The Effect of N-Acetylcysteine on Creatinine Measurement: Protocol for a Systematic Review

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Abstract

Background: N-acetylcysteine (NAC) is an antioxidant which can regenerate glutathione and is primarily used for acetaminophen overdose. It is also a potential therapy to prevent iatrogenic acute kidney injury or slow the progression of chronic kidney disease. It has been considered in this context by many studies with mixed results. Notably, a biological-mechanism rationale for a protective effect of NAC has never been adequately reported. Among conflicting reports, there appears to be evidence that NAC may artificially lower measured serum creatinine without improving kidney function, potentially by assay interference. Given these mixed results, a systematic review of the literature will be conducted to determine whether there is an effect of NAC on kidney function measured with serum creatinine.

Objective: To determine the effect of NAC on kidney function.

Design: A systematic review and meta-analysis.

Settings: Prospective studies, with administration of NAC, in the absence of any other change in kidney function (such as contrast administration or surgery).

Patients: Adult humans aged 18 years old or more, either healthy volunteers or with chronic kidney disease, were administered with NAC. Populations having little to no kidney function such as in end-stage kidney disease will be excluded.

Measurements: Serum creatinine and/or cystatin C measurements before and after NAC administration.

Methods: An information specialist will assist in searching MEDLINE, EMBASE, and the Cochrane CENTRAL databases to identify all study types including randomized controlled trials, and prospective cohort studies reporting change in serum creatinine after NAC administration. Two reviewers will independently screen the titles and abstracts of the studies obtained from the search using predefined inclusion criteria and will then extract data from the full texts of selected studies. The weighted mean difference will be calculated for change in creatinine with NAC, using random-effects analysis. Quality assessment will be done with the Cochrane Risk of Bias tool for randomized trials and the Newcastle-Ottawa Scale for observational studies.

Results: The outcome of interest is kidney function as reported by either change in serum creatinine and/or serum cystatin C measurement for randomized trials or comparing baseline (pre-NAC dose) values and those following the NAC dose.

Limitations: Possible heterogeneity and publication bias and lack of mechanistic data.

Conclusions: This systematic review will provide a synthesis of current evidence on the effect of NAC on serum creatinine measurement. These findings will provide clinicians with guidelines and serve as a strong research base for future studies in this field.

Systematic review registration: This review is registered with PROSPERO, CRD42017055984

Abrégé

Contexte: La N-acétylcystéine (NAC) est un antioxydant capable de régénérer le glutathion et principalement utilisé pour traiter les cas de surdose d’acétaminophène. La NAC pourrait également s’avérer efficace comme traitement préventif de l’insuffisance rénale aiguë iatrogénique ou pour ralentir la progression de l’insuffisance rénale chronique. Cette substance a fait l’objet de plusieurs études dans ce contexte, mais les résultats demeurent mitigés. Notamment, il reste toujours à rapporter adéquatement une justification de l’effet protecteur de la NAC sur la base d’un mécanisme biologique. Parmi les rapports contradictoires, certaines données montreraient que la NAC abaisse artificiellement les valeurs de créatinine sérique mesurées sans améliorer la fonction rénale, potentiellement par interférence de l’essai. À la lumière de ces résultats
divergents, une revue systématique de la littérature sera effectuée pour déterminer si la NAC produit un effet sur la fonction rénale mesurée par la créatinine sérique.

Objectif: Mesurer l’effet de l’administration de NAC sur la fonction rénale.

Type d’étude: Une revue systématique de la littérature et une méta-analyse.

Cadre: Les études prospectives avec administration de NAC sans autres changements dans la fonction rénale; l’administration d’un produit de contraste ou une intervention chirurgicale, par exemple.

Sujets: Des adultes, volontaires sains ou atteints de néphropathie chronique, ayant reçu de la NAC. Seront exclues les populations dont la fonction rénale est faible ou inexistante; notamment, les cas d’insuffisance rénale terminale.

Mesures: Des mesures de la créatinine sérique et/ou de la cystatine C faites avant et après l’administration de NAC.

