N-acetylcysteine to reduce renal failure after cardiac surgery: a systematic review and meta-analysis

[Étude méthodique et méta-analyse : la N-acétylcystéine dans la réduction de l'insuffisance rénale à la suite d'une chirurgie cardiaque]

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Purpose: To assess the effect of N-acetylcysteine (NAC) on acute renal failure and important clinical outcomes after cardiac surgery.

Methods: Two reviewers performed literature searches, using EMBASE and PubMed, of randomized controlled trials investigating the renoprotective effect of N-acetylcysteine in cardiac surgery. Treatment effects were calculated as relative risks (RR) with 95% confidence intervals (CI). Heterogeneity and publication bias were assessed using the I^2 test and funnel plots, respectively. Meta regression was performed to assess the effect of baseline renal function and the use of aprotinin on renal function.

Results: Seven randomized controlled trials (RCTs) ($n = 1000$) were identified. No study could demonstrate, either independently or meta-analytically, an improvement in the postoperative increase in creatinine, mortality (RR 0.93, 95% CI 0.4 to 2.07), renal failure requiring renal replacement therapy (RR 1.01, 95% CI 0.49 to 2.12), myocardial infarction (RR 0.88, 95% CI 0.36 to 1.88), atrial fibrillation (RR 0.88, 95% CI 0.70 to 1.10), or stroke (RR 0.69, 95% CI 0.27 to 1.69). There was a small, though significant increase in postoperative blood loss among patients treated with NAC (weighted mean difference 119 mL 95% CI 51, 187). After meta regression neither increase in postoperative creatinine ($r^2 = 0.33$) nor renal replacement therapy ($r^2 = 0.04$) was associated with the baseline creatinine or with NAC dose ($r^2 = 0.04$).

Conclusion: This analysis did not find that treatment with NAC was associated with clinical renal protection during cardiac surgery, or improvement in other clinical outcomes.

Objectif : Évaluer l'effet de la N-acétylcystéine (NAC) sur l'insuffisance rénale aiguë et les événements cliniques majeurs après une chirurgie cardiaque.

Méthode : Deux analystes ont réalisé des recherches de littérature dans les bases de données EMBASE et PubMed pour trouver des études randomisées contrôlées étudiant l'effet néphroprotecteur de la N-acétylcystéine en chirurgie cardiaque. Les effets thérapeutiques ont été calculés en tant que risques relatifs (RR) avec des intervalles de confiance (IC) de 95 %. L'hétérogénéité et le biais de publication ont été évalués à l'aide du test I^2 et de graphiques en entonnoir (« funnel plots »), respectivement. Une méta-régression a été réalisée afin d'évaluer l'impact de la fonction rénale de base et de l'utilisation d'aprotinine sur la fonction rénale.

Résultats : Sept études randomisées contrôlées (ERC) ($n = 1000$) ont été identifiées. Aucune étude n'a pu démontrer, de façon indépendante ou par méta-analyse, une amélioration dans l'élévation postopératoire de la créatinine, de la mortalité (RR 0,93, IC 95 % 0,4 à 2,07), de l'insuffisance rénale nécessitant une transplantation rénale (RR 1,01, IC 95 % 0,49 à 2,12), d'infarctus du myocarde (RR 0,88, IC 95 % 0,36 à 1,88), de fibrillation auriculaire (RR 0,88, IC 95 % 0,70 à 1,10), ou d'accident vasculaire cérébral (RR 0,69, IC 95 % 0,27 à 1,69). Il y a eu une petite augmentation, tout de même significative, des pertes sanguines postopératoires chez les patients traités avec la NAC (différence moyenne pondérée 119 mL IC 95 % 51, 187). Après la méta-régression, il n'y pas eu d'association entre l'augmentation de la créatinine postopératoire ($r^2 = 0,33$) ou la transplantation rénale ($r^2 = 0,04$) et la créatinine de base ou la dose de NAC ($r^2 = 0,04$).

CAN J ANESTH 2008 / 55: 12 / pp 827-835

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This investigation was supported by funds from the R. Fraser Elliot endowment.

Conflicts of interest: None declared.

