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Araştırma/*Research Article*

Comparison of the Intraoperative Hemodynamic Effects of Remifentanil and Fentanyl in Pediatric Cardiac Surgery Anesthesia

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Pediyatrik Kalp Cerrahisi Anestezisinde Remifentanil ve Fentanilin İntraoperatif Hemodinamik Etkilerinin Karşılaştırılması

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ABSTRACT

Objective: *The aim of this prospective observational study was to compare the hemodynamic effects of remifentanil and fentanyl, which are used as intraoperative analgesics in pediatric cardiac surgery.*
Methods: *Patients were divided into two groups as those who received continuous intravenous remifentanil infusion (Group R) or intermittent intravenous fentanyl for intraoperative analgesia (Group F). These groups were compared in terms of hemodynamic characteristics and intraoperative complications.*
Results: *The most common congenital cardiac pathology observed in the patients included in the study was ventricular septal defects (32%). Intraoperative complications occurred in 21 (40%) patients, and ventricular fibrillation was the most common complication (n=6; 11.5%). When the patients in both groups were compared in terms of intraoperative hemodynamic indicators, the mean arterial pressure values of the patients in Group R after sternotomy were significantly lower than those of the patients in Group F (p=0.034). No statistically significant difference was found between the two groups in terms of other hemodynamic indicators. When the two groups were compared in terms of intraoperative complications, the difference was not statistically significant although the number of patients with complications was higher in Group F (p=0.1).*
Conclusion: *As a result of this study, it was found that remifentanil was as effective as fentanyl in maintaining intraoperative hemodynamic stability in patients undergoing pediatric cardiac surgery.*

Keywords: *cardiovascular anesthesia, congenital heart disease, fentanyl, opioid analgesics, remifentanil*

ÖZ

Amaç: *Bu prospektif gözlemsel çalışmanın amacı, pediyatrik kalp cerrahisinde intraoperatif analjezik olarak kullanılan remifentanil ve fentanilin hemodinamik etkilerini karşılaştırmaktı.*
Yöntem: *Hastalar intraoperatif analjezi amacıyla sürekli intravenöz remifentanil infüzyonu uygulananlar (Grup R) ve aralıklı intravenöz fentanil uygulananlar (Grup F) üzere iki gruba ayrıldı. Gruplar hemodinamik özellikler ve intraoperatif komplikasyonlar açısından karşılaştırıldı.*
Bulgular: *Çalışmaya dahil edilen hastalarda en sık görülen doğumsal kalp patolojisi ventriküler septal defektlerdi (% 32). İntraoperatif komplikasyonlar 21 hastada (%40) meydana geldi ve en sık görülen komplikasyon ventriküler fibrilasyondu (6 hasta, %11,5). Her iki gruptaki hastalar intraoperatif hemodinamik göstergeler açısından karşılaştırıldığında, Grup R'deki hastaların sternotomi sonrası ortalama arteriyel basınç değerleri Grup F'deki hastalara göre anlamlı olarak düşüktü (p=0,034). Diğer hemodinamik göstergeler açısından iki grup arasında istatistiksel olarak anlamlı bir fark bulunamadı. İki grup intraoperatif komplikasyonlar açısından karşılaştırıldığında, Grup F'de komplikasyon gelişen hasta sayısı daha yüksek olmasına rağmen fark istatistiksel olarak anlamlı değildi (p=0,1).*
Sonuç: *Bu çalışma sonucunda pediyatrik kalp cerrahisi geçiren hastalarda intraoperatif hemodinamik stabilitenin sağlanmasında remifentanilin fentanil kadar etkili olduğu saptanmıştır.*

Anahtar kelimeler: *fentanil, kardiyovasküler anestezi, konjenital kalp hastalıkları, opioid analjezikler, remifentanil*

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INTRODUCTION

Anesthesia for pediatric cardiac surgery is one of the most challenging applications of anesthesia because of the presence of physiological mechanisms in pediatric patients that are very different from those in adults and the complex surgical procedures it involves. The quality of surgical repair, effects of cardiopulmonary bypass, and postoperative care process are the main factors affecting morbidity and mortality in patients, especially in surgical procedures performed for congenital heart diseases. A carefully planned and applied anesthesia regime is another crucial factor [1]. The risk of morbidity and mortality in pediatric cardiac surgery is at least two to three times more than that of cardiac surgery in adults [2]. Therefore, the selection and appropriate dosing of drugs used in anesthesia for pediatric cardiac surgeries are vital issues.

