Kardiologia Polska 2018; 76, 1: 99–106; DOI: 10.5603/KP.a2017.0183 ISSN 0022–9032

ARTYKUŁ ORYGINALNY / *ORIGINAL ARTICLE*

The effect of intravenous N-acetylcysteine on prevention of atrial fibrillation after coronary artery bypass graft surgery: a double-blind, randomised, placebo-controlled trial

Aria Soleimani[1], Mohammad Reza Habibi[1], Farshad Hasanzadeh Kiabi[1], Abbas Alipour[2], Valiollah Habibi[3], Soheil Azizi[4], Amir Emami Zeydi[5], Fatemeh Bozorg Sohrabi[6]

[1]Department of Anaesthesiology, Faculty of Medicine, Mazandaran University of Medical Sciences, Sari, Iran
[2]Department of Epidemiology, Faculty of Medicine, Mazandaran University of Medical Sciences, Sari, Iran
[3]Department of Cardiac Surgery, Faculty of Medicine, Mazandaran University of Medical Sciences, Sari, Iran
[4]Department of Pathology, Faculty of Paramedicine, Mazandaran University of Medical Sciences, Sari, Iran
[5]Department of Medical-Surgical Nursing, Faculty of Nursing and Midwifery, Mazandaran University of Medical Sciences, Sari, Iran
[6]Mazandaran Heart Centre, Mazandaran University of Medical Sciences, Sari, Iran

Abstract

Background: Atrial fibrillation (AF) is one of the most frequently occurring dysrhythmias after coronary artery bypass graft (CABG) surgery.

Aim: The aim of this study was to evaluate the effect of intravenous N-acetylcysteine (NAC) on the prevention of AF after CABG surgery.

Methods: In a double-blind, randomised controlled trial, a total of 150 patients who were scheduled for on-pump CABG surgery were randomly assigned into two groups. In group A, patients received an intravenous NAC infusion (50 mg/kg) after induction of anaesthesia. These patients additionally received two intravenous doses of NAC on postoperative days 1 and 2. Patients in group B received normal saline (as a placebo) with the same volume, during the same time interval. During the first three days after surgery, postoperative AF (POAF) was assessed by continuous electrocardiogram monitoring; serum high-sensitivity C-reactive protein (hsCRP) level was also assessed before and three days after surgery.

Results: During follow-up, 17 patients (17/141, 12.1%) developed POAF. POAF occurred in four (5.6%) patients in the NAC group and 13 (18.8%) patients in the placebo group (OR 0.23; 95% CI 0.08–0.82; $p = 0.02$). In the multivariable logistic regression analysis, the only predictor of AF after CABG surgery was the use of NAC (OR 0.21; 95% CI 0.06–0.73; $p = 0.01$). Also, the hsCRP level trend in the NAC group was different from the trend in the control group (group time interaction or interaction effect) ($p < 0.001$).

Conclusions: It seems that perioperative intravenous NAC therapy can be effectively used to reduce inflammation and the incidence of POAF after CABG surgery.

The clinical trial registration number: IRCT2015040921669N1

Key words: atrial fibrillation, coronary artery bypass graft, N-acetylcysteine, arrhythmias

Kardiol Pol 2018; 76, 1: 99–106

Address for correspondence:
Farshad Hasanzadeh Kiabi, Assistant Professor, Department of Anaesthesiology, Imam Khomeini hospital, Mazandaran University of Medical Sciences, Sari, Iran, tel: +98 1133326262, fax: +98 1133268915, e-mail: hasanzadehkiabi@gmail.com
Received: 02.03.2017 **Accepted:** 03.08.2017 **Available as AoP:** 20.09.2017

INTRODUCTION

Atrial fibrillation (AF) is one of the most frequent dysrhythmias observed after coronary artery bypass graft (CABG) surgery [1], with an incidence that has ranged from 3% to 50% in previous studies [2]. Postoperative AF (POAF) is associated with decreased long-term survival as well as an increased risk of various complications, including post-surgical stroke, multi-organ failure, haemodynamic disturbances, palpitation, and thromboembolism in patients undergoing CABG surgery [2, 3]. These adverse events can lengthen hospital stays and in turn increase hospital costs [1, 2]. As such, to date many strategies have been attempted to prevent POAF after CABG surgery. However, the current success rates of preventive strategies — and the progress in terms of developing more advanced and effective strategies — has been disappointing so far, with POAF incidence remaining high [2, 4].

