N-acetylcysteine for the prevention of postoperative atrial fibrillation: a prospective, randomized, placebo-controlled pilot study

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Aims
Oxidative stress has recently been implicated in the pathophysiology of atrial fibrillation (AF). The aim of the present study was to evaluate the effects of antioxidant agent N-acetylcysteine (NAC) on postoperative AF.

Methods and results
The population of this prospective, randomized, double-blind, placebo-controlled study consisted of 115 patients undergoing coronary artery bypass and/or valve surgery. All the patients were treated with standard medical therapy and were randomized to NAC group (n = 58) or placebo (saline, n = 57). An AF episode >5 min during hospitalization was accepted as endpoint. During follow-up period, 15 patients (15/115, 13%) had AF. The rate of AF was lower in NAC group compared with placebo group (three patients in NAC group [5.2%] and 12 patients in placebo group [21.1%] had postoperative AF; odds ratio [OR] 0.20; 95% confidence interval [CI] 0.05 to 0.77; P = 0.019). In the multivariable logistic regression analysis, independent predictors of postoperative AF were left atrial diameter (OR, 1.18; 95% CI, 1.06–1.31; P = 0.002) and the use of NAC (OR, 0.20; 95% CI, 0.04–0.91; P = 0.038).

Conclusion
The result of this study indicates that NAC treatment decreases the incidence of postoperative AF.

Keywords
N-acetylcysteine • Cardiac surgery • Atrial fibrillation

Introduction
Postoperative atrial fibrillation (AF) is the most frequent arrhythmia after cardiac surgery with the incidence ranging from 10 to 65%.1 It is associated with cerebrovascular accidents, hypotension, pulmonary oedema, longer hospital stays, increased cost of the procedure, and mortality.1 In spite of surgical and pharmacological advances, the frequency of this arrhythmia is increasing, most likely because of rising proportions of elderly patients undergoing cardiac surgery.2

Recent investigations have suggested that oxidative stress and inflammation may contribute to the pathophysiology of AF.3–7 It has been shown that administration of antioxidant vitamin C attenuates inflammation and decreases the incidence of AF after both cardioversion8 and cardiac surgery.9

N-acetylcysteine (NAC) is an antioxidant, mucolytic agent and has beneficial effects in chronic pulmonary disease,10,11 which is a risk factor for postoperative AF.12 Pre-treatment of cardiac surgery patients with NAC may prevent postoperative pulmonary atelectasis13 and may improve systemic oxygenation. Thus, theoretically, NAC may be a useful antioxidant agent that can be used for the prevention of postoperative AF. Although a recent study14 showed that NAC did not decrease the rate of postoperative complications, including arrhythmias, however, to the best of our knowledge, no previous studies have used postoperative AF as a primary outcome variable. Therefore, we hypothesized

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that administration of NAC would reduce the incidence of postoperative AF.

**Methods**

**Study population**

A total of 128 consecutive patients undergoing cardiac surgery in our centre between February 2005 and April 2006 were screened for eligibility. To be included in the study, patients needed to be referred for primary elective coronary artery and/or valve surgery, >18 years of age and in normal sinus rhythm. Exclusion criteria included prior coronary revascularization or heart valve surgery, emergency surgery, New York Heart Association class III or IV congestive heart failure, history of AF, hyperthyroidism, inflammatory diseases except coronary artery disease, infection, a left atrium size >70 mm, electrolyte imbalance, age <18 years old, and ejection fraction <0.25. Of the 128 patients evaluated, 13 were excluded because of previous AF (n = 11) or postoperative hypokalemia (n = 2). Therefore, the population of this study consisted of 115 patients undergoing primary elective coronary artery bypass graft and/or valve surgery.

