TOPICAL AMIODARONE TO PREVENT POSTOPERATIVE ATRIAL FIBRILLATION: NEED FOR FURTHER STUDY

To the Editor:

Postoperative atrial fibrillation (AF) is a common complication after cardiac surgery that increases hospital stay and the risk of stroke.[1] Prophylactic systemic administration of amiodarone in the perioperative period prevents postoperative AF[2]; however, its challenging side-effect profile limits its routine and widespread use as prophylaxis.[3] It was therefore with great interest that we recently read the report by Feng and colleagues[4] describing their success in applying a topical amiodarone-releasing hydrogel on the atrial surface during coronary artery bypass grafting operations. Feng and colleagues[4] randomly assigned 100 patients to receive either usual care or the addition of amiodarone 1 mg/kg mixed with Co-Seal (Baxter Healthcare, Deerfield, Ill) diffusely sprayed over the left and right atrial epicardium before sternal closure. Feng and colleagues[4] reported a significant reduction in the incidence of postoperative AF with topical amiodarone (usual care vs amiodarone, 26% vs 8%; $P < .01$). In contrast to the challenges associated with systemic amiodarone, Feng and colleagues[4] noted no safety concerns associated with the amiodarone-releasing hydrogel application.

Feng and colleagues[4] are to be congratulated for an elegant study, even if the study population was relatively small. Moreover, the design was limited by the absence of blinding, a clear randomization process, or a placebo therapy to serve as a control. Nevertheless, the results of the pilot study were striking, and after its publication we began to apply the therapy to all our subsequent cardiac surgical patients with no previous history of AF. We applied the therapy in a manner similar to that described by Feng and colleagues,[4] except that we increased the dose to 150 mg for all patients (instead of 1 mg/kg). All patients were followed up with telemetry after surgery. Although we were enthusiastic at first, we ultimately were disappointed with our experience. The rate of AF among 100 consecutive patients who served as historical controls was not different from the rate of AF among the subsequent 50 patients who were treated with topical amiodarone (usual care vs amiodarone, 29% vs 36%; $P = .46$). The difference remained nonsignificant even when we adjusted for covariates (age, sex, and length and complexity of surgery) with logistic regression (odds ratio, 1.5; $P = .28$) and when we limited the sample to only patients undergoing coronary artery bypass grafting (usual care vs amiodarone, 27% vs 38%; $P = .36$).

In contrast to Feng and colleagues,[4] we could not find a similar benefit in our patient population, putting the generalizability of their results in question. We would be pleased to learn from Feng and colleagues[4] whether they are continuing to study the use of topical amiodarone and also whether they are embarking on a larger trial to confirm the findings from their initial pilot study. Alternatively, have they begun to apply this therapy widely in their practice? On the basis of our experience, in light of its cost and the unclear benefits, we believe that the subject of topical amiodarone requires further study, limiting its routine use at present.

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References

1. Guarnieri T, Nolan S, Gottlieb SO, Dudek A, Lowry DR. Intravenous amiodarone for the prevention of atrial fibrillation after open heart surgery: the Amiodarone Reduction in Coronary Heart (ARCH) trial. *J Am Coll Cardiol*. 1999;34:343-7.
2. Bagshaw SM, Galbraith PD, Mitchell LB, Sauve R, Exner DV, Ghali WA. Prophylactic amiodarone for prevention of atrial fibrillation after cardiac surgery: a meta-analysis. *Ann Thorac Surg*. 2006;82:1927-37.
3. Patel AA, White CM, Gillespie EL, Kluger J, Coleman CI. Safety of amiodarone in the prevention of postoperative atrial fibrillation: a meta-analysis. *Am J Health Syst Pharm*. 2006;63:829-37.
4. Feng XD, Wang XN, Yuan XH, Wang W. Effectiveness of biatrial epicardial application of amiodarone-releasing adhesive hydrogel to prevent postoperative atrial fibrillation. *J Thorac Cardiovasc Surg*. 2014;148:939-43.

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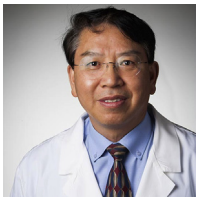

CONSIDERATIONS FOR THE SUCCESS OF TOPICAL AMIODARONE TO PREVENT POSTOPERATIVE ATRIAL FIBRILLATION

Reply to the Editor:

My coauthors and I thank Beau and Kulik for their letter and for their efforts to address this significant problem in cardiothoracic surgery—specifically, postoperative atrial fibrillation. I applaud the investigators for their attempts to corroborate results from clinical studies such as ours, because this is a critical to the scientific

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process and ultimately leads to advances in the care of our patients. I would like to stress the importance of the application of the hydrogels, as outlined in our methods section,[1] because we believe that the concentration of the amiodarone and the complete exposure to the left atrial surface are key components to the results that we saw with this treatment.

We are continuing to study the clinical efficacy of epicardial application of drug-releasing hydrogels, and we also recently completed a study on topical triamcinolone hydrogels in a similar clinical model. These results have recently been submitted to the *Journal* for consideration. Our ongoing early results strongly support the belief that epicardial delivery options may become a breakthrough therapy for preventing postoperative atrial fibrillation.

I encourage Beau and Kulik to continue their studies of postoperative atrial fibrillation, because their robust patient volume would readily support a prospective, randomized, controlled trial that could contribute significantly to the medical literature. The results in their study, however, I found very surprising because there was such a high rate of postoperative atrial fibrillation in the study group versus the control group (38% vs 27%), even if the covariates were adjusted. This may be attributable to the following reasons: (1) There was a limited study sample and an aging study group. (2) The mixture of amiodarone powder with COSEAL (Baxter Healthcare, Deerfield, Ill) was found to be time-consuming, and the preparation requires every particle to be dissolved into hydrogels, otherwise efficacy will be adversely affected. (3) The diffuse spraying over the left atrial posterior wall, left atrial appendage, and left atrial dome across the transverse sinus with deep Trendelenburg position is essential. (4) Finally, a high dosage of amiodarone may cause epicardial chemical inflammation, which may lead to new-onset atrial fibrillation.

Of course, a number of issues may affect absorption of topical agents on the epicardial surface. On the basis of our multiple studies showing suboptimal coronary venous sinus blood concentration of amiodarone with topical amiodarone hydrogels, we are therefore currently embarking on a pivotal study with nanotechnology needle arrays for atrial epicardial amiodarone delivery to prevent postoperative atrial fibrillation.

Our team will continue to explore these and other options for the management of postoperative atrial fibrillation. We look forward to further contributions from Beau and Kulik, adding to the management algorithm of this difficult clinical problem.

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Reference

1. Feng XD, Wang XN, Yuan XH, Wang W. Effectiveness of biatrial epicardial application of amiodarone-releasing adhesive hydrogel to prevent postoperative atrial fibrillation. *J Thorac Cardiovasc Surg*. 2014;148:939-43.

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