N-acetylcysteine's renoprotective effect in cardiac surgery: A systematic review and meta-analysis

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Abstract

ABSTRACT Background/Objective: To examine N-acetylcysteine's renoprotective effect in adult cardiac surgery Methods: PubMed, Ovid Medline, and Embase were searched for randomised controlled trials published between January 1990 and November 2019 that investigated the effect of N-acetylcysteine in preventing acute kidney injury in patients undergoing cardiac surgery. Cochrane Library was searched to identify any prior systematic review or meta-analysis. Eligibility Criteria: Randomised controlled trials that assessed the effect of N-acetylcysteine in comparison to placebo by measuring the incidence of acute kidney injury. Two independent reviewers extracted the data and assessed the risk of publication bias of included studies. Results: Overall meta analytic estimates of all 10 included trials was controversial, showing that N-acetylcysteine did not have a significant effect (odds ratio: 0.84, 95% confidence interval 0.64 to 1.10). However further meta analytic estimates comparing the dosage and timing of NAC administered suggested that the administration of high dosages of NAC perioperatively would have significant benefit in preventing acute kidney injury. Conclusion: This study suggests that N-acetylcysteine must be administered at high dosages perioperatively to have a significant effect in reducing the incidence of acute kidney injury. However, only one out of the 10 included trials administered NAC high dosages perioperatively. Although it is worth noting that it is the only included trial to show a significant benefit in reducing the incidence of acute kidney injury (odds ratio: 0.30, 95% confidence interval 0.11 to 0.81), further studies should be conducted to confirm the renoprotective effect of administering high dosages of NAC perioperatively.

Introduction

Description of Condition

Acute Kidney Injury (AKI) is a common and serious complication after cardiac surgery [1]. Specifically, acute kidney injury is mostly caused by the usage of cardiopulmonary bypass during coronary artery bypass grafting (CABG) and valvular surgery. [2] The incidence of acute kidney injury might also be dependent on the clinical characteristics of patients undergoing cardiac surgery, such as reduced left ventricular function, presence of congestive heart failure or an elevated preoperative serum creatinine. Acute Kidney injury does not have a universal definition. The three most popular consensus definitions are Acute Dialysis Quality Initiative's "RIFLE" criteria, the Acute Kidney Injury Network (AKIN) criteria and the Kidney Disease Improving Global Outcomes (KDIGO) criteria [3]. These criteria are based on percentage increase in serum creatine concentration over baseline, absolute increase in serum creatine concentration or urine volume. [4] The pathogenesis of AKI after CPB is multifactorial, and is mostly due to hypoperfusion, reperfusion

injury, activation of the systematic inflammatory response, and/or low cardiac output. [5] Reperfusion will result in the formation of reactive oxygen species, resulting in injury to tissue. [6] The activation of the systematic inflammatory response is mostly due to the exposure of blood to the extracorporeal CPB circuit, resulting in the activation of the immune system, which is also mediated by the generation of reactive oxygen species. This results in increased recruitment of neutrophils, macrophages and lymphocytes into the renal parenchyma, leading to AKI. [7]

Description of Intervention

N-acetylcysteine (NAC) is well recognized for its antioxidant and free radical scavenging properties [8] in addition to acting as a vasodilator [9]. Hence, theoretically, NAC is able to counteract several mechanisms of kidney injury during cardiac surgery, namely the systemic inflammatory response, free radical injury and ischemia. [10]

Many randomised controlled trials have been conducted on different measures to prevent acute kidney injury. These measures range from different pharmacological therapies, such as fenoldopam or pentoxifylline, to surgical techniques such as off pump cardiopulmonary bypass to remote ischemic preconditioning. However, among the randomised controlled trials conducted on different preventive measures, the administration of N-acetylcysteine was the most promising measure with the greatest number of randomised controlled trials conducted on its usage. Hence this review was conducted to assess the overall effect of N-acetylcysteine based on past randomised controlled trials.

