European Review for Medical and Pharmacological Sciences 2016; 20: 1140-1148

Sedoanalgesia for cardioversion: comparison of alfentanil, remifentanil and fentanyl combined with propofol and midazolam: a prospective, randomized, double-blind study

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Abstract. – OBJECTIVE: Electrical cardioversion (EC) is a short but painful procedure to restore sinus rhythm. The aim of this study is to compare the effect of fentanyl, remifentanil and alfentanil in association with propofol and midazolam for elective EC.

PATIENTS AND METHODS: Ninety-nine patients older than 18-years, American Society of Anesthesiologists I/II/III grades undergoing elective EC were randomized into 3 groups. All patients received 2 mg midazolam and propofol (0.5 mg/kg). Group A received alfentanil (5 μg/kg i.v. bolus), Group F received fentanyl (0.5 μg/kg i.v. bolus) and Group R received remifentanil (0.25 μg/kg i.v. bolus). Hemodynamics and respiratory variables [Heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), SpO_2, respiratory rate (RR)], and Modified Aldrete recovery score (MARS) were assessed at six different time points (baseline, right after EC, and 3rd min, 5th min, 10th min, 30th min following EC). Also, induction times (time to reach RSS to 5) and recovery times (time to reach MARS to 8) were recorded. The incidence of respiratory depression, bradycardia, hypotension and adverse effects were also recorded.

RESULTS: Hemodynamic variables were similar in all groups. SpO_2 values in Group R were significantly lower at 3rd min ($p = 0.005$). Induction and recovery times were longest in Group F. There were significant differences at 3rd, 5th and 10th minute MARS values between groups. The incidence of hypotension and bradycardia were similar in all groups ($p > 0.05$) but respiratory depression was higher in Group R ($p = 0.047$).

CONCLUSIONS: Propofol alfentanil combination has more beneficial advantages in their rapid onset, early recovery time and less respiratory depression than remifentanil and fentanyl.

Key Words:
Atrial fibrillation, Alfentanil, Remifentanil, Fentanyl, Cardioversion, sedoanalgesia, Propofol, Recovery.

Introduction

Atrial fibrillation (AF) is the most common sustained heart rhythm disorder, with an incidence of 5% to 10% in patients over 65 years of age[1]. Prevalence and incidence of AF are increasing, and restoring sinus rhythm remains a goal for the clinicians[2].

Electrical cardioversion (EC) still continues to have an important role in daily practice, especially in the setting of AF management. EC may be performed in elective or emergency settings according to the patient's clinical condition and the causing cardiac arrhythmia. Since the procedure is painful, it requires sedation and analgesia, usually via intravenous agents[3,4]. Anesthetic agents used for EC should provide procedure related amnesia, adequate analgesia, fast induction and early recovery time and should also have lower side effects on cardio-respiratory system[5].

Various short-acting drugs such as midazolam, diazepam, thiopental, etomidate, propofol and opioids like fentanyl, alfentanil or combinations of these drugs have been tested for this purpose. Each of these drugs has some advantages and disadvantages[6]. Propofol is the most commonly used short-acting anesthetic agent in ambulatory anesthesia. However, it is usually combined with short-acting opioids in painful ambulatory proce-

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dures like EC due to negligible analgesic effect[7]. Fentanyl, remifentanil and alfentanil are short-acting and rapid onset opioid agonists that have similar dose-dependent effects and side-effects[8,9]. Although there were many studies involving binary comparison of opioids in combination with intravenous anesthetics for EC, to the best of our knowledge, there is no study comparing the efficacy of these three short-acting agents[6,7].

The aim of this study is to determine and compare time to onset of adequate sedation, recovery times, effectiveness, and side effects of fentanyl, remifentanil and alfentanil in association with propofol and midazolam, in patients with atrial fibrillation scheduled for elective EC.

Patients and Methods

Patient Selection

After obtaining Clinical research approval from General Directorship of Medicine and Pharmacy of Ministry of Health (April 16 2014; 26247029-514-04-01; 2014-AKD-39) Ethics Committee, this randomized and prospective double-blinded study was performed in Gulhane Military Medical Academy, Ankara, Turkey. A signed written consent was obtained from all patients before they recruited to the study in coronary and cardiovascular intensive care units between May 2014 and November 2015. This study corresponds to the principles summarized in the Declaration of Helsinki.

