



Effect of perioperative intravenous amiodarone on cardioversion of atrial fibrillation early after video-assisted thoracoscopic surgical ablation: Study protocol for a double-blind randomized controlled trial

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ABSTRACT

Introduction: Video-assisted thoracoscopic surgical (VATS) ablation is widely performed in surgical areas to treat atrial fibrillation (AF), which is minimally invasive and highly effective. Amiodarone, known as a class III antiarrhythmic agent, has the greatest potential to maintain sinus rhythm of AF. At present, few studies focused on the efficacy of perioperative intravenous amiodarone in the VATS ablation of AF. Therefore, the trial is designed to investigate the effect of perioperative amiodarone infusion on cardioversion of AF early after VATS ablation.

Methods: and analysis: This will be a prospective, randomized, double-blind, controlled trial. The trial is to enroll 182 patients aged 18–70 years who will undergo VATS ablation of AF. All eligible participants will be randomly allocated to either the amiodarone or placebo group by using the block randomization in a 1:1 ratio. The primary endpoint will be freedom from atrial arrhythmias 24 h after the VATS procedure and be assessed using the Kaplan-Meier method. All data will be analyzed in accordance with the intention-to-treat principle.

Discussion: The clinical trial has been designed to investigate the efficacy of perioperative intravenous amiodarone on cardioversion of AF early after VATS ablation. We are hoping to demonstrate that perioperative infusion of amiodarone could improve the maintenance of sinus rhythm 24 h after VATS ablation.

1. Introduction

Atrial fibrillation (AF) is one of the most common cardiac arrhythmias in the clinical setting. The prevalence rate of AF is approximately 1% in patients <60 years of age, whereas up to 12% in those between 75 and 84 years of age [1]. More than one third of patients with AF are ≥80 years of age [2]. The risk factors include age, female gender, hypertension, diabetes mellitus, hyperthyroidism, obstructive sleep apnea syndrome etc [3]. Due to the social aging and increasing morbidity of underlying diseases, it is estimated that the prevalence is expected to double in the next 25 years [4].

AF is correlated with a higher incidence of mortality, cardiovascular events, and stroke than sinus rhythm. Studies showed that the cardiovascular death occurs 2 to 4.4 times higher in patients with chronic AF

[5,6]. The stroke is commonly seen in AF patients, especially in the elderly, which seriously reduces the quality of life and adds the medical burdens. Moreover, AF patients with uncontrolled ventricular rate are prone to develop tachycardia-induced cardiomyopathy, resulting in the occurrence of systolic dysfunction [7]. Therefore, the proactive and reasonable management of AF and complications caused by AF could greatly improve the patients' prognosis.

The rhythm control is one part of the therapies in AF patients [4]. There are various methods to convert AF including antiarrhythmic drugs, electrical conversion, catheter ablation and surgical operations. In 1987, the Maze procedure, now known as the Cox-Maze (CM) procedure, was firstly performed by Dr. James Cox which was a benchmark surgery to reliably convert AF through surgical ways [8]. However, due to its complexity and technical difficulty, the procedure was refined over

Abbreviations: VATS, video-assisted thoracoscopic surgical; AF, atrial fibrillation; CM, Cox-Maze; PVI, pulmonary vein isolation; LAA, left atrial appendage; DEA, desethylamiodarone; ECG, electrocardiograph; IBP, invasive arterial blood pressure; BIS, bispectral index; PETCO₂, end tidal CO₂; TEE, transesophageal echocardiogram; ICU, intensive care unit; RF, radiofrequency ablation; SAE, severe adverse events; ICE, the Institutional Ethics Committee.

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several iterations with changes to both lesion sets and replacement of the incisional lesions with a combination of bipolar radiofrequency ablation and cryoablation. The latest iteration of this procedure has been termed the CM-IV procedure [9]. For lone AF, the CM-IV procedure can be performed through bilateral mini-thoracotomy incisions or via a video-assisted thoracoscopic approach.

In 2005, Dr. Randall Wolf first performed the Wolf Mini Maze procedure utilizing a video-assisted thoracoscopic surgical (VATS) ablation, which is a minimally invasive surgical approach to convert AF. In the procedure, the bilateral epicardial pulmonary vein isolation (PVI) and exclusion of the left atrial appendage (LAA) were carried out and 91.3% of the patients were free of AF during the three-month follow-up [10]. Thereafter, the VATS ablation for AF has been more and more widely conducted in surgical areas. A meta-analysis of 13 studies with 699 patients showed the clinical outcomes of VATS ablation for AF compared with catheter ablation [11]. Across all categories of AF, VATS ablation has a better success rate than does catheter ablation. For paroxysmal AF, catheter ablation presents similar results to VATS ablation but has less morbidity. For long-standing persistent AF, the results of VATS surgery are clearly superior. For persistent AF, considering the efficacy and safety, it is controversial which of the two approaches is better. Furthermore, during the VATS ablation, the LAA could be resected simultaneously avoiding thromboembolic events owing to AF, which could not be achieved in the catheter ablation. Therefore, VATS ablation plays a significant role in the cardioversion of AF.