Méthodologie: Un documentariste spécialisé assistera les recherches dans les bases de données MEDLINE, EMBASE et Cochrane CENTRAL afin de répertorier tous les types d’essais, y compris les essais contrôlés à répartition aléatoire, et toutes les études de cohorte prospectives faisant état d’une variation de la créatinine sérique à la suite de l’administration de NAC. À l’aide de critères d’inclusion prédéfinis, deux réviseurs seront indépendamment chargés de trier les titres et abrégés des études répertoriées lors de la revue de la littérature. Ils devront ensuite extraire les données des textes des études qui auront été retenues. Une analyse des effets aléatoires sera utilisée pour calculer la moyenne pondérée des écarts pour les variations observées dans les mesures de créatinine en présence de NAC. La qualité des essais aléatoires sera évaluée à l’aide de l’outil Cochrane sur le risque de biais, et celle des études observationnelles sera mesurée avec l’échelle de Newcastle-Ottawa.

Résultats: Le principal résultat d’intérêt est la fonction rénale telle que rapportée soit par un changement dans les mesures de créatinine sérique et/ou de la cystatine C dans les essais à répartition aléatoire, soit en comparant les valeurs mesurées avant et après l’administration d’une dose de NAC.

Limites: L’hétérogénéité des données, de possibles biais de publication et un manque de données mécanistiques.

Conclusion: Cette revue systématique offrira une synthèse des données probantes actuelles sur l’effet de la NAC sur les mesures de créatinine sérique. Ces résultats fourniront des lignes directrices aux cliniciens et serviront de bases solides pour les recherches futures dans ce domaine.

Keywords
N-acetylcysteine, kidney function, serum creatinine, serum cystatin C, acute kidney injury

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Background

N-acetyl cysteine (NAC) is an antioxidant which can regenerate glutathione and is primarily used for acetaminophen overdose. However, it has also been tested in prevention of acute kidney injury (AKI) in different settings, such as postoperative AKI and contrast induced AKI (CI-AKI) with mixed results, mainly using change in serum creatinine levels before and after NAC treatment as the outcome. Nevertheless, given the low cost and lack of side effects, NAC has been recommended for use by the Kidney Disease Improving Global Outcomes (KDIGO) guidelines in the context of CI-AKI. Additionally, although NAC is generally recommended for patients with chronic kidney disease (CKD), with an eGFR < 60 ml/min/1.73 m$^2$ in clinical practice, the supporting evidence has been inadequate. A recent systematic review from the Agency for Healthcare Research and Quality (AHRQ) also supports its use for CI-AKI prophylaxis. At present, there are over 20 ongoing trials testing the efficacy of NAC for prevention of acute kidney injury (AKI) in various settings (contrast AKI, perioperative AKI, drug-induced AKI) as well as in CKD for slowing progression or preserving residual kidney function. Therefore, a significant body of research is in progress and the outcome of these large and expensive trials may quantitatively resolve the effectiveness of NAC for preventing CI-AKI. Notably, a biological mechanism or rationale for a protective effect of NAC has never been satisfactorily reported.

Among conflicting reports, there appears to be evidence that NAC may artificially lower measured serum creatinine
without improving kidney function, by interference with the enzymatic laboratory test. If a dose of medication or some other treatment reduces serum creatinine levels via interference, this may incorrectly be interpreted as representing increased kidney excretion and improved organ functioning.

Given these mixed results, a systematic review of the literature will be conducted to determine the effect of N-acetylcysteine (NAC) on serum creatinine. The review methodology, as described below, is designed to tease out potential nuances regarding characteristics of the patient population, NAC route of administration, and measurement of kidney function biomarkers.

Methods

Study Design

The specific objectives are to summarize available evidence on direct effect of NAC, through various routes of administration without dose limitation, on kidney function as measured by serum creatinine. This systematic review will be performed to determine whether there is a direct effect of NAC on serum creatinine. It will adhere to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement, using the Cochrane Risk of Bias (RoB) 2.0 tool for individually randomized, parallel group trials, and the Newcastle-Ottawa Scale (NOS) for observational studies for quality assessment. This protocol is reported in accordance with the PRISMA-P 2015 checklist (see Supplementary Material).

Eligibility Criteria

Type of studies. This systematic review will consider all studies exploring the potential effect of NAC on human kidney function as quantified by baseline and follow-up serum creatinine and/or serum cystatin C measurements. Randomized controlled trials, crossover randomized controlled trials, and prospective before/after NAC dose single-arm protocols will be included. Existing systematic reviews and meta-analyses will be excluded, but their bibliographies and more recent citing articles will be cross-referenced to strengthen our literature search. Studies that are not clinical trials (e.g., observational study, case series) will be excluded. Studies without outcome measures (e.g., serum creatinine, cystatin C) will be excluded. Trials of using NAC as a protective agent to prevent AKI (e.g., CI-AKI or postoperative AKI) will also be excluded.