Accepted for publication August 12, 2008.

Revision accepted September 30, 2008.

Conclusion : Cette analyse n'a pas démontré que le traitement avec la NAC a été associé à une protection rénale clinique pendant la chirurgie cardiaque, ni d'amélioration dans les autres événements cliniques.

Acute kidney injury (AKI) or renal impairment is an established complication of cardiac surgery occurring with an incidence up to 30%, depending on the definition. In recent years it has become obvious that postoperative renal dysfunction and failure does not merely represent an inconvenient complication prolonging intensive care treatment, infectious complications and hospitalization, but that AKI directly contributes to risk of mortality.¹⁻⁴

Predisposing factors for the development of AKI after cardiac surgery are well documented and include advanced age, preoperative renal impairment, emergent/urgent or re-do surgery, complexity of the surgery, cardiopulmonary bypass duration, diabetes, congestive heart failure, left ventricular dysfunction, bleeding and blood product transfusion, preoperative use of intra-aortic balloon pump and chronic obstructive pulmonary disease.^{1,2,4-14}

Pharmacological interventions to prevent AKI after cardiac surgery have been extensively investigated. To date, no agent has conferred renal protection.¹⁵⁻³⁹ Considerable interest has developed in the potential for N-acetylcysteine (NAC) to exert a renoprotective effect in patients undergoing cardiac surgery. Due to the beneficial effect of NAC on contrast nephropathy and its purported anti-inflammatory effects, several studies were undertaken to evaluate the renoprotective effects after cardiac surgery.⁴⁰⁻⁴⁵ At this point, none of these studies has been able to demonstrate a significant benefit; although, taken individually, they were relatively small and underpowered to demonstrate an effect on the need for renal replacement therapy (RRT). Therefore, we conducted a systematic review and meta-analysis of the randomized controlled trials (RCTs) utilizing NAC in cardiac surgery requiring cardiopulmonary bypass, to determine the effect of NAC on AKI and on other important clinical outcomes.

Methods

This review adhered to the QUOROM recommendations.⁴⁶

Search strategy

Two reviewers (F.N. and W.S.B.) searched PubMed (up to May 2008) and EMBASE (1980 to May 2008),

FIGURE 1 QUORUM diagram and search strategy.

and PubMed for RCTs comparing N-acetylcysteine to placebo in cardiac surgery. The text words and medical subject headings included: *N-acetylcysteine*, *cardiac surgery*, *cardiopulmonary bypass/CPB/CABG*, *high-risk*, *renal dysfunction*, *renal failure*, *renoprotection*. Included trials had to report any of the following outcomes: death, stroke, myocardial infarction, atrial fibrillation, or acute renal failure. The outline of the search strategy is seen in Figure 1.

Quality assessment and data abstraction

Two reviewers (F.N. and W.S.B.) performed quality assessment and data abstraction. Randomized controlled trial quality was rated with regard to randomization, allocation concealment, blinded outcome assessment, and dropouts. Data were abstracted on death, acute renal failure, RRT/dialysis, stroke, infarction, atrial fibrillation, red cell transfusion and reoperation. We accepted the outcome definitions used by the original researchers. A 25% increase from baseline serum creatinine was used as a surrogate measure of renal outcome by authors of all included studies. For the purpose of this meta-analysis and for consistency, we have adopted this surrogate measure in defining AKI.

