Pre-versus postoperative tramadol instillation: both are effective for decreasing pain and/or agitation in pediatric adenotonsillectomy

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Aim: The present study aimed to investigate the possible influence of nasopharyngeal preoperative or postoperative tramadol instillation on postoperative pain and agitation in pediatric patients undergoing adenoidectomy, with or without tonsillectomy and tube placement.

Materials and methods: Ninety pediatric patients were included in the study. Induction of anesthesia was achieved with 2.5 mg kg^{-1} propofol and 0.6 mg kg^{-1} rocuronium bromide. To maintain the anesthesia, 2%–2.5% sevoflurane in an oxygen-N_2O mixture (FiO_2 = 35%) was administered. In Group I (n = 30), 1 mg kg^{-1} tramadol was given 10 min before adenoidectomy, and in Group II (n = 30) it was administered 10 min after adenoidectomy was achieved on the adenoid tissue. Saline, at the same volume, was injected as a control in Group III (n = 30). Patients were evaluated for postoperative pain, agitation score, and modified Aldrete score (MAS) in recovery.

Results: When compared with the treatment groups, pain scores and analgesic requirements in the control group significantly increased (P < 0.001). Agitation scores were also significantly higher in the same group. Time-related MASs were significantly lower in the control group in the early recovery period.

Conclusion: Preoperative or postoperative tramadol instillation administered to the adenoidectomy area significantly decreased postoperative analgesic requirements and agitation.

Key words: General anesthesia, sevoflurane, agitation, tramadol

1. Introduction

Adenoidectomy and tonsillectomy operations are among the most frequent surgeries performed for the pediatric population in an outpatient setting. Pain in the postoperative period remains the major determinant of morbidity and should be reduced without increasing the side effects. Surgery is performed in the preschool period in the great majority of patients, and there is a prominent incidence of volatile anesthetic-induced agitation (1).

Sevoflurane is the volatile anesthetic of choice in the pediatric population due to its smooth mask induction and early recovery profile properties. Emergence agitation is the phenomenon largely linked with the use of sevoflurane. Although it can also be observed without surgery, such as in imaging studies, pain seems to be one of the contributing factors (2). Agitation may influence surgical outcomes by delaying discharge, increasing complications, and consuming the time of the recovery staff.

Tramadol is considered a weak opioid analgesic that also has serotonin and noradrenaline reuptake inhibition (3). It is also suggested for postoperative pain relief after

minor surgeries because of its local anesthetic properties (4). Drop formulation is one of the commercially available forms of the drug. Tramadol has been largely investigated to determine the doses of intravenous (i.v.) or peritonsillar infiltration for postoperative pain relief in pediatric patients undergoing adenoidectomy or tonsillectomy (5–8). Although mucosal application is associated with faster peak plasma concentrations with long-lasting analgesic levels (9), there are limited data about its clinical use in this regard.

The absorption of tramadol after oral administration was demonstrated to be faster in a study investigating the pharmacokinetics of the oral form of the drug in pediatric patients aged 4 to 7 years. The peak plasma level was reached at about 30 min and the analgesic concentration, considered as 100 ng mL^{-1}, was maintained throughout 6.8 h. The faster metabolism of pediatric patients and active metabolites that augment μ-receptor affinity were cited as factors that contributed to this increased effect (9). When compared with the placebo, tramadol ointment in a dose of 3 mg kg^{-1} before dental intervention was demonstrated

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to provide marked analgesia in pediatric patients without respiratory depression (10). Although a lower dose was applied at the surgical site, effective analgesia was also observed in our study by means of decreasing supplemental analgesics and agitation in the postoperative period, with similar recovery profiles.

The objectives of this study were to investigate tramadol instillation to the adenoid tissue before or after surgical ablation versus a placebo and to compare the postoperative analgesic effects and possible influence on agitation in pediatric patients undergoing adenoidectomy and/or tonsillectomy, with or without tube placement.

