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Original Article

Comparison of effect of intravenous ketamine, peritonsillar infiltration of tramadol and their combination on pediatric post-tonsillectomy pain: A double-blinded randomized placebo-controlled clinical trial

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Abstract

In this study, the aim was the evaluation of effect of intravenous (IV) administration of ketamine, peritonsillar infiltration of tramadol and their combination for control of post-operative pain in comparison with single use of each drug in children undergoing tonsillectomy. One hundred and twenty children, aged 2-15 years, selected for elective adenotonsillectomy were enrolled in the study. We divided the patients into four groups of 30 each, Group I: received IV ketamine 0.5 mg/kg, Group II: received peritonsillar infiltration of tramadol 2 mg/kg, Group III: received IV ketamine 0.5 mg/kg added to peritonsillar tramadol 2 mg/kg and Group IV: received IV and peritonsillar infiltration of 0.9% saline. We utilized the Children's Hospital of Eastern Ontario Pain Scale (CHEOPS) recorded each 15 min after surgery to the first h and then each 2 , 4, 6, 8, 16, 24 h to assess pain levels postoperatively. The analysis of data showed that Group III had significantly lower CHEOPS scores than another three groups (P<0.001), while both Groups I and II had the same ranged scores, which were not statistically significant (P>0.05). During 24 h after surgery, the first time for analgesic requirement was higher in Group III in comparison with other groups (P<0.001). Combined use of IV ketamine 0.5 mg/kg with peritonsillar infiltration of tramadol 2 mg/kg provided better and more prolong analgesic effects compared with using each drug alone in patients undergoing tonsillectomy.

Keywords: Tonsillectomy; Ketamine; Postoperative pain; Tramadol

INTRODUCTION

Pain is one of the most consequential problems which are caused subsequent to the invasive procedures. According to the several researches, the management of post operative pain in children is poor and tonsillectomy as a common surgical procedure usually results in a significant pain in children often compel a regional anesthesia technique for postoperative pain control (1,2). Management of this sort of pain is a difficult task and could remain even over 4 days after the surgery that results in poor oral intake, long hospital stay, and a delay in return to the normal activities (3,4).

Some methods are available to relieve and control the acute postoperative pain. The analgesic effect of morphine which commonly results in some side effect such as postoperative nausea and vomiting (PONV) has been compared with other analgesic drugs (5,6). Peritonsillar infiltration of bupivacaine 0.5% alone or in combination with epinephrine has caused lower recovery room pain scores and opioid requirements (7,8).

Previous studies have shown that administration of small doses of intravenous ketamine before or after surgery can decrease diclofenac and acetaminophen consumption after tonsillectomy (9,10). It has also shown that peritonsillar infiltration of tramadol is a successful method to provide superior analgesia for the first 4 h after tonsillectomy (11).

In our clinical experience, we noted that using intravenous ketamine in combination with peritonsillar infiltration of tramadol can apparently prolong the analgesic efficacy of tramadol. However, to the best of our

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knowledge, any controlled study to address this subject has not yet been reported. We, therefore, designed the present randomized, double blinded, placebo controlled study to compare the effect of combination of intravenous low dose ketamine with peritonsillar infiltration of tramadol with administration of single dose of each drug on the postoperative pain relief after tonsillectomy in children.

MATERIALS AND METHODS

Following obtaining approval from the Isfahan University of Medical Sciences (project number: 289291) and written informed consent from the parents, 120 children ages 2-15 years with ASA of physical status I or II, scheduled for elective tonsillectomy were recruited in this study. The study was performed from September 2010 through November 2011 in Kashani hospital, city of Isfahan, Iran. All of children were randomly arranged in 4 groups with a sample size of 30 patients in each group. All operations were performed by one surgeon who was blind to the study drug by using a standardized snare dissection technique. Patients who developed bleeding or hypersensitivity to tramadol or ketamine were excluded from the study.

All patients received a standard anesthetic protocol including premedication with atropine 0.006 mg/kg and midazolam 0.1 mg/kg, induction with thiopental sodium 5 mg/kg and atracurium 0.5 mg/ kg, and maintenance with nitrous oxide (50%) in oxygen (50%) and isoflurane (1.2%). Children also received fentanyl citrate (1 μg/kg) and metoclopramide (0.25 mg/kg) intravenously. Ordinary monitoring including ECG, noninvasive blood pressure, oxygen saturation, and end-tidal CO2 was used.

