Medical Journal of Australia

MJA The Medical Journal of Australia

RESEARCH

Early Cessation of Acetylcysteine Treatment After Paracetamol Overdose (NACSTOP 2): A Non-Inferiority Randomised Controlled Trial

Anselm Wong[1,2] | Richard McNulty[3,4] | Sarah E. Hodgson[1] | Naren Gunja[4,5] | Andis Graudins[2,6]

[1]Austin Health, Melbourne, Victoria, Australia | [2]Monash University, Melbourne, Victoria, Australia | [3]Blacktown and Mount Druitt Hospital, Sydney, New South Wales, Australia | [4]The University of Sydney, Sydney, New South Wales, Australia | [5]Western Sydney Toxicology Service, Sydney, New South Wales, Australia | [6]Monash Health, Melbourne, Victoria, Australia

Correspondence: Anselm Wong (anselm.wong@austin.org.au)

Received: 21 April 2025 | **Revised:** 18 September 2025 | **Accepted:** 18 September 2025

Keywords: drug overdose | pharmaceutical preparations | poisoning | toxicology

ABSTRACT

Objectives: To determine whether ceasing acetylcysteine treatment for adults with acute paracetamol overdose after at least 12 h of the two-bag acetylcysteine regimen is non-inferior to providing the full 20-h two-bag regimen.

Study Design: Open label, non-inferiority randomised controlled trial.

Setting: Emergency departments of six Australian metropolitan hospitals (four in Melbourne, two in Sydney), 1 December 2019–31 July 2024.

Participants: Adults who required acetylcysteine treatment following single or staggered paracetamol ingestions whose serum alanine transaminase (ALT) level was below 40 IU/L on presentation, and whose ALT levels were below 40 IU/L and serum paracetamol concentrations below 20 mg/L after 12 h of acetylcysteine treatment.

Intervention: *Control group* (standard care): two-bag intravenous acetylcysteine regimen (200 mg/kg over 4 h, followed by 100 mg/kg over 16 h). *Intervention group*: Acetylcysteine stopped at least 12 h after treatment initiation and the 20-h infusion period completed with intravenous compound sodium lactate.

Main Outcome Measures: Difference in ALT level between presentation and 20 h after acetylcysteine treatment initiation; non-inferiority was defined as the upper limit of the 95% confidence interval (CI) of the difference between median changes in ALT level for the intervention and control groups being less than 3 IU/L.

Results: Of 2830 people who presented with paracetamol overdose, 860 received acetylcysteine treatment; 186 people who met both the presentation and 12-h acetylcysteine treatment blood test inclusion criteria (median age, 17 years; interquartile range [IQR], 16–23 years; 162 women [87%]) were randomly assigned to the intervention (93 participants) and control groups (93 participants). Median acetylcysteine infusion time in the intervention group was 13 h (IQR, 13–13 h). The median change in ALT level between arrival and 20 h after starting intravenous acetylcysteine treatment was similar for the intervention (−1 IU/L; IQR, −4 to 1 IU/L) and control groups (0 IU/L; IQR, −2 to 2 IU/L); the difference in median change (−1 IU/L; 95% CI, −2 to 1 IU/L) was consistent with the non-inferiority criterion. No patients developed hepatic injury or hepatotoxicity.

Conclusion: An abbreviated acetylcysteine treatment regimen was non-inferior to the standard 20-h two-bag regimen for people with paracetamol overdose who were at low risk of hepatic failure.

Trial Registration: ACTRN12619001549112 (prospective)

Plain Language Summary

The known

A 20- to 21-h acetylcysteine treatment regimen has been used for more than four decades to treat all people with paracetamol overdose despite differences in hospital presentation characteristics.

The new

A shorter acetylcysteine regimen was found to be as safe as the 20-h regimen in a randomised controlled trial.

The implications

The shorter acetylcysteine regimen can be used when people with paracetamol overdose are at low risk of liver injury. Future guidelines should consider adopting this practice.

1 | Introduction

Paracetamol overdose is the pharmaceutical most frequently implicated in poisoning in developed countries [1]. It is involved in 50% of overdoses in the United Kingdom (100,000 hospital presentations per annum) [2] and is the most frequent reason for calls to poisons information centres in Australia [3]. Paracetamol overdose is the most frequent cause of acute liver failure in developed countries [1].