TABLE I Assessment of study quality

STUDY	Randomized method	Concealment	Blinding	Intention to treat	Treatment effect assumed for calculating sample size
Burns <i>et al.</i> ⁴⁰ JAMA 2005	1:1 Computer generated alternating blocks of 4 and 6	Drugs prepared In pharmacy	Patients Clinicians Data collectors	Yes	50% reduction in primary outcome (event rate decrease from 30% to 15%)
Ristikankare <i>et al.</i> ⁴¹ Br J Anaesth 2006	No details	Drugs prepared and randomized in pharmacy	Patients Clinicians	Yes	30% reduction in urine NAG
Haase <i>et al.</i> ⁴³ Crit Care Med 2007	1:1 Computer generated blocks of 10	Yes	Patients Clinicians Data collectors and Analysts	Yes	30 mmol difference in serum creatinine
El-Hamamsy <i>et al.</i> ⁴² JTCVS 2007	Not given	Not given	Patients Clinicians	Yes	25% reduction in troponin T
Wijesundera <i>et al.</i> ⁴⁴ Can J Anesth 2007	1:1 Computer generated numbers in blocks of 4	Drugs prepared and randomized in pharmacy	Patients Clinicians Data collectors	Yes	5% change in eGFR
Sisillo <i>et al.</i> ⁴⁵ Crit Care Med 2008	1:1 Random generated number	No details	Patients Clinicians	Yes	40% reduction in ARF
Barr <i>et al.</i> ⁴⁷ Crit Care Med 2008	Not given	Drugs prepared and randomized in pharmacy	Patients Clinicians	Yes	25% improvement in creatinine clearance

ARF = acute renal failure; NAG = N-acetyl- β -D-glucosaminidase, AKI = acute kidney injury, eGFR = estimated glomerular filtration rate.

Analyses

We employed Review Manager 4.2.10 (Cochrane Collaboration) to combine treatment effects among studies with the same design. All analyses were performed on an intention-to-treat basis. Effects on dichotomous outcomes were expressed as relative risk (RR) with 95% confidence intervals (CI). Continuous outcomes were expressed as weighted mean differences with 95% CI. Heterogeneity was assessed with the I-statistic. In all analyses the random-effects model was used. Statistical significance was defined by a two-tailed $P \leq 0.05$. For the purposes of this meta-analysis, the outcomes compared were increase in serum creatinine by 25% from baseline mortality, RRT, blood transfusion, re-exploration, atrial fibrillation, myocardial infarction and stroke. For analysis the effects of baseline creatinine and dose of NAC on the outcomes we used meta-regression.^A Meta-regression was performed using

S-plus/R statistical software and the MiMa function.^B Funnel-plots were used to assess for publication bias.

Results

The search strategy identified seven trials enrolling 1,000 patients.^{40-45,47} The details of the quality of the studies identified are outlined in Table I. All studies were RCTs, and analyzed on the basis of intention-to-treat. Six of the seven trials were blinded.

The design and characteristics of the studies are shown in Table II. There was variability in the NAC dosing regimens used across the seven trials, with the average dose received ranging from 100 mg to 1000 mg·hr⁻¹. Inclusion criteria of all the studies except one, selected patients at moderate-to-high risk of developing postoperative renal injury. Other patient characteristics were similar across all studies. The pri-

A Meta-regression is a tool which can be used to measure the variability of a given response. By assessing the effects of a covariate, (in this case both baseline creatinine and the dose of NAC) on the outcome of interest, (in this case the odds ratio of post operative renal failure), we can measure the extent that this covariate explains the heterogeneity. The r^2 has been used to measure the extent to which a covariate explains the hetero-

geneity. In this analysis we found a large degree of heterogeneity in the baseline creatinine of the study populations and the dose of NAC used in the studies.

B Veichtbauer: MiMa: An S-plus/R function to fit meta-analytic mixed-random-and fixed effects models [computer and software manual] Available from URL; <http://www.wvbauer.com> (accessed Feb 9/2007).

TABLE II Patient characteristics, dosing of N-acetylcysteine and outcome measures of included studies

