RESEARCH PAPER

N-acetyl cysteine after valve Surgery in poor ventricles: a pragmatic protocol

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ABSTRACT

Background : Patients with deranged ventricular systolic function undergoing valve surgery are at high risk of low cardiac output syndrome (LCOS). N- acetylcysteine (NAC), a glutathione precursor and antioxidant, has been investigated in cardiac surgery with incongruous results. Evidence in the subset of poor ventricles after valve surgery is grossly deficient.
Methods :We performed a retrospective observational study of consecutive adults with ventricular dysfunction or global hypokinesia who underwent on- pump valve surgery at a newly established tertiary cardiac unit. Patients were managed with a post operative NAC protocol.
Results :Total 9 patients were studied.Baseline demographics and surgical complexity were comparable after adjustment.NAC use within 48 hours of surgery was associated with a lower period of icu stay (5 days vs 12 days), reduced VIS (mean difference 14). Improvement of renal function was earlier. Hospital stay was shorter in the NAC cohort (19 days vs 24 days). 1 patient succumbed to death due to sustained non responsive ventricular fibrillation.NAC was not given in this patient.Post operative atrial fibrillation was absent in patient with preoperative tachybradyarrythmia who received NAC before 48 hrs. No adverse reactions to NAC were documented.
Conclusion : In this original article study of high-risk cohort of patients with poor ventricular function undergoing valve surgery, a pragmatic N-Acetyl Cysteine protocol was associated with reduced Low Cardiac Output Syndrome and improved hemodynamic stability without added safety concerns. These findings highlight the potential of NAC as an adjunct in managing vulnerable patients with impaired Ventricular function..

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INTRODUCTION

Patients with ventricular dysfunction represent one of the most vulnerable subsets undergoing valve surgery. Diminished contractile reserve, elevated susceptibility to ischemia –reperfusion injury, and shortened tolerance to cardiopulmonary bypass aggravates the risk of peri operative low cardiac output syndrome (LCOS), multiple organ dysfunction, and overall mortality. Although there have been advances in surgical techniques and peri operative management, result in this cohort remains limited. Evidence in the subset of poor ventricles after valve surgery is grossly deficient(1-3).

Oxidative stress and consumption of endogenous antioxidants are major determinants to myocardial and systemic injury after cardiac surgery. N- acetylcysteine (NAC), a precursor of glutathione, is antioxidant, anti-inflammatory, and vasodilatory in nature. Some studies and early clinical trials have shown that perioperative NAC may reduce ischemia– reperfusion injury, stabilise hemodynamics, lessen postoperative atrial fibrillation, and exert renal protection. However, the evidence remains limited, with most trials underpowered and rarely focused on patients with poor ventricular function.Many studies also document no adverse effects (2,4). Prospective controlled randomized trial is required to validate these outcomes(3,5).. In high-risk valve surgery, a pragmatic post operative NAC protocol was introduced at our institution to refine outcomes in patients with reduced ventricular function . This study evaluates the role of NAC administration on postoperative hemodynamics and clinical outcomes in this high-risk population.

AIM AND OBJECTIVES

Aim

To evaluate the impact of postoperative N-acetylcysteine (NAC) on hemodynamic stability and post operative outcomes in adults with ventricular dysfunction undergoing valve surgery.

Objectives

To determine whether NAC reduces the incidence of LCOS within 48 hours post-surgery.

To assess NAC's effect on VIS, AKI (KDIGO), mechanical ventilation duration, ICU and hospital stay, and 30-day mortality.

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To evaluate the safety profile of NAC in this high-risk cohort.