Ninety-nine patients older than 18 years of age with American Society of Anesthesiologists (ASA) I/II/III grade having ejection fraction more than 35% and undergoing elective EC were included the study. Pregnancy, known allergy to study drugs and egg, chronic medication with opioids or sedatives, alcohol or drug abuse, neuropsychiatric diseases, and emergency cardioversions were accepted as exclusion criteria. Patients with hemodynamic instability, unstable angina or severe circulatory failure, and patients receiving intravenous medications (vasodilators, inotropic agents), or mechanically ventilated were also excluded.

Randomization

Randomization was performed when a new patient scheduled for elective EC was reported. Patients were randomly assigned to 3 groups and each of them comprised 33 patients. Group A (propofol, midazolam with alfentanil), Group R (propofol, midazolam with remifentanil), or Group F (propofol, midazolam with fentanyl). Randomization was performed by sequentially numbered envelopes. Anesthesia team and the cardiologist who performed EC were all blind to the study drugs that combined with propofol. The same anesthesia team and cardiologist performed all ECs. The study drugs were prepared by another anesthesiologist and the team was not informed which drug was used. All patients were distributed randomly into three groups, each consisting equal number of patients. Patients were not informed about the groups that they were involved.

Medication and Cardioversion

Patients were prepared for the EC with an intravenous (iv) cannula, 5-lead electrocardiogram (ECG), pulse oximetry (SpO_2) and non-invasive blood pressure (NIBP). For a possible emergency situation endotracheal intubation equipment and emergency drugs were kept ready at the bedside. All patients were pre-oxygenated for three minutes before premedication. Oxygen (5 L/min) was administered via nasal cannula until the end of the procedure excluding the time of cardioversion.

All patients received 2 mg midazolam (Zolamid, Defarma, Ankara, Turkey) for premedication which was followed by propofol (Propofol, Fresenius, Istanbul, Turkey) (0.5 mg/kg) for induction. Following these two drugs, Group A received alfentanil (Rapifen, Johnson & Jonhson, Istanbul, Turkey) (5 μg/kg i.v. bolus), Group F received fentanyl (Talinat, Vem, Istanbul, Turkey) (0,5 μg/kg i.v. bolus) and Group R received remifentanil (Ultiva, GlaxoSmithKline, Istanbul, Turkey) (0.25 μg/kg i.v. bolus) to provide an adequate level of sedation (patient exhibits a sluggish response to light glabellar tap or loud auditory stimulus) and analgesia with spontaneous breathing. Then the patients were cardioverted with biphasic current at 150J following sequential shocks of 200J if necessary.

Data Collection

Hemodynamics and respiratory variables [HR, systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), SpO_2, respiratory rate (RR)], and Modified Aldrete recovery scores[10] (MARS) were recorded throughout the procedure at six different time points (baseline, right after EC, and 3rd min, 5th min, 10th min, 30th min following EC).

Furthermore, time for initiation of sedation (time to reach Ramsay Sedation Score[11] (RSS) score to 5) and recovery time (time to reach MARS to 8 or more) were recorded.

Analgesia level was evaluated by using a numeric pain rating scale from 0 to 10. All patients were questioned to indicate on the scale the intensity of pain experienced (0 = no pain, 10 = worst pain) after reaching of MARS to 8.

The incidence of adverse effects such as hypotension, bradycardia, and respiratory depression, nausea, vomiting and itching was recorded. We defined hypotension as more than 30% fall in baseline SBP, bradycardia as HR < 50/bpm and respiratory depression was considered when RR < 8/min or apnea > 20 s occurred.

Following EC, cardiologist and the patients (just before discharge) were questioned to report satisfaction on a scale from 1 to 5 (1: not satisfied and 5: very satisfied).

