

The efficacy of scheduled cardioversion in atrial fibrillation. Comparison of two schemes of treatment: electrical versus pharmacological cardioversion

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Introduction and objectives. Atrial fibrillation is an arrhythmia with high morbidity and mortality. Restoring sinus rhythm is one of the principle objectives in its management. The present study aimed to assess the efficacy of scheduled cardioversion on atrial fibrillation by comparing two different therapeutic approaches: electrical vs. pharmacological cardioversion.

Patients and method. Two hundred thirty patients with atrial fibrillation of more than 48 hours duration and requiring sinus rhythm restoration were included. One hundred forty-four patients underwent external electrical cardioversion and 86 patients received quinidine. We analyzed the rate of success, duration of hospital stay, complications and clinical and echocardiographic variable that might predict success.

Results. Sinus rhythm was restored in 181 of 230 patients (79%). The rate of success was 77% (111/144 patients) in the electrical group and 81% (70 of 86 patients) in the pharmacological group (NS). In 13 pharmacological group patients for whom the first attempt failed attempt, a second attempt with electrical cardioversion was made and was successful in 8 patients (61%). No embolic complication was recorded and only two electrical disturbances were seen. Only atrial fibrillation lasting less than 8 weeks was associated with a higher success rate ($P < .01$).

Conclusions. Scheduled cardioversion in atrial fibrillation is an effective technique with a high success rate and a very low rate of complication. Electrical cardioversion and pharmacological cardioversion with quinidine are similarly effective, although the latter involves a longer hospital stay.

Key words: *Atrial fibrillation. Defibrillation. Antiarrhythmia agents.*

Eficacia de la cardioversión programada en la fibrilación auricular. Comparación de dos esquemas de tratamiento: cardioversión eléctrica frente a cardioversión farmacológica

Introducción y objetivos. La fibrilación auricular es una arritmia con una elevada morbimortalidad. Restablecer el ritmo sinusal es uno de los objetivos principales en su manejo. El objetivo del presente estudio es evaluar la eficacia de la cardioversión programada en la fibrilación auricular comparando dos estrategias: la cardioversión eléctrica y la farmacológica.

Pacientes y método. Se incluyeron 230 pacientes consecutivos con fibrilación auricular de más de 48 h de evolución tributarios de intento de reversión a ritmo sinusal. En 144 casos se realizó cardioversión eléctrica externa y en 86 farmacológica con quinidina, analizándose el porcentaje de éxito alcanzado, la estancia hospitalaria, las complicaciones y una serie de variables clínicas y ecocardiográficas que permitieran predecir un mayor éxito en la cardioversión.

Resultados. Se consiguió restablecer el ritmo sinusal en 181 de 230 pacientes (79%). En el grupo eléctrico el porcentaje de éxito fue del 77% (111/144 casos) y en el grupo farmacológico del 81% (70/86 casos; $p = ns$). En 13 pacientes del grupo farmacológico en los que fracasó el primer intento se realizó posteriormente cardioversión eléctrica, que fue eficaz en 8 casos (61%). No se produjo ninguna complicación embólica y sólo dos eléctricas. Únicamente la presencia de una duración de la fibrilación auricular menor de 8 semanas se asoció a un mayor éxito ($p < 0,01$).

Conclusiones. La cardioversión programada en la fibrilación auricular es una técnica eficaz, con una alta tasa de éxitos y un muy bajo índice de complicaciones. La eficacia es similar entre la cardioversión eléctrica y la farmacológica, aunque con una mayor estancia hospitalaria en el grupo farmacológico.

Palabras clave: *Fibrilación auricular. Cardioversión. Agentes antiarrítmicos.*

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ABBREVIATIONS

AF: atrial fibrillation

ECV: electrical cardioversion

PCV: pharmacological cardioversion

INTRODUCTION

Atrial fibrillation (AF) is the most frequent arrhythmia, with a prevalence of 5% in patients over 65 years and an incidence that increases with age. Patients with AF have a greater morbidity and mortality,⁵⁻⁷ and an increased risk of embolic events, which leads to a high percentage of permanent disability in survivors of stroke. The recovery and maintenance of sinus rhythm has several potential benefits: an improved functional capacity and hemodynamic situation, relief of symptoms and reduction of the risk of embolism. For that reason, this is one of the main goals of cardiologists when treating patients with AF.

