Anaesth Intensive Care 2006; **34:** 353-357

Comparison of Remifentanil and Fentanyl in Anaesthesia for Elective Cardioversion

F. MALTEPE*, E. KOCAAYAN†, B. S. UGURLU‡, B. AKDENIZ§, S. GUNERI**

Dokuz Eylul University Medical School, Department of Anesthesiology and Reanimation, Department of Cardiovascular Surgery, Department of Cardiology, Izmir, Turkey

SUMMARY

This prospective, randomized, double-blind study was designed to compare the recovery characteristics of remifentanil and fentanyl in combination with propofol for direct current cardioversion. Patients undergoing elective cardioversion received either intravenous fentanyl 1 μg/kg (n=33) or remifentanil 0.25 μg/kg (n=30) and propofol was titrated to a Ramsay sedation score of 5 by slow intravenous injection. Heart rate, systolic, diastolic and mean blood pressures decreased significantly following sedation in both groups but did not show a significant difference between the groups. Time to answer a question (306±83 vs 383±131s, mean±SD, P=0.014) and time to sit up (412±90 vs 511±126s, P=0.002) were significantly shorter in the remifentanil group compared to the fentanyl group. Side-effects and patient discomfort were similar for both groups. Remifentanil can be used as a suitable supplement to propofol for direct current cardioversion and may provide a faster recovery profile than fentanyl.

Key Words: remifentanil, fentanyl, cardioversion, propofol, sedation, recovery

External electrical cardioversion is often performed to restore sinus rhythm in patients with atrial arrhythmia that is resistant to pharmacologic therapy. Electrical direct current (DC) cardioversion is extremely painful, frightening, stressful and unpleasant[1]. Elective, cardiovascularly stable patients need to be deeply sedated or anaesthetized for this procedure[1-3]. A variety of short-acting drugs such as diazepam, midazolam, etomidate, thiopentone, propofol and fentanyl or combinations of these drugs have been used during cardioversion[4-9]. Despite its hypotensive effect, propofol is currently the most commonly used short acting anaesthetic for DC cardioversion[10]. Propofol provides rapid and brief anaesthesia but has negligible analgesic effect. It is prudent to combine propofol with a short-acting opioid to provide analgesia during this extremely painful procedure[1]. Remifentanil is an opioid agonist with rapid onset and ultra-short duration of action. Its effects and side-effects are dose-dependent and similar to other opioids[11,12]. With its reported brief and powerful analgesic and sedative properties it may provide a comfortable cardioversion procedure and faster recovery. Despite its potential benefits, there are no previous reports of the use of this relatively new agent for cardioversion. The aim of this study was to assess and compare early recovery characteristics of fentanyl and remifentanil in association with propofol, in patients with atrial arrhythmia scheduled for elective DC cardioversion.

METHODS

Sixty-three ambulatory patients with atrial fibrillation of less than 24 hours duration, who were scheduled for external DC cardioversion after fasting for 5 hours were entered into the study, which was approved by the Dokuz Eylul University Hospital Ethics Committee. All patients gave their written informed consent. Patients less than 18 years of age, or American Society of Anesthesiologists (ASA) physical status >3, or with potentially difficult airway problems or a body mass index (BMI)>35 kg/m^{2}were excluded.

DC cardioversion was performed in the coronary care unit. ECG, heart rate (HR), pulse oximetry (SpO_2) and non-invasive blood pressure were monitored. No premedication was given. All patients were pre-oxygenated for two to three minutes before induction of anaesthesia. Oxygen 6 l/min

*M.D., Associate Professor, Department of Anesthesiology and Reanimation.
†M.D., Department of Anesthesiology and Reanimation.
‡M.D., Associate Professor, Department of Cardiovascular Surgery.
§M.D., Assistant Professor, Department of Cardiology.
**M.D., Professor, Department of Cardiology.

Address for reprints: Yard. Doç. Dr Fikret Maltepe, Dokuz Eylul Universitesi Tıp Fakultesi, Anestezi ve Reanimasyon Anabilim Dalı, Inciraltı 35340, Izmir, Turkey.

