

■ Research Article

## The effect of preemptive analgesia on emergence delirium in tonsillectomy and adenotonsillectomy operations

### *Adenotonsillektomi ve Tonsillektomi operasyonlarında preemtif analjezinin derlenme deliryumu üzerine etkisi*

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#### Abstract

**Aim:** Emergency delirium (ED) is a phenomenon of unknown etiology, mostly seen in young children, characterised by aggressive behaviour, lack of eye contact and lack of awareness of the environment. It has been shown to have many causes, but head and neck surgery, inhaled agents and post-operative pain are the most common. The most sensitive scale available is the Paediatric Anaesthesia Emergency Delirium (PAED) scale.

Preemptive analgesia is the interruption of pain pathways before the painful stimulus occurs, and its effectiveness in post-operative analgesia has been confirmed by many studies. This study was designed with the hypothesis that post-operative pain reduced by preemptive analgesia would reduce ED.

**Material and Methods:** After ethics committee approval, 96 patients aged 2-7 years undergoing adenotonsillectomy and tonsillectomy were randomised into two groups. Analgesics were administered to the preemptive group before induction and to the intra-operative group 15 min after the start of operation. In the recovery room, ED was assessed using the PAED scale and pain scores were assessed using the Face, Legs, Activity, Cry, Consolability (FLACC) scales. FLACC>7 was pain and PAED>10 was considered emergence delirium.

**Results:** PAED and FLACC scores were significantly lower in the preemptive group. There was a significant difference in the incidence of ED between the two groups only at 5 minutes ( $p<0.01$ ). Heart rate was significantly lower in the preemptive group intraoperatively ( $p<0.01$ ).

**Conclusions:** In children undergoing adenotonsillectomy and tonsillectomy, preemptive analgesia reduced postoperative pain scores and delirium scores, but did not reduce the incidence of recovery delirium.

**Keywords:** Emergence delirium, postoperative pain, preemptive analgesia, tonsillectomy.

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## Öz

**Amaç:** Derlenme deliryumu etiyojisi tam olarak bilinmeyen, çoğunlukla küçük çocuklarda görülen, agresif davranışlar, göz teması eksikliği ve çevrenin farkında olmamakla karakterize bir fenomendir. Birçok sebepten kaynaklanabileceği gösterilmiş ancak en çok baş-boyun cerrahisi, inhaler ajanlar ve postoperatif ağrı suçlanmaktadır. Değerlendirmek için bazı skalalar kullanılır. Duyarlılığı en yüksek olan Pediatrik Anestezi Deliryum Skalası olan "PAED" (Pediatric Anesthesia Delirium Scale)'dir. Preemptif analjezi, ağrı yollarının henüz ağrılı uyaran oluşmadan kesilerek engellenmesidir ve postoperatif analjezi için etkinliği birçok çalışma ile doğrulanmıştır. Bu çalışma: preemptif analjezi yöntemi ile azaltılan postoperatif ağrının derlenme deliryumunu azaltacağı hipotez edilerek planlanmıştır.

**Gereç ve Yöntemler:** Etik kurul onayı alındıktan sonra adenotonsillektomi ve tonsillektomi operasyonu geçirecek, 2-7 yaş arası 96 hasta iki gruba randomize edildi. Analjezikler preemptif gruba indüksiyondan önce, intraoperatif gruba ise operasyonun başlamasından 15 dakika sonra uygulandı. Derlenme ünitesinde derlenme deliryumu PAED skalası ile, ağrı skorları çocuğun yüz ifadesi, bacakların pozisyonu, hareketleri, ağlaması ve avutulabilmesi değerlendirilerek yapılan "FLACC" (Face, Legs, Activity, Cry, Consolability) ağrı değerlendirme skalası ile değerlendirildi. FLACC>7 ağrı ve PAED> 10 derlenme deliryumu kabul edildi.

**Bulgular:** Preemptif grupta PAED ve FLACC skorları istatistiksel olarak anlamlı düşük bulundu ancak derlenme deliryum gelişme insidansı açısından iki grup arasında sadece 5.dakikada anlamlı fark saptandı ( $p<0.01$ ). Preemptif grubun intraoperatif tüm ölçüm zamanlarında nabız değerleri anlamlı düşük saptandı ( $p<0.01$ ).

**Sonuç:** Adenotonsillektomi ve tonsillektomi operasyonu geçiren çocuklarda uygulanan preemptif analjezi, postoperatif ağrı skorlarını ve deliryum skorlarını azaltmış ancak derlenme deliryum gelişme insidansını azaltmamıştır.

