

## Effectiveness of biatrial epicardial application of amiodarone-releasing adhesive hydrogel to prevent postoperative atrial fibrillation

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**Objective:** Postoperative atrial fibrillation (POAF) is the most frequent complication arising after cardiac surgery, occurring in 30% of cases. Amiodarone is the most effective drug for prophylaxis and treatment. However, because of significant extracardiac side effects, only high-risk patients are eligible for prophylactic amiodarone therapy. We performed a randomized prospective study of 100 patients undergoing cardiac surgery with epicardial application of amiodarone-releasing hydrogel to determine the effectiveness of preventing POAF.

**Methods:** After institutional review board approval, 100 patients, from January 2012 to July 2013, who had undergone cardiac surgery, were randomized to 2 equal groups. The study group received poly-based hydrogel with amiodarone sprayed diffusely over the epicardium. The control group underwent the procedure without the spray. Continuous telemetry monitored for POAF, and amiodarone levels in the atria, plasma, and tissue were measured postoperatively. Daily electrocardiographic parameters were measured until postoperative day 14.

**Results:** The incidence of POAF was significantly less in the study group, with 4 of 50 patients (8%) incurring atrial fibrillation compared with 13 of 50 patients (26%) in the control group ( $P < .01$ ). The mean amiodarone concentrations in the atria ( $12.06 \pm 3.1$ ) were significantly greater than those in the extracardiac tissues ( $1.32 \pm 0.9$ ;  $P < .01$ ). The plasma amiodarone levels remained below the detection limit ( $<8 \mu\text{g/mL}$ ) during the 14 days of follow-up. Bradycardia was observed less in the study group ( $76 \pm 29$ ) than in the control group ( $93 \pm 18$ ;  $P < .01$ ).

**Conclusions:** Epicardial application of amiodarone-releasing adhesive hydrogel is a less invasive, well-tolerated, quick, and effective therapeutic option for preventing POAF at minimal risk of extracardiac adverse side effects. (*J Thorac Cardiovasc Surg* 2014;148:939-43)

Postoperative atrial fibrillation (POAF) is the most frequent complication arising after cardiac surgery, occurring in 30% of cases.<sup>1,2</sup> It increases patient mortality and morbidity, hospitalization duration, and healthcare resource usage. 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 efficacy, amiodarone therapy has several disadvantages, including the requirement of a loading period, interactions with many other drugs, and, most importantly, serious extracardiac side effects, such

as thyroid dysfunction, pulmonary toxicity, and hepatic toxicity.<sup>3,4</sup> These have been, in part, attributed to the relatively high drug concentrations required with systemic administration.

The concept of local amiodarone delivery to the myocardium has been investigated in several animal studies using intrapericardial infusion of amiodarone solutions.<sup>5,6</sup> They were able to minimize the ventricular and extracardiac adverse effects of amiodarone and made a loading period superfluous. Although the results are encouraging, most arrhythmias require a longer treatment duration. Long-term catheter-based intrapericardial infusion could increase the risk of infection and fibrosis. This approach is also not applicable to 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 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.<sup>7,8</sup> 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, because,

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### Abbreviations and Acronyms

AF	= atrial fibrillation
CABG	= coronary artery bypass grafting
PEG	= polyethylene glycol
POAF	= postoperative atrial fibrillation

despite diffusion to other heart chambers through leakage to the pericardial fluid, the amiodarone concentration of the biatrial myocardium remains very high.

CoSeal Surgical Sealant (Baxter Healthcare, Deerfield, Ill) is used in a wide range of surgical specialties, including cardiac procedures, primarily for prevention of pericardial adhesions and anastomotic bleeding. These agents consist of 2 biodegradable synthetic polyethylene glycol (PEG) polymers that are mixed at application, forming a strong hydrogel that vigorously adheres to tissue.<sup>9</sup> These properties make this biomatrix attractive as a vehicle for local drug delivery. Lidocaine mixed with this hydrogel has been shown to reduce postoperative pain after breast augmentation.<sup>10</sup> The hydrogel has also been used to deliver nerve growth factor, stem cells, and chemotherapeutic agents.<sup>11</sup> From these studies, we reasoned that the addition of amiodarone to this hydrogel would produce a drug-releasing matrix capable of suppressing atrial tachyarrhythmias and the systemic drug levels would remain low, even in the presence of effusion or pericardial drainage. The purpose of the present prospective study was to evaluate the efficacy of amiodarone-loaded hydrogels applied to the atria to prevent POAF.