2. Materials and methods

This prospective, randomized, placebo-controlled study was performed after obtaining approval from the Local Ethics Committee and informed consent from parents or caregivers (No: 2009-206). The study was conducted in the Anesthesiology and Otorhinolaryngology Departments of the Kırıkkale University School of Medicine from January 2010 to March 2011.

Ninety pediatric patients, aged between 3 and 16 years and with American Society of Anesthesiologists (ASA) physical status I or II, were allocated to 3 groups, each group containing 30 patients.

Patients with chronic systemic disorders such as renal insufficiency, respiratory disease, or heart failure; neurological or psychiatric disorders that influence cognition; use of analgesics within the 2 days before the surgery; a known allergy to the study drugs; or parental refusal were excluded from the study. Randomization was performed using shuffled opaque envelopes chosen before the surgery.

Patients received 0.5 mg kg^{-1} oral midazolam in 20 mL of strawberry juice 30 min before arrival to the holding area. Venous access was performed on the dorsum of the hand after applying EMLA cream (ASTRA, Södertalje, Sweden) and a solution containing 1/3 glucose with saline mixture was started at a dose of 4 mL kg^{-1} h^{-1}. Patients were monitored, including an electrocardiogram at V_5, noninvasive blood pressure measurements, oxygen saturation, body temperature, and end-tidal CO_2 after intubation. The other anesthetic gas concentrations were followed continuously and recorded every 5 min (Datex-Ohmeda Cardiocap 5, Helsinki, Finland).

The induction of anesthesia was achieved with 2.5 mg kg^{-1} propofol containing 1 mg mL^{-1} lidocaine and 0.6 mg kg^{-1} rocuronium bromide. Endotracheal intubation was performed with an appropriate reinforced tube and sevoflurane with an end-tidal concentration of 2%–2.5% in an oxygen-N_2O mixture (FiO_2 = 35%) was administered for maintenance. Unless otherwise indicated, a muscle relaxant was administered only during the induction. Sevoflurane concentration was adjusted according to the heart rate or blood pressure values in order to maintain them within limits of approximately 10% of the preoperative measurements. Patients were mechanically ventilated with a tidal volume of 8 mL kg^{-1} and the frequency was adjusted to maintain an end-tidal CO_2 level of around 4–4.5 kPa. Patients were positioned for surgery and an oral retractor was applied. A solution of 1 mg kg^{-1} tramadol was administered 10 min before (Group I) as a preemptive treatment or 10 min after bleeding control was achieved (Group II), or an equal volume of saline was administered to the adenoid tissue 10 min before adenoidectomy (Group III controls) while the uvula was retracted using an insulin injector (1 mL = 100 U) extended with a 20-G prefilled i.v. cannula without an introducer. The injectors were filled with an undiluted form of the tramadol (100 mg = 1 mL) or saline in units corresponding to the body weights. Tonsillectomy or tube placements were performed after adenoidectomy and all surgeries were performed by the same technique. The study drugs and controls were prepared in a separate room by an investigator who did not participate in any of the later observations. Residual muscle relaxation was antagonized using 10 μg kg^{-1} atropine sulfate with 30 μg kg^{-1} neostigmine. Endotracheal tubes were removed according to the objective criteria of the extubation (able to hold head and neck up for at least 5 s, squeeze hand, protrude tongue) and adequate respiration (tidal volume ≥ 6 mL kg^{-1}, respiratory rate > 10 breaths min^{-1}) after suction was performed with care. Respiratory complications including bronchospasm, laryngospasm, or cough and other complications such as nausea, vomiting, or bleeding from surgical sites were recorded. Patients were observed while supplemental oxygen at 2–3 L min^{-1} was maintained with a mask until cooperation was achieved, and they were then transferred to the recovery room. Patients were monitored and vital findings were recorded every 5 min and oxygen was continued until discharge to the ward.