Traditionally, two types of cardioversion have been described, external electrical and pharmacological. Recently, internal electrical cardioversion has been introduced into clinical practice and its initial results have been much better than those of external cardioversion, although its use is still not very widespread due to its greater technical complexity. The recent development of defibrillators that can deliver a bi-phase rectilinear pulses (as opposed to the traditional monophasic pulses) has also helped to improve the success rate with reduce the energy applied. Although both classic types of cardioversion, pharmacological and external electrical, have been shown to be effective in restoring sinus rhythm, we have found no large studies comparing the effectiveness of both strategies. On the other hand, both techniques have advantages and disadvantages. Pharmacological cardioversion (PCV) is generally recommended in AF of less than 48 h evolution in patients with good hemodynamic tolerance and no relevant structural heart disease, with or without ventricular dysfunction, as well as in persistent AF as an alternative to electrical cardioversion (ECV). The drugs usually used belong to groups Ia, Ic and III of the Vaughan-Williams classification. ECV is indicated principally in cases of AF with poor hemodynamic tolerance, as first-line treatment of paroxysmal and persistent AF or when PCV fails. Generally speaking, ECV is more effective than PCV in cases of longstanding AF. Both require clinical monitoring of the patient, although it must be stricter in the case of ECV, which is carried out under deep sedation. Another advantage of PCV versus ECV is its lower cost. The

aims of the present study are *a)* to compare the effectiveness and safety of both strategies in the case of chronic or persistent AF, and *b)* to identify clinical or echocardiographic markers related with successful cardioversion.

PATIENTS AND METHOD

The present prospective study included 230 consecutive patients who were selected in two provincial hospitals (Hospital General de Alicante and Hospital General de Elche) between February 1997 and January 2000. Patients had chronic or persistent AF of more than 48 h evolution and were candidates for the recovery of sinus rhythm by elective cardioversion according to the criterion of the cardiologist. This is a comparative study of experimental nature without randomization. Most of the patients came from the outpatient clinics and, to a lesser extent, directly from the emergency area. Hemodynamically unstable patients who required urgent electrical cardioversion were excluded. Two main treatment groups were created, one assigned to synchronized external ECV, which was constituted by patients selected exclusively from the Hospital General de Alicante (144 patients), and the other was assigned to PCV with quinidine and formed by patients selected from the Hospital General de Elche (86 patients). Thirteen patients assigned to the pharmacological group without success, then assigned to a second attempt at CV by electrical discharge, which was performed at the same hospital. All patients signed an informed consent form before CV was performed. The duration of the arrhythmia was determined by considering the time of onset of symptoms or of the abrupt deterioration of previously existing symptoms. In patients in whom the exact moment of onset of symptoms (15.2% overall, 35 of 230 patients, with similar percentages in each group; 13.9% in the pharmacological group versus 15.9% in the electrical group) was not clear, the duration of arrhythmia was not considered in the analysis. In every case, oral anticoagulation with acenocoumarol was begun at least 3 weeks before cardioversion, maintaining a stable range of anticoagulation, with INR 2.0-3.0 according to present recommendations. Most patients took medication to control heart rate, basically beta-blockers, calcium antagonists, and digoxin, in a regimen established by the cardiologist responsible for the patient. All patients were hospitalized the day before cardioversion and underwent a differential blood count, basic biochemistry, and chest radiograph, as well as an electrocardiogram that confirmed the persistence of AF. In all patients, an echocardiographic study was made (Hewlett-Packard Sonos 2500, Andover, Massachusetts) with M-mode

bidimensional analysis to determine the ventricular diameters, wall thickness (septum and posterior wall), and size of the left atrium in the longitudinal parasternal plane. In addition, the existence of structural valve anomalies and significant cardiac valve disease was evaluated by continuous pulsed color Doppler study. Left ventricular mass was calculated with the Devereux formula, and related with the patient's body surface.

