Use of N-acetylcysteine to reduce post-cardiothoracic surgery complications: a meta-analysis

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Summary
Post-cardiothoracic surgery (CTS) complications (e.g. myocardial injury, renal dysfunction, atrial fibrillation) may occur as a result of enhanced systemic inflammation, perhaps provoked by an oxidative stress response. N-acetylcysteine (NAC) is a free radical scavenger antioxidant agent that may attenuate this physiologic response and reduce post-CTS complications. Thus, a meta-analysis was performed to help characterize the potential beneficial effects of perioperative NAC administration in patients undergoing CTS. A systematic literature search in MEDLINE, EMBASE and the Cochrane Library was conducted through April 2008. A search strategy using medical subject headings and text keywords was performed. Results are reported as odds ratios or weighted mean differences with accompanying 95% confidence intervals (CIs). Studies were pooled using a fixed-effect model. The primary outcomes included atrial fibrillation (AF), myocardial infarction (MI), stroke, acute kidney injury (AKI), need for renal replacement therapy (RRT), mortality and total hospital length-of-stay (LOS). Upon meta-analysis of 13 trials (\(n = 1338\) subjects), the use of NAC appeared to statistically significantly lower the odds of developing post-CTS AF by 36% (95%CI 2—58%) (\(n = 6\) studies). This corresponded to an 8% (1—15%) pooled risk difference and a number-needed-to-treat of 13. NAC did not appear to significantly alter any of the other meta-analysis endpoints. The exclusion of the study utilizing only oral NAC therapy and the study with lower internal validity did not affect the overall conclusions of our meta-analysis. Currently, the most compelling data for using NAC in CTS patients is in post-CTS AF prevention. However, additional, larger randomized controlled trials evaluating this and other postoperative complication endpoints are needed.

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1. Introduction
The use of cardiopulmonary bypass (CPB) during cardiothoracic surgery (CTS), and the systemic exposure to these non-biologic surfaces, has been shown to provoke an oxidative stress response [1—3]. Oxidative stress can activate inflammatory processes causing systemic inflammation [4]. The use of CPB can increase serum markers including total peroxide, reactive oxidative metabolites, C-reactive protein (CRP) and interleukin-6 [5,6]. This may contribute to the development of post-CTS complications including myocardial injury [7,8], renal dysfunction [9] and atrial fibrillation (AF) [10,11]. Thus, agents with antioxidant properties may attenuate the oxidative stress [12—15] and resultant inflammation [2,3,16—18] seen in patients undergoing CTS and potentially reduce postoperative complications.

N-acetylcysteine (NAC) is a free radical scavenger antioxidant agent that reduces cellular oxidative damage [7,8,19]. In patients, NAC has been shown to reduce ischemia/reperfusion injury. In a canine model, NAC has been shown to prevent myocardial infarction extension after reperfusion and subsequent reperfusion arrhythmias [8]. Since inflammation is one of the proposed mechanisms of post-CTS AF, NAC may prevent post-CTS AF [20—25].

Several studies [13—15,20—29] have been conducted using NAC in patients undergoing CTS, with various postoperative complications being reported. These studies included relatively small numbers of patients and showed mixed results. This may be a result of low power to detect these differences and the pooling of results may clarify these areas of ambiguity. Thus, we performed a meta-analysis of relevant randomized clinical trials to determine the pooled effect of NAC use on post-CTS complications.
2. Materials and methods

2.1. Study selection

Three investigators (WLB, MWA, CIC) conducted a systematic literature search of MEDLINE from 1966 through April 2008, EMBASE from 1990 through April 2008 and the Cochrane Library for all relevant articles. The medical subject headings (MeSH) and key words N-acetylcysteine, NAC, acetylcysteine, mucosamt, and cardiac surgery, cardiothoracic surgery, open heart surgery, cardiopulmonary bypass, CPB, coronary artery bypass graft, CABG, CAB, valve surgery, valvular surgery were used. Results were limited to human studies and randomized controlled trials. A manual search of references from reports of clinical trials or review articles was performed to identify additional relevant studies. All three investigators independently reviewed all relevant articles, with disagreement resolved by consensus. Trials were included for analysis if they met the following inclusion criteria: randomized, controlled trials evaluating NAC use in CTS with adequately reported data on the incidence of at least one of the following postoperative endpoints: (1) atrial fibrillation; (2) myocardial infarction (MI); (3) stroke; (4) acute kidney injury (AKI) defined as either an increase in serum creatinine of at least 0.5 mg/dl and/or a 25% increase from baseline; (5) need for renal replacement therapy (RRT); (6) mortality or (7) total hospital length-of-stay (LOS). Studies using NAC in cardioplegia solutions only were excluded from this analysis.

