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Demonstration of analgesic effect of intranasal ketamine and intranasal fentanyl for postoperative pain after pediatric tonsillectomy

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ABSTRACT

Objective: Tonsillectomy is one of the oldest and most commonly performed surgical procedure in otolaryngology. Postoperative pain management is still an unsolved problem. In this study, our aim is to demonstrate the efficacy of intranasal ketamine and intranasal fentanyl for postoperative pain relief after tonsillectomy in children.

Material and method: This randomized-controlled study was conducted to evaluate the effects of intranasal ketamine and intranasal fentanyl in children undergoing tonsillectomy. Tonsillectomy performed in 63 children were randomized into three groups. Group I received: Intravenous paracetamol (10 mg/kg), Group II received intranasal ketamine (1.5 mg/kg ketamine), Group III received intranasal fentanyl (1.5 mcg/kg). The Children's Hospital of Eastern Ontario Pain Scale (CHEOPS) and Wilson sedation scale scores were recorded at 15, 30, 60 min, 2 h, 6hr, 12 h and 24 h postoperatively. Patients were interviewed on the day after surgery to assess the postoperative pain, nightmares, hallucinations, nausea, vomiting and bleeding.

Results: Intranasal ketamine and intranasal fentanyl provided significantly stronger analgesic affects compared to intravenous paracetamol administration at postoperative 15, 30, 60 min and at 2, 6, 12 and 24 h in CHEOPS ($p < 0.05$). Sedative effects were observed in three patients in the intranasal ketamine administration group. No such sedative effect was seen in the groups that received intranasal fentanyl and intravenous paracetamol in Wilson Sedation Scale ($p < 0.05$). Cognitive impairment, constipation, nausea, vomiting and bleeding were not observed in any of the groups.

Conclusion: This study showed that either intranasal ketamine and intranasal fentanyl were more effective than paracetamol for postoperative analgesia after pediatric tonsillectomy. Sedative effects were observed in three patients with the group of intranasal ketamine. There was no significant difference in the efficacy of IN Ketamine and IN Fentanyl for post-tonsillectomy pain.

1. Introduction

Tonsillectomy is one of the earliest and most commonly performed operations in Otorhinolaryngology [1]. Tonsillectomy operation may cause complications, such as postoperative sore throat, swallowing difficulty, bleeding and agitation in pediatric patients [2]. Post-operative pain after tonsillectomy operation has great importance. It may prolong patients' discharge time from the hospital and may cause re-hospitalization to control the pain with intravenous treatment [3]. There are many studies in the literature regarding how to alleviate postoperative pain after tonsillectomy. In these studies, different drug applications were tried such as opioids, non-opioids, NSAIDs, steroids and ketamine utilizing different application methods of intravenous, subcutaneous, rectal and peritonsillary infiltration are applied [2–5].

Intranasal (IN) analgesia provides safe and timely relief of pain without any discomfort and avoid delay oral administration [6–8]. IN pharmacokinetics of drug administration allows therapeutic drug levels and adequate analgesia with reduced drug absorption rate and minimal side effects. IN drug application is often used instead of parenteral opioids to provide analgesia in children [7], [9].

IN Ketamine has a bioavailability of 45–50% and has been shown to be an effective analgesic without dissociative and sedative effects at a dose of 1.5 mg/kg (50 mg/ml) [10–12]. IN Fentanyl has a bioavailability of 77%, the most commonly used and investigated IN analgesic [13], [14]. 1.5 μg/kg (50 μg/ml) of IN fentanyl has been shown to have an analgesic equal to 0.1 mg/kg IV morphine [7].

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In this study, it was aimed to evaluate the efficacy IN ketamine and IN fentanyl in pediatric patients for post-tonsillectomy pain in the postoperative period.

2. Material and method

This is a prospective study, the approval dated 01/02/2017 and decision number 3/24 was received from the local ethics committee. Sixty-three patients present to the Otorhinolaryngology Department with age range of 2–14 years, who had tonsillectomy/adeno-tonsillectomy, were included in the study and written informed consents by their parents were received.

Fentanyl and ketamine sprays are not commercial products. It was prepared by our pharmacist in considering the previous studies [10]–[14]. We used them separately without mixing. The cases were divided into three groups to check for post-operative analgesia: Intravenous paracetamol (Group 1), IN fentanyl (Group 2), and IN ketamine (Group 3). Anesthesia was maintained with 1% isoflurane and 50:50% Oxygen (O): Nitric oxide (NO). Group 1 received 10 mg/kg IV paracetamol during induction, Group 2 received 1.5 mg/kg (50 mg/ml) IN ketamine and Group 3 received 1.5 mcg/kg (50 μg/ml) IN fentanyl. In all three groups, the drugs were administered at the same dose three times a day for one day [15]. 1 puff nasal spray has 7.5 mcg. We planned 1 puff nasal spray for every 5 kg. For example, 3 puffs were applied as nasal spray for a 15 kg child. Patients with pathology such as chronic sinusitis, cold and rhinitis, concha hypertrophy, nasal polyposis, septum deviation, mucociliary clearance and atrophic rhinitis were excluded from the study.