**Study design**

The aim of this prospective, randomized, double-blind, placebo-controlled study was to assess the effects of NAC in the prevention of the postoperative AF. A patient flow diagram is given in Figure 1. All the patients were treated with standard medical therapy and were randomized to NAC group (n = 58; intravenous infusion for 1 h before the procedure at a dose of 50 mg/kg, followed by intravenous infusion for 48 h after the operation at a dose of 50 mg/kg/day) or placebo (saline, n = 57). In the literature, NAC has been given at a dose of 50–150 mg/kg bolus before the surgery and 12.5 mg/kg over 12 h, and 40 mg/kg/day over 24 h after the surgery. In the present study, we used the similar doses as given in the previous studies. However, to test the effects of its longer administration, we infused it for 1 h preoperatively and 48 h postoperatively.

**Operative procedures**

All the procedures were performed through midline sternotomy incision. All patients received scopolamine and morphine for premedication, and fentanyl and pancuronium for induction of anaesthesia. Isoflurane was used as an inhalational anaesthetic agent. In patients in whom cardiopulmonary bypass was performed, aortic and right atrial 2-staged cannulation, systemic hypothermia (32°C), and antegrade-repeated blood cardioplegia into the coronary circulation and a monolymph membrane oxygenator were used. Right atrial 2-staged cannulation was used in the aortic valve replacement group, and two venous cannulations were used in the mitral valve replacement group. Valve exposure was performed through the aorta in the aortic valve replacement group and through left atriotomy in the mitral valve replacement group. In beating heart operations, cardiac stabilizers were used. Patients with mechanical prostheses were anticoagulated with warfarin.

**Follow-up for postoperative atrial fibrillation**

After completion of the surgical procedure, patients were admitted to the intensive care unit and when their haemodynamic and respiratory functions were stable, they were transferred to the wards. Rhythm was monitored continuously during the operation and during the first 2 postoperative days in the intensive care unit. In the wards, patients were monitored with a 12-lead electrocardiography. An electrocardiography was obtained two times a day routinely and when the patient developed new-symptom or if physical examination revealed a tachycardia or irregular rhythm. All occurrences of AF were confirmed by diagnostic findings on 12-lead electrocardiography. Two blinded cardiologists assessed the electrocardiography. The rhythm was monitored during hospitalization. AF was defined as an irregular narrow complex rhythm (in the absence of bundle branch block) with absence of discrete P-waves. An AF episode lasting longer than 5 min was accepted as endpoint.

![Figure 1 Patient flow diagram](image-url)
N-acetylcysteine for the prevention of postoperative AF

Statistical analysis

Calculation of the number of patients needed was based on the assumption of 30% rate of postoperative AF in placebo group and 75% risk reduction with NAC treatment. To observe a significant difference with an alpha level of 0.05 and a power of 0.80, it was necessary to include 55 patients in each group. A total of 115 patients undergoing primary elective coronary artery bypass graft and/or valve surgery constituted the study population of primary interest for the statistical analysis.

Categorical variables were compared with χ² test and with Fisher’s exact tests in case of an expected frequency of <5. Continuous variables were expressed as mean ± SD and categorical variables were presented as percentages. Continuous variables were compared with Student’s t-test for normally distributed values and with Mann–Whitney U-test for abnormally distributed values. Kaplan–Meier method with log-rank test was used to calculate the actuarial curves for the incidence of postoperative AF during hospitalization. Predictors of postoperative AF were determined by logistic regression analysis. The strength of association between variables and occurrence of AF was represented by odds ratios (ORs) and their accompanying 95% confidence intervals (CIs).

Demographic characteristics and procedural profile shown in Tables 1 and 2 were evaluated. In order to prevent the chance predictors to be included in the final model, we employed an epidemiological approach and factors that have been regarded as potential predictors or have been shown to be multivariable predictors of postoperative AF in the previous studies have been accepted as potential predictors of the outcome. Therefore, age, gender, ejection fraction, left atrial enlargement, a history of AF, congestive heart failure, diabetes mellitus, myocardial infarction, hypertension, treatment with beta-blockers, treatment with angiotensin-converting enzyme inhibitors, valve surgery, duration of cross-clamp, duration of cardiopulmonary bypass,18–20 and NAC, which is the agent of interest in the present study, have been accepted as potential predictors of postoperative AF. These potential predictors were evaluated in univariable analysis and factors with P < 0.10 (left atrial enlargement, valve surgery, use of statin, and use of NAC) were then entered into a multivariable logistic regression analysis. Before the multivariable regression analysis, we performed curve estimation, and found that the best model is the linear model for estimating the development of AF for all continuous variables.