Amiodarone is a class III antiarrhythmic agent with multiple electrophysiological effects, which has been used clinically in the management of both atrial and ventricular arrhythmias. Through hepatic metabolism, amiodarone is transformed to desethylamiodarone (DEA), which has the property of antiarrhythmic effects. Amiodarone is highly lipid soluble and is widely stored in fat, muscle, skin, liver and lungs with a very long elimination half-life, averaging about 58 days [12]. The predominant antiarrhythmic effect of amiodarone is the inhibition of IKr and IKs channels leading to a prolongation of myocardial repolarization homogeneously. Amiodarone also slows heart rate and atrioventricular nodal conduction through inhibiting calcium channel and β -receptor. In addition, it also prolongs refractoriness and reduces intracardiac conduction velocity by blocking sodium channel [13,14].

Of all antiarrhythmic drugs currently used in AF, amiodarone has the greatest potential to maintain sinus rhythm [15,16]. The study of Vardas et al. presented that restoration of sinus rhythm in patients after one-month receiving amiodarone therapy is twice that of patients treated with placebo (80.05% vs 40%, $p < 0.0001$) [17]. Compared with other antiarrhythmic drugs, amiodarone can be safely administered in severe heart failure [18], coronary artery disease [19] and left ventricular hypertrophy. In the catheter ablation of AF, amiodarone can also show an effective outcome after a short-term use. Kettering et al. enrolled patients undergoing catheter ablation of AF and studied short-term use of amiodarone on long-term maintenance of sinus rhythm. The results showed that adjunctive short-term amiodarone therapy improves the success rate after catheter ablation of persistent AF during 2-year follow-up [20].

Despite lots of amiodarone researches in catheter ablation, few articles concentrated on the amiodarone administration in VATS ablation. In the research by Ad et al. [21], patients were randomized to receive or not receive amiodarone orally after surgical ablation. The freedom from atrial arrhythmias was higher in patients receiving amiodarone by the end of 3-month follow-up (81.4% vs 47.7%, $P < 0.001$). However, there are no relevant research data on perioperative intravenous amiodarone in VATS ablation especially very short-term results after the procedure.

Therefore, we designed this clinical trial to explore the outcomes of perioperative intravenous amiodarone on cardioversion of atrial fibrillation 24 h after VATS ablation.

2. Materials and methods

2.1. Study design and setting

This study is a prospective, single-center, randomized, double-blinded, placebo-controlled clinical trial to investigate effect of perioperative intravenous amiodarone on cardioversion of atrial fibrillation 24 h after video-assisted thoracoscopic surgical ablation. The study will be conducted in the First Affiliated Hospital of Nanjing Medical University, Nanjing, China. A schematic of the trial protocol is presented in Fig. 1.

2.2. Study population

One hundred and eighty-two patients who meet the eligibility criteria below will be recruited and randomly divided into two groups, including amiodarone group (group A) and placebo group (group P), 91 cases in each group. Informed consent will be obtained from all participants.

2.2.1. Inclusion criteria

Patients included in the trial are as follows:

1. Subjects undergoing VATS ablation for AF.
2. Aged between 18 and 70 years old.
3. Nonvalvular AF.
4. American Society of Anesthesiologists (ASA) class I-III.
5. New York Heart Association (NYHA) class I-III.

2.2.2. Exclusion criteria

Patients fulfilling one or more of the following criteria will not be included:

1. Preoperative use of class I or III antiarrhythmic drugs.
2. $QTc \geq 480$ ms or $QT \geq 500$ ms.
3. Mean heart rate of 24 h < 50 beats/min.
4. Left atrial diameter > 50 mm.
5. Left ventricular ejection fraction $< 30\%$.
6. With high grade or III° atrioventricular block.
7. With thyroid dysfunction.
8. With rheumatic valvular disease.
9. Previous valvular replacement or valvuloplasty.
10. With left atrial appendage thrombosis.
11. With electrolyte imbalances.
12. With hepatic or renal dysfunction.
13. With pulmonary fibrosis.
14. Allergic to amiodarone.