2.2. Validity assessment

The following methodological features, most relevant to the control of bias, were assessed: randomization and masking of treatment allocation and blinding. All studies were reviewed and evaluated by three reviewers (WLB, ELB, CIC), with disagreement resolved by consensus.

2.3. Data abstraction

All data was independently abstracted by three investigators (MWA, ELB, CIC) through the use of a standardized data abstraction tool. Disagreements were resolved by consensus. The following information was sought from each article: author identification, year of publication, study design (randomized, placebo or active controlled, blinded or open-label), study population, sample size, duration of patient follow-up, NAC regimen used (route, dosing regimen, and total cumulative dose given), type of surgery performed (coronary artery bypass graft [CABG], valve, or combination surgery), label), study population, sample size, duration of patient follow-up, NAC regimen used (route, dosing regimen, and total cumulative dose given), type of surgery performed (coronary artery bypass graft [CABG], valve, or combination surgery), use of CPB, definitions of and data for aforementioned study endpoints. Attempts were made to contact authors of included studies in order to clarify or collect additional data.

2.4. Statistical analysis

The estimates of AF, MI, stroke, AKI, need for RRT and mortality in the NAC and placebo groups were treated as dichotomous variables and total hospital LOS was treated as continuous variable. Information from individual trials was combined using a general inverse variance-based method, which incorporates a fixed-effect model and assumes that studies under examination share a common true effect size, that the sampling distribution of these effects is normal, and that all the variability is due to sampling error (homogeneity assumption). In this model, the weights of individual studies correspond to the inverse of the total variance for each study. The pooled estimates of effect were reported as either odds ratio (ORs) (for dichotomous data) or weighted mean differences (WMDs) (for continuous data) with accompanying 95% confidence intervals (CIs). Calculations of ORs are problematic for individual studies with an absence of events in the treatment and/or placebo group. For these studies, a nominal value (0.5) was added in all 2 x 2 cells to enable calculation of ORs.

The assumption of homogeneity (presence or absence of statistical heterogeneity) was tested with both the Cochrane Q and I² statistics. We decided a priori that in the case the assumption of homogeneity was rejected for any endpoint (Q statistic p < 0.10 or I² > 50%) a random-effects model would be applied to estimate the variance component associated with between-study variation for that endpoint. According to this method, the variance for each individual study in the meta-analysis is the sum of within- and between-study components of the variance. The assumption of homogeneity was not rejected for any endpoint, thus only the results of fixed-effects models are reported in this paper.

Egger’s weighted regression statistics and a visual inspection of funnel plots were used to assess the presence of publication bias. The funnel plot is a pictorial representation of each study plotted by its effect size (OR) on the horizontal axis and variance (standard error of the log OR) on the vertical axis. If the plot represents an inverted symmetrical funnel then publication bias less likely. Inversely, if no inverted plot is seen, a greater likelihood of publication bias exists [30].

To establish the effect of heterogeneity between studies on the conclusions of this meta-analysis, subgroup and sensitivity analyses were conducted where applicable. The effect of variations in the route of administration, surgical technique (on- or off-pump CPB surgery) and methodological quality (excluding studies not specifying the use of double-blinding and placebo-control) were assessed.

All statistics were performed using StatsDirect statistical software, version 2.4.5 (StatsDirect, Cheshire, UK).

3. Results

The initial search yielded 37 potential literature citations. Of these, only 18 were randomized, controlled trials in humans. Five of the 18 were excluded for reasons depicted in Fig. 1. Thus a total of 13 randomized, controlled trials [13–15,20–29] (evaluating n = 1338 subjects) were included in this meta-analysis. A detailed summary of each included study, including surgery type and the NAC dosing regimen used can be found in Table 1.

