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Original Research Article

Antazoline for termination of atrial fibrillation during the procedure of pulmonary veins isolation

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ABSTRACT

Purpose: Pulmonary vein isolation is a well established method of definite treatment of atrial fibrillation (AF). Periprocedural onset of AF usually terminates spontaneously within minutes, but not in all cases. Antazoline is an antihistaminic agent with antiarrhythmic properties. The aim of our retrospective study was to evaluate the efficacy of antazoline in termination of AF in patients undergoing pulmonary vein isolation.

Materials and methods: Consecutive 141 patients who received antazoline to terminate AF during pulmonary vein isolation were analyzed. The antazoline was administered at the rate of 30–50 mg/min (max. 500 mg) after the circumferential ablation in the ostia of pulmonary veins and before confirmation of isolation. Success was defined as restoration of sinus rhythm within 20 min after antazoline infusion.

Results: The efficacy of antazoline was 83.6% in paroxysmal and 31.1% in persistent AF patients. Clinical variables that were independently predictive of antazoline ineffectiveness were female (odds ratio [OR]: 4.35; 95% confidence interval [CI]: 1.26–14.3; $p = 0.018$) and AF at the beginning of procedure (OR 28.4; 95% CI 3.89–208.0; $p = 0.001$). Due to antazoline related side effects infusion was discontinued in 7 patients (5%).

Conclusions: Antazoline seems to be safe agent in termination of AF in patients undergoing pulmonary vein isolation. We also observed satisfying efficacy, which needs to be proved in a randomized clinical trial.

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1. Introduction

Pulmonary vein isolation is established method of treatment of atrial fibrillation (AF). AF may occur during the procedure hindering the verification of successful isolation of pulmonary veins. Periprocedural onset of AF usually terminates spontaneously within minutes, but not in all cases. Particularly, it is uncommon in patients with persistent AF. In such cases rapid conversion to sinus rhythm may be achieved by electrical cardioversion (ECV). However, it requires general anaesthesia and does not prevent from immediate AF recurrence. The pharmacological cardioversion (PCV) of AF to sinus rhythm (SR) may be achieved by administration of class IA, IC and III antiarrhythmic drugs: flecainide, ibutilide, dofetilide, propafenone or amiodarone [1]. Beta-adrenergic blocking agents alone are not considered suitable for PCV due to their low or lack of efficacy [1]. Another drug for rapid PCV of AF is vernakalant [2,3].

Antazoline is an antihistaminic agent with antiarrhythmic quinidine-like properties [4,5]. In some countries it is registered for intravenous termination of cardiac arrhythmias. It has been used for many years for rapid termination of AF [6,7]. In Poland it has registration for using it for termination of supraventricular arrhythmias – it was used according to this registration. However, due to the lack of large randomized trials the drug is not listed in any of the formal guidelines. Antazoline prolongs the action potential duration and lowers its amplitude, prolongs duration of phase 0, reduces phase 4 of resting potential and reduces excitability of cardiac tissue. Clinically, antazoline lowers the velocity of intra-atrial conduction, prolongs the atrial refraction period and may improve atrioventricular conduction allowing fast ventricular response to supraventricular arrhythmias [4,8].

There are no widely known, randomized clinical trials evaluating the antiarrhythmic effect of antazoline. Published studies are mainly single-arm clinical trials with no control group or a different series of cases where antazoline was administered

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either orally or intravenously in different doses and in different arrhythmias. These studies suggested high efficacy of antazoline in rapid conversion of AF to SR if administered intravenously up to the cumulated dose of 350 mg. Most adverse effects were observed after cumulated doses exceeding 250 mg and they were mainly comprised of mild hypotension, hot flushes and mild tachycardia. Antazoline can unmask the underlying sick sinus syndrome or atrio-ventricular block [4,8–12]. According to information from the trials journal there is one randomized trial, which is being currently conducted [13].

2. Methods

This is a retrospective, non-randomized, no placebo – controlled observational study. Consecutive 141 patients who received antazoline to terminate AF during isolation of pulmonary veins between January 2009 and April 2013 were analyzed retrospectively. The persistent AF was diagnosed when it lasted longer than 7 days. The antazoline was administered during the procedure in the electrophysiological laboratory after the isolation of pulmonary veins and before confirmation of isolation. We based on medical notes to collect demographic and clinical data. The total dose of antazoline required for sinus rhythm restoration was recorded. Early success was defined as restoration of sinus rhythm within 20 min after antazoline infusion. The 20 min results from the time when patient stays in the electrophysiology laboratory. Afterwards the patient is moved to the intensive care unit and observed for 12 h.

