Journal of Experimental and Clinical Medicine
https://dergipark.org.tr/omujecm

Clinical Research

J. Exp. Clin. Med., 2019; 36(3): 81-85
doi: 10.5835/jecm.omu.36.03.003

The effect of intravenous N-acetyl cysteine on the incidence of postoperative atrial fibrillation in coronary artery bypass graft surgery patients

Elif Coskun Sungur[a*], **Levent Altinay**[b], **Mustafa Buyukates**[c]

[a] *Department of Cardiovascular Surgery, Ankara City Hospital, Ankara, Turkey*
[b] *Department of Cardiovascular Surgery, Dıskapı Yıldırım Beyazıd Education and Research Hospital, Ankara, Turkey*
[c] *Department of Cardiovascular Surgery, Faculty of Medicine, Selcuk University, Konya, Turkey*

ARTICLE INFO

Article History
Received 24 / 12 / 2019
Accepted 05 / 01 / 2020
Online Published 10 / 02 / 2020

*** Correspondence to:**
Elif Coskun Sungur
Department of Cardiothoracic Surgery,
Ankara City Hospital,
Ankara, Turkey
e-mail: drelfco@gmail.com

Keywords:
Arrhythmia
Coronary artery bypass surgery
N-acetyl cysteine
Postoperative ftrial fibrillation
Postoperative complication

ABSTRACT

Atrial fibrillation is the most frequent arrhythmia after open heart surgery. The aim of this study was to determine the effect of intravenous (IV) N-acetyl cysteine (NAC) administration in the early postoperative period of coronary artery bypass (CABG) surgery on the incidence of postoperative atrial fibrillation (POAF). A total of 60 patients who had undergone isolated CABG surgery between June 2014 – July 2015 in our clinic included in this retrospective study. The patients divided into two groups: Group 1 (n=30) included the patients who had been administered standard saline solution infusion and Group 2 (n=30) included the patients who had been administered IV NAC (10mg/kg) infusion while they were under mechanical ventilation support. All patients were administrated oral 600 mg NAC once a day for 5 days after weaning from mechanical ventilation support. The ECG's were evaluated for POAF by the same cardiovascular surgeon who was blinded for patient groups. POAF was seen in 12 (40%) patients in Group 1 and 4 (13%) patients in Group 2. The POAF incidence was significantly higher in Group 1 (p=0.020). We think that administration IV NAC is an effective way to prevent the POAF after CABG surgery.

1. Introduction

Atrial fibrillation (AF) is the most common form of cardiac arrhythmia after coronary artery bypass graft (CABG) surgery and it is frequently seen in the early postoperative period (Soleimani et al., 2014). Although the incidence of postoperative atrial fibrillation (POAF) changes according to the surgical procedure, perioperative attributes of the patients, monitorization methods and the definition of AF accepted by the researchers, it is reported to be between 3 – 50% in the literature (Gholipour Baradari et al., 2016).

There is an increasing number of studies proving the role of oxidative stress and inflammatory reactions in the pathophysiology of POAF. The anti-oxidants reduce the level of intracellular oxidative stress molecules which occur after the CABG surgery. N-acetyl cysteine (NAC) is a promising molecule in the prevention of POAF with its anti-oxidant and anti-inflammatory effects in addition tothe well-known mucolytic effect of it (Kazemi et al., 2013). The aim of this study was to determine the effect of intravenous (IV) NAC administration on prevention of POAF after CABG surgery.

2. Material and methods

We have been administrating NAC intravenously as a medication protocol in the postoperative period of the CABG patients while they are under mechanical ventilation support in our intensive care unit (ICU) since 2015. We had set up two groups selected from the patients who underwent open heart surgery before and after the application of the NAC protocol. The inclusion criteria were having been undergone isolated CABG surgery, having preoperative normal sinus rhythm. The exclusion criteria were having been undergone concomitant cardiac surgery other than CABG and having any kind of preoperative arrhythmia. The incidence of POAF in the groups was evaluated in both groups in the early postoperative period.

A total of 60 patients included in this retrospective study who underwent isolated CABG surgery between June 2014 - July 2015 in Bulent Ecevit University Department of Cardiovascular Surgery. The patients divided into two groups: Group 1 (n=30) included the patients who had been administered standard saline solution infusion and Group 2 (n=30) included the patients who had IV NAC (10 mg/kg) while they were under mechanical ventilation support. All patients were administrated oral 600 mg NAC once a day for 5 days after weaning from mechanical ventilation support. Routine postoperative laboratory findings and standard 12-lead electrocardiograms (ECG) of the patients were recorded. The ECGs were evaluated for POAF by the same cardiovascular surgeon who was blinded for the patient groups. Also the demographical data, comorbidities, preoperative medications, preoperative echocardiography (ECHO) results of the patients were evaluated as well as the operative and postoperative data such as postoperative medications, intra-aortic balloon pump applications, cardiopulmonary bypass (CPB) times, aortic cross-clamp times and postoperative anti-arrhythmic medications.

