Original Article

Evaluation of the Effects of Peritonsillar Infiltration of Tramadol–Ketamine Combination Versus Tramadol Alone on Posttonsillectomy Pain in Children

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Abstract

Introduction: Tonsillectomy is associated with significant pain and post-operative pain control is often unsatisfactory. This study sought to evaluate the effect of peritonsillar infiltration of tramadol–ketamine combination, tramadol alone and ketamine alone on post-tonsillectomy pain in children. **Patients and Methods:** A randomized double-blinded interventional study involving 90 patients aged 3-15 years of American society of anesthesiologists I or II physical status scheduled for elective adenoidectomy, tonsillectomy or adenotonsillectomy at JUTH was conducted. Patients were randomized into one of three groups: group I received tramadol 2mg/kg, group II received ketamine 1mg/kg plus tramadol 2mg/kg and group III received ketamine 1mg/kg only all made up to 2mls with normal saline and 1ml given per tonsillar bed. All patients had standard general anaesthesia with endotracheal intubation and monitoring. Data was analyzed using Epi-info version 7.1.5 with p £ 0.05. **Result:** The analysis of data showed that the mean ages of the participants in group I, II and III were 5.70±2.00, 5.69±3.22 and 4.47±2.01 years respectively (p-value=0.091). Group II had significantly lower pain scores, longer time to first request of analgesia, earlier oral intake and discharge from the hospital compared to the group that received either tramadol or ketamine alone. Minimal side effects were noted across all the groups in the study. **Conclusion:** Peri-tonsillar infiltration of tramadol-ketamine combination immediately after tonsillectomy (but before extubation of patients) significantly decreased post-tonsillectomy pain without increasing the incidence of side effects compared to tramadol or ketamine alone in children undergoing adenotonsillectomy.

Keywords: *Adenotonsillectomy, tramadol, ketamine, postoperative pain, peritonsillar infiltration*

Introduction

Tonsillectomy is associated with significant pain, and postoperative pain control is often unsatisfactory.[1] The pain following tonsillectomy is typically prolonged, relatively constant, and rated as moderate-to-severe in intensity.[2] Inadequate pain control leads to decreased oral intake, which results in dehydration, readmission for pain control, extended hospital stays, and increased cost, and the continued pathologic responses to pain may lead to chronic pain in adulthood.[3] Managing acute postoperative pain is a major challenge for practitioners, given that more than 80% of patients report pain after surgery, and 75% report the pain as moderate, severe, or even extreme.[4] Ketamine and tramadol have been found to have local anesthetic properties.[5,6] Ketamine acts peripherally by blocking sodium and potassium currents in peripheral nerves[7]; whereas nerve conduction effects of opioids have also been demonstrated in both clinical and animal studies.[6] This study sought to evaluate the effect of peritonsillar infiltration of tramadol–ketamine combination, tramadol alone, and ketamine alone on posttonsillectomy pain in children.

Materials and Methods

This study was a prospective, randomized double-blinded interventional study carried out in the Modular Theatre of the Jos University Teaching Hospital, Jos, Plateau State, North Central Nigeria. Inclusion criteria included children 3–15 years old, with an American society of anesthesiologists physical status of I or II and whose surgery will be completed within 1 h. Children excluded from this study were those with hepatic or renal disease, asthmatics, hypersensitivity to study drugs,

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or those with respiratory tract infection. Sample size was calculated from the formula for comparison of means in experimental study designs.[8]

$$n = \frac{2(Z_{\alpha}+Z_{\beta})^2 (s1^2+s2^2)}{(\mu\ 1-\mu\ 2)^2}$$

Where, n = minimum sample size per group, Z_{α} = point of normal distribution corresponding to a significance level of 95%, which has a value of 1.96, Z_{β} = point of normal distribution power of 90%, which has a value of 1.28, s1 = standard deviation of outcome variable from a similar study, s2 = standard deviation of outcome variable in control group, and µ1–µ2 = mean difference. Substituting the standard deviation and mean difference from a previous study[9] and an attrition rate of 25% as reported by Idoko *et al*.[10] gives a sample size of 30 per group and a total sample size of 90 children.

Randomization via allocation concealment into groups I, II, and III was employed to assign the patients to study groups. Group I received peritonsilar infiltration of tramadol 2 mg/kg made up to 2 mL with normal saline, Group II received infiltration of ketamine 1 mg/kg plus tramadol 2 mg/kg made up to 2 mL with normal saline, and Group III received peritonsillar injection of ketamine 1 mg/kg alone made up to 2 mL with saline. Those whose calculated drug dose of more than 2 mL were still given 2 mL to ensure uniformity across all the groups in the study in keeping with similar studies.[11-13] The investigator reviewed all the patients preoperatively in the ward a day before the procedure to ascertain fitness for surgery after which demographic characteristics were taken preceded by obtaining informed verbal and written consent from parents or guardians.

