Original Research

Adding Fentanyl to Etomidate Fails to Reduce Painful Recall of External Direct Current Cardioversion in Adults: A Randomised Trial

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Key words: **Atrial fibrillation, anaesthesia, adverse effects, analgesics, opioid, electric countershock.**

Manuscript received: November 4, 2013;
Accepted: May 13, 2014.

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Introduction: External electrical cardioversion under hypnotics, even when combined with opioids, has been consistently described as distressing or painful. The main objective of the present study was to determine if adding an opioid to a hypnotic, in comparison to the same hypnotic alone, would decrease the incidence of unpleasant or painful recall during anaesthesia for external electrical cardioversion.

Methods: This was a single-centre, prospective, randomised, double-blinded clinical trial that took place from September 2011 to March 2012. Fifty-two adult patients with persistent atrial fibrillation, scheduled for external direct current cardioversion, were enrolled. Exclusion criteria were age >80 years, previous cardiac surgery, implanted pacemaker or defibrillator, and haemodynamic instability. Patients received intravenously either (group EF) fentanyl 50 μg and after 60 s etomidate 0.1 mg/kg, or (group E) only etomidate 0.1 mg/kg. If the patients did not lose their eyelid reflex, repeated doses of etomidate 4 mg were given. Cardioversion was attempted with an extracardiac biphasic electrical shock from 200 to 300 J, at most three times. The primary endpoint was recall of something unpleasant or painful. Secondary outcome measures were predictors of the requirement for repeat doses of etomidate, and the number of shocks needed.

Results: Fifty-one patients (35 male, 16 female), aged 62.1 ± 10.2 years, completed the study. There were no differences between group EF and group E regarding recall (unpleasant recall 0 vs. 2 patients, p=0.235; painful recall 1 vs. 0 patients, p=0.510). The administration of etomidate alone was a significant predictor for subsequent repeated doses of etomidate (p=0.049, odds ratio 4.312, 95% confidence interval 1.007-18.460). The number of shocks needed to restore sinus rhythm did not differ between the groups (p=0.846).

Conclusions: In the present study, the addition of fentanyl to etomidate did not diminish distressing or painful experience during anaesthesia for external cardioversion.

External direct current cardioversion (DCC) is an effective method for converting atrial fibrillation (AF) to sinus rhythm.[1] The procedure is described as painful and distressing; therefore, general anaesthesia is needed.

Most of the anaesthetic regimens for DCC mainly consist of sedative or hypnotic drugs without the addition of an analgesic.[2-8] However, more recently it was shown that anaesthetic protocols that include opioids did not prevent patients from reporting recall of unpleasant or painful experiences.[9-11]

Aiming to evaluate whether an analgesic drug could decrease the incidence of unpleasant or painful recall after DCC, we conducted a prospective randomised controlled trial to compare anaesthesia with fentanyl plus etomidate to etomidate

alone. The main outcome parameter was unpleasant or painful recall of the cardioversion. Secondary outcome parameters were predictors for the requirement of repeated doses of etomidate, the number of shocks needed, haemodynamic stability, anaesthesia-related side effects and rapidity of anaesthesia induction and awakening.

Methods

Ethics

The research protocol for this study was approved (6147/2-5-2011) by the Ethics Committee of the University Hospital of Heraklion, Greece (Chairperson Prof. D. Georgopoulos) on 19 September 2011. All patients gave their written informed consent to participate in the study. The investigation conformed with the Declaration of Helsinki.

Study design

This was a prospective, randomised, double-blinded clinical study of two anaesthesia regimens with 1:1 randomisation for external DCC in patients with persistent AF.

Patient selection

Adult patients with persistent AF who were scheduled for DCC in a public tertiary hospital were eligible to participate and were enrolled by the participating cardiologists. The patients' inclusion criteria were age between 18-80 years, being on an acenocoumarol regimen that resulted in an international normalized ratio between 2.5 and 3.5 for at least one month, being euthyroid, and having normal electrolyte concentrations and an empty stomach. Exclusion criteria were age >80 years, previous cardiac surgery, implanted pacemaker or defibrillator, and haemodynamic instability.

The diagnosis of AF was made from the surface electrocardiogram (ECG) according to the accepted criteria: fluctuation of the baseline without regular P or F waves and totally irregular RR intervals. The duration of AF was assessed at the patient's entry into the study and was based on medical records and existing ECGs.

