was assessed using a 3-point scale: 0, no bleeding; 1, a mild to moderate bleeding without haemodynamic disorder; 2, a severe bleeding with haemodynamic disorder. In the case of full awareness, stable haemodynamic status, ability to maintain the air way, return of air way reflexes and no bleeding at the surgery site, the patient was discharged at the end of the operation day.

The data were analysed using SPSS software program, version 11.5, for Windows (SPSS Inc., Chicago, IL). Values were noted as average and standard deviation. Chi-square test and Mann-Whitney U-test were used for statistical analysis when appropriate. A P values <0.05 was considered as statistically significant.

Results

A total of 110 children (55 in each group) were included in the study. No patient was excluded from the study. There were no statistically significant differences between the

groups for sex (male/female: M, 31/24 and S, 29/26), age (mean: M, 8.96 and S, 7.96; median of 8 for both) and weight (mean: M, 28.31 with minimum and maximum respectively 10 and 75; S, 22.96 with minimum and maximum respectively 15 and 35). All mCHEOPS values at postoperative 1st, 2nd, 3rd and 6th hour significantly decreased in both groups (M: from 4.3 to 2.35; S: from 3.54 to 1.62). The average score of pain was lower in group M and this difference was statistically significant ($P<0.001$) (Table 2).

Considering bleeding, significant difference between the amounts of bleeding was observed in each group at 1st, 2nd, 3rd and 6th hour post-operation. Average bleeding between the two groups did not show significant differences ($P=0.27$) (Table 3); however, the bleeding score assessment was down to decimal point with most below 1 which indicates the bleeding severity was mostly recorded as 0, i.e. no bleeding.

Incidence of laryngeal spasm in the recovery room was evaluated; considering $P=0.23$ there was no significant difference between the two groups (Table 4).

Acetaminophen consumption, which was given at any time with a pain score of more than 5, was significantly lower at the 1st and 2nd hour post-surgery in group M ($P<0.001$), but no significant difference was found between the two groups at 3rd and 6th hour after surgery ($P=0.618$). The total amount of acetaminophen consumption in group M during the 6-hour assessment was generally lower than group S (Table 5). One patient in group M and two in group S needed to take acetaminophen two times.

Discussion

Finding an ideal pain management method for post-tonsillectomy pain and also a medication or method that may reduce the chance of postoperative bleeding is a real challenge in otolaryngology. They cause discomfort during the postoperative period and their control is often inadequate. Several randomised double blind studies claimed antibiotics effectiveness in reducing pain and halitosis by using antibiotics.[17] Postoperative steroids and even homeopathic drugs are suggested in some studies.[18-20]

Topical solutions are being widely tested to improve or block post-tonsillectomy pain. Tisseel bovine fibrin sealant is described to promote earlier return to normal activity.[21] Vaiman et al found that patients improved in swallowing and pain reduction after the use of Quixil as a haemostatic

Table 1 Modified CHEOPS scoring

Item structure	Parameter	Score
Crying	No crying	0
	Crying, moaning	1
	Screaming	2
Facial expression	Smiling	0
	Neutral	1
	Grimacing	2
Verbal expression	Positive statement	0
	Negative statement	1
	Complaining of pain	2
Torso	Neutral	0
	Variable, tense, upright	1
	Stretched	2
Legs	Neutral	0
	Kicking	1
	Stretched, continues move	2

Table 2 mCHEOPS scores for the study groups (mean±S.D.)

Time of assessment postoperatively	Group M	Group S	*P*-value
Recovery room	3.02±2.03	2.75±1.83	0.64
1 hour	1.62±1.42	3.51±1.85	0.00
2 hours	1.29±0.85	2.84±1.48	0.00
3 hours	0.93±0.99	1.22±1.04	0.10
6 hours	1.05±1.38	0.62±0.62	0.17

Table 3 Bleeding scores for the study groups (mean±S.D.)

Time of assessment postoperatively	Group M	Group S	*P*-value
1 hour	0.11±0.31	0.29±0.45	0.01
2 hours	0.07±0.26	0.04±0.18	0.40
3 hours	0.00±0.00	0.02±0.13	0.31
6 hours	0.05±0.22	0.00±0.00	0.08

Table 4 Laryngospasm incidence of the patients

Laryngospasm	Positive	Negative
Group M	8 (14.5%)	47 (85.5%)
Group S	14 (25.5%)	41 (74.5%)

