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Age Effect on Efficacy and Side Effects of Two Sedation and Analgesia Protocols on Patients Going through Cardioversion: A Randomized Clinical Trial

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Abstract

Background: Cardioversion (CV), a painful procedure, requires sedation and analgesia. Although several sedation agents currently are in use for CV, data on age-specific efficacy and side effects of midazolam and propofol have been limited.

Objectives: To compare the efficacy and side effects of midazolam and propofol in patients of two different age groups, younger than 65 years and 65 years and over, who were going through CV.

Methods: Seventy consented patients with CV indications caused by atrial fibrillation were included in this clinical trial. The participants were placed into four groups by using a stratified randomization method: patients aged younger than 65 years who were receiving midazolam (n = 12) or propofol (n = 11) and patients 65 years and over who were receiving midazolam (n = 25) or propofol (n = 22). Medications were administered by slow intermittent bolus injections. During CV, time to reach Ramsay Sedation Scale level 5 (RSS-5; induction time); time to reach RSS-2 (recovery time); and side effects including desaturation, apnea, and changes in hemodynamic parameters were recorded by a person blinded to the patient treatment allocation.

Results: Mean induction time was similar in all four groups. Mean recovery time (min ± SD) was shorter in both propofol groups when compared with both midazolam groups: 18.8 (±4.06) and 40.33 (±20.8) in the group younger than 65 years and 18.2 (±5.12) and 54.2 (±20.85) in the group 65 years or older, respectively ($p < 0.001$). Older participants in each medication group needed less medication than younger patients. There were no hemodynamic differences between the groups. Desaturation was higher in both midazolam groups as compared with individuals in the age-matched propofol groups (both $p < 0.05$). Patient reactions were less in propofol groups with similar joules during CV procedures than were those in the midazolam groups.

Conclusions: Propofol appears to be a better choice for CV sedation in elders because of its short recovery time, fewer side effects, and its more comfortable sedative effect.

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Cardioversion (CV), a painful procedure, requires sedation and analgesia. A good sedative agent for CV should have a fast induction and recovery time, low cardiovascular and respiratory side effects, an amnesic effect, and an affordable price. Almost all sedative agents have been tested for this purpose. Preexisting conditions such as previous myocardial infarction, congestive heart failure, angina, hypertension, chronic renal failure, chronic hepatic insufficiency, electrolyte imbalance, other concurrent medications, and the age of the patient have been considered in the selection of agents.[1–10] Midazolam and propofol frequently have been used for CV sedation.[11–17] However, different studies report different application techniques, doses, and side effects,[2–4,6–8,10,12,15,18–21] and data on age-specific efficacy and side effects of midazolam and propofol when used in procedural sedation have been limited.[4,6] This study aimed to compare the efficacy and side effects of slow intermittent bolus injections

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of midazolam and propofol in patients of two different age groups, younger than 65 years and 65 years and over, who were undergoing CV at Ramsey Sedation Scale level 5 (RSS-5).[22]

METHODS

Study Design

This was a randomized, blinded clinical trial. Permission from the institutional review board of Dokuz Eylul University Medical Facility was obtained. All patients consented to participate in the study.

Study Setting and Population

The current study was conducted in the emergency department (ED) and coronary care unit (CCU) of the university between March 2002 and October 2002. Patients included in the study were at least 18 years of age, had 90% or higher peripheral oxygen saturation while breathing room air and were free from any respiratory problems, had a sufficient preprocedural fasting period, were undergoing an elective CV because of atrial fibrillation, and were able to provide a written informed consent. Uncooperative patients and those with liver and renal insufficiency, with electrolyte imbalance, with acute respiratory symptoms, with chronic obstructive pulmonary disease, with blood pressure less than 90/60 mm Hg, or with obscure cardiac rhythms, and those who were taking digoxin, beta blockers, or heparin were excluded.

Study Protocol

Randomization was achieved by first doing a stratification on age and then using computer software to generate random numbers. Fentanyl citrate (Abbott Laboratories, Chicago, IL) was used on all participants for preprocedural analgesia. The dosage of fentanyl was reduced by half in the ≥65 years group, because of the well-known and documented increased side effects of opioids in elders.[14,15] Midazolam (Dormicum; Roche Ltd, Basel, Switzerland) or propofol (Diprivan; Astra Zeneca, Macclesfield, Cheshire, UK) was used for sedation. All patients, after consenting to participate in the study, received oxygen at 4 L/min, starting 3 minutes before CV. After that, they received sedative medications according to their randomized allocations.