Although the exact mechanism of POAF has not been fully elucidated, it is believed that oxidative stress and inflammation play important roles in its development [1, 4, 5]. Evidence from published studies has demonstrated that cardiac surgery activates a vigorous inflammatory response, stimulating initiation of the complement system and the release of inflammatory markers [5, 6]. Moreover, several studies have confirmed a significant association between two markers of inflammation, interleukin (IL)-6, and C-reactive protein (CRP) and the development of AF, supporting the potential benefit of anti-inflammatory and antioxidant therapy in the prevention of AF [4–6].

N-acetylcysteine (NAC) is a mucolytic, antioxidant, and anti-inflammatory agent that might diminish cellular oxidative damage and systemic inflammation during cardiac surgery [7]. Theoretically, NAC may be a potential anti-inflammatory and antioxidant agent for the prevention of POAF after cardiac surgery [8]. Some studies have suggested the existence of a positive effect for NAC in the prevention of POAF after cardiac surgery [8], although these findings were not confirmed by other studies [9, 10]. Additionally, a recent meta-analysis recommends additional studies to evaluate the efficacy of NAC in the prevention of POAF as a primary endpoint [7]. The current study aims to evaluate the effect of intravenous NAC on prevention of AF after CABG surgery given the importance of POAF prevention and the contradictory findings yielded by previous studies.

METHODS

Patient selection

After obtaining approval from the institutional Ethics Committee and informed, written consent from patients, a total of 150 adult patients of both sexes (age, 35–75 years), who were scheduled for elective CABG surgery using cardiopulmonary bypass (CPB) were included in this double-blind, randomised, placebo-controlled clinical trial. The study was carried out between August 2015 and April 2016 and registered in the Iranian Registry of Clinical Trials Database (IRCT2015040921669N1).

Patients with a history of previous cardiac surgery, prior treatment with antiarrhythmic medications (except beta-blockers), a history of heart failure with ejection fraction (EF) < 30%, left atrium size > 55 mm, obstructive sleep apnoea, a need for more than four grafts, renal failure (serum creatinine > 1.5 mg/dL on two consecutive tests), liver dysfunction (hepatic enzymes elevated over 1.5 times the normal value), a history of chronic obstructive pulmonary disease (COPD), hyperthyroidism, grade II to III atrioventricular block, serum pH < 7.25 or > 7.55, or who experienced myocardial infarction (MI) after surgery were excluded from the study. Additionally, we excluded patients who required a pacemaker or re-operation for any reason, as well as those who had postoperative haemodynamic instability (defined as mean arterial pressure < 60 mm Hg and heart rate < 50 bpm or > 110 bpm).

Intervention

Patients who fulfilled the inclusion criteria were randomly divided into groups A and B (75 patients in each group) using a sealed envelope technique with a computer-generated random numbering system with the help of a nurse anaesthetist who was blinded to the study groups. In group A, after induction of anaesthesia, patients received intravenous NAC infusion at a dose of 50 mg/kg, diluted to a total volume of 50 cc of normal saline, over a period of 30 min. Furthermore, these patients received two intravenous doses of 50 mg/kg NAC (with each dose occurring over a period of 30 min) on days 1 and 2 after surgery. Patients in group B received normal saline (as a placebo) with the same volume at the same time interval. All pharmaceutical preparations were done by an anaesthesiology resident who was not involved in the conduct of the study.

Anaesthesia and CPB protocol and surgical procedure

Protocols for anaesthesia, CPB, and surgery were identical for all patients in both groups. Anaesthesia was induced with combinations of midazolam, sufentanil, and pancuronium bromide. After intubation, the lungs were mechanically ventilated with oxygen. Anaesthesia was maintained with moderate doses of sufentanil and midazolam supplemented with propofol (50–75 μg/kg/min). Tracheal intubation was facilitated with atracurium 0.6 mg/kg. A bispectral index (BIS) score between 40 and 60 was considered adequate to ensure adequate anaesthesia depth. Standard median sternotomy was performed, and the right atrium and ascending aorta were cannulated for CPB.

Heparin was given at an initial dose of 300 IU/kg to achieve an activated clotting time (ACT) of > 480 s. At the end of CPB, the effect of the heparin was reversed using a full dose

of protamine chloride to achieve an ACT of < 120 s. Non-pulsatile CPB was performed using a membrane oxygenator, an open cardiotomy reservoir, and uncoated tubing systems. A colloid solution of hydroxyethyl starch (Voluven; Fresenius Kabi, Germany) without any blood products was used as the priming solution. During CPB, the minimum and maximum allowed haematocrit levels were 20% and 24%, respectively. Moderate hypothermia (32°C) was used during CPB. Mean arterial blood pressure was maintained between 60 mm Hg and 80 mm Hg. Alpha-Stat acid — base management was used for all patients.