Accepted for publication on February 1, 2006.

was administered via a simple facemask until the end of the procedure. Patients were rapidly cardioverted with monophasic current at 150J following adequate sedation. Sequential shocks of 200J, if necessary, were rapidly delivered under the same sedation.

Patients were admitted to the study as they presented. Randomization was performed for each patient by chance (coin toss) by the primary investigator. Patients were entered into either intravenous fentanyl (Group FEN) or remifentanil (Group REM). Fentanyl and remifentanil were diluted in unmarked 5 ml syringes prior to study. All anaesthetics were given by the same anaesthetist (EK) who was blinded to the drug used. The observers were also blinded to the drug being used. A stop-watch was started at the onset of induction of anaesthesia. Group FEN received fentanyl 1 μg/kg IV over 20s and group REM received remifentanil 0.25 μg/kg IV over 20s for analgesia. After injection of the opioid, propofol was injected (approximately 1 mg/s) until patients responded only sluggishly to verbal stimuli and to light glabellar touch (Ramsay sedation score of 5). The total propofol dose was recorded. Patients were then synchronously defibrillated using a Hewlett Packard codemaster XL defibrillator. If sinus rhythm was not restored, a second or third shock was delivered in rapid succession (Figure 1).

Non-invasive blood pressure, HR, respiratory rate and SpO_2 measurements were recorded at five time points: 1—at the start of the procedure (preinduction), 2—prior to cardioversion, 3—immediately after cardioversion, 4—at eye-opening to verbal commands, 5—once the patient was able to sit up.

After cardioversion, the anaesthetist stimulated the patients by calling their names and asking them to open their eyes and breathe deeply. When the patient opened his/her eyes appropriately, the time was recorded by a second observer. Recovery times were recorded from cessation of propofol injection. After eye-opening, patients were asked repeatedly how they were feeling. When the patient answered the question clearly, the second recovery time was recorded. The patient was then encouraged to sit up. When the patient actively sat up with light support, the third recovery time was recorded. Patients were questioned for recollection of the actual cardioversion event, pain and other unpleasant sensations. The number of shocks, the total amount of energy, the number of patients in which sinus rhythm could not be restored, and the incidence of adverse effects (apnoea, cough, abnormal movement and post procedure nausea and vomiting) were recorded. After full recovery, patients were questioned on their experiences of cardioversion.

Data were analysed using SPSS (Version 11.0) for Windows. Student's t test and repeated measures ANOVA were used for continuous variables and the chi-square test was used for nominal data. A P value of <0.05 was considered significant.

The primary outcome was recovery time difference. The power of the study to detect a difference in the time to being able to answer a question was 80%.

RESULTS

There were 33 patients in the fentanyl and 30 patients in the remifentanil groups. Group number disparity was caused by the randomization method as none of the enrolled patients were excluded. There was statistically no significant difference between the groups in regard to age, sex, weight, body mass index, left ventricle ejection fraction or ASA physical status (Table 1).

The mean propofol dose required to obtain adequate sedation was 0.88±0.48 mg/kg in the FEN group and 0.90±0.43 mg/kg in the REM group. This was not a statistically significant difference (Student's t test $P=0.859$).