ECV was carried out under deep sedation with diazepam and etomidate i.v., ECG follow-up, and continuous pulse oximetry. It began with a discharge of 100, 200 or 300 joules (according to the criterion of the cardiologist in charge of cardioversion) with the defibrillator paddles in standard anteroapical position. If the first discharge was ineffective, shocks were repeated at progressively higher energies up to a maximum of 4 shocks (200, 300, and 360 joules, respectively). PCV was carried out with quinidine sulfate, administering an oral dose of 300 mg every 6 h the first 2 days, followed by a 600-mg dose every 6 h for 48 h more, which was discontinued when sinus rhythm was restored. After this time, patients who remained in AF were included in the ECV protocol. The presence of a stable sinus rhythm was defined as success after the procedure and before releasing the patient.

After cardioversion, the anticoagulation state of the patient was recorded, as estimated by the INR value. These records were completed by a physician not involved in the cardioversion process, and done after the procedure. The anticoagulation level was considered adequate when the INR was 2.0 to 3.0. Patients were followed-up for a month after cardioversion to detect delayed embolic events.

The following variables were analyzed:

1. Techniques: total quinidine dose and days of treatment in the pharmacological group; number of dis-

charges, maximum and total energy in the electrical group; duration of hospital stay and complications in both groups.

2. Clinical variables: Age, sex, history of previous AF, time since onset of AF (in weeks), presence of hypertension, and body mass index.

3. Echocardiographic variables: Size of left atrium, presence of structural heart disease, shortening fraction, left ventricular ejection fraction, and cardiac mass.

Statistical analysis

The qualitative variables are expressed as percentages and the quantitative ones are expressed as mean and standard deviation. The normal distribution of the quantitative variables analyzed was confirmed by the Kolmogorov-Smirnov test. To analyze the different variables, parametric tests were used. The chi-square test was used to compare two qualitative variables. To determine the association between quantitative and qualitative variables, the Student *t* test was used. To study possible confusion variables, a multiple logistic regression model was made. A *P* of less than 0.05 was considered statistically significant. The strength of the association of the factors associated with greater success was estimated by calculating the *odds ratio* (OR) with the EpiInfo statistical program and Cornfield method to establish 95% confidence intervals (CI).

RESULTS

The clinical and echocardiographic characteristics of the study population, overall and by assigned treatment groups, are described in Table 1. The groups were similar in clinical and echocardiographic characteristics. A tendency was found towards a greater inci-

TABLE 1. Baseline clinical and echocardiographic characteristics of the study population

	Overall	ECV	PCV	P
Age (years)	63.3±10.0	64±10.1	63±8.3	NS
Sex (M/W)	112/118	73/71	39/47	NS
Mass (g)	258±123	254±91	268±174	NS
CMI (g/m ²)	127±40	128±38	126±42	NS
LA (mm)	42.5±6.4	41.9±6.1	43.6±6.5	.06
EF (%)	63.1±6.5	62.1±10.3	65.3±6.9	.08
Shortening fraction (%)	34.3±7.4	32.8±7.1	37.0±6.3	.08
Time of AF (weeks)	25.5±83.9	15.4±27.9	58.6±158.7	NS
Previous AF (%)	37.0	42.7	27.0	.09
AHT (%)	41	38	50	.07

LA indicates left atrium; ECV, electrical cardioversion; PCV, pharmacological cardioversion; M, men; W, women; EF, ejection fraction; AHT, hypertension; BMI, cardiac mass index; mass, left ventricular mass; AF, atrial fibrillation.

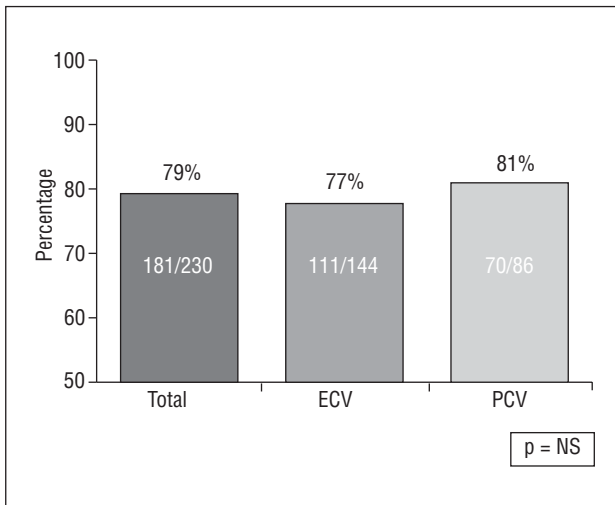


Fig. 1. Success rate after cardioversion. In the center of the columns is indicated: successful cardioversion/total number of patients. ECV indicates electrical cardioversion; PCV, pharmacological cardioversion.