Material and Methods

Data Sources, Search Strategy, and Study Selection

Two reviewers searched MEDLINE (1990 to May 2020), EMBASE (1990 to May 2020), PUBMED (1990 to May 2020) for randomized controlled studies that compared any form of usage of NAC to placebo in adult patients (age above 18) undergoing cardiac surgery. The following search terms were employed to source for eligible studies: NAC, N-acetylcysteine, Cardiac surgery, Cardiac surgical procedures, Cardiac, Heart, Renal, Kidney, Acute Kidney Injury and Acute Renal failure. There was no language restriction but only papers written in English were included.

Inclusion Criteria

To be included, all studies had to assess the effect of NAC on the primary outcome of acute kidney injury after adult cardiac surgery. Only relevant randomised controlled trials conducted in the past 30 years (1990-2020) that were related to the search terms were included. Acute kidney injury was defined as more than or equal to a 25-percentage increase in serum creatine concentration over baseline.

Exclusion Criteria

Studies evaluating the effects of NAC in noncardiac surgical settings (such as contrast induced nephropathy, endothelial function, and so on) and those that did not report the specified renal outcomes were excluded. Studies that lacked details on the timing and duration of administration of NAC or the exact amount of dosage administered were excluded. Studies of a small sample size, defined as having less than 10 patients in each arm of the randomised controlled trial, were also excluded.

Data Analysis

Data was analysed by Review Manager 5.3. Dichotomous data from individual studies were analysed to calculate individual odds ratio with 95% confidence interval ($p < 0.05$) according to inverse variance model. Statistical heterogeneity was analyzed using heterogeneity $\chi 2$ (Cochrane Q) statistic. Treatment effects were analyzed with the random-effects model.

Results

Selection Process

Details of the flow of study identification are detailed in a Prisma chart shown in Figure 1. Database searches yielded a total of 277 citations after removing duplicate citations. 256 irrelevant citations were excluded based on abstract and title. After further assessment of the full text of the remaining citations, 11 were excluded due to not meeting the requirements of the selection criteria. These studies were excluded for the following reasons: studies reported only on serum creatine levels (n = 4), studies reported only on estimated glomerular filtration rate (n=2), studies reported on outcomes other than the incidence of acute kidney injury (n=2), studies reported on the usage of NAC in comparison to other drugs (n=2), studies reported on the usage of NAC with other drugs (n=1). Our analysis finally identified 10 eligible studies comprising 1,242 patients (623 NAC group; 619 control group) Characteristics of the included studies are summarized in Supplemental Table 1.

Risk of Bias Assessment

The quality of the included studies was assessed by the Jadad scale. Supplemental Table 2 details the scores of each individual study. All included studies were assessed to have a low risk of bias.

Primary Outcome measures

Meta-analytic estimate showed that a positive trend towards preventing acute kidney injury in patients treated with NAC. There was moderate statistical heterogeneity (I2= 31%) among the studies for any of the primary outcomes. Overall results showed that the effect of NAC in preventing acute kidney injury after adult cardiac surgery was controversial, as showed in Fig 2 (OR: 0.84, 95% CI: 0.64-1.10). As such, overall meta analytic estimates showed that NAC did not have a significant effect, however 1 study showed that NAC had significant benefits.

Perioperative usage of N-acetylcysteine was examined in 5 studies. Intraoperative to postoperative usage of NAC was examined in 5 studies where NAC was administered after the induction of anaesthesia and administered for 12 to 24hrs post operatively. Meta-analytic estimates of perioperative usage and intraoperative to postoperative usage are detailed in Fig 3 and Fig 4.

High dosage of NAC was administered in 5 studies, where generally, the dosage administered was 150mg/kg for 15 minutes, 50mg/kg for the next 4 hours, and 100 mg/kg for the next 16 to 20 hours. Low dosage of NAC was administered in 5 studies, where the total dosage administered ranged from 2400ml to 8400ml. The format of the dosages reported varied depending on the study. These characteristics of the studies are summarized in Supplemental Table 3. Meta-analytic estimates of high dosage and low dosage of NAC administered are detailed in Fig 5 and Fig 6.