Statistical Analysis

Data were analyzed with SPSS version 22.0 (IBM Corp., NY, USA). Categorical variables were expressed as frequencies and percentages; continuous variables were expressed as mean ± standard deviation. Parametric comparison between groups performed by one-way ANOVA, paired samples *t*-test, and non-parametric comparison performed by Kruskal-Wallis and Wilcoxon tests. Change for variables in different measures compared with repeated measures analysis of variance. Categorical variables compared by chi-square test or Fisher's exact test. A *p* value of less than 0.05 was considered to be statistically significant.

Results

A total of 99 patients were included in this prospective, randomized double-blind study, with 33 patients in each of the three groups. There were no statistically significant differences in demographic characteristics among groups A, R and F (Table I).

Baseline hemodynamic variables were similar among groups. After the induction of anesthesia, there was a decrease in HR, SBP, DBP and MBP in all groups (paired *t*-test $p < 0.05$). There were also no significant differences in the mean values at each time points after EC ($p > 0.05$) within groups (Table II).

Preprocedural SpO_2 values were similar in all groups. After induction, there was a decrease in oxygen saturation at all time points. However, this was more prominent at the 3rd min ($p = 0.005$). When the groups were compared with each other, there was a statistically significant decrease in Group R at the 3rd minute (p=0.009 Group R *vs*. A, $p = 0.018$ Group R *vs*. F). Changes in mean SpO_2 values were shown in Figure 1.

When duration of the onset of sedation was compared, the time to reach RSS to 5 was the longest in Group F ($p < 0.01$). Although there was no statistical difference between Groups A and R, time to reach RSS 5 duration was shorter in Group R. Data of the groups were shown in Table II.

When post EC recovery data were evaluated, there was a significant difference between groups for the duration to reach MARS to 8 (p=0.001). This duration was faster in Group R and longest in Group F. When binary comparisons were performed, there was statistically significant difference between Group R *vs*. F, and Group A *vs*. F. But the difference between Group A and Group R was not statistically significant. Data related MARS was shown in Table III.

There was statistically difference at 3rd, 5th and 10th minute MARS values between groups. However, no significant difference was observed at right after and 30th min after EC ($p > 0.05$) within

Table I. Demographic data of patients

	Group A (n = 33)	Group R (n = 33)	Group F (n = 33)	*p*-values
Age (year)	58.72 ± 13.59	50.12 ± 15.77	56.96 ±16.31	0.058
Gender (male/female)	15/18	18/15	15/18	0.695
Weight (kg)	78.18 ± 15.66	79.54 ± 13.35	74.60 ± 12.75	0.338
Height (cm)	168.09 ± 7.26	169.24 ± 9.56	167.00 ± 8.07	0.554
ASA (I/II/III)	6/18/9	11/16/6	5/20/8	0.246

ASA: American Society of Anesthesiologists. Values are mean ± SD or actual numbers.

Table II. Hemodynamic parameters of groups.

