Role of Prophylactic N-Acetylcysteine Supplementation on Postoperative Outcomes in Patients Undergoing Elective Double-Valve Replacement (Aortic and Mitral Valve)

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ABSTRACT

Aims and Objectives: The incidence of postoperative liver dysfunction is high in patients undergoing double-valve replacement – mitral and aortic valve replacement (DVR). This study aims to evaluate N-acetylcysteine's free radical scavenging property (NAC) to prevent postoperative liver dysfunction in these patients, thus affecting overall clinical outcomes.

Methods: A single-center, prospective, randomized, double-blinded interventional study of 60 patients divided into two groups of 30 each. Group N received prophylactic intravenous NAC, and Group C received volume-matched 5% dextrose. Data comprised demographics, liver function tests (LFT), renal function tests (RFT), vasoactive-inotropic scores (VIS) score, and C-reactive protein (CRP) at various time intervals. Postoperative parameters such as ventilation duration, length of stay in ICU (LOS-ICU), length of hospital stay (LOHS), atrial fibrillation (AF), acute kidney injury (AKI) requiring hemodialysis, and mortality were noted. Statistical analysis was performed with the Student's *t*-test and Chi-square test (SPSS 22 software).

Results: All postoperative LFT parameters (total bilirubin, serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvate transaminase (SGPT), and alkaline phosphatase (ALP)) were significantly lower ($P < 0.05$) at 24, 48, and 72 hours in Group N compared to Group C. RFT and VIS scores were lower in Group N; however, were not statistically significant except for Serum Creatinine at 48 hours ($P = 0.0478$). Ventilation duration ($P = 0.0465$) and LOS-ICU ($P = 0.0431$) were significantly lower in Group N. Other outcomes like AF, LOHS, and mortality were lower in Group N but were not statistically significant.

Conclusion: Our study showed that prophylactic administration of NAC in patients undergoing DVR is associated with a reduction in the incidence of postoperative liver dysfunction with a positive impact on postoperative outcomes.

Keywords: Cardiopulmonary bypass, hepatic dysfunction, high liver enzymes, N-acetylcysteine

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INTRODUCTION

Despite advancements in cardiopulmonary bypass (CPB) and cardiac surgery techniques, the incidence of postoperative liver dysfunction remains high in patients undergoing cardiac surgeries using CPB.[1] The spectrum of dysfunction may vary from a temporary increase in the bilirubin levels to a full-blown liver failure, which can have a negative impact on the postoperative outcomes in terms of morbidity, mortality, and costs.[2] The causes of

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these adverse events are complex and multifactorial, and pump-induced inflammation plays a significant role.[3,4]

N-acetyl cysteine (NAC) is an antioxidant agent extensively studied for its potential to prevent postoperative kidney injury and atrial fibrillation (AF) after cardiac surgery.[5] However, there is a paucity of research regarding its utility in preventing liver dysfunction. The results of the studies on its effectiveness on the outcomes are inconclusive owing to the differences in patient inclusion criteria, surgery type, and NAC administration route and dose.[5,6]

This study investigates the effect of prophylactic intravenous NAC administration on postoperative outcomes in patients undergoing double-valve replacement surgery.

OBJECTIVES

The primary objective of this study was to assess the effect of NAC on liver dysfunction, as measured by the absolute values of LFTs during the first three postoperative days. Secondary objective was to analyze the NAC effect on other perioperative outcomes including mortality.

PROCEDURE

Study design

This was a single-center, prospective, randomized, double-blinded interventional study of 60 patients divided into two groups of 30 each. After obtaining institutional ethics committee approval, the study was registered in CTRI (CTRI-REF/2023/12/076812). Written informed consent was obtained from all subjects. The study was conducted over 6 months (June 2023 to December 2023).

Inclusion and exclusion criteria

Sixty patients between the ages of 18 and 65 years, comprising both sexes, who underwent elective DVR (aortic and mitral valve replacement) with or without tricuspid repair were included in our study. The study excluded individuals who had known drug allergies to NAC. It also excluded those who required emergency cardiac surgery or inotropic support during the preoperative period. Additionally, subjects who required additional coronary artery bypass grafting or tricuspid valve replacement, those with severe left ventricular or right ventricular (RV) dysfunction, severe pulmonary hypertension, and patients with existing end-stage renal disease or end-stage liver disease were also excluded from the study.

