IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 15, Issue 11 Ver. IV (November. 2016), PP 94-100
www.iosrjournals.org

Analgesic Efficacy of Topical Tramadol in the Control of Postoperative Pain in Children after Tonsillectomy: A Double Blind, Prospective, Randomized, Controlled Study

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Abstract:
Background: *Adequate postoperative analgesia following tonsillectomy in children is still a challenge. Recently the use of topical analgesia at tonsillectomy site is being developed as a modality of analgesia. Survey across the literature gives a very sparse data regarding efficacy of topical tramadol application. Hence we conducted this study to evaluate the effects of topical tramadol on postoperative pain in children undergoing tonsillectomy*
Methods: *A double blind, prospective, randomised, controlled clinical trial was conducted in 56 children between 4 and 12 years scheduled for elective tonsillectomy or adenotonsillectomy, who were randomized into two groups. Group T received swabs soaked in tramadol 2 mg/kg diluted in 10 ml saline and Group C swabs soaked in saline 10 ml, which were applied for 5 min in the tonsillar fossa after tonsillectomy. All patients received oral paracetamol (20 mg/kg) in form of pediatric suspensions/tablets at 6 hrs postoperatively, repeated every 6 hrly for 3 days. Injection diclofenac 1.5mg/kg infusion was given as rescue analgesic. Postoperative pain(FLACC score Face, Legs, Activity, Cry, Consolability), rescue analgesic requirement and other complaints like fever, nausea, vomiting, otalgia were noted on the 1^{st} , 4^{th} , 12^{th} , 18^{th} , 24^{th} , 48^{th} hrs , 3^{rd} day, 4^{th} day and 7^{th} day postoperatively.*
Results: *Postoperative pain scores were significantly low in the tramadol group(Group T) as compared to the control group (Group C) at the 4^{th} , 12^{th} , 18^{th} , 24^{th} and 48^{th} hr postoperatively ($P<0.001$). Pain scores were comparable in the rest of the hours and days $P>0.05$. The difference in rescue analgesic requirement was highly significant, $P<0.001$. The total number of doses of rescue analgesic received in the first 48 hrs postoperatively was significantly higher in Group T (56) as compared to Group C (12), $P<0.001$.*
Conclusions: *Topical tramadol application is a simple, safe, economic and effective modality for analgesia in children undergoing tonsillectomy. It significantly reduced pain scores as well as rescue analgesic consumption postoperatively.*
Keywords: *Tonsillectomy, analgesia, rescue, topical tramadol.*

I. Introduction

Of all the ENT surgeries performed in children, tonsillectomy/adenotonsillectomy is the commonest surgery. Significant pain associated with tonsillectomy is reported in 20-50% of children undergoing tonsillectomy[1]. Pain can be devastating to the child, affecting its nutrition, longer hospital stay, longer duration of abstinence from school. Despite the use of various surgical techniques adequate postoperative analgesia is still a challenge[2]. Systemic analgesics and opioids though frequently used may have undesired side effects like respiratory depression can be hazardous after tonsillectomy. These adverse effects justify investigators to develop alternate strategies for analgesia.

Topical approaches have the advantage of local pain control with minimal systemic side effects and good patient acceptability. Local anaesthetics, anti-inflammatory agents and opioids are given in solution form by rinsing the oral cavity for oropharyngeal pain control[3].

Tramadol is formulated as a racemic mixture with enantiomer having different opioid receptor binding properties, monoaminergic reuptake inhibition and metabolic pathways. Mechanism of action of topical tramadol is similar to that of hydrophillic local anesthetics[4]. Tramadol exerts its sensory blocking action by a mechanism similar to that of local anesthetics in the form of blocking voltage dependent sodium channels[5] and potassium channels[6]

Studies have been carried out in which topical swab application of local anaesthetics (bupivacaine[7], levobupivacaine[8], ropivacaine[9]) have been applied. Similarly lidocaine, ketamine and morphine in the form of spray at tonsillar fossa were found effective for postoperative analgesia[10]. However there is scarcity of data which establish the efficacy of topical tramadol[3] application for postoperative analgesia.