Study	Inclusion Criteria	Dose of N-acetylcysteine	Primary outcome	Secondary outcomes
Burns <i>et al.</i> ⁴⁰ JAMA 2005	High risk for AKI 2 of : Creatinine > 120 $\mu\text{mol}\cdot\text{L}^{-1}$ Grade 3-4 left ventricular function Age > 70 Diabetes, Complex surgery	600 mg X 4 Induction Weaning from CPB 12 hr postoperatively 24 hr postoperatively	Incidence of AKI - absolute increase in serum creatinine of 44 μmol or a 25% increase over baseline. Postoperative 5 days	In hospital mortality RRT, MI, stroke Infection, ICU stay Hospital stay
Ristikankare <i>et al.</i> ⁴¹ Br J Anaesth 2006	Creatinine > 100 μmol Excluded: Dialysis, prior treatment, Serum creatinine > 400 $\mu\text{mol}\cdot\text{L}^{-1}$	Bolus 150 $\text{mg}\cdot\text{kg}^{-1}$ 50 $\text{mg}\cdot\text{kg}^{-1}$ for 4 hr 100 mg for 16 hr	Incidence of AKI - increase in NAG/ creatinine ratio > 30%. Postoperative 5 days	30 day mortality RRT, ICU stay
Sisillo <i>et al.</i> ⁴⁵ Crit Care Med 2008	Calculated Cr Cl (Cockcroft-Gault) 60 $\text{mL}\cdot\text{min}^{-1}$ Excluded patients with RRT	Bolus 1200 mg Then 1200 mg x 3 q 12 hr	Incidence of AKI - increase in serum creatinine > 25% from baseline in first 72hr Postoperative 72 hr	Mortality Maximal change in creatinine clearance Doubling of serum creatinine. RRT, MI, mechanical ventilation ICU stay
El-Hamamsy <i>et al.</i> ⁴² J Thorac Cardiovasc Surg 2007	Primary CABG. Excluded emergency, AMI < 3/52, Redo, > 80 yr, ejection fraction < 20%	Oral bolus T-1 600 mg 150 $\text{mg}\cdot\text{kg}^{-1}$ <i>iv</i> bolus 12.5 $\text{mg}\cdot\text{kg}^{-1}$ over 24 hr levels	Troponin T levels-25% reduction in postoperative levels	Rate of MI (CKMB > 50% +/- Q waves) Renal function (creatinine) Bleeding Low cardiac output syndrome Arrhythmias, mean CKMB levels
Haase <i>et al.</i> ⁴³ Crit Care Med 2007	High risk for AKI, 1 or more of: > 7, Creat > 120 $\mu\text{mol}\cdot\text{L}^{-1}$, NYHA III/IV, Valve/complex/redo surgery IDDM. Excluded: ESRD Creat > 300 $\mu\text{mol}\cdot\text{L}^{-1}$, emergency	300 $\text{mg}\cdot\text{kg}^{-1}$ <i>iv</i> over 24 hr	Absolute change in serum creatinine of 50 $\mu\text{mol}\cdot\text{L}^{-1}$. Postoperative 5 days	Relative change in serum creatinine Peak creatinine Absolute / relative change in cystatin C Urinary output, RRT Mechanical ventilation Chest tube drainage, Reoperation Atrial fibrillation, ICU stay Hospital stay, mortality
Wijesundera <i>et al.</i> ⁴⁴ Can J Anesth 2007	Age > 18 Elective CABG +/- valve surgery eGFR (Cockcroft-Gault < 60 $\text{mL}\cdot\text{min}^{-1}$) Excluded: Creat. > 300 $\mu\text{mol}\cdot\text{L}^{-1}$ or RRT IABP or vasoactive meds	100 $\text{mg}\cdot\text{kg}^{-1}$ <i>iv</i> bolus Then 20 $\text{mg}\cdot\text{kg}^{-1}\cdot\text{hr}^{-1}$ until 4 hr after CPB	72 hr % change in eGFR. Postoperative 72 hr	Incidence of ARF (absolute increase in serum creatinine of 44 μmol or a 25% increase over baseline) RRT, Vasoactive meds IABP, Transfusion Atrial fibrillation, stroke
Barr <i>et al.</i> ⁴⁷ Crit Care Med 2008	Age > 18 Elective/urgent/emergency surgery. eGFR (Cockcroft-Gault < 40 $\text{mL}\cdot\text{min}^{-1}$) Excluded: Hemodialysis	Oral T-1 1200 mg preop oral 600 mg 4 hr preop Oral 600 mg postop	Absolute change in eGFR Postoperative 72 hr	Weight change postoperative 72 hr eGFR T+14 ICU stay Hospital stay RRT Mortality

AKI = acute kidney injury, AMI = acute myocardial infarction; ARF = acute renal failure; CABG = coronary artery bypass graft; CKMB = creatinine kinase MB, CPB = cardiopulmonary bypass, eGFR = estimated glomerular filtration rate, ESRD = end-stage renal disease; IABP = intraaortic balloon pump, ICU = intensive care unit; IDDM = insulin-dependent diabetes mellitus MI = myocardial infarction, NAG = N-acetyl- β -D-glucosaminidase; RRT = renal replacement therapy.

