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Feasibility of a cardiologist-only approach to sedation for electrical cardioversion of atrial fibrillation: A randomized, open-blinded, prospective study ☆

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ABSTRACT

Background/objectives: Sedation with propofol should be administered by personnel trained in advanced airway management. To overcome this limitation, the use of short acting benzodiazepines by cardiologists spread widely, causing concerns about the safety of this procedure in the absence of anesthesiology assistance. The aim of the study was to compare feasibility of a cardiologist-only approach with an anesthesiologist-assisted sedation protocol during elective direct-current cardioversion (DCC) of persistent atrial fibrillation (AF).
Methods: This prospective, open-blinded, randomized study included 204 patients, which were admitted for scheduled cardioversion of persistent AF, and randomized in a 1:1 fashion to either propofol or midazolam treatment arm. Patients in the propofol group underwent DCC with anesthesiologist assistance, while patients in the midazolam group saw the cardiologist as the only responsible for both sedation and DCC.
Results: Twenty-three adverse events occurred: 13 in the propofol group and 10 in the midazolam group ($p =$ NS). Most of them were related to bradyarrhythmias and respiratory depressions. There was no need of intubation or other advanced resuscitation techniques in any of these patients. No differences were found regarding procedure tolerability and safety endpoints between the two groups. DCC procedures with anesthesiology support were burdened by higher delay from scheduled time and higher costs.
Conclusions: Sedation with midazolam administered by cardiologist-only appears to be as safe as sedation with propofol and anesthesiologist assistance. Adverse events were few in both groups and easily handled by the cardiologist alone. A cardiologist-only approach to sedation provides less procedural delay, thus being easier to schedule and correlated with fewer costs.

1. Introduction

Despite its old origin in the early 1960s, [1] direct current cardioversion (DCC) is still the most effective and widely used method for restoring sinus rhythm in patients with persistent atrial fibrillation (AF) [2,3]. DCC is preferred over anti-arrhythmic drugs because of its high rate of success, lower risk of pro-arrhythmia and shorter overall procedure duration. However, DCC is a painful procedure requiring sedation and analgesia. Although a variety of agents may be employed for the provision of sedation, the most popular agent used in this setting is propofol, an intravenous hypnotic–amnestic drug exclusively administered by trained professionals such as anesthesiologists [4]. To overcome this limitation, the use of short acting benzodiazepines for procedural sedation and analgesia (PSA) spread widely, following general recommendations and international guidelines regarding PSA management by non-anesthesiologists [5–7]. Nowadays, recent AF guidelines provide no specific recommendations concerning PSA for DCC, [8,9] and many concerns still exist about the safety of this procedure in the absence of anesthesiology assistance [10].

The purpose of this prospective, open-blinded, randomized study is to compare safety, tolerability, efficacy, and costs of a cardiologist-only approach with a more traditional anesthesiologist-assisted deep sedation protocol during elective DCC of persistent AF.

2. Methods

2.1. Study population

This prospective, randomized, open-blinded, single-center study included 204 patients, admitted to our center from February 2011 to November 2013. Inclusion criteria were age ≥18 years, and hospital admission for scheduled elective cardioversion of persistent AF. The only exclusion criterion was a known or suspected allergy or adverse

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reaction to either midazolam or propofol. No patients were excluded based on concomitant diseases, such as obesity, chronic obstructive pulmonary disease and liver or renal failure, in order to test safety, tolerability and efficacy endpoints on a "real-life" population. The present study has been approved by our local Ethic Committee. All patients gave their written informed consent. Anticoagulation management of all patients before and after DCC was performed according to current European guidelines [8,11].