On the day of surgery, all patients had standard general anesthesia with endotracheal intubation. Analgesia was achieved with intravenous paracetamol 15 mg/kg and fentanyl 1.5 mcg/kg. All the surgical procedures were performed using the same blunt dissection technique (Boyle-Davis technique). During the procedure and period of anesthesia, hemodynamic parameters were monitored every 5 min, and analgesic drugs administered were also documented. The anesthetic assistant drew the research drugs into appropriate syringes such that the investigator was not aware of what he was injecting into the peritonsillar fossa. At the completion of the surgery, haemostasis was secured using bipolar diathermy and their airway was suctioned. Peritonsillar infiltration of study drugs was carried out in accordance with the randomly assigned group of the patient. The tonsillar bed and peritonsillar tissues on both sides were infiltrated by the investigator in collaboration with the ENT surgeon using the fanwise injection from superior to inferior poles of the fossa. All patients were extubated awake in the lateral position, airway suctioning of secretions was done, and patients were transferred to the recovery room in the tonsillar position.

In the recovery room, oxygen was administered by simple face mask at 2–3 L/min. Assessment of vital signs at the time of admission (oxygen saturation, non-invasive blood pressure, and pulse rate) and then every 5 min until discharge from the postanesthesia care unit to the ward was carried out. These were used to deduce the postanesthesia recovery score at each level of the monitoring using the modified Aldrete's scoring system.[13]

The research assistant assessed pain using the faces rating scale when the patients were fully awake for those within the ages of 3–7 years and numerical rating scale for children 8 years old and above. This was done every 10 min for the first hour and then every 2 h for the next 12 h. The pain assessment continued in the ward 2 hourly for a period of 12 h postoperatively. Rescue analgesia with intravenous tramadol 1 mg/kg and paracetamol 10 mg/kg was used for patients with pain score of at least 4 using both scales. The time to first analgesic, commencement of oral intake, and discharge from the hospital and total analgesic administration over a 24-h period were recorded. The data collected were entered and analyzed using Epi-info version 7.1.5 (CDC, Atlanta, Georgia, 2018). Data were presented as tables and charts as appropriate. *P*-value of 0.05 or less was considered statistically significant. Ethical clearance

Table 1: Demographic characteristics of study participants

Variable	Group I	Group II	Group III	Statistics		
Age in years (mean ± SD)				ANOVA		*P*-value
	5.70 ± 2.00	5.69 ± 3.22	4.47 ± 2.02	2.465		0.091
Age category (number/percent)					χ^2	*P*-value
≤7 years	20 (66.7)	23 (76.7)	25 (83.3)	68 (75.6)	2.286	0.319
≥8 years	10 (33.3)	7 (23.3)	5 (16.7)	22 (24.4)		
Sex (number/percent)					χ^2	*P*-value
Male	21 (70.0)	26 (86.7)	22 (73.3)	69 (76.7)	2.609	0.271
Female	9 (30.0)	4 (13.3)	8 (26.7)	21 (23.3)		
BMI category (number/percent)					F-test	*P*-value
Underweight (<18.0)	30 (100.0)	27 (90.0)	29 (96.7)	86 (95.6)	3.025	0.318
Normal (18.0–24.9)	0 (0.0)	3 (10.0)	1 (3.3)	4 (4.4)		

ANOVA: analysis of variance, SD: standard deviation

Table 2: Comparison of postoperative median pain score (Wong-Baker Scale) among children aged 7 years and below

Time period	Study groups			Kruskal–Wallis	*P*-value
	Group I	Group II	Group III		
	Median (range)	Median (range)	Median (range)		
Baseline	0 (0–0)	0 (0.0)	0 (0.0)	0.000	1.000
10 min	0 (0–0)	0 (0–0)	0 (0 - 0)	0.000	1.000
20 min	0 (0–0)	0 (0–2)	0 (0–2)	6.199	0.045*
30 min	0 (0–2)	0 (0–2)	2 (0–2)	24.906	0.001*
40 min	0 (0–3)	1 (0–4)	2 (1–4)	24.514	0.001*
60 min	2 (1–4)	1 (0–4)	3 (1–4)	10.767	0.005*
2 h	3 (2–6)	2 (1–4)	4 (3–9)	30.278	0.001*
4 h	6 (5–8)	4 (2–5)	5(0–10)	16.502	0.001*
6 h	0 (0–4)	7 (4–9)	2 (0–6)	47.752	0.001*
8 h	0 (0–8)	0 (0–9)	2 (0–8)	10.170	0.006*
10 h	0 (0–2)	0 (0–2)	0 (0–6)	14.389	0.001*
12 h	0 (0–2)	0 (0–1)	0 (0–5)	8.664	0.013*