Secondary Outcomes

Three secondary outcomes, in hospital mortality, requirement for renal replacement therapy and length of stay (LOS) in ICU were also assessed. Regarding in hospital mortality, a total of 1055 patients in 8 of studies were observed. Meta-analytic estimates for in hospital mortality showed that there was no statistically significant difference between patients treated with NAC and without, as showed in Fig 7 (OR: 0.85, 95% CI: 0.43-1.68)

Regarding the requirement for renal replacement therapy, a total of 686 patients in 4 of the studies were assessed. Meta-analytic estimates did not show any significant benefit of NAC in reducing the requirement for renal replacement therapy as showed in Fig 8 (OR: 1.05, 95% CI: 0.38-2.92)

Seven studies (1042 patients) reported length of stay in ICU. All studies reported the exact length of stay in ICU except one study which reported the number of patients that had an ICU stay longer than 4 days. Three studies reported the mean length of stay and standard deviation. Two studies reported the median length of stay and interquartile range. One study reported the median length of stay and total range. For meta analytic estimates to be conducted, a normal distribution had to be assumed for the three studies that reported the median length of stay. Thus, the median was approximated to be the mean, and standard deviation was approximated by dividing the interquartile range by 1.35 and the total range by 4. Meta

analytic estimates of studies that reported the mean and standard deviation and studies with approximated mean and standard deviation were conducted separately. Both meta analytic estimates did not show any benefit of NAC in reducing the length of stay in ICU as showed in Fig 9A (Mean Difference: 0.27, 95% CI: -2.25-2.79) and Fig 9B (Mean Difference: 0.00, -0.27-0.27).

Publication Bias

Publication bias was assessed by Review Manager V5.3 and a funnel plot for the analysis of complication rate is shown in Fig. 10. The symmetrical funnel plot indicated a low risk of publication bias.

Discussion

It is intriguing that despite NAC's well documented effect as an antioxidant, vasodilator and free radical scavenger, overall data analysis was inconclusive in showing that NAC could provide significant renal protection in major cardiac surgery. In addition, NAC has been shown to be effective in preventing radiocontrast nephropathy [11] and protecting renal function after cardiopulmonary bypass [12], possibly by inhibiting transforming growth factor beta1 (TGFβ1) [13]. Animal models have also shown the administering of NAC would reduce total, cortical, and medullary vascular resistance by 7% to 10%, improving renal function [14] which further suggests that NAC would confer protection against acute kidney injury after cardiac surgery.

It is likely that the main reason for the controversial effect of NAC is due to the different dosage administered, timing when NAC was first administered, and the overall duration. Firstly, NAC effect on preventing renal failure was also more pronounced in studies where it was administered at a much higher dosage. All 5 studies that reported higher doses of NAC [16] [17] [18] [19] [20] showed a trend pointing towards the reno-protective effect of NAC, with an odds ratio of less than 1. This is further supported when meta analytic estimates of NAC administered at high dosage (Fig 5) were compared to that of low estimates (Fig 6). The odds ratio of all studies that administered high dosages of NAC was at 0.66 (95% CI: 0.44-1.01) while that of studies that administered low dosages of NAC was at 0.98 (95% CI: 0.67-1.42). Secondly, NAC's effect on preventing against renal failure was more pronounced in studies where it was administered perioperatively. In 2 studies conducted by Prasad [15] and Santana [16], perioperative usage of NAC resulted in a decrease in incidence of renal failure, with an odds ratio of 0.73 and 0.30 respectively. It is also worth noting that the study conducted by Santana and associates showed a significant benefit in perioperative usage of NAC (OR: 0.30, 95% CI: 0.11-0.81). However, when meta analytic estimates of all perioperative usages of NAC (Fig 3) was compared to that of intraoperative to postoperative usages of NAC (Fig 4), the trend seems to show that intraoperative to postoperative usage of NAC had a more pronounced effect (OR: 0.71, 95% CI: 0.50-0.99) as compared to perioperative usage of NAC (OR:0.95, 95%CI: 0.55-1.63). However, this is likely due to the fact that a low dosage was administered in all three studies on the perioperative usage of NAC that had an odds ratio of more than one, resulting in the overall meta analytic estimate incorrectly favouring intraoperative to postoperative usage of NAC. Therefore, it is likely that the reno-protective effect of NAC is best elicited when administered in high doses perioperatively. It is worth noting that among all 10 studies, only 1 study reported the administration of high doses of NAC perioperatively [16], and that study was the sole study to show a significant benefit (OR: 0.30, 95% CI: 0.11-0.81). This study was accorded a greater weightage compared to other studies due to it having a significant number of patients and being of better scientific design, as a double blind randomised controlled trial.