Acetylcysteine (*N*-acetylcysteine, NAC) is used as an antidote to prevent hepatotoxicity after paracetamol overdose [4]. For more than 40 years, the intravenous acetylcysteine protocol in these cases involved three-bag infusion over 20–21 h [4]. However, frequent prescribing and dispensing errors result from dose calculation errors and incorrect infusion rates; adverse drug reactions related to histamine release during the large initial acetylcysteine loading dose (bag 1) are also frequent [5]. A two-bag acetylcysteine regimen, with the loading dose infused over 4 h but providing the same total acetylcysteine dose, has simplified the treatment regimen and reduced the incidence of severe histamine reactions from 10% to 4% [6, 7].

The 20-h infusion period, based on the desire to treat the patient for at least five paracetamol elimination half-lives, was selected in an era when serum paracetamol concentrations could not readily be assessed [8]. The treatment duration was therefore the same for all patients requiring acetylcysteine treatment, regardless of the ingested paracetamol dose. Notably, a large group of patients at low risk of hepatotoxicity may not require such prolonged treatment [9]. Few studies have evaluated abbreviated intravenous acetylcysteine treatment regimens [10, 11].

We undertook a multicentre cluster-controlled pilot study (the NACSTOP trial) of reducing the duration of the treatment regimen from 20 to 12 h for all people who presented with paracetamol overdose and were at low risk of developing hepatotoxicity [12]. We found that the abbreviation of acetylcysteine treatment was safe for all patients in the intervention group. However, larger randomised studies are required to validate the safety and benefits of the regimen. The aim of the study we report in this article was to validate the findings of the NACSTOP trial in a randomised controlled trial that included a larger study group.

2 | Methods

2.1 | Study Design and Setting

We conducted an open label, multicentre, non-inferiority randomised controlled trial of whether ceasing acetylcysteine treatment for adults with paracetamol overdose after at least 12 h of the two-bag acetylcysteine regimen is non-inferior to the full 20-h two-bag regimen. We included adults who presented to the emergency departments of six metropolitan hospitals (Austin Hospital, Monash Medical Centre, Dandenong Hospital and Casey Hospital in Melbourne; Westmead Hospital and Blacktown Hospital in Sydney), supported by inpatient toxicology units, during 1 December 2019–31 July 2024. The trial was prospectively registered with the Australian New Zealand Clinical Trials Registry (ACTRN12619001549112; 11 November 2019). We report our study according to the CONSORT 2025 statement for randomised controlled trials [13].

2.2 | Participant Selection

Adults and children (10 years or older) who attended the six emergency departments with single or staggered paracetamol overdoses that required acetylcysteine treatment and who met the inclusion criteria were recruited for the study. Definitions for ingestion type (single or staggered) and treatment criteria corresponded to Australian and New Zealand paracetamol treatment guidelines (paracetamol concentration on or above the 150 mg/L at 4 h threshold line of the modified Rumack–Matthew nomogram for single acute ingestions) [14]. Staggered ingestions are defined as multiple ingestions over more than 2 h for the purpose of deliberate self-poisoning. People were recruited during the first 12 h of acetylcysteine treatment, as initial treatment was identical for the two treatment groups.

2.3 | Inclusion and Exclusion Criteria

We included people who required acetylcysteine treatment following single or staggered paracetamol ingestions and with serum alanine transaminase (ALT) levels below 40 IU/L on presentation, as well as ALT levels below 40 IU/L and serum paracetamol concentrations below 20 mg/L (< 132 μmol/L) after 12 h of acetylcysteine treatment.

We excluded people who presented with a history of repeated non-intentional supratherapeutic ingestion of paracetamol (as defined by the Australian and New Zealand paracetamol treatment guidelines: more than 10 g over 24 h or more than 6 g/day over 48 h) [14]. We also excluded people who had also ingested alcohol or sedating drugs, had ingested modified release paracetamol, people with pre-existing liver disease (history or abnormal liver function test results) and pregnant women. If after 12 h of acetylcysteine treatment the ALT level exceeded 40 IU/L or the paracetamol concentration exceeded 20 mg/L (132 μmol/L),

the patient received the full acetylcysteine course but was excluded from the study.

2.4 | Participant Consent

All participants provided written consent to participation after discussion with a study investigator familiar with the study. People were given the participant information and consent form to read if they required acetylcysteine treatment and were allowed time to consider their involvement in the trial and follow-up. They provided consent prior to blood collection for tests undertaken 12 h after acetylcysteine treatment initiation.

