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Klinik Çalışma

Effects of Remifentanil and Fentanyl on Postoperative Pain and Recovery in Fast-Tract Cardiac Surgery

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SUMMARY

Objective: *The effectiveness of remifentanil infusion and fentanyl bolus provided by patient-controlled analgesia on postoperative pain and recovery of patients undergoing pre-planned fast-track cardiac surgery was studied.*

Material and Methods: *Anaesthesic combination of sevofloran and remifentanil were applied to 42, ASA II group patients undergoing fast-track coronary artery bypass graft surgery. Patients were divided into two groups. In Group 1 (remifentanil group), 0.1 μg kg^{-1} min^{-1} remifentanil infusion was given postoperatively by patient-controlled analgesia device. In Group 2, fentanyl was administered at 10 μg kg^{-1} loading dose 5 minutes before the end of surgery. After fentanyl administration, fentanyl bolus protocol was started to be applied at 0.1 μg kg^{-1} bolus dose with 8 minutes lockout time. Pain scores, sedation levels and additional analgesic requirements were recorded for the first 4 hours at every 15 minutes and then at 12., and 24. hours postoperatively.*

Results: *There was no difference between groups as for analgesic effectiveness. The sedation levels were lower postoperatively during the first two hours in Group 1. After two hours, sedation levels were similar between the two groups.*

Conclusion: *Remifentanil can be used at analgesic doses during the recovery period of patients undergoing fast-track cardiac surgery.*

Key words: *coronary by-pass, fast-track, postoperative pain*

ÖZET

Fast-track Kardiyak Cerrahide Remifentanil ve Fentanilin Postoperatif Ağrı ve Derlenme Üzerine Etkilerinin Karşılaştırılması

Amaç: *Çalışmamızda "fast-track" kardiyak cerrahi planlanan hastalarda, hasta kontrollü analjezi yöntemiyle fentanil bolus ve remifentanil infüzyon uygulamasının postoperatif ağrı ve derlenme üzerine etkilerinin karşılaştırılması amaçlandı.*

Gereç ve Yöntem: *Sevofluran ve remifentanil anestezisi uygulanan, "fast-track" koroner baypas cerrahisi geçirecek ASA II grubu 42 hasta çalışmaya dahil edildi. Hastalar rastgele iki gruba ayrıldı. Grup 1 (remifentanil grubu), 0.1 μg kg^{-1} min^{-1} postoperatif hasta kontrollü analjezi cihazı ile remifentanil infüzyon verilen grup. Grup 2, (fentanil grubu) cerrahi bitiminden 5 dakika önce 1 μg kg^{-1} fentanil bolus verilen grup. Fentanil bolus uygulamasından sonra fentanil bolus protokolü 0.1 μg kg^{-1} bolus doz ve 8 saat kilit süresi olacak şekilde düzenlendi. Postoperatif ilk 4 saatte her 15 dk. da bir, 12. ve 24. saatlerde ağrı skorları, sedasyon skorları ve ek analjezik gereksinimleri kaydedildi.*

Bulgular: *Analjezik etkinlik açısından iki grup arasında fark yoktu. Grup 1'de sedasyon seviyesi ilk 2 saat içinde daha düşük bulundu. İkinci saatten sonra sedasyon seviyeleri iki grup arasında benzerdi.*

Sonuç: *"Fast-track" kardiyak cerrahi geçiren hastaların derlenme döneminde postoperatif ağrıyı önlemede analjezik dozda remifentanil kullanılabilir.*

Anahtar kelimeler: *koroner baypas, fast-track, postoperatif ağrı*

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INTRODUCTION

The aim of the fast-track cardiac surgery anaesthesia is to provide early extubation and rapid recovery with selection of suitable anaesthesia method and agent.

At fast-track technique, early wake up at the end of operation and throbbing pain makes the technique difficult. Therefore, postoperative pain management must be planned and started at the beginning [1,2].

Although application of high dose opioids in cardiac surgery provides sufficient hemodynamic control and analgesia until postoperative period, it causes delayed extubation, long term mechanical ventilation, prolonged intensive care and hospitalization. Fast-track cardiac anesthesia technique can provide early extubation and rapid recovery with selection of suitable anaesthesia method and agents. Early extubation is likely with the improved anaesthesia, and also myocardial protection and postoperative homeostasis is possible [1-3].