One of the drug groups that are frequently used in pediatric cardiac anesthesia is opioid analgesics. Opioids are analgesic drugs that are used to prevent the response to painful stimulations during the surgical procedure. One of the most important reasons why these drugs are preferred as analgesics in pediatric anesthesia is that they do not cause myocardial depression [3,4]. Due to this characteristic, opioid analgesics such as fentanyl and sufentanil are commonly used in the induction and maintenance of anesthesia in pediatric patients with limited cardiac reserve [1,5]. It has been emphasized in some studies that, in addition to fentanyl and sufentanil, remifentanil is as effective as other opioids and provides even better hemodynamic stability in open heart surgical procedures [6,7]. However, most of these studies are conducted in adult patients, and only a limited number of studies are available in the literature on the use of remifentanil in pediatric patients undergoing cardiac surgery.

The most important characteristic of remifentanil is that it creates a strong analgesic effect by quickly relieving pain without disturbing hemodynamics [8]. However, since it is rapidly inactivated by nonspecific esterases in blood and tissue, it does not accumulate in the body even in long-term and high-dose applications, unlike other opioids [5,9]. Furthermore, remifentanil metabolism does not involve the kidney and liver, making it preferable as an intraoperative analgesic in patients with kidney and liver failure [6]. In addition to these positive characteristics, remifentanil, like fentanyl, may cause a dose-dependent decrease in heart rate, arterial blood pressure, and cardiac output [6].

Based on this information, we designed this study based on the idea that the use of remifentanil as an intraoperative analgesic may be as effective as other opioids in pediatric cardiac surgery cases, and we aimed to compare the intraoperative hemodynamic effects of fentanyl and remifentanil in pediatric patients undergoing open heart surgery. Secondly, it was aimed to compare fentanyl and remifentanil in terms of intraoperative complication development and postoperative inotrope requirement in this patient group.

MATERIAL and METHODS

Study Design, Population, and Data

This prospective observational study was performed at SBÜ Gazi Yaşargil Education and Research Hospital between November 2019 and January 2021, following ethics committee approval (10/25/2019; 359). All relatives of the patients were informed about the study, and informed consent was obtained from the parents. The study was conducted in accordance with the 2008 Helsinki Declaration.

The study included pediatric patients aged 0–10 years who had congenital cardiac pathologies and underwent American Society of Anesthesiologists grade II–III and elective open cardiac surgery. Patients outside the specified age range; those requiring urgent surgery; those who underwent any surgery other than congenital heart surgery repair; patients who admitted to American Society of Anesthesiologists grade IV; and those with severe left ventricular dysfunction and major organ damage (e.g., patients with acute–chronic renal failure, acute-chronic hepatic failure, or severe lung disease, etc.) were excluded from the study.

During the study, pediatric cardiac surgery patients were operated by five different anesthesiologists and four pediatric cardiac surgery specialists. While some anesthesiologists preferred fentanyl as an intraoperative analgesic, others preferred remifenta-

nil. After determining the number of patients required as a result of the power analysis, the patients were divided into two groups, according to the type of intraoperative analgesic used and evaluated accordingly, without any randomization. Patients who received fentanyl constituted Group F (n=25), whereas patients who received remifentanil comprised Group R (n=27). Along with demographic data of both groups such as age, sex, and body surface area, preoperative and intraoperative heart rate, mean arterial pressure, central venous pressure, surgery duration, anesthesia duration, cross-clamp duration, cardiopulmonary bypass duration, right and left near-infrared spectroscopy values, urine output, whether modified ultrafiltration was applied, intraoperative complications, and inotropes applied after cardiopulmonary bypass were recorded. The effects of fentanyl and remifentanil on intraoperative hemodynamic indicators were evaluated using preoperative heart rate and mean arterial pressure values, as well as heart rate, mean arterial pressure, and central venous pressure measurements obtained after intraoperative intubation, after skin incision, after sternotomy, after cardiopulmonary bypass, and before transfer to the intensive care unit.