2.5 | Randomisation

A randomisation sequence was generated using Stata 15 and participants were allocated 1:1 to the intervention and control arms by a trial statistician not involved with recruitment. Random permuted blocks of sizes 2, 4 and 6 were employed to ensure approximate balance of treatment allocation within each arm. Study envelopes with the intervention or control assignment were prepared by a study investigator not involved with recruitment. Study investigators involved in enrolment did not have access to the random allocation sequence. Participants were assigned after it had been established they met the study inclusion criteria.

2.6 | Blinding

The decision to cease acetylcysteine treatment after paracetamol overdose relies on normal biochemical markers (e.g., ALT <40 IU/L). The primary outcome measured in this trial was correspondingly based on biochemical testing performed in the pathology laboratory at the respective hospitals, minimising recording and analytical bias. The pathologists undertaking testing were blinded to the study and the interventions. Treating clinicians and participants were not blinded to treatment, as the treatment infusion changes would have made blinding difficult. The randomised controlled trial was therefore undertaken as an open label study. The statisticians who performed the trial statistical analyses were blinded to allocation.

2.7 | Interventions

Treatment for all people who met the Australian and New Zealand treatment guidelines criteria (paracetamol concentration above the treatment nomogram line [14]) commenced with the standard two-bag regimen (200 mg/kg acetylcysteine intravenous over 4 h, then 6.25 mg/kg/h acetylcysteine for up to 16 h) (Figure 1). If after 12 h of acetylcysteine treatment their serum ALT level was below 40 IU/L and their serum paracetamol concentration below 20 mg/L, the patient, after providing consent to trial participation, was randomly allocated to treatment in one of the two trial arms:

- Intervention group: after at least 12 h, acetylcysteine infusion was ceased, and 1 L compound sodium lactate or 0.9% sodium chloride solution was administered intravenously over 8 h.
- Control group (standard treatment): patients received acetylcysteine (in 500 mL 0.9% sodium chloride, 6.25 mg/kg/h for up to 8 h) to complete 20 h of acetylcysteine intravenous treatment; that is, continuation of the second 16-h infusion bag.

For safety reasons, if the ALT level exceeded 40 IU/L or have doubled at the end of the 20-h infusion for either group, acetylcysteine infusion was restarted (6.25 mg/kg/h) and continued until acetylcysteine cessation criteria were met [14]. For

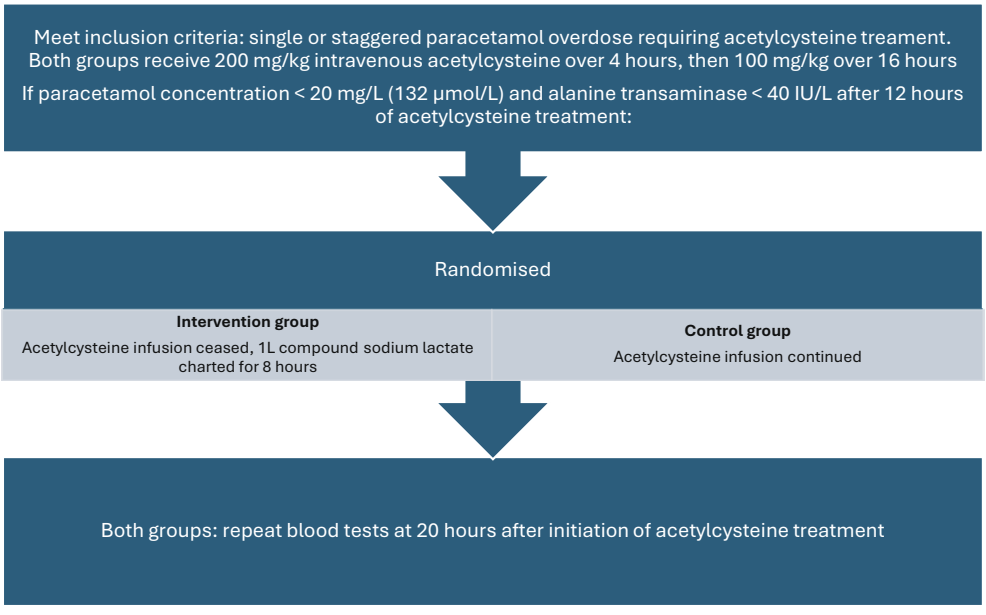

FIGURE 1 | The NACSTOP-2 trial enrolment and procedure [13].

people who did not meet the blood test inclusion criteria 12 h after the initiation of acetylcysteine treatment, it was continued according to the standard treatment protocol (two-bag 20-h regimen).

