Original Article

Preemptive peritonsillar infiltration with bupivacaine in combination with tramadol improves pediatric post-tonsillectomy pain better than using bupivacaine or tramadol alone: A randomized, placebo-controlled, double blind clinical trial

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Abstract

Background: Post-tonsillectomy pain is one of the most common problems after anesthesia, therefore use of a good anesthesia technique with minimum side effect is an important aim. This study was performed to compare the efficacy of peritonsillar infiltration of bupivacaine, tramadol and combination of bupivacaine-tramadol in post-tonsillectomy pain.

Materials and Methods: In a double blind trial 120 ASA I and II children condidated for tonsillectomy were randomized into four groups: Peritonsillar infiltration with bupivacaine 1 mg/kg in Group B, tramadol 2 mg/kg in Group T, combination of bupivacaine-tramadol in Group BT and saline in Group C was done.

Results: Until 60 minutes in the recovery room, control of pain in the first three groups were better than Group C ($P < 0.05$) and in the third group it was better than others. Four hours after surgery, control of pain was better in the second and third groups in comparison to Groups B and Group C ($P < 0.05$) and was better in the third group in comparison to the second group. Then, 24 hours after that, only in the group III the control of pain was effective ($P < 0.05$).

Conclusions: In this study we showed that peritonsillar infiltration with combination of bupivacain-tramadol provided less post surgery pain compared with infiltration of bupivacaine and tramadol alone in adenotonsillectomy of children.

Key Words: Adenotonsillectomy, bupivacaine, children, post surgery pain, tramadol

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INTRODUCTION

The pain after tonsillectomy is a problem that has to be solved.[1]

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Oro-pharynx cavity and tonsils are nerved by trigeminal and glossopharyngeal nerves, which lead to sensory area in cortex of brain.[2] Elective tonsillectomy and adenoidectomy are performed in an out-patient way. So using a suitable analgesic method for reducing pain is very important.[2-5] Different drugs like non-steroid anti-inflammatory drugs, opioids, corticosteroids along with the surgical techniques and topical anesthesia are used to reduce pain.[6] It is observed that reducing post adenoidectomy pain with analgesic drugs have a notable effect on patients.[7] For example, NSAIDs are caused GIB, or Opioids are caused respiratory depression, nausea and vomiting.[7] In some published articles, some kind of complications of topical anesthesia, in deep and high dosage are mentioned. Like paraplegia of vocal cord, deep cervical abscess and brain-stem shock.[8] So using suitable anesthetic method with the least side effects is very important.

Tramadol is a central analgesic that was effective to reduce pain. This drug is a racemic or any kind of enantiomers combination that shows different kinds of properties of opioid receptors, inhibit absorption of monoaminergics.[8,10] Tramadol have methyl group on phenyl that justifies low potency of that in the face of opioid receptors.

At first it was reported that tramadol is selective for m, d and k receptors. But at last it was proved that it is selective only for m receptors. M1 metabolite of tramadol had more desire to opioid receptors in comparison to the injectable form of drug.[7] Previously thought was that tramadol has its affect only in central way but recent studied have shown that we can use it in a topical way.[8,9]

Bupivacaine is used as a topical analgesic widely. In terms of construction it is very similar to lidocain except amine group of butylpyridine.[10] This drug is a suitable combine for long acting anesthesia. Considering that, till now, there was no research on the preemptive effect of bupivacaine and tramadol combination in post-tonsillectomy pain.[17-20] So we performed this study to compare the analgesic effect of peritonsillar infiltration of bupivacaine in combination with tramadol with using bupivacaine or tramadol singly in a placebo controlled study.

MATERIALS AND METHODS

After obtaining institutional approval from Ethic committee of our university and taking written informed consent from the patients, this randomized, double blind placebo controlled study was performed on 120 children with ASA I and II in a age range of 5 to 15 years who were candidate for tonsillectomy with or without adenoidectomy from 21 December 2010 to 21 October 2012 in Kashani hospital.

The other inclusion criteria were patients without acute pharyngeal infection, allergy to bupivacaine or tramadol, acute and active infection of respiratory tract with fever and rhonchi, constant use of sedative or analgesic hypnotic, peritonsillar abscess, renal disease, liver disease, asthma and coagulation disorders. If the technique of anesthesia was changed or there was bleeding during operation which necessitated reoperation, the patient was excluded from the study.

These patients were randomly divided into four groups.

- Group 1 received peritonsillar injection of bupivacaine 0.5% (1 mg/kg) in adrenalin 1:200 000 in a volume of 3 cc with normal saline (N/S)
- Group 2 received peritonsillar infiltration of tramadol 2 mg/kg in a volume of 3 cc in N/S
- Group 3 received peritonsillar infiltration of tramadol 2 mg/kg and bupivacaine 1 mg/kg in adrenalin 1:200 000 in a volume of 3 cc
- Group 4 received peritonsillar infiltration of N/S in a volume of 3 cc.