METHODOLOGY

Sixty patients were randomly divided into two groups using computer-generated random numbers: 30 patients were assigned to Group N, who received prophylactic intravenous (iv) NAC (150 mg/kg at induction and 150 mg/kg infusion in the postoperative intensive care unit for 24 hours), and 30 patients were assigned to Group C, who received an equal volume of 5% dextrose. The consort diagram is described in Figure 1.

As per the institutional protocol, anesthetic management for these patients was standardized intraoperatively and postoperatively, with the same surgical and anesthesia teams responsible for perioperative management. The night before surgery, premedication with 150 mg of oral ranitidine was administered. For anesthetic induction, IV midazolam (0.1 mg/kg), IV fentanyl (2-5 mcg/kg) with aliquots of propofol (50-100 mg), and IV vecuronium (0.1 mg/kg) were used, while sevoflurane and time-bound doses of IV fentanyl and IV vecuronium were used for anesthetic maintenance. CPB aspects were consistent, such as priming solution, flow rate, hypothermia, and myocardial protection. The perfusion pressure was maintained at approximately 60 mmHg, and packed red blood cell concentrates were transfused when the hematocrit value decreased below 25% during CPB. Blood products, such as random donor platelets and fresh frozen plasma, were administered as required. The administration

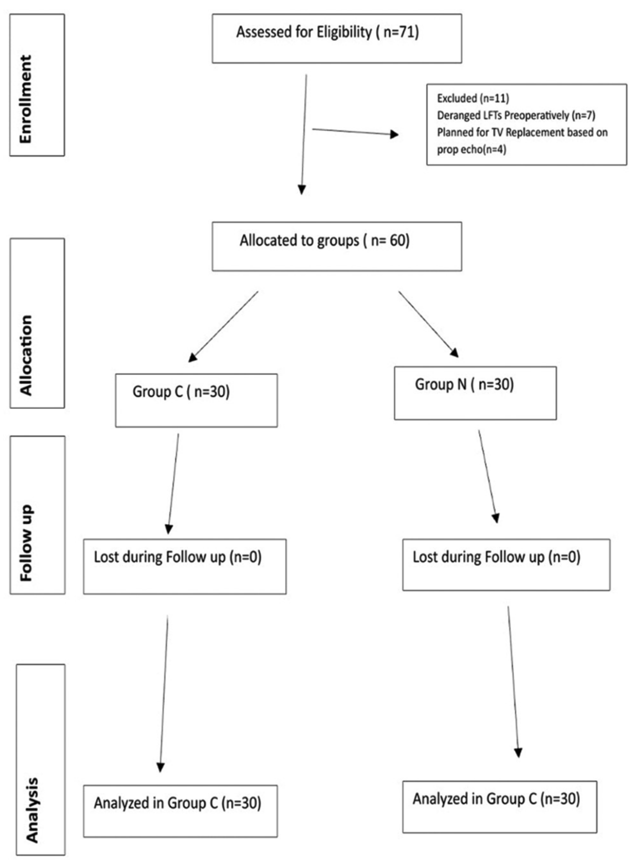

Figure 1: Consort Diagram

of inotropes and vasopressors was adjusted based on mean arterial pressure, heart rate, central venous pressure, and echocardiographic parameters as per the institutional protocol, both during and after surgery. The postoperative period was marked by the implementation of standardized pain management and weaning protocols tailored to each patient's specific needs. Routine echocardiography was performed to assess postoperative cardiac function and rule out any complications.

The study collected demographics, comorbidities, echocardiographic parameters, and EUROSCORE II data.[7] Intraoperative parameters such as CPB time, aortic cross-clamp (ACC) time, and adverse events were also noted. The study measured five parameters of liver function tests (LFTs), which included serum total, direct, and indirect bilirubin (TB, DB, and IB, respectively), as well as serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvate transaminase (SGPT), and alkaline phosphatase (ALP). Renal function parameters were also measured, including serum creatinine, urea, and C-reactive protein (CRP). These parameters were measured preoperatively (baseline) and on the first to third postoperative days (24 h, 48 h, and 72 h). Vasoactive-inotropic scores (VIS) were calculated at various time points.[8] The study also noted early postoperative outcomes, such as ventilation duration, length of stay-intensive care unit (LOS-ICU), length of hospital stay (LOHS), and mortality as well as postoperative atrial fibrillation (POAF) requiring treatment and acute kidney injury (AKI) requiring Hemodialysis (HD). Acute postoperative liver dysfunction was identified as an increase in the liver enzymes SGOT and SGPT by ten times from the baseline values, and hyperbilirubinemia was considered when the serum bilirubin level was more than 3 mg/dl.[9,10]

Sample size calculation and statistics

It was based on the results of previous studies, wherein the expected reduction in hepatic dysfunction after prophylactic administration of NAC was reported to be 50%, and the overall prevalence of hepatic dysfunction in patients undergoing cardiac surgery with CPB was about 20%.[11] Using alpha = 0.05 and power (1 – beta) of 0.80, the calculated sample size was 24 patients in each group. We included 30 in each group for better validation.