2.8 | Measurements

Blood was collected for assessment at three time points:

- admission (on arrival): paracetamol concentration, ALT, electrolytes and creatinine;
- 12 h after initiation of acetylcysteine treatment: paracetamol concentration, ALT, electrolytes and creatinine levels and international normalised ratio (INR); and
- 20 h after initiation of acetylcysteine treatment: paracetamol concentration, ALT, electrolytes and creatinine levels and INR.

We attempted to phone all participants 14 days after discharge from hospital to ascertain that they were alive and to ask about nausea, abdominal pain and re-presentations to hospital. If the person had re-presented to hospital, all available related blood test, and imaging results were recorded. Medical records were checked for re-presentations to hospital of people who could not be contacted by phone.

2.9 | Outcomes

The primary outcome was the absolute difference in ALT level between presentation and 20 h after the initiation of acetylcysteine treatment.

The secondary outcomes were hepatic injury (defined as doubling of serum ALT level and ALT exceeding 100 IU/L 20 h after the commencement of acetylcysteine infusion) and the need for further acetylcysteine treatment; peak INR exceeding 2; and development of hepatotoxicity (defined as ALT exceeding 1000 IU/L) recorded before hospital discharge. Adverse reactions to acetylcysteine, including non-allergic gastrointestinal (nausea, vomiting) or systemic (rash, hypotension wheeze, angioedema) anaphylactic reactions, were assessed and recorded by nursing staff before hospital discharge.

We also collected information on paracetamol ingestion type (dose and formulation), other ingested substances (e.g., opioids, antihistamines) and demographic characteristics of participants. Information about death within 14 days of hospital discharge was collected by follow-up phone call for a post hoc analysis. Data were collected in a case report form and transferred to a secure electronic Excel (Microsoft) spreadsheet, as were laboratory test results transcribed from electronic hospital databases (Cerner and Symphony).

The data safety and monitoring board comprised three reviewers, independent of the study group, who regularly monitored clinical outcomes and liver enzyme results for each participant.

2.10 | Sample Size Calculation

In NACSTOP, the mean difference in ALT level between presentation and 20 h after acetylcysteine treatment initiation was 2 IU/L (standard deviation (SD), 6 IU/L; 95% confidence interval [CI], −10 to 14 IU/L) [12]. As half the upper limit of the 95% CI was 7 IU/L, a non-inferiority margin of 7 IU/L or less should be chosen. In NACSTOP 2, the non-inferiority margin of 3 IU/L used to assess efficacy with regard to the primary outcome and was found to be a suitable clinical significance boundary. If there were no difference in outcome between the standard and intervention treatment groups, 174 participants (87 per group) would be required for 95% power to detect that the upper limit of a one-sided 95% CI (equivalent to a 90% two-sided CI) was below the non-inferiority limit of 3 IU/L. Allowing 10% attrition for failure and non-compliance with the study protocol, we planned to enrol 200 participants (100 per group).

2.11 | Statistical Analysis

All analyses were performed in SAS 9.4. For the primary outcome, non-inferiority was established if the upper limit of the 95% CI of the difference between the intervention and control groups in the median change in ALT level between admission and 20 h after acetylcysteine treatment initiation was less than the pre-defined non-inferiority margin of 3 IU/L. Post hoc analyses included tests of normality of the continuous ALT data (Kolmogorov–Smirnov test); as the data were not normally distributed, we used non-parametric methods for analysis. Differences in medians (with 95% CI) were calculated using the Hodges–Lehmann estimator and method.

Pre-defined comparisons of the statistical significance of differences in secondary outcomes were performed using the Student's *t*-test for normally distributed continuous variables and the Mann–Whitney *U* test for non-normally distributed continuous variables. All analyses were intention-to-treat analyses.

2.12 | Ethics Approval

The study was approved by the Monash Health Human Research Ethics Committee (MONH-262715). The study was conducted in accordance with the Declarations of Helsinki and Istanbul. Written consent to participation was provided by all participants.

3 | Results

During the study period, 2830 people presented with paracetamol overdose at the six hospitals, of whom 860 received acetylcysteine treatment (Figure 2). Two hundred people eligible for the trial on presentation consented to participation in the trial. Fourteen were excluded because they did not meet the 12-h acetylcysteine treatment blood test inclusion criteria (Supporting Information), and 186 people were randomly assigned to the intervention (93 participants) and control groups