Pain was assessed using a verbal rating scale (VRS) scored between 0 (no pain) to 10 (worst pain imaginable) every 1 h for the first 4 h. An intravenous infusion of paracetamol, at a dose of 10 mg kg^{-1}, was given in cases of VRS ≥ 4, which were treated with 5 or 10 mg i.v. meperidine (according to body weights of ≤30 kg or >30 kg), repeated if required. Agitation was assessed by an independent observer during the recovery period as according to Aono et al. (1) and scored as: 1 = calm, 2 = not calm but easily calmed, 3 = moderately agitated or restless, and 4 = combatively excited or disoriented. A modified Aldrete score (MAS) (11) was recorded during the same period, and complications or side effects in the recovery room were also noted. Patients were accepted as eligible to transfer to the ward when there was no complication such as nausea, vomiting, cardiovascular instability, or

respiratory insufficiency within the past 30 min and patients were calm, sitting, and staying unaided according to their age. Patients were discharged following the surgical visit on the same day when patients were calm and cooperative, pain scores were decreased, and there was no bleeding from the surgical site. A telephone interview was performed with parents 24 h after the operation in order to determine whether there were further complications, like sleep disturbance or problems with food or fluid intake.

2.1. Statistical analysis

Statistical analyses were performed using a package program (SPSS for Windows 15.0, SPSS Inc., Chicago, IL, USA). Our preliminary data indicated that at least 26 patients were required to determine any difference between supplemental analgesic consumption within 24 h with an α of 0.05 and β of 90%. Each group therefore consisted of 30 patients, to account for possible dropouts. Side effect profiles and differences including sex or ASA physical status were evaluated using contingency tables and chi-square and Fisher exact tests. Continuous variables were analyzed using 1- or 2-way ANOVA and with repeated measures when indicated, followed by Tukey's test for post hoc comparison. The Mann–Whitney U test and Bonferroni correction were used for nonparametric data. A P-value of less than 0.05 was considered as statistical significant.

3. Results

All patients were eligible to complete the study and were included in the further analyses. Groups were similar with respect to age, weight, and sex distribution and ASA physical status, except that height was higher in Group III (P < 0.05) when compared with the other groups (Table 1). The indications for surgery and duration of surgery and anesthesia are shown in Table 2. The study groups were comparable according to these variables.

Table 1. Patient demographics and American Society of Anesthesiologists (ASA) physical status, *: P < 0.05.

	Group I (n = 30)	Group II (n = 30)	Group III (n = 30)
Age (years)	7.2 ± 2.6	5.6 ± 3.1	7.4 ± 3.5
Height (cm)	107 ± 16	103.3 ± 23.8	122.3 ± 21.4*
Weight (kg)	25.5 ± 10.9	21.1 ± 8.6	27 ± 13.6
Sex (F/M)	16/14	12/18	13/17
ASA status (I/II)	28/2	29/1	28/2

Table 2. Operation indications and periods of anesthesia, surgery, recovery, and pain scales, *: P < 0.05.

	Group I (n = 30)	Group II (n = 30)	Group III (n = 30)
Types of surgery			
A	15	9	16
T	3	3	2
A + T	5	11	8
A + TP	7	7	4
Duration of anesthesia (min)	55.5 ± 26.5	54.1 ± 20.8	51.9 ± 20.2
Duration of operation (min)	48.9 ± 23.8	49.8 ± 19.7	39.2 ± 19.5
Time to open eyes (min)	6.2 ± 3.2	7.4 ± 3.5	13.8 ± 5.1
Time to consolation (min)	8.9 ± 3.8	11.2 ± 5.8	7.9 ± 3.2
Time to cooperation (min)	15.9 ± 9.4	16 ± 7.2	19.9 ± 6.3
VRS 0	1.7 ± 1.4	2.1 ± 1.3	4.3 ± 1.8*
VRS 1	1.3 ± 1.0	1.6 ± 1.0	2.9 ± 1.4*
VRS 2	0.9 ± 0.7	1.3 ± 0.9	1.8 ± 0.9*
VRS 3	0.6 ± 0.6	0.9 ± 0.7	1.3 ± 0.6*
VRS 4	0.4 ± 0.6	0.5 ± 0.7	1.0 ± 0.6*

A: Adenoidectomy, T: tonsillectomy, TP: tube placement, VRS: verbal rating scales.

