

# Remifentanil-Propofol versus Fentanyl-Propofol for Circumcision Operations in Pediatric Ambulatory Surgical Patients

## Pediyatrik Ambulatuvar Cerrahi Hastaların Sünnet Operasyonlarında Remifentanil-Propofole karşı Fentanil Propofol

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**Abstract:** Circumcision is the most frequent surgical procedure performed worldwide. The present study aimed to compare the efficacy and safety of fentanyl vs. remifentanil in pediatric patients undergoing circumcision procedure. A total of 120 boys, who were ASA (American Society of Anesthesiologists) I-II and underwent circumcision procedure, were retrospectively evaluated. Induction for anesthesia was provided using propofol that using 0,5-1 µg kg<sup>-1</sup> (n=60) in Group F and using remifentanil 0,5-1 µg kg<sup>-1</sup> (n=60) in Group R. After monitoring the patients and recording hemodynamic parameters and complications the findings every 30 minutes in peroperative and the recovery room, the patients were then followed for 6 hours. A total of 120 boys at the age of 0-2 years old who were underwent circumcision procedure, were retrospectively evaluated. The groups were comparable in terms of age, body weight, height, ASA physical status and duration of surgery that was not statistically significant. Recovery time from anesthesia was statistically significantly shorter in the remifentanil-propofol (Group R) as compared to the fentanyl-propofol (Group F). While vomiting was the most common complication in Group F, bradycardia was the most common complication in Group R. Comparison of the frequencies of complications between the groups revealed no difference in terms of bradycardia, bronchospasm, respiratory depression and allergic reaction. In conclusion, based on the results of the present study, we recommend using remifentanil-propofol in this pediatric age group but also underline the necessity of close monitoring of these patients for the potential side effects.

**Keywords:** pediatric, circumcision, remifentanil, fentanyl

**Özet:** Sünnet dünya genelinde en sık uygulanan cerrahi işlemdir. Fentanil, remifentanil ve propofol pediatri pratiğinde bu amaç için en yaygın kullanılan ilaçlardır. Bu çalışmada sünnet yapılan çocuk hastalarda fentanil veya remifentanil uygulamasının etkinliğini ve güvenilirliğinin karşılaştırılması amaçlandı. Sünnet cerrahisi uygulanan ASA I-II, 120 erkek çocuk (American Society of Anesthesiologists), retrospektif olarak çalışmaya alındı. Hastalara propofol 2-3 mg kg<sup>-1</sup> sonrasında Grup F'ye fentanil 0,5-1 µg kg<sup>-1</sup> (n=60), Grup R'ye remifentanil 0,5-1 µg kg<sup>-1</sup> (n=60) kullanılarak induksiyon yapıldı. Anestezi idamesinde sevofluran 4 L dk<sup>-1</sup> %50 hava ve oksijen %3-4 kullanıldı. Peroperatif ve derlenme ünitesinde hemodinamik verileri ve komplikasyon kayıtları alındıktan sonra hastalar 6 saat boyunca çocuk cerrahi servisinde takip edildi. Sünnet cerrahisi uygulanan 0-2 yaş, 120 erkek çocuk hastanın gruplar arasında yaş, vücut ağırlığı, boy, ASA fiziksel durumu ve operasyon süreleri arasında istatistiksel olarak fark yoktu. Remifentanil-propofol alan Grup R hastalar, Grup F alanlara göre uyanma süresi istatistiksel olarak önemli oranda kısaydı. Grup F'de kusma en sık görülen komplikasyon iken, Grup R'de ise bradikardi idi. Gruplar komplikasyon gelişimi sıklığı bakımından karşılaştırıldığında bradikardi, bronkospazm, solunum depresyonu ve alerjik reaksiyon sıklığı açısından gruplar arasında fark gözlenmedi. Sonuç olarak sünnet cerrahisi uygulanan pediatrik hastaları değerlendirdiğimiz bu çalışmada; remifentanil-propofol kullanımının bu yaş grubunda önermekle birlikte olası yan etkiler açısından hastaların yakından izlenmesinin gerekliliğini de vurgulamayı amaçladık.