**Anahtar Kelimeler:** parasetamol, tonsillektomi, ortaya çıkma deliryum, analjezi

## Introduction

Emergent delirium (ED) is a phenomenon of unknown etiology characterised by loss of cooperation, hyperactive behaviour and perceptual changes often observed in children and adolescents on recovery from anaesthesia. Although it is usually observed in the first 20 minutes after the end of anaesthesia, it can occur as early as 5 minutes and as late as 45 minutes [1,2,3].

It is thought that 2-6 years of age, male children, anxious parents, head and neck surgery, inhalation agents and postoperative pain may be responsible for the etiology of ED [4-7]. It is characterised by crying, kicking, lack of eye contact and general lack of awareness of the environment in children [6]. Several scales are available for assessment, but the Paediatric Anaesthesia Emergence Delirium (PAED) scale has the highest sensitivity (91%) [7]. Preemptive analgesia aims to reduce the intensity and duration of pain by preventing the onset of central sensitisation before the noxious stimulus that causes pain occurs, and may also delay its onset [8,9,10]. This method provides analgesia prior to skin incision, preventing the generation of pain signals and contributing to post-operative analgesia. This has been demonstrated in published studies in a variety of surgical situations [11,12]. As

postoperative pain and ED are thought to be related, effective analgesia is expected to reduce the incidence of delirium.

In this study, we aimed to compare the effects of analgesia on postoperative ED and pain relief in children undergoing adenotonsillectomy and tonsillectomy by administering analgesia at two different times before the operation (preemptive) and intraoperative.

Hypothesis: We believe that preemptive analgesia may have a reducing effect on ED.

## Material and Methods

### Ethics

This study was approved by the our training and research hospital clinic research ethics committee (CREC) under number 2023/07. The parents of the patients were informed prior to surgery and their written informed consent was obtained. The study was conducted in accordance with the tenets of the Declaration of Helsinki.

### Study design

This is a randomised, controlled, double-blind, single-centre study to evaluate the effect of the timing of analgesic administration on postoperative emergency delirium



in patients undergoing elective adenotonsillectomy and tonsillectomy. Patients were divided into two groups: preemptive and intraoperative.

### Participants

Patients undergoing elective adenotonsillectomy and tonsillectomy, American Society of Anaesthesiologist (ASA) physical status 1-2 group, aged 2-7 years were included in the study. Children of parents who refused to participate in the study, older than 7 years, with a history of allergy to the drugs used, liver and kidney disease, asthma, bleeding diathesis, children with attention-deficit/hyperactivity disorders, psychiatric diseases and mental retardation were excluded from the study.

### Management of anaesthesia

All patients were premedicated with 0.05 mg/kg midazolam. After approximately 10 minutes, the patients were taken to the operating room for standard monitoring of peripheral oxygen saturation (spO<sub>2</sub>), electrocardiogram (ECG) and non-invasive blood pressure (NIBP).

In the preemptive group, 15 mg/kg intravenous (IV) paracetamol was administered before the induction drugs. Induction was then performed with 2 mg/kg fentanyl, 2.2 mg/kg propofol, 0.6 mg/kg rocuronium IV. Patients were intubated and anaesthesia maintained with 2% sevoflurane, 50% O<sub>2</sub>/N<sub>2</sub>O. All patients received 0.2 mg/kg dexamethasone IV.

In the intraoperative group, all steps were performed in the same order. However, 15 mg/kg paracetamol was administered 15 minutes after the start of surgery.

At the end of surgery, all patients were awakened with sugammadex and taken to the recovery room, and parents were allowed to accompany their children and comfort them.

### Outcomes

The incidence of ED in patients is the primary outcome. Secondary outcome measures are the results of the PAED (Paediatric Anaesthesia Emergency Delirium) scale used to assess ED and the FLACC (Face, Legs, Activity, Crying, Consolation) scale used to assess pain scores [7,13].

Patients' age, weight, ASA, and haemodynamic data were recorded. FLACC and PAED scores were recorded by a blinded recovery nurse at 5, 10, 20 and 30 minutes after arrival in the recovery unit. The nurse was trained in the scales used.

The PAED scale has five items: 1; eye contact, 2; intention

of actions, 3; awareness of environment, 4; anxiety and 5; inconsolability. Items 1, 2 and 3 are scored as follows: 4: none, 3: very little, 2: a little, 1: a lot, 0: extreme. Items 4 and 5 are scored in reverse order. A PAED score of  $\geq 10$  was defined as ED.

