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RESEARCH ARTICLE

Clinical pharmacy intervention post tonsillectomy: a randomized control trial

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Abstract *Back ground* Pain control in pediatric patients undergoing tonsillectomy remains a dilemma. Tramadol and ketamine are reported to be an effective analgesic. *Aim of the study* To evaluate the effect of peritonsillar infiltration of tramadol in combination with ketamine versus peritonsillar infiltration of tramadol posttonsillectomy. *Setting* Specialty hospital in Jordan. *Method* Sixty children, aged 7–12 years, selected for tonsillectomy were enrolled in the study. We divided the patients into two groups 30 of each, Group I: received peritonsillar saline and peritonsillar infiltration of tramadol 2 mg/kg, Group II: received peritonsillar infiltration of ketamine 1.0 mg/kg added to peritonsillar tramadol 2 mg/kg. *Main outcome measure* Hemodynamic stability, pain scale, first request of analgesia, total analgesics consumption and post-operative nausea and vomiting (PONV) side effects were recorded 24 h after surgery. *Results* The analysis of data showed that Group II had significantly lower face pain scale, longer time for first request of analgesia, and better hemodynamic stability than GI ($p < 0.001$). On the other hand the total analgesics requirements, time of surgery, and PONV showed no significant differences between the two groups. *Conclusion* Combined use of peritonsillar infiltration of ketamine 1.0 mg/kg with tramadol 2 mg/kg provided prolong analgesic effects, less pain with no side effect, and better hemodynamic stability compared with using tramadol alone in patients undergoing tonsillectomy.

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Impact of findings on practice

- The combined use of peritonsillar infiltration of ketamine with tramadol provides a prolonged analgesic effects in children undergoing tonsillectomy.
- The combined use of peritonsillar infiltration of ketamine with tramadol prolonges the time to the first request for analgesia.

Introduction

Tonsillectomy is a common surgical procedure in children. Their intra operative hemodynamic stability, the severity of their post-operative pain and the requirements for subsequent analgesic consumption, are all major challenges for the surgical team. Using different anesthetic strategies during surgery may positively influence subsequent analgesic requirements [1, 2]. There are many studies that have investigated the control of post-tonsillectomy pain using different drugs, such as intravenous opioids, non-steroidal anti-inflammatory drugs (NSAIDs), steroids, ketamine, as well as peritonsillar injection of local anesthetics, opioids and ketamine [1, 3–5].

Tramadol is an analgesic, acting as an opiate agonist that principally affects mu receptors, and to a smaller extent kappa and sigma receptors, and also inhibits serotonin and norepinephrine reuptake [1, 5, 6]. Its analgesic potency is 5 times lower than morphine [1, 5], but it has a lower risk of dependency and respiratory depression, without any

reported serious toxicity [1, 5]. However, its side effects include: nausea, vomiting, dizziness, sweating, anaphylactic reactions, increased intra-cerebral pressure, blood pressure, and lowering the heart rate. It can also lower the seizure threshold [1, 5, 6].

On the other hand, ketamine hydrochloride is a nonbarbiturate, intravenous anesthetic. Its anesthetic and analgesic effects are mediated primarily by a noncompetitive antagonism at *N*-methyl-D-aspartic acid (NMDA) receptors. This drug has a preference for mu receptors, the stimulation of which is responsible for the analgesic effect of a low dose of ketamine, and this it is believed produces an opioid sparing effect during the postoperative use of analgesics. The drug affects blood pressure and the pulse rate which are frequently elevated following the administration of ketamine alone. This blood pressure elevation begins shortly after its administration, reaching a maximum within a few minutes and usually returns to pre-anesthetic values within 15 min of cessation of its administration [7, 8].

Peritonsillar infiltration of tramadol has been shown to be a successful method to provide superior analgesia for the first 4 h after tonsillectomy [5]. Low dose ketamine was used pre-incisional for tonsillectomy surgery and showed a postsurgical decrease in consumption of diclofenac and acetaminophen. [9, 10].

To our knowledge, the combination of peritonsillar infiltration ketamine with tramadol to control post tonsillectomy has not been previously reported. This paper investigates whether a new anesthetic strategy for this procedure can be suggested.

Aim of the study

To design and conduct a randomized, double blind, study to compare the effect of peritonsillar infiltration of tramadol in combination with low dose peritonsillar infiltration of ketamine versus peritonsillar infiltration of tramadol, posttonsillectomy under the auspices of a clinical pharmacist. The investigational primary endpoint was to test the hemodynamic stability during the surgery, while the secondary endpoints were to investigate: the cumulative analgesics consumption 24 h after the surgery, the severity of postoperative pain using the face scale, and full term [post-operative nausea and vomiting (PONV)] side effects.

