INTRODUCTION

Atrial fibrillation (AF) is a rapid, irregular rhythm associated with absence of P wave on ECG. AF has a higher frequency after cardiac surgery with a range of 10-65%. Studies carried out in Pakistan have reported frequency of 15%. It depends on different factors including surgery type, perioperative management, monitoring methods etc. AF increases the hospital stay of patients and mortality. Different studies have therefore, focused on methods to decrease frequency of atrial fibrillation so as to reduce the complications arising from post operative AF (POAF). Currently beta blockers and amiodarone are used for this purpose. However, side effects associated with these require careful monitoring. Studies have demonstrated high levels of inflammatory cytokines and oxidative stress to be responsible for POAF.

N-acetylcysteine (NAC) has antioxidant and anti-inflammatory properties, and can counter oxidative stress and inflammatory response in cardiac surgery. Studies have focused on use of NAC for prevention of POAF. Even it has been used to treat POAF. Most of other studies have focused on its intravenous use. NAC also results in decreasing frequency of post cardiac surgery reperfusion injury, hence adding to its benefits.

METHODOLOGY

It was a quasi-experimental study, conducted at Adult Intensive Care Unit (ITC) of Armed Forces Institute of Cardiology over a period of 06 months...
Pre-operative N-Acetyl Cysteine

after receiving approval from Institutional Ethical review board. (IERB# 18/5/R&D/2021/106)

Sample Size: A total of 146 patients were included in this study with prevalence of 10.56%. Sample size was calculated keeping confidence level at 90% and power at 80%.6

Inclusion Criteria: All patients, male and female, undergoing elective CABG were included in the study, having age between 30 to 70 years.

Exclusion Criteria: However, any patient with history of arrhythmia including AF, Thyroid dysfunction, ejection fraction less than 25%, any valvular lesion, dilated left atrium, dilated left ventricle, dilated right atrium, dilated right ventricle or having right atrial tear during surgery were excluded from the study.

The recruitment of patients was done using Non-Probability consecutive sampling. After inclusion of the patients in study, informed consent was obtained from them. Patients were equally divided into two groups by using envelope method. One group was given standard treatment (control group) while other group was named as NAC group (experimental group). 1.2 grams of NAC was started in divided doses, three times a day, 48 hours before surgery in NAC group. All patients received medication as recommended by hospital guidelines. Bed side monitor with 3 lead ECG continuous monitoring was used once these patients were received from operation theatre. Post operatively, medication was given using nasogastric tube.

Medication was continued for 72 hours after procedure, and monitoring was in place till that time. Serum Potassium was maintained between 4.5 and 5 mEq/L, PaO2 greater than 80 mm Hg, and PaCO2 less than 40 mm Hg in all patients. Any episode of AF was noted by Nurse in charge of patient, and Doctor in charge of ICU was notified immediately.

Statistical Analysis: Descriptive statistics were calculated with the help of SPSS-21. Descriptive stats were reported as Mean±SD. Categorical variables were reported as frequency and percentage. Chi square test was used to determine association between different variables.

RESULTS

A total of 146 patients included in the study through non probability consecutive sampling having mean age 55.27±7.3 yrs. Majority of the study population was male i.e., 127(87%) and 19(13%) were females (Figure-1).

Patients were divided into two groups; Group-I was NAC group and Group-II was a control group by having 73(50%) patients in each group. Patients were equally divided into two groups. 28(19.2%) patients had atrial fibrillation while 11 (7.5%) patients had ventricular premature contractions (VPC) as shown in Table-I.

Table-I: Descriptive Statistics of Study Population (n=146)

| Variables | Frequency | Percentages % |
|-----------|-----------|---------------|
| Gender    |           |               |
| Male      | 127       | 87%           |
| Female    | 19        | 13%           |
| Group     |           |               |
| NAC       | 73        | 50%           |
| Control   | 73        | 50%           |
| AF        |           |               |
| Yes       | 28        | 19.2%         |
| No        | 118       | 80.8%         |
| VPC       |           |               |
| Yes       | 11        | 7.5%          |
| No        | 135       | 92.5%         |

Pearson’s chi-square test was applied to compared the both groups, there was no statistically significant difference between ages (p=0.784), gender (p=0.461), frequency of atrial fibrillation (p=0.207) and ventricular premature contractions (VPC) (p=0.347) with both of the groups as depicted in Table-II.

Table-II: Comparison of Both Groups with AF, Gender, VPC and Age

| Variables | Group (n=146) | p-value |
|-----------|---------------|---------|
| AF        |               |         |
| Yes       | 11(15.1%)     | 17(23.3%) | 0.207 |
| No        | 62(44.9%)     | 56(76.7%) |
| Gender    |               |         |
| Female    | 8(11%)        | 11(15.1%) | 0.461 |
| Male      | 65(89%)       | 62(85%)  |
| VPC       |               |         |
| Yes       | 4(5.5%)       | 7(9.6%)  | 0.347 |
| No        | 69(94.5%)     | 66(90.4%) |
| Age in Yrs (Mean±SD) | 55.41±7.3 | 55.08±7.1 | 0.784 |

Out of 73(50%) patients from each group; the mean age of NAC group was 55.41±7.3 yrs and of
control group was 55.08±7.1 yrs (p=0.784). Genderwise distribution of NAC group was 8(11%) females and 65(89%) males while in control group 11(15%) females and 62(85%) were males. AF was found to be 11(15%) and 17(23.3%) in NAC and control group respectively. In NAC group, VPC was 4(5.5%) and in control group it was 66(90.4%) as shown in Figure-2 & Table-II.