All included trials were conducted between the years of 2003 and 2008 and had sample sizes ranging from 20 to 295 patients. All but two studies [15,20] were double-blinded and placebo-controlled. The study by Orhan and colleagues [20] stated they blinded the surgeon and internist, but no placebo...
was used. Sucu and colleagues used a saline control, but the extent of blinding, if any, was unclear. All the patients in 8 of the 13 studies underwent CTS using CPB, in the remaining 5 studies [24–26,28,29] a small percentage of patients (1–7%) underwent off-pump surgery. Six studies [13–15,20,21,23] enrolled patients undergoing CABG surgery only, while seven allowed valve patients to be enrolled [22,24–29]. Six studies

### Table 1

Characteristics of included randomized, controlled trials.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Double-blinding</th>
<th>Control group</th>
<th>Percent on-pump</th>
<th>Surgery type</th>
<th>NAC regimen used (route, dose, duration)</th>
<th>Study endpoints reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ozaydin, 2008 (n = 115)</td>
<td>Yes</td>
<td>Placebo</td>
<td>95%</td>
<td>C/2BG and/or valve</td>
<td>50 mg/kg IV 1 h before surgery and 50 mg/kg/day for 48 h post-CTS</td>
<td>Atrial fibrillation stroke, mortality, LOS</td>
</tr>
<tr>
<td>Adabag, 2008 (n = 102)</td>
<td>Yes</td>
<td>Placebo</td>
<td>93%</td>
<td>C/2BG and/or valve</td>
<td>600 mg PO × 14 doses starting 1200 mg IV at anesthesia induction every 12 h × 3</td>
<td>AKI, RRT, mortality, LOS</td>
</tr>
<tr>
<td>Sisillo, 2008 (n = 254)</td>
<td>Yes</td>
<td>Placebo</td>
<td>90%</td>
<td>C/2BG and/or valve</td>
<td>150 mg/kg IV bolus at first incision, then 25 mg/kg/h × 24 h</td>
<td>Atrial fibrillation AKI, RRT, stroke, mortality</td>
</tr>
<tr>
<td>Wijeysundera, 2007 (n = 175)</td>
<td>Yes</td>
<td>Placebo</td>
<td>98%</td>
<td>C/2BG and/or valve</td>
<td>50 mg/kg IV after anesthesia induction</td>
<td>Atrial fibrillation mortality, LOS</td>
</tr>
<tr>
<td>Haase, 2007 (n = 60)</td>
<td>Yes</td>
<td>Placebo</td>
<td>100%</td>
<td>C/2BG and/or valve</td>
<td>150 mg/kg IV bolus after anesthesia induction, then 50 mg/kg IV over 4 h</td>
<td>Atrial fibrillation AKI, RRT, mortality</td>
</tr>
<tr>
<td>El-Hamamy, 2007 (n = 100)</td>
<td>Yes</td>
<td>Placebo</td>
<td>100%</td>
<td>C/2BG</td>
<td>600 mg PO 1 day pre-CTS, 150 mg/kg IB bolus at first incision, then 12.5 mg/kg/h × 24 h</td>
<td>Atrial fibrillation stroke, MI, mortality, LOS</td>
</tr>
<tr>
<td>Orhan, 2006 (n = 20)</td>
<td>No</td>
<td>Routine treatment</td>
<td>100%</td>
<td>C/2BG</td>
<td>150 mg/kg IV bolus after anesthesia induction</td>
<td>Atrial fibrillation mortality, LOS</td>
</tr>
<tr>
<td>Ristikankare, 2006 (n = 77)</td>
<td>Yes</td>
<td>Placebo</td>
<td>100%</td>
<td>C/2BG</td>
<td>100 mg/kg IV bolus after anesthesia induction, then 50 mg/kg IV over 4 h</td>
<td>Atrial fibrillation AKI, RRT, stroke, mortality</td>
</tr>
<tr>
<td>Burns, 2005 (n = 295)</td>
<td>Yes</td>
<td>Placebo</td>
<td>99%</td>
<td>C/2BG and/or valve</td>
<td>600 mg IV at anesthesia induction and CPB weaning, then 600 mg IV at 12 and 24 h after CPB dose</td>
<td>AKI, RRT, stroke, mortality</td>
</tr>
<tr>
<td>Sucu, 2004 (n = 40)</td>
<td>Unclear</td>
<td>Unclear</td>
<td>100%</td>
<td>C/2BG</td>
<td>25 mg/kg every 12 h for 3 days pre-CTS, 100 mg/kg in CPB prime, then 20 mg/kg/h until end of CPB</td>
<td>MI</td>
</tr>
<tr>
<td>Fischer, 2004 (n = 40)</td>
<td>Yes</td>
<td>Placebo</td>
<td>100%</td>
<td>C/2BG</td>
<td>100 mg/kg in CPB prime, then 20 mg/kg/h day at 24 h post-CPB</td>
<td>RRT, MI, mortality</td>
</tr>
<tr>
<td>Eren, 2003 (n = 20)</td>
<td>Yes</td>
<td>Placebo</td>
<td>100%</td>
<td>C/2BG</td>
<td>100 mg/kg for 1 h before CPB, then 40 mg/kg/h day duration</td>
<td>Atrial fibrillation stroke, MI, mortality</td>
</tr>
<tr>
<td>Tossios, 2003 (n = 40)</td>
<td>Yes</td>
<td>Placebo</td>
<td>100%</td>
<td>C/2BG</td>
<td>100 mg/kg in CPB prime, then 20 mg/kg/h day at 24 h post-CPB</td>
<td>MI, mortality</td>
</tr>
</tbody>
</table>