Ethical approval

The full study design was submitted to the Ethical Committee of the Specialty Hospital, Amman, Jordan for their consideration. After due consideration they gave their formal permission for the study to be carried out.

Basically, written informed consent was obtained from the parents of 60 children whose ages ranged between 7 and 12 years and who were scheduled to undergo elective tonsillectomy.

Methods

Experimental procedure

All the children were assessed for their ASA physical status. To detect a reduction in pain score of 1–2 U (SD 0.7–0.8), which is in agreement with several studies, with a two-sided 5 % significance level and a power of 80 %, a sample size of 30 patients per group (60 total) was necessary, given an anticipated dropout rate of 5 %. The 60 children were randomly divided into two groups of 30 children per group disregarding age and gender.

All operations were performed by one surgeon, using a standardized snare dissection technique, who was blind to the study drug protocol. The same nursing staff were responsible for recording the pain scores and were also unaware of the drug protocol. The results of patients who developed bleeding or hyper-sensitivity to tramadol or ketamine were excluded from the final study.

Clinical pharmacist's role

An independent clinical pharmacist, who was not involved in the surgery, created the experimental protocol for the study and the drugs which were to be used. This pharmacist provided the patients with simple information about the disease and drug therapy pre-, intra-and post-operatively.

Before the operation they attempted to allay patients' fears and apprehensions and to minimize the consequences of the painful surgical experience, checked the patients wellbeing and health condition, and monitored medication consumption prior to the surgery, if such existed.

On the evening before surgery, they instructed the patients how to use the face pain scale.

The clinical pharmacist investigated and recorded all the details of the potential drug allergic responses and major side effects if exist, and analyzed both the primary and the secondary endpoints of the study.

Technique of anesthesia

All patients received a standard anesthetic protocol including premedication with midazolam 0.1 mg/kg, induction was achieved with propofol 1–2 mg/kg and atracurium 0.4 mg/kg, and maintenance with nitrous oxide (50 %) in oxygen (50 %) and sevoflurane (1–2 %). The

children also received fentanyl citrate (1 μg/kg) intravenously.

Before tonsillectomy, children were randomly assigned to receive either, peritonsillar saline and peritonsillar tramadol (2 mg/kg in 3 ml of normal saline; 1.5 ml dose volume per tonsil) (Group I, n = 30), or peritonsillar ketamine (1.0 mg/kg) and tramadol (2 mg/kg in 3 ml of normal saline; 1.5 ml per tonsil) (Group II, n = 30).

All medications dose volumes and dosages of ketamine [11] and tramadol [12] were based on two previous studies [9, 11].

Randomization was arranged by shuffled, sealed, opaque, and numbered envelopes.

The same surgeon performed all the injections with a 25-gauge needle mounted and the tonsil 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.

Quantitative measurements made during the operation

Assessment of hemodynamic stability

The heart rate, mean arterial blood pressure, ECG, noninvasive blood pressure, oxygen saturation, and end-tidal CO_2 were recorded throughout the 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 surgery time (the time from surgical incision to removal of mouth gag) was recorded by an observer blinded to the study drugs.

Assessment of pain

In the recovery room the assessment of patients' pain scores were performed using a face pain rating scale [7] at 0, 15, 30, 60 min and 6, 12, and 24 h after the operation in the ward. A nurse who was unaware to the randomization recorded the pain scores. If the pain score was >4, IV acetaminophen in the PACU, and acetaminophen 20–40 mg/kg suppository in the ward was administered.

The pain score was divided into 4° in the following way: 0 where patient did not complain of pain, 1 is a mild degree of pain, 2 and 3 is a moderate pain degree, and 4 and 5 is severe pain.

First request of analgesia

The time (minutes) to the first request for analgesia and additional analgesic requirements was recorded. All patients were discharged on postoperative day one.

Side effect and adverse drug reaction

All adverse effects, including nausea, vomiting and hallucination were recorded.

Statistical analysis

All statistical analyses were performed using SPSS (version 17) All data were expressed as mean ± SD and were analyzed using the Student's *t* test and where appropriate the Kruskal–Wallis test. A p value <0.05 was considered statistically significant.

Results

The two groups studied were comparable as regards sex, age, weight, duration of surgery and anesthesia. The analysis showed that there were no significant differences between the numbers of males and females in their respective groups and also for comparisons made between GI and GII for their ages, and body weight. In the absence of any significant differences being found between the groups they were subsequently considered as one group despite their apparent gender and age differences Table 1.

After the pre-operative tests, patients were found to be free of any major systemic disease and they were fit to be operated upon according to the criteria used by the anesthesiologists involved in this study. No patients were excluded from the study due to any problem as bleeding or drug hypersensitivity.