**DISCUSSION**

NAC has been studied for reduction of POAF a lot in other countries. Studies about its efficacy are contradictory in nature. The drug has demonstrated antioxidant and anti-inflammatory effects, which caught the attention of researchers. Orhan G,11 studied the effect of NAC for myocardial ischemia-reperfusion injury and found that Tumor necrosis factor-alpha levels and creatinine kinase-MB levels were significantly less in NAC group as compared to control. Shafiei et al. also studied the role of NAC in reducing early post operative reperfusion injury after CABG, and concluded that it has significant effect.12 Systematic review and meta-analysis by Sher Ali Khan and his colleagues demonstrated the potential NAC carries in reduction of reperfusion injury after CABG.13 Apart from these effects, NAC has shown improvement in systemic oxygenation and decreasing the frequency of acute lung injury after CABG surgery.14,15 Some researchers have also stated that NAC decreases the frequency of mechanical ventilation in Covid-19 patients.16 Others have pointed to the protective effects of NAC against acute kidney injury following CABG surgery.17

Regarding AF, Ozaydin and his colleagues studied the role of NAC for conversion of Post operative AF to sinus rhythm and recommended using it.8

However, our study differs from this study as we have studied the preventive role of NAC in Post operative AF after CABG. We included 146 patients, and divided them into equal groups of 73. 11 patients in NAC group had POAF, whereas 17 patients in control group had POAF. Statistically speaking, the difference is insignificant. Another observation was that patients in NAC group had lower frequency of ventricular premature contractions (VPC). 4 patients in NAC group developed VPCs whereas 7 patients in control group developed VPCs. The difference between the two groups is statistically insignificant.

Kazemi and his colleagues,18 used 1.2 G of oral NAC in 240 patients. They started giving medicine 48 hours prior to CABG and continued it for 72 hours after surgery. Though frequency of POAF was less in NAC group, the difference was not statistically significant. Also, they reported that length of stay, morbidity and mortality were similar between placebo and NAC group. Regarding the groups characteristics, Kazemi and colleagues reported that NAC group had more age, acute coronary syndrome (ACS) and hypercholesterolemia. Certain studies have shown that risk of atrial fibrillation is high in ACS and hypercholesterolemia.19,20 This raises the possibility that these factors may also have played their role.

El-Hamamsy and his colleagues,21 conducted a randomized controlled trial to study the effect of NAC in regards to different factors including 30 day mortality, MI, Low cardiac output syndrome, Supra-ventricular arrhythmia, ventricular arrhythmia and AF. They concluded that prophylactic NAC did not prove beneficial in regards to these factors which were studied. However, the frequency of AF was actually less in NAC group as 7 out of 50 patients developed AF, in contrast to 12 out of 50 patients in control group.

Keeping these studies in mind, meta analysis of Khan and his colleagues highlight the importance of NAC for its preventive role during coronary artery reperfusion. There was reduction in cardiac troponin, POAF, length of stay in ICU and improvement in EF.22

**LIMITATIONS OF STUDY**

Small sample size was the main study restriction that can have an impact on the findings. Additionally, the lack of randomization limits the study’s capacity to establish a causal relationship between an intervention and its effects.

**CONCLUSION**

This study shows that NAC decreases the frequency of Post-operative atrial fibrillation and ventricular premature contractions, but the decrease is statistically insignificant in Pakistani population. However, keeping in view other beneficial effects of NAC, we would recommend more studies on this subject in Pakistani population.
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Conflict of Interest: None.

Author’s Contribution

Following authors have made substantial contributions to the manuscript as under:

SARAS: Manuscript writing, Concept, review, manuscript writing
SMHK: Intellectual contribution, idea, intellectual contribution
SAH: Intellectual contribution, data analysis, review
HK: Data analysis, interpretation, editing
SSN: Formatting, data management, review of articles
SKZK: Intellectual contribution, data analysis, review of articles

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

REFERENCES

1. 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(1):52. Published 2014. doi:10.1186/1471-2258-14-52.

2. Gill BUA, Jahanzeb, Ramzan M, Abbas T, Zafar MJ, Javaid A. Frequency of atrial fibrillation in post operative coronary artery bypass grafting surgery. Pak Heart J 2014;47(5):141-144.

3. Maisel WH, Rawn JD, Stevenson WG. Atrial fibrillation after cardiac surgery. Ann Intern Med 2001; 135(1): 1061-1073.

4. Patel D, Gillinov MA, Natale A. Atrial fibrillation after cardiac surgery: where are we now? Indian Pacing Electrophysiol J. 2008; 8(1): 281–291.