The study was performed in the electrophysiology laboratory of the University Hospital of Heraklion, Greece.

Study protocol

Pulse oximeter, non-invasive blood pressure monitor and 3-lead ECG were applied as recommended.[12,13] Patients were pre-oxygenated for three minutes prior to induction of anaesthesia, while breathing spontaneously via a simple face mask. Drugs were injected via an 18 or 20 gauge peripheral intravenous (i.v.) catheter in the forearm with an ongoing infusion of Lactated Ringer's solution. Patients were randomly allocated, using a computer-generated random list, to one of the two groups, as follows: group EF received a bolus of fentanyl 50 μg i.v., and after 60 s etomidate 0.1 mg/kg i.v. over a period of 30 s; group E received only the same amount of etomidate, again over 30 s. If the patients did not lose their eyelid reflex, repeated doses of etomidate 4 mg i.v. were given in both groups. Patients were not told which type of anaesthesia they would receive, nor were the cardiologists informed about the allocation. The anaesthesiologists were un-blinded. Once the eyelid reflex was lost, DCC was attempted with an extracardiac biphasic electrical shock ranging from 200 to 300 J (Zoll). If sinus rhythm was not restored, a second or at most a third shock was delivered. In case of apnoea, manual ventilation with a Mapleson system was performed. If obstruction of the upper airway occurred, a jaw thrust and chin lift manoeuvre were applied. At the end of DCC patients were repeatedly requested to open their eyes and were asked simple questions about their name and age. After full recovery, the patients were asked by the cardiologists about unpleasant or painful recall of the procedure and pain during the i.v. drug injection.

Data collection

For each patient, the following data were collected: age, sex, height, weight and American Society of Anesthesiologists Physical Status (ASA) classification. Systolic blood pressure, heart rate and oxygen saturation were recorded immediately before and again after anaesthesia induction with an adequate depth of anaesthesia. The ejection fraction of the left ventricle and the dimension of the left atrium were obtained using pre-procedural echocardiography, according to standard methods. The number of shocks needed, or the failure to restore sinus rhythm were also recorded. Recall of something unpleasant or painful and the occurrence of apnoea, upper airway obstruction, or myoclonus were noted. The time intervals from the end of the injection of the initial dose of etomidate

until (a) loss of consciousness, (b) first shock, (c) eyes opening, and (d) ability to answer simple questions were determined.

Randomisation

Simple randomisation with a 1:1 allocation ratio to the groups EF and E was applied using a computer-generated random sequence, prepared by a registered nurse not otherwise involved in the study. The group assignment was prepared in sequentially numbered, opaque and sealed envelopes. Corresponding envelopes were opened by the anaesthesiologist after enrolment of the patients, immediately before the anaesthesia induction.

Blinding

Patients and cardiologists were blinded to the study group. Only the anaesthesiologists were aware of the allocation so that they could perform the anaesthetic accordingly and be prepared for potential side effects of the fentanyl administration.

Statistical analysis

A power analysis was performed *a priori* based on the results of a previous study[14] using G*Power 3.[15] Based on the proportions of recall of 0 and 25% for the EF and the E group, respectively, an alpha-error of 0.05 and a power of 0.80, a sample size of 52 was calculated with a one-tailed test to yield a statistically significant difference. The statistical analysis was performed using SPSS Statistics v. 19.0. Normally distributed interval variables were expressed as mean ± SD, ordinal parameters and those with non-normal distribution as median (min-max), and categorical variables as frequencies. Inter-group comparisons were performed using the independent-samples t-test or Fisher's exact test, as appropriate. The comparisons regarding the primary outcome were performed as both per-protocol and intention-to-treat analysis. Logistic regression analysis was employed to evaluate potential predictors of the requirement for repeat doses of etomidate.

Results

Fifty-one patients (35 male, 16 female), aged 62.1 ± 10.2 years, were included in the per-protocol analysis (Figure 1). One patient in the EF group was excluded because of protocol violation, as the etomidate dose was given immediately after the fentanyl administra-