***Group 1* (n = *12*).** Patients younger than 65 years received 1 μg/kg of intravenous (IV) fentanyl. Three minutes later, they received 2 mg of midazolam (1 mL = 1 mg) IV over 20–30 seconds, until they reached RSS-5. They then received 1 mg of midazolam every 2 minutes.

***Group 2* (n = *11*).** Patients younger than 65 years received 1 μg/kg of IV fentanyl. Three minutes later they received 20 mg of propofol IV (1 mL = 10 mg) over 20–30 seconds, until they reached RSS-5. They then received 20 mg of propofol every 2 minutes.

***Group 3* (n = *25*).** Patients ≥ 65 years received 0.5 μg/kg of IV fentanyl. Three minutes later, they received 2 mg of midazolam (1 mL = 1mg) IV over 20–30 seconds, until they reached RSS-5. They then received 1 mg of midazolam every 2 minutes.

***Group 4* (n = *22*).** Patients ≥ 65 years received 0.5 μg/kg of IV fentanyl. Three minutes later they received 20 mg of propofol IV (1 mL = 10 mg) over 20–30 seconds, until they reached RSS-5. They then received 20 mg of propofol every 2 minutes.

Cardioversion was performed by using a defibrillator (Nihon Kohden, 02326; Nihon Kohden, Tokyo, Japan) when the patient reached the RSS-5 level. CV was started with 100 J; when necessary the voltage was increased to 200, 300, and 360 J. It was applied a maximum of five times.

Two final-year medical residents from the emergency and anesthesiology departments (IP and MP) administered the medication and recorded induction time, recovery time, and side effects of the medications. The researcher who collected the data was blinded to patient treatment allocation. Blinding was achieved by obscuring the patient's arm from the person collecting information. A third-year cardiology resident, who had previously had extensive experience with the procedure, performed CV. A study nurse obtained the randomization scheme from a computer and prepared the medication. To make randomization and blinding work, all contributing personnel in the intervention and data collection procedures were trained on all steps before the study, and they were available 24 hours, 7 days per week during the study. The study personnel monitored participants by using a pulse oximeter for SpO_2 (Spacelabs Medical, Inc. Issaquah, WA), an automatic sphygmomanometer for blood pressure, and a rhythm monitor for heart rate and rhythms during the intervention.

The modified RSS was used to measure the level of sedation.[12,23,24] This scale has six levels. There are three levels for awake: level 1 indicates the patient is anxious, agitated, or restless; 2 means the patient is cooperative, oriented, tranquil; 3 means the patient responds to verbal stimuli. There are three levels for when the patient has greater level of sedation and is asleep: 4 indicates the patient only responds to pain; 5 indicates a sluggish response to pain; and 6 indicates no response to pain.

All medications needed during the CV were recorded. Additionally, the patient's pulse, systolic blood pressure (sBP), diastolic blood pressure (dBP), and oxygen saturation (SpO_2) were recorded at baseline (0 min), after every 5 minutes for the first 30 minutes, and at 45 and 60 minutes. The RSS was recorded every minute in the first 20 minutes, then at 25, 30, 45, and 60 minutes. Close observations continued for all patients for up to 90 minutes. Desaturation was defined as blood oxygen level lower than 95%. Apnea was defined as a period of respiratory arrest lasting 20 seconds or longer.[13,23]

Patient reactions to CV were recorded as 0 = no reaction, 1 = painful face expression, eye opening and incomprehensible speaking, 2 = pointing to the painful areas, and 3 = responding rationally or body movements. Patient satisfaction subsequently was evaluated with a questionnaire including Likert-type questions.

Data Analysis

SPSS 10.0 for Windows (SPSS Inc., Chicago, IL) was used for statistical analysis. Data were summarized as means (±SD) and *n* (%). Kruskal-Wallis, Mann-Whitney U, chi-square, and Fisher's exact tests were used for overall and post hoc comparisons. Analysis of

variance–repeated measures analysis was a method of choice for repeating data. Values of p that were less than 0.05 were considered statistically significant.

