Clinical efficacy of epicardial application of drug-releasing hydrogels to prevent postoperative atrial fibrillation

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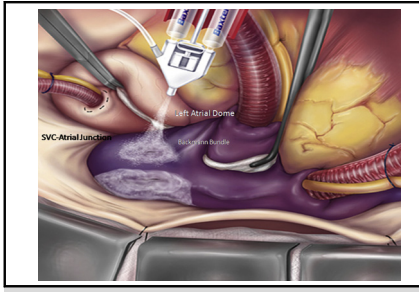
ABSTRACT

Objective: Postoperative atrial fibrillation is the most frequent complication arising after cardiac surgery, occurring in 40% of cases. The treatment of postoperative atrial fibrillation with epicardial amiodarone/corticosteroid hydrogel delivery can increase efficacy and reduce side effects. To further evaluate whether amiodarone hydrogel is superior to corticosteroid hydrogel or placebo, we performed a randomized prospective study in 150 patients with coronary artery bypass grafting to compare the effectiveness with different epicardial drug approaches in the postoperative period.

Methods: After institutional review board approval, 150 patients, from January 2012 to July 2014, who had undergone cardiac surgery were randomized to 3 equal groups. Group I received poly-based hydrogel with amiodarone, and group II received poly-based hydrogel with triamcinolone. Both hydrogels were sprayed diffusely over the biatrial epicardium. The control group underwent the procedure with only hydrogel spray. Continuous telemetry monitored for postoperative atrial fibrillation, and amiodarone or triamcinolone levels in the atria, plasma, and tissue were measured postoperatively. Daily electrocardiographic parameters were measured until postoperative day 14.

Results: The incidence of postoperative atrial fibrillation was significantly less in group I, with 4 of 50 patients (8%) incurring atrial fibrillation compared with 11 of 50 patients (22%) in group II and 13 of 50 patients (26%) in the control group ($P < .01$). The mean amiodarone and triamcinolone concentrations in the atria ($12.06 \pm 3.1/1.5 \pm 0.7$) were significantly greater than those in the extracardiac tissues ($1.32 \pm 0.9/0.2 \pm 0.4$; $P < .01$). The plasma amiodarone and triamcinolone levels remained below the detection limit (<8 μg/mL and <0.2 μg/mL) during the 14 days of follow-up. Bradycardia was observed less in the control group (93 ± 18) than in study group I (76 ± 29; $P < .01$).

Conclusions: Epicardial application of amiodarone-releasing adhesive hydrogel is a less-invasive, well-tolerated, quick, and effective therapeutic option for preventing postoperative atrial fibrillation with minimal risk of extracardiac adverse side effects. However, there was no clinical evidence that epicardial corticosteroid prevented postoperative atrial fibrillation. (J Thorac Cardiovasc Surg 2016;151:80-5)



Epicardial application of drug-releasing adhesive hydrogel.

Central Message

Epicardial application of drug-releasing adhesive hydrogel is an effective therapeutic option for preventing postoperative AF.

Perspective

Epicardial application of amiodarone-releasing adhesive hydrogel is a less-invasive, well-tolerated, quick, and effective therapeutic option for preventing POAF with minimal risk of extracardiac adverse side effects. However, there was no clinical evidence that epicardial corticosteroid prevented POAF.

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Postoperative atrial fibrillation (POAF) is the most frequent complication arising after cardiac surgery, occurring in 44% of cases.[1,2] The pathophysiologic mechanism of POAF remains unknown. It increases patient mortality and morbidity, hospitalization duration, and healthcare resources. Currently, the available conventional therapies for preventing POAF are suboptimal. Amiodarone, a class III antiarrhythmic medicine, is the most effective drug for prophylaxis and treatment. Clinical studies have demonstrated the efficacy of oral and intravenous amiodarone therapy to prevent POAF. Despite its superior

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Abbreviations and Acronyms
AF = atrial fibrillation
CABG = coronary artery bypass grafting
IPC = intrapericardial
PEG = polyethylene glycol
POAF = postoperative atrial fibrillation

efficacy, amiodarone therapy has several disadvantages, including requirement of a loading period, interactions with many other drugs, and, most important, serious extracardiac side effects, such as thyroid dysfunction, pulmonary toxicity, and hepatic toxicity.[3,4]

Considerable experimental and clinical evidence suggest that POAF is multifactorial. Facilitating factors can be classified as acute factors caused by the surgical intervention (inflammation) and chronic factors related to structural heart disease. Cardiac surgery, especially when accompanied by cardiopulmonary bypass, causes a systemic inflammatory response that may be in part responsible for POAF. Complement, C-reactive protein complex levels, and white blood cell count—markers of an inflammatory reaction—are increased in patients after cardiac surgery. Elevated C-reactive protein complex and C-reactive protein complex-complement levels after cardiac surgery are predictive of POAF.[5] The utility of anti-inflammatory agents for preventing POAF also has been studied in experimental animals and clinically. Prednisone given orally prevents inducible atrial flutter in a canine sterile pericarditis model.[6] A similar study showed that corticosteroids decreased the frequency and duration of atrial fibrillation (AF) in an animal model of cardiac surgery.[7] Two prospective, randomized clinical trials of perioperative corticosteroids showed a significant reduction in POAF.[8]