The effectiveness of remifentanil infusion and fentanyl bolus provided by patient-controlled analgesia on postoperative pain and recovery of patients undergoing fast-track cardiac surgery were studied in this report.

MATERIALS and METHODS

This study was conducted with the approval of Hospital Education Coordination Committe and the consent of the patients. Forty-two patients, aged between 35-60 years were included in the study. Two patiens were excluded from the study because of technical failure or surgical complication.

The patients were informed about the operation and the intensive care the day before the operation. The patients were informed that they couldn't talk as they wake up since they were going to stay intubated for a short time. They were asked to use their fingers to score the pain ranging 0-10 (0=least; 10=worst). The patients were also informed about the patient-controlled analgesia (PCA) device. Medications were continued until the operation day. All patients were premedicated with 10 mg diazepam p.o. the night before the operation and with 0.1 mg kg^{-1} morphine-SO4 i.m. one hour before the operation. All patients were monitorized with ECG, pulse oximetry and invasive arterial blood pressure and cathetherized through two peripheral veins in the operation room. One catheter was used only for remifentanil infusion. At anesthesia induction 2 mg kg^{-1} propofol, 0.5 μg kg^{-1} remifentanil, 0.15 mg kg^{-1} pancuronium, and 1 mg kg^{-1} 2 % lidocain was used. After intubation the patients were ventilated with the mixture of oxygen (FiO_2=0.4) and sevoflurane (2 %) so that $PaCO_2$ will range between 35-45 mmHg. Then, central venous catheter (into internal jugular vein), urethral catheter and rectal probe were inserted. Remifentanil infusion rates were 0.5 μg $kg^{-1}min^{-1}$ after anesthesia induction, 0.25 μg $kg^{-1}min^{-1}$ after sternotomy, 0.125 μg $kg^{-1}min^{-1}$ at the entry of perfusion, 0.25 μg $kg^{-1}min^{-1}$ at termination of the perfusion and this last dose was maintained until the end of surgery. Sevoflurane concentration was 2 % until the onset of perfusion and applied at 1 % with vaporizator on oxygen pump during perfusion. Pancuronium was not used except for induction. Cardiopulmonary by-pass technique was applied to all patients with Medos Hilite Oxygenator (7000 membran type) in standard conditions. The pump flow was calculated with the formula: body surface x 2.4. According to surgeon's choice, middle hypothermic (<32°C), low hypothermic (32-36°C) or normothermic (36°C) cardiopulmonary bypass (CBP) procedures were performed. The patients were warmed up to 36.5°C at the end of CPB.

The patients were randomized in two groups. The doctors who followed the patient at the operation room and those who scored the patients's perception of pain were blinded to the groups. Remifentanil infusion was started in Group 1 (remifentanil group) at the dose 0.1 μg $kg^{-1}min^{-1}$ with PCA device. Fentanyl was given to patients in Group 2 at the loading dose of 1 μg kg^{-1} (fentanyl group) with PCA device 5 minutes before the end of surgery. After fentanyl administration, fentanyl bolus protocol was started at 0.1 μg kg^{-1} bolus dose with 8 minutes lockout time. A nonsteroidal antiinflamatory agent (75 mg diclofenac sodium) was administered to all patients when pain scores were 4 or higher at any time during the study period.

Age, sex, myocardial infarction experienced during the last three months, left ventricular ejection fraction, cross clamping time, partial by-pass time, body temperature and total remifentanil dose were recorded. In the postoperative period, systolic and diastolic arterial blood pressures (SAP, DAP), heart rates (HR), pain scores, sedation levels, additional analgesic requirements, complications such as nausea and