Time point	Parameter	Group A (n = 33)	Group R (n = 33)	Group F (n = 33)	*p*-values
Preinduction (baseline)	HR (bpm)	111.63 ± 22.69*	115.60 ± 20.87*	115.66 ± 19.75*	0.676
	SBP (mm/Hg)	131.57 ± 17.57*	127.21 ± 17.74*	127.75 ± 16.68*	0.540
	DBP (mm/Hg)	80.93 ± 10.74*	77.75 ± 12.10*	77.60 ± 11.73*	0.419
	MBP (mm/Hg)	97.69 ± 13.19*	92.87 ± 11.74*	94.84 ± 14.03*	0.324
Right after EC	HR (bpm)	77.12 ± 13.86*	75.36 ± 14.01*	72.45 ± 11.33*	0.349
	SBP (mm/Hg)	116.187 ± 16.79*	115.69 ± 12.08*	115.18 ± 17.77*	0.967
	DBP (mm/Hg)	71.87 ± 11.69*	68.87 ± 9.21*	69.66 ± 13.03*	0.545
	MBP (mm/Hg)	85.45 ± 11.92*	83.42 ± 11.67*	85.63 ± 16.16*	0.759
3rd minute	HR (bpm)	74.57 ± 11.26*	72.21 ± 9.30*	71.78 ± 9.60*	0.484
	SBP (mm/Hg)	116.84 ± 16.70*	115.60 ± 12.90*	112.69 ± 16.88*	0.543
	DBP (mm/Hg)	67.84 ± 9.88*	67.66 ± 9.90*	66.72 ± 10.61*	0.890
	MBP (mm/Hg)	83.54 ± 11.72*	82.81 ± 11.53*	84.72 ± 14.12*	0.823
5th minute	HR (bpm)	72.27 ± 10.72*	72.24 ± 12.54*	70.54 ± 9.81*	0.770
	SBP (mm/Hg)	118.09 ± 17.97*	113.90 ± 14.25*	113.06 ± 16.77*	0.414
	DBP (mm/Hg)	70.84 ± 12.40*	70.30 ± 9.98*	68.96 ± 11.36*	0.786
	MBP (mm/Hg)	86.03 ± 12.86*	84.30 ± 10.59*	87.36 ± 22.70*	0.746
10th minute	HR (bpm)	73.81 ± 11.11*	71.96 ± 11.89*	71.15 ± 9.03*	0.588
	SBP (mm/Hg)	118.81 ± 16.16*	115.87 ± 13.27*	112.93 ± 15.76*	0.292
	DBP (mm/Hg)	69.84 ± 10.44*	70.18 ± 8.65*	66.93 ± 9.55*	0.323
	MBP (mm/Hg)	84.57 ± 9.82*	84.87 ± 9.57*	83.15 ± 11.28*	0.766
30th minute	HR (bpm)	73.36 ± 11.26*	71.42 ± 7.68*	70.63 ± 8.62*	0.410
	SBP (mm/Hg)	122.42 ± 15.03*	118.81 ± 11.58*	116.21 ± 12.44*	0.160
	DBP (mm/Hg)	73.78 ± 11.01*	70.78 ± 7.97*	68.78 ± 8.82*	0.097
	MBP (mm/Hg)	88.69 ± 10.78*	86.87 ± 8.93*	86.81 ± 10.16*	0.315

HR: Heart Rate, SBP (Systolic Blood Pressure), DBP (Diastolic Blood Pressure), MBP (Mean Blood Pressure).Values are mean ± SD.* Test for repeated measurements, comparison within group, values significantly different to baseline.

groups. MARS values of Group A and R were superior to Group F at 3rd, 5th and 10th minutes. MARS values at the 5th minute of Group A were significantly better than Group R ($p = 0.035$). Detailed data of MARS values for six time points were summarized in Figure 2.

The prevalence of hypotension and bradycardia were similar in all groups ($p > 0.05$) but respiratory depression was higher in Group R ($p = 0.047$). Respiratory depression was observed in 10 patients of Group R, 3 in Group A and 4 in Group F but none of the patients needed bag-mask ventilation. When respiratory depression compared as a binary comparison in three groups, we determined the number of patients with respiratory depression in Group R was higher than Group A ($p = 0.03$). There was no statistically significant difference between Group A and Group F ($p > 0.05$), and Group R and Group F ($p > 0.05$) (Table IV).

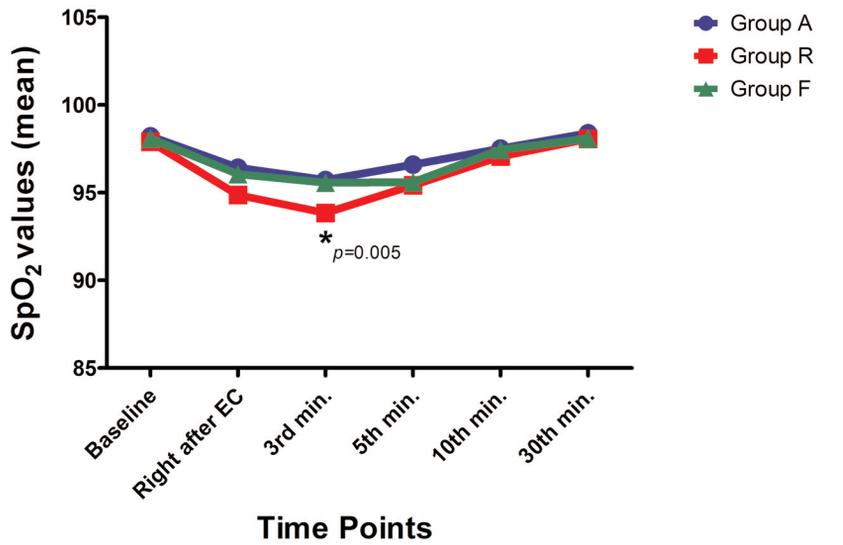
The success rate of cardioversion, mean number of required shocks, pain scores, cardiologists and patient satisfaction scores were comparable and there was no significant difference between groups ($p > 0.05$) (Table IV).