On the FLACC scale, each category is scored between 0 and 2 and the total score is between 0 and 10. 0: the child is calm and relaxed, 1-3: the child is slightly disturbed, 4-6: the child is in moderate pain, 7-10: the child is in severe pain.

As rescue analgesia, 10 mg/kg metamizole was planned for FLACC 7 and above. All patients received 4 x 1 (10 mg/kg) paracetamol for postoperative analgesia.

### Sample size

In the power analysis performed using G-Power 3.1.9.7, the 2-sample Z-test was performed with 90% power, 0.05 error and sample size as the reference, and the number of samples was calculated as 40 in each group with 90% power, taking the study by Xue Yang et al. [14] on reducing emergency delirium by 30% as an example. Taking into account a loss of 20%, the study was designed with 48 patients in each group and a total of 96 patients.

### Randomisation

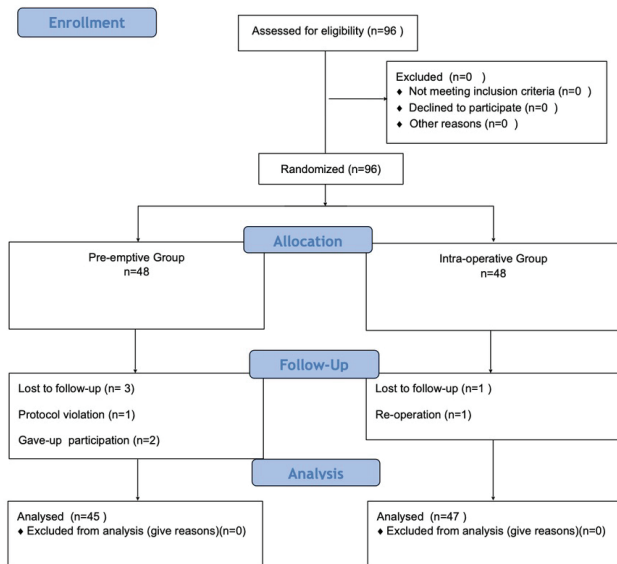
Patients were randomly assigned by placing the papers prepared on the computer with the numbers 1 and 2 in a sealed envelope and having their families draw lots. The patients and the nurse who performed the postoperative follow-up were blinded to the groups.

### Statistics

Statistical analyses were performed with IBM SPSS (Statistical Package for the Social Sciences) v23. Normality analysis of the data was performed with Shapiro-Wilk test. Normally distributed data were analyzed with Independent Sample T-test and non-normally distributed data were analyzed with Mann Whitney-U test. Qualitative data were compared with Pearson chi-square test. Data were presented as number (n) and percentage (%), mean  $\pm$  SD and median (min - max). Statistical significance value was accepted as  $p < 0,05$ .

### Results

Our study was completed with the analysis of 92 patients. In the preemptive group, one patient was excluded because of protocol violation and two patients were excluded due to their parents withdrawal from the study. In the intraoperative group one patient. In the intraoperative group, one patient was excluded because of re-operation (Figure 1).

**CONSORT 2010 Flow Diagram**

**Figure 1:** CONSORT 2010 flow diagram CONSORT: Consolidated Standards of Reporting Trials

There were 46 girls and 46 boys among the 92 patients. 45 (49%) patients received preemptive and 47 (51%) intraoperative paracetamol. The gender and age distribution was normal and similar between the two groups. There was no statistically significant difference. Weight, ASA and operating time were similar. There was no statistically significant difference between the use of preemptive analgesia and sex, age and other demographics (Table 1).

**Table 1.** Comparison of demographic and clinical characteristics of the groups

Parameters	Preemptive Group (n=45)	Intraoperative Group (n=47)	p value
Age (years) mean±SD	5.3 ± 1.7	6 ± 1	0.566
Weight (kg) mean±SD	23.5 ± 7.5	24.7 ± 8.7	0.690
ASA ps median (min-max)	1 (1 - 1)	1 (1 - 1)	1.000
Sex ; Male n (%)	26 (57.8)	20 (42.6)	0.144
Female n (%)	19 (42.2)	27(57.4)	
Operation Time(min) mean±SD	46.2 ± 17.2	46.7 ± 12.6	0.470

ASA ps: American Society of Anesthesiologist physical status, SD: Standart Deviation

The primary outcome was the incidence of ED. The preemptive group had a lower incidence of ED than the intraoperative group at all times, but there was a statistically significant

difference between the two groups at 5 minutes, 17.8% in group 1 and 38.3% in group 2 (p=0.0029) (Table 2). PAED scores were statistically significantly lower in the preemptive group at 5, 10 and 30 minutes (p:0,026, p:0,025, p:0,025) (Table 3). FLACC values were significantly lower in the preemptive group at 20 and 30 minutes (p:0,03,p:0,01) (Table 4). Among the intraoperative data, only the heart rate values were statistically significantly lower in the preemptive group at all time points (p<0.01) (Table 5). For the other data, no difference was found.