Preoperative and intraoperative routine

The patients were evaluated in the ward where they were hospitalized the day before the surgery as a routine procedure. Their pre-anesthetic physical examinations were performed, lab tests were evaluated, parents were informed, and the parents' consent was obtained for anesthesia. Preoperative blood and blood product preparations were made according to patient characteristics and type of surgery. Necessary preoperative consultations were requested.

After the patients were taken to the operating room, they were monitored with electrocardiogram, pulse oximeter, and noninvasive blood pressure measurements. For induction of anesthesia, propofol (1-3 mg/kg, intravenous) was administered as a general anesthetic, fentanyl (1-2 µg/kg) as an analgesic, and rocuronium (0.6-0,9 mg/kg) as a neuromuscular blocker to the patients in both groups. For patients weighing less than 10 kg, midazolam (1-2 mg/kg) was administered as an intravenous anesthetic agent instead of propofol for induction of anesthesia. In cases where peripheral venous access is difficult to obtain, induction of anesthesia was achieved with 3.5-4% sevoflurane. After the patients were intubated, they were connected to a mechanical ventilator in a pressure-controlled mode. Invasive arterial blood pressure monitoring and central venous pressure monitoring were performed in all patients. Near-infrared spectroscopy monitoring was performed in the patients before the surgical procedure started. In both groups, anesthesia was continued with 2% sevoflurane (inhaler agent concentration was adjusted according to the heart rate and mean arterial pressure of the patients), 50% O_2, and 50% air mixture. In addition, while intravenous fentanyl at a dose of 1 µg/kg was administered every 30 µg/kg/min minutes to the patients in Group F for the maintenance of intraoperative analgesia, the patients in Group R were administered intravenous remifentanil at a dose of 0.02-0.2 µg/kg/min as a continuous infusion. Remifentanil dose was started at a dose of 0.1. The infusion rate was decreased and increased according to the changes in the hemodynamic status (such as hypotension, bradycardia). When hemodynamic changes such as hypotension or bradycardia developed in patients, the cause was first investigated (such as mechanical ventilator connections, appropriate fluid replacement, and surgical complication). After the appropriate fluid replacement was provided, the concentration of sevoflurane and the dose of opioid used for maintenance was reduced. However, when there was no improvement, inhaler agent and opioid were completely discontinued, and then inotropic support (dopamine, noradrenaline) was started. The remifentanil infusion administered to the patients was discontinued after the surgical procedure was completed. All patients were transferred to the intensive care unit without being extubated.

Statistical Analysis

G-Power software (version 3.1.9.4; University of Kiel, Kiel, Germany) was used to calculate the required sample size based on a previous study. The minimum number of patients required was 52 (25 in the fentanyl group and 27 in the remifentanil group), assuming a two-tailed alpha error of 0.05, power of 0.80, allocation ratio of N2/N1=1.1, and effect size of 0.8.

SPSS 16.0 software for Windows (SPSS Inc., Chicago, IL, USA) was used for the statistical analysis.

Continuous data are expressed as mean and standard deviation; categorical data are expressed as frequency and percentage. The categorical data of the groups were compared using the chisquare and Fisher exact tests. The Shapiro-Wilk test was used to determine whether the numerical data were normally distributed. Student's t-test was used to analyze data with a normal distribution, while the Mann – Whitney U test was used to analyze non-normally distributed data. In all comparisons, $p < 0.05$ was considered significant.