**Anahtar Kelimeler:** pediatri, circumcision, remifentanil, fentanil

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## 1. Introduction

Male circumcision is the surgical removal of the foreskin, which is one of the most widely performed surgical procedures worldwide. Despite the fact that it is widely performed for religious reasons, it can be performed also for medical reasons such as phimosis and paraphimosis (1-4).

Children are the ideal patients for ambulatory surgery and anesthesia procedures. Small interventions such as adenoidectomy and circumcision are the most frequently performed ambulatory procedures (3-5). Fentanyl and propofol are the drugs used widely for this purpose in pediatrics practice. Fentanyl is a rapid-onset opioid agent reaching to peak activity in 3-5 minutes with mean duration of action nearly 30-45 minutes, which is 10 minutes for pediatric patients. Remifentanyl is a potent opioid alternative for fentanyl with rapid-onset and much shorter activity lasting for nearly 3-10 minutes (6-9). The present study aimed to compare the efficacy and safety of fentanyl vs. remifentanyl in pediatric patients undergoing circumcision procedure.

## 2. Methods

After obtaining approval of the local ethics committee, 120 boys at the age of 0-2 years old, who were ASA (American Society of Anesthesiologists) I-II and underwent circumcision procedure, were retrospectively evaluated and enrolled. Patients with hemorrhagic diathesis detected on physical examination, and the patients with history of endocrine disorder, cardiac disease and neurological disease were excluded. In all patients, premedication was provided with 0.3-0.5 mg kg<sup>-1</sup> midazolam (Dormicum®, Deva, Istanbul, Turkey) given via oral route 30 minutes prior to the procedure. The patients were admitted to the operating room and underwent IV cannulation after they were monitored; induction of anesthesia was achieved using propofol (Propofol 2%®, Fresenius Kabi, Bad Hamburg, Germany) 2-3 mg kg<sup>-1</sup> and fentanyl (Talinat®, Vem, Istanbul, Turkey) 0.5-1 µg kg<sup>-1</sup> in 60 boys (Group F) and using propofol 2-3 mg kg<sup>-1</sup> and

remifentanyl (Ultiva®, Glaxo Smith Kline, Istanbul, Turkey) 0.5-1 µg kg<sup>-1</sup> in the remaining 60 boys (Group R). Thereafter, an appropriate laryngeal mask was placed. Sevoflurane (Sevorane® Likit 100%, AbbVie, Queenborough, Kent, England) 4 L dk<sup>-1</sup> 50%, air and oxygen 3-4% (MAC (Mean Alveolar Concentration) 1.1-1.3) were used for the maintenance of anesthesia. In case the patients showed body movements, additional 0.5-1 mg kg<sup>-1</sup> propofol was administered. ECG, pulse oximetry and non-invasive blood pressure monitoring were performed in all patients both before the procedure and every 5 minutes after the procedure in the recovery room. Postoperative analgesia was provided using 10-20 mg/kg rectal paracetamol and dorsal penile nerve block. After monitoring for 30 minutes in the recovery room, the patients were then followed-up in the pediatric surgery clinic.

### *Statistical analysis*

The analysis of data was done using SPSS for Windows 23 package program. While evaluating the study data, descriptive statistics were presented as mean and standard deviation (Mean, SD). Comparison of the quantitative data between the groups was done by Mann Whitney U test. Comparison of categorical variables between the groups was done by chi-square test; continuous variables with normal distribution were evaluated using One Way Analysis of Variance, while continuous variables without normal distribution were evaluated using Kruskal-Wallis Variance Analysis. Statistical significance was evaluated at the level of  $p < 0.05$ .

## 3. Results

A total of 120 boys at the age of 0-2 years old were enrolled into the study. The mean age of the patients was  $14 \pm 10$  months. The mean body weight was  $12.6 \pm 3.8$  kg, height was  $78 \pm 8$  cm and mean duration of surgery was  $14.9 \pm 2.6$  minutes. Sixty boys in Group F received propofol/fentanyl, while 60 boys in Group R received propofol/remifentanyl. The groups

were comparable in terms of age, body weight, height, ASA physical status and duration of surgery. Demographic and clinical characteristics of the groups are summarized

in Table 1. Time to recovery from anesthesia was statistically significantly shorter in the remifentanyl-propofol groups as compared to the fentanyl-propofol group.