The randomization was performed with using random-allocation software.

Peritonsillar injection was performed in a fan-wise way from upper pole to lower pole before surgical incision (pre-emptive). Syringes prepared in the same form and volume by person who had no information about study group. Peritonsillar injection also performed by surgeon who was not inform from group allocation. For premedication, midazolam 0.1 mg/kg IV was administered 15 minutes before induction of anesthesia. Routine monitoring were electrocardiography, non-invasive blood pressure, pulse oxymetry and capnography. General anesthesia was induced by using 0.02 mg/kg atropine, 5 mg/kg thiopental and 2 μg/kg fentanyl. Intratracheal intubation was facilitated by 0.5 mg/kg atracurium. $EtCO_2$ was kept between 30 and 40 mmHg. Maintenance of anesthesia was done by isoflurane 1.25% and N_2O 50% in O_2 50%. At the end of the surgery all the anesthetic drugs was discontinued and the patients were extubated after resumption of consciousness and reflexes. The residual neuromuscular block was reversed by 0.05 mg/kg neostigmine and 0.02 mg/kg atropine. After 1 hour if the patient didn't have bleeding, he or she was discharge from the post-anesthesia care

unit (PACU). After arriving to the PACU, the severity of post-tonsillectomy pain was evaluated in 15, 30, and 60 minutes. Evaluation of the pain was continued in 4, 8, 16, and 24 hours by using obtaining pain scale [Table 1]. If the severity of pain was more than 3, the patient was given 15 mg/kg rectal acetaminophen. Level of consciousness was recorded by a 4-stage grading in the mentioned times:

- Open their eyes by their own
- Open their eyes by calling
- Open their eyes by shaking
- Do not open their eyes.

Also, duration of anesthesia (the time from induction of anesthesia till discontinuation of anesthetic drugs), duration of surgery (the time from beginning surgery till ligation of the last suture), extubation time (the time from discontinuation of anesthetic drugs till extubation), heart rate, mean arterial blood pressure, the first time of asking rescue analgesic, the amount of rescue analgesic used, the first time of drinking and eating, nausea, vomiting and needing anti-vomiting drug during the first 24 hours was also recorded. If nausea and vomiting happened, 0.5 mg/kg metoclopramide was administered.

The statistical analysis was done by using SPSS version 16.0 (SPSS Inc., Chicago, IL, USA). The continuous variables were analyzed by using analysis of variance. *Post hoc* analysis was performed by using the Bonferroni test. The Kruskal-Wallis test was used for analysis of difference between four groups with respect to non-parametric variables. If there was a significant difference, the Mann-Whitney U-test was used for analysis of differences between the groups in pairs. The Chi-square test was used for analysis of categorical data. Data were presented as mean ± SD or numbers. A P value less than 0.05 was considered statistically significant.

Table 1: Objective pain scale

Observation criteria	Points
Blood pressure	
±10% of preoperative value	0
>20% of preoperative value	1
>30% of preoperative value	2
Crying	
Not crying	0
Crying, but stop with tender	1
Loving care	-
Crying without stopping, does not	-
Respond to tender, loving care	2
Movement	
None	0
Restless	1
Trashing around	2
Agitation Asleep or calm	0
Mild agitation	1
Hysterical	2
Verbalization asleep or state no pain	0
Of pain state there in pain	
But cannot localize	1
Can localize pain	2

Table 2: Descriptive data of children included in the study

Variables	Group B	Group T	Group BT	Group C	*P* value
Gender					
Male	16	14	13	12	0.759
Female	14	16	17	18	
Age (years)	7.7±3.4	7.2±3.0	7.2±3.2	8.2±4.3	0.658
Weight (kg)	23.5±10.0	25.6±7.4	20.0±7.4	24.2±14.0	0.180
Surgical operation					
Tonsillectomy	12	12	11	11	0.756
Adenoidectomy	13	16	14	12	
Adenotonsillectomy	5	2	5	7	

Data are presented as mean±SD or numbers. No significant difference was noted among four groups (P>0.05). Group B=Received bupivacaine; Group T=Received tramadol; Group BT=Received bupivacaine-tramadol; Group C=Received saline

RESULTS

In this study, 120 children with ASA I and II, in the average age of 5 to 15 years, who were candidate for tonsillectomy with or without adenoidectomy entered and randomly divided into four groups [Figure 1].

From all these patients, 55 (45.8%) were men and 65 (54.2%) were women, there was no significant difference between them according to age and sex (P = 0.759) [Table 2].