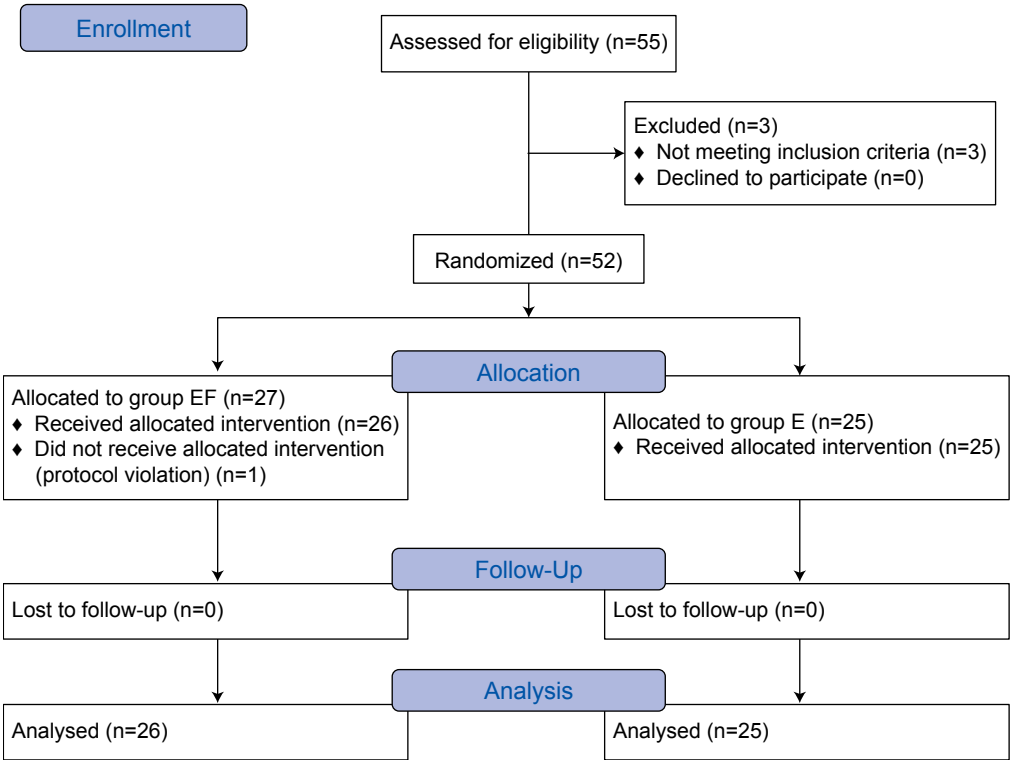

Figure 1. Flow chart showing the progress of the patients through the study.

tion instead of 60 s later. Forty-five patients were on beta-blockers and 36 were on amiodarone therapy, without inter-group differences. Patients' characteristics and their vital signs before anaesthesia induction are presented in Table 1.

Three patients in total had recall of the procedure. Two in the E group had recall of something unpleasant, while one patient in the EF group recalled something painful. The inter-group differences regarding recall of something unpleasant and something painful were not statistically significant (p=0.235 and p=0.510, respectively). An additional intention-to-treat analysis including the 27 patients originally assigned to the EF group yielded a similar, non-significant result (p=0.226 and p=0.519, respectively).

Logistic regression analysis revealed that the administration of etomidate alone was a significant predictor for subsequent repeated doses of etomidate (Table 2). The odds of a patient in group E needing a repeated dose of etomidate were four times those for a patient in group EF. In contrast, the basic characteristics of the patients and their cardiac performance were not predictors of the need for repeat doses (Table 2).

Patients with successful DCC needed 1 (1-3) shock, without inter-group differences (Table 3). Patients in whom sinus rhythm was restored had a slightly greater left ventricular ejection fraction compared to those with unsuccessful DCC (Table 3). This difference was not statistically significant. Nor did the success of DCC depend on age, sex, or the dimension of the left atrium (Table 4).

Table 1. Patients' characteristics and vital signs before anaesthesia induction. Values are mean ± standard deviation or frequencies.

	Etomidate + Fentanyl (n=26)	Etomidate (n=25)	p
Age (years)	62.27 ± 9.28	61.92 ± 11.21	0.904
Sex (m/f)	15/11	20/5	0.132
Height	169.7 ± 9.5	173.2 ± 7.3	0.150
Weight	88.4 ± 15.1	88.8 ± 18.3	0.930
ASA (2/3/4)	13/10/3	12/11/2	0.852
SBP (mmHg)	138.5 ± 18.1	149.1 ± 22.6	0.072
Heart rate (min^{-1})	86.3 ± 20.8	90.0 ± 18.4	0.507
SpO_2 (%)	98.1 ± 1.8	97.7 ± 1.7	0.427

ASA – American Society of Anesthesiologists Physical Status classification; SBP – systolic blood pressure

Table 2. Predictors of the requirement for repeat doses of etomidate. Univariate logistic regression analysis.