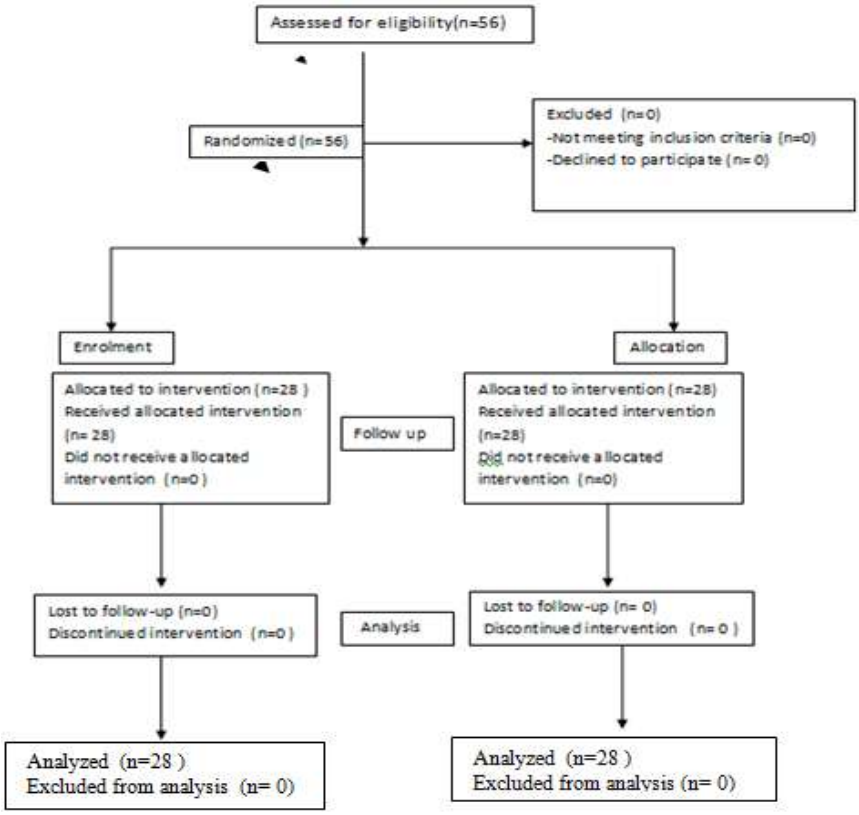
Therefore we carried out present study to test the hypothesis whether topical application of tramadol at the tonsillectomy site after completion of surgery could reduce postoperative pain.

II. Materials And Methods

A double blind, prospective, randomised, controlled clinical trial was designed and approved by the faculty of ethics committee. Informed written consent from parents of 56 children aged between 4 and 12 years, ASA I–II, of both sexes, suffering from recurrent tonsillitis, chronic tonsillitis, tonsillo-adenoid syndrome, scheduled for elective tonsillectomy or adenotonsillectomy were randomised by opaque sealed envelope technique into two groups, Group T(Tramadol) and Group C(Control) with 28 patients in each group(Consort flow diagram)

Consort flow diagram

Pain was assessed by FLACC[11] (Face, Legs, Activity, Cry, Consolability) scale, which uses five components to assess pain. Minimum score is 0 and maximum score is 10. Score of >4 indicates pain. Reduction of FLACC score in the trial group from 8 to <4 would be expected. To obtain a result that is statistically significant with a power of 80% and an α error of <0.05, a total of 56 subjects were required in 2 groups (28 in each). Primary outcome of the study was pain score. Secondary outcomes were rescue analgesic consumption and postoperative complaints.



Flacc Behavioral Scale[11]

CATEGORIES	FLACC SCORING		
	0	**1**	**2**
Face	No particular expression or smile	Occasional grimace or frown,withdrawn,disinterested.	Frequent to constant frown, clenched chin
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 cry (awake or asleep)	Moans or whimpers occasional complaint	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
How to use the FLACC; **In patients who are awake:** observe for 1 to 5 minutes or longer. Observe legs and body uncovered. Reposition patient or observe activity. Assess body for tenseness and tone. Initiate consoling interventions if needed.			
In patients who are asleep: observe for 5 minutes or longer. Observe body and legs uncovered. If possible, reposition the patient. Touch the body and assess for tenseness and tone			

All surgeries were performed by the same surgeon who was blind to the study drugs used. Patients with a known history of allergy, sensitivity, or contra-indication to opioids or local anesthetic, renal or liver impairment, acute pharyngeal infection, a history of asthma, or clotting disorder were excluded.