Repeated measures ANOVA showed a signifi-

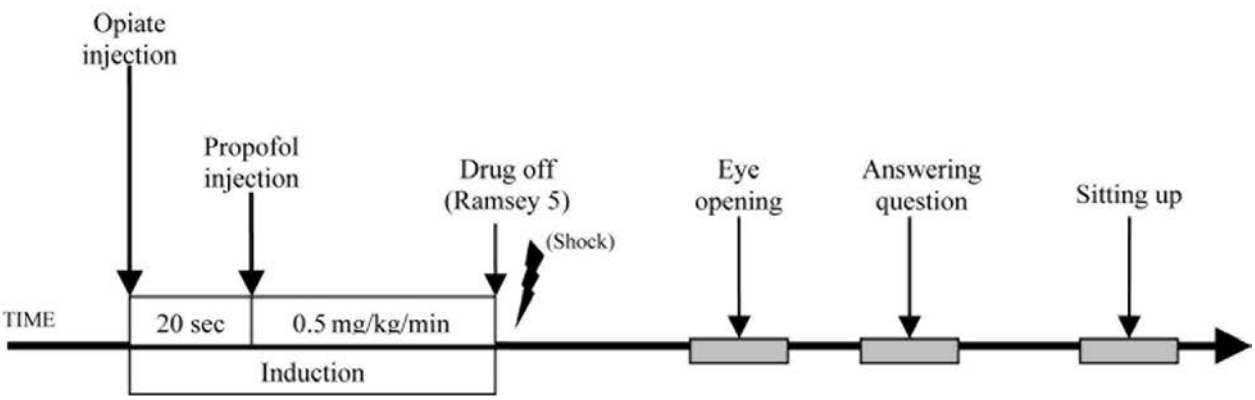


FIGURE 1: Design of the study.

TABLE 1
Demographic data of patients in fentanyl (FEN) and remifentanil (REM) groups

	FEN group (n=33)	REM group (n=30)	*P*
Age (y)	65±11	64±12	0.677
Gender; male/female	12/21	17/13	0.777
Body weight (kg)	73±12	71±13	0.532
Left ventricle EF(%)	56±8	54±9	0.363
ASA score(II/III)	30/3	23/7	0.296

Values are mean±SD or actual numbers.

cant difference in mean arterial pressures between different time points ($P<0.001$) but there was no significant difference between the groups (Student's t test $P=0.574$). In both FEN and REM groups, mean arterial pressures decreased significantly with the induction of anaesthesia (paired t test $P<0.001$). Blood pressures remained slightly lower compared to starting values in both groups (Figure 2). In none of the patients did systolic arterial pressure decrease to less than 80 mmHg and none of the patients required treatment for hypotension. With induction of anaesthesia, heart rates decreased significantly. After conversion to sinus rhythm and during the recovery period, heart rates were significantly lower in both groups (paired t test $P<0.001$) compared with initial rates (Figure 3). However, bradycardia (HR <50 bpm) was not observed in any of the patients.

Brief periods of apnoea were observed in both groups (2/33 with fentanyl and 5/30 with remifentanil). The difference between the two groups was not significant (chi square $P=0.243$), although the study was not adequately powered to assess this outcome. These episodes of apnoea were transitory and responded well to verbal stimulation. None of the patients required assisted ventilation and no patient had an apnoea period lasting longer than 20s in either group. Mean S_PO_2 measurements were similar for both groups and none of the patients had an S_PO_2 value lower than 92%.

Cardioversion was successful during the initial attempt in 60% of patients in the FEN group and 63% in the REM group. The mean number of shocks was 1.78 per patient in the FEN group and 1.68 in the REM group. Overall cardioversion was successful in 85% of the patients in the FEN group and 97% of the patients in the REM group ($P=0.078$) (Table 2).

Mean induction times were similar for both groups (Table 2). Time to opening of eyes was shorter in the REM group but the difference did not reach statistical significance. Full recovery was achieved more rapidly in the remifentanil group. Time to

TABLE 2
Induction and recovery characteristics of patients receiving fentanyl (FEN) or remifentanil (REM)

	FEN group (n=33) Mean±SD	REM group (n=30) Mean±SD	*P*	95% confidence interval of the difference	
				Lower	Upper
Induction time (seconds)	121±24	123±23	0.791	–19	25
Time to eye-opening (seconds)	260±119	237±69	0.394	–30	77
Time to answering question (seconds)	383±131	306±83	0.014	16	137
Time to sitting up (seconds)	511±126	412±90	0.002	33	158