Variable	β Regression coefficient	Significance	Exp(β) Odds ratio	95% CI for Exp(β) Lower	Upper
Study group (group E)	1.462	0.049	4.312	1.007	18.460
Age	-0.014	0.666	0.986	0.925	1.051
Sex (male)	0.405	0.588	1.500	0.346	6.501
Left ventricular ejection fraction	-0.012	0.627	0.988	0.939	1.039
Maximum left atrial dimension	0.042	0.584	1.043	0.897	1.214

Table 3. Details of echocardiographic findings and external direct current cardioversion. Values are mean ± standard deviation or frequencies.

	Etomidate + Fentanyl (n=26)	Etomidate (n=25)	p
Left ventricular ejection fraction (%)	54.0 ± 14.6	52.9 ± 10.8	0.750
Left atrial dimension (mm)	42.4 ± 3.7	44.5 ± 4.8	0.087
Number of shocks needed to restore sinus rhythm:			0.846
1	18	17	
2	3	5	
3	1	1	
Number of patients with unsuccessful cardioversion (n)	4	2	0.668

Table 4. Characteristics of patients with successful and unsuccessful direct current cardioversion. Values are mean ± standard deviation or frequencies.

	Sinus rhythm restored (n=45)	Sinus rhythm not restored after three attempts (n=6)	p
Age (years)	62.3 ± 10.4	60.3 ± 8.9	0.655
Sex (m/f)	33/12	2/4	0.069
Left ventricular ejection fraction (%)	54.1 ± 12.8	48.5 ± 11.6	0.313
Left atrial dimension (mm)	43.5 ± 4.5	43.7 ± 3.6	0.916

The systolic arterial blood pressure did not fall in any patient by more than 15% of the baseline value before anaesthesia induction. The mean change after anaesthesia induction was -0.5% (95% confidence interval, CI -2.8-1.7%; min-max -14.6-18.5%. Apnoea needing manual ventilation and obstruction of the upper airway needing jaw thrust and chin lift manoeuvres were observed in 29% and 47% of all patients, respectively, without significant inter-group differences (p=0.220 and p=0.404). No patient experienced a decrease in oxygen saturation to below 94%. Myoclonus occurred in 29% and 31% of patients in groups EF and E, respectively (p=0.776). Five patients in group EF, compared to 4 patients in group E, reported a painful i.v. injection (p=1.0).

The time intervals needed for anaesthesia induction, first cardioversion and awakening were slightly shorter in group EF, but without statistical significance compared to group E (Table 5).

Discussion

Analgesic requirement

This prospective, randomised, controlled study evaluated whether the addition of an analgesic to the hypnotic agent can prevent distressing or painful experience during anaesthesia for external DCC. Our results show that the incidence of unpleasant or painful recall did not differ significantly between the study groups with and without fentanyl. This is in agreement with the results of Miner et al, who compared propofol with and without alfentanil for short painful procedures in an emergency department and failed to show a lower incidence of recall for the group with the opioid.[9] Nevertheless, there are a number of differences between the present study and Miner's study that should be considered. Most of the 145 patients investigated by Miner et al were undergoing orthopaedic procedures, while only five underwent electrical cardioversion.[9] Also, results regarding painful recall might be biased, as pre-existing pain in Miner's study was treated with a considerable dose of morphine.[9] As far as we know, the present study is the first to compare the combination of a hypnotic and an analgesic with the same hypnotic alone in a prospective, randomised way, exclusively in patients undergoing DCC. Cardiological patients, in contrast to the mainly traumatological population in Miner's study, might have impaired cardiac performance and could react in a different way to various drugs. Regarding the anaesthetics in particular, while in Miner's study propofol with and without alfentanil was tested,[9] we chose to investigate etomidate with and without fentanyl for several reasons. First, etomidate plus fentanyl, as an anaesthetic protocol for DCC, has proven to ensure haemodynamic stability in contrast to propofol plus fentanyl,[14] and even in comparison to only propofol.[10] Second, alfentanil, when compared to fentanyl, may

Table 5. Time intervals needed for anaesthesia, cardioversion and awakening, in patients who underwent external direct current cardioversion. Values are mean ± standard deviation.