Calculation of the sample size was performed using InStat (Graph-Pad). Other analyses were performed using SPSS 9.0 (SPSS Inc., Chicago, IL, USA). A P-value of <0.05 (two-tailed) was considered significant.

Results

Study population

A total of 115 patients (24 women; mean age 58 ± 10 years; range, 25–78) were included in this prospective, randomized, double-blind, placebo-controlled study. Of which, 107 patients underwent only coronary artery bypass graft, three patients underwent coronary artery bypass graft and mitral valve replacement, one patient underwent coronary artery bypass graft and aortic valve replacement, one patient underwent aortic valve replacement, and three patients underwent mitral valve replacement. Demographic characteristics were given in Table 1. Procedural variables were similar in both groups (Table 2). No potential side effects attributable to NAC were recorded (e.g. nausea, vomiting, stomatitis, and urticaria).

Postoperative atrial fibrillation

During follow-up, 15 patients (15/115, 13%) developed postoperative AF. The rate of AF was lower in the NAC group compared...
Control for other therapies potentially affecting atrial fibrillation

The effect of NAC on postoperative AF was also evaluated after control for other confounding therapies. After control for beta-blockers (Mantel–Haenszel common OR, 0.17; 95% CI, 0.04–0.69; \( P = 0.01 \)), statins (Mantel–Haenszel common OR, 0.18; 95% CI, 0.04–0.71; \( P = 0.01 \)), and angiotensin-converting enzyme inhibitors (Mantel–Haenszel common OR, 0.20; 95% CI, 0.05–0.76; \( P = 0.01 \)), NAC still significantly decreased the risk of developing postoperative AF.

Duration of hospitalization

Mean postoperative hospital stay was similar in both groups (\( P = 0.82 \), Table 3).

Postoperative complications

The incidence of postoperative complications was similar in both groups (\( P = 0.74 \), Table 3). Four patients in the NAC group (acute renal failure, \( n = 1 \); cerebrovascular accident, \( n = 1 \); congestive heart failure, \( n = 1 \); and bleeding requiring transfusion, \( n = 1 \)) and five patients in the control group (mortality, \( n = 2 \); pericardial tamponade requiring reinsertion of sternum, \( n = 1 \); mediastinitis, \( n = 1 \); and pneumothorax, \( n = 1 \)) had postoperative complications.

Discussion

Main findings

The main finding of this study is that the rate of postoperative AF is lower in the NAC group compared with the placebo group.

Oxidative stress, atrial fibrillation, and remodelling

Classically, channel-blocking drugs and beta-blockers are used to decrease the rate of postoperative AF as suggested by current guidelines.\(^2\) However, the efficacy of these drugs is not very high and their use is limited by their side effects.

In the recent years, investigations performed on the pathophysiology of AF have brought about ‘non-channel-blocking drugs’ as promising novel approach. In this regard, previous studies have shown that there is an association between oxidative stress and AF.\(^3,6–9\)

Oxidative stress is caused by an increase in reactive oxygen species and is associated with a more oxidized cellular redox state, as measured by the loss of glutathione.\(^21\) High amounts of reactive oxygen species can cause DNA damage, apoptosis, and myocyte dysfunction.\(^1,22\) In the previous studies, it has been shown that there is a substantial oxidative damage in atrial fibrillation.
myofibrils of patients with AF, and that genes associated with the production of reactive oxygen species are up-regulated in these patients. Atrial tachy-pacing was found to be associated with decreased tissue levels of vitamin C, increased protein nitration indicating enhanced oxidative stress and shortened atrial effective refractory period. In animal model, AF was associated with increased nicotinamide adenine dinucleotide phosphate (NADPH) oxidase activity and superoxide production in a previous study. Kim et al. have shown that NADPH oxidase, NO synthase, and mitochondrial oxidases contribute to atrial oxidative stress and electrical remodelling in AF patients. Rac1 GTPase, which activates superoxide producing NADPH oxidase, has been found to be overexpressed in mouse model of AF. Finally, in a recent study, oxidative stress markers were shown to be associated with AF.