Continuous variables were presented as mean (SD) and compared between groups using either a Student's *t*-test or a Mann–Whitney U test. Categorical data, presented as frequency and percentages, were compared using a Chi-squared test. Analysis of variance was employed to analyze variables measured at repeated time points. A *P* value less than 0.05 was considered statistically significant. Data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 22.

RESULTS

The demographic data are displayed in Table 1 and were comparable between the two groups. Additionally, the EUROSCORE II was also similar ($P = 0.6546$). Six subjects required tricuspid valve repair in Group N, while five patients in Group C. CPB and ACC times were identical between the two groups.

As shown in Figure 2, the baseline liver function test values were comparable between the two groups. At 24, 48, and 72 h, all the parameters were elevated above the baseline values in both groups. All parameters in Group C were significantly higher than those in Group N at all time points ($P < 0.05$). Postoperative liver dysfunction was observed in both groups but was statistically significant in group C. [Group N vs. Group C: total bilirubin: 6.66% vs. 46.6% ($P = 0.005$), SGOT – 13.3% vs 53.3% ($P = 0.0011$), SGPT – 16.6% vs. 53.3% ($P = 0.0031$), respectively].

The baseline renal function parameters were comparable between the two groups. However, these values increased over time in both groups. Group C had higher values than Group N, but the difference was not statistically significant, except for serum creatinine at 48 h ($P = 0.0478$). Additionally, both groups experienced increased CRP values from their baseline values, with Group N always having lower CRP values. However, this was not statistically significant, except at 24 h ($P = 0.0058$). The VIS scores, assessed at various time intervals, were similar between the two groups ($P > 0.05$). RFT's, CRP, and VIS scores among the two groups are depicted in Figure 3.

Table 1: Demographic, comorbidities, and other comparison between two groups

	Group N	Group C	*P*
AGE (in years)	38.3±9.625	38.3±11.008	0.9801
BMI (in Kg/m^2)	27.61±4.406	27.16±4.206	0.687
SEX, Male (*n*)	21	18	0.5883
Female (n)	9	12	
HTN (*n*)	7	9	0.7703
SMOKER (*n*)	8	6	0.7602
ALCOHOL (*n*)	8	5	0.5308
PREOPERATIVE AF (*n*)	7	9	0.7703
NEEDING TV REPAIR (*n*)	6	5	1
EUROSCORE II	3.49±5.06	4.07±4.93	0.6546
CPB TIME (in min)	142.8±39.98	142.5±42.012	0.9724
ACC TIME (in min)	93.73±28.025	91.83±29.433	0.7988
Blood product Transfusion (>3 units)	4 (13.7%)	3 (10%)	0.6602
Massive transfusion	0	0	

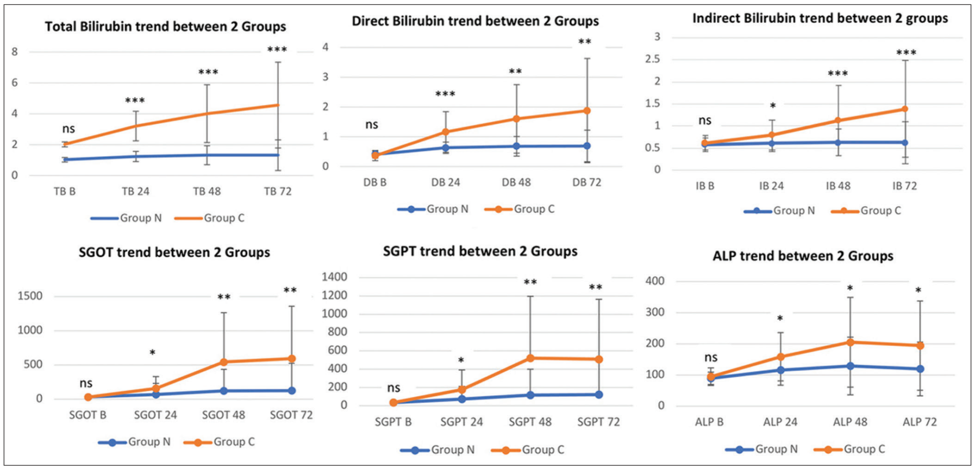

Figure 2: Trends of LFTs between two groups at various time points. *P* value represented in figure: (ns = Not significant; * = *P* value < 0.05; ** = *P* value < 0.01; *** *P* value < 0.001)