There were no hemodynamic alterations, including heart rate or mean arterial blood pressure, that required medication during the surgery or in the early postoperative period. There was no significant difference between the study groups (data not shown).

Analgesic requirement in the postoperative period was significantly increased in the control group, and 16 patients received paracetamol and/or meperidine treatment in this group. On the other hand, none of the patients in the 2 treatment groups required additional analgesics in the early postoperative period when compared with the control group (P < 0.001).

Recovery profiles, including time to open eyes and time to consolation and cooperation, were similar between the treatment groups (Table 2). Verbal rating scales between the study groups are also indicated in Table 2. Pain scores were significantly higher at all time intervals in Group III when compared with the treatment groups.

Agitation scores were significantly higher in the control group at 0 min (P = 0.009 between Group I and Group III), 10 min (P = 0.028 between Group II and Group III), 20 min (P < 0.001 between Group I and Group III), 30 min (P < 0.001 between Groups I and II compared to Group III), 45 min (P < 0.001 between Group I and Group III), and

60 min (P = 0.005 between Group I and Group III) when compared to the preoperative and postoperative tramadol treatment groups (Figure 1).

The MASs were significantly lower in the control group at 0 min (P < 0.001 between Groups I and II compared to Group III), 10 min (P < 0.001 between Groups I and II compared to Group III), and 20 min (P < 0.01 between Groups I and II compared to Group III). Time-related changes in MASs are shown in Figure 2.

There was no significant difference with respect to side effect profiles (Table 3). No further complication or side effect, sleep disturbance, or difference in food or fluid intake was determined in the first postoperative day via telephone interview.

4. Discussion
Our results indicated that tramadol instillation to the adenoid tissue before or after the operation decreased pain, agitation, and analgesic consumption in pediatric patients undergoing adenoidectomy with or without tonsillectomy. Patients in the treatment groups also had higher MAS values, indicating that patients in these groups recovered faster than the controls. Although a limited number of individuals were included, this efficacy in tonsillectomy
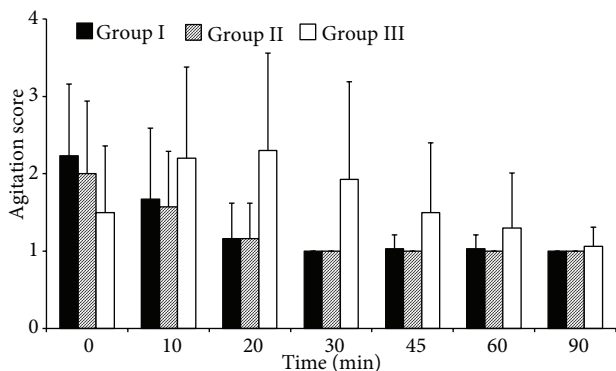

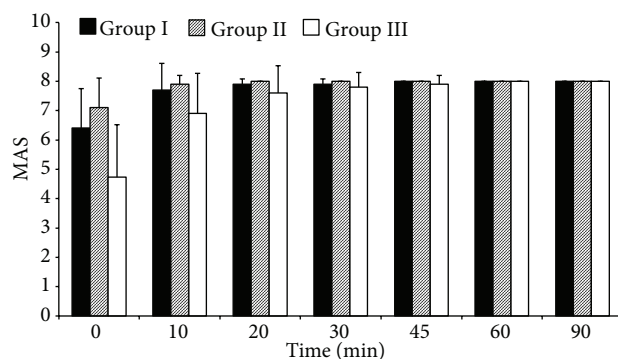**Figure 1.** Agitation scores of groups in the early postoperative period, *: P < 0.05.

Figure 2. Modified Aldrete scores of the groups during recovery, *: P < 0.05.

Table 3. Side effects and additional analgesic requirements of the groups, *: P < 0.001.