vomiting, tremor, pruritis, respiratory depression and apnea, wake- up times, amount of drainage, urine outputs, extubation times, intensive care unit, and hospital discharge times were recorded every 15 minutes during the first 4 hours and then 12., and 24. hours, postoperatively. Pain scores were assessed with Numeric Rating Scale (NRS) and sedation levels were assessed with Ramsay Sedation Scoring. Patients were ventilated simultaneously at intermittent mandatory ventilation mode in the intensive care room, and when spontaneous respiration became stronger, ventilation was maintained with continuous positive airway pressure (CPAP) until extubation criteria were met. Patients were extubated at CPAP mode but not taken into T system. Respiration parameters were followed by arterial blood gas measurements, and respiratory complications (atelectasia, pneumothorax) were recorded. The patients were discharged from the clinic, if hemodynamic stability was achieved in ambulatory patients who could be nourished orally without any evidence of infection.

DATA AND STATISTICAL ANALYSIS

Patients' data were coded using SPSS for Windows 10.0.1. program. Genders and side effects of two groups were compared with chi -square test. Hemodynamics, pain and sedation scores of two groups were compared with Student-t test for parametric data, and with Mann-Whitney U test for nonparametric data. Eighteen different times parametric data were compared with repeated measures analysis of variance and nonparametric data with Friedman's test. Post hoc tests were performed to find the pairs causing intra-, and intergroup differences. For all tests, $p<0.05$ was considered statistically significant.

RESULTS

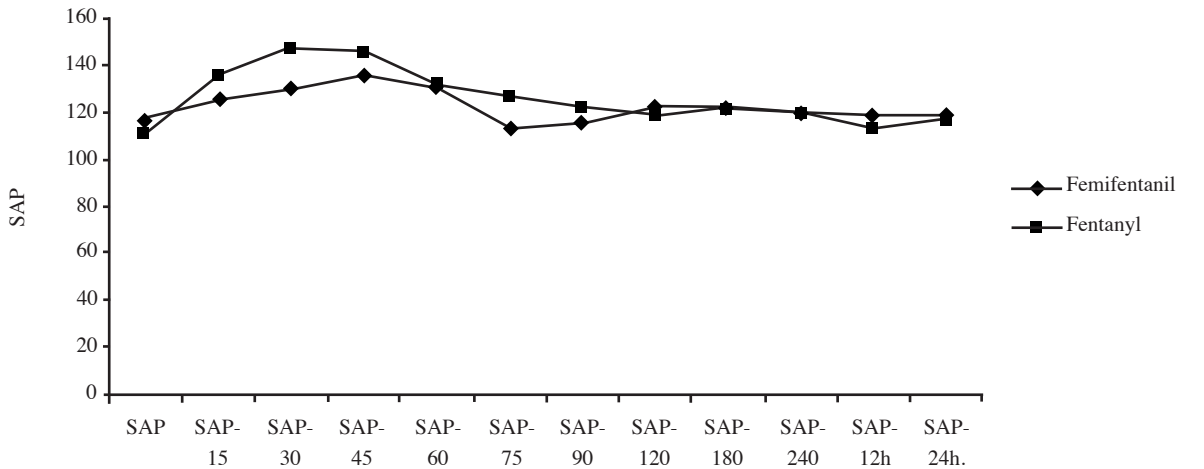
Statistically significant differences were not found between the groups with respect to demographic (age, sex and weight) characteristics. Former MI incidence, cross- clamping, partial bypass and operation times were significantly higher in Group 1 when compared with Group II, $p<0.05$. Ejection fraction was lower in Group 1. Minimal temperature in perfusion period was -also significantly lower in Group 1 ($p<0.05$) (Table 1).

Table 1. The demographics of groups.

	Group 1	Group 2	p
Sex (M/F)	20/0	18/2	p<0.147
Age (year)	48.15	48.62	p<0.799
Weight (kg)	77.9	77.05	p<0.783
EF (%)	55.8	63.4	p<0.000
Former MI (present/absent)*	12/8	5/15	p<0.025
Cross clamp time (min)*	35.1	24.8	p<0.007
By-pass time (min)*	60	39.6	p<0.001
Operation time (min)*	213.15	161	p<0.000
Temperature (°C)*	31.2	32.2	p<0.036