**Table 1.** Demographic characteristics of the groups

Variables	Group F (n=60) Mean±SD	Group R (n=60) Mean±SD	P
Age, month	16 ± 8	15 ± 9	0.459
Body weight, kg	12.7 ± 4.3	12.4 ± 3.4	0.427
Height, cm	78 ± 8	79 ± 7	0.627
Duration of surgery, min	15.2 ± 3.2	14.6 ± 2.1	0.572
Time of recovery, min	9.4 ± 3.2	4.2 ± 2.8	0.001

*SD, standard deviation*

All of the patients were evaluated in terms of the complications of anesthesia during the procedure and in the first 6 hours after the procedure. Vomiting, the most common complication in Group F, was seen in 7 patients (11%), whereas it was seen in only one patient in Group R. Bradycardia was the most common complication in Group R and seen in 5 patients, whereas it was seen in 3 patients in Group F. Comparison of the complications between the groups revealed no difference in terms of the frequency of bradycardia, bronchospasm, respiratory depression and allergic reaction. Vomiting was statistically significantly more frequent in Group F vs. Group R, whereas intraoperative

bradycardia was more prevalent in Group R vs. Group F, but it was not statistically significant (Table 2). Atropine 0.01 mg kg<sup>-1</sup> was administered in the patients with bradycardia, and bradycardia did not occur again. Allergic reaction, which was seen in 5 patients in Group F and 4 patients in Group R, was in the form of mild urticarial rash. It did not recur after a single dose of 1 mg kg<sup>-1</sup> antihistamine administration (pheniramine hydrogen maleate). Bronchospasm resolved spontaneously in the patients suffering from bronchospasm in both groups. None of the children developed serious complication during or after the procedure.

**Table 2.** Distribution of anesthesia-related complications among groups

Variables	Group F (n=60) n (%)	Group R (n=60) n (%)	P
Bronchospasm	3 (5)	2 (3.3)	0.475
Respiratory depression	2 (3.3)	1 (1.6)	0.346
Vomiting	7 (11)	1(1.6)	0.003
Allergic reaction	5 (8.3)	4 (6.6)	0.489
Bradycardia	3 (5)	5 (8.3)	0.136

#### 4. Discussion

Although circumcision for medical reasons is performed due to certain indications, it is more frequently performed because of religious and cultural beliefs (2-5). In a survey evaluating the anesthesiologists' opioid drug

preferences during circumcision procedure in children, which is the most appropriate group of patients for ambulatory anesthesia, it was reported that propofol and fentanyl have been used in the substantial proportion of the cases

but that remifentanil has been preferred much lesser (10). In the present study, we observed that fast-acting remifentanil has been successfully used in 0-2-year-old pediatric patients undergoing ambulatory circumcision surgery with faster recovery from anesthesia and lower side effects as compared to the children receiving fentanyl. This study was considered worth presenting because there is no study yet in the literature comparing these two opioid analgesics in the pediatric patients undergoing circumcision procedure.

Sevoflurane is an inhalation agent halogenated with fluorine. It is a potent inhalation anesthetic that provides rapid induction and the control of depth of anesthesia allowing rapid recovery from anesthesia because of its low solubility character. Sevoflurane provides adequate muscle relaxation for intubation following inhalation induction. Moreover, contrary to the other halothanes, it does not depress myocardial contractility in children (11-12). We as well used sevoflurane, which is recommended most in childhood in the literature, for the maintenance of anesthesia following induction in both groups.

Propofol is the most widely used sedative agent in pediatric patients owing to rapid onset and short action as well as easy titration during anesthesia care. It is usually used in combination with an opioid analgesic to reduce surgical procedure-related discomfort. Propofol infusion syndrome, which is a rarely encountered but very serious condition resulting in death, can occur due to long-term use of high-dose propofol in critical pediatric patients (13,14). Nevertheless, it was demonstrated that using propofol for short-term surgical procedures in healthy children does not cause this syndrome (15). In the present study group, we did not encounter this very rare condition because study inclusion criteria comprised the condition of being healthy, and duration of surgical procedure was short.