Follow-up for POAF

In this study, POAF was defined according to the European Society of Cardiology guideline as any dysrhythmia that represents the electrocardiogram (ECG) characteristics of AF lasting at least 30 s on a rhythm strip or 12-lead ECG [11]. Postoperatively, patients in both groups were carefully and continuously monitored during their stays in the intensive care unit (ICU) and after being transferred to the coronary care unit (CCU). In the presence of any suspicious rhythms on continuous ECG monitoring, as visually detected by the intensive care nurse practitioners, a 12-lead ECG was recorded for assessment by two independent cardiologists blinded to the treatment assigned.

Other clinical, laboratory, and demographic measures

Prior to, immediately after, and on days 1, 2, and 3 after surgery (at 8:00 a.m. each day), venous blood samples were taken from all patients to assess the levels of blood urea nitrogen (BUN) and creatinine. Moreover, prior to and on the third day after the surgery, blood samples were obtained for evaluation of the high-sensitivity (hs) CRP level. Other information was recorded in data collection forms. This information included age, sex, body mass index, preoperative EF, history of MI, diabetes, right coronary artery involvement, duration of cross-clamping, duration of CPB, duration of mechanical ventilation, and the amount of blood received during surgery. All patients underwent control echocardiography within three days after the surgery to provide a frame of reference.

Endpoints of the study

The occurrence of AF during the study period after CABG surgery was considered the primary endpoint of the study. The secondary endpoints included the postoperative variations of hsCRP levels, the length of ICU and hospital stay, and the incidence of major adverse cardiac and clinical events (MACCE), which was defined as the occurrence of any of the following complications during the perioperative period: acute MI, non-fatal cardiac arrest, unstable angina pectoris, heart failure, postoperative stroke, and death.

Statistical analysis

We used the Shapiro-Wilk test to determine whether data were normally distributed or not. Comparisons of the descriptive baseline characteristics of the two groups (NAC and control) were presented as mean (standard deviation [SD]) values or as percentages. Chi-square or Fisher's exact tests were used to compare two groups of categorical data; for continuous data, t-tests or the Mann-Whitney U test were used. The primary efficacy data related to AF after surgery was examined using intention-to-treat analysis. The predictors of AF were assessed with univariable and multivariable binary logistic regression analysis. General Linear Model levels of EF, CRP, creatinine, and BUN between two groups were compared by repeated-measurement analysis of variance (ANOVA) tests. The compound symmetry assumption was assessed using Mauchly's sphericity test. The time groups' cross-product (an interaction term) was considered as group differences in their response over time with the baseline values (age) as a covariate in this model. A significance level of 5% (alpha = 0.05) was used for all statistical tests. Data were analysed using IBM (Armonk, New York, USA) SPSS statistics version 16 and Stata version 12.

RESULTS

A total of 168 patients who were referred for CABG surgery to our hospital were screened during the study period. Of these, 12 patients did not meet the inclusion criteria and six patients declined to participate in the study. Of the 150 patients allocated between the two groups, three and six patients from group A (NAC group) and group B (control group), respectively, were lost to follow-up during the study period. A total of 141 patients (NAC group, n = 72; control group, n = 69) completed the present study, and data from all these patients were analysed (Fig. 1).

The basic demographic and clinical characteristics of the two groups are presented in Table 1. The results show that no statistically significant difference existed between the two study groups ($p > 0.05$). The procedural characteristics (variables) of the two groups are shown in Table 2. These variables were not statistically significant between groups ($p > 0.05$).

During follow-up, 17 patients (17/141, 12.1%) developed POAF. The rate of AF was lower in the NAC group compared to the control group (four [5.6%] patients in the NAC group and 13 [18.8%] patients in the placebo group had POAF; OR 0.23; 95% CI 0.08–0.82; $p = 0.02$; Table 3). The mean duration of surgery as well as the length of stay in the ICU and hospital were not different between groups ($p > 0.05$). Table 4 shows the demographic and procedural characteristics in patients with and without POAF. These characteristics were not different between the two groups ($p > 0.05$).

