

Postoperative atrial fibrillation, oxidative stress, and inflammation

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Abstract: Postoperative atrial fibrillation is the most common complication of cardiac surgery. It is associated with increased complication rates. Recent trials have suggested that inflammation and oxidative stress have key roles in the pathophysiology of atrial fibrillation. Current evidence evaluating the use of antiinflammatory and antioxidant agents, including statins, corticosteroids, N-acetylcysteine, vitamin C, and fish oil, to prevent postoperative atrial fibrillation is promising. However, larger randomized, controlled trials comparing different dose regimens are needed.

Key words: Coronary artery bypass grafts, atrial fibrillation, inflammation, oxidative stress

Postoperatif atriyal fibrilasyon, inflamasyon ve oksidatif stress

Özet: Postoperatif atriyal fibrilasyon kardiyak cerrahinin en sık görülen komplikasyonudur ve artmış komplikasyon riski ile ilişkilidir. Son zamanlarda yapılan araştırmalar inflamasyon ve oksidatif stresin atriyal fibrilasyon patofizyolojisinde anahtar rol alabileceğini göstermiştir. Statinler, kortikosteroidler, N-asetil sistein, vitamin C ve balık yağı gibi antiinflamatuvar ve antioksidan ajanların postoperatif atriyal fibrilasyon sıklığını üzerine etkisini araştıran çalışmalarda ümit verici bulgular elde edilmesine rağmen; kesin birşey söylemek için farklı doz rejimlerinin kullanıldığı büyük randomize kontrollü çalışmalara ihtiyaç vardır.

Anahtar sözcükler: Koroner arter bypass cerrahisi, atriyal fibrilasyon, inflamasyon, oksidatif stress

Introduction

Postoperative atrial fibrillation (POAF) is the most common complication of cardiac surgery. It is associated with cerebrovascular accidents, hemodynamic disorders, longer hospital stays, increased procedural cost, and mortality (1,2). Classically, ion channel blockers are used for the treatment of this arrhythmia. However, in spite of the use of these agents, the frequency of this arrhythmia is increasing, most likely because of the rising proportion of elderly patients undergoing cardiac surgery. Therefore, investigations in this area are ongoing. Recent investigations have suggested that the renin-angiotensin system (3,4), inflammation (5-9), and oxidative stress (10-12) play key roles in the pathophysiology of atrial fibrillation (AF). Oxidative stress and inflammation may cause electrical and/or structural atrial remodeling and increase the risk of AF (13). Similarly, cardiac surgery has been shown to be associated with increased inflammatory response (5,14) and oxidative stress (15), and this is where antiinflammatory agents could prevent the development of POAF. In this review, we focus on the evidence supporting the use of agents that block inflammation and oxidative stress for the prevention of POAF.

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Statins and POAF

Statins have antiinflammatory (16-18), antioxidant (19), and antiarrhythmic effects (20), and also play a role in extracellular matrix modulation (21). In previous small retrospective studies, statins have been found to be effective in preventing AF after cardiac surgery (22-24). In the ARMYDA-3 study (17), the largest randomized study, 40 mg/day of atorvastatin decreased the incidence of POAF compared to a placebo. Although peak C-reactive protein (CRP) levels were not different between the placebo and atorvastatin groups, CRP levels were higher in the patients that developed AF compared to those who did not develop AF (17). Analysis from the PROVE IT-TIMI 22 and the A to Z trial did not show decreased incidence of AF with high doses of statins compared to low doses (25). However, PROVE IT-TIMI 22 and the A to Z trial were performed in patients with acute coronary syndromes, not postoperative patients. On the other hand, Kourliouros et al. (26) showed that simvastatin at 40 mg/day and atorvastatin at 40 mg/day demonstrated the greatest effect on POAF, and low-dose statins (simvastatin or atorvastatin at 10 mg/day) did not influence POAF rates. Another small randomized study performed by Ji et al. included 140 patients (27) and showed that atorvastatin at 20 mg/day significantly reduced the incidence of POAF and the postoperative CRP level compared to a placebo.