After thorough pre-anesthetic evaluation and appropriate fasting according to age, all patients were given oral midazolam 0.5 mg/kg (preservative free midazolam hydrocloride syrup 2mg/ml; Ranbaxy Pharmaceutical Inc.) 10 minutes before intravenous cannulation.

Routine monitoring (ECG, noninvasive blood pressure, pulse rate, oxygen saturation and temperature) was used. Patient was premedicated with glycopyrrolate (0.01mg/kg), tramadol (2mg/kg), ondansetron (0.1mg/kg) given intravenously. After induction with intravenous propofol 2 mg/kg and atracurium 0.5 mg/ kg, patient was intubated with an appropriate sized, cuffed/uncuffed, naso-tracheal tube under direct laryngoscopy using magill forceps. Anesthesia was maintained with O_2 and N_2O (50:50 ratio), propofol 2 mg/kg/h and atracurium 0.1mg/kg intermittently.

After tonsillectomy but before reversal, swabs soaked in tramadol 2 mg/kg diluted in 10 ml saline (Group T) or saline 10 ml (Group C) were applied in tonsillar fossa for 5 min. Then patient was reversed using Inj. neostigmine 0.08 mg/kg and Inj. glycopyrrolate 0.02 mg/kg IV. The trachea was extubated after proper oropharyngeal suctioning, removal of tonsillar swabs and adequate reversal of muscle power.

The time of application of topical swabs at tonsillar site at the end of surgery was considered as 0 hrs. Data related to postoperative analgesia were recorded referring to this time of 0 hrs. Along with pain, other postoperative complaints like fever, nausea, vomiting, otalgia, pain were noted at 1^{st} , 4^{th} , 12^{th} , 18^{th} , 24^{th} , 48^{th} hrs , 3^{rd} day, 4^{th} day and 7^{th} day postoperatively and treated accordingly.

Injection diclofenac (1.5mg/kg) diluted in 50 ml saline, infusion over 15 min was given as a rescue analgesic, when the patient complaints of pain or FLACC >4 or both, any time after surgery within the first 48 hrs with a minimum duration of 6 hours between each dose.

All patients received oral paracetamol (20 mg/kg) and amoxicillin (45 mg/kg) in form of pediatric suspensions/tablets at 6 hrs postoperatively which was repeated every 6 hourly. Amoxicillin was given for 5 days and paracetamol for 3 days as a routine clinical protocol in our setup.

Data were entered and analysed with the help of MS Excel, EPi info 6 and SPSS 12.0. Qualitative or categorical data like patient distribution according to sex, age, airway assessment, indication for surgery, type of surgery performed, FLACC score, rescue analgesic requirement, post-operative complaints and complications were presented as number (proportion) and compared with Chi-square test. Quantitative or continuous variables like age, weight, duration from induction to placement of swabs were presented as mean ± SD and compared using student 't' test. A post hoc test was used to assess intergroup differences, $P<0.05$ was considered as statistically significant.

III. Results

There was no statistically significant differences between age, gender, body weight, surgeries performed and duration from induction to placement of swabs($P>0.05$) (Table 1).

Postoperative pain, as assessed by FLACC was lower at all time intervals in Group T as compared to Group C. The reduction in FLACC score reached a statistical significance at 4^{th}, 12^{th}, 18^{th}, 24^{th} & 48^{th} hrs($P<0.001$). There was no significant difference in postoperative pain in two groups at 1^{st} hr and after 48 hrs (i.e. at 3^{rd}, 4^{th}, 7^{th} day)($P>0.05$)(Table 2).

The total number of doses of rescue analgesic was significantly higher in Group T (56) as compared to Group C (12), P=0.0005.