2.3. Randomization and blinding

Before anesthetic induction, the enrolled participants who meet the eligibility criteria will be randomly allocated in a 1:1 ratio to two groups, namely group A (treated with amiodarone) and group P (placebo control). Block randomization will be used with a block size of 4, which will be implemented with SPSS 22.0 (IBM, New York, Armonk, USA) by an independent statistician, and the randomization numbers will be given to an external data manager with no involvement in the study procedures and concealed on password-protected computer.

When a patient meets the eligibility criteria, the external data manager will return the corresponding allocation to the nurse anesthetist. The drugs will be prepared by the nurse anesthetists according to the allocation information, packaged with the same looking and labelled with numbers and injected by the anesthesiologists. Both anesthesiologists and patients will be blinded to the regimen. The anesthesiologist will be notified of the study group by the nurse anesthetists in case of emergency. However, the nurse anesthetists have no role in assessing the

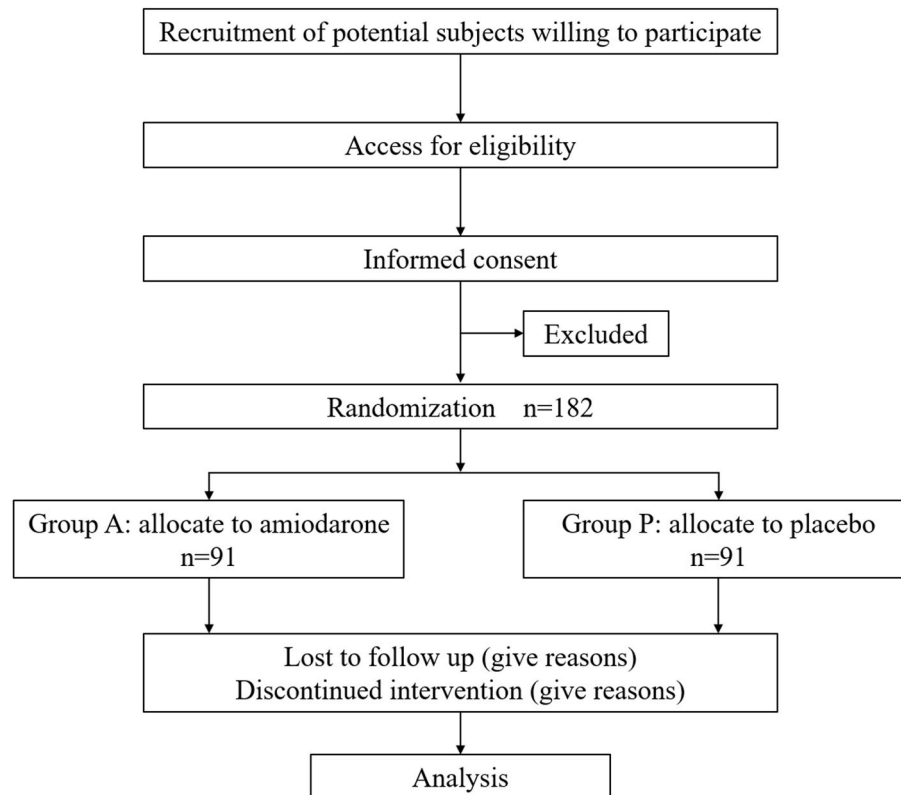


Fig. 1. Trial flow chart.

treatment actions, analyzing or interpreting the data.

2.4. Interventions

2.4.1. Treatment regimen of amiodarone

In the present study, the administration regimen is bolus dose plus maintenance dose. After the induction of anesthesia and before the skin incision, the bolus dose is administered intravenously from the central veins. The maintenance dose is continuously pumped immediately after the bolus dose is given, and is maintained for 24 h in total. In group A, the bolus dose is 150 mg of amiodarone, which is pumped in 5 min. The maintenance dose is the infusion of amiodarone at 1 mg/min for 6 h, and then at 0.5 mg/min for the remaining 18 h [4]. In group P, both the bolus and maintenance doses are given the same volume of normal saline with the same administration speed as those in group A.