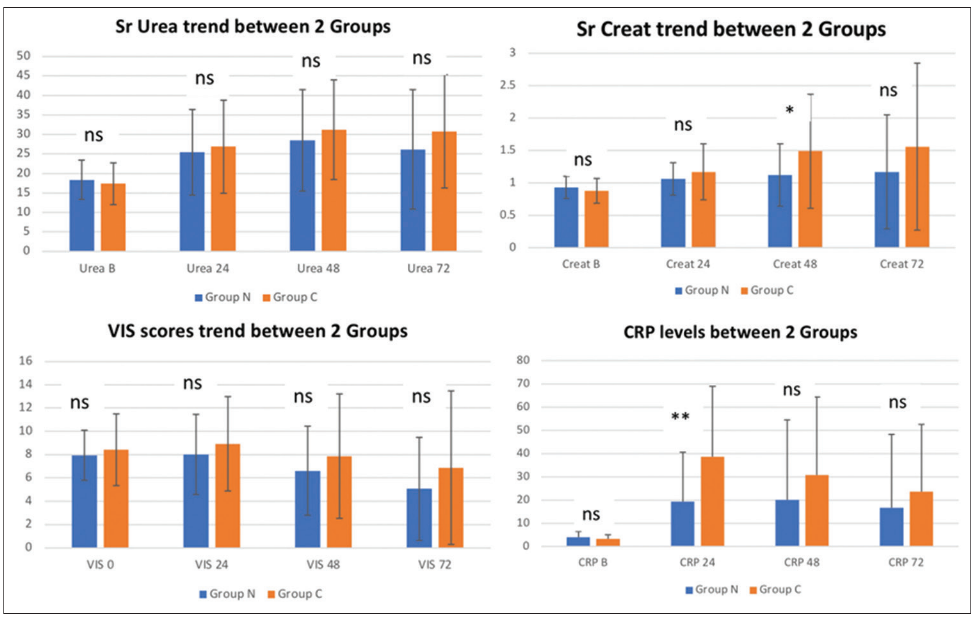

Figure 3: Trends of RFTs (S. Urea and S. Creat), VIS score, CRP levels between two groups at various time points. *P* value represented in figure: (ns = Not significant; * = *P* value < 0.05; ** = *P* value < 0.01; *** *P* value < 0.001)

The early postoperative outcomes of the patients after surgery are summarized in Figure 4. The duration of ventilation and LOS-ICU were significantly shorter in Group N than in Group C (P = 0.0465 and 0.0431, respectively). While the LOHS, mortality rate, the incidence of POAF requiring treatment, and number of patients requiring hemodialysis for AKI were lower in Group N, these differences were not statistically significant.

DISCUSSION

The present study revealed that all liver function parameters, including total bilirubin, direct and indirect bilirubin, SGOT, SGPT, and ALP, increased from the baseline values in both groups. The homeostasis milieu of the liver is compromised during cardiac surgery, mainly when CPB is employed, as it imposes considerable physiological, immunological, and metabolic demands on the liver.[3] Hepatic dysfunction following cardiac surgery can result from various factors, such as congestion, decreased perfusion, and hemolysis, which can manifest as a transient elevation in LFTs to severe ischemic liver failure, often referred to as shock liver.[12] Several factors, such as the number of valves replaced, duration of ACC, and duration of CPB, can increase the likelihood of liver injury after cardiac surgery.[13] Patients undergoing DVR may be particularly at high risk due to these risk factors. We have investigated the effects of prophylactic NAC on postoperative liver dysfunction in such a vulnerable cohort. Our study revealed that Group N had significantly