In total 46 patients had tonsillectomy (38.3%), 55 patients had adenoidectomy (48.8%) and 19 patients had adenotonsillectomy (15.8%) and there was no meaningful difference between them (P = 0.756) [Table 2].

Mean of age, weight, duration of surgery, duration of anesthesia, duration till awareness, extubation time, duration of recovery room stay, frequency of nausea and vomiting were not significantly different among 4 groups (P > 0.05) [Tables 3-5]. The first time of eating, the first time of asking for additional analgesic had significant difference between four groups (P < 0.05). The dosage of metoclopramide usage was not significantly different among four groups (P > 0.05) [Table 3]. Level of consciousness, diastolic blood pressure, systolic blood pressure, and heart rate at different times were not significantly different between four groups. There was significant difference in severity of pain in different time intervals in four groups (P < 0.05) [Table 4].

Table 3: Comparison of data related with duration of anesthesia and awakening time and other parameters in four study groups

Variables	Group B	Group T	Group BT	Group C	*P* value
Surgical time (min)	62.0±8.6	62.7±7.7	59.7±8.2	60.9±10.2	0.571
Anesthesia time (min)	72.3±8.4	70.4±8.8	71.1±8.7	70.4±12.8	0.824
Awakening time (min)	21.6±6.4	19.6±4.5	21.0±2.6	20.5±6.7	0.534
Extubation time (min)	6.0±3.0	6.0±2.7	4.7±1.9	5.2±3.0	0.133
Recovery time (min)	35.7±10.6	36.1±9.2	33.1±13.4	35.8±11.3	0.715
First time (hours) of drinking and eating	6.6±1.6	6.8±1.7	5.3±1.5*	6.6±1.3	0.001
Metoclopramide dose	0.6±1.5	1.1±2.0	0.5±1.1	0.5±1.0	0.379

Data are presented as mean±SD. No significant difference was noted among four groups (P>0.05). Group B=Received bupivacaine; Group T=Received tramadol; Group BT=Received bupivacaine-tramadol; Group C=Received saline

Table 4: Severity of pain in four groups

Variables	Times of postoperative	Group B	Group T	Group BT	Group C
	0 min	4.3±2.7*	4.3±1.7*	1.0±2.0**	6.0±3.0
	15 min	2.3±2.7*	2.4±1.8*	0.6±1.9**	4.2±2.6
At recovery	30 min	2.1±2.5*	2.0±1.6*	0.4±1.5**	3.7±2.8
	60 min	2.0±2.2*	2.0±1.5*	0.3±1.5**	3.5±2.4
	4 h	2.3±1.9	1.5±1.4*	0.2±1.0**	2.9±2.0
At ward	8 h	1.8±1.8	1.8±1.3	0.2±1.0**	1.8±2.0
	16 h	1.2±1.5	1.4±1.2	0.1±1.0**	2.0±2.0
	24 h	1.5±1.2	1.5±1.0	0.1±0.4**	1.9±1.5

Data are presented as mean±SD. Group B=Received bupivacaine; Group T=Received tramadol; Group BT=Received bupivacaine-tramadol; Group C=Received saline. *P<0.05 *vs.* Group C; **P<0.05 *vs.* Group B, Group T and Group C

Table 5: Postoperative complication in four groups

Variables	PONV	Group B	Group T	Group BT	Group C	*P* value
Vomiting	Yes	5	8	6	6	0.811
	No	25	22	24	24	
Nausea	Yes	5	6	6	4	0.888
	No	15	24	24	26	

Data are presented as numbers. No significant difference was noted among four groups (P>0.05). Group B=Received bupivacaine; Group T=Received tramadol; Group BT=Received bupivacaine-tramadol; Group C=Received saline. PONV=Postoperative nausea and vomiting

Until 60 minutes in the recovery room, control of pain in the first three groups were better than Group C ($P < 0.05$) and in the third group was better than others. Four hours after surgery, control of pain was better in the second and third group in comparison to Groups B and Group C ($P < 0.05$) and was better in third group in comparison to second group. Till 24 hours after that, only in the group III the control of pain was effective ($P < 0.05$) [Table 4].

DISCUSSION

In this study we compared the pre-emptive effect of bupivacaine and tramadol on post adeno-tonsillectomy. Our results showed that combination of bupivacaine and tramadol had better effect on pain in comparison to either alone. This is while the side effects like nausea, vomiting, respiratory tract obstruction had no significant difference.

Tramadol is a central analgesic that was effective to reduce pain. This drug is a racemic or any kind of enantiomers combination that shows different kinds of properties of opioid receptors, inhibit absorption of monoaminergics.[8] Tramadol have methyl group on phenyl that justify low potency of that in the face of opioid receptors.[10]

Ugar *et al.*[11] showed that peritonsillar infiltration of tramadol had better pain-reducing effect in comparison to intramuscular tramadol within the first hour after surgery.