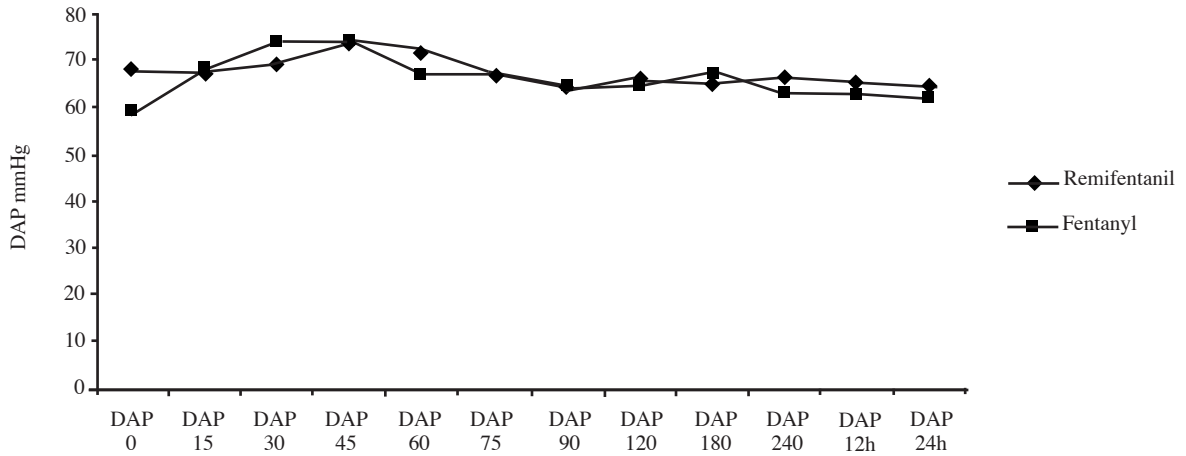
Abbreviation; M: Male, F: Female, MI: Myocardial infarction
** P<0.05 was determined as significance.*

There were no significant differences in hemodynamic parameters (SAP, DAP, HR) at postoperative 0, 15, 30, 45, 60, 75, 90, 120, 180 and 240. min. and 12 and



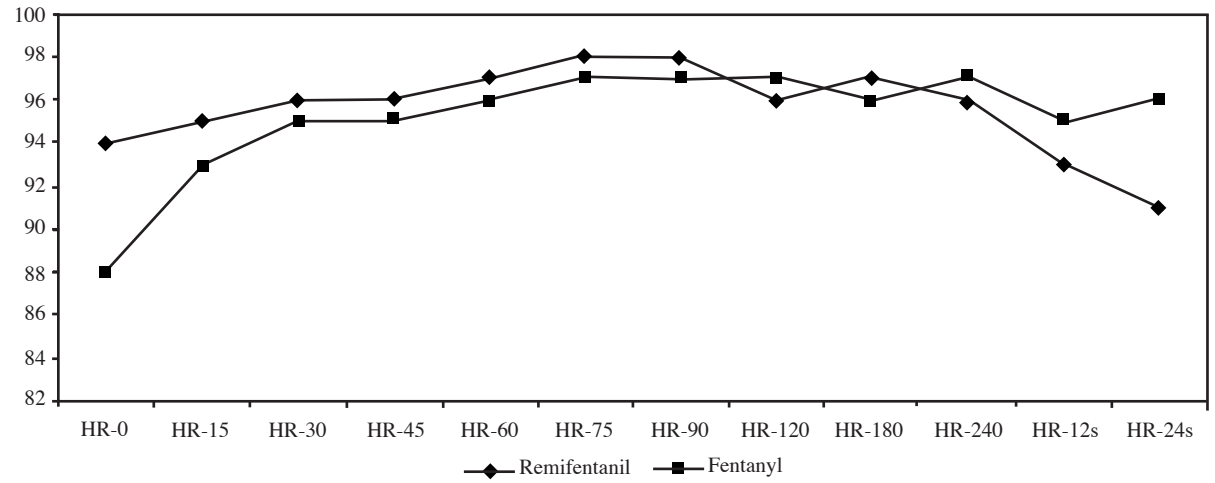
Graphic 1. Postoperative sistolic arter pressure changes between groups.