2.4.2. Anesthesia protocols

All the patients will fast for 8 h and abstain from water for 4 h preoperatively and receive standardized general anesthesia. In the operating room, the patients will be routinely monitored including 5-lead electrocardiograph (ECG), peripheral blood oxygen saturation, invasive arterial blood pressure (IBP), bispectral index (BIS) and end tidal CO₂ (P_{ET}CO₂), which will be recorded every 3 min in each patient's Electronic Medical Record. In order to prevent sudden cardiovascular events during the procedure, the patients are pasted with surface defibrillation pads. The induction of anesthesia will be performed as the followings successively: 0.05 mg/kg midazolam, 0.3 mg/kg etomidate, 0.15 mg/kg cis-atracurium, and 4–6 µg/kg fentanyl. Approximately 5 min after induction, patients will be intubated with the double-lumen endobronchial tube and ventilated to maintain P_{ET}CO₂ at 35–45 mmHg. Then, the ultrasound-guided central vein catheterization will be conducted via the right internal jugular or subclavian vein. Thereafter, transesophageal echocardiogram (TEE) will be examined to exclude the LAA thrombus. The maintenance of anesthesia will be inhalation of sevoflurane 1%–2%

and continuous pump of propofol 1–2 mg/kg/h, remifentanyl 0.2–0.3 µg/kg/min, and cis-atracurium 0.05–0.1 mg/kg/h. During anesthesia maintenance, the BIS will be maintained between 40 and 60. After the procedure, the patients will be transferred to intensive care unit (ICU) with the single endotracheal tubes until meeting the extubation criteria. The patients in the ICU will receive the standardized management of postoperative recovery.

2.4.3. Surgical operations

The VATS procedure is performed to achieve an electrically PVI bilaterally. A bipolar radiofrequency ablation (RF) and RF generator system (AtriCure, Inc, Cincinnati, Ohio) is used to achieve linear, transmural ablation lesions. The two-sided sets of pulmonary veins are encircled and ablated on the left atrium by using the epicardial-placed bipolar RF clamp. The left atrial roof and posterior lines are performed to link the pulmonary vein lesions by using the bipolar RF pen (AtriCure, Inc, Cincinnati, Ohio). The ligament of Marshall is also taken down in all patients. During the procedure, LAA management is performed by 60-mm stapler exclusion (Medtronic, Inc, Minneapolis, Minnesota) or clip closure (AtriCure, Inc, Cincinnati, Ohio) when deemed feasible. TEE is examined to verify the effect of LAA management. The electrical isolation of pulmonary veins is confirmed after completion of the lesion sets. At the end of the procedure, patients who do not achieve sinus rhythm will undergo biphasic electric cardioversion once or twice, of which the first energy is 150 J and the second is 200 J. All the procedures are performed by the same surgical group.

2.5. Endpoints

The primary endpoint is freedom from atrial arrhythmias 24 h after the VATS procedure. The freedom from atrial arrhythmias is defined as no atrial tachyarrhythmias including AF, atrial flutter or atrial tachycardia lasting for more than 30 s at the time of observation.

The secondary endpoints will include freedom from atrial

arrhythmias at the end of the procedure; heart rate, blood pressure and heart rhythm in two groups before anesthetic induction (Ti0), before bolus dosage (Ti1), immediately after bolus dosage (Ti2), after excision of LAA (Ti3), after the left PVI (Ti4), after the right PVI (Ti5), and at the end of the procedure (Ti6); the speed of inotropic agents and vasoactive agents at Ti1 to Ti6; the total dosages of inotropic agents and vasoactive agents during the procedure; heart rate, blood pressure and heart rhythm immediately back to ICU unit (Tp0), 1 h (Tp1), 6 h (Tp2), 12 h (Tp3), 18 h (Tp4), and 24 h (Tp5) after the procedure; the length of mechanical ventilation, ICU stay and hospitalization stay; the dosages and category of any other antiarrhythmic agents; heart rhythm and mean heart rate at the time of discharge.

2.6. Sample size estimation

The sample size is calculated based on the primary endpoint: freedom from atrial arrhythmias 24 h after the VATS procedure, using PASS 15.0 (NCSS, Kaysville, Utah, USA). According to the studies published, maintenance rate of sinus rhythm early after surgical ablation ranges from 69.2% to 89% [22–24]. We assumed the 24-h postoperative freedom from atrial arrhythmias would be 70% in the placebo-controlled group and amiodarone could improve the rate by 25%. Therefore, the rate of freedom from atrial arrhythmias would be 87.5% in the amiodarone group. To reach statistical significance with a power of 80% and an α of 0.05 (2-sided), 82 patients are assessed to be needed in each group. Assuming a 10% drop-out or missing data rate, we will recruit 91 patients in each group for a total of 182 patients.