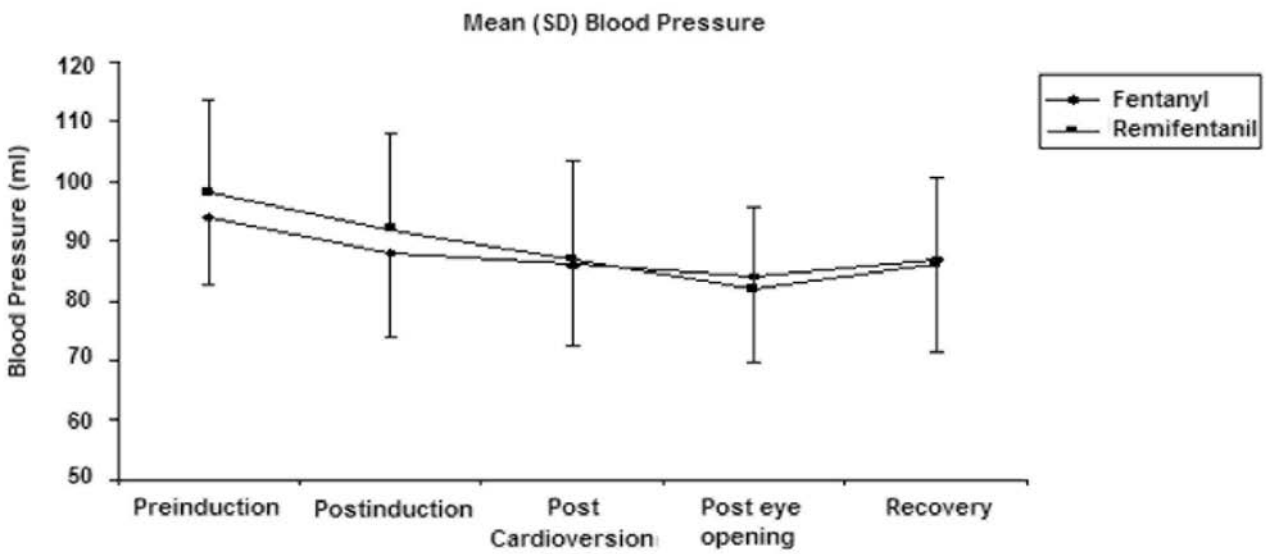


FIGURE 2: Mean blood pressures at different intervals in the two groups.

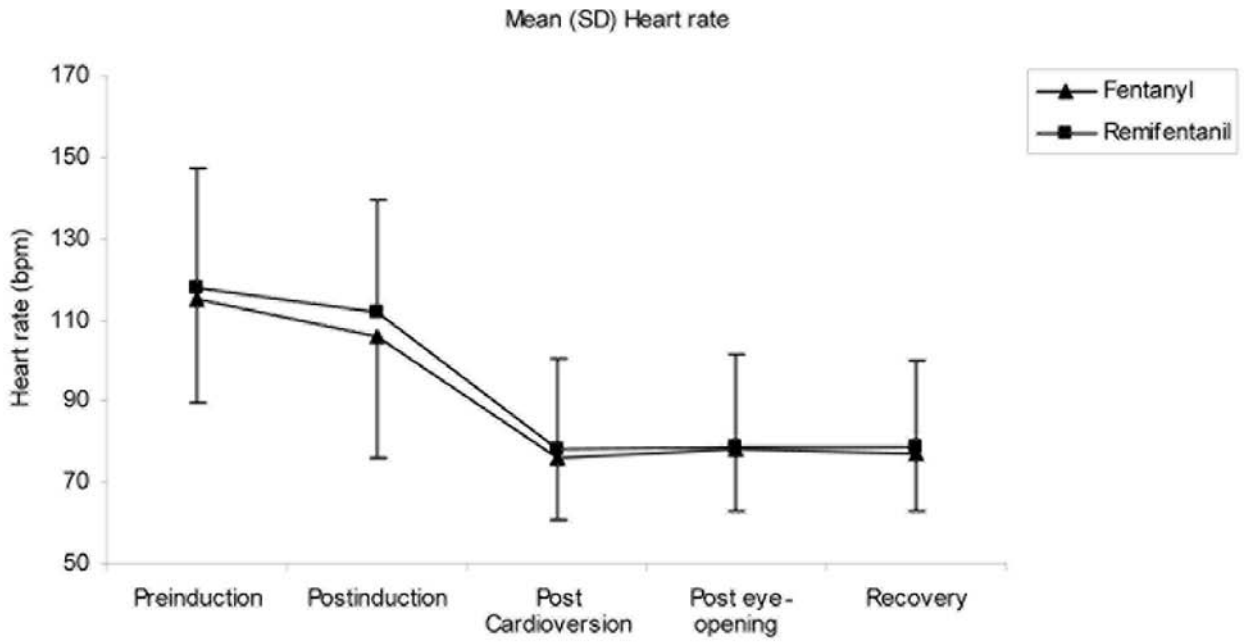


FIGURE 3: Heart rates of patients in fentanyl and remifentanil groups in different time intervals.

answer a question was significantly shorter in the REM group (306±83s) compared to the FEN group (383±13s, Student's t test P=0.014). Similarly, time to sitting up was also significantly reduced in the REM group (412±90s) compared to the FEN group (511±126s, Student's t test P=0.002) (Table 3).