Patient population. This review will consider prospective clinical trial studies of adult humans aged 18 years old or more, receiving NAC with prior and subsequent serum measurement creatinine and/or cystatin C. The patient population will include healthy volunteers or CKD patients, defined as the presence of kidney damage (urinary albumin excretion of ≥ 30 mg/day) or decreased kidney function (estimated glomerular filtration rate < 60 mL/min/1.73m²). Patients with minimal to none kidney function, for example, end-stage kidney disease (ESKD), and/or those requiring renal replacement therapy such as dialysis or transplantation will be excluded. Patient populations receiving contrast agents and those simultaneously undergoing surgery will be excluded from the study to avoid potential for kidney function due to CI-AKI or other acute kidney injury.

Intervention. The exposure to be assessed is NAC (oral administration and/or intravenous injection, without restriction on dose).

Comparator. For randomized controlled trials, patients receiving NAC will be compared to those receiving placebo. For single-arm prospective cohort studies, data on change in creatinine from baseline (i.e. before and after NAC administration) will be extracted.

Information Sources and Search Strategy

A comprehensive systematic search will be performed using standard electronic databases including MEDLINE, EMBASE, and the Cochrane CENTRAL Library. Databases will be searched in all available time, from the oldest literature to the search date (1947 to July 2018). An information scientist (AD) will help design the search strategy and conduct the search (see Table 1 for preliminary strategy). Cross-reference bibliographies and citations of published

| Table 1. MEDLINE Search Strategy |
|----------------------------------|
| **Medline Search Algorithm** |
| 1. Acetylcysteine/ |
| 2. (acetylcysteine or n-acetylcysteine or n-acetyl cysteine).tw.kw. |
| 3. I or 2 |
| 4. exp Kidney Function Tests/ or ((renal or kidney) adj2 function$).tw.kw. |
| 5. Creatinine/ or Cystatin C/ or Urea/ |
| 6. (creatinine or urea or albumin or cystatin c or gfr or glomerular filtration rate$).tw. |
| 7. or/4-6 |
| 8. 3 and 7 |
| 9. Prospective Studies/ |
| 10. prospective$.tw. |
| 11. randomized controlled trial.pt. |
| 12. controlled clinical trial.pt. |
| 13. randomi?ed.ab. |
| 14. placebo.ab. |
| 15. clinical trials as topic.sh. |
| 16. randomly.ab. |
| 17. trial.ti. |
| 18. or/9-17 |
| 19. 8 and 18 |
works will be conducted to identify additional potential studies. Non-English literatures will be excluded.

**Study Records**

**Data management and selection process.** Pertinent articles identified by our search strategy will be reviewed systematically. Two authors (O.J.C., J.W.H.) will independently screen abstracts, and remove studies clearly meeting exclusion criteria in a first-round of analysis. Articles not excluded outright via abstract analysis will be downloaded as full-text documents and scrutinized again in a second review stage (by O.J.C., J.W.H.) for inclusion/exclusion criteria (Table 2). Any disagreement regarding article inclusion will be solved by in-person meeting to attempt consensus and if necessary will be forwarded to a third reviewer (S.H.) for adjudication.

**Data collection process.** A data extraction template will be created by the principal investigator (S.H.) in Microsoft Excel and modified by feedback from two independent reviewers (O.J.C. and J.W.H.) to ensure that complete data is obtained. O.J.C. and J.W.H. will perform data extraction from selected manuscripts and compare for consistency. In cases with disagreement, consensus will be attempted via further discussion, and input by a third reviewer (S.H.) if necessary. Reviewers will not be blinded to the authors or journals during this process.

**Data Items**

Data extraction will proceed for the selected studies after secondary screening. The following data will be extracted for analysis—“human” factors related to the manuscripts (research group, country of origin, year of publication, and funding source), study design (Randomized Control Trial [RCT], crossover RCT, before/after single arm), patient population (healthy volunteers vs CKD, sample sizes, sex, age, presence of other comorbid conditions such as diabetes), NAC details (oral vs intravenous, dose (total and frequency), control group (placebo-controlled vs no medicine), and kidney-function serum biomarker measurements (creatinine and/or cystatin C, pre-NAC + controls baseline levels vs post-NAC + controls follow-up measurements, and follow-up times), methods used for measuring the biomarkers (Jaffe vs enzymatic creatinine), and associated statistical quantities such as significance (P values) and precision (confidence intervals). If the methodology is not clear, authors will be contacted for further information. Lastly, cointerventions and adverse events will serve as other variables for data extraction.