P-value: 0.27

Table 5 Postoperative analgesic requirement for the study groups

Time of assessment postoperatively	Acetaminophen consumption in Group M		Acetaminophen consumption in Group S		*P*-value
	Positive	Negative	Positive	Negative	
1 hour	2 (3.6%)	53 (96.4%)	22 (40%)	33 (60%)	<0.001
2 hours	0 (0%)	55 (100%)	10 (18.2%)	45 (81.8%)	<0.001
3 hours	1 (1.8%)	54 (98.2%)	3 (5.5%)	52 (94.5%)	0.618
6 hours	3 (5.5%)	52 (94.5%)	1 (1.8%)	54 (98.2%)	0.618
Total	6 (2.7%)	214 (97.3%)	36 (16.4%)	184 (83.6%)	<0.001

coating on the tonsillar beds when evaluated by electromyography after tonsillectomy.[22] On the other hand, some studies did not substantiate a significant beneficial effect of fibrin glue in postoperative pain control or as a haemostatic agent and thus found no indication for the routine use of it in tonsillectomy.[23, 24]

C-fiber afferents located in the peritonsillary space are believed to mediate post-tonsillectomy pain; hence, in order to prevent the nociceptive impulses, local anesthetics can be used to decrease pain by blocking the sensory pathways. As a result, injecting a variety of medications to the tonsillar beds (like bupivacaine, levobupivacaine, ketamine) has been used for that purpose. Many studies claimed that peritonsillary infiltration of bupivacaine decreased post-tonsillectomy pain;[8-10] however, Nikandish et al reported peritonsillar injection of pethidine and bupivacaine not to affect the dynamic pain state in the first 24 hours after snare-dissection tonsillectomy.[25] Besides, Akoglu et al[9] reported ropivacaine and bupivacaine infiltration to have equal efficacy in post-tonsillectomy pain relief. levobupivacaine also decreased the postoperative analgesic requirement and it decreased more significantly when magnesium was added to levobupivacaine.[26] Results from this study were consistent with our study which could imply the impact of magnesium sulfate on pain relief after surgery; magnesium sulfate provided significant decrease in additional analgesic consumption.

In other studies ketamine was demonstrated to have a potent analgesic effect by central blockage of perception of pain with sub-anesthetic doses.[2,3,26,27] The findings obtained in these studies were consistent with ours. NMDA receptors activation found in dorsal horn of spinal cord is considered as the cause of changes in CNS resulting in provocation of pain and decreased pain threshold.[28,29] Ketamine, like magnesium sulfate is an NMDA receptor antagonist and it is believed that they both involve in pain adjustment mechanisms through blocking of NMDA receptors. The regulation of calcium influx into the cell may be another reason for antinociceptive effects of magnesium. Considering no incidence of nausea and sedation (which are of central complications of ketamine) it seems the pain relieving effect is due to peripheral mechanisms; which are the same about magnesium.

O'Flaherty et al reported no decrease in pain or analgesic consumption in children undergoing tonsillectomy in 24 hours post-operation when pretreated with a small dose of ketamine and/or magnesium.[30] This was not consistent with the results of our study which may be because of magnesium sulfate pharmacokinetics and pharmacodynamics; its onset of effect is immediately after the onset of the intravenous injection and the duration of effectiveness is 30 minutes. Basically this time is spent during the operation and in the recovery room; hence, during the 24 hours of monitoring after the operation, the effectiveness of the drug is not expected to be found.

Laryngospasm is frequently observed in children after upper airway surgeries like adenotonsillectomy, with an incidence of approximately 20%.[31] Intravenous magnesium has been reported in the treatment of acute bronchospasm in paediatrics[25] We did not observe any significant differences in our two groups.

Being a calcium antagonist, magnesium has a muscle relaxant effect which suggests a higher risk of bleeding; however, in a study on the effects of magnesium sulfate on bleeding time in women with threatened preterm labor, no significant difference in bleeding time and platelet count before and after treatment with magnesium sulfate was observed.[32] In our study, there was no increase in normal post-operative bleeding and no acute side effect was observed in the therapeutic dose.

Conclusions

Results in this study suggested that topical administration of magnesium sulfate at tonsillar bed after surgery reduced postoperative pain degree, reduced the number and amount of analgesic (acetaminophen) consumption and had no effect on laryngeal spasms. Besides, there was no increase in post-operative bleeding. Generally, it would benefit children undergoing adenotonsillectomy to receive topical magnesium sulfate postoperatively which is available and has a very low risk of postoperative bleeding but improved analgesic profiles.

Arranging similar studies with higher sample size for meaningful statistical evaluation, comparison of different methods of administration of magnesium sulfate (topical, intravenous, intramuscular and tonsillar bed injection) in efficacy and incidence of complications, determining blood levels after administration of magnesium sulfate and its role in effectiveness and similar studies in adults can be in perspective views.

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