Fentanyl is a synthetic opioid agonist derived from meperidine. Drug interactions are in question for fentanyl as it is a substrate of hepatic cytochrome enzymes. Owing to its

being lipid-soluble, it rapidly passes through the blood-brain barrier causing rapid-onset of action. Both the analgesic and respiratory depressant activities of this drug are prolonged with multiple doses and continuous administration (10,15-16). It is also used to provide postoperative analgesia in painful surgical procedures (6-8). Fentanyl does not lead to histamine secretion as it does not generate active metabolite, hence, it enables hemodynamic stability as compared to morphine. It rarely causes dose-dependent rigidity in the chest wall (6-9,16).

Analgesic efficacy of remifentanil, a selective opioid agonist, is similar to that of fentanyl. Remifentanil, which is structurally different, is hydrolyzed into the metabolites by non-specific plasma and tissue esterases. Rapid-onset and short activity due to this property are responsible for non-cumulative effects and rapid recovery. The anesthesia can be started in 60-90 sec with remifentanil in the cases a temporary analgesic efficacy is targeted (16,17). Remifentanil-associated potential side effects are unlikely with correct usage. Slow administration and avoiding repeated administrations can prevent development of bradycardia, hypotension and chest wall rigidity (7-9). In a study conducted with newborns receiving fentanyl and remifentanil, no difference was determined between the groups in terms of mean intubation time as well as total laryngoscopy time, time to the spontaneous breathing, heart rate, blood pressure, oxygen saturation and the number of attempts made for intubation. Different from fentanyl, remifentanil was associated with chest wall rigidity in two patients. This side effect was explained by the remifentanil dose's being  $> 3$  mcg/kg<sup>(6)</sup>. In the present study, the most common side effect in the group receiving remifentanil was bradycardia, which did not recur in any of the patients after a single dose of atropine administration. Chest wall rigidity was not encountered in any of the patients receiving remifentanil.

The mean extubation time with remifentanil is 8-13 minutes due to its rapid-onset and short activity. Remifentanil is used in the newborns and pediatric patients for sedation and analgesia during flexible bronchoscopy,

endoscopy, cardiac electrophysiological studies, premature retinopathy and bone marrow aspiration procedures (5-8,10,17). In the present study, time to recovery from anesthesia was significantly shorter in the patients receiving remifentanyl as compared to the patients receiving fentanyl, which is consistent with the literature.

Nausea and vomiting are the most common documented side effects of fentanyl in childhood. Likewise, these side effects are frequently encountered also in adults. Remifentanyl is associated with lower incidence of nausea and vomiting as compared to fentanyl. Less commonly, seizures, arrhythmia and hypersensitivity can be seen as well (5-8,13). In a study, the frequency of postoperative vomiting was evaluated in a pediatric patient group undergoing strabismus surgery and vomiting was determined in one of every two patients. Reevaluating the frequency of vomiting with different opioids, number of vomiting attacks per patient was found to be lower in the remifentanyl group as compared to the fentanyl group. The authors stated that remifentanyl is less anti-emetic than fentanyl (18). In the present study, consistent with the literature, vomiting was the most common side effect in the fentanyl group. Studies in the literature suggest propofol as a drug with anti-emetic efficacy (19). Opioid-related vomiting and vomiting-like situations have been reported more frequently (6-8,13,16-18). Lower rate of vomiting in the present study vs. the literature might have resulted from propofol used for the management of

anesthesia. Again, consistent with the literature, vomiting as a side effect was more common in the patients receiving fentanyl as compared to the patients receiving remifentanyl.

No difference was determined between the frequencies of bronchospasm, which was encountered in both groups. In the literature, there was no study comparing fentanyl with remifentanyl in terms of respiratory problems. Bronchospasm usually occurs due to allergy, malposition of the endotracheal tube, airway irritation, and aspiration related to the laryngeal mask (20). Nevertheless, although a recent study reported lower prevalence rate for bronchospasm after LMA vs. intubation, it was similar to that reported in the present study (21).

## 5. Conclusion

Along with the development of ambulatory pediatric anesthesia procedure, the targets of providing patient hemodynamics and minimal side effect, rapid patient discharge, and patient preparation for discharge from the hospital with a reasonable cost have been the main factors in determining the anesthesiologists' anesthetic selection. In the present study, we evaluated for the first time the most appropriate opioid analgesic for the pediatric patients undergoing ambulatory circumcision procedure; although we recommend using remifentanyl in this age group as it is associated with fast recovery from anesthesia, we also intended to underline the necessity of close patient monitoring for the potential side effects.

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