RESULTS

The mean age of the 52 patients included in the study was 17.06 ± 24.6 months. The most common congenital cardiac pathologies observed in pediatric patients undergoing surgery were ventricular septal defects (32%), patent ductus arteriosus (28%), tetralogy of fallot (23%), and atrial septal defects (19%), in order. In addition, seven patients (13%) had total anomalous pulmonary venous return, and six patients (11%) had hypoplastic left heart syndrome, which are rarer cardiac pathologies. Intraoperative complications were observed in 21 patients (40%), the most common intraoperative complications were ventricular fibrillation (six patients, 11.5%), atrioventricular block (five patients, 9.6%), and bradycardia (five patients, 9.6%). In addition, intraoperative cardiac arrest developed in two patients, and short-term cardiopulmonary resuscitation was performed in these patients. The demographic characteristics and preoperative data of the patients are presented in Table 1. When the patients in Group F and Group R were compared in terms of demographic, as well as preoperative and intraoperative characteristics, it was determined that the mean age of the patients in Group R was lower than that in Group F and that the patients in this group consisted of more male patients than expected. In addition, it was found that the duration of cardiopulmonary bypass was significantly higher in patients in Group R than those in Group F (p=0.03) (Table 1).

When both groups were compared in terms of intraoperative hemodynamic indicators, the mean arterial pressure values after sternotomy of the patients in Group R were significantly lower than those of the patients in Group F (p=0.034). There was no significant difference between the two groups in terms of other parameters (Table 2, Figures 1 and 2).

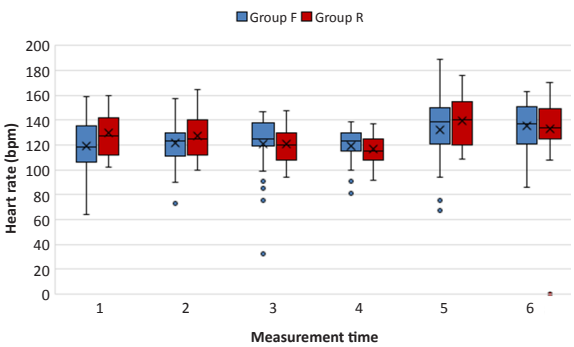

Figure 1. Effects of drugs on intraoperative heart rate.

Tablo 1. Comparison of demographic, preoperative and intraoperative characteristics of patients.

Characteristic	All patients (n=52) Mean±SD	Grup F (n=25) Mean±SD	Group R (n=27) Mean±SD	p value
Age (month)	17,06±24,6	20,06±26,0	14,2±23,3	0,5
Body surface area (m^2)	0,46±0,19	0,46±0,17	0,46±0,21	0,97
Gender				0,026
Female	27 (51,9%)	17 (68%)	10 (37,0%)	
Male	25 (48,1%)	8 (32%)	17 (63,0%)	
Preoperative heart rate (beats/minute)	124,76±19,5	119,6±20,7	129,5±17,5	0,06
Preoperative MAP* (mmHg)	57,9±16,4	58,3±15,9	57,5±17,2	0,86
Preoperative NIRS†-Right	65,4±8,92	64,7±9,6	66,07±8,2	0,6
Preoperative NIRS-Left	64,6±12,25	64,9±15,2	64,3±8,8	0,85
Surgery time (minute)	309,9±80,2	304,6±88,3	314,8±73,4	0,61
Anesthesia time (minute)	365,1±90,5	358,6±94,9	371,2±87,7	0,44
Cardiopulmonary bypass time (minute)	149,8±73,8	130,3±59,3	168±82,08	0,03
Cross- clamp time (minute)	85,3±47,4	72,6±45,6	97,1±46,8	0,18

**Mean arterial pressure; †Near infrared spectroscopy*

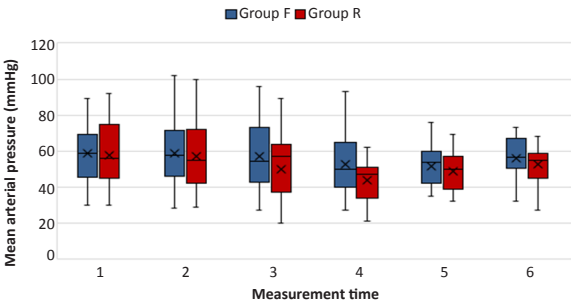

Figure 2. Effects of drugs on intraoperative mean arterial pressure.

Patients in both groups were compared in terms of other intraoperative characteristics (urine output, near-infrared spectroscopy, modified ultrafiltration, intraoperative complications, and inotrope support requirement). There was no significant difference between the two groups in terms of urine output, right and left near-infrared spectroscopy values, modified ultrafiltration, and inotrope support requirement. Although the number of patients with intraoperative complications was higher in Group F, the difference was not statistically significant (p=0.1) (Table 3).