RESULTS

Seventy-four participants were randomized into four groups during the eight-month study period. Because of difficulties in data collection, one patient in the propofol–younger than 65 years group, and three patients in the propofol–65 years or older group were excluded from the analysis. There were no significant differences among groups in terms of patient sociodemographic factors and other characteristics (Table 1). The mean induction time (minutes ± SD) did not differ among the groups (8.08 ± 1.67, 8.36 ± 1.85, 7.12 ± 1.16, 7.86 ± 1.88, group 1 through group 4, respectively; overall p = 0.22). Mean recovery time (minutes, ±SD) was shorter in both propofol groups when compared with those in both midazolam groups (18.8 ± 4.06 and 40.33 ± 20.8 in the younger than 65 years group, p < 0.001; and 18.2 ± 5.12 and 54.2 ± 0.85 in the ≥65 years group, p < 0.001; overall p < 0.001).

The average (±SD) amount of midazolam used to reach RSS-5 among patients 65 years and older was significantly less than that in younger patients (2.8 ± 0.76 mg vs. 3.91 ± 0.51 mg, p < 0.001). The amount of propofol used to reach RSS-5 between the different age groups was not statistically different. The average (±SD) total amount of midazolam used during CV was significantly lower in group 3 than group 1 (3.32 ± 1.10 mg vs. 5.0 ± 1.59 mg; p = 0.003). There was no difference between groups 2 and 4 in terms of the total propofol used during the procedure. With regard to desaturation, group 1 was different from group 3: 2 patients (18.2%) desaturated vs. 16 (64.7%; p = 0.01) desaturated. In group 2, desaturation occurred in 1 patient (9.1%); 4 patients (19.0%) desaturated in group 4 (p = 0.02; overall p = 0.001). One patient in groups 1 and 2, six patients in group 3, and two patients in group 4 experienced apnea during the procedure (overall p = 0.39). Figures 1 and 2 present graphical analyses by total drug dose of apnea and desaturation, respectively, for these patients. The side effects of midazolam are much more prominent in the elder patient group. All younger patients in the two medication groups were satisfied with the procedure, whereas two patients in the two older groups were unsure (Table 2).

Although both systolic and diastolic blood pressures during the procedures were decreased in all groups, changes in systolic and diastolic blood pressures by time among the four groups did not show any statistically significant difference (p-value for sBP = 0.6; p-value for dBP = 0.7). The patient reactions to CV at different voltage levels were evaluated by comparing the percentages of reactions with different intensity among the groups. The patients in both midazolam groups showed more serious reactions in the concomitant energy levels (data not shown).

DISCUSSION

The current study compared the efficacy and side effects of midazolam and propofol for CV sedation in two different age groups of patients. Although these medications were found to be very comparable in many aspects related to efficacy and side effects, propofol performed better in several ways in the elder group. It has been reported elsewhere that because of pharmacological differences in the geriatric population, the dosages of midazolam and propofol for sedation need to be reduced.[6,8,10,21,25–27] Midazolam also has been reported to have more side effects in elders, leading to late hospital discharges and long recovery time.[4,6,7,10,28–30] Findings from the current study mostly are comparable with those of previous reports.

Several studies have reported different induction times for different sedative agents used for CV. This could be caused by pharmacokinetic differences in medications, medication administration techniques, different dosages, concomitant medications, and the patients' personal habits.[4,11,17,31,32] Goldner et al. compared 1 mg/kg propofol bolus with 1 mg of midazolam bolus combined with 1–2 mg of morphine. They found that the average time to reach RSS-5 was 3 (±2) minutes for propofol and 9 (±4) minutes for midozolam.[17] David et al. compared 100 mg/min of propofol, 5 mg/min of midazolam, and 50 mg/min of methohexital infusions, and they reported induction times of 1.64 (±0.3), 2.7 (±1.1), and 1.7 (±0.4) minute, respectively.[31] The time to reach RSS-5 was shorter in this study than in our study. Possible reasons for this difference are the higher dosage of medication that these investigators used and the waiting time (3 min) after fentanyl administration in our study. We did