TABLE III Outcomes

Comparison or outcome	Studies	Participants	Statistical method	Effect estimate	Test for heterogeneity I^2
Mortality	7	1000	RR random (95% CI)	0.93 [0.41,2.07]	6.0%
Renal replacement therapy	7	1000	RR random (95% CI)	1.01 [0.49,2.12]	0%
Baseline creatinine	7	1000	WMD random (95%CI)	0.02[-0.5,0.10]	60.7%
>25% increase creatinine from baseline	7	1000	RR random (95% CI)	0.80 [0.62,1.05]	0%
Use of aprotinin	6	710	RR random (95%CI)	1.53 [0.53,4.53]	93.1%
Postoperative blood loss	4	415	WMD Fixed 95% CI	119 [51,187]	32.1%
Reexploration	6	923	RR random (95% CI)	1.32 [0.71,2.45]	0%
Low output state	6	753	RR random (95% CI)	0.78 [0.43,1.43]	0%
Stroke	4	532	RR random (95% CI)	0.71 [0.28,1.80]	0%

RR = relative risk; CI = confidence interval; WMD = weighted mean difference.

FIGURE 2 Forrest plot: The effect of N-acetylcysteine and the relative risk of a 25% rise in postoperative creatinine. The diagram is subdivided by the use of aprotinin. The relative risk is calculated using the random effects model. Each square represents the weighting of that study in the overall relative risk; the lines represent the 95% confidence interval. Heterogeneity is calculated using the I^2 test.

mary study endpoint was the development of AKI in all but one of the studies. There was some variation in the definition and markers of AKI, but all studies reported a 25% increase in serum creatinine from baseline. Increase in serum creatinine by 25% is a surrogate measure of renal failure.^{48,49} Secondary outcome measures varied, but all seven studies reported RRT and mortality. The studies varied with regard to the time period over which the change in renal

function occurred, ranging from 72 hr^{44,45} to five days postoperatively.^{40,41,43}

Table III summarizes the results of the meta-analysis. This analysis did not demonstrate any significant effects of NAC on outcomes. N-acetylcysteine was neither protective nor deleterious in its impact on an increase in serum creatinine by 25% from baseline (RR 0.80, 95%CI 0.62 to 1.05). There was no statistically significant difference between treatment and con-

FIGURE 3 Meta-regression: Showing the relationship between preoperative creatinine expressed in $\text{mg}\cdot\text{dl}^{-1}$ and the log odds ratio for the proportion of patients with a 25% postoperative increase in creatinine. The size of the bubbles around each point reflects the weighting that the study has on the overall relationship. The regression relationship is expressed as r^2 .

trol groups in the requirement for RRT (RR 1.01, 95% CI 0.49 to 2.12), the prevalence of which was 2.8%. There was wide variance in baseline creatinine between studies. A meta-regression analysis shows no significant relationship between preoperative serum creatinine and postoperative change in creatinine (Figure 3). However, there is a possibility that the beneficial effect of NAC is greater for patients with higher preoperative creatinine. This was not seen for RRT or for mortality. There is also a possibility that aprotinin use may counteract the beneficial effect of NAC (Figure 2). When studies are divided by frequency of the use of aprotinin, studies in which nearly all patients received aprotinin had a RR of renal failure of 1.0, while the two studies where aprotinin was never used had a RR of 0.76 (95% CI .57–1.03). In-hospital death occurred in 14 of 503 patients receiving treatment with NAC and 18 of 497 control patients (RR 0.93, 95% CI, 0.41 to 2.07).

Four studies measured postoperative blood loss. There was a small, though significant increase in postoperative blood loss among patients treated with NAC (weighted mean difference 119 mL 95% CI 51, 187). There was no indication of publication bias (Figure 4).