Intra operative and post-surgical analysis

The duration of the surgery and the total analgesics requirements did not show any significant differences between the two groups, while the HR and MAP was more stable in GII comparing to GI, first request of analgesia was significantly ($p < 0.03$) shorter in GI comparing to Group II, and the pain scale score was significantly lower for GII comparing to GI Table 2.

Table 1 Demographic characteristics of patients, baseline HR and MAP

	GI (n = 30)	GII (n = 30)	p value
Sex (M/F)	14/16	17/13	0.98 NS
Wt. (kg)	29.9 ± 10.1 kg	28.1 ± 9.3	0.91 NS
Age (years)	9.7 ± 2.2	9.5 ± 2.5	0.86 NS
Baseline heart rate	88 ± 2.3	87 ± .7	0.73 NS
Baseline MAP	82.3 ± 1.1	81.7 ± 1.9	0.067 NS

NS not significant

Potential for drug allergic responses and adverse effects

No statistical differences were observed between the two groups in terms of the incidence of vomiting or nausea, and no hallucination were recorded.

The face scale scores were significantly different between the two groups ($p < 0.05$) (Fig. 1).

Discussion

In the world literature, clinical pharmacist interventions in the 'surgery room' is still limited. This study applied a pharmaceutical care intervention to tonsillectomy, in response to the suggestion of PC Gordon who suggested in the South African Society of Anesthesiologists that they should be more involved with pharmacists to their mutual advantage [13]. Hadi et al. have applied clinical pharmacy intervention program in the surgery room in two previous studies [2, 14].

Hemodynamically, the HR and MAP were significantly lower in GI as compared to GII. Several studies showed that peritonsillar infiltration of tramadol causes arterial hypotension and bradycardia with iv anesthetic agents either propofol or thiopental [1, 15]. Adding a low dose of ketamine to GII gave us better and more suitable hemodynamic stability results.

Another study [7] has confirmed that, using low dose of ketamine led to less tachycardia and hypertension and no incidence of side effects such as post-operative hallucinations and delirium that may induced by higher dose. The finding that the HR and MAP did not decrease below the normal values may be explained by previous reports where catecholamine release by ketamine has been reported to commonly cause both tachycardia and hypertension [7].

Pain following tonsillectomy is one of the most important complaints and has several unwanted consequences such as excessive use of analgesics, longer period of hospitalization, intolerance to diet, which can lead to nutritional problems, and subsequently poorer quality of life [4, 5].

Our results showed that the combined use of peritonsillar infiltration of ketamine with tramadol lowered the postoperative pain scores and prolonged the first request of analgesia than using peritonsillar infiltration of tramadol alone. Atef and Fawaz [5] showed that peritonsillar infiltration of tramadol (2 mg/kg) improved postoperative pain for 4 h, while in our study it was similar to that of Honarmand et al. [16] who used the combination of tramadol with intravenous administration of ketamine (0.5 mg/kg) where analgesic effect was prolonged from 4 to 24 h after the operation with no significant adverse effects.

On the other hand, in our study we have used peritonsillar infiltration of ketamine, not i.v. ketamine to avoid any

Table 2 Clinical measurements made during tonsillectomy surgery for GI and GII

	GI	GII	*p* value
Duration of surgery (min)	27.4 ± 6.3	28.1 ± 6	0.63 NS
Heart rate (beats per min)	60 ± 12	70 ± 7	0.02*
MAP (mmHg)	72 ± 5	80 ± 5	0.01*
Time for first patient analgesia request during 24 h in the ward (min)	3.9 ± 1.9	7.6 ± 1.6	0.03*
Total acetaminophen dose (g)	1.8 ± 1	1.1 ± 0.3	0.52 NS
PONV n (%)	3 (20)	2 (13.3)	0.57 NS