2.2. Peri-procedural assessment

After collecting clinical history and performing physical examination, blood samples were drawn in order to obtain complete blood count, sodium and potassium blood levels, serum creatinine levels, and coagulation profile. An electrocardiogram (ECG) was performed at admission, before sedation, after recovery, and the day after DCC. Standard 12-lead ECGs were acquired at a paper speed of 25 mm/s and a scale of 10 mm/mV (Cardioline Delta 60 Plus, Vignate, Milano, Italy). A transthoracic echocardiogram was performed in all patients (Vivid 7 Pro, GE-Vingmed Ultrasound, Horten, Norway), and left atrial diameter, left ventricular dimension, and ejection fraction were recorded. Monitoring of heart rate, brachial systolic and diastolic blood pressure and oxygen saturation was started before PSA administration and continued up until 2 h after complete recovery (Agilent M3046A, Agilent Technologies, Milan, Italy). After complete recovery, each patient was asked to indicate on a visual analog scale (VAS) the pain and emotional distress associated with the cardioversion procedure. The scales were 100 mm horizontal lines anchored with "no pain or distress" at the leftmost end and "worst imaginable pain and/or distress" at the rightmost end. Tolerability was then assessed measuring the distance in mm between the beginning of the scale and the patient's mark, thus giving a value from 0 to 100, as previously reported [12].

2.3. Cardioversion

Enrolled patients were randomized in a 1:1 fashion to either propofol or midazolam treatment arm. Patients in the propofol group underwent DCC with anesthesiologist assistance. Both a cardiologist and an anesthesiologist were present during cardioversion procedure, and the anesthesiologist was responsible for propofol administration. Propofol 1 mg/kg i.v. was administered as an initial loading dose, following by subsequent doses of 0.5 mg/kg every 3 min until a satisfactory response (modified Ramsay sedation scale 4 or 5) was achieved [13]. In very elderly patients a loading dose of 0.8 mg/kg was used instead. No other drugs were used in combination with propofol in order to induce or maintain PSA. Patients in the midazolam group underwent DCC without anesthesiologist assistance, and the cardiologist was the only responsible for both PSA and cardioversion. Midazolam 3 mg i.v. was administered as a first starting dose, with subsequent doses of 2 mg i.v. every 2 min until a satisfactory response (modified Ramsay sedation scale 4 or 5) was achieved [13]. Oxygen supplementation with a 100% oxygen mixture and saline infusion through a peripheral intravenous line were granted to all patients during the whole procedure. Once the optimal level of sedation was achieved, up to three R-wave synchronized shocks were delivered according to a step-up protocol. The first 150 J shock was delivered with paddles in the antero-apical position. If ineffective, a second 200 J shock was delivered maintaining the same paddle position. If both shocks were ineffective, a third 200 J shock was delivered using self-adhesive pads in the antero-posterior position [8,14]. All shocks were delivered using a biphasic defibrillator (Zoll M-Series, Zoll Medical Corporation, Chelmsford, MA, USA). At the end of the procedure, 1 mg of flumazenil i.v. was administered by the cardiologist for all patients in the midazolam group. No patient switched from propofol to midazolam arm and vice-versa during the study. All patients' vital signs were monitored for at least 2 h after the procedure, and an anesthesiologist was readily available for any possible emergency regarding patients in the midazolam group.

2.4. Study endpoints

The primary safety endpoint was the incidence of adverse events requiring medical or pharmacological intervention. Trivial or transient adverse events that required no medical intervention were not taken into account. At least one of the authors supervised every DCC procedure, and was responsible for event report. All suspected adverse events were discussed by all authors and adjudicated by consensus.

The primary efficacy endpoint was tolerability of the procedure as assessed by the patient using the VAS system.

Secondary endpoints included: a) variations of vital status parameters (blood pressure, heart rate, and blood oxygen saturation) during DCC procedure; b) total duration of the procedure, defined as the time from sedation induction to complete recovery (Ramsay sedation scale 1); c) monitoring time, defined as the time from the start of the procedure to the end of active monitoring (as retrospectively assessed by nursing notes); d) procedural delay (calculated in minutes as the difference between the scheduled time for DCC and the actual time when the procedure was performed); e) length of hospitalization, assessed in hours; e) incidence of AF recurrence up to 24 h after cardioversion.

2.5. Cost analysis

In order to define direct costs related to DCC, total cost was defined as the sum of material costs, personnel costs and hospitalization costs. All the materials and drugs needed for the DCC procedure were listed, and their cost added up according to the price list used in the "Ospedali Riuniti" University Hospital of Ancona, Italy from February 2011 to November 2013. The cost of each intravenous drug employed was considered equal to the cost of the total number of vials opened during the hospitalization, as residual i.v. drugs were discarded after each procedure. The hourly wage of every health worker attending each procedure was multiplied by total duration of the procedure (in hours) and every wage added together in order to define personnel-related cost. The average cost of a 24-hour hospitalization in our clinic considering AF as main diagnosis (249.1 €) was multiplied by total hospitalization length in order to define hospitalization-related cost of each DCC procedure. Median total cost for effective procedure was calculated as median total cost of DCC in each group multiplied by total number of procedures performed and divided by actual number of DCC resulting in a conversion to sinus rhythm lasting more than 24 h. Indirect costs were not taken into account.