To assess the independent predictive effect of NAC on POAF, multivariable logistic regression was performed, with adjustment for age in the final model (Table 5). As shown in

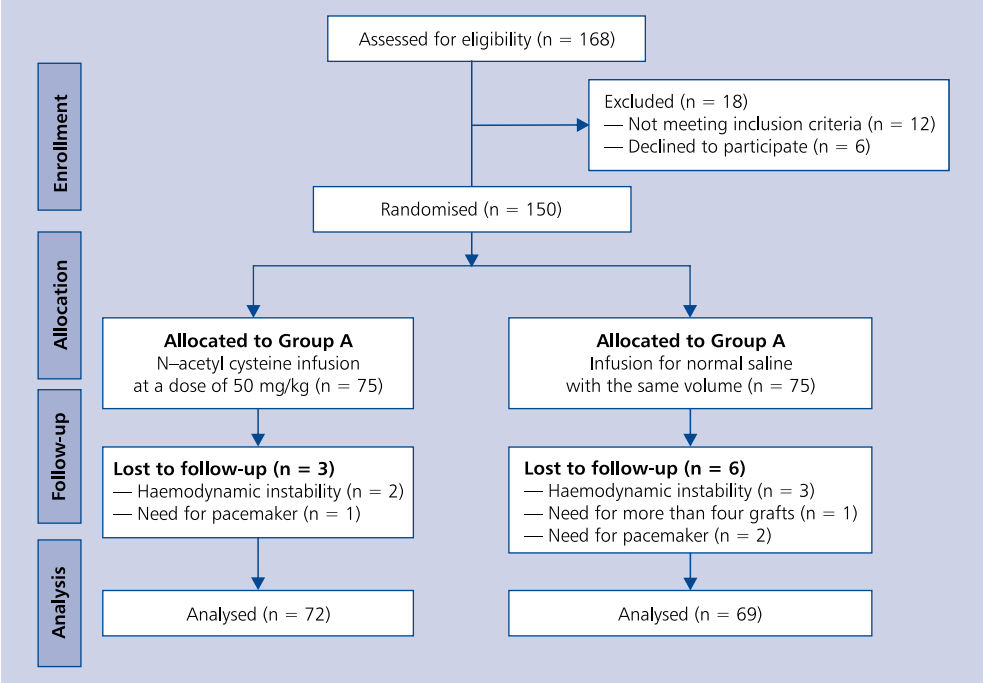

Figure 1. Flow chart of the study

Table 1. Demographic and clinical characteristics of the two study groups

Variable		Group of study		p
		NAC (n = 72)	Control (n = 69)	
Age [years]		62.36 ± 8.85	60.7 ± 8.43	0.26
Female gender		33 (45.8%)	35 (50.7%)	0.62
Body mass index		27.25 ± 5.2	26.88 ± 5.27	0.68
Diabetes mellitus	Proportion	30 (41.7%)	25 (36.2%)	0.61
	Duration [years]	3.56 ± 6.2	2.77 ± 4.68	0.51
History of hypertension	Proportion	47 (65.3%)	41 (59.4%)	0.49
	Duration [years]	5.31 ± 6.06	4.86 ± 5.47	0.65
Previous history of MI		12 (16.7%)	10 (14.5%)	0.82
Cigarette smoking	Proportion	11 (15.3%)	14 (20.3%)	0.51
	Pack years	2.28 ± 8.51	2.42 ± 6.28	0.44
Opium addiction	Proportion	6 (8.3%)	7 (10.1%)	0.78
	Duration [years]	1.01 ± 3.77	1.35 ± 4.67	0.69

Values expressed as mean ± standard deviation or number (per cent); MI — myocardial infarction; NAC — N-acetylcysteine

Table 5, the use of NAC (OR 0.23; 95% CI 0.069–0.751; $p = 0.015$) decreased the odds of POAF. Table 6 shows the mean and SD values of the pre- and post-operation EF, hsCRP, creatinine, and BUN of each group. There was a statistically significant time trend (within-subject differences or time effect) regardless of the study group ($p < 0.001$). The trend for the hsCRP level in the NAC group was different from that in the control group (group time interaction or interaction effect) ($p < 0.001$). EF, creatinine, and BUN trends were similar between two groups of study (no interaction effect).

No significant side effects related to NAC administration were observed during the study period. Also, no MACCE were observed in either the NAC or the control groups until discharge from the hospital.

Table 2. Procedural characteristics of patients in both groups

	Group of study		p
	NAC (n = 72)	Control (n = 69)	
Cross-clamp duration	41.85 ± 14.57	38.26 ± 13.32	0.13
Pump duration	71.54 ± 18.86	68.41 ± 18.17	0.32
Graft number	3.42 ± 0.8	3.3 ± 0.75	0.39
Graft type:			0.54
LIMA	0 (0%)	2 (2.9%)	
Saphenous vein	2 (2.8%)	2 (2.9%)	
LIMA + saphenous vein	69 (95.8%)	64 (92.8%)	
RIMA + saphenous vein	1 (1.4%)	1 (1.4%)	
Ventilation time	9.03 ± 3.02	9.75 ± 3.94	0.23