*Statistically significant

Table 3: Comparison of postoperative median pain score (numerical rating scale) among children aged 8 years and above

Time period	Study groups			Kruskal–Wallis	*P*-value
	Group I	Group II	Group III		
	Median (range)	Median (range)	Median (range)		
Baseline	0 (0–0)	0 (0.0)	0 (0.0)	0.000	1.000
10 min	0 (0–0)	0 (0–0)	0 (0–0)	0.000	1.000
20 min	0 (0–2)	0 (0–1)	0 (0–0)	2.104	0.349
30 min	0 (0–1)	0 (0–2)	1 (0–2)	2.188	0.335
40 min	1.5 (1–2)	1 (0–3)	2 (0–3)	2.007	0.367
60 min	1.5 (1–4)	1 (0–2)	3 (0–4)	3.781	0.151
2 h	3.5 (1–4)	2 (2–3)	7 (2–8)	7.826	0.020*
4 h	7 (5–9)	5 (2–7)	0 (0–7)	10.734	0.005*
6 h	0 (0–0)	5 (0–10)	0 (0–2)	14.698	0.001*
8 h	0 (0–0)	0 (0–3)	0 (0–2)	3.071	0.215
10 h	0 (0–0)	0 (0–3)	0 (0–2)	4.812	0.090
12 h	0 (0–0)	2 (0–3)	1 (0–2)	11.352	0.003*

*Statistically significant

Table 4: Comparison of mean time to first analgesia and mean time to commencement of oral liquid intake

Variable	Study groups			ANOVA	*P*-value
	Group I	Group II	Group III		
	Mean ± SD	Mean ± SD	Mean ± SD		
Time to first analgesia (hours)	3.34 ± 0.97	5.47 ± 1.20	2.92 ± 1.10	47.048	0.0001*
Time to commencement (hours)	2.84 ± 1.67	2.54 ± 1.16	3.96 ± 1.79	6.576	0.002*

ANOVA: analysis of variance, SD: standard deviation
*Statistically significant

was obtained from the Research Ethics Committee of Jos University Teaching Hospital.

Results

All patients enrolled into this study were included in the final analysis. Children in the three study groups were comparable with respect to age (P = 0.091). There was variable number of sex distribution across study groups with an overall 76.7% being males and 23.3% being females. Mean body weight and BMI were also comparable across the study groups (P = 0.318) [Table 1]. With regard to the pain scores among children 7 years old and below, group II had the lowest comparative median pain score at 4 h, and pain scores at this time required rescue analgesia. The differences in median pain scores were statistically significant at different time periods across all groups [Table 2]. Children 8 years old and above in group II had a comparative lowest median pain scores in the first 2 h. There was no statistically significant difference in the pain scores across

Table 5: Comparison of mean dose of additional analgesic among groups according to weight status

Variable	Study groups			ANOVA	*P*-value
	Group I	Group II	Group III		
	Mean ± SD	Mean ± SD	Mean ± SD		
Weight < 20 kg					
Dose of **PCM (mg)	351.79 ± 228.91	207.39 ± 80.80	470.00 ± 94.80	19.354	0.001*
Dose of tramadol (mg)	35.03 ± 23.03	20.83 ± 7.97	46.64 ± 8.10	19.723	0.001*
Weight ≥ 20 kg					
Dose of PCM (mg)	535.00 ± 141.70	432.50 ± 166.94	524.00 ± 169.94	1.596	0.220
Dose of tramadol (mg)	53.25 ± 14.38	38.42 ± 14.95	56.80 ± 7.16	5.008	0.013*

ANOVA: analysis of variance
*Statistically significant. **PCM: Paracetamol

Table 6: Distribution of side effects among study groups

Variables	Study groups			Total, *n* (%)	Fisher's exact	*P*-value
	Group I	Group II	Group III			
	n (%)	*n* (%)	*n* (%)			
Postoperative nausea and vomiting					2.719	0.326
Yes	0 (0.0)	2 (6.7)	0 (0.0)	2 (2.2)		
No	30 (100.0)	28 (93.3)	30 (100.0)	88 (97.8)		
Bleeding					1.840	1.000
Yes	0 (0.0)	1 (3.3)	0 (0.0)	1 (1.1)		
No	30 (100.0)	29 (96.7)	30 (100.0)	89 (98.9)		
Hallucination					1.840	1.000
Yes	0 (0.0)	0 (0.0)	1 (3.3)	1 (1.1)		
No	30 (100.0)	30 (100.0)	29 (96.7)	89 (98.9)		
Fever					1.886	0.770
Yes	1 (3.3)	2 (6.7)	0 (0.0)	3 (3.3)		
No	29 (96.7)	28 (93.3)	30 (100.0)	87 (96.7)		

all the groups within the first hour following peritonsillar injection [Table 3].