The concept of local amiodarone/corticosteroid delivery to the myocardium has been investigated in several animal studies by intrapericardial (IPC) infusion of amiodarone/steroid solutions.[9,10] This approach is not applicable in the postoperative patient because the pericardium is usually left open and in communication with a mediastinal drain. Along with bleeding and effusions, any drug solution instilled at the time of surgery would be rapidly evacuated. A few studies researching the effectiveness of the topical application of a biodegradable disc with amiodarone or amiodarone-eluting bilayered patch have reported encouraging results.[11,12] However, the amount of exposure to the atrial epicardial surface is often limited using those applications. Biatrial epicardial application of drug-releasing hydrogel might offer the advantage of a more localized (biatrial targeted) drug delivery.

Surgical sealant CoSeal (Baxter Healthcare, Fremont, Calif) consists of 2 biodegradable synthetic polyethylene glycol (PEG) polymers that are mixed at the time of application, forming a strong hydrogel that vigorously adheres to tissue.[13,14] These properties make this biomatrix attractive as a vehicle for local drug delivery.[15] We reasoned that addition of amiodarone/steroid to this hydrogel would produce a drug-releasing matrix capable of suppressing atrial tachyarrhythmias while systemic drug levels remain low. The purpose of this prospective study is to evaluate the efficacy of amiodarone versus corticosteroid-loaded hydrogels applied to the atria to prevent POAF.

MATERIAL AND METHODS

After institutional review board and ethical research committee approval, 150 patients undergoing conventional coronary artery bypass grafting (CABG) were randomized to 3 equal groups after obtaining informed consent. Group I received poly-based hydrogel with amiodarone, and group II received poly-based hydrogel with triamcinolone. Both hydrogels were sprayed diffusely over the biatrial epicardium. The control group underwent the procedure with the hydrogels spray only. Patients were excluded if they had a history of pacemaker/automatic internal cardiac defibrillator or significant preoperative events developed, such as cardiogenic shock or ventricular tachyarrhythmias (Table 1).

CoSeal Surgical Sealant, a sprayable polymeric matrix, was obtained via Baxter Healthcare. The kit is composed of 2 synthetic PEGs, a dilute hydrogen chloride solution, and a sodium phosphate/sodium carbonate solution. Amiodarone hydrochloride powder (Sigma-Aldrich, St Louis, Mo) 1 mg/kg bodyweight or triamcinolone acetonide (Sandoz Inc, Princeton, NJ) 0.5 mg/kg was first added to the PEG powder and then mixed with solutions until the drug was completely dissolved. All patients underwent dissection of the superior vena cava–atrial junction area and the free left atrial anterior wall, which was adjacent to the transverse sinus (Bachmann's bundle area). Temporary epicardial atrial and ventricular pacing wires were inserted in all patients at the end of surgery. Before the sternum was closed, hydrogels were sprayed diffusely in a thin layer onto the exposed epicardial surfaces with a Co_2 driver set over the right atrial lateral wall, left atrial appendage, and transverse sinus area (Figure 1). The pericardium was approximated with interrupted suture, and a single mediasternal chest tube was placed retromediastinal above the pericardium. The myocardial venous blood sampling was obtained from the coronary venous sinus under fluoroscopic control during postoperative day 3, right atrial endomyocardial biopsy was performed from areas adjacent to the fossa ovalis for measurements of myocardial amiodarone/triamcinolone concentration, and abdominal extraperitoneal adipose tissue within the chest tube site was biopsied during chest tube removal on postoperative day 3. Amiodarone/triamcinolone plasma concentrations were also measured in the blood drawn from a peripheral vein during postoperative days 2 and 5. The amiodarone and triamcinolone assays were performed by the standard method of high-performance liquid chromatography (HP-Series 1090, Hewlett Packard, Palo Alto, Calif). A cardiac enzyme panel was measured on postoperative days 1, 3, and 5, and before discharge to monitor the local atrial myocardial injury. Continuous telemetry was monitored for POAF. Daily complete blood count and electrocardiography parameters (RR, PQ, QT, and maximal Tpeak-Tend intervals, and P and QRS widths) were measured until postoperative day 14. After the operation, the patient in the control group received intravenous or oral amiodarone for new-onset AF. Electrical cardioversion was performed before hospital discharge in any patient who was not in normal sinus rhythm.

All values are expressed as the mean ± standard deviation. Statistical analysis comparing the data between the 2 groups was performed with the chi-square test for categoric variables. Continuous variables were compared by means of 2-tailed Student *t* tests and Kruskal–Wallis test