Table 1
Demographic and Clinical Characteristics of Participants at Baseline

	<65 Years of Age		≥65 Years of Age		
Variable	Group 1 Midazolam (*n* = 12)	Group 2 Propofol (*n* = 11)	Group 3 Midazolam (*n* = 25)	Group 4 Propofol (*n* = 22)	Total (*N* = 70)
Age in years, mean (±SD)	55.0 (9.94)	55.27 (10.0)	75.04 (5.13)	73.18 (5.31)	67.91 (11.39)
Gender (*n*, women/men)	5/7	7/4	14/11	10/12	36/34
Weight in kg, mean (±SD)	74.25 (9.71)	73.27 (11.79)	70.64 (13.55)	71.82 (11.40)	72.04 (11.85)
CV number, mean (±SD)	2.17 (1.19)	2.18 (0.87)	2.28 (1.40)	2.50 (1.14)	2.31 (1.20)
EF, mean (±SD)	54.91 (11.36)	50.20 (10.80)	51.95 (14.59)	56.89 (11.01)	53.71 (12.34)
Low EF (%)	2 (16.7)	2 (18.2)	5 (20)	3 (13.6)	12 (17.1)
Left atrium diameter, mean (±SD)	4.46 (0.41)	4.59 (0.42)	4.36 (0.34)	4.27 (0.41)	4.36 (0.42)

CV = cardioversion; EF = ejection fraction.