DISCUSSION

This study demonstrated that intravenous continuous remifentanil infusion can be used as an analgesic in pediatric patients undergoing cardiac surgery without compromising intraoperative hemodynamic stability. The results obtained were similar to those patients administered with intermittent intravenous fentanyl. In addition, although it was not statistically significant, it was found that less intraoperative complications developed in patients who received remifentanil than in those who received fentanyl.

In previous studies, it has been reported that the use of opioid analgesics in combination with other anesthetic agents in general anesthesia provides analgesia without disturbing hemodynamic stability by reducing cardiovascular depression [7,10]. This provides an important advantage in cases where hemodynamic stability can be lost very quickly such as in pediatric cardiac surgery. Opioids affect the heart rate, inotropic state, vascular function, and cellular adaptation to ischemic damage through opioid receptors located outside the central nervous system [11]. Consequently, undesirable hemodynamic

Tablo 2. Comparison of the intraoperative hemodynamic data of groups.

Characteristic	All patients (n=52) Mean±SD	Grup F (n=25) Mean±SD	Group R (n=27) Mean±SD	p value
After entubation				
Heart rate (beats/minute)	124,5±18,2	121,4±18,7	127,3±17,7	0,24
Mean arterial pressure (mmHg)	57,5±18,03	57,9±17,5	57,1±18,8	0,87
CVP* (mmH_2O)	6,05±3,07	5,52±2,95	6,55±3,15	0,22
After skin incision				
Heart rate (beats/minute)	121,6±19,8	122,3±24,6	120,9±14,5	0,8
Mean arterial pressure (mmHg)	53,8±19,4	57,8±21,3	50,1±17,1	0,15
CVP (mmH_2O)	6,21±3,1	5,8±2,53	6,59±3,55	0,36
After sternotomy				
Heart rate (beats/minute)	118,4±12,6	120,7±13,5	116,4±11,6	0,22
Mean arterial pressure (mmHg)	48,3±15,3	53±17,3	44±11,8	0,034
CVP (mmH_2O)	5,65±3,01	5,24±2,36	6,03±3,51	0,37
After cardiopulmonary bypass				
Heart rate (beats/minute)	136,4±22,8	133,4±26	139,2±19,5	0,36
Mean arterial pressure (mmHg)	50,3±10,7	51,9±11,4	48,8±10	0,3
CVP (mmH_2O)	6,98±3,38	7,0±3,55	6,96±3,28	0,9
Before transfer to ICU†				
Heart rate (beats/minute)	136,4±22,4	137,4±17,8	135,4±26,3	0,74
Mean arterial pressure (mmHg)	54,2±10,9	56,08±11,8	52,4±10	0,24
CVP (mmH_2O)	7,8±3,4	7,92±3,91	7,7±2,91	0,82

**Central venous pressure; †Intensive care unit*

Tablo 3. Comparison of the intraoperative characteristics of the groups.

	All patients (n=52) Mean±SD	Grup F (n=25) Mean±SD	Group R (n=27) Mean±SD	p value
Initial values at the start of the operation				
Urine output (ml)	14,5±33,05	16,9±26,4	12,4±38,5	0,17
NIRS*-Right (%)	65,4±8,92	64,7±9,6	66±8,2	0,6
NIRS-Left (%)	64,6±12,2	64,9±15,2	64,3±8,8	0,85
The values at the end of operation				
Urine output (ml)	281,5±259,1	305,6±278,2	259,2±243,1	0,46
NIRS-Right (%)	69,1±8,4	67,1±8,8	70,9±7,8	0,1
NIRS-Left (%)	69,9±8,8	68,4±9,2	71,3±8,3	0,23
Modified ultrafiltration (Yes/No)	22/30	10/15	12/15	0,74
Complication (Yes/No)	21/31	13/12	8/19	0,1
After CPB† inotrop support				
Adrenaline (Yes/No)	31/21	14/11	17/10	0,6
Noradrenaline (Yes/No)	13/39	7/18	6/21	0,63
Dopamine (Yes/No)	29/23	15/10	14/13	0,55
Milrinone (Yes/No)	50/2	23/2	27/0	0,22

**Near infrared spectroscopy; †Cardiopulmonary bypass time*

changes such as hypotension and bradycardia may sometimes occur depending on the type and dose of opioid medication used in patients [11]. These undesirable effects may cause more serious problems, especially in pediatric patients with congenital heart disease, due to pharmacokinetic changes in the drugs [12]. However, remifentanil stands out among opioids as a suitable option for pediatric patients with congenital heart disease due to its metabolism that is independent of age and organ functions [12].