CABG: coronary artery bypass grafting; CPB: cardiopulmonary bypass; CTS: cardiothoracic surgery; IV: intravenous; MI: myocardial infarction; n: number of patients; PO: by mouth.

a Extent to which of blinding was attempted was unclear, study does not use the use of a saline control.

b Study states surgeon and internists were blinded.
therapy [29] and the study with weaker methodology (not double-blinded and placebo-controlled) [20] did not affect the overall conclusions of our meta-analysis. Unpublished data were obtained for one study [25] for the AKI endpoint. When this data was incorporated into the AKI analysis, no significant changes were seen in our results [odds ratio, 0.87 (95% CI 0.67–1.13)].

4. Comment

In this meta-analysis of 13 randomized, controlled trials [13–15,20–29], patients receiving perioperative NAC had lower odds of developing post-CTS AF, but did not appear to derive statistically significant benefits for any other meta-analysis endpoint. Of note, trends towards reductions in the

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Base-case analysis</th>
<th>Excluding studies with weaker methodologies*</th>
<th>Excluding studies using oral NAC only</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dichotomous variables (results presented as odds ratios with 95% confidence intervals)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post-CTS AF</td>
<td>0.64 (0.42, 0.98) (n = 6)</td>
<td>0.63 (0.43, 0.99) (n = 5)</td>
<td>0.64 (0.42, 0.98) (n = 6)</td>
</tr>
<tr>
<td>AKI</td>
<td>0.86 (0.66, 1.12) (n = 6)</td>
<td>0.86 (0.66, 1.12) (n = 6)</td>
<td>0.81 (0.61, 1.08) (n = 5)</td>
</tr>
<tr>
<td>RRT</td>
<td>0.99 (0.50, 1.95) (n = 7)</td>
<td>0.99 (0.50, 1.95) (n = 7)</td>
<td>0.92 (0.44, 1.90) (n = 6)</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.81 (0.34, 1.95) (n = 5)</td>
<td>0.81 (0.34, 1.95) (n = 5)</td>
<td>0.81 (0.34, 1.95) (n = 5)</td>
</tr>
<tr>
<td>MI</td>
<td>0.73 (0.34, 1.57) (n = 7)</td>
<td>0.78 (0.35, 1.71) (n = 6)</td>
<td>0.73 (0.34, 1.57) (n = 7)</td>
</tr>
<tr>
<td>Mortality</td>
<td>0.71 (0.41, 1.31) (n = 12)</td>
<td>0.73 (0.40, 1.31) (n = 11)</td>
<td>0.74 (0.40, 1.37) (n = 11)</td>
</tr>
<tr>
<td>Continuous variables (results presented as a weighted mean difference with 95% confidence interval)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Length-of-stay</td>
<td>0.07 (0.28, 0.42) (n = 4)</td>
<td>−0.06 (−0.82, 0.70) (n = 3)</td>
<td>0.08 (0.27, 0.43) (n = 3)</td>
</tr>
</tbody>
</table>

AF: atrial fibrillation; AKI: acute kidney injury; CTS: cardiothoracic surgery; MI: myocardial infarction; NAC: N-acetylcysteine; RRT: renal replacement therapy.

analysis has demonstrated that NAC reduces the risk of renal dysfunction [26,34,35]. A recent meta-analysis showed that NAC significantly reduces the risk of developing post-CTS AF (hazard ratio: 0.71 to 0.86) [35]. We do not believe that publication bias significantly affected our results, as the funnel plot could not rule out the presence of publication bias, even when conducting this sensitivity analysis where we re-analyzed our results without the study by Ozaydin and colleagues [25].