** Stastically significant change according former value in the group. (p<0.05), SAP: Systolic arterial pressure*



Graphic 2. Postoperative diastolic arter pressure changes between groups.

** Stastically significant change according former value in the group. (p<0.05), DAP: Diastolic arterial pressure*



Graphic 3. Postoperative heart rate (HR) changes between groups.

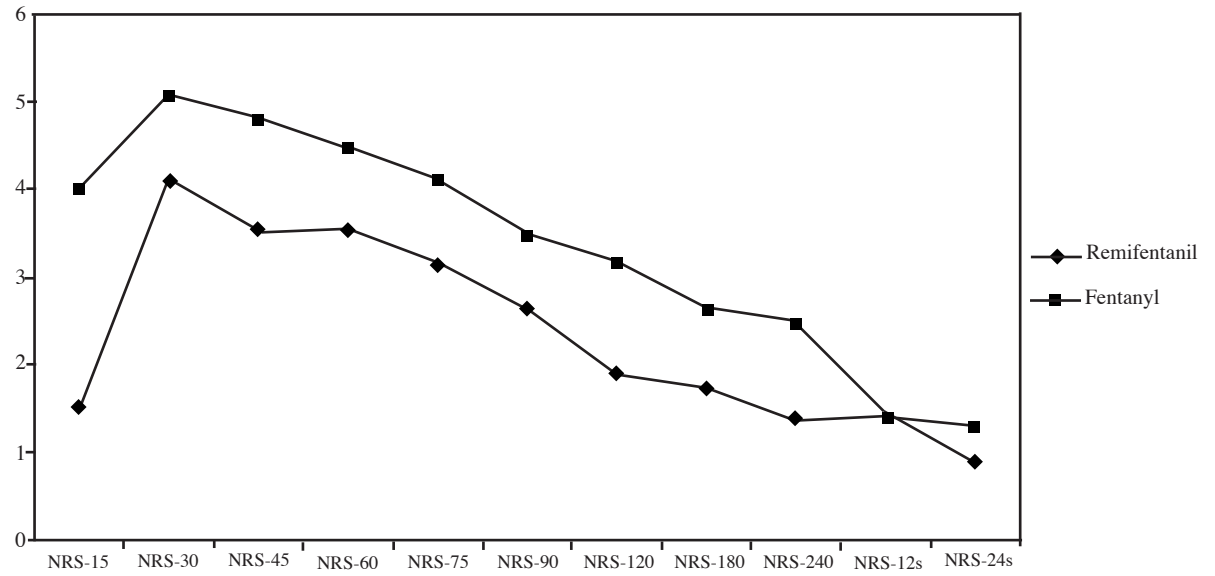
24. hrs between the two groups. There were no differences in hemodynamic parameters within Group 1. In Group 2, SAP and DAP at 15. min. were higher than those at 0. min. SAP and DAP at 30. min. were higher than those at 15. min., but SAP and DAP at 60. min. were significantly lower than those at 45. min., p<0.05, (Graphics 1, 2, 3).

NRS scores in Group 1 were lower during the first postoperative 4 hours (Graphic 4). But the difference between groups was not statistically significant (Graphic 4). Four additional analgesics were required for each group. Diclofenac sodium was administered mostly during the first 4 hrs in Group 2 but given after the first 4 hrs in Group 1, (Graphic 5).

Ramsay sedation scores during the first 2 hours in the intensive care unit were significantly lower in Group 1 (p<0.05). These scores were equal between the two groups after 2 hours, (Graphic 6).

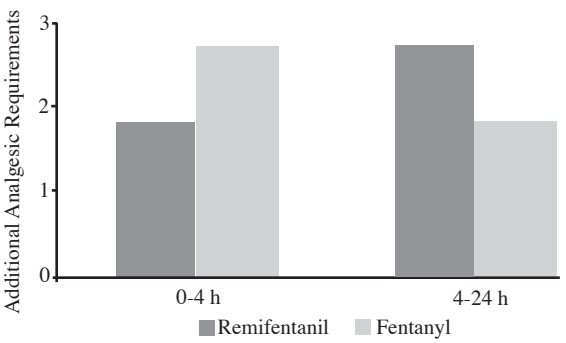
Postoperative complications like nausea, vomiting, ECG changes, pruritis, tremor, respiratory depression and apnea were not different between the two groups. Nausea was observed in 5 patients in Group 1 and 7 patients in Group 2. Two patients from both groups had tremor, 2 patients respiratory depression and 1 patient had ECG changes in Group 1, (p<0.05).