Values are presented as scores for PONV

NS not significant

* Significant

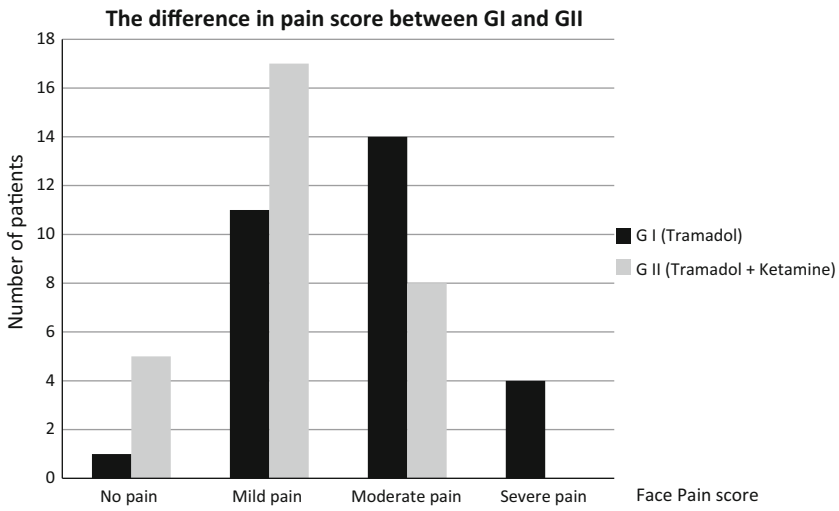

Fig. 1 The difference in pain score between GI and GII. The overall pain score in GII, was significantly lower than GI

sedation effect this route would cause. Dal and Elven showed that low dose ketamine (0.5 mg/kg^{-1}) given i.v. or by peritonsillar infiltration perioperatively provides efficient pain relief without significant side effects in children undergoing adenotonsillectomy but children in i.v. ketamine group had significantly higher sedation scores than peri-tonsillar ketamine group in immediate postoperative period [4].

Furthermore another study showed that oral ketamine provided ineffective postoperative analgesia and caused more salivation, while intramuscular ketamine produced sedation and reduced pain on swallowing but failed to provide effective postoperative analgesia [17].

Ketamine has both peripheral and central effects. During peritonsillar infiltration, ketamine perhaps brought about its analgesic effects through the blockade of sodium and potassium channels in the peripheral nerve (tonsillar nerve) [18]. In pre-clinical studies, peripheral local ketamine was shown to have an anti-hyperalgesic effect [19].

In our study using peritonsillar infiltration of tramadol combined with ketamine in low dose did not show any significance PONV side effect versus using peritonsillar infiltration of tramadol alone. Other studies have showed that using intravenous tramadol in children undergoing adenotonsillectomy caused PONV [20, 21]. Demiraran et al. [22] have demonstrated that wound infiltration with tramadol improved post-operative pain relief better than bupivacaine after herniotomy in children.

Peritonsillar infiltration of local anesthetics, such as bupivaciane can cause complications such as bilateral paralysis of vocal cords and severe obstruction of upper airways, acute pulmonary edema (vagus and hypoglossal block), deep neck abscesses, and brainstem stroke, which have been seen after deep infiltration and high doses of local anesthetics [3, 23].

Tramadol has been shown to block nerve conduction like a local anesthetic, but with a weaker effect than that of lidocaine. Its anesthetic action is reported to be mediated by a non-opioid receptor dependent mechanism that is different from that of lidocaine [24, 25]. Local anesthetic efficacy of intradermal and subcutaneous tramadol has been shown in previous controlled clinical trials [26–28]. Therefore, local infiltration of the tramadol to the peritonsillar region is expected be beneficial in decreasing tonsillectomy pain by utilizing two separate modes of action: firstly by its local anesthetic and secondly by its analgesic effect following systemic absorption from the peritonsillar region.

It is also suggested that tramadol might have a different mechanism from that of lidocaine for producing conduction block [24]. 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 using of local anesthetics in the peritonsillar area is to cause an increase rate of bleeding.

On the other hand, Ugur et al. [1] have compared the effect of peritonsiller infiltration of tramadol with intramuscularly tramadol, and they confirmed that its efficiency was better than same dose of tramadol given intramuscularly.

All analgesic methods have some potential drawbacks. Opioids can cause postoperative respiratory complications and sedation, whereas nonsteroidal anti-inflammatory drugs increase the risk of bleeding, which might require repeated surgeries to control homeostasis [1, 4, 5, 26]. In this study we have used paracetamol post operatively which another study showed to have adequate analgesia in this condition [4].

Negus and colleagues showed that the combination of oral midazolam and intravenous morphine can cause upper respiratory airway obstruction [27]. In spite of the fact that NSAIDs have no obstructive effects on airways, but some of them like ibuprofen could increase the risk of postoperative bleeding [25, 28]. This is of importance that no significant complications following combined use of tramadol and ketamine were observed.

Further studies could be carried out to achieve an understanding as to how to reduce tramadol's systemic effects which are responsible for PONV.

Conclusion

The administration of low dose peritonsillar infiltration of ketamine (1.0 mg/kg) before surgical excision appears to reduce pain and prolong analgesic efficacy of tramadol (2 mg/kg) alone. Combining tramadol and ketamine in a low dose assured better hemodynamic stability; and prevented PONV in children undergoing tonsillectomy.

We highly recommend using peritonsiller infiltration of tramadol combined to peritonsiller infiltration ketamine as a routine therapy for post tonsillectomy pain management.

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Conflicts of interest There are no conflicts of interest.

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