Each patient underwent transesophageal echocardiography before the procedure. During the pulmonary vein isolation each patient was treated with intravenous infusion of unfractionated heparin under the control of activated clotting time (ACT) with a target of 300–400 s.

In polish summary of product characteristics there is information that dose from 100 up to 300 mg should be infused in 3–10 min. Higher doses are acceptable in intensive care units. In our lab antazoline was administered intravenously at a rate of 30–50 mg/min until either maximal cumulative dosage was obtained (500 mg) or sinus rhythm was restored or presence of side effects was observed – in most of the cases 400 mg were delivered. A 12-lead electrocardiogram, intracardiac recordings and blood pressure were continuously monitored. If the SR was not restored, the confirmation of isolation of pulmonary veins was performed during AF. The infusion was also stopped in case of QTc interval >550 ms or QRS > 140 ms; symptomatic bradycardia or heart rate <40 beats/min; symptomatic hypotension or systolic blood pressure <85 mm Hg; new bundle branch block, any ventricular tachycardia, any *Torsades de pointes* (TdP) or ventricular fibrillation; one or more sinus pauses of >5 s or complete heart block; or intolerable side effects.

Antazoline was contraindicated when a patient had severe underlying cardiac disorder defined as previous myocardial infarction, heart failure symptoms in NYHA class above II or markedly reduced left ventricular ejection fraction <40%. Also significant hypotension (systolic blood pressure <90 mm Hg) was a contraindication since the drug may cause hypotension. The metoprolol intravenously was administered if high ventricular rate emerged during antazoline infusion. The decision of metoprolol infusion was left to the discretion of the operator. There were no other antiarrhythmic drugs used in this study.

2.1. Statistical analysis

Categorical and continuous variables were presented as percentages and median value with interquartile range respectively. To analyze the risk predictors of AF persistence after antazoline infusion in the whole group, a univariate and multivariate logistic regression analyses were performed. In univariate analyses all clinical and procedural factors were included. To reduce the number of variables in multivariate analysis only factors with p-value lower than 0.1 in univariate analyses were considered. Statistical significance was noted for p-values lower than 0.05. All analyses were performed using SAS software, version 9.2.

3. Results

3.1. Study group characteristics

A total of 141 patients, who received antazoline to terminate AF during isolation of pulmonary veins between January 2009 and April 2013 were included in the study. Those were patients with paroxysmal (n = 67) and persistent (n = 74) AF. In the paroxysmal AF (PAF) group, 11 patients had an onset of AF before the procedure and in 56 the AF was induced during pulmonary vein isolation. Median duration of persistent AF was 9 months interquartile range (IQR): 4.5–24 months. The median age in the analyzed group was 57 years (IQR: 49–63) and 73.0% of patients were male. The most common comorbidity was hypertension (69.3%). In 22.7% of patients AF was the only condition. The patient demographics and differences between patients who responded and did not respond (total efficacy) to antazoline are summarized in Table 1.

Table 1
Baseline characteristic of patients.

	Total (n = 141)	Early efficacy		
		Antazoline effective (n = 79)	Antazoline ineffective (n = 62)	p
Female	27.0%	20.3%	35.5%	0.06
Age	57 (49–63)	57 (49–63)	57 (49–64)	0.99
Duration of procedure (min)	155 (130–195)	150 (130–195)	170 (130–195)	0.11
AF before procedure	60.2%	35.4%	91.9%	<0.0001
Dose of antazoline	400 (225–400)	300 (200–400)	400 (400–500)	<0.0001
Addition of metoprolol	13.5%	8.8%	19.4%	0.08
Serum level of fibrinogen	310 (262–364)	296 (262–360)	337 (284–385)	0.08
Persistent AF	52.5%	29.1%	82.3%	<0.0001
Hypertension	69.3%	65.8%	73.8%	0.35
Diabetes mellitus	12.1%	12.7%	11.3%	1.0
Mitral valve disease	2.8%	2.5%	3.2%	1.0
Lone AF	22.7%	25.3%	19.4%	0.42
History of hyperthyroidism	18.4%	19.0%	17.7%	1.0
Hyperlipidaemia	27.0%	20.2%	35.5%	0.06

AF, atrial fibrillation.

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