Eye opening and extubation times between groups was significantly different (p<0.037 and p<0.001).



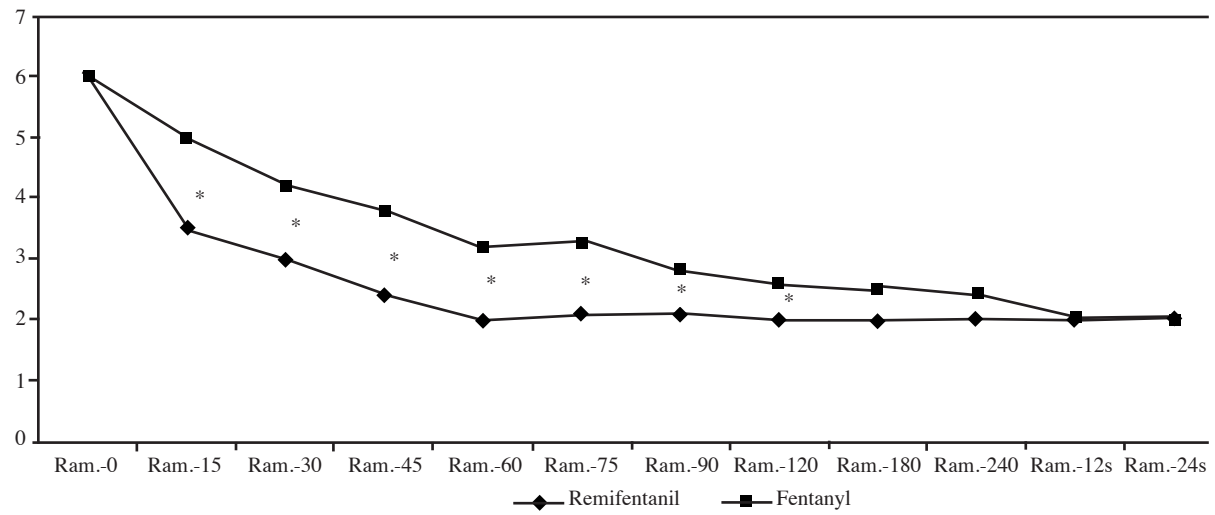
Graphic 4. Time related median NRS values between groups.

NRS: Numerical Rating Scale



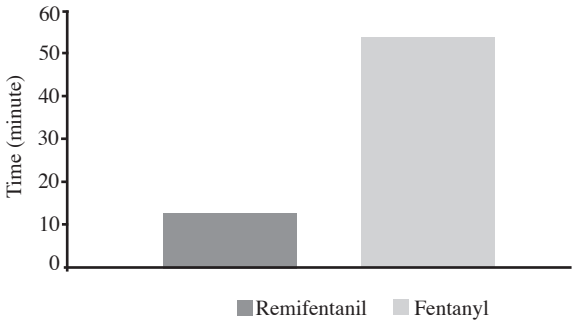
Graphic 5. Additional analgesic requirements of groups.

Time to eye opening was 12.5 minutes in Group 1 and 53.5 minutes in Group 2 and extubation time was 136 minutes in Group 1 and 265 minutes in Group 2, (Graphics 7, 8). Median time passed in the intensive care unit was 25 hours in Group 1 and 27 hours in Group 2. Time to patients' discharge was 6.78 and 7 days in Groups 1 and 2, respectively. The difference was not significantly different between groups (Graphics 9, 10).