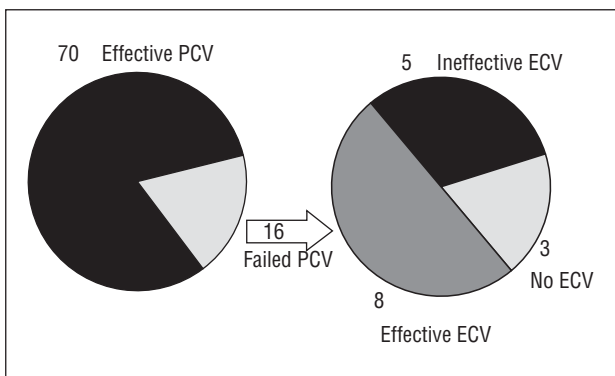


Fig. 2. Electrical cardioversion after failed pharmacological cardioversion. Next to the sectors is indicated the absolute number of patients. PCV indicates pharmacological cardioversion; ECV, electrical cardioversion.

dence of hypertension, larger left atrium, and greater ejection fraction in the pharmacological group and more previous episodes of paroxysmal AF in the electrical group, although none of them reached statistical significance. The drugs that the patients were taking at the time of inclusion in the study were digitalis (40%), beta-blockers (25.2%), calcium antagonists (25.6%), amiodarone (16.9%), flecainide (2.6%), and sotalol (4.3%). No significant differences were found between intervention groups (pharmacological to electrical), in previous drug treatment, or when comparing the successful or unsuccessful CV groups.

In Figure 1 are shown the percentages of success achieved after cardioversion, overall and by treatment groups. Of 16 patients in the pharmacological group who did not recover sinus rhythm, 13 were referred for a second cardioversion attempt using electrical shock,

which resulted in recovery of sinus rhythm in 8 of them (61% success) (Figure 2). This, added to the percentages of success obtained previously, resulted in an overall post-cardioversion success rate of 82% (189 of 230 patients). No statistically significant differences were found in the variables analyzed between the groups with successful and failed cardioversion (Table 2). There were no differences in the presence and number of previous episodes of AF, or the presence of hypertension or structural heart disease, including the presence of mitral valve disease. The same analysis was repeated separately in both the pharmacological and electrical groups, comparing the subgroups of successful and unsuccessful cardioversion in each group, but no significant difference was found between the variables analyzed. Since the duration of AF had a very large standard deviation, a cut-off point was established at the average value (8 weeks). In both the overall group and ECV subgroup, patients with a duration of AF of less than 8 weeks had a higher rate of conversion to sinus rhythm ($P < .01$ for both). Nevertheless, in the PCV subgroup, the duration of AF was still not a predictive factor of success. In multivariate analysis, only duration of AF less than 8 weeks had a significant isolated influence on the success of cardioversion ($P < .01$), with an OR of 3.31 (95% CI, 1.40-7.91).

In the electrical group, a single discharge sufficed to achieve sinus rhythm in 46% of patients, two discharges in 31%, three in 21%, and four in only 2% of patients. This indicates that conversion was achieved most often after the first discharge and progressively decreased with the number of discharges administered. In 55 patients, cardioversion began at 100 J and was effective in 16.4% of cases. In 76 patients, cardioversion began at 200 J and was effective in 55.3% of cases. In the rest of the patients (n=13) it began at 300 J and was effective in 77% of cases. PCV with quinidine was successful on the first day of treatment in 44% of cases, on the second day in 34%, on the third day in 14%, and on the fourth day of treatment in only 8%. The mean hospital stay in the electrical group was 1.00 day, and 1.96 ± 1.06 days in the pharmacological group ($P < .01$).