Values expressed as mean ± standard deviation or number (per cent); LIMA — left internal mammary artery; NAC — N-acetylcysteine; RIMA — right internal mammary artery

Table 3. Follow-up profiles of patients in both groups

Variable	Group of study		p
	NAC (n = 72)	Control (n = 69)	
Occurrence of AF	4 (5.6%)	13 (18.8%)	**0.02**
Duration of surgery [h]	4.12 ± 0.76	4.05 ± 0.67	0.59
Length of ICU stay [day]	2.82 ± 0.88	2.88 ± 0.83	0.66
Length of hospital stay [day]	8.81 ± 2.88	9.22 ± 3.31	0.43

Values expressed as number (per cent) or mean ± standard deviation; AF — atrial fibrillation; ICU — intensive care unit; NAC — N-acetylcysteine

Table 4. Demographic and clinical characteristics in patients with and without postoperative atrial fibrillation

Variable	Atrial fibrillation after surgery		p
	Yes (n = 17)	No (n = 124)	
Age [years]	64 ± 6.73	61.21 ± 8.86	0.21
Female gender	9 (52.9%)	59 (47.6%)	0.8
Body mass index	27.53 ± 5.72	27 ± 5.2	0.52
Diabetes mellitus	7 (41.2%)	48 (38.7%)	0.85
History of HTN	10 (58.8%)	78 (62.9%)	0.75
Previous history of MI	3 (17.6%)	19 (15.3%)	0.73
Smoking	3 (17.6%)	22 (17.7%)	0.99
Pack years of smoking	2.15 ± 5.72	2.38 ± 7.7	0.91
Opium addiction	2 (11.8%)	11 (8.9%)	0.7
NAC administration	4 (23.5%)	68 (54.8%)	**0.02**

Values expressed as mean ± standard deviation or number (percent); HTN — hypertension; MI — myocardial infarction; NAC — N-acetylcysteine

Table 5. Multivariable logistic regression analysis predicting the effect of N-acetylcysteine (NAC) on postoperative atrial fibrillation, adjusted for age

	Standard error	Odds ratio (95% CI)	p
NAC administration	0.611	0.23 (0.069–0.751)	0.015
Age	0.032	0.95 (0.895–1.014)	0.128

CI — confidence interval

DISCUSSION

We evaluated the effect of intravenous NAC on the prevention of AF after CABG surgery. One of the major findings of this study was that patients receiving intravenous NAC had a significantly lower incidence of POAF as well as lower hsCRP concentrations compared to the control group.

In a study by Ozaydin et al. [8], which assessed the effects of NAC in the prevention of POAF in patients undergoing

Table 6. Mean ± standard deviation of ejection fraction (EF), high-sensitivity C-reactive protein (CRP), creatinine, and blood urea nitrogen (BUN) at pre- and post-operation times in both groups

Variable		Time				p	
		Before	Day 1	Day 3	Day 5	Time effect	Interaction effect
EF	NAC	51.07 ± 6.2	–	49.03 ± 6.44	–		
	Control	51.72 ± 5.96	–	48.29 ± 6.08	–	< 0.001	0.21
hs-CRP	NAC	3.25 ± 2.80	–	30.39 ± 9.60	–		
	Control	3.43 ± 2.19	–	39.19 ± 7.48	–	< 0.001	< 0.001
Creatinine	NAC	1.05 ± 0.20	1.12 ± 0.24	1.07 ± 0.27	0.99 ± 0.24		
	Control	1.03 ± 0.18	1.11 ± 0.25	1.02 ± 0.19	0.97 ± 0.19	< 0.001	0.44
BUN	NAC	15.79 ± 3.85	20.19 ± 5.77	22.31 ± 9.22	16.63 ± 6.21		
	Control	15.54 ± 4.34	20.16 ± 5.81	20.73 ± 8.37	16.16 ± 7.54	< 0.001	0.6

NAC — N-acetylcysteine

CABG and/or valve surgery, it was shown that intravenous administration of NAC before and until two days after surgery significantly reduced POAF incidence. The multivariable logistic regression analysis from this study indicates that the use of NAC was an independent predictor of POAF [8], which is consistent with our study. The results of another study by Ozaydin et al. [8] that compared the efficacy of carvedilol, metoprolol, or carvedilol plus NAC in the prevention of POAF after cardiac surgery indicated that intravenous infusion of NAC one hour before surgery (followed by its concomitant infusion with carvedilol for two days after the surgery) significantly reduced the incidence of POAF compared to the use of either agent as monotherapy. Furthermore, using NAC plus carvedilol was associated with significantly lower oxidative stress and inflammation as well as reductions in the length of hospital stay compared with metoprolol [12, 13].