If AF occurred, the following standard up-to-date treatment protocol was applied independently from the study: 150 mg IV bolus amiodarone was administered followed by an infusion at the rate of 15mg/kg for 24 hours. If the amiodarone treatment was ineffective, then electrical cardioversion was performed to regulate the heart rhythm. If the heart rhythm was successfully converted to normal sinus rhythm (NSR) then oral amiodarone therapy was administered for 30 days and if not, heart rate control was done by administration of oral beta-blockers or calcium channel blockers. The protocol of the study was summarized in Fig.1.

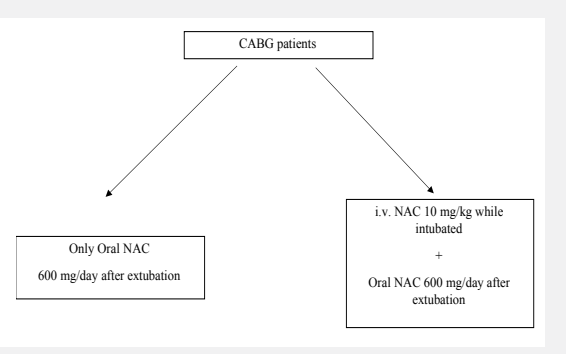

Fig. 1. The study protocol.

2. Results

The demographical data of the groups were presented in Table 1 and they were similar between the groups except the number of hypertensive patients was significantly higher in Group 1 (p=0.020) and the mean BMI was significantly higher in Group 2 (p<0.000).

Table 1. Demographical data SD: Standard deviation; BMI: Body mass index; DM: Diabetes mellitus; HT: Hypertension; HL: Hyperlipidemia; COPD: Chronic obstructive pulmonary disease.

	Group 1 (n=30)	Group 2 (n=30)	P value
Age (years) (Mean±SD)	65.73±8.18	64,87±8.35	0.686
Male (n)(%)	21 (70)	22 (73)	0.774
BMI (kg/m²) (Mean±SD)	23.10±2.65	28.09±4.48	<0.000
DM (n) (%)	14 (46.7)	11 (36.7)	0.432
HT (n)(%)	26 (86.7)	18 (60)	0.020
Smoking (n)(%)	23 (76.7)	17 (56.7)	0.100
HL (n)(%)	11 (36.7)	11 (36.7)	1.000
COPD (n)(%)	6 (16.7)	8 (26.7)	0.542
Thyroid dysfunction(n)(%)	2 (6.7)	2 (6.7)	1.000

In Group 1, mean preoperative ejection fraction (EF) was 51.50±9.04%, preoperative left atrium (LA) mean diameter was 3.99±0.45 cm, preoperative mean SPAP was 35.31±9.76 mmHg and mean preoperative interventricular septum (IVS) thickness was 1.21±0.11 cm. In Group 2, mean preoperative EF was 49.67±8.04%, preoperative LA mean diameter was 3.84±0.44 cm, preoperative mean SPAP was 28.13±5.6 mmHg, mean preoperative IVS thickness was 1.19±0.15 cm. The preoperative mean SPAP was significantly higher in Group 1 (p=0.016, Table 2).

Mean aortic cross-clamping time was 70.97±28.91 min and mean CPB time was 113.83±48.78 min in Group 1 and 64.20±19.61 min and 99.70±29.84 min respectively in Group 2. There was no significant difference of these values between the groups (p=0.566 and 0.282 respectively). Postoperative inotropic agent support was needed in 10 (33.3%) patients in Group 1 and 5 (16.7%) patients in Group 2. There was no

Table 2. Preoperative ECHO findings. SD: Standard deviation; EF: Ejection fraction; LA: Left atrium; SPAP: Systolic pulmonary artery pressure; IVS: Interventricular septum.

Preoperative data	Group 1 (30)	Group 2 (30)	P value
EF (Mean±SD)(%)	51.50±9.04	49.67±8.04	0.410
LA diameter (Mean±SD)	3.99±0.45	3.84±0.44	0.223
SPAP (Mean±SD)	35.31±9.76	28.13±5.6	0.016
IVS thickness (Mean±SD)	1.21±0.11	1.19±0.15	0.744

significant difference of this data between the groups (p=0.136). The procedural data is presented in Table 3.

Table 3. Comparison of the perioperative data. SD: Standard deviation; XCL: Aortic cross-clamp.