2.7. Statistical analysis

All data will be analyzed using SPSS 22.0 (IBM, New York, Armonk, USA) and in accordance with the intention-to-treat principle, beginning immediately after randomization. All statistical tests will be considered significant if P value <0.05. Only two-sided tests will be used. Baseline characteristics will be described and compared by using the Chi-square or Fisher exact tests for the categorical variables and 2-sample t tests or Wilcoxon rank sum test depending on the normality of the data distribution for the continuous variables. The continuous variables will be described by mean and standard deviation if normally distributed or median and interquartile range if not. The normality of distributions will be checked graphically and using the Komolgorov-Smirnov test. If there is a violation of distribution assumption, appropriate transformation will be used. The categorical variables will be expressed as frequencies and percentages.

2.7.1. Primary endpoints

Freedom from atrial arrhythmias 24 h after the VATS procedure will be estimated by the Kaplan-Meier method and compared by using the log-rank test. Cox proportional hazards models will be used to identify significant predictors of atrial arrhythmia recurrence.

2.7.2. Secondary endpoints

For the secondary endpoints, heart rate and blood pressure will be compared between two groups by using repeated ANOCVA model during different observation times intraoperatively and postoperatively. Other continuous secondary endpoint variables will be compared between two groups by using 2-sample t tests or Wilcoxon rank tests depending on the normality of the data distribution. The Chi-square test or Fisher's exact test will be used to compare categorical secondary endpoint variables.

2.7.3. Missing data

If data are missing at random, the analyses will be carried out using multiple imputations. The multiple imputation procedure will be based on all available data for that patient and be conducted using the chained equation approach. If data are not missing at random, the analyses will

be conducted using available data with appropriate interpretational reservations. We will also evaluate the data using intention-to-treat principle and per-protocol data set and compare the analysis results to estimate reliability of our analytical results.

2.8. Severe adverse events

Severe adverse events (SAE) are defined as the followings: cardiac arrest requiring chest compression, severe bradycardia (heart rate <40bpm) with no amelioration of inotropic drugs or atropine, severe hypotension (systolic blood pressure <70 mmHg) with no amelioration of vasoactive drugs, high grade or III° atrioventricular block with no amelioration with atropine or requiring temporary pacing, and torsades de pointes caused by elongation of QT interval (QT > 500 ms or QTc >480 ms). If any of the SAEs happens, the infusion will be discontinued immediately and the SAE will be recorded and reported to the Institutional Ethics Committee (ICE) for clinical research of the First Affiliated Hospital of Nanjing Medical University.

2.9. Data collection and management

The data will be collected from paper case report forms (manually counter checked with source files by the data entry personnel) by the investigator and given to the statistician to analyze the data. The data will be recorded by their specific ID number instead of participant's name throughout the study unless otherwise specified. Access to data will be restricted to the investigators who signed the confidential disclosure agreement or to the institutional or governmental auditors during the study. All original documents and files will be archived for at least 5 years to allow inspection after the trial has ended. The process will be monitored by the ICE.

2.10. Study status

The trial will start patient recruitment in August 2020, and the recruitment will continue until March 2023.

3. Discussion

AF is the most common arrhythmia encountered in clinical practice and remains one of the major causes of stroke, heart failure, cardiovascular morbidity and mortality worldwide. VATS ablation has been increasingly accepted for the treatment of patients with AF because of its high efficacy compared with percutaneous ablation and minimally invasive character [25,26]. Amiodarone, known as class III antiarrhythmic agent, has the properties of converting AF and maintaining the sinus rhythm and can also be administered in patients with structural heart diseases. In patients receiving catheter ablation, oral use of amiodarone can reduce the early recurrence of AF [27], and atrial arrhythmia related hospitalization and cardioversion rates [28]. However, few researches concentrated on the use of amiodarone after VATS ablation, especially perioperative infusion of amiodarone.

Due to the research status so far, we design the clinical trial in order to investigate the efficacy of perioperative intravenous amiodarone on cardioversion of AF early after VATS ablation. With this trial, we are hoping to demonstrate that perioperative infusion of amiodarone could improve the maintenance of sinus rhythm 24 h after VATS ablation.

Authors' contributions

Yin Fang conceived of the study. Yin Fang and Zhenfeng Zhang participated in its design and coordination. Yin Fang, Zhenfeng Zhang, Chanjuan Gong and Yu Chen collected references and developed the protocol. Chanjuan Gong and Yu Chen performed statistics analysis. Yin Fang and Zhenfeng Zhang drafted the manuscript. All authors participated, read and approved the final manuscript.

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Ethics approval

This study has been approved by the Institutional Ethics Committee of the First Affiliated Hospital of Nanjing Medical University (2020-SR-114) and registered with the Chinese Clinical Trial Registry (ChiCTR2000035031).

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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