2.6. Statistical analysis

According to sample size calculation, a population of ≥98 subjects in each group would have a >80% power to show that the primary safety endpoint (adverse events requiring medical or pharmacological intervention) for the cardiologist-only group was at least as low as the rate for the control group, considering a difference ≥5% between the two groups as clinically significant (with $\alpha = 0.05$) and an expected rate ranging from 5.8% to 38.3%, according to previous studies on similar populations [15–17]. Quantitative variables were checked for normality by the Kolmogorov–Smirnov test. ANOVA adjusted by age and sex was used to compare normally distributed quantitative variables. Kruskal–Wallis ANOVA was used to compare non-normally distributed quantitative variables. Categorical variables were assessed by using χ^2 analysis. General linear model for repeated measures was used to assess time-dependent changes of blood pressure, heart rate and oxygen saturation. SPSS 13.0 for Windows (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Values of $p < 0.05$ were taken as statistically significant.

3. Results

3.1. General population

The whole population consisted of 204 patients, 100 of which were randomized to propofol and 104 to midazolam. General characteristics of the population are shown in Table 1. There were no significant differences between the two groups in terms of risk factors, concomitant

Table 1
General characteristics of the population.

Variable	Total population (n = 204)	Propofol group (n = 100)	Midazolam group (n = 104)	p-Value
Male gender (n, %)	135 (66.2)	72 (72)	63 (60.6)	.085
Age (years)	68.4 ± 9.3	68.5 ± 8.6	68.3 ± 10.0	.883
BMI (kg/m^2)	27.7 ± 5.2	27.4 ± 6.2	27.9 ± 4.1	.488
Hypertensive cardiomyopathy (n, %)	157 (77)	76 (76)	81 (77.9)	.749
Ischemic cardiomyopathy (n, %)	31 (15.2)	11 (11)	20 (19.2)	.099
Valvular cardiomyopathy (n, %)	19 (9.3)	8 (8)	11 (10.6)	.117
COPD (n, %)	36 (17.6)	20 (20)	16 (15.4)	.387
Previous thyroid disorders (n, %)	21 (10.3)	13 (13)	9 (8.6)	.549
eGFR (ml/min)	68.2 ± 18.2	69.6 ± 19.0	66.8 ± 17.4	.288
Potassium (mEq/l)	4.2 ± .4	4.3 ± .5	4.1 ± .4	.170
INR	2.5 ± .7	2.4 ± .6	2.5 ± .7	.761
LAD (mm)	47.1 ± 5.7	46.6 ± 5.1	47.5 ± 6.2	.378
LVEDD (mm)	55.0 ± 9.9	55.5 ± 10.9	54.5 ± 8.8	.574
LVESD (mm)	38.4 ± 9.6	38.1 ± 9.5	38.6 ± 9.9	.757
LVEF	55.7 ± 13.7	55.8 ± 14.6	55.5 ± 13.0	.903
Class I AADs (n, %)	11 (5.4)	3 (3)	8 (7.7)	.081
Amiodarone (n, %)	89 (43.6)	40 (40)	49 (47.1)	.306
β-blockers (n, %)	125 (61.3)	61 (61)	64 (61.5)	.937
Number of previous AF episodes	1.2 ± .7	1.3 ± .7	1.2 ± .7	.853
Previous DCC performed (n, %)	72 (35.3)	36 (36)	36 (34.6)	.775
Previous PC performed (n, %)	19 (9.3)	9 (9)	10 (9.6)	.404

AAD: anti-arrhythmic drug; BMI: body mass index; COPD: chronic obstructive pulmonary disease; DCC: direct-current cardioversion; eGFR: estimated glomerular filtration rate; INR: international randomized ratio; LAD: left atrial diameter; LVEDD: left ventricular end-diastolic diameter; LVESD: left ventricular end-systolic diameter; LVEF: left ventricular ejection fraction; PC: pharmacological cardioversion.