Other possible explanations for NAC's inconsistent effect on renal function could be due to differences in off pump and on pump coronary artery bypass grafting which could result in varying effects of NAC in attenuating immune responses due to the fact that the systematic inflammatory response is more likely to be activated when exposed to extracorporeal CPB circuit only found in on pump coronary artery bypass grafting. The multifactorial pathophysiology of acute kidney injury after cardiac surgery could suggest that other mechanisms unaffected by NAC could have resulted in renal failure despite administration of NAC, such as low cardiac output and decreased reperfusion pressure. Lastly, for studies which focused on patients with chronic kidney disease or moderate renal insufficiency undergoing cardiac surgery, the effect of NAC may be insufficient in protecting renal function since renal function was already compromised prior to cardiac

surgery.

One limitation worth mentioning is that due to studies using different metrics to report dosages administered, discretion was used to decide which dosage was considered high or low.

Other findings

It is worth mentioning that one of the studies excluded, [21] also showed a significant reduction in incidence of acute kidney injury when carvedilol, a beta blocker, is administered with N-acetylcysteine (OR: 0.42, 95% CI: 0.23,0.79) However, it is likely that the main effect is due to N-acetylcysteine, since there was a decreased incidence of acute kidney injury in patients that were administered both N-acetylcysteine and carvedilol as compared to patients that were only administered carvedilol. More importantly, N-acetylcysteine was administered perioperatively at high dosages, which further suggests that the NAC's effect on preventing renal failure is maximised when administered perioperatively at high dosages.

Conclusion

Meta-analysis of the effects of N-acetylcysteine in preventing acute kidney injury after cardiac surgery is questionable due to the different dosage and different treatment time periods across different studies. However, further analysis shows that perioperative high dosages of N-acetylcysteine showed a significant protective effect in preventing renal failure after adult cardiac surgery. Therefore, analysis of primary outcomes confirms the protective effect of N-acetylcysteine. It is recommended that N-acetylcysteine should be administered with beta blockers such as carvedilol to maximise patient outcomes. Further randomized controlled trials should be conducted to examine the effects of administering high dosages of N-acetylcysteine with beta blocker agents perioperatively. This would better elucidate the benefits of administering N-acetylcysteine in order to maximise patient outcomes.

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Figure Legends

Fig 1: Flow chart of study identification

Fig 2: Meta analytic estimates of acute kidney injury comparing Experiment (NAC) to Control

Fig 3: Meta analytic estimates of acute kidney injury comparing perioperative usage to Control

Fig 4: Meta analytic estimates of acute kidney injury comparing intraoperative usage to Control

Fig 5: Meta analytic estimates of acute kidney injury comparing high dosage to Control

Fig 6: Meta analytic estimates of acute kidney injury comparing low dosage to Control

Fig 7: Meta analytic estimates of in hospital mortality comparing Experiment (NAC) to Control

Fig 8: Meta analytic estimates of requirement for renal replacement therapy comparing Experiment to Control

Fig 9A: Meta analytic estimates of LOS in ICU comparing Experiment to Control (Mean and SD not approximated)

Fig 9B: Meta analytic estimates of LOS in ICU comparing Experiment to Control (Mean and SD approximated)

Fig 10: Funnel plot of complication

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