Although there is a limited number of publications in the literature on the use of remifentanil and other opioids in pediatric cardiac surgery, there are studies on the use of remifentanil and other opioids in adult cardiac surgery and other surgeries. Huang et al. evaluated 152 pediatric patients with atrial septal defect and emphasized that remifentanil-based fast-track anesthesia was as effective as fentanyl-based routine anesthesia in intraoperative device closure of atrial septal defect operations [8]. They reported that there was no difference between the two groups in terms of intraoperative hemodynamic values [8]. Khanykin et al. have reported in their study examining 64 adult patients who underwent cardiac surgery that remifentanil did not have an adverse effect on myocardial function. It was found to be equally effective and safe as low-dose fentanyl administration; however, it had no advantage over low-dose fentanyl administration [3]. In another study conducted on adults, Lison et al. compared remifentanil and sufentanil in fast-track cardiac surgery anesthesia, and as a result of the study, they reported that remifentanil was more effective than sufentanil in suppressing the response to surgical stimulations in these cases [5]. However, it was emphasized that postoperative pain management should be planned carefully in patients who received remifentanil [5]. In our study, there was no significant difference between remifentanil and fentanyl groups in terms of hemodynamic values measured after intraoperative intubation, skin incision, sternotomy, cardiopulmonary bypass, and before transfer to intensive care unit. Only mean arterial pressure value measured after sternotomy was lower in the remifentanil group. Based on these results, we believe that continuous intravenous remifentanil infusion provides as good intraoperative hemodynamic stability as intermittent intravenous fentanyl administration does in pediatric cardiac surgery anesthesia.

Cardiovascular complications that may develop due to fentanyl and its analogs (such as sufentanyl, remifentanil, alfentanil), which are synthetic opioids, may occur mostly in case of administration of these drugs at high doses [7,11,13,14]. Among these complications, the most common are various arrhythmias (such as bradycardia and tachycardia), hypotension, and more rarely, hypertension [13]. Fentanyl and opioids, which are its analogs, are known to have mini-

mal effects on the cardiovascular system [14]. In addition, hypotension and prolongation of the QT interval as a result of a decrease in cardiac output and stroke volume are rare side effects at high doses [14]. The most common intraoperative complications in our study were ventricular fibrillation, atrioventricular block, and bradycardia, and these complications were more common in the fentanyl group. We believe that these complications did not develop directly due to the medication. This is because the patients included in the study were those who already had congenital heart diseases and underwent serious surgical repair. The risk of developing complications was high because of their existing conditions and the procedures performed. Although the difference in the incidence of intraoperative complications between the two groups was not statistically significant, the lower rate of complications in the remifentanil group led us to believe that remifentanil may be a more appropriate choice than fentanyl in pediatric patients undergoing cardiac surgery. However, it is clear that more studies are needed on this subject.

Based on the results of this study, it was found that remifentanil, one of the most commonly used opioid analgesics in general anesthesia, is as effective as fentanyl in providing intraoperative hemodynamic stability in pediatric patients undergoing cardiac surgery. Moreover, patients who received remifentanil developed less intraoperative complications.

This study has several limitations. The first is that the study was single-centered. Prospective studies on the subject with larger patient series and involving multiple centers may provide clearer results. Another limitation of our study was the age of the participants. Pediatric patients aged 0–10 years were included in our study. Performing the study separately in newborns and other pediatric age groups may potentially lead to different results. However, pediatric cardiac surgeries are already performed rarely and in a limited number of centers; therefore, this will take a considerable amount of time. We will conduct further studies on this topic in the coming years.

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