Vomiting, nausea or itching was not observed in any patients and also none of the patients in the study required resuscitation, inotropes or ventilator support.

Discussion

To our knowledge, this is the first study, which compares the effect of three widely used opioids with propofol and midazolam combination in patients undergoing elective cardioversion. The current study shows that low dose concentrations of fentanyl, alfentanil and remifentanil provide an effective sedation and analgesia induced by low dose propofol and midazolam which can be used safely for EC. However, there are some differences that were highlighted as following.

Propofol is widely used for sedation during the performance of different ambulatory procedures. When propofol is used as a sole agent for procedures requiring sedation, analgesia and early recovery; patients may develop unwanted experiences like panic attack, fear and pain, and these adverse events may not be predicted[12]. Also,



	Group A		Group R		Group F	
	Mean	SD	Mean	SD	Mean	SD
Baseline	98.21	1.51	97.90	1.75	98.09	1.72
Right after EC	96.42	2.94	94.87	3.14	96.06	3.26
3rd min.	95.72	2.60	93.84	2.88	95.57	2.00
5th min.	96.60	2.10	95.42	2.61	95.60	2.16
10th min.	97.51	2.00	97.06	1.98	97.45	1.48
30th min.	98.39	0.89	98.06	1.36	98.09	1.44

Figure 1. Comparison of mean SpO_2 values in all groups at time points.

Table III. Initiation of sedation and Post EC recovery data.

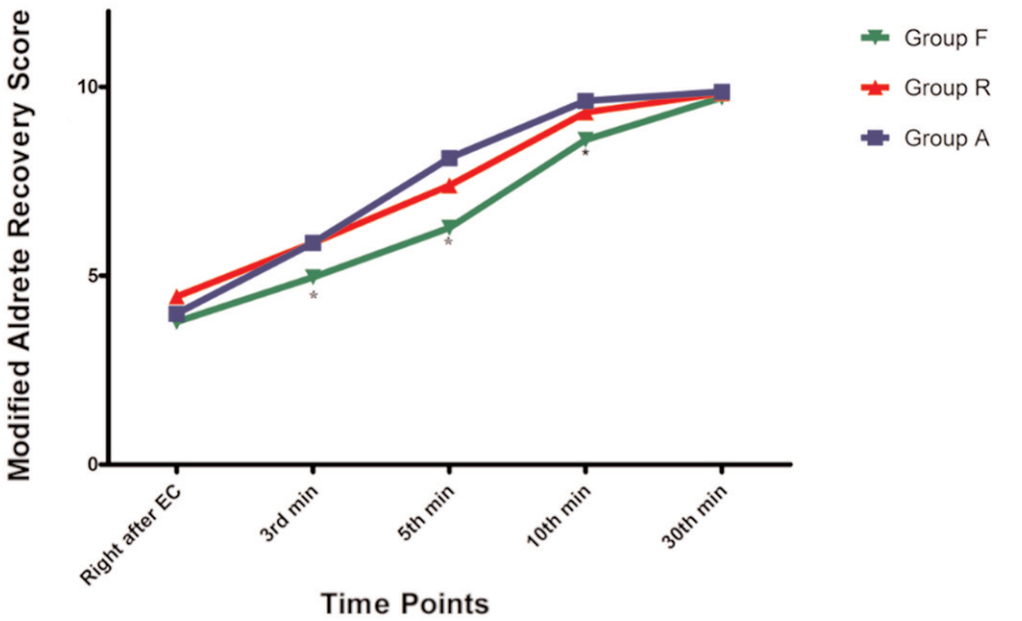
	Group A (n = 33)	Group R (n = 33)	Group F (n = 33)	*p*-values
RSS to 5 duration (sec.)	42.757 ± 13.740	42.424 ± 9.67	62.393 ± 25.39	< 0.05[a,b,c]
MARS to 8 duration (sec.)	335.66 ± 106.45	321.30 ± 98.52	473.45 ± 265.0	0.001[d,e,f]