The difference in the mean time to first analgesic requirement was statistically significant ($P = 0.001$) across study groups with patients in group II having the longest time of 5.47 ± 1.20 h [Table 4]. Patients in group II had the earliest time to commencement of oral liquid intake, which was a statistically significant finding ($P = 0.002$) [Table 5]. Patients in group II had the lowest additional analgesia compared with the other groups in the first 24-h postoperative period. This finding was statistically significant for patients weighing less than 20 kg and in those weighing more than 20 kg with significant levels of 0.001 and 0.013, respectively [Table 6]. Concerning side effects of treatments across study groups, there was no statistically significant difference with respect to postoperative nausea and vomiting ($P = 0.326$), bleeding and hallucination ($P = 1.000$ each, respectively), and fever ($P = 0.770$) [Table 7].

Discussion

Our study showed that the combination of peritonsillar infiltration of tramadol–ketamine after the surgical removal of the tonsils significantly lowered the postoperative pain scores for up to 6 h compared with either tramadol alone or ketamine alone. This means that the pain-free period was longer in group II (tramadol–ketamine combination) than either tramadol and ketamine groups. The pain control seen in group II may be due to the additive effects of ketamine and tramadol as against single drugs used in groups I and III. A similar study found lower pain scores in tramadol–ketamine combination group than the tramadol alone group.[9] Although the result did not show the time period in which the pain scores were taken, it showed an increased number of participants having no pain to mild pain in the tramadol–ketamine combination group compared with the tramadol group. The study also found that fewer children had moderate-to-severe pain in the combination group compared with the single-therapy group.

Another study also found lower visual analogue scale pain score in the tramadol–bupivacaine group compared with the bupivacaine alone group, tramadol alone group, and the control group.[14] Although this study was done in adults and on a day case basis, it showed the advantage of combination therapy over monotherapy and supports the concept of preemptive and multimodal analgesia.

The time to first analgesia request in this index study based on pain score was longer in the tramadol–ketamine combination group than the tramadol-alone or ketamine-alone groups. A study reported by Atef and Fawaz[15] found a longer duration of action in the tramadol group than normal

saline for up to 4 h after peritonsillar injection. Patients in the study also had preincisional infiltration of the study drugs, whereas in the index study, the peritonsillar injection was done after surgery but before extubation. A similar study, where preincisional infiltration of the study drugs was done, also found prolonged duration to first request of analgesia in the group that received drug combination compared with the groups that received single therapy.[16] This is considerably longer (8.4 h) than the time to first request of analgesia in our study. This may be due to that in their study, ketamine was given intravenously, whereas tramadol was given via peritonsillar route. This could be due to both systemic and local effects of the drugs, which may have been responsible for the long duration seen in their study. It was expected that the duration of analgesia in our study should have been longer than the duration observed with their study, since the risk of removing some of the tissues infiltrated with the study drugs was avoided our study.

The quality of pain control influences postoperative recovery, optimal mobilization, and dietary intake. Our study found that the commencement of oral intake was earlier in the group that had tramadol–ketamine combination compared with those in the other groups who had either drug alone. The fact that the children were able to take orally earlier in the combination group showed better pain control compared with the other groups. The advantage of early oral feeding is that the children will mobilize and ambulate earlier than those who had delayed oral feeding. In addition, good oral feeding will result in earlier wound healing, and risk of infection will be lower. Early ambulation will lead to less morbidity, earlier discharge from the hospital, and better parental satisfaction. This indicates that the time to oral intake depends on the presence or absence of pain and the efficacy of the analgesic drug given to patients. The study done by Honarmand *et al*.[16] also showed earlier intake in patients who received combination therapy than monotherapy. Their study showed earlier intake in all the groups compared with our study, which may be attributed to that both intravenous and peritonsillar routes were used in their study as against only the peritonsillar route used in the index study. The findings in our study agree with that of Shamendra *et al*.,[17] which showed that the peritonsillar infiltration of various drugs reduced posttonsillectomy pain and improved earlier oral intake. In their study, the group that received combination therapy had increased number of the participants taking orally at the fourth hour compared with the groups that received single therapy. Other studies also showed reduced pain on swallowing after tonsillectomy following the peritonsillar infiltration of ketamine or tramadol.[12,18] These effects were noticed to be greater in the group of patients who received drug combination than those who received single therapy across all time period studied. Good postoperative analgesia permits early return to feeding, which reduces the risk of agitation, infection, sleep deprivation, and altered daily activity.