### METHODS

A total of 100 patients scheduled to undergo coronary artery bypass grafting (CABG) from January 2012 to July 2013 were randomized and prospectively enrolled in the present study. The institutional review board and ethical research committee approved the study, and all patients provided informed consent. Patients were excluded if they had a history of pacemaker or automatic internal cardiac defibrillator placement or if significant preoperative events developed, such as cardiogenic shock or ventricular tachyarrhythmia. The 100 patients (60 men, 40 women; mean age,  $52 \pm 9$  years), who were undergoing conventional on-pump CABG, were randomized to 2 equal groups. The study group received CoSeal-based hydrogel with amiodarone sprayed diffusely over the biatrial epicardium. The control group underwent CABG without amiodarone spraying (Table 1).

A sprayable polymeric matrix, CoSeal Surgical Sealant was obtained from Baxter Healthcare. The kit includes 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, was first added to the PEG powder and then mixed with the solutions until the powder had completely dissolved. These components form a hydrogel. All patients primarily underwent on-pump CABG. Triple radiofrequency pulmonary vein epicardial circumferential isolation was performed in 5 patients who had been diagnosed with paroxysmal atrial fibrillation (AF; 3 in the study group, 2 in the control group). 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 (Backmann'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, the hydrogel was sprayed diffusely using a carbon dioxide driver set over the right atrial lateral wall, left atrial appendage, and transverse sinus area. The pericardium was approximated with interrupted sutures, and a single mediastinal chest tube was placed retromediastinally above the pericardium. Myocardial venous blood sampling was obtained from the coronary venous sinus under fluoroscopic control during postoperative day 3. Also, right atrial endomyocardial biopsy was performed from areas adjacent to the fossa ovalis for measurement of the myocardial amiodarone concentration. Finally, abdominal extraperitoneal adipose tissue within the chest tube site was biopsied during chest tube removal on postoperative day 3. The amiodarone plasma concentrations were also measured using blood drawn from a peripheral vein during postoperative days 2 and 5. The amiodarone and desethylamiodarone assays were done using 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 local atrial myocardial injury. Continuous telemetry was used to monitor for POAF. Daily electrocardiographic parameters (RR, PQ, and QT intervals, maximal intervals between the peak and end of the T wave, and P and QRS widths) were measured until postoperative day 14. Postoperatively, the patients in the control group received either intravenous or oral amiodarone for new-onset atrial fibrillation. Electrical cardioversion was performed before hospital discharge for any patient who was not in normal sinus rhythm.

All values are presented as the mean  $\pm$  standard deviation. Statistical analysis comparing the data between the 2 groups was performed with the chi-square test for categorical variables. Continuous variables were compared using 2-tailed Student *t* tests and the Kruskal-Wallis test, as appropriate. The collected data were analyzed using the number cruncher statistical systems software (NCSS, Kaysville, Utah).

### RESULTS

No epicardial amiodarone hydrogel-related complications occurred. The greatest incidence of troponin T detection was observed in 2 patients (2%) in the study group with preoperative acute myocardial infarction. Transient bradycardia requiring temporary pacing developed in 7 patients in the study group. The overall hospital mortality was 1%. Stroke occurred in 1 patient (1%), and 5 patients underwent reoperation for bleeding (5%). The mean follow-up period was  $6 \pm 9$  months (range, 1-14). The incidence of POAF was significantly less in the study group, with 4 of 50 patients (8%) developing POAF compared with 13 of 50 patients (26%) in the control group ( $P < .01$ ). In the study group, the coronary venous sinus blood concentration of amiodarone ( $10.09 \pm 3.6 \mu\text{g/mL}$ ) was far greater than that in the peripheral plasma ( $1.43 \pm 1.6 \mu\text{g/mL}$ ;  $P < .01$ ). The plasma concentrations of both amiodarone and desethylamiodarone remained below detection limits ( $<8 \mu\text{g/mL}$ ) during the 14 days of follow-up. The right atrial myocardium concentration of desethylamiodarone ( $12.06 \pm 3.1 \mu\text{g/g}$ ) was significantly greater than that in the abdominal adipose tissue ( $1.32 \pm 0.9 \mu\text{g/g}$ ;  $P < .01$ ). The mean heart rate averaged  $76 \pm 29$  beats/min within 7 days in study group compared with  $93 \pm 18$  beats/min in the control group ( $P < .01$ ). The QT intervals increased from  $401 \pm 44$  ms before

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