Before tonsillectomy, children were randomly assigned to receive IV ketamine (0.5 mg/kg, Rotexmedica, Tritta, Germany) and peritonsillar saline (3 ml of normal saline; 1.5 ml per tonsil) (group I, n=30), IV saline and peritonsillar tramadol (2 mg/ kg in 3 ml of normal saline; 1.5 ml per tonsil) (group II, n=30), IV ketamine (0.5 mg/kg) and peritonsillar tramadol (2 mg/ kg in 3 ml of normal saline; 1.5 ml per tonsil) (group III, n=30); IV and peritonsillar saline (group IV, n=30).

All medications were 3 ml in volume and dosage of ketamine (4) and tramadol (6) (Chemidarou Industrial Company, Tehran, Iran) was based on the previous studies (4,9). Randomization was arranged by shuffled, sealed, opaque, and numbered envelopes.

In four groups, an independent anesthesiologist, who was not involved in the medication or surgery, prepared the studied drugs. The same surgeon who also was blinded to the given medication performed all the injections with a 25-gauge needle mounted to the syringe. The tonsillar bed and peritonsillar tissues on both sides were infiltrated by using the same technique with fan-wise injections from the superior and inferior poles of the fossa.. The infiltrate was free of adrenaline and the bed of adenoid and the bodies of the tonsil were not injected. We recorded heart rate, systolic, diastolic, mean arterial blood pressure, and peripheral oxygen saturation at 15 min intervals throughout the procedure. Removal of the mouth gag was performed at the end of operation. At the end of the surgery, neuromuscular blockade was reversed by IV neostigmine 0.04 mg/kg and IV atropine 0.02 mg/kg. Then after, anesthesia was discontinued and the tracheal tube removed in the operating room when airway reflexes were returned. The extubation time (the time from discontinuation of anesthesia drugs to tracheal extubation), the duration to anesthesia (the time from induction of anesthesia to discontinuation of anesthetic drugs) and surgery time (the time from surgical incision to removal of mouth gag) were recorded by an observer blinded to the study drugs.

In the recovery room the assessment of patients' pain scores were performed using a modified Children's Hospital of Eastern Ontario Pain Scale (mCHEOPS) (Table 1) (6) at 0, 15, 30 min, and 1, 2, 4, 12, 16, and 24 h after the operation. A nurse who was unaware to the randomization succession recorded the pain scores. If the pain score was greater than 5, we administered rectal acetaminophen 20 mg/kg. The time to the first request for analgesia and additional analgesic requirements was recorded. All patients were discharged on

Table 1. Modified CHEOPS scoring

Score	*0*	*1*	*2*
Cry	No cry	Crying, moaning	Scream
Facial	Smiling	Neutral	Grimace
Verbal	Positive Statement	Negative Statement	Suffering from pain another complement
Torso	Neutral	Variable, taut, Upright	Stretched
Legs	Neutral	Kicking	Stretched, continuous move

*CHEOPS:Children'sHospital Eastern Ontario Pain Scale.

postoperative day 1. A four-point sedation score (0 = eyes open spontaneously; 1 = eyes open to speech; 2 = eyes open when shaken; 3 = unarousable) (12) was also measured at 0, 15, 30 min and 1, 2, 4, 12, 16, and 24 h postoperatively. All adverse effects, including nausea, vomiting, and hallucination were recorded.

Nausea and vomiting scores were determined as follows: 0 = absent, 1 = nausea and 2 = vomiting. Dysphagia was graded on a scale from 0 to 4 points (0, no dysphagia; 1, dysphagia for regular solids; 2, dysphagia for soft solids; 3, dysphagia including liquids; and 4 complete dysphagia including saliva) (13). Parents satisfaction was graded on the basis of : 0 = poor, 1 = fair, 2 = good, 3 = excellent).