All patients tolerated the procedure well and had no complaints. Injection site pain, nausea, vomiting or bronchospasm were not observed in any patient.

DISCUSSION

The ideal anaesthetic agent for DC cardioversion should produce rapid loss of consciousness, should have some analgesic properties and its effect should be brief with rapid recovery. It should have no effect on cardiac contractility or rhythm and should produce minimal side-effects such as laryngospasm, nausea or vomiting[1]. Propofol, while not perfectly suited, is widely used for cardioversion. Its effect is rapid, it obtunds laryngeal reflexes and it redistributes quickly with rapid offset of effect[3]. In a recent survey conducted in the United Kingdom it was reported that 90% of surveyed hospitals used propofol as the anaesthetic agent of choice for cardioversion, but in 43% of the hospitals it was combined with a short-acting opioid[10]. Combining propofol with a short-acting opioid is a good alternative for providing adequate patient sedation and analgesia without increasing side-effects[13, 14].

Fentanyl is frequently used with propofol for short painful procedures under sedation and has a relatively rapid offset with duration of effect of about 30 minutes[14,15]. The usual dose for fentanyl for this setting is 1-2 μg/kg[13-15]. Remifentanil on the other hand is four to ten times more potent than fentanyl and is cleared in five to ten minutes after a single intravenous dose[12,16]. Remifentanil has been used for various procedures under sedation such as electroconvulsive therapy and insertion of a laryngeal mask at doses between 0.25 and 1 μg/kg. A dose of 0.25 μg/kg has been deemed adequate for most brief procedures[17,18]. When combined with propofol, remifentanil at 1 μg/kg can even facilitate endotracheal intubation[19]. For these reasons we chose to use fentanyl 1 μg/kg and remifentanil 0.25 μg/kg for this study.

In studies of DC cardioversion with propofol as the sole anaesthetic agent, recovery times have shown a great deal of variation. As expected, recovery times usually correspond to the total administered dose of propofol and method of administration. Herregods et al administered a propofol dose of 1 mg/kg over 120s and reported mean times for opening eyes, answering a question and sitting up of 4.7, 6.7 and 9.4 minutes respectively[2]. When propofol was used as a bolus dose of 1.69 mg/kg by Gale et al, mean awakening time was 11 minutes[7]. Karthikeyan et al maintained a target-controlled infusion of 6 μg/ml with a total propofol dose of 2.7 mg/kg and reported a mean time to eye-opening of 12.3 minutes[4]. On the other hand, when a total propofol dose of 0.64 mg/kg was administered by Hullander et al, mean time to awakening was reduced to 4.5

minutes[5]. In our study mean times to opening eyes, answering a question and sitting up in the REM group were 4.2, 5.8 and 7.8 minutes. Recovery times were shorter than most of the studies with propofol as a single agent. This decrease in recovery time is probably caused by the lower dose of propofol necessary in our study, as our mean propofol dose was lower than 1 mg/kg. Recovery times in our study are comparable to previous studies with similar propofol doses.

Our study found a significant difference between fentanyl and remifentanil in regard to recovery times. While time to eye-opening did not show a statistical significance, time to answer a question, and time to sit up were significantly shorter in the remifentanil group. A similar conclusion was reached by Vuyk et al when the effects of various opioids in combination with propofol were compared[13]. In our study, patients in the remifentanil group achieved full recovery (able to sit up) more than one and a half minutes earlier than the fentanyl group. While a one and a half minute difference may not be important for a long procedures, it may be important for short procedures such as for DC cardioversion.