The high-risk for or currently diagnosed with chronic kidney disease, which is in agreement with another recently published meta-analysis [37]. We did observe a non-significant 14% decline in the odds of patients having AKI (defined as at least a 0.5 mg/dl or 25% increase in serum creatinine), and while we did not see an effect on the need for RRT with NAC, data suggests that even a minimal increase in serum creatinine (>0.5 mg/dl) was associated with a substantial decrease in 30-day survival [hazard ratio: 5.76 (95%CI 3.86—8.61)] [35].

NAC, a source of sulphydryl groups, stimulates glutathione synthesis, enhances glutathione S-transferase activity, promotes detoxification, and acts directly on reactive oxidant radicals [38]. It is known that myocardial ischemia in general is characterized by a reduction in cellular sulphydryl levels, and that CPB during CTS stimulates leucocytes to produce oxygen free radicals, both leading to oxidative damage during reperfusion [38,39]. Various studies have demonstrated the ability of NAC administration to attenuate the reactive oxygen species-mediated myocardial stress induced by the CPB, and increase glutathione levels, preventing oxidoinflammatory damage [13,15,39,40]. These properties make NAC a potentially useful therapeutic option for preventing commonly encountered post-CTS complications such as kidney injury and atrial fibrillation, given their known etiology related to oxidative stress and inflammation-related damage [9—11,13,40].

There are some limitations to this meta-analysis that should be noted. First, for the post-CTS AF endpoint, the utilization of higher intensity beta-blockade and amiodarone prophylaxis was not the standard amongst most constituent studies [20—25]. As such, the adjunctive use of NAC in addition to these proven prophylactic strategies is not known. However, the use of an adjunctive prophylactic strategy that might further prevent post-CTS AF without reducing blood pressure or heart rate would be advantageous [41]. The results of this meta-analysis support further research of this kind. This is especially true since NAC may be able to reduce other CTS complications as well, although our meta-analysis was not powered to determine whether this is actually true. Secondly, while studies utilized different NAC doses and schedules, we were unable to assess this heterogeneity on CTS outcomes, thus we cannot discern the optimal NAC dosing from our meta-analysis. Next, we did include non-double-blinded, non-placebo-controlled studies. Such studies are often subject to additional biases and thus thought to have a lower internal validity. While we felt it was advantageous to include these trials in order to provide additional power to our meta-analysis, we did conduct sensitivity analysis whereby we re-analyzed our results including only the studies utilizing the more rigorous double-blind, placebo-controlled design. No noteworthy changes in any of the study endpoints were noted upon conducting this sensitivity analysis, thus strengthening our confidence in the meta-analysis’ conclusions. Finally, as with any meta-analysis, the potential for publication bias is a concern. While visual inspection of our meta-analysis’ funnel plot could not rule out the presence of publication bias, review of Egger’s weighted regression funnel plot statistics suggest that it was unlikely that publication bias significantly affected our study results.
4.1. Recommendations for future research

As mentioned above, only trends toward reductions in stroke, MI and mortality were seen in our meta-analysis. More work needs to be done to evaluate these endpoints in larger trials using standard definitions before any definitive conclusions can be made. At a minimum, it appears reasonable to assume that post-CTS AF can be reduced with NAC without significantly increasing a patient’s risk of these detrimental endpoints. However, the exact dose of NAC to use and the optimal length of therapy are still unknown. Thus, future studies should directly compare various doses of NAC, including varying lengths of therapy (perhaps extending it through postoperative day 4 in order to cover the most vulnerable period for AF development). These studies should also evaluate the impact of adding NAC on top of already proven therapies for preventing post-CTS AF, including beta-blockers, amiodarone and potentially HMG-CoA reductase inhibitors [42].

5. Conclusions

NAC appears to be a promising but not proven strategy for reducing post-CTS complications. Currently, the most compelling data for using NAC in CTS patients is in post-CTS AF prevention. However, additional, larger randomized controlled trials evaluating this and other postoperative complication endpoints are needed.

References