**Table 2.** Comparison of ED incidence between groups according to postoperative time points

Time points	Preemptive Group (n=45)	Intraoperative Group (n=47)	p value
5.min	8 (17.8)	18 (38.3)	0.029
10.min	5 (11.0)	11 (23.4)	0.120
20.min	1 (2.2)	3 (6.4)	0.328
30.min	0 (0)	3 (6.4)	0.085

n (%), ED: Emergence Delirium, min: minute

**Table 3.** Comparison of PAED scores between groups according to postoperative time points

Time points	Preemptive Group(n=45)	Intraoperative Group(n=47)	p value
5.min	3 (0 - 17)	8 (0 - 15)	0.026
10.min	2 (0 - 15)	6 (0 - 15)	0.025
20.min	2 (0 - 11)	4 (0 - 15)	0.084
30.min	1 (0 - 7)	3 (0 - 15)	0.025

median (min-max), PAED: Paediatric Anaesthesia Emergency Delirium, min: minute

**Table 4.** Postoperative FLACC scores between groups according to postoperative time points

Time points	Preemptive Group(n=45)	Intraoperative Group(n=47)	P value
5.min	2 (0 - 7)	3 (0 - 8)	0.184
10.min	2 (0 - 7)	3 (0 - 8)	0.170
20.min	2 (0 - 5)	2 (0 - 6)	0.034
30.min	1 (0 - 5)	2 (0 - 6)	0.010

median (min-max), FLACC :Face, Legs, Activity, Cry, Consolability, min: minute

**Table 5:** Intraoperative heart rates between the groups

Time points	Preemptive Group		Intraoperative Group		p value
	n	(mean±SD)	n	(mean±SD)	
HR 0.min	45	115 ± 13	45	124 ± 13	0.003
HR 10.min	45	115 ± 11	45	126 ± 12	<0.001
HR 20.min	45	115 ± 12	45	125 ± 13	<0.001
HR 30.min	42	111 ± 13	45	123 ± 12	<0.001
HR 40.min	28	113 ± 14	37	122 ± 12	0.011
HR 50.min	18	113 ± 13	21	126 ± 14	0.007
HR 60.min	10	116 ± 13	13	125 ± 16	0.284

HR: Heart Rate, SD: Standard Deviation, min: minute

## Discussion

In this study, the effect of preemptive analgesia on the development of postoperative recovery delirium was evaluated. Low incidence was found at all measured time points, but the incidence of ED development at 5 minutes postoperative was statistically significant in favour of the preemptive group. PAED and FLACC scores were also significantly lower in the preemptive group at all time points measured.

The adenotonsillectomy and the tonsillectomy are the most common surgical procedures performed in childhood. Tonsillectomy is defined as a surgical procedure that completely removes the tonsil with its capsule by dissection of the peritonsillar space between the tonsil capsule and the muscle wall, with or without adenoidectomy [15]. Adenoidectomy is the removal of the adenoid by shaving with a curette inserted through the mouth into the nasopharynx [16]. Postoperative management of these operations is quite difficult and the main problems are pain, bleeding and ED. During recovery, dehydration as a result of pre-operative hunger and dryness of the throat and the desire for water may be a trigger for pain and delirium in children [12,17].

Children show restless behaviour on awakening from anaesthesia, but some of this is related to pain and some to ED. Although the incidence of ED is reported to be 10-80%, the actual incidence of ED is 10-20% [4,5]. This rate ranges from 13-26% in cases of ear, nose and throat (ENT) [18]. Children may cry and scream in an agitated state, injure themselves or staff, and dislodge catheters and surgical drains. As a result of all these serious complications, the length of hospital stay can be prolonged [12,18,19]. However, it is also possible that children with post-operative pain will scream and try to get the vascular lines removed. In our daily practice it is difficult to differentiate. It has been highlighted that 15% of children experience pain and ED together [3]. Sikich et al. [7] stated that

ED should be suspected if the child has "no eye contact" and is "not aware of his/her surroundings" when interpreting the scales. In their study, Somanini and Shi et al. [20,21] used PAED and FLACC scores. They emphasised that pain and delirium are two conditions that are not easily differentiated and showed that the FLACC score increased in correlation with the PAED.