With using MedCalc 9.0 statistical software, it was calculated that 30 patients in each group would have 80% power for detection of 21% difference in the CHEOPS scoring between Group III with Group IV at a 5% significance level. Statistical analyses performed with SPSS 17 for Windows using one-way analysis of variance (ANOVA) (for repeated continuous variables) with post hoc comparisons using the Bonferroni multiple range test, and chi-squared tests (for categorical variables) when appropriate. Kruskal-Wallis test was used for analysis of median in four groups. Mann-Whitney test was used for analysis of non-parametric variables in each two groups if necessary. A value of $P<0.05$ was considered statistically significant.

RESULTS

No patient was excluded from the study due to any problem. Four groups of patients did not indicate any significant differences with respect to the demographic data, duration of surgery or anesthesia and extubation time (Table 2).

There was no statistical differences among four groups in HR, SPO_2 level, SAP, DAP and MAP during surgery, in the PACU, and the first 24 h after operation.

Statistical differences were not observed between 4 groups in incidence of vomiting or nausea ($P>0.05$), but dysphagia was significantly lower in group III compared with the other three groups ($P<0.0001$) (Table 3).

The median of sedation scores were significantly different among four groups at the time of arrival to the post-anesthesia care unit (PACU) and 15 min after that ($P<0.05$) (Table 4). The patients in Group I and Group III which received IV ketamine was more sedated at the time of arrival to the PACU compared with Group II and Group IV ($P<0.05$) (Table 4).

The CHEOPS scores were significantly lower in Group III compared with Group I, Group II, and Group IV at all times after operation till 24 h ($P<0.05$) (Table 5). The postoperative pain was significantly lower in Group I compared with Group IV till 24 h after operation but it was significantly higher in comparison with Group III ($P<0.05$) (Table 5). The CHEOPS scores were significantly lower in Group II compared with Group IV till 4 h after operation ($P<0.05$) (Table 5).

The first time of analgesic requirement was significantly higher in group III compared with the other groups ($P<0.001$) (Table 6). The mean dosage of additional analgesic used was significantly lower in Group III compared with the other groups ($P<0.001$) (Table 6). Time to the first oral intake of analgesics was significantly lower in Group III compared with Group IV while this variable was not

Table 2. Demographic data of patients, duration of surgery, duration of anesthesia, and extubation time for the four groups

Variable	Group I	Group II	Group III	Group IV
Age (year)	7.33 ±3.2	8.3 ±2.8	7.8 ±3.2	8 ±4.3
Weight (kg)	24.7±10.3	23.5±9.9	22.9±9.3	22.1±13.4
Sex (M/F)	17/13	18/12	14/16	16/14
Duration of surgery (min)	55.5±4.4	55.6±4	56.7±7.3	57±6.3
Duration of anesthesia (min)	71±39.6	70.4±40.7	69.5±14.7	68.6±11.4
Extubation time (min)	10.7±24	13.8±21.5	12.4±5	12.6±8.7

Data are presented as mean ± SD or numbers. Group I, received IV ketamine 0.5 mg/kg and peritonsillar saline; Group II, received IV saline and peritonsillar tramadol 2 mg/ kg; Group, III, received IV ketamine 0.5 mg/kg and peritonsillar tramadol 2 mg/ kg; Group IV, received IV and peritonsillar saline. No significant difference was noted between four groups.

Table 3. Incidence of nausea, vomiting and dysphagia in four study groups

Group	PONV	Abdominal pain	Dysphagia (0/1/2/3/4)	No of postoperative events
Group I (n = 30)	10 (33.3)	0	0/1/13/14/2 † (0/3.3/46.7/6.7)	20 (66.7)
Group II (n = 30)	9 (30.0)	0	7/5/3/2/13† (23.3/16.7/10/6.7/43.3)	21 (70.0)
Group III (n = 30)	7 (23.3)	1 (3.3)	22/2/2/3/1* (73/6.7/6.7/10/3.3)	23 (76.7)
Group IV (n = 30)	11 (36.7)	3 (10.0)	0/0/0/9/21 (0/0/0/30/70)	19 (63.3)
P value	P > 0.05	P > 0.05	P < 0.0001	P > 0.05

Data are presented as numbers (%). PONV = postoperative nausea vomiting. Group I, received IV ketamine 0.5 mg/kg and peritonsillar saline; Group II, received IV saline and peritonsillar tramadol 2 mg/ kg; Group III, received IV ketamine 0.5 mg/kg and peritonsillar tramadol 2 mg/ kg; Group IV, received IV and peritonsillar saline.* P<0.05 vs other three groups. † P< 0.05 vs. Group IV.