	Group 1 (30)	Group 2 (30)	P value
XCL time(min) (Mean±SD)	68.40±29.17	64.20±19.61	0.516
CPB time (min) (Mean±SD)	108.97±43.26	99.70±29.84	0.338
Postoperative inotropic agent support (n)(%)	10 (33.3)	5 (16.7)	0.136
Mechanical ventilation support time (hr) (Mean±SD)	14.13±9.07	13.27±5.79	0.994

Mean time of postoperative mechanical ventilation support was 14.13±9.07 hr in Group 1 and 13.27±5.79 hr in Group 2 (p=0.994). Mean time of postoperative ICU follow-up was 9.23±3.67 days in Group 1 and 8.83±2.87 days in Group 2 (p=0.799). Mean total length of stay time in hospital was 12.37±2.15 days in Group 1 and 11.93±3.47 days in Group 2 (p=0.071). There was no significant difference of these data between the groups. Postoperative atrial fibrillation was seen in 12 (40%) patients in Group 1 and 4 (13.3%) patients in Group 2. The POAF incidence was significantly higher in Group 1 (p=0.020). The data is represented in Table 4.

Table 4. Comparison of the effect of NAC on POAF incidence and hospitalization time. AF: Atrial fibrillation; ICU: Intensive care unit.

	Group 1 (n=30)	Group 2 (n=30)	P value
Postoperative AF (n)(%)	12 (40)	4 (13.3)	0.020
ICU follow-up time (days) (Mean±SD)	9.23±3.67	8.83±2.87	0.799
Total hospitalization time (days) (Mean±SD)	12.37±2.15	11.93±3.47	0.071

Statistical analysis

The PASW (Predictive Analytics Software) Statistics for Windows v18 programme was used for statistical analyses. Percent rates were calculated for qualitative data. Mean values and standard deviation were calculated for quantitative data. The normality of the distribution of the data was tested with Shapiro-Wilk test. Normally distributed data were analysed with t-test and non-normally distributes qualitative data were analysed with Pearson's Chi-square test and quantitative data were analysed with Mann-Whitney U test. P value <0.05 was accepted as statistically significant.

3. Discussion

According to the results of this study, we can say that NAC reduces the incidence of postoperative arrhythmic complications after isolated CABG surgery. Also the ICU follow-up times and the in-hospital stay times tend to be lower after NAC administration although it was not statistically significant.

Postoperative atrial fibrillation is mostly benign in nature but it sometimes causes unwanted events that prolong the hospitalization time which increases the medical expenses. Thus many treatment modalities have been applied to prevent and/or cure the POAF (Baradari et al., 2016). It is believed that the reactive oxidative metabolites that rise in blood after CBP cause oxidative stress and systemic inflammation. Thus the drugs which have anti-oxidant and anti-inflammatory effects can be used to prevent POAF in cardiothoracic surgery (Kazemi et al., 2013)

NAC is a mucolytic, anti-oxidant and anti-inflammatory agent which can reduce the cellular oxidative injury and systemic inflammation in cardiovascular surgery (Liu et al., 2014). It is a free radical scavenger which reduces the myocardial ischemic/reperfusion injury. Because of the major role of oxidative stress in POAF pathogenesis, many studies were conducted to determine the anti-arrhythmic effect of NAC (Baker et al., 2009).

In four meta-analyses including NAC, it was reported that NAC could reduce the incidence of POAF with its potential anti-arrhythmic effect but it could not reduce the time of ICU follow-up and the time of hospitalization significantly (Baker et al., 2009; Gu et al., 2012; Ali-Hassan-Sayegh et al., 2014; Liu et al., 2014). But the meta-analysis of the studies in which NAC was used for a short time and the studies in which NAC was used for a longer time is different in the literature. It may be caused by the anti-inflammatory effect of NAC. It is generally accepted that POAF has usually been seen in postoperative 2nd or 3rd days and the levels of the inflammatory cytokines are at maximum in these days (Mathew et al., 2004; Cairns et al., 2011). Soleimani et al also prolonged the IV administration of NAC until postoperative 2nd day in their study. They reported that this NAC administration protocol did not reduce the times of ICU follow-up and hospitalization but they managed to achieve a 13.2% reduction in POAF incidence (Soleimani et al., 2018).

In a randomized placebo controlled study conducted by Ozaydın et al., it was reported that NAC administration significantly reduced the incidence of POAF after CABG and/or heart valve surgery (Ozaydın et al., 2008). NAC administration was started 1 hr before the surgery and continued for 48 hrs postoperatively in this study. This could be the reason that explained the attribute of this study's being the only study which reported the high rate reduction ability of NAC on POAF incidence.

In our study, there was no significant difference of total mechanical ventilation support times between the groups and NAC was administered orally for 5 days after surgery in both groups. We think that the reduction in POAF incidence in our study could not be due to total NAC administration time but be due to administration of NAC in the early postoperative period in which the CPB stimulated inflammatory cytokine blood levels were at maximum.