Discussion

This meta-analysis of seven well designed RCTs suggests that NAC does not confer renal protection in patients undergoing cardiac surgery. It has no significant impact on a 25% increase from baseline serum creatinine, which is a surrogate for acute renal failure necessitating RRT. The prevalence of RRT in these studies was 2.8%. Renal replacement therapy rates have previously been reported at 1.3–2.2% in derivation and validation cohorts.⁵⁰ The relatively high RRT rate in these studies most likely reflects the inclusion of patients at moderate-to-high risk for developing AKI

FIGURE 4 Funnel plot.

in the postoperative period. N-acetylcysteine was not associated with a reduction in RRT rates.

In addition, other important clinical outcomes such as perioperative mortality, stroke, myocardial infarction and atrial fibrillation were not improved by treatment with NAC. Somewhat surprisingly, our analysis found that there was increased postoperative blood loss in patients receiving NAC. A possible mechanism for this effect may be related to a direct anti-aggregating effect on human platelets through an increased bioavailability of platelet nitric oxide.⁵¹ N-acetylcysteine has also been found to potentiate the inhibition of platelet aggregation by nitroglycerin.⁵²

This analysis has several limitations. The meta-analytic tool is best used for hypothesis generation rather than hypothesis testing. Meta-analysis can be unreliable when multiple small studies, as seen in this analysis, are combined. Publication bias does not appear to be an issue in this study, as funnel plots show clearly that negative studies have been included (Figure 4). The quality of included trials is unlikely to have biased treatment effects since six studies were double-blinded, or evaluator-blinded. Allocation concealment was generally well described, abrogating the likelihood of increasing estimates of treatment benefit. Despite this meta-analysis, existing data still lack adequate power to conclusively determine whether NAC improves or worsens outcomes.

Meta-analysis is weakest and most controversial when studies disagree and there is heterogeneity. In our meta-analysis, the outcomes chosen for comparison are clinically important which is reflected in their repeated use by investigators of outcome after cardiac surgery. While our sample size is relatively small, there was little heterogeneity between the studies in terms of inclusion criteria or measured outcomes, although there is some variation in surrogate measures of outcome, definitions, and local practice guidelines. This analysis is further complicated by the issues surrounding perioperative blood loss and aprotinin. Aprotinin

was administered in five of the seven studies analyzed, either routinely⁴² or when the patient was deemed to be at high risk for bleeding^{43,44} or in accordance with local institution policy in operation at the time. This analysis does not allow us to fully assess the effect that aprotinin may have had in these studies. Aprotinin use was moderate, being used in approximately 43% of the studied patients, and was equally distributed between groups of the two trials which universally used NAC. There was no effect of NAC on postoperative creatinine. However, in the two trials where no patients received aprotinin, NAC was associated with a smaller proportion of patients who had a postoperative rise in creatinine (RR 0.78 95% CI 0.59–1.08 $P = 0.08$). We can only speculate as to whether rates for renal failure, reoperation or transfusion were affected by the use of aprotinin.^{53–56} Finally, this meta-analysis cannot evaluate the interrelationship between preexisting renal dysfunction, the dosages of NAC, and the renal toxicity that may have been conferred with aprotinin. Heterogeneity in baseline creatinine and NAC dosages may account for the lack of significance in NAC effect. Further clarification on the effects of NAC might be provided by an individual patient data meta-analysis.

In conclusion, this analysis suggests there is no renal protection with NAC in cardiac surgery patients. However, we are unable to fully assess the effects of NAC dosage, the use of aprotinin, and baseline renal function and the interrelationship of these factors on outcomes. Future trials, if undertaken, could address this issue, if designed to include large numbers of patients with similar baseline renal function receiving the same dosing regimen of NAC. In the meantime, individual patient data meta-analysis within existing studies may provide answers.

Acknowledgements

We sincerely thank the authors who responded in a very timely manner to our requests for additional information related to their respective studies. Drs. Burns and Chu provided the unpublished data on aprotinin. Dr. El-Hamansay provided details on renal failure, and on the incidence of bleeding. We thank Dr. Marenzi for confirming that aprotinin was not used in any of their patients. Finally, to Dr. Barr, for providing the unadjusted creatinine values and details of blood loss.

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