5. Fuster V, Ryden LE, Cannon DS, Crijns HJ. ACCF/AHA/HRS focused updates incorporated into the ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. Circulation 2011; 2011(123): e269–e367.

6. Elahi MM, Flatman S, Matata BM. Tracing the origins of postoperative atrial fibrillation: the concept of oxidative stress-mediated myocardial injury phenomenon. Eur J Cardiovasc Prev Rehabil 2008; 15(1): 735–741.

7. Wang G, Bainbridge D, Martin J. N-acetylcysteine in cardiac surgery: do the benefits outweigh the risks? A meta-analytic reappraisal. J Cardiothorac Vasc Anesth 2011; 25(1): 268–275.

8. Soleimani A, Habibi MR, Hasanazadeh Kibi F, Alipour A, Habibi V, Azizi S, Emami Zeydi A, Sohrabi FB. 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.

9. Ozaydin M, Erdogan D, Yucel H, Peker O, Icli A, Akcay S, et al. N-acetyl cysteine for the conversion of atrial fibrillation into sinus rhythm after cardiac surgery: a prospective, randomized, double-blind, placebo-controlled pilot study. Int J Cardiol 2013; 165(3): 580-583. doi: 10.1016/j.ijcard.2012.09.031.

10. Bartekova M, Barancik M, Ferenczyova K, Dhalia NS. Beneficial Effects of N-acetylcysteine and N-mercaptopropionylglycine on Ischemia Reperfusion Injury in the Heart. Curr Med Chem 2018; 25(3): 355-366. doi: 10.2174/092986732466170608111917.

11. Orhan G, Yapici N, Yulek M, Sargin M, Senay S, Yalcin AS, Aykaç Z, Aka SA. 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.

12. Shafei E, Bahtoo M, Raj P, Ostovar A, Iranpour D, Akbarzadeh S, Shahryari H, Anvaripour A, Tahmasebi R, Netticadan T, Movahed A. Effects of N-acetyl cysteine and melatonin on early reperfusion injury in patients undergoing coronary artery bypass grafting: A randomized, open-labeled, placebo-controlled trial. Medicine (Baltimore) 2018; 97(30): e11383. doi: 10.1097/MD.0000000000011383.

13. Khan SA, Campbell AM, Lu Y, An L. N-Acetylcysteine for Cardiac Protection During Coronary Artery Reperfusion: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Front Cardiovasc Med 2021; 8(1):752939.

14. Eren N, Cakir O, Oruc A, Kaya Z, Erdinc L. Effects of N-acetylcysteine on pulmonary function in patients undergoing coronary artery bypass surgery with cardiopulmonary bypass. Perfusion 2003; 18(6): 345-350. doi: 10.1119/01/2676591036p696oa.

15. Kim JC, Hong SW, Shin JK, Yoo KJ, Chun DH, Kwak YL. Effect of N-acetylcysteine on pulmonary function in patients undergoing off-pump coronary artery bypass surgery. Acta Anaesthesiol Scand 2011; 55(4): 452-459. doi: 10.1111/j.1399-6576.2011.02407.x.

16. Assimakopoulos SF, Aretha D, Komninos D, Dimitropoulou D, Lagadinou M, Leonidou L, et al. N-acetylcysteine reduces the risk for mechanical ventilation and mortality in patients with COVID-19 pneumonia: a two-center retrospective cohort study. Infect Dis (Lond) 2021; 53(11): 847-854. doi: 10.1080/23744235.2021.1945675.

17. Savluk OF, Guzelmeric F, Yavuz C, Cevirme D, Gurcu E, Ogus H, et al. N-acetylcysteine versus Dopamine to Prevent Acute Kidney Injury after Cardiac Surgery in Patients with Preexisting Moderate Renal Insufficiency. Braz J Cardiovasc Surg 2017; 32(1): 8-14. doi: 10.21470/1678-9741-2016-0028.

18. Kazemi B, Akbarzadeh F, Safaei N, Yaghoubi A, Shadvar K. 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.

19. Lee JH, Kim S, Lee W. New-onset paroxysmal atrial fibrillation in acute myocardial infarction: increased risk of stroke?BMJ Open 2020; 10(1): e039600.

20. Roh E, Chung HS, Lee JS, Kim JA, Lee YM, Hong SH, et al. Total cholesterol variability and risk of atrial fibrillation: A nationwide population-based cohort study. PLoS One 2019; 14(4): e0215687. doi: 10.1371/journal.pone.0215687.

21. El-Hamamsy I, Stevens LM, Carrier M, Pellerin M, Bouchard D, Demers P, Cartier R, Page P, Perrault LP. 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.

22. Khan SA, Campbell AM, Lu Y, An L, Alpert JS, Chen QM. N-Acetylcysteine for Cardiac Protection During Coronary Artery Reperfusion: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Front Cardiovasc Med 2021; 8:752939. doi: 10.3389/fcvm.2021.752939.