The effects of statins on AF, including AF after cardiac surgery, have been examined in 4 metaanalyses. A metaanalysis performed by Liu et al. (28) included 10 observational and 6 randomized studies with 7041 patients and showed that statins decreased AF rates. This favorable effect was greatest in the postoperative patients (relative risk reduction, 0.39). Another metaanalysis of 6 randomized studies included 2 studies with cardiac surgery and found that, although statins were beneficial in secondary AF prevention, their effect on new-onset AF or POAF was not statistically significant (29). Liakopoulos et al. (30) included 13 trials in their metaanalysis (3 randomized controlled trials, 10 observational trials; a total of 17,643 patients) and reported that preoperative statin therapy was associated with a reduction in the incidence of POAF. In addition, the beneficial actions of statins on POAF persisted after pooled analysis of risk-adjusted treatment effects

from randomized controlled trials and observational trials (odds ratio, 0.64). In the metaanalysis by Patel et al. (31), which included 14 trials, it was found that statins decreased AF rates by 58% in a postoperative patient group.

On the other hand, 3 retrospective studies, 2 large and 1 small, were unable to show any positive effects of statins on POAF (32-34). In a large retrospective study, Virani et al. (32) showed that preoperative statin therapy was not associated with decreased incidence of POAF in 4044 patients undergoing cardiac surgery, including patients with low ejection fraction. Patients with low ejection fraction and patients undergoing valve surgery are at higher risk for POAF. In the study population of Virani et al. (32), 12% of the patients had ejection fraction below 0.35 and 34% of the patients underwent valve surgery, very high percentages. In another large retrospective study, Miceli et al. (33) evaluated the effects of statins on POAF in 8946 patients (6321 of whom received preoperative statins) undergoing isolated coronary artery bypass grafting. Interestingly, the study showed that POAF rates were actually higher in the statin group (19.5%) compared with the nonstatin group (15.8%), and statin use was a positive independent predictor of POAF (odds ratio, 1:31). Our observational study, which included 590 patients, was in agreement with the studies of Virani et al. (32) and Miceli et al. (33), and showed that statin use was not associated with low POAF rates (34). The studies of Virani et al. (32) and Miceli et al. (33) and our study (34) were retrospective, and different statins were used at different doses. The beneficial effects of statins may be dependent on the dose and statin used.

N-acetyl cysteine and POAF

N-acetylcysteine (NAC) is a free-radical-scavenging antioxidant agent that reduces cellular oxidative damage (35). In our previous randomized study (36), we showed that NAC decreases the incidence of POAF. Our observational study (34) also indicated that NAC was associated with low incidence of POAF. A metaanalysis performed by Baker et al. (35) evaluated the effects of NAC on prevention of postoperative complications after cardiac surgery. In the subgroup analysis of 6 trials, which reported POAF as endpoints, the use of NAC significantly decreased the risk of developing POAF (36%) (35).

Corticosteroids and POAF

Halonen et al. (37) showed that corticosteroids decreased the incidence of POAF and, similarly, serum CRP levels. A metaanalysis of 9 randomized controlled trials suggested positive effects of perioperative corticosteroid use on AF occurrence and on length of hospital stay after cardiac surgery (38). One recent randomized double-blind study on the effects of corticosteroids on the development of POAF did not show any beneficial effects of corticosteroids on POAF and inflammation, but it was a small study (39).

Vitamin C and POAF

Carnes et al. (15) showed that ascorbate attenuates electrical remodeling and decreases the incidence of POAF, and Eslami et al. (40) supported these findings.

Polyunsaturated fatty acids and POAF

Reports about the effects of polyunsaturated fatty acids (PUFAs) on AF are controversial. In a randomized study (41), it was observed that 2 g/day of N-3-polyunsaturated fatty acid administration before elective bypass surgery reduced the incidence of POAF and the length of hospital stay. In a study by Heidt et al. (42), perioperative infusion of PUFAs (soya oil at a daily dose of 100 mg/kg) was associated with a significantly lower incidence of POAF and a shorter hospital stay. On the other hand, Saravanan et

al. (43) showed that fish oil at 2 g/day did not reduce postoperative AF burden.

Comments

While the current evidence evaluating the effects of antiinflammatory and antioxidant agents in preventing POAF is promising, the question of whether these agents are effective in reducing POAF rates has not yet been clearly answered. The questions of which statin at what dose, the ratio of eicosapentaenoic acid to docosahexaenoic acid in fish oil, and the dose and ideal treatment duration for other antiinflammatory and antioxidant agents also need to be answered. To address each of these questions, larger randomized controlled trials with comparisons of different dose regimens are needed.

Conclusion

Although benefits deriving from the use of antiinflammatory and antioxidant agents, including statins, corticosteroids, N-acetylcysteine, vitamin C, and fish oil, for prevention of POAF have been shown in observational and randomized studies and metaanalyses, there is significant heterogeneity among the studies. Larger randomized studies would provide us with more information and lead to a better understanding of the actions of these agents on POAF.

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