Table 4. Sedation scores of four groups in the PACU

	Group I (0/1/2/3)	GroupII (0/1/2/3)	Group III (0/1/2/3	Group IV (0/1/2/3)	P-value
0 min	1/5/21/3*	4/15/11/0	2/3/24/1*	5/15/8/2	0.00
15 min	3/8/18/1*	13/16/1/0	5/5/18/2*	11/15/3/1	0.00
30 min	17/13/0/0	12/18/0/0	13/16/1/0	9/16/3/2	0.06
60 min	9/17/4/0	8/16/6/0	3/23/4/0	5/19/3/3	0.47

PACU = Post-anesthesia care unit. Group I, received IV ketamine 0.5 mg/kg and peritonsillar saline; Group II, received IV saline and peritonsillar tramadol 2 mg/ kg; Group III, received IV ketamine 0.5 mg/kg and peritonsillar tramadol 2 mg/ kg; Group IV, received IV and peritonsillar saline. P<0.05 vs. Group IV and Group II.

Table 5. Postoperative mCHEOPS scoring in four groups

	At PACU (min)				After discharge from PACU (h)					
	0	15	30	60	2	4	6	8	16	24
G I	5.3±0.8‡	5.0±0.6‡	4.5±0.6‡	4.1±0.6‡	3.5±0.8‡	3.0±0.6‡	1.5±0.8‡	1.6±0.8‡	1.6±0.8‡	1.6±1.1‡
G II	4.0±1.1†	3.5±1.4†	3±1.3†	2.4±1.4†	2.1±1.2†	1.8±0.9†	2.0±0.9	2.2±1.1	2.1±1.0	2.0 ± 0.9
G III	2.6±2.7*	1.8±3.1*	1.2±2.9*	1.0±2.6*	0.7±2.2*	0.7±2.1*	0.5±2.1*	0.6±0.9*	0.64±1.1*	0.6±1.2*
G IV	8.2±0.6	7.6±0.7	7.1±0.7	6.8±1.4	5.2±1.6	4.3±1.7	2.8±1.5	2.8±1.5	2.8±1.4	2.9 ± 1.8
P	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00

Data are presented as mean ± SD. PACU = Post-anesthesia care unit. G I, received IV ketamine 0.5 mg/kg and peritonsillar saline; G II, received IV saline and peritonsillar tramadol 2 mg/ kg; G III, received IV ketamine 0.5 mg/kg and peritonsillar tramadol 2 mg/ kg; G IV, received IV and peritonsillar saline.* P<0.05 vs. Group IV and Group II.* P<0.05 vs. Group I, Group II, and Group IV. † P<0.05 vs. Group IV. ‡ P<0.05 vs. Group IV.

Table 6. The first time for rescue analgesic, dosage of rescue analgesic, first time to the oral intake and parent satisfaction score in the four groups

	Group I	Group II	Group III	Group IV	*P* value
The first time for analgesic requirement (h)	5.9 ± 1.3*	5.9 ± 1.2*	8.4 ± 1.5†*	1.8 ± 1.0	0.000
Dosage of additional analgesic used (mg)	167.3 ± 30.6*	245.6 ± 30.4	21.7 ± 9.6†*	268.2 ± 24.7	0.000
Time to the first oral intake (min)	84.0 ± 14.5	84.0 ± 13.9	54.0 ± 16.9*	128.0 ± 11.6	0.005
Satisfaction Score (good + excellent, %)	23.3*	53.3*	90.0†*	0.0	0.000

Data are presented as mean ± SD. Group I, received IV ketamine 0.5 mg/kg and peritonsillar saline; Group II, 30 received IV saline and peritonsillar tramadol 2 mg/ kg; Group III, received IV ketamine 0.5 mg/kg and peritonsillar tramadol 2 mg/ kg; Group IV, received IV and peritonsillar saline..* $P<0.05$ vs. Group IV. † $P<0.05$ vs. Group I and Group II.

significantly different with placebo in Group I and Group II (Table 6).