N-acetylcysteine, as described above, is a potentially safe antioxidant that possesses preventive and therapeutic effects in the inflammatory conditions, and its side effects are similar to (or less than) placebo [7, 8]. The degree to which these effects contribute to prevention of POAF are related to the characteristics of the patient population and other factors. Kazemi et al. [9] evaluated the effect of high-dose oral NAC that was initiated two days before surgery and continued for three days after surgery for prevention of POAF in patients undergoing cardiac surgery. The results of the study do not support the preventive efficacy of NAC on POAF, postoperative morbidity or mortality, or duration of hospitalisation. Additionally, a study by Wijeysundera et al. [14] did not support the efficacy of perioperative intravenous administration of NAC in the prevention of POAF in patients with moderate pre-existing renal insufficiency, and who underwent CABG and/or valve surgery with CPB. In that study, POAF was not the primary endpoint variable, which may potentially confound the results of the study. Moreover, NAC was administered after induction of anaesthesia, followed by a continuous infusion until 4 h after CPB. In our study, the duration of NAC administration was extended until the second postoperative day. Extending the duration of NAC therapy until postoperative day 2 to 3 is probably the best approach because previous studies have indicated that inflammatory cytokines are at their highest levels on postoperative days 2 and 3. This finding is consistent with the higher incidence of POAF during the first two to three days after surgery [1, 7].

The results of our study showed that NAC therapy was associated with significantly lower levels of hsCRP as a strong marker of postoperative systemic inflammation. Although the precise underlying mechanisms involved in AF development after CABG have not been fully clarified, inflammation and oxidative stress are among the major contributing factors [1, 4]. Evidence suggested that CPB-induced inflammation is interconnected with atrial remodelling, which is associated with the development of AF [6, 15, 16].

It has previously been demonstrated that intravenous administration of NAC during surgery can significantly reduce CPB-induced ischaemia-reperfusion injury in patients undergoing CABG. Clinical studies provide significant support for decreasing hsCRP levels using short-term oral or intravenous NAC therapy [17]. In a study by Song et al. [18], aiming to evaluate the efficacy of perioperative NAC administration in prevention of acute kidney injury (AKI) after off-pump CABG surgery, intravenous administration of NAC during induction of anaesthesia and until postoperative day 1 was not able to prevent AKI, with no statistically significant differences observed between NAC and the control group in terms of reducing hsCRP levels [18]. However, another study by Aldemir et al. [19] confirmed the efficacy of intravenous NAC therapy in prevention of AKI in elderly patients undergoing CABG. Additionally, several studies have indicated the effectiveness of NAC in the pulmonary function of patients

undergoing CABG. Erdil et al. [20] confirmed the efficacy of NAC in the prevention of pulmonary dysfunction in patients with COPD undergoing on-pump CABG surgery. Another study demonstrated that intravenous infusion of NAC before and one day after CPB can significantly improve systemic oxygenation and decrease lung injury in patients undergoing on-pump CABG surgery [21].

The results of our study showed that perioperative intravenous administration of NAC does not reduce the length of ICU and hospital stay in patients undergoing CABG surgery. In a systematic review by Ali-Hassan-Sayegh et al. [22], polyunsaturated fatty acids and vitamin C (an antioxidant) were shown to reduce the length of hospital stay in patients undergoing cardiac surgery; however, NAC therapy did not have this effect. Several side effects have also been reported for NAC, including fever, haemolysis, cutaneous eruptions, moderate neutropaenia, and wheezing [19]. None of the side effects related to NAC administration were observed in our study. In a study by Wijeysundera et al. [23], it was shown that perioperative NAC therapy in patients undergoing cardiac surgery, who had moderate pre-existing renal insufficiency, was associated with increased blood loss and utilisation of blood products. Conversely, another study revealed that preoperative NAC therapy was not associated with increasing postoperative blood loss or interference with other bleeding parameters in patients undergoing cardiac surgery [24].

Limitations of the study

This study has some limitations. First, we did not investigate the oxidative stress-related parameters that may contribute to the incidence of POAF. In this study, we used NAC at a dose of 50 mg/kg, with infusion occurring after induction of anaesthesia as well as on days 1 and 2 postoperatively. Further studies should be performed to evaluate the efficacy of larger doses of NAC or the length of time from NAC administration. Another limitation of this study was that while the two groups were given propofol by continuous infusion for maintenance of anaesthesia and propofol has potent anti-arrhythmic properties [25], the dosages per kg body weight of this drug may be unequally distributed between groups, and thus may be a confounding variable. Finally, the results might be influenced by unknown variables; however, we tried to match confounding factors.