Apnoea is a potential problem with combinations of propofol and opioids as short-acting opioids, by themselves, may cause apnoea at higher doses[16]. In our study, none of the patients had apnoea longer than 20 seconds or required ventilatory support. Successful conversion to sinus rhythm was higher in the remifentanil (97%) group compared to fentanyl (85%), although the study was not designed or powered to assess this outcome. Propofol dose and haemodynamic parameters were similar between groups.

In conclusion, our findings suggest that both fentanyl and remifentanil can be safely used in combination with propofol for elective DC cardioversion. Use of remifentanil may facilitate a slightly faster recovery.

REFERENCES

1. Stoneham MD. Anaesthesia for cardioversion. Anaesthesia 1996; 51:565-570.
2. Herregods LL, Bossuyt GP, De Baerdemaeker LE et al. Ambulatory electrical external cardioversion with propofol or etomidate. J Clin Anesth 2003; 15:91-96.
3. Harrison SJ, Mayet J. Physician administered sedation for DC cardioversion. Heart 2002; 88:117-118.
4. Karthikeyan S, Balachandran S, Cort J, Cross MH, Parsloe M. Anaesthesia for cardioversion a comparison of sevoflurane and propofol. Anaesthesia 2002; 57:1114-1149.
5. Hullander RM, Leivers D, Wingler K. A comparison of propofol and etomidate for cardioversion. Anesth Analg 1993; 77:690-694.
6. Gupta A, Lennmarken C, Vegfors M, Tyden H. Anaesthesia for cardioversion: A comparison between propofol, thiopentone and midazolam. Anaesthesia 1990; 45:872-875.
7. Gale DW, Grissom TE, Mirenda JV. Titration of intravenous anesthetics for cardioversion: A comparison of propofol, methohexital and midazolam. Crit Care Med 1993; 21:1509-1513.
8. Fennelly ME, Powell H, Galletly DC, Whitwam JG. Midazolam sedation reversed with flumazenil for cardioversion. Br J Anaesth 1992; 68:303-305.
9. Canessa R, Lema G, Urzua J, Dagnino J, Concha M. Anesthesia for elective cardioversion:a comparison of four anaesthetic agents. J Cardiothorac Vasc Anesth 1991; 5:566-568.
10. James S, Broome IJ. Anaesthesia for cardioversion. Anaesthesia 2003; 58:291-292.
11. Burkle H, Dunbar S, Van Aken H. Remifentanil: A novel, short-acting, μ-opioid. Anesth Analg 1996; 83:646-651.
12. Westmoreland CL, Hoke JF, Sebel PS et al. Pharmacokinetics of remifentanil (G187084B) and its major metabolite (G190291) in patients undergoing elective inpatient surgery. Anesthesiology 1993; 79:893-903.
13. Vuyk J, Mertens M, Olofsen E, Burm A, Bovill J. Propofol anesthesia and rational opioid selection determination of optimal EC50-EC95 propofol-opioid concentrations that assure adequate anesthesia and a rapid return of consciousness. Anesthesiology 1997; 87:1549-1562.
14. Lysakowski C, Dumont L, Pelerini M, Clergue F, Tassonyi F. Effects of fentanyl, alfentanil, remifentanil and sulfentanil on loss of consciousness and bispectral index during propofol induction of anesthesia. Br J Anaesth 2001; 86:523-527.
15. Baily PL, Egan TD, Stanley TH. Intravenous opioid anesthetics. In: Miller RD eds. Anesthesia. Philadelphia, Churchill Livingstone 2000: pp. 273-376.
16. Litman RS. Conscious sedation with remifentanil during painful medical procedures. J Pain Symptom Manage 2000; 19;468-471.
17. Lee MP, Kua JS, Chiu WK. The use of remifentanil to facilitate the insertion of the laryngeal mask airway. Anesth Analg 2001; 93:359-362.
18. Recart A, Rawal S, White PF, Byerly S, Thornton L. The Effect of remifentanil on seizure duration and acute hemodynamic responses to electroconvulsive therapy. Anesth Analg 2003; 96:1047-1050.
19. Trabold F, Casetta M, Duranteau J et al. Propofol and remifentanil for intubation without muscle relaxant: the effect of the order of injection. Act Anaesthesiol Scand 2004; 48:35-39.