The parent satisfaction score was significantly higher in Group III compared with Group I, Group II and Group IV ($P<0.05$) (Table 6). There was no significant difference in incidence of postoperative nausea and vomiting (PONV) in four groups. There was no case of hallucination, dysphoria, diplopia or any psychological adverse effects after operation in any patient.

DISCUSSION

One of the most important issues for patients undergone tonsillectomy is to provide a safe and effective analgesia and appropriate pain managements. Some methods of pain control can cause post-tonsillectomy comp-lications.

Our results showed that combined use of peritonsillar infiltration of tramadol with intravenous ketamine lowered postoperative pain scores better than using each drug separately. Atef and coworkers (11) showed that peritonsillar infiltration of tramadol (2 mg/kg) improved postoperative pain till 4 h, while our study showed that combination of tramadol with intravenous administration of ketamine (0.5 mg/kg) prolonged analgesic effect from 4 h till 24 h after operation with no significant adverse effects.

Negus and colleagues (14) showed that the combination of oral midazolam and intravenous morphine can cause upper respiratory airway obstruction. In spite of the fact that non-steroidal anti-inflammatory drugs (NSAIDs) have no obstructive effects on airways, but some of them like ibuprofen could increase the risk of postoperative bleeding (15,16). This is of importance that no significant complications following combined use of tramadol and ketamine were observed.

Previous studies have indicated that tramadol has local anesthetic properties (17-20). Kapral and coworkers (19) showed that addition of tramadol to mepivacaine would significantly prolong the duration of both sensory block to pinprick and motor block following axillary block. Demiraran and colleagues (21) demonstrated that wound infiltration with tramadol improved posto-perative pain relief better than bupivacaine after herniotomy in children.

The site of action of tramadol is suggested to be on the nerve endings (19). It was shown that tramadol affects sensory and motor nerve conduction by a mechanism similar to that of lidocaine which acts on voltage-dependent sodium channel for producing axonal block (22). It is also suggested that tramadol might have a different mechanism from that of lidocaine for producing conduction block (23). This additional mechanism is related to the calcium ion concentration in the plasma. The presence of a large Ca^{+2} concentration increased activity of tramadol while decreased the activity of lidocaine. It must be emphasized that peritonsillar tissue is rich of blood vessels and the action of tramadol suggested that is via systemic effect.

A probable disadvantage of the use of local anesthetics in the peritonsillar area is an increase of bleeding. No patients in our study showed the increase in blood loss.

It was shown that the use of small dose of intravenous ketamine (0.5 mg/kg) before or after surgical procedure could reduce the

frequency or even the use of rescue analgesia in pediatric population underwent tonsillectomy (9). It has also been shown that ketamine can act as a potent noncompetitive N-methyl-dimethyl-aspartate receptor (NMDA) antagonist which reduces the rescue analgesic used during postoperative period (24).

Our study showed that the time to first oral intake was shorter in Group III compared with Group IV. Also, parent satisfaction score was better in Group III compared with the other groups. These results can be attributed to the potentiation of the effect of the analgesic combination. The combined use of tramadol and ketamine in our study may involve hyperalgesic activation of the NMDA-receptor-mediated pain pathway (25,26). Blockade of NMDA receptors by ketamine probably attenuated tramadol-induced hyperalgesia and enhanced and prolonged the duration of the antinociceptive activity of the tramadol (27).

The analgesic efficacy of tramadol may be due to the systemic absorption of its peritonsillar infiltration. Thus, we could not conclude if tramadol exerts its analgesic effect totally by systemic absorption. This could have been elucidated if we had measured the plasma concentration of tramadol.

CONCLUSION

In conclusion, intravenous administration of low dose of ketamine (0.5 mg/kg) before surgical incision appears to prolong analgesic efficacy of peritonsillar infiltration of tramadol (2 mg/kg) and to improve oral intake and parent satisfaction in comparison with use of each drug on their own without important side effects in pediatric population undergoing tonsillectomy.

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