The quantity of rescue and additional analgesias given to the children in the present study was lower in those who received drug combination compared with those who received monotherapy. The children were categorized into two based on their weight (less than 20 kg, and 20 kg and above). The quantity of additional analgesia was lower in the tramadol–ketamine group than the other groups irrespective of the weight category the child belonged to across all time period. This could be due to the additive effect of the study drugs rather than the weight. It also shows that the weight of the participants in the study had little influence on drug consumption. Combination (multimodal) therapy may be a major factor to explain the lower additional analgesia seen in group II. The participants in the other groups had higher total analgesic consumption likely because the children had monotherapy, and this controlled their pain for a shorter duration comparatively. The additional analgesic doses in the index study were lower than those reported by Hadi and Sbeitan,[9] which also showed a reduction in additional analgesia in the combination group compared with the other groups, which had monotherapy. However, their study used only paracetamol for the rescue analgesia, whereas we used paracetamol and tramadol, and they did not consider the influence of weight on analgesic consumption. A similar study also showed a reduction in the quantity of additional analgesics in those who received drug combination than single therapy.[16] A much lower dose of rescue analgesia was given to the children in the group that received tramadol–ketamine combination compared with the other groups, which received single-drug therapy. Multimodal postoperative pain treatment including non-steroidal anti-inflammatory drugs, regional anesthesia, and opioid is currently believed to be the gold standard.[19] The quality of analgesia is greater, drug dose reduced, and side effects are minimal.

The occurrence of side effects was minimal across all the groups in the present study indicating that peritonsillar infiltration of analgesic drugs is a good alternative technique of pain control following adenotonsillectomy. None of the complications was statistically significant across the groups. The occurrence of postoperative nausea and vomiting only affected children in group II and none in the other groups in the study. The children did not receive any form of antiemetic prophylaxis during the period of the study. The incidence of postoperative nausea and vomiting recorded in our study may be due to the use of fentanyl and tramadol for intra- and postoperative analgesias, the use of intraoperative volatile anesthetic (isoflurane), the surgery itself or possibly the combination of tramadol–ketamine enhanced nausea, and vomiting compared with the use of either drug alone. It has been noted that adenoidectomy and tonsillectomy are surgical procedures associated with

a high incidence of postoperative nausea and vomiting.[12,20] A study in Nigeria[20] reported an incidence of 16.8%, which is higher than the index study. Hadi and Sbeitan[9] also reported higher proportions than that in our study, and they noted an incidence of 13.3% for the group that received the combined use of tramadol and ketamine and 20% in the group that received tramadol alone, suggesting the association between opioid and postoperative nausea and vomiting.

The index study reported a case of posttonsillectomy bleeding that responded to conservative management without blood transfusion. Our study used the same experienced surgeon throughout the period of the research and the same surgical technique using bipolar diathermy, which may have accounted for the low incidence of postoperative bleeding seen in our study. Hallucination also occurred in the index study affecting a child in group III in which ketamine alone was used. This is in contrast to the study done by Ayotallahi and Baghianimoghadam,[11] which reported an incidence of hallucination of 11.9%, affecting only those who received ketamine alone. This is not surprising because it is common knowledge that ketamine is associated with hallucination. Hallucination may be associated with agitation, which increases the incidence of physical injury.[21] Coadministration of opiates or tramadol intraoperatively can reduce the amount of ketamine required for anesthesia and, therefore, reduce the incidence and duration of postoperative hallucinations. Hallucinations can be reduced by premedicating the patient with benzodiapines and by recovering the patient in a quiet area.[22]

Limitations

Assessing pain in children could be prone to assessment bias, as hunger, thirst, or any other discomfort may be interpreted as pain in children.

Another limitation was the inability to measure the plasma level of the drugs injected to quantify buccal absorption in the study setting.

Conclusion

This study showed that the peritonsillar infiltration of tramadol–ketamine combination after adenotonsillectomy significantly decreased posttonsillectomy pain in children without increasing the incidence of side effects. Furthermore, the need for additional analgesic consumption and the time to the commencement of oral intake were reduced leading to earlier hospital discharge.

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Conflicts of interest

There are no conflicts of interest.

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