Another study was done by Moghadam *et al.*[12] that showed that peritonsillar infiltration of bupivacaine significantly reduced postoperative pain till 4 hours.

Gosh *et al.*[13] showed that peritonsillar injection of tramadol had better effect on reduction of postoperative pain.

Atef *et al.*[14] showed that submucosal infiltration of tramadol 2 mg/kg before extubation significantly reduced postoperative pain. Their conclusion was similar to Akkaya *et al.* study.[15] Akkaya study showed that in all patients who were under adenotonsillectomy surgery, peritonsillar infiltration of tramadol maintains efficient pain relief and lower incidence of nausea and vomiting.

In total, different studies showed reduction of pain by infiltration of bupivacaine after surgery for more than 10 days.[13,14] But some studies, did not confirm this.[15,16] According to different kinds of complications of topical peritonsillar anesthesia, we decided to have two kinds of topical anesthesia.

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At first it was reported that tramadol is selective for m, d and k receptors. But at last it was proved that it is selective only for m receptors. M1 metabolite of tramadol had more desire to opioid receptors in comparison to the injectable form of drug.[7] It was previously thought that tramadol has its affect only

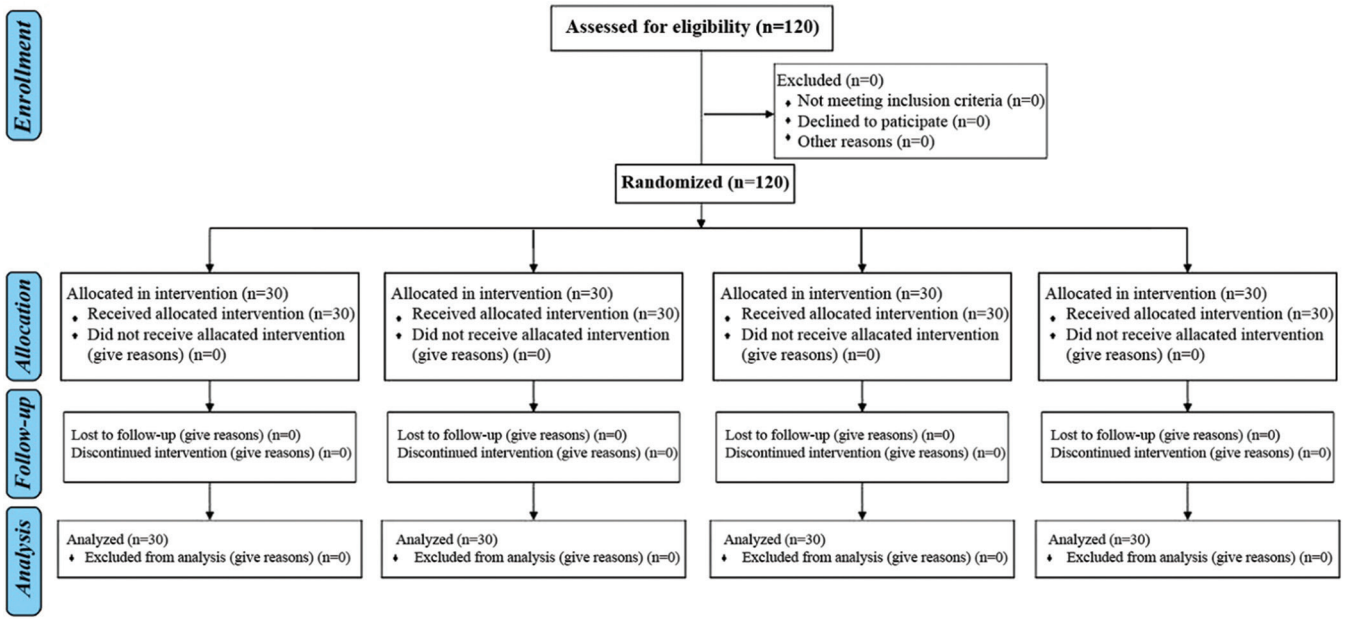

Figure 1: Study flowchart

in a central way but recent studied have shown that we can use it in a topical way.[8,9]

Bupivacaine is used as a topical analgesic widely. In terms of construction it is very similar to lidocain except amine group of butylpyridine. This drug is a suitable combine for long acting anesthesia. Considering that, till now, there was no research on the pre-emptive effect of bupivacaine and tramadol combination in post-tonsillectomy pain.[17-20] So we performed this study to compare the analgesic effect of peritonsillar infiltration of bupivacaine in combination with tramadol with using bupivacaine or tramadol singly in a placebo controlled study.

In this study, we concluded that a combination of peritonsillar injection of bupivacaine and tramadol has better effect in comparison to each of them individually. The only limitation of this study was not measuring the plasmatic level of drugs.

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