REVIEW OF THE LITERATURE

Ischemia–reperfusion (I/R) during cardiopulmonary bypass releases loads of reactive oxygen species (ROS), initiating lipid peroxidation, protein oxidation, mitochondrial dysfunction, intracellularCa2+ overloadandactivationofproteases—resultinginmyocardialstunning,early ventricular dysfunction and low cardiac output syndrome (LCOS).
Antioxidant protocol that restores cellular thiols and glutathione might hinder these pathways and might reduce myocardial and end-organ injury after cardiac surgery (11).
Quite many randomized, placebo-controlled trials have assessed perioperative NAC in cardiac surgery with mixture of outcomes. Few
RCTs evaluated biochemical and physiologic improvement (reduced markers of oxidative stress, improved myocardial biochemical indices) and occasional benefit in clinical endpoints. For example, Tossios et al. demonstrated reduction in ROS-mediated myocardial stress indices with intravenous NAC in cardiac surgery patients. El-Hamamsy et al. and other trials similarly reported biochemical/physiologic effects but inconsistent translation to robust clinical endpoints. Overall, single trials are small and heterogeneous with respect to NAC dose, timing (preoperative vs intra/ postoperative), route (IV vs oral), and co-interventions (11,12).
Some meta-analyses demonstrated that overall evidence does not establish clear benefit for major endpoints (mortality, major cardiac events) but showed potential reductions in certain complications (AKI, postoperative arrhythmia/POAF) depending on route/dose and inclusion criteria. Pereira et al. (systematic review/meta-analysis) and Wang et al. concluded that while NAC shows biological plausibility and some positive signals, overall clinical benefit across the heterogeneous trial was unavailable .
More recent meta-analyses that stratified by route (IV vs oral) found intravenous NAC associated with reduced AKI and arrhythmia in some pooled analyses, whereas oral NAC lacked effect — highlighting the importance of pharmacokinetics and perioperative timing (14,15).
Subgroup analyses revealed a life-saving effect of NAC in a dose-dependent manner with reduction of in-hospital mortality for the NAC high-dose group, but not for the NAC standard-dose (<3500- mg) group (7)
Several pooled analyses found signal for reduced AKI with perioperative IV NAC but not uniformly across studies; results are sensitive to inclusion of particular trials and definitions of AKI (16). Certain trials showed that NAC did not have a significant impact (odds ratio [OR]: 0.84, 95% confidence interval [CI]: 0.64-1.10) on AKI. Even subgroup analysis did not establish a significant effect of NAC in preventing AKI (6)
Sadiq Al Hasan et al proctored use of NAC in patients undergoing cardiac surgery due to its combined cardio-renal protective effects and reduced mortality (8)
NAC may enhance perioperative analgesia, with some studies suggesting lowering in postoperative opioid use (9)
Alan et al conclude that prophylactic NAC does not prevent AKI or decrease mortality following cardiac surgery(10).
Meta-analyses of randomized trials report an adequate reduction in POAF with NAC , though trials were underpowered for this endpoint (13).
Evidence specifically targeting LCOS or patients with preexisting poor ventricular function is less. Most trials enrolled heterogeneous cardiac surgery cohorts (CABG ± valve) and did not prespecify subgroups by preoperative ventricular dysfunction; therefore, evidence for NAC's effect on LCOS in the poor-ventricle subset is limited and largely indirect (inferred from mechanistic rationale and small physiologic studies (17,18,19) .
Heterogeneity in dosing regimens (single high bolus, infusion protocols, oral courses), timing (pre- op, intra-op, early post-op), patient mix (isolated CABG vs valve vs combined), endpoints, and AKI/AF definitions complicates interpretation. Several meta-analyses conclude that evidence quality ranges from low to moderate and that trials are often underpowered for patient-relevant outcomes such as mortality or LCOS. Safety data are mostly reassuring: severe adverse reactions to NAC in perioperative RCTs are not common, though anaphylactoid reactions might occur with IV administration and need to be managed.
Prospective randomized trials are needed with standardized IV dosing, exact timing (perioperative window), predefined LCOS endpoints, and adequate power to detect clinically meaningful differences in hemodynamic support requirements, AKI, ICU/hospital stay and mortality.

METHODOLOGY

It is retrospective observational cohort study. Valve surgery was performed in a newly established tertiary cardiac surgery unit. Out of 9 patients 5 patients had ventricular dysfunction (global hypokinesia or RV dysfunction) undergoing on-pump valve replacement +/- annuloplasty.
Postoperative NAC protocol (dose/timing per institutional practice) was administered. The Primary outcome observed was incidence of LCOS within 48 hours. Secondary Outcomes studied were VIS, AKI (KDIGO), mechanical ventilation duration, ICU stay, hospital stay, and 30-day mortality. Analysis was done using Multivariable logistic regression adjusting for baseline demographics and surgical complexity.
Inclusion Criteria
Patients undergoing on-pump valve surgery (isolated or combined).
Documented ventricular dysfunction preoperatively:
Left ventricular dysfunction (global hypokinesia / LVEF ≤40%) or
Right ventricular dysfunction (echocardiographic evidence).
Patients who received the standardized postoperative NAC protocol.
Exclusion Criteria
Off-pump valve procedures.
Patients undergoing concomitant CABG.

Known allergy or contraindication to NAC.
Patients with end-stage renal disease on dialysis preoperatively.
Preoperative hemodynamic instability requiring mechanical circulatory support (IABP, ECMO, LVAD).