Sympathetic hyperactivity, ischaemia/reperfusion injury, or tachyarrhythmias occurring during cardiac surgery can cause an increase in cytosolic calcium levels via the L-type Ca channel, which in turn increases reactive oxygen species, and thereby causes oxidative stress. Oxidative stress causes down-regulation of L-type calcium channels and transient outward current (Ito), changes which are known to occur in atrial electrophysiological remodelling. By its effects on gene expression, oxidative stress may also alter myocardial structure and cause structural remodelling. Electrophysiological and structural remodelling causes initiation/perpetuation of AF.

Table 4 Comparison of demographic characteristics and procedural profile in patients with and without postoperative atrial fibrillation

<table>
<thead>
<tr>
<th>Variable</th>
<th>Without AF (n = 100)</th>
<th>With AF (n = 15)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, year</td>
<td>58 ± 10</td>
<td>60 ± 10</td>
<td>0.5</td>
</tr>
<tr>
<td>Male gender</td>
<td>81 (81)</td>
<td>10 (66.7)</td>
<td>0.3</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>32 (32)</td>
<td>5 (33.3)</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>57 (57)</td>
<td>9 (60)</td>
<td>1</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>51 ± 11 (25–70)</td>
<td>49 ± 10 (32–62)</td>
<td>0.5</td>
</tr>
<tr>
<td>Left atrial diameter (mm)</td>
<td>38 ± 4 (27–51)</td>
<td>44 ± 9 (32–67)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Clinical presentation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stable AP</td>
<td>43 (43)</td>
<td>7 (46.7)</td>
<td>0.9</td>
</tr>
<tr>
<td>Unstable AP/Non ST-elevation MI</td>
<td>33 (33)</td>
<td>5 (33.3)</td>
<td></td>
</tr>
<tr>
<td>ST-elevation MI</td>
<td>24 (24)</td>
<td>3 (20)</td>
<td></td>
</tr>
<tr>
<td>Pre- and postoperative medications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>92 (92)</td>
<td>12 (80)</td>
<td>0.15</td>
</tr>
<tr>
<td>Metaprolol</td>
<td>86 (86)</td>
<td>11 (73.3)</td>
<td>0.3</td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>1 (1)</td>
<td>1 (6.7)</td>
<td></td>
</tr>
<tr>
<td>Atenolol</td>
<td>3 (3)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Carvedilol</td>
<td>2 (2)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Statin</td>
<td>87 (87)</td>
<td>10 (66.7)</td>
<td>0.06</td>
</tr>
<tr>
<td>Angiotensin-converting enzyme inhibitor</td>
<td>66 (66)</td>
<td>10 (66.7)</td>
<td>1</td>
</tr>
<tr>
<td>Acetyl salicylic acid</td>
<td>99 (99)</td>
<td>15 (100)</td>
<td>1</td>
</tr>
<tr>
<td>NAC</td>
<td>55 (55)</td>
<td>3 (20)</td>
<td>0.01</td>
</tr>
<tr>
<td>Procedure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary artery bypass surgery</td>
<td>96 (96)</td>
<td>11 (73.3)</td>
<td>0.01</td>
</tr>
<tr>
<td>Valve replacement alone or combined with bypass surgery</td>
<td>4 (4)</td>
<td>4 (26.7)</td>
<td></td>
</tr>
<tr>
<td>Beating heart surgery</td>
<td>6 (6)</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Use of left internal mammarian artery</td>
<td>89 (89)</td>
<td>11 (73.3)</td>
<td>0.1</td>
</tr>
<tr>
<td>Revascularized vessel number</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single-vessel</td>
<td>20 (20)</td>
<td>1 (6.7)</td>
<td>0.18</td>
</tr>
<tr>
<td>Two-vessel</td>
<td>34 (34)</td>
<td>5 (33.3)</td>
<td></td>
</tr>
<tr>
<td>Three-vessel</td>
<td>33 (33)</td>
<td>5 (33.3)</td>
<td></td>
</tr>
<tr>
<td>Four-vessel</td>
<td>11 (11)</td>
<td>2 (13.3)</td>
<td></td>
</tr>
<tr>
<td>Duration of cardiopulmonary bypass (min)</td>
<td>99 ± 29</td>
<td>101 ± 14</td>
<td>0.8</td>
</tr>
<tr>
<td>Duration of aortic cross-clamping (min)</td>
<td>55 ± 17</td>
<td>54 ± 11</td>
<td>0.8</td>
</tr>
</tbody>
</table>