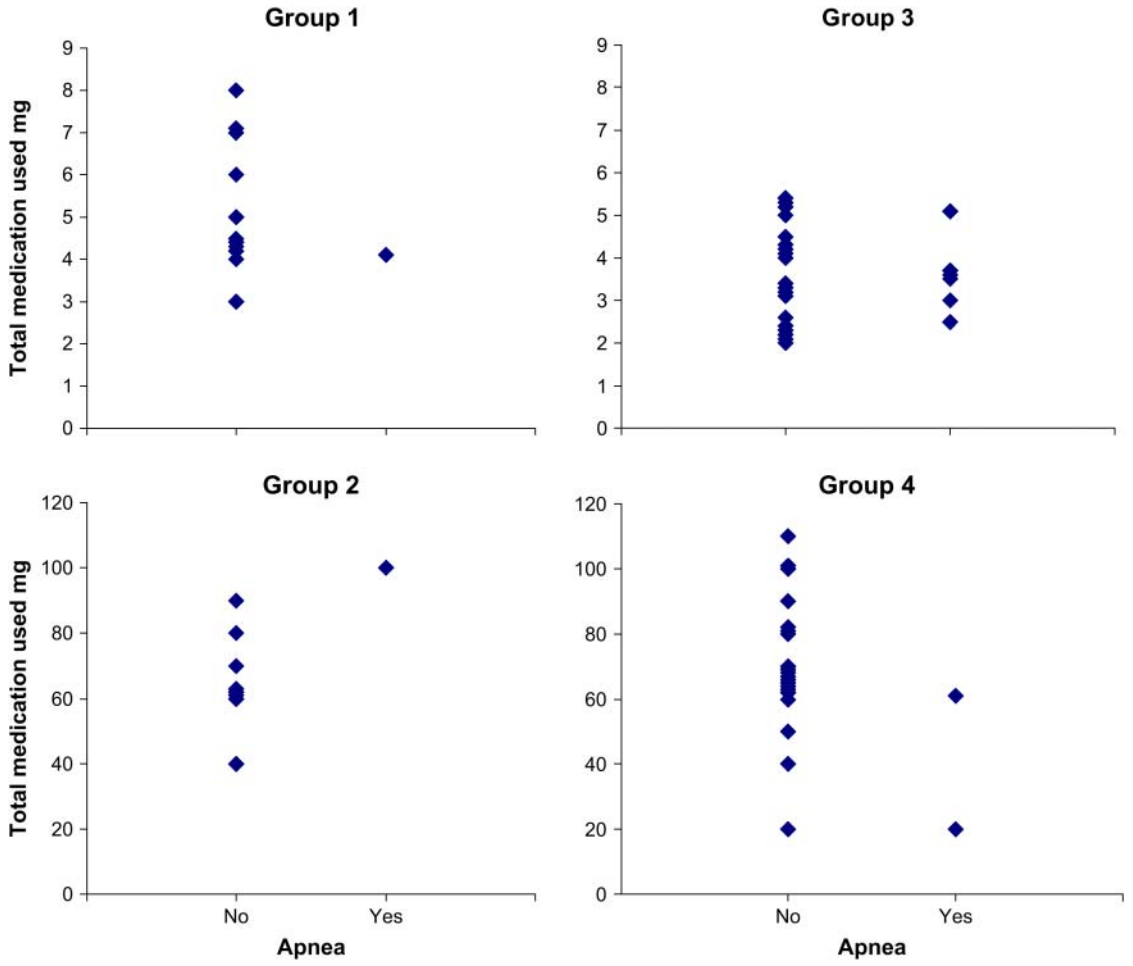

Figure 1. Apnea by total drug dose in each age group. Group 1: younger than 65 years of age and receiving midazolam; group 2: younger than 65 years of age and receiving propofol; group 3: 65 years of age or older and receiving midazolam; and group 4: 65 years of age or older and receiving propofol.

not observe any difference in terms of the induction time among our study groups.

Short recovery time is an important advantage of a sedative agent for CV in a busy ED. Fennelly et al. reported more than 90 minutes of sedation time with 13.9 mg of midazolam.[18] Khan et al. found one-hour sedation time in most patients, but two-hour sedation time in some at a midazolam dosage of between 2.6 mg and 16 mg.[12] Greenblatt et al. found that the half-life of midazolam is longer in elder patients.[6] The present study showed that older patients receiving midazolam had longer recovery times with lower doses of the medication. This needs to be taken into account when using midazolam in elder patients.

Studies using propofol for sedation at boluses of 1 and 1.5 mg/kg reported the occurrence of up to 30% apnea and hypotension.[4,13,14,16,20] Fennelly et al. compared midazolam plus flumazenil, with midazolam plus placebo. They found excessive desaturation, low arterial blood pressure, and two hours more of sedation in the midazolam plus placebo group.[18] Gupta et al. compared propofol, midazolam, and thiopental. They observed a 30% occurrence of apnea in both propofol and thiopental groups, and 40% of the patients showed SpO_2 of less than 95% in the propofol and midazolam groups.[16] Bailey et al. compared midazolam, fentanyl, and midazolam plus fentanyl among volunteer young males.[7] They used a level of SpO_2 of less than 90% to describe desaturation and a 15-second respiratory arrest to describe apnea. Fifty percent of the fentanyl group showed desaturation, but there were no observed apnea events. The midazolam plus fentanyl group showed even more desaturation in addition to apnea incidents (11 of 12 patients).[7] The older midazolam group showed the highest rate of desaturation. Although fentanyl dosage in our study was much lower than that in the study of Bailey et al., higher desaturations can be interpreted as the age effect, the additive effect of midazolam plus fentanyl, or both. Therefore, the use of fentanyl plus midazolam in older individuals requires more caution.

Several studies have indicated that patients' reactions may complicate CV procedures.[1,19,32] Payen et al. evaluated patient reactions by using a Behavioral Pain Scale[33] and reported that the medication dosage can be adjusted by this scale. Ammer et al. applied low-voltage intracardiac CV. With increasing energy level, patient reactions increased, and more midazolam was needed.[34] Gupta et al. also reported that CV patients under midazolam anesthesia showed flexion of their arms and legs. This increased physician dissatisfaction with the procedure.[19]