	Group I (n = 30)	Group II (n = 30)	Group III (n = 30)
Laryngospasm	1	-	1
Throat pain	3	-	-
Pain on swallowing	2	-	-
Shivering	1	-	-
Nausea	2	-	3
Vomiting	1	-	1
Delirium	-	1	4
Additional analgesics	-	-	16*

patients indicates the possible spread of the drug to the surgical area.

The analgesic effect of i.v. tramadol has been largely investigated in pediatric patients undergoing adenotonsillectomy, with varying success. In their study, Ozköse et al. (5) indicated that relatively lower doses of i.v. tramadol administration (0.5 or 1 mg kg^{-1}) after induction of anesthesia were found to be equally effective for decreasing tonsillectomy pain in pediatric patients. When compared with morphine, the analgesic effect of tramadol for posttonsillectomy pain relief given through a patient-controlled analgesia device was lower in the early postoperative period, but the incidence of nausea increased with morphine (6). Although the postoperative analgesic effects of 1 and 2 mg kg^{-1} tramadol or 0.1 mg kg^{-1} morphine after induction of anesthesia were found to be comparable, the incidence of nausea and vomiting increased with morphine (75% and 40%, respectively) in pediatric patients undergoing tonsillectomy (7). In another study, the analgesic effects of 0.1 mg kg^{-1} morphine, or 1.5 mg kg^{-1} tramadol given during the induction of anesthesia were superior to those of ketamine at 0.5 mg kg^{-1} in pediatric adenotonsillectomy operations (12).

Peritonsillar tramadol infiltration after tonsillectomy was shown to be more effective than a placebo for decreasing pain and supplemental analgesic requirements in the early postoperative period (8). In their study, Akkaya et al. (13) compared i.v. administration of 2 mg kg^{-1} tramadol with peritonsillar infiltration, and tramadol infiltration was determined to be superior with respect to pain score, analgesic requirements, and side effects including nausea and vomiting. On the other hand, this route of administration is invasive and carries potential complications in the postoperative period, such as increased postoperative bleeding and respiratory distress by compromising the airway or with inadvertent vascular entry.

Surgical trauma leads to the dual phenomena of peripheral and central sensitization. The result is a state of neuronal hyperexcitability, the so-called "wind-up phenomenon", which could partially explain postoperative painful states. Preemptive analgesia blocks the nociceptive stimuli before surgery, but the timing for postoperative analgesia is controversial. In a study of pediatric patients undergoing hypospadias surgery, there was no significant difference between effects of pre- and postoperative tramadol administrations on analgesic periods or side effect profiles (14). Our results also indicated no additional benefit with using preemptive tramadol before surgery. However, the facts that tramadol was well absorbed and analgesia occurred in both of the treatment groups indicated proper timing. In addition, the possible influence of local anesthetic properties may influence the outcome due to using relatively lower doses in this study. The analgesic influence of tramadol may increase due to the disposing site being in close vicinity to the brain. In a previous study, our study group also demonstrated efficacy of epidural tramadol infiltration in lumbar microdiscectomy (15). On the other hand, addition to the local anesthetic solution has neither influenced the characteristics of motor and sensorial blockade nor increased the duration of analgesia (16). These results also indicate that the importance of the site of action might come from pain afferents directly to the spinal cord, which does not happen during plexus blockade. In addition to the alleviation of pain, agitation may also decrease with the interaction of enantiomers of tramadol on monoaminergic and serotonergic mechanisms. The latter mechanisms might be involved to a lesser extent in light of the higher MAS values observed in the treatment groups, but not in the increased agitation that might be involved with higher doses of tramadol or interaction with other drugs (17). The influence of tramadol on agitation and sedation will need to be determined with further studies.

In conclusion, tramadol implementation directly to the adenoid, before or after surgery, decreased pain and agitation in pediatric patients undergoing adenoidectomy with or without tonsillectomy and tube placement. This route of tramadol administration is easy and noninvasive, without increasing the side effects.

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