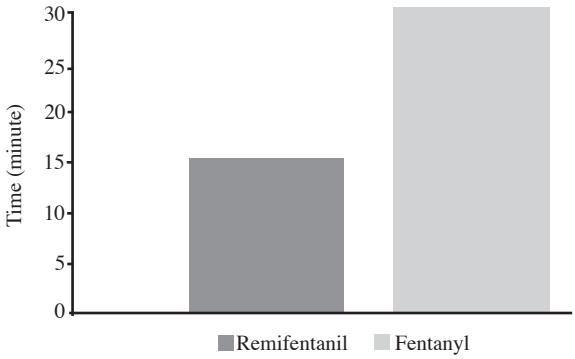
Graphic 6. Median Ramsey Sedation Scores.

** Stastically significant differance between the groups. (p<0.05)*

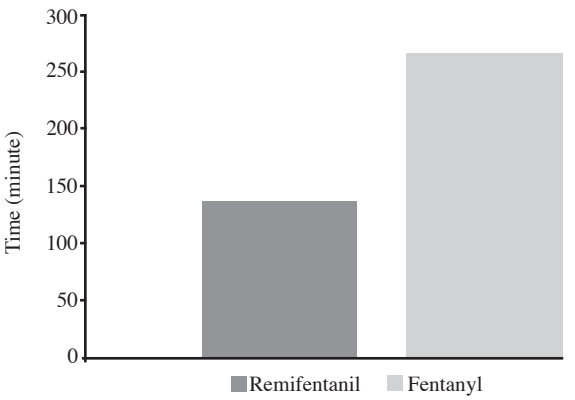


Graphic 7. Wake Up Time (WUT).

**W.U.T. was stastically significant lower in remifentanyl group than fentanyl group (p<0.05).*

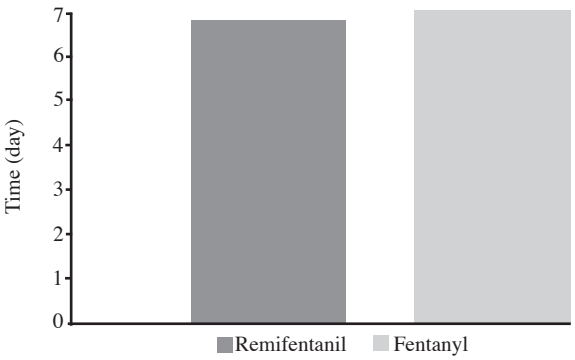


Graphic 9. Intensive care unit exit times (leaving times from intensive care unit).



Graphic 8. Extubation time.

**Extubation time was significantly was lower in remifentanyl group than in fentanyl group (p<0,05).*



Graphic 10. The difference between discharge days.

DISCUSSION

Aim of the fast-track cardiac surgery anaesthesia is to provide early extubation and rapid recovery with selection of suitable anaesthesia method and agent. In the fast-track technique, early wake up at the end of operation and throbbing pain makes the technique difficult to apply. Therefore, postoperative pain management must be planned and started at the beginning.

High dose fentanyl has been used for years in cardiac surgery. Epidural administration of fentanyl is the preferred method in the postoperative pain management. Although epidural administration in cardiac surgery is known in many centers all around the world for more than twenty years, its usage is not common [(4)]. The most important restriction in its usage is the increased risk of epidural hematoma as a result of anticoagulation during cardiac surgery. Intravenous fentanyl administration is not preferred due to respiratory depression, nausea,vomiting and muscle rigidity during the postoperative period. Also, its intravenous administration, compared to other postoperative analgesia methods, provides inadequate analgesia. Due to the effects of intravenous administration, analgesic agent must be carefully selected.

Remifentanil infusion was compared with fentanyl bolus administration in the present study. According to Pande et al. [(5)], appropriate selection and titration of anesthetic agents, standardized surgical procedure, postoperative normothermia and pain control must be achieved for the fast-track technique. In the fast-track cardiac surgery, it has been shown that early extubation can be performed easily with stable anaesthesia provided by a volatile and an opioid agent. This technique is the key factor of early extubation [(6)]. In a multicenter study, Searle et al. [(7)] reported that the sevoflurane and isoflurane combination with fentanyl is acceptable for cardiac anaesthesia in patients with low risk undergoing elective CABG surgery.