**Outcomes and Prioritization**

The outcome of interest will include kidney function as reported by either change in serum creatinine and/or serum cystatin C measurement for randomized trials or comparing baseline (pre-NAC dose) values and those following the NAC dose.

**ROB in Individual Studies**

The explicit aim of our systematic review will be to objectively determine whether there is a direct effect of NAC on human kidney function, in the absence of concomitant kidney injury. Therefore, this study will assess whether the design and implementation of studies included in our review meet quality standards required to infer association between controlled NAC administration and measured kidney function biomarkers (serum creatinine and/or cystatin C). Quality of studies and potential for biases will be examined.
independently by two authors (O.J.C. and J.W.H.) using standard tools such as Cochrane “Risk of Bias” for randomized studies and NOS for observational studies. A table comprised of study characteristics will illustrate the results from this methodology quality assessment.

**Data Synthesis**

If data heterogeneity, methodological quality, and apparent study biases are of sufficient quality to allow it, data will be pooled from the included studies into a meta-analysis using the Comprehensive Meta-analysis (Biostat Inc. Version 3 Engleside, NJ). The weighted mean difference will be calculated for change in creatinine with NAC, using random-effects analysis. Cochran’s Q and I² statistics will be conducted to assess data homogeneity regarding the effect of NAC administration on kidney function biomarkers. If there is significant statistical heterogeneity, it will be explored with subgroup analysis and univariate meta-regression. Correction factor for multiple comparisons will be considered in the event of missing outcome measurements, when applicable.

**Meta-Bias Assessment**

Additional analyses that will be performed include sensitivity and univariate meta-regression analyses to assess the effects of clinical factors (dose of NAC) and sociodemographic (proportion of diabetes) characteristics reported in included studies on the meta-analyses estimates. Subgroup analyses will be conducted based on route of NAC (oral versus intravenous), method of creatinine measurement (Jaffe vs non-Jaffe methods). Funnel plot methodology, utilizing visualization of the asymmetry and Egger’s statistics, will be used to identify publication bias.

**Discussion**

There has been much research activity investigating potential protective effects of NAC on kidney function. There is considerable heterogeneity when meta-analyses are conducted, and overall the last quantitative synthesis reports a benefit with NAC use in CI-AKI, but a large subsequent trial found no such benefit. Clearly there is a need for an analysis of the direct effects, if any, of NAC on kidney function for studies considering direct effect of NAC, with the present systematic review being the first such article to our knowledge. The current practice guidelines suggest NAC be used as an oral prophylactic agent among patients at increased risk of CI-AKI, but admittedly on imperfect evidence with the low cost and lack of apparent side effects weighing heavily in this advocacy. While NAC may be relatively inexpensive on a per-dose basis, the cost associated with using it routinely and in large quantities in the clinical acute and chronic kidney injury setting is enormous. Additionally, if there is assay interference, this aspect should be taken into account when using NAC in clinical practice and assessing kidney function.

This systematic review will provide clinicians with strong foundational evidence on which to gauge the effectiveness of NAC on adult kidney function, and whether or not standard clinical practice requires change in the setting of preventing AKI via administration of NAC.

**List of Abbreviations**

NAC, N-acetylcysteine; AHRQ, Agency for Healthcare Research and Quality; AKI, Acute Kidney Injury; CI-AKI, Contrast-Induced Acute Kidney Injury; CKD, Chronic Kidney Disease; ESRD, End-stage Renal Disease; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT, Randomized Control Trial.

**Ethics Approval and Consent to Participate**

This is a protocol for a systematic review of published literature. There will be no direct patient contact, and ethics approval is not necessary.

**Consent for Publication**

All authors read and approved the final version of this manuscript.

**Availability of Data and Material**

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

**Author Contributions**

S.H., A.A., and C.M. did the initial design; A.D. has developed the search strategy with contribution from S.H.; S.H., J.M., O.C. wrote the initial draft of this manuscript; all authors read and approved the final manuscript.

**Declaration of Conflicting Interests**

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