Propofol is an anaesthetic agent which has a strong anti-arrhythmic effect and it may affect the incidence of POAF (Krzych et al., 2009). It was administered as IV infusion for anaesthesia maintenance in both of our groups. The total administered doze equivalence of this agent between the groups may be biased to Group 2 because the mean BMI was significantly higher in Group 2. The significant low level of POAF incidence in Group 2 in our study may be due to this propofol effect.

NAC has a good safety profile (Kazemi et al., 2013). In our study, the IV dose of NAC was very low according to other studies in the literature and we did not observe any side effects or complications caused by NAC infusion.

Limitations of the study

We did not monitor and evaluate the levels of oxidative stress related markers in blood which could affect the incidence of POAF. We did not measure and evaluate the effect of concomitant administration of NAC and other well-proven POAF preventive drugs such as beta-blockers, amiodarone, etc. on POAF incidence. Also the optimal dose and the optimal treatment time of NAC is still unknown. We suggest that more studies should be conducted on this subject. Also we think that the definition of POAF should be standardized and larger scale studies should be conducted with a primary end point of POAF incidence.

It seems that NAC is a promising drug to prevent the postoperative arrhythmic complications of open heart surgery but it is not well-proven. We think that IV NAC administration in the postoperative period of high risk CABG patients should be considered as a preventive treatment against POAF.

REFERENCES

Ali-Hassan-Sayegh, S., Mirhosseini, S.J., Rezaeisadrabadia, M., Dehghan, H.R., Sedaghat-Hamedani, F., Kayvanpour, E., Popov, A.F., Liakopoulos, O..J., 2014. Antioxidant supplementations for prevention of atrial fibrillation after cardiac surgery: An updated comprehensive systematic review and meta-analysis of 23 randomized controlled trials. Interactive Cardio. Vas. Thorac. Surg. 2014, 646–654.

Baker, W.L, Anglade, M.W, Baker, E.L,White, C.M, Kluger, J., Coleman, C.I., 2009. Use of N-acetylcysteine to reduce post-cardiothoracic surgery complications: A meta-analysis. Eur. J. Cardio-Thoracic Surgery. 35, 521-527.

Cairns, J.A., Connolly, S., McMurtry, S., Stephenson, M., Talajic, M., 2011 Canadian Cardiovascular Society atrial fibrillation guidelines 2010: Prevention of stroke and systemic thromboembolism in atrial fibrillation and flutter. Can. J. Cardiol. 27, 74–90.

Gholipour Baradari, A., Emami Zeydi, A., Ghafari, R., Aarabi, M., Jafari, M., 2016. 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. 34, 276–282.

Gu, W.J., Wu, Z.J., Wang, P.F., Aung, L.H., Yin, R.X., 2012. N-acetylcysteine supplementation for the prevention of atrial fibrillation after cardiac surgery: A meta-analysis of eight randomized controlled trials. BMC. Cardiovascular Disorders. 12, 10.

Kazemi, B., Akbarzadeh, F., Safaei, N., Yaghoubi, A., Shadvar, K., Ghasemi, K., 2013 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. 36, 1211–1219.

Krzych, L.J., Szurlej, D., Bochenek, A., 2009. Rationale for propofol use in cardiac surgery. J. Cardiothorac. Vasc. Anesth. 23, 778–885.

Liu, X.H., Xu, C.Y., Fan, G.H., 2014. Efficacy of N-acetylcysteine in preventing atrial fibrillation after cardiac surgery: A meta-analysis of published randomized controlled trials. BMS. Cardiovascular Disorders. 14, 52.

Mathew, J.P., Fontes, M.L., Tudor, I.C, Ramsay, J., Duke, P., Mazer, C.D., Barash, P.G., Hsu, P.H., Mangano, D.T., 2004. Investigators of the ischemia research and education foundation; Multicenter study of perioperative ischemia research group. A multicenter risk for atrial fibrillation after cardiac surgery. JAMA. 291, 1720-1729.

Ozaydin, M., Peker, O., Erdogan, D., Kapan, S., Turker, Y., Varol, E., Ozguner, F., Dogan, A., Ibrisim, E., 2008. N-acetylcysteine for the prevention of postoperative atrial fibrillation: A prospective, randomized, placebo-controlled pilot study. Eur. Heart. J. 29, 625–631.

Soleimani, A., Hasanzadeh Kiabi, F., Emami Zeydi, A., Reza Habibi, M., 2014. Can white blood cell count be used as a predictor of atrial fibrillation following cardiac surgery? A short literature review. Anadolu Kardiyol. Derg.14, 216–217.

Soleimani, A., Habibi, M.R., Kiabi, F.H., Alipour, A., Habibi, V., Azizi, S., Emami Zeydi, A., Sohrabi, F.B., 2018. The effect of intravenous N-acetylcysteine on prevention of atrial fibrillation after coronary artery bypass graft surgery: A double-blind, randomised, placebo-controlled trial. Kardiologia. Polska. 76, 99–106.