After remifentanil administration, spontaneous respiration and extubation is possible, because the effect of this agent terminates at 3-10. minutes after completion of infusion. Royston et al. [8], reported that the interval between the end of infusion and spontaneous respiration was not affected by the infusion time. The timing of postoperative pain management is important because of lack of remifentanil's residual analgesic effect [9]. During the fast-track cardiac anesthesia remifentanil provided safe and stable operating conditions and facilitated earlier tracheal extubation. However, postoperative pain management should be planned carefully [10]. No difference was found for pain scores and also for additional analgesic requirements between groups in this study. But additional analgesic requirement was higher 4 hours after the end of infusion in Group1 and during the first 4 hours in Group 2. It was observed that 1 μg kg^{-1}min^{-1} remifentanil infusion and PCA fentanil bolus administration were effective for analgesia. Robert et al. [11] used fast-track anaesthesia protocol with remifentanil and fentanyl in pediatric cases and did not found any difference between postoperative analgesic requirements.

In the study of Calderon et al. [9] two different doses of remifentanil were compared in severe postoperative pain management. They reported that two different remifentanil doses hadn't made a significant difference in patients undergoing major surgery (like thoracotomy and laparotomy) with severe or moderate pain, but additional analgesic requirement was higher in the low dose group. In a former study by Bowdle et al. [12], 0.05 - 0.15 μg kg^{-1}min^{-1} remifentanil infusion was administrated during the first postoperative 30 minutes and they reported that adequate analgesia was achieved at a rate of 78 percent. In a similar study, Yarmush et al. [13] found that the incidence of effective and reliable postoperative pain control after extubation was 58 % when remifentanil infusion was administrated at a dose of only 0.125 μg kg^{-1}min^{-1} (range 0.05-0.23 μg^{-1} kg^{-1} min^{-1}). In another study, intraoperative remifentanil was terminated at the end of surgery, and intratechal morphine was administrated for the management of postoperative pain after application of remifentanil based fast-track anaesthesia protocol with excellent analgesia outcomes [14].

During the surgery in remifentanil group SAP in the CPB exiting period was lower than fentanyl group. The reasons for this may be related to lower ejection fractions, and longer cross-clamping, and perfusion times, and also higher incidence of former MI episodes experienced in the remifentanil group.

Some of remifentanil's side effects are respiratory depression, apnea, nausea and vomiting. The incidence of apnea and respiratory depression ranged between 14 % (Yarmush et al) [13] and 29 % (Bowdle et al) [12]. In our study, these two side effects were observed in one patient in Group 1. However, they were not observed in any patient in Group 2.

Remifentanil was administered while the patient was intubated in the intensive care unit. The use of remifentanil as an analgesic was not previously studied at postoperative 4 hours after fast-track CABG. The use of remifentanil in the early postoperative period necessitates close observation and intensive care to provide the balance between respiratory depression and titration of analgesic effects [12-16]. Remifentanil infusion was found effective for postoperative analgesia, this type of pain management may be suitable only under conditions of strict monitorization. The bolus doses of remifentanil for postoperative analgesia are related with high incidence of respiratory depression [12,16,17]. It has been observed that remifentanil infusion and fentanyl have similar effects on postoperative pain. The use of remifentanil and fentanyl in the postoperative period did not affect the time passed in the intensive care unit and discharge times.

Akhtar et al [18], attemped to identify the causes of delayed extubation in patients planned for fast tract extubation during cardiac surgery. Major contributing factors for delayed extubation were identified by this audit. These factors need to be targeted accordingly by modifications in intraoperative management protocol.

In this study, eye opening and extubation times were different between two groups. Although anesthesia tecniques were the same, this difference in eye opening and extubation times may originate from application of 10 μg kg^{-1} fentanil bolus administration at the end of surgery. Recovery, cooperation, orientation and sedation levels required to obey the orders were provided earlier with remifentanil infusion compared with fentanyl and supplemental analgesic require-

ments during the first 4 hour-period was lower in remifentanil group.

In conclusion, remifentanil has similar analgesic effects as fentanyl and provides better sedation levels. Remifentanil can be used safely at analgesic doses without the risk of respiratory depression during the postoperative period of cardiac surgery patients.

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