During first 12 hrs postoperatively, only 4(14.29%) patients of Group T required rescue analgesic (1 dose) as compared to 25(89.29%) patients of Group C [16(57.14%) -1dose, 9(32.14%)- 2 dose], the difference was highly significant, P=0.0004. Thus number of rescue analgesic doses required during first 12 hrs postoperatively was significantly higher in Group C (34 doses) as compared to Group T (4 doses), P=0.0003.

During 12-24 hrs postoperatively, significantly higher number of patients of Group C (75%, n=21) required rescue analgesic as compared to only 5(17.86%) patients in Group T, P=0.0003. However, patients of both groups required only 1 dose. Rescue analgesic requirement during 12-24 hrs postoperatively was significantly higher in Group T(21) as compared to Group C(5) P=0.0004. During 24-48 hrs postoperatively rescue analgesic was required by 3(10.72%) patients of Group T and 1(3.57%) patients of Group C, which was statistically comparable, P=0.067.

When overall rescue analgesic requirement was observed during first 48 hrs postoperatively, it was found that only 11(39.29%) patients of Group T[10(35.71%) - 1 dose; 1(3.57%) – 2 doses] required rescue analgesic as compared to all 28(100%) patients in Group C[6(21.42%) – 1 dose; 16(57.14%) – 2 doses; 6(21.42%) – 3 doses]. The difference was highly significant, P=0.0005. (Table 3).

Incidence of other postoperative complaints like nausea, vomiting, fever, otalgia and post-tonsillectomy bleeding (requiring re-exploration) were statistically comparable during 7 days in two groups, P>0.05 (Table 4).

Table-1 Distribution of patients according to demographic parameters

	Group T (n=28)	**Group C (n=28)**	**P-value**
Age (yrs)	7.78±2.09	9.21±2.33	0.122(NS)
Sex (M/F)	19/9	15/13	0.67(NS)
Body weight(Kgs)	14.03±5.22	15.14±5.55	0.82(NS)
Surgery (Adenotonsillectomy/ Tonsillectomy)	17/11	14/14	0.74(NS)
Duration from induction to placement of swabs(mins)	40.17±10.84	39.82±10.84	0.122(NS)

NS - Not Significant

Table 2 Comparison of post-operative pain as assessed by Face, Leg, Activity, Cry, Consolability (FLACC) score

Time interval	**FLACC**	**Group T**	**Group C**	**P-value**
1st hr	**Mean±SD**	0.21±0.62	0.21±0.38	0.142
	Range	0-2	0-2	(NS)
4th hr	**Mean±SD**	1.21±0.73	2.82±2.11	**0.0004**
	Range	0-3	1-6	**(HS)**
12th hr	**Mean±SD**	1.39±1.19	4.54±0.92	**0.0008**
	Range	0-6	2-6	**(HS)**
18th hr	**Mean±SD**	1.36±1.37	4.54±0.92	**0.0006**
	Range	0-4	1-6	**(HS)**
24th hr	**Mean±SD**	1.29±1.21	4.39±1.23	**0.0004**
	Range	0-4	3-6	**(HS)**
48th hr	**Mean±SD**	0.68±0.82	4.29±0.85	**0.0003**
	Range	0-3	1-4	**(HS)**
3rd day	**Mean±SD**	0.89±0.69	1.29±1.58	0.122
	Range	0-2	0-4	(NS)
4th day	**Mean±SD**	0.54±0.74	1.14±1.11	0.132
	Range	0-2	0-4	(NS)
7th day	**Mean±SD**	0.14±0.39	0.18±0.52	0.134
	Range	0-1	0-4	(NS)

NS - Not Significant; HS – Highly Significant

Table 3: Comparison of rescue analgesic requirements at various time intervals during first 48 hours postoperatively in the two groups