Of 103 patients in which the state of anticoagulation was analyzed at the time of cardioversion, 82% of the patients had an adequate INR level between 2.0 and 3.0 and 18% had an INR of less than 2.0. In spite of this, no embolic complications were found during the acute phase or the next month of follow-up. Only 2 patients presented arrhythmic complications during the cardioversion process: an episode of bradycardia that required pharmacological treatment in the electrical group and a *torsade des pointes* in the group treated with quinidine.

TABLE 2. Analysis of clinical and echocardiographic variables. Differences between the group with effective cardioversion and the group with ineffective cardioversion

	Effective	Ineffective	P
Age (years)	64.0±9.3	62.0±10.2	NS
Mass (g)	257±138	268±95	NS
CMI (g/m ²)	125±45	128±30	NS
LA (mm)	42.1±5.9	44.1±7.7	NS
EF (%)	63.1±9.7	61.9±10.0	NS
Shortening fraction (%)	33.9±7.1	33.3±7.0	NS
Time of AF (weeks)	25.0±97.6	29.7±2.2	NS
Previous AF (%)	35.2	43.8	NS
AHT (%)	44.3	30.2	.08

LA indicates left atrium; EF, ejection fraction; CMI, cardiac mass index; mass, left ventricular mass; AF, atrial fibrillation.

DISCUSSION

Current recommendations for the treatment of persistent AF indicate that we should try to recover sinus rhythm by external or pharmacological electrical cardioversion if the clinical profile of the patient allows. However, this recommendation is being debated and a discussion is underway as to which of the following two options is best: cardioversion and aggressive efforts to maintain sinus rhythm, or control of heart rate in the presence of baseline AF.

Another current topic of debate is the potential benefit, in terms of improved quality of life, of recovering sinus rhythm in persistent or chronic AF. A recently published study, the PIAF study, found no differences in this point, although the group assigned to amiodarone treatment for rhythm control achieved sinus rhythm initially in only 23%, versus 56% for electrical cardioversion. In addition, there were 25% of withdrawals from treatment with amiodarone. A multicenter trial in course, the AFFIRM study, is attempting to answer these questions. Until these studies conclude, most authors feel that an attempt must be made to recover sinus rhythm, PCV being most useful in patients with paroxysmal AF of less than 48 h evolution. From this time on, its effectiveness greatly diminishes. In this case and in patients with chronic AF, the use of ECV as a preliminary strategy is advised.

Our results confirm a high rate of effectiveness for the conversion to sinus rhythm of patients with persistent AF (the mean duration of the arrhythmia in our group was 25 weeks). The success rate was similar with both strategies but, since it was not a randomized study, a critical analysis must be made to compare the effectiveness of the two strategies. The rates of conversion to sinus rhythm by ECV that we obtained were similar to those seen in previously published series. Nevertheless, in the PCV group the results were better than expected in view of previous studies,

which have reported success rates of about 50% for quinidine. The differences between studies in the success rates of quinidine seem to be due to differences in the groups analyzed, fundamentally the time since onset of AF (which suggests that quinidine is less beneficial in AF of less than 48 h evolution) and the different pharmacological regimes used. Quinidine is a classic antiarrhythmic drug, which was much used in the past and has fallen into disuse due to its lower effectiveness and greater proarrhythmic risk, especially for *torsade des pointes*, which occurs in 2% to 8.5% in different studies. The meta-analysis of Coplen et al indicates a higher incidence of death with quinidine versus placebo. Nevertheless, this study has important limitations because the groups of patients were very heterogeneous and had a higher incidence of baseline heart disease. A recent meta-analysis that analyzed the long-term use of this drug found a low mortality rate, similar to that obtained with drugs considered safer. Therefore, the main problem of proarrhythmia (fundamentally in the form of *torsade des pointes*) and sudden death with quinidine seems to be limited to the first days of treatment, especially in the subgroup of patients with depressed systolic function. In addition, this side effect is not dose-dependent, the appearance of which depends on individual drug tolerance (idiosyncratic reaction). In our group we found a success rate similar to that obtained with ECV, and a very low rate of arrhythmic complications, only one case of *torsade des pointes* in 86 patients treated (1.16%).