	Etomidate + Fentanyl (n=26)	Etomidate (n=25)	p
Time from injection of induction agents until (s)			
– Loss of consciousness	56.5 ± 50.2	69.8 ± 65.4	0.419
– First shock	68.9 ± 58.9	91.5 ± 63.5	0.193
– Opening of eyes	198.4 ± 142.4	219.8 ± 146.9	0.600
– Answering simple questions	252.8 ± 154.2	321.4 ± 145.0	0.108

produce more pronounced bradycardia and more muscle rigidity, probably leading to hypoventilation, hypoxaemia, hypercapnia, and difficulty with manual bag-mask ventilation.

It is difficult to compare the results of the present study with other investigations, as most other studies of anaesthetic regimens for DCC have not systematically evaluated the possible benefit of adding an opioid to a hypnotic over the same hypnotic alone. For example, in two studies, patients had received either the combination hypnotic plus opioid or another type of hypnotic without opioid.[10,11] In particular, propofol was compared to the combination etomidate plus fentanyl in one study,[10] and to midazolam in combination with morphine in the other study.[11] In another investigation of midazolam, one third of patients also received pethidine in a non-randomised way at the discretion of the physician, without any explanation of which was the decisive factor for the pethidine administration.[17] Furthermore, it was not reported whether unpleasant recall of the procedure was related to withholding pethidine.[17]

We observed a tendency toward a lower total etomidate dose in the EF group, which is in accordance with the known reduction of the required dose of etomidate after fentanyl administration,[18] as in the vast majority of these patients optimal conditions for DCC were established just after the predetermined fixed doses of fentanyl and etomidate. In contrast, almost 40% of the patients in group E needed one or more repeat doses of etomidate, which was a practical disadvantage of our etomidate-only protocol. In particular, the need for repeat doses in the present study was unpredictable, as it was unrelated to the patients' characteristics and their cardiac function. The need for titration of the adequate induction dose has also been shown in other studies of DCC under various sedative or hypnotic agents, such as midazolam, diazepam, propofol, etomidate and thiopental.[4,6-8,17] An inverse correlation between the required dose and age was only reported in studies investigating benzodiazepines,[6,7,17] whereas in other studies no attempt was made to correlate the need for repeat doses with patient characteristics or the anaesthetic technique.[4,8] To avoid the need for repeat doses, considerably higher induction doses have been used—which, however, have led to a marked blood pressure decrease.[2,3,5]

Side effects of anaesthesia

Systolic arterial blood pressure remained stable in all patients, as was expected given the findings of a previous study.[14] A considerable proportion of the patients needed a jaw thrust and chin lift manoeuvre and/or manual ventilation. These anticipated side effects of the drugs regarding airway patency and respiration did not led to a clinically significant desaturation. Respiratory support was not necessary for more than one min and was easily provided by the attending anaesthesiologist. Myoclonic movements after etomidate injection did not interfere with ECG interpretation, nor did they delay DCC. Their incidence in the present study was much lower than otherwise reported, which can be explained by the lower dose of etomidate used in the present study.[19,20] The occurrence of local pain on etomidate injection might have been decreased by the use of etomidate in an emulsion of medium and long-chain triglycerides;[19,21] however, this formulation is currently not available in Greece.

Study design and limitations

We decided to keep the anaesthesiologists un-blinded to the allocation for practical and also for safety reasons. However, the patients and the cardiologists were left unaware of the treatment assignment, in order to eliminate potential bias among the physicians who assessed the subjective outcomes.

Smaller or arbitrary time periods for the drug administration might have led to insufficient or inconsistent time for the fentanyl effect and thereby to an unforeseeable influence on the outcome parameters. However, by strictly adhering to our methodology, we ensured that the application of the first DCC in group EF occurred on average 160 s after the fentanyl administration. Thus, the maximum effect of fentanyl, which is described to be 2-3 minutes after intravenous injection,[22] was already achieved at the time of cardioversion. The results of the present study might be valid only for the specific time span between the fentanyl and the etomidate administration and for the particular fentanyl dose chosen.

Another limitation of the present study is the small number of events regarding the main outcome, which may have led to an increased probability of a β-error.

Conclusion

The present study showed that the addition of fentanyl to etomidate for DCC did not decrease patients' reporting of pain or of something unpleas-

ant after awakening from the procedure. Nevertheless, the combination of fentanyl with etomidate provided slightly faster and considerably more predictable anaesthesia induction. In contrast, significantly more patients in the etomidate group needed one or more repeat doses to establish adequate conditions for DCC.

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