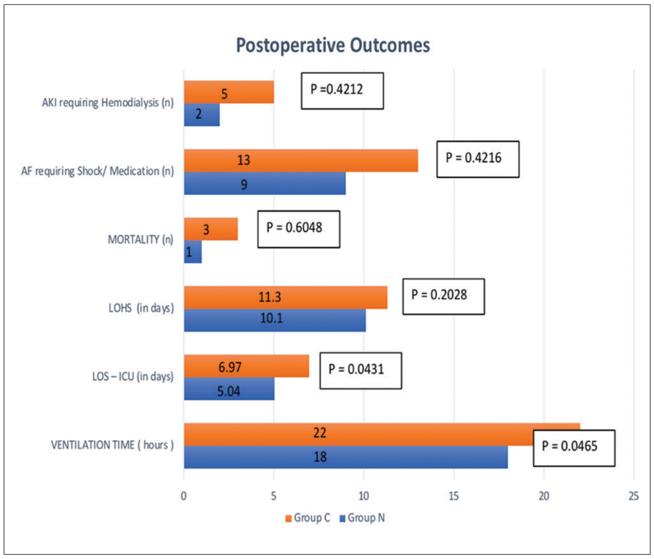

Figure 4: Postoperative outcomes between two groups

lower LFT elevations than the control group. Systemic inflammatory response syndrome and oxidative stress from CPB can contribute considerably to postoperative hepatic injury. NAC is a free radical scavenger and antioxidant agent that can reduce cellular oxidative damage and has been shown to reduce ischemia/reperfusion injury.[14] These properties of NAC may explain its beneficial effects in Group N.

Group N had a statistically lower incidence of postoperative liver injury than Group C (total bilirubin: 6.6% vs 46.6%, SGOT: 13.3% vs 53.3%, SGPT: 16.6% vs 53.3%, respectively). These findings are consistent with the incidence in previous studies (Kumar *et al.*[11] and Faust *et al.*,[15] which showed an incidence of around 40% and 35.1%, respectively). Ischemic hepatitis, a type of liver injury that occurs during cardiac surgery, is caused by cellular and centrilobular sinusoid ischemia, which results from the cessation of hepatic microcirculation at critical levels and subsequent reperfusion. Group N had a lower incidence of liver injury due to the potential vasodilatory effect of NAC on hepatic microcirculation, as it may enhance the effect of nitric oxide on guanylate cyclase, leading to the formation of 3',5'-guanosine monophosphate and avoiding ischemia.[16] A study by Sabzi *et al.*[17] showed a much lower incidence of hyperbilirubinemia (approximately 7%). Still, they did not include patients who underwent complex and combined surgery, which are often associated with liver injury and require preventive measures.

The present study showed that the incidence of AKI requiring hemodialysis, POAF requiring treatment, and CRP levels were lower in Group N than in Group C, but the difference was not statistically significant. The administration of NAC might have contributed to these results by attenuating reactive oxygen species-mediated myocardial stress induced by CPB and increasing glutathione levels, thereby preventing oxidative inflammatory damage.[18] However, meta-analyses have shown varied results in terms of statistical significance, as the optimal NAC dose and duration of therapy in the postoperative period to prevent these complications have not been standardized, as in our study.[5,19]

The postoperative outcomes of ventilation duration, LOS-ICU, LOHS, and mortality were better in Group N than in Group C. Ventilation duration and LOS-ICU were significantly longer in Group C. The elevated liver function parameters in Group C may explain these differences. Previous research by Wang *et al.*[20] showed that an immediate increase in aminotransferases can predict morbidity and mortality after cardiac surgery. Collins *et al.*[21] suggested that a single measurement of serum total bilirubin on the second day after surgery could identify patients with unfavorable postoperative outcomes. The better postoperative outcomes in Group N may have also been influenced by the lower prevalence of POAF and more favorable renal function parameters.

CONCLUSION

The present study revealed that prophylactic administration of NAC in patients undergoing DVR is associated with a reduction in the incidence of postoperative liver dysfunction, positively impacting postoperative outcomes.

Limitations and future recommendations

The present study, being a single-center study with limited sample size, suggests that further multicenter trials with larger sample sizes are imperative. To avoid the potential impact of preoperative liver function abnormalities, severe left or RV dysfunction, and severe pulmonary hypertension on postoperative outcomes, we excluded patients with these conditions. Future studies should include such patients to evaluate the benefits of NAC in this population. Additionally, the present study did not assess the effect of the concomitant use of NAC and other proven prophylactic drugs for POAF, such as beta-blockers and amiodarone, in patients with valvular heart disease who often have preoperative atrial arrhythmias that may worsen after surgery.

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Conflicts of interest

There are no conflicts of interest.

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