[a]Within group comparison $p < 0.05$ Group F *vs.* A; [b]Within group comparison $p < 0.05$ Group F *vs.* R; [c]Within group comparison $p = 0.992$ Group A *vs.* R; [d]Within group comparison $p = 0.005$ Group F *vs.* A; [e]Within group comparison $p = 0.002$ Group F *vs.* R; [f]Within group comparison $p = 0.940$ Group A *vs.* R.

Table IV. Complications and clinical parameters of groups.

	Group A (n = 33)	Group R (n =33)	Group F (n = 33)	*p*-values
Apnea	3	10	4	0.047
Hypotension	2	2	3	0.858
Bradycardia	0	1	1	0.600
Success rate	30	32	31	0.587
Number of shock	1.3 ± 0.63	1.27 ± 0.57	1.33 ± 0.59	0.844
Cardiologists' satisfaction	4.21 ± 0.73	4.27 ± 0.57	4.03 ± 0.80	0.457
Patients' satisfaction	4.21 ± 0.59	3.96 ± 0.52	4.27 ± 0.76	0.095
Pain scores	2.15 ± 0.97	2.15 ± 0.93	2.12 ± 1.11	0.99

Values are mean ± SD or actual numbers.



	Group A (n=33)	Group R (n=33)	Group F (n=33)	*p* values
Right after EC.	4,00±1,11	4,45±1,48	3,78±1,16	0.150
3rd min.	5,87±1,36	5,87±1,76	4,96±1,21	0.021[a,b,c]
5th min.	8,12±1,59	7,39±1,34	6,27±1,68	<0.05[d,e,f]
10th min.	9,63±0,48	9,33±0,64	8,60±1,53	0.001[g,h,i]
30th min.	9,87±0,33	9,84±0,36	9,72±0,45	0.244

a.Within group comparison p=0.012 Group F *vs.* A b.Within group comparison p=0.021 Group F *vs.* R

c.Within group comparison p=0.768 Group A *vs.* R d.Within group comparison p<0.05 Group F *vs.* A

e.Within group comparison p=0.007 Group F *vs.* R f.Within group comparison p=0.035 Group A *vs.* R

g.Within group comparison p<0.05 Group F *vs.* A h.Within group comparison p=0.030 Group F *vs.* R

i.Within group comparison p=0.052 Group A *vs.* R

Figure 2. Comparison of mean SpO_2 values in all groups at time points.

higher doses of propofol can be life-threatening with cardiac, respiratory and airway management problems[13]. Combining propofol with a short-acting low dose opioid is a good alternative for providing satisfactory sedation and analgesia without increasing side-effects[14-16]. Drugs having a rapid onset and short duration of action with rapid recovery should be selected. The association of opioids and propofol has many advantages: it decreases the pain caused by the propofol injection; it decreases the discomfort and pain during the procedure. Furthermore, they decrease the amount of propofol that can lead to rapid recovery and decrease the risk of the side effects. Propofol decreases nausea and vomiting due to opioids[17]. Many opioids such as fentanyl[13,18], alfentanil[13], sufentanil[19] and remifentanil[20] added to propofol with different degrees of success.