In our study, the rate of ED was generally below 26%, in line with the literature. Only at the 5th minute in the PACU we observed a rate of 38.3%. This rate can be considered real, but it can also be considered that the evaluator may have given a high value due to the similarity of PAED and FLACC scores. In our postoperative data, FLACC scores were generally high in patients with high PAED scores.

Since it is believed that postoperative pain and recovery delirium are related to each other, many studies have been conducted with different analgesics. As a result of these studies, it has been shown that the time of analgesia is more important than the type of analgesics and that preemptive analgesia is effective in postoperative analgesia [11]. Zielinski et al. [22] reported that they reduced postoperative pain scores by giving paracetamol along with oral premedication, and they believed that preemptive analgesia should be used in ENT surgery. We administered intravenous paracetamol to both groups and although the postoperative pain scores were not very high, they were significantly lower in the group that received preemptive analgesia.

Similarly, El fattah [23] stated that triple preemptive analgesia used in the multimodal analgesia protocol reduced postoperative pain scores and analgesic requirements, and intraoperative heart rate was found to be significantly lower. In our study, heart rates were found to be significantly lower in the preemptive group at all intraoperative follow-ups. Our opinion is that the use of analgesia before skin incision prevented the formation of pain signals and therefore the intraoperative heart rate was low.



McHale B et al. [24] argued that preemptive administration of ibuprofen and paracetamol in ENT cases had no effect on postoperative pain scores. In a review of a large number of studies, Jorgen B et al. [25] argued that although preemptive analgesia has an effect on acute postoperative pain, it has no clinical significance and the only way to prevent sensitivity of the nociceptive system is to completely block all types of pain signals from the moment of incision until wound healing.

Acetaminophen and ibuprofen are recommended in clinical practice guidelines for intraoperative and postoperative analgesia in ENT surgery in children, especially for tonsillectomy. Single-dose intravenous dexamethasone has been shown to be effective for postoperative analgesia and its use has been recommended [22]. We administered a single dose of dexamethasone in both the preoperative and intraoperative groups in our study protocol. As both groups were included in the protocol, we did not observe any difference.

Paracetamol is an effective postoperative analgesic. It is metabolized in the liver and toxicity occurs in very high doses. It is well tolerated and provides adequate analgesia in children undergoing tonsillectomy [22]. Both groups received paracetamol and postoperative pain scores were not high in either group. At the 20th and 30th minute, the pain scores of our preemptive group were significantly lower, and we were able to observe the effect of preemptive analgesia on the post-operative pain scores.

Several studies have been conducted on the effectiveness of reducing preoperative anxiety to reduce the incidence of ED. Premedication and psychological approaches have been found to reduce PAED scores [26]. We have pre-medicated all of our patients, and our incidence of ED has been within the expected range. Based on studies showing that hearing parents' voices and feeling parents' presence when children come to the recovery unit reduces ED by making them less alienated from the environment [27-28], we considered this in our study design and parents were taken with children after they came to the recovery unit.

ED may occur despite effective treatment of postoperative pain. It may also occur in the absence of painful stimuli. There have been studies of ED in children sedated for painless procedures such as magnetic resonance imaging and strabismus. In these studies, ED in children was attributed to prolonged fasting and thirsting periods, and it was observed that delirium decreased when fasting and thirsting periods were shortened or when oral intake was opened early [29]. Whereas in a counter-

study conducted by Özdemir et al. [30] in tonsillectomy, it was shown that fasting had no effect on delirium. We did not receive records on this, but most of our crying children had thirst-related complaints in our observations.

There have been various studies on the mechanism of development and prevention of ED, but there is no consensus on a definite algorithm for its prevention or successful elimination

## Conclusions

In this study, the use of preemptive analgesia for the prevention of postoperative pain to reduce the incidence of ED development, in which many factors play a role in its etiology, we showed that the method was effective in preventing pain, but we could not show its effectiveness in the incidence of ED development. Our conclusion is that the incidence of ED cannot be reduced by postoperative pain relief alone. We are of the opinion that there is a need for the establishment of algorithms in this area.

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