Time interval	**Number of doses**	**Number of patients**		**P-value**
		Group T (n=28)	**Group C (n=28)**	
0-12 hrs	No. of patients requiring rescue	4(14.29%)	25(89.29%)	**0.0004 HS**
	Patient distribution according to no. of doses	4(14.29%)	16(57.14%)	
	1 dose			
	2 doses	0(0.00%)	9(32.14%)	
	Total doses of rescue analgesic	4	34	**0.0003 HS**
>12-24 hrs	No. of patients requiring rescue analgesic	5(17.86%)	21(75%)	**0.0004 HS**
	Patient distribution according to no. of doses			**0.0003**
	1 dose	5(17.86%)	21(75%)	**HS**
	2 doses	0(0.00%)	0(0.00%)	
	Total doses of rescue analgesic	5	21	**0.0004 HS**
>24-48 hrs	No. of patients requiring rescue	3(10.72%)	1(3.57%)	
	Patient distribution according to no. of doses			
	1 dose	3(10.72%)	1(3.57%)	
	2 doses	0(0.00%)	0(0.00%)	
	Total doses of rescue analgesic	3	1	0.067 NS
0-48 hrs	No. of patients requiring rescue analgesic	11(39.29%)	28(100%)	**0.032 S**

	Patient distribution according to no. of doses			
	1 dose	10(35.71%)	6(21.42%)	
	2 doses	1(3.57%)	16(57.14%)	
	3 doses	0(0.00%)	6(21.42%)	
	Total doses of rescue Analgesic	12	56	**0.0005 HS**

Table 4 Comparison of Post-operative complaints in both the groups

Complaints	**1st day**		**2nd day**		**3rd day**		**4th day**		**7th day**	
	Group		**Group**		**Group**		**Group**		**Group**	
	T	**C**	**T**	**C**	**T**	**C**	**T**	**C**	**T**	**C**
Nausea	8	5	0	0	0	0	2	2	0	0
Vomiting	7	9	2	2	0	0	0	0	0	0
Fever	3	4	3	1	0	1	0	0	0	0
Otalgia	2	2	2	3	1	1	1	0	0	0
Post-tonsillectomy bleeding	1	1	0	0	0	0	0	0	0	0

IV. Discussion

Pain after tonsillectomy is a very agonising and an unpleasant experience for both, patients as well as the parents in the perioperative period. Throat pain, referred otalgia and bleeding after tonsillectomy contribute to making recuperation prolonged. It is thus necessary to provide adequate analgesia, to relieve the agony of pain and reduce incidence of bleeding since increased vascular congestion of head and neck associated with crying may precipitate bleeding.

The oropharynx and the tonsillar fossae are exquisitely sensitive. They are well innervated locally by the branches of the trigeminal and glossopharyngeal nerves and are highly represented in the somatic cerebral cortex.[12] During surgery, pain impulses entering the central nervous system, creates a hyperexcitable state inspite of general anaesthesia. Blockage of these impulses by preoperative analgesic drugs, infiltration or topical administration of various groups of drugs have preemptive analgesic effect.

Many treatment modalities for post-tonsillectomy pain have been used, ranging from systemic opioids to different surgical techniques, even radiation.[13]

Several investigators have evaluated the effect of pre-incisional and postoperative injection of local anaesthetics at tonsillar site, on postoperative pain following tonsillectomy [14,15]. With regards to the results of the cited studies, there exist three different ways of applying the local anaesthetics: pre-incisional peritonsillar infiltration [16,17] post-tonsillectomy wound infiltration [18,19] post-tonsillectomy packing with soaked local anaesthetic gauze [7]

At present it is not clear which application method is the most effective, because of the wide range of results, i.e., from "no difference"[18] to "highly significant difference".[16] A systematic review of the literature by the Cochrane Institute could not verify any evidence that the use of perioperative local anaesthetic in patients undergoing tonsillectomy improves postoperative pain control. [15]

Topical application of drugs in the tonsillar fossae for postoperative analgesia after tonsillectomy has been evaluated previously using bupivacaine,[7] levobupivacaine[8] and ropivacaine.[9]

Oghan F[9] et al (2008) used 1% ropivacaine hydrochloride soaked swabs packed in tonsillar fossae in the test group and the control group received saline-soaked swabs. Mc-Grath's face scale was used to compare the two groups in respect of pain control. Kadar A A[7] et al (2003) used gauze soaked in 2ml of 0.5 % bupivacaine solution and kept in the tonsillar fossae in situ for five minutes after tonsillectomy in the right tonsillar fossae (subject fossae). The left fossae (control fossae) were packed with the similar tonsillar swab soaked in 0.9% normal saline. The main outcome measure was severity of pain by using visual analogue score. There was significant difference between subject and control fossae scores at all the stages up to discharge of patients, showing better pain relief with bupivacaine $P<0.05$. Only at first hour there was no significant pain-relieving effect seen in ropivacaine group ($P>0.05$). The other hours and days there were statistically significance between the two groups ($P<0.001$).