Pain levels were evaluated by The Children's Hospital of Eastern Ontario Pain Scale (CHEOPS) established by McGrath et al. [16] (Fig. 1). In this postoperative pain evaluation, behavior scoring (crying score, facial impression, verbal complaints, position and movement of the body, response when the wound was touched, and whether the child pointed to the wound) was assessed by an experienced observer. The sedative condition was evaluated with the Wilson sedation scale [17] (Fig. 2). The post-operative values for CHEOPS at minutes 15-30-60, hours 2-6-12-24 and for Wilson sedation scale at minutes 15-30-60 and hours 2-6-12-24 were obtained from the patient files. Postoperative pain, sedation and side effect measurements were recorded objectively by a blinded observer.

3. Result

This study included 63 pediatric cases (25 females (39.7%); 38 males (60.3%)) who were treated in our clinic during February–July 2017. The patients were divided into 3 groups.

Group 1 (Intravenous paracetamol) consisted of 20 cases, with a mean age of 5.4 ± 2.8 years. Group 2 (IN fentanyl) consisted of 23 cases with a mean age of 5.9 ± 2.5 years. Group 3 (IN ketamine) included 20 cases, with a mean age of 5.2 ± 1.9 years. The Tukey HSD test results comparing the mean age, sex, weight, operation duration and anesthesia duration of all groups did not reveal any statistically significant difference ($p > 0.05$) (Table 1). Cognitive impairment, constipation, nausea and vomiting were not observed in any of the groups.

Modified Children's Hospital of Eastern Ontario Pain Scale

Score	0	1	2
Cry	No cry	Crying, moaning	Scream
Facial	Smiling	Neutral	Grimace
Verbal	Positive statement	Negative steatement	Suffering from pain, another complement
Torso	Neutral	Variable, taot, upright	Stretched
Legs	Neutral	Kicking	Stretched, continuous move

Fig. 1. Modified Children's hospital of Eastern Ontario pain scale.

Wilson Sedation Scale

Score	Degree of sedation
1	Fully awake, orientated
2	Lethargic
3	Opens eyes with verbal stimulus
4	Opens eyes with moderate pain
5	Does not respond moderate pain

Fig. 2. Wilson sedation scale.

Table 1
Comparison among groups on the basis of age, weight, operation duration and anesthesia duration.

Variables	Group 1	Group 2	Group 3	P
Sex				0.102
Male	11	15	12	
Female	9	8	8	
Age; (median)	5.4 ± 2.8	5.9 ± 2.5	5.2 ± 1.9	0.604
Age; (range)	3–14	2–12	2–10	
Weight	23,09 ± 4,02	21,17 ± 4,37	24,87 ± 7,01	0.674
Operation duration (min)	31,67 ± 5,15	31,27 ± 6,05	32,13 ± 3,96	0.872
Anesthesia duration (min)	38,13 ± 3,62	39,13 ± 4,96	40,33 ± 3,84	0.219

One-Way ANOVA- Tukey HSD test (*$P < 0.05$, **$P < 0.001$).

Based on a comparison among groups on the basis of CHEOPS, there was a statistically significant difference in Groups 2 and 3 compared to Group 1 at 15, 30, 60 min and at 2, 6, 12 and 24 h ($p < 0.05$) (Table 2) (Fig. 3). In this respect Groups 2 and 3 had comparable CHEOPS results.

Based on a comparison among groups on the basis of Wilson sedation scale, there was a statistically significant difference in Groups 1 and 2 compared to Group 3 at 15, 60 min and at 2 h ($p < 0.05$) (Table 3). In this respect Groups 1 and 2 had comparable Wilson Sedation Scale results.

4. Statistical analysis

Statistical analyses was carried out using the Statistical Package for the Social Sciences version 13.0 software for Windows (SPSS Inc, Chicago, Illinois, USA). All quantitative variables were estimated using measures of central location (i.e. mean and median) and measures of dispersion (i.e. standard deviation (SD)). The data were specified as average ± standard deviation. To compare the data, the One-Way ANOVA- Tukey HSD test was used. $P < 0.05$ was considered statistically significant. Descriptive statistics presented as mean, standard deviation and 95% confidence intervals.

5. Discussion

Postoperative tonsillectomy analgesia is still an ongoing unresolved hot topic requiring effective treatment solutions in the literature. Inadequate analgesia causes complications and discomforts such as postoperative sore throat, swallowing difficulty, aspiration, delayed discharge [2]. Paracetamol is preferred for postoperative analgesia but its use alone does not always produce adequate analgesia. NSAID provides effective analgesia but increases the risk of bleeding and the patient can be re-operated for bleeding control [18].

Ketamine is an intravenous anesthetic agent from the phencyclidine group. Because of the effect of NMDA receptor antagonist, it provides central synthesis and opioid resistance. It binds to the mucin receptor on the spinal cord and brain and has an analgesic effect [19]. Since its formulation in 1960, Ketamine has been used for various indications such as sedation for painful procedures [20]. There are many studies showing the analgesic efficacy of perioperative Ketamine in the acute