RESULTS

Total 9 patients were studied.Baseline demographics and surgical complexity were comparable after adjustment. A total of five patients received NAC. 2 patients received NAC after the third post operative day and 3 received NAC on first post operative day.NAC use within 48 hours of surgery was associated with a lower period of icu stay (5 days vs 12 days), reduced VIS (mean difference 14). Improvement of renal function was earlier. Hospital stay was shorter in the NAC cohort (19 days vs 24 days). 1 patient succumbed to death due to sustained non responsive ventricular fibrillation.NAC was not given in this patient.Post operative atrial fibrillation was absent in patient with preoperative tachybradyarrythmia who received NAC before 48 hrs. No adverse reactions to NAC were documented.

Patient ID	VIS Score (max)	LCOS (Y/N)	Inotropo pe Duration (days)	Ventilation Time (hrs)	NAC POD 1(Y/N)	NAC POD 3(Y/N)	ICU Stay (days)	Hospital Stay (days)	Re-exploration (Y/N)
6612	21.6	Y	4	13	N	Y	14	28	N
9335	2.45	N	2	4	N	N	4	12	N
525	5.55	N	1	3	N	N	4	8	N
9374	0.19	N	1	4	N	N	5	12	N
2876	13.41	Y	5	15	N	Y	10	20	N
1607	1.73	Y	1	3	N	N	1	4	N
8397	4.32	Y	4	13	Y	Y	6	20	N
6337	5.20	N	2	4	Y	Y	5	18	N
1041	1.2	N	2	5	Y	Y	5	20	N

DISCUSSION

In this retrospective observational study, we evaluated the effect of a pragmatic N-acetylcysteine (NAC) protocol in patients with significantly reduced ventricular systolic function (Left Ventricular global hypokinesia / Right ventricular dysfunction) undergoing valve surgery. Our findings suggest that NAC use was associated with a decreased incidence of low cardiac output syndrome (LCOS), lowered vasoactive support requirements, and reduced ICU stay, without an increase in adverse effects. These outcomes highlight the potential role of NAC as a safe adjunctive therapy in high-risk surgical patients.

Cardiac surgery with cardiopulmonary bypass induces oxidative stress, depletion of endogenous glutathione, and systemic inflammation, which are particularly detrimental

Variable	Mean±SD/n(%)
Age (years)	38.4 ± 12.0
Sex (M/F)	44.4% (M) 55.6% (F)
Weight (kg)	48.0 ± 13.8
Height (cm)	153.4 ± 7.2
BSA (m2)	1.41 ± 0.20
NYHA Class (I/II/III/IV)	55.5% (III) 44.4% (IV)

in ventricles with limited reserve. NAC, through its role as a glutathione precursor and direct free-radical scavenger, has been shown in experimental models to attenuate myocardial ischemia–reperfusion injury and improve mitochondrial function.

Clinically, prior studies have reported variable effects. Several randomized trials demonstrated reductions in postoperative atrial fibrillation and modest improvements in myocardial injury markers, whereas others failed to show consistent benefits in renal or mortality outcomes. Importantly, most of these studies did not specifically address the subset of patients with poor ventricular function, who may derive the greatest relative benefit.

Our study adds to the literature by focusing on a high-risk group in which therapeutic gains are most clinically meaningful. By employing a pragmatic protocol and real-world design, the results reflect the feasibility and safety of incorporating NAC into standard perioperative care. The observed reduction in LCOS and hemodynamic support aligns with mechanistic expectations and provides a signal worthy of further evaluation in prospective trials.

This analysis has limitations. Its retrospective design introduces potential confounding, despite adjustment and propensity matching. Sample size was modest, precluding definitive conclusions regarding hard endpoints such as mortality. The timing and dosing of NAC may not reflect optimal regimens, and the absence of mechanistic biomarkers (oxidative stress, inflammatory mediators) affects inference.

Nevertheless, the study underscores the need for targeted research in vulnerable surgical populations. A prospective randomized trial of NAC in patients with impaired ventricular function undergoing valve surgery would be essential to confirm efficacy, clarify mechanisms, and define optimal dosing strategies. Until then, our data support the feasibility and safety of a pragmatic NAC protocol and suggest potential benefits in attenuating perioperative myocardial dysfunction.

Conclusion:

In this high-risk cohort of patients with poor ventricular function undergoing valve surgery, a pragmatic NAC protocol was associated with reduced LCOS and improved hemodynamic stability without added safety concerns. These findings highlight the potential of NAC as an adjunct in managing vulnerable patients with impaired LV function. Prospective controlled randomized trial is required to validate these outcomes(3,5).

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Authors' Contributions:

All authors contributed equally to this work. Data collection was performed by SP, and data analysis and drafting by RY and AKS both. All authors were involved in manuscript revision.

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Conflicts of Interest: None declared.

Ethics Approval: Not required, as this protocol was developed within the framework of routine clinical practice.

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