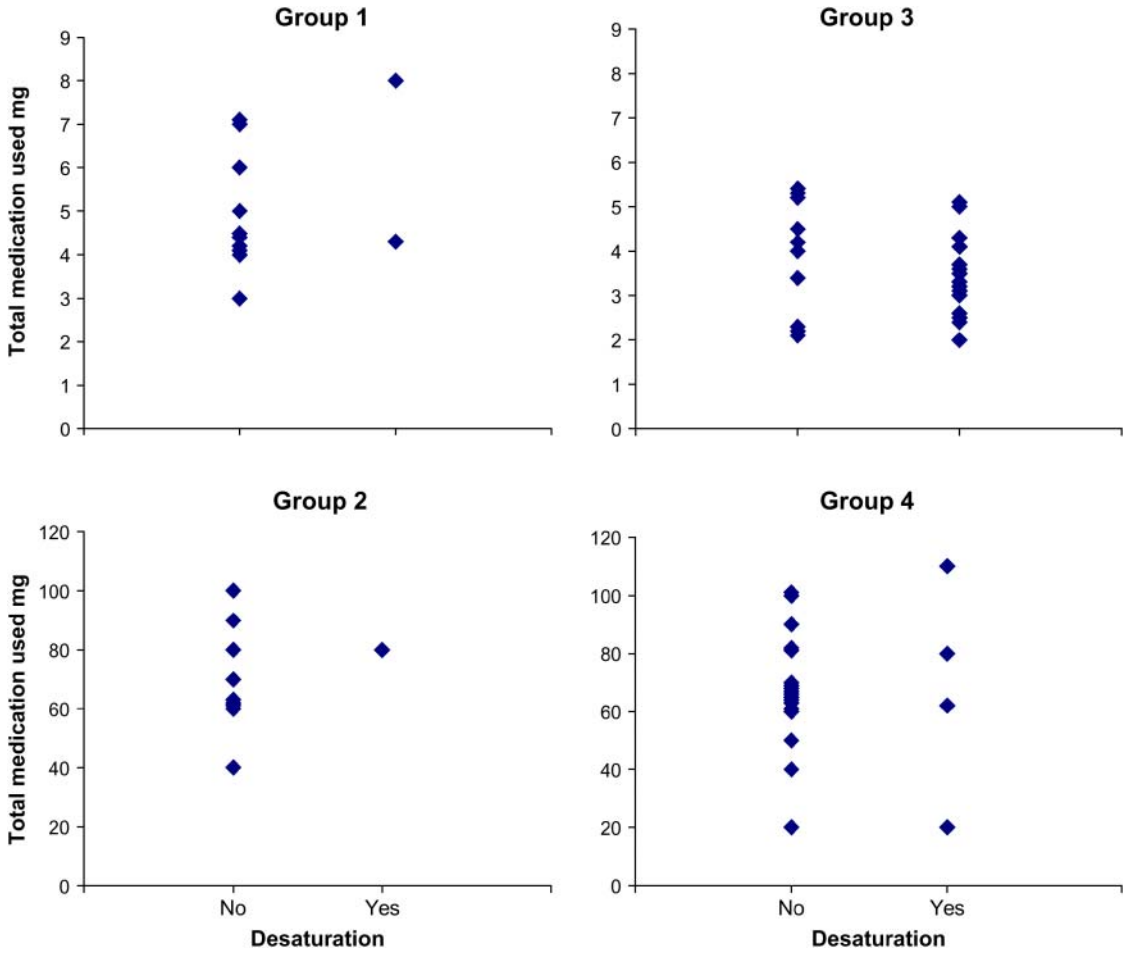

Figure 2. **Desaturation by total drug dose in each age group. Group 1: younger than 65 years of age and receiving midazolam; group 2: younger than 65 years of age and receiving propofol; group 3: 65 years of age or older and receiving midazolam; and group 4: 65 years of age or older and receiving propofol.**

Table 2
Comparisons of Groups by Age and Type of Medication

Outcome	<65 Years of Age		≥65 Years of Age		Overall p-value*
	Group 1 Midazolam (n = 12)	Group 2 Propofol (n = 11)	Group 3 Midazolam (n = 25)	Group 4 Propofol (n = 22)	
Time (min) to reach RSS-5, mean (±SD)	8.08 (1.67)	8.36 (1.85)	7.12 (1.16)	7.86 (1.88)	0.22
Time (min) to reach RSS-2, mean (±SD)	40.33 (20.8)†	18.18 (4.06)†	54.20 (20.85)‡	18.22 (5.12)‡	<0.001
Amount of medication (mg) needed to reach RSS-5, mean (±SD)	3.91 (0.51)§	55.45 (17.52)	2.80 (0.76)§	50.45 (15.26)	—
Total medication (mg) used during the procedure, mean (±SD)	5.00 (1.59)§	67.27 (19.02)	3.32 (1.10)§	65.00 (22.83)	—
Desaturation n (%)	2 (18.2)§	1 (9.1)	16 (64.7)§‖	4 (19.0)‖	0.001
Apnea n (%)	1 (8.3)	1 (9)	6 (24)	2 (9.1)	0.39
Patient dissatisfaction (n)	0	0	2 not sure	2 not sure	—
Event recall, n (%)	0 (0)	1 (9.1)	4 (16)	1 (4.5)	—