We must emphasize that, of all clinical and echocardiographic parameters analyzed, only duration of AF of less than 8 weeks was predictive of successful cardioversion, both overall and in the ECV subgroup. No differences were found in the PCV subgroup, possibly due to the high success rate and size of the sample. Nevertheless, it was not possible to identify subgroups of patients who benefit more from one strategy than the other. This could be related with a sample size that

was too small to find significant differences, or with the possibility that the factors traditionally implicated in the reappearance of AF (age, hypertension, systolic dysfunction, left atrial size) are not directly related with the immediate success of cardioversion. Likewise, the practical absence of relevant structural heart disease, as indicated by the echocardiographic parameters within normal range in our group, could explain these findings.

In the ECV group, we found that 98% of the patients who recovered sinus rhythm did so with fewer than 4 electrical shocks, the success rate after a single discharge being 46%. Nevertheless, the number of patients who benefited from a fourth shock is low (2 of 35 patients in our group). The success rate was greater with higher initial discharges. In patients in which cardioversion began with 100 J, the failure rate was very high and a new discharge was required, thus increasing the final total energy. Nevertheless, when the initial discharge was 200 J, the success rate was greater and the total energy applied was less than in those that began with 100 J. These findings justify the present tendency to initiate electrical cardioversion at 200 J. On the other hand, in the pharmacological group, almost 80% of patients who recover sinus rhythm do so in the first 2 days of treatment, which is why it is not useful to prolong treatment longer. If after 2 days of failed treatment, it is advisable to continue with ECV, which reduces the hospital stay. In this subgroup, the rate of conversion was high, so the failure of one technique does not seem to predict the failure of the other and it seems justified to attempt ECV after a preliminary failure. In our study, PCV was not attempted in any patient in which ECV had failed, which is why results cannot be extrapolated to the other treatment. On the other hand, although the overall cost of PCV is accepted as lower, our study found that the hospital stay was longer, twice as long as in the ECV group ($P<.05$). In addition, PCV has the disadvantage that the moment of recovery of sinus rhythm is unforeseeable, and may occur as long as four days after initiating treatment.

It is necessary to emphasize the very low incidence of embolic complications after cardioversion in both the electrical and pharmacological groups. No immediate embolic event (in the first 3 days post-cardioversion) took place, although it was found *a posteriori* that 18% of the patients were not correctly anticoagulated. This could be due to the fact that these incorrectly anticoagulated patients had an INR between 1.7 and 2.0, which could have been sufficient to prevent embolic events. In fact, in the work of Hylek, et al.⁵¹ patients with non-rheumatic AF who were anticoagulated and had an INR between 1.6 and 1.9 presented a 75% lower embolic risk than patients who were not

anticoagulated. Our patients were followed-up for one month after cardioversion, because it has been reported that embolic events can appear up to 20 days after cardioversion, although 90% of embolisms appear in the first 3 days. No late embolisms were recorded either. These findings illustrate the controversy over this point. No randomized study has clarified if an INR below 2.0 in a given moment forces CV to be delayed 3 weeks longer. In spite of this, it seems prudent to control anticoagulation before carrying out cardioversion and to delay it another 3 weeks if low-grade of anticoagulation is evidenced, even at the expense of prolonging the duration of AF and its harmful effect on atrial functionality.

We must note that a possible limitation of the study is the selection bias, which has been assumed voluntarily by not including patients with scant possibilities of success with cardioversion (chronic AF of long duration and grossly dilated left atrium, in excess of 60 mm), because these patients were not referred for cardioversion by their cardiologists.

CONCLUSIONS

Elective cardioversion is an effective technique, with a high rate of initial success in the treatment of the chronic or persistent AF in patients without left ventricular dysfunction and with no major dilation of the left atrium. The effectiveness of the electrical and pharmacological modalities of cardioversion is similar, although the hospital stay is longer in pharmacological cardioversion. After the failure of PCV, it seems to be useful to try ECV. The complication rate is low and similar in both strategies. According to our results, both therapeutic modalities are valid and the decision to choose one or the other will depend on the experience of the cardiologist.

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