CONCLUSIONS

In conclusion, it seems that perioperative intravenous NAC therapy can be effectively used to reduce inflammation and the incidence of POAF after CABG surgery. We believe that intravenous NAC therapy should be considered by clinicians for prevention of POAF in patients undergoing on-pump CABG surgery, especially in higher-risk patients.

Acknowledgements

The financial support of the Research Deputy of Mazandaran University of Medical Sciences (No. 1759) is gratefully acknowledged. Also, the authors wish to thank all the study participants for their tremendous cooperation and support.

Conflict of interest: *none declared*

References

1. Soleimani A, Hasanzadeh Kiabi F, Emami Zeydi A, et al. Can white blood cell count be used as a predictor of atrial fibrillation following cardiac surgery? A short literature review. Anadolu Kardiyol Derg. 2014; 14(2): 216–217, doi: 10.5152/akd.2014.5301, indexed in Pubmed: 24566487.
2. Gholipour Baradari A, Emami Zeydi A, Ghafari R, et al. A double-blind randomized clinical trial comparing different doses of magnesium in cardioplegic solution for prevention of atrial fibrillation after coronary artery bypass graft surgery. Cardiovasc Ther. 2016; 34(4): 276–282, doi: 10.1111/1755-5922.12198, indexed in Pubmed: 27225338.
3. Soleimani A, Habibi MR, Hasanzadeh Kiabi F, et al. Opium addiction as a novel predictor of atrial fibrillation after cardiac surgery. Int Cardiovasc Res J. 2012; 6(3): 96, indexed in Pubmed: 24757601.
4. Hu YF, Chen YJ, Lin YJ, et al. Inflammation and the pathogenesis of atrial fibrillation. Nat Rev Cardiol. 2015; 12(4): 230–243, doi: 10.1038/nrcardio.2015.2.
5. Huang CX, Liu Yu, Xia WF, et al. Oxidative stress: a possible pathogenesis of atrial fibrillation. Med Hypotheses. 2009; 72(4): 466–467, doi: 10.1016/j.mehy.2008.08.031, indexed in Pubmed: 19103473.
6. Augoustides JGT. The inflammatory response to cardiac surgery with cardiopulmonary bypass: should steroid prophylaxis be routine? J Cardiothorac Vasc Anesth. 2012; 26(5): 952–958, doi: 10.1053/j.jvca.2012.05.001, indexed in Pubmed: 22765991.
7. Liu XH, Xu CY, Fan GH. Efficacy of N-acetylcysteine in preventing atrial fibrillation after cardiac surgery: a meta-analysis of published randomized controlled trials. BMC Cardiovasc Disord. 2014; 14: 52, doi: 10.1186/1471-2261-14-52, indexed in Pubmed: 24739515.
8. Ozaydin M, Peker O, Erdogan D, et al. N-acetylcysteine for the prevention of postoperative atrial fibrillation: a prospective, randomized, placebo-controlled pilot study. Eur Heart J. 2008; 29(5): 625–631, doi: 10.1093/eurheartj/ehn011, indexed in Pubmed: 18263874.
9. Kazemi B, Akbarzadeh F, Safaei N, et al. Prophylactic high-dose oral-N-acetylcysteine does not prevent atrial fibrillation after heart surgery: a prospective double blind placebo-controlled randomized clinical trial. Pacing Clin Electrophysiol. 2013; 36(10): 1211–1219, doi: 10.1111/pace.12190, indexed in Pubmed: 23731362.
10. El-Hamamsy I, Stevens LM, Carrier M, et al. Effect of intravenous N-acetylcysteine on outcomes after coronary artery bypass surgery: a randomized, double-blind, placebo-controlled clinical trial. J Thorac Cardiovasc Surg. 2007; 133(1): 7–12, doi: 10.1016/j.jtcvs.2006.05.070, indexed in Pubmed: 17198774.
11. Camm AJ, Kirchhof P, Lip GYH, et al. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). Eur Heart J. 2010; 31(19): 2369–2429, doi: 10.1093/eurheartj/ehq278, indexed in Pubmed: 20802247.