Fentanyl is frequently used with propofol for short, painful procedures under sedation and has a relatively rapid offset with duration of effect about 30 minutes[16,21]. The usual dosage of fentanyl for this setting is 1-2 μg/kg[15,16,21]. Alfentanil is less lipid soluble than fentanyl. This allows less tissue accumulation and, therefore, greater binding of plasma concentrations to opioid receptors and more rapid onset of effects[15]. On the other hand, Remifentanil is four to ten times more potent than fentanyl and it is cleared in five to ten minutes after a single intravenous dose[15,16,21,22]. A dosage of 0.25 μg/kg has been deemed adequate for most brief procedures[23]. For these reasons, we decided to use 0.5 μg/kg fentanyl, 0.25 μg/kg remifentanil and 5 μg/kg alfentanil for this study.

In studies of EC with propofol and opioids, induction times have shown similarities which were about 2 minutes[6,24]. In our study, induction times were not similar to the literature. The difference may be explained by the addition of midazolam to all groups for premedication. The addition of small doses of midazolam to propofol and opioids for brief procedures like EC not only reduces the need for higher drug doses, but also provides an earlier onset time of induction and also effective anxiolysis without any additional side effects. In our study, we evaluated the induction times with duration needed to reach RSS 5. When the groups were compared duration to RSS 5 was significantly longer for fentanyl group. This result was consistent with the literature[6,20].

Apnea is a serious problem with combinations of propofol and short-acting opioids especially for remifentanil[22]. The combination of remifentanil and propofol has synergistic effects which cause serious respiratory depression[25]. In our study, remifentanil produced more respiratory events with a significant effect on SpO_2, especially at the beginning of sedation (3rd minute). However, these episodes were transitory and responded to tactile and vocal stimulation. None of the patients required bag-mask ventilation or mechanical ventilation support. These clinical findings are in concordance to other studies[6,23].

Differences in recovery times between remifentanil and fentanyl in EC have already been studied in the literature. Maltepe et al[6] found that the recovery after propofol-remifentanil combination was faster than the propofol-fentanyl combination. Our recovery times were shorter than most of the studies with propofol-opioid combinations in the literature[26-28]. This situation can be explained by the use of lower doses of propofol (0.5 mg/kg) in the present study. Although the level of sedation produced by all drugs was sufficient enough for EC, recovery times with fentanyl were longer when compared to alfentanil and remifentanil (150 seconds longer than alfentanil and 138 seconds longer than remifentanil). 150 seconds of duration may not be an important time for long procedures, but it is an important time for short procedures like EC.

In Group F, aldrete recovery score was significantly less than remifentanil and alfentanil groups at 3rd, 5th and 10th minutes. But the difference in alfentanil and remifentanil groups was not significant excluding 5th-minute time point which was better in alfentanil group. We found similar MARS at 30th-minute results for all groups after EC suggesting that none of these drugs delayed discharge of patients.

In the present study, successful cardioversion to sinus rhythm was achieved with similar shock requirements. There were no statistically significant different results with data related to these parameters

Cardiologist and patients satisfaction scores were similar and high in all groups. This indicates that sedoanalgesia is the essential requirement for a comfortable and safe EC experience for the patients.

In studies of EC with opioid combinations[28-31], there were documented adverse effects such as nausea and vomiting during and after anesthesia. None of the patients experienced nausea and vomiting during and after anesthesia in our study. This may be explained due to the antiemetic effects of propofol itself and the lower dose of opioid used in the study. In the literature there is only one study, which compares propofol and two opioids. The adverse events observed in this study are in accordance with us. This emphasizes that using lower doses of opioids at subanesthetic levels with combining propofol prevents nausea-vomiting and increases the patients' quality of recovery.

Conclusions

Our study for the first time compared 3 opioids in the literature. Our results showed that all study drugs (fentanyl, remifentanil and alfentanil) provide adequate sedoanalgesia for EC. These short-acting widely used opioid agents can

be safely used in combination with propofol and midazolam. All drugs provided rapid onset of anesthesia and perfect conditions for EC. But there were significant differences for recovery times. Use of remifentanil may provide a faster recovery, but may cause more respiratory depression can be seen. Propofol alfentanil combination not only gives the advantage of rapid onset for sedation and analgesia, but also provides early recovery and less respiratory depression than remifentanil and fentanyl.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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