* Comparisons of continuous variables among the four groups were performed by using Kruskal-Wallis test, and comparisons of categorized variables were performed by using chi-square test. Post hoc comparisons were performed only if the overall p-value was significant. The Mann Whitney U for continuous and Fisher's exact test for categorical variables were used for post hoc testing.
† $p < 0.05$, comparison of group 1 and group 2.
‡ $p < 0.05$, comparison of group 3 and group 4.
§ $p < 0.05$, comparison of group 1 and group 3.
‖ $p < 0.05$, comparison of group 3 and group 4.

In our study, the patients in midazolam groups showed more serious reactions with the concomitant energy levels than did those patients receiving propofol. Perhaps propofol provided greater muscle relaxation so that there was less evidence of a reaction to CV. This has a potential to increase physician satisfaction. Additionally, after receiving CV with 300 and 360 J, patients in the midazolam groups reported recall of the procedure. This suggests that midazolam failed to create an amnestic reaction in patients receiving CV at high joule levels.

Titration technique was the method of patient sedation used in the present study. This approach reduced the total amount and the side effects of medications. In short procedures like CV, infusion of sedatives has been recommended previously.[1,2,15,31,32] Hullander et al. used propofol infusions (starting with a 50 mg/min infusion and with repeating CVs, increasing to 100 mg/min) to get the benefits of fast recovery and low cardiovascular side effects from the medication. They reported that the appropriate propofol dosage for induction was 1.4 ± 0.3 mg/kg.[32] However, other studies reported that the cardiovascular and respiratory side effects of propofol were independent from the administration technique.[2,4,24,31,32] Peacock et al. administered propofol at different infusion rates (25, 50, and 100 mg/min) and reported that the induction time was reduced as the medication dosage increased. However, the amount of propofol necessary for a successful procedure increased as well.[4] In the present study, we believe that titration of the medication reduced side effects of medications, lessened the total amount of medication used, and also (unlike continuous infusion) required fewer personnel; therefore, it was more cost-effective.

There is no consensus on the use of analgesic before CV. One supportive study included 44 patients receiving 1.5 μg/kg of fentanyl as well as thiopental (3 mg/kg), etomidate (1.5 mg/kg), propofol (1.5 mg/mg), or midazolam (0.15 mg/kg).[14] In another study, the researchers used 1 mg/kg propofol or 1.5 mg/kg thiopental, in addition to 2 μg/kg of fentanyl in 24 patients.[15] However, Khan and Malhhotra did not use any analgesic in addition to midazolam (2.6–16 mg).[12] Hullander et al. also did not use any analgesic in their study comparing etomidate (8 mg/min infusion) and propofol (50 mg/min infusion).[32] On the basis of these reports and our previous experience, fentanyl was chosen for analgesia for the present study. Its short, strong, and antagonizable effect were factors in this decision.[32] Fentanyl dosage was kept to a minimum to reduce the additive negative cardiac effect between benzodiazepines and narcotic analgesics.[15,31,35] The dosage was reduced by half in the older age group, as well.

This study also found a significant amount of chest pain at 6 and 24 hours after CV (15 of 47 patients). Many of these individuals needed extra analgesic. Especially with repeated CVs, patient analgesic was needed to prevent chest pain, and pain should be evaluated for the following 24 hours.

LIMITATIONS

One limitation of this study is that data for four patients in the propofol groups were not collected because of extraordinary clinical activity in the ED that made data collection very difficult. Despite a large sample size in our study compared with many previous studies, our small sample size could be a shortcoming, especially in the case of the negative results, such as not finding any difference in induction time or rate of apnea among the medication groups. However, we employed a randomized and blinded clinical trial design to attempt to answer the study question reasonably.

CONCLUSIONS

In summary, propofol appears to be a more appropriate choice for CV sedation, especially in older individuals, because of its short recovery time, fewer side effects, and more comfortable sedative effects.

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