In our study postoperative pain scores were significantly low in the tramadol group(Group T) as compared to the control group (Group C) at the 4^{th} , 12^{th} , 18^{th} , 24^{th} and 48^{th} hr postoperatively ($P<0.001$). Pain scores were comparable in the rest of the hours and days, $P>0.05$. The difference in rescue analgesic requirement was highly significant, $P<0.001$.The total number of doses of rescue analgesic was significantly higher in Group T (56 doses) as compared to Group C (12 doses), $P<0.001$. This pattern of delayed and longer duration analgesic effect might probably be because of topical administration to the tonsillar fossa and dilution of tramadol[3].

Akbay et al[3] (2010) used swabs soaked in 2mg/kg tramadol diluted in 10ml saline and applied to both tonsillar fossae for 5 min (Tramadol group) and compared it with swabs soaked in 10 ml saline (saline group). McGrath's face scale (happy–sad nine-face scale) was used for pain assessment. Pain scores were found to be significantly lower at the 21st hour and on postoperative day seven in the tramadol group compared with the control group ($P < 0.05$). Mean daily pain scores ranged from Day 1: 0.34 ± 0.21 to Day 7: 0.11 ± 0.08 in the tramadol group and Day 1: 0.53 ± 0.14 to Day 7: 0.42 ± 0.15 in the control group.

Ugar M B[20] et al compared infiltration anesthesia with tramadol (2 mg/kg) to the peritonsillar area (INF group), intramuscular analgesia with tramadol (2 mg/kg) (IM group), and the placebo controls (PL group). Visual analog scale (VAS) scores for pain was used. VAS scores on awakening were significantly better in INF than PL group ($P = 0.015$). The difference between IM and PL groups was not significant. Number of children that required analgesics was significantly more in the PL group compared to the INF group($P = 0.005$), whereas the difference between PL and IM groups was not statistically significant. They found efficacy of infiltrated tramadol was better than same dose of tramadol given intramuscularly.

Jou et al[21] reported that tramadol affects sensory and motor nerve conduction by a similar mechanism to that of lidocaine, which acts on the voltage-dependent sodium channel leading to axonal blockage. Mert et al[22] proposed that tramadol might have a mechanism different from that of lidocaine for producing conduction blocks; the presence of a large calcium concentration increases tramadol's activity, whereas it reduces lidocaine's activity. Pang et al[23] suggested a sensory block to pinprick, touch, and cold at the intradermic injection site of 5% tramadol similar to 1% lidocaine. Altunkaya[24] investigated local anesthetic effects of tramadol with prilocaine in sixty patients undergoing excision of cutaneous lesions. They suggested that tramadol has a local anesthetic effect similar to 2% prilocaine when used intradermally. They showed that 5% tramadol may be a good choice for minor surgery, because of its sufficient local anesthetic and analgesic effects. In another study they investigated the efficacy of tramadol for relieving postoperative pain in minor surgery (lipoma excision and scar revision). They found the time span before taking first analgesic medication was longer for the tramadol group than for the lidocaine group.[25]

Postoperative complaints effects like nausea, vomiting, fever, otalgia and post-tonsillectomy bleeding were noted in our study, with a minimal incidence which was comparable in the two groups.

We conclude that topical application of 5% tramadol (2 mg/kg diluted in 10 ml saline) for 5 min after tonsillectomy in the tonsillar bed is an effective method of reducing postoperative pain in children undergoing tonsillectomy/adenotonsillectomy, resulting in significant reduction in rescue analgesic requirement. It's a simple, safe, economic and effective modality for analgesia in children undergoing tonsillectomy. We further recommend to evaluate tramadol in various concentrations and routes for its efficacy in tonsillectomies.

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