Values are mean ± SD (range) or n (%). Abbreviations: AP, angina pectoris; MI, myocardial infarction.
Modulation of oxidative stress in atrial fibrillation

Antioxidant vitamin C has been shown to decrease reactive oxygen species production and improve recovery from ischaemic injury. Korantzopoulos et al. have shown that vitamin C reduces the early recurrences after cardioversion of AF and attenuates inflammation. It was proposed that beneficial effect of vitamin C was mainly based on the prevention of electrical remodelling. Carnes et al. have shown that vitamin C attenuates atrial pacing-induced peroxynitrite formation and electrical remodelling and decreases the incidence of postoperative AF in a dog model. On the other hand, Shirotta-Takeshita et al. failed to demonstrate a favourable effect of vitamin C or vitamins C and E in combination, on AF promotion by atrial tachy-pacing in dogs.

Previous studies

N-acetylcysteine is a free radical scavenger antioxidant agent that reduces cellular oxidative damage. It has been shown that NAC may reduce ischemia/reperfusion injury, reperfusion arrhythmias, and/or extension of infarction. The combination of NAC and reperfusion therapy for acute myocardial infarction in man has also been shown to be associated with less oxidative stress and better preservation of left ventricular function. Although El-Hamamsy et al. were unable to show any beneficial effects of NAC on outcome of patients undergoing cardiac surgery, however, they did not use postoperative AF as a primary outcome variable.

Potential mechanisms of the beneficial effects of N-acetylcysteine on postoperative atrial fibrillation

The main mechanism of action of NAC is its antioxidant actions. NAC is a glutathione precursor; by entering cells and being hydrolyzed to cysteine, it stimulates glutathione synthesis. In addition, it may scavenge several reactive oxygen species including hypochlorous acid (HOCl), peroxynitrous acid (ONOOH), hydroxyl radical (OH), and hydrogen peroxide (H2O2). Treatment of cardiac myocytes with NAC has been shown to increase iNa density and therefore, reverse disease-induced (including AF) remodelling of ion currents.

It also has anti-inflammatory actions through the reduction of the production of pro-inflammatory cytokines. It may block rennin–angiotensin system and/or atrial remodelling via its anti-inflammatory and antioxidant actions.

N-acetylcysteine decreases ischemia-reperfusion injury, and is beneficial in the treatment of chronic lung disease, which is a risk factor for postoperative AF. It is also a sulphydryl donor and it potentiates the vasodilator effects of nitroglycerin and antagonens-converting enzyme inhibitors. Its protective effect of on nitric oxide oxidation may prevent the occurrence of acute myocardial infarction. Since hypertension and ischaemia are risk factors for postoperative AF, beneficial effects of NAC might partly be explained by its anti-ischaemic and vasodilator actions.

Study limitations

Sample size was small. We did not evaluate the laboratory parameters of oxidative damage that may associate with postoperative AF. Our follow-up method after first 2 days of operation is relatively insensitive; therefore, we might have missed some asymptomatic paroxysmal AF recurrences during follow-up. However, we excluded the patients with a previous history of AF; therefore, we speculated that the occurrence of a new-onset AF lasting >5 min would be expected to cause symptoms.

Conclusion

The result of this study indicates that NAC treatment decreases the incidence of postoperative AF. This result supports the idea of the relationship between oxidative stress and AF, and possible favourable effects of antioxidants in patients with AF. Large clinical studies are needed to clarify this issue.

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Conflict of interest: none declared.

References