12. Ozaydin M, Icli A, Yucel H, et al. Metoprolol vs. carvedilol or carvedilol plus N-acetyl cysteine on post-operative atrial fibrillation: a randomized, double-blind, placebo-controlled study. Eur Heart J. 2013; 34(8): 597–604, doi: 10.1093/eurheartj/ehs423, indexed in Pubmed: 23232844.
13. Ozaydin M, Peker O, Erdogan D, et al. Oxidative status, inflammation, and postoperative atrial fibrillation with metoprolol vs carvedilol or carvedilol plus N-acetyl cysteine treatment. Clin Cardiol. 2014; 37(5): 300–306, doi: 10.1002/clc.22249, indexed in Pubmed: 24477817.
14. Wijeysundera DN, Beattie WS, Rao V, et al. N-acetylcysteine for preventing acute kidney injury in cardiac surgery patients with pre-existing moderate renal insufficiency. Can J Anaesth. 2007; 54(11): 872–881, doi: 10.1007/BF03026790, indexed in Pubmed: 17975231.
15. Sucu N, Cinel I, Unlu A, et al. N-acetylcysteine for preventing pump-induced oxidoinflammatory response during cardiopulmonary bypass. Surg Today. 2004; 34(3): 237–242, doi: 10.1007/s00595-003-2699-8, indexed in Pubmed: 14999536.
16. Orhan G, Yapici N, Yuksel M, et al. Effects of N-acetylcysteine on myocardial ischemia-reperfusion injury in bypass surgery. Heart Vessels. 2006; 21(1): 42–47, doi: 10.1007/s00380-005-0873-1, indexed in Pubmed: 16440148.
17. Saddadi F, Alatab S, Pasha F, et al. The effect of treatment with N-acetylcysteine on the serum levels of C-reactive protein and interleukin-6 in patients on hemodialysis. Saudi J Kidney Dis Transpl. 2014; 25(1): 66–72, indexed in Pubmed: 24434384.
18. Song JW, Shim JK, Soh S, et al. Double-blinded, randomized controlled trial of N-acetylcysteine for prevention of acute kidney injury in high risk patients undergoing off-pump coronary artery bypass. Nephrology (Carlton). 2015; 20(2): 96–102, doi: 10.1111/nep.12361, indexed in Pubmed: 25384603.
19. Aldemir M, Koca H, Baki ED, et al. Effects of N-acetyl cysteine on renal functions evaluated by blood neutrophil gelatinase-associated lipocalin levels in geriatric patients undergoing coronary artery bypass grafting. The Anatolian Journal of Cardiology. 2015, doi: 10.5152/anatoljcardiol.2015.6287.
20. Erdil N, Eroglu T, Akca B, et al. The effects of N-acetylcysteine on pulmonary functions in patients undergoing on-pump coronary artery surgery: a double blind placebo controlled study. Eur Rev Med Pharmacol Sci. 2016; 20(1): 180–187, indexed in Pubmed: 26813472.
21. Eren N, Cakir O, Oruc A, et al. Effects of N-acetylcysteine on pulmonary function in patients undergoing coronary artery bypass surgery with cardiopulmonary bypass. Perfusion. 2003; 18(6): 345–350, doi: 10.1191/0267659103pf696oa, indexed in Pubmed: 14714769.
22. Ali-Hassan-Sayegh S, Mirhosseini SJ, Rezaeisadrabadi M, et al. Antioxidant supplementations for prevention of atrial fibrillation after cardiac surgery: an updated comprehensive systematic review and meta-analysis of 23 randomized controlled trials. Interact Cardiovasc Thorac Surg. 2014; 18(5): 646–654, doi: 10.1093/icvts/ivu020, indexed in Pubmed: 24556447.
23. Wijeysundera DN, Karkouti K, Rao V, et al. N-acetylcysteine is associated with increased blood loss and blood product utilization during cardiac surgery. Crit Care Med. 2009; 37(6): 1929–1934, doi: 10.1097/CCM.0b013e31819ffed4, indexed in Pubmed: 19384218.
24. Wesner AR, Brackbill ML, Sytsma CS. Effect of preoperative N-acetylcysteine on postoperative blood loss parameters in cardiac surgery patients. Int J Vasc Med. 2011; 2011: 859020, doi: 10.1155/2011/859020, indexed in Pubmed: 21761005.
25. Krzych LJ, Szurlej D, Bochenek A. Rationale for propofol use in cardiac surgery. J Cardiothorac Vasc Anesth. 2009; 23(6): 878–885, doi: 10.1053/j.jvca.2009.05.001, indexed in Pubmed: 19577484.

Cite this article as: Soleimani A, Habibi MR, Hasanzadeh Kiabi F, et al. The effect of intravenous N-acetylcysteine on prevention of atrial fibrillation after coronary artery bypass graft surgery: a double-blind, randomised, placebo-controlled trial. Kardiol Pol. 2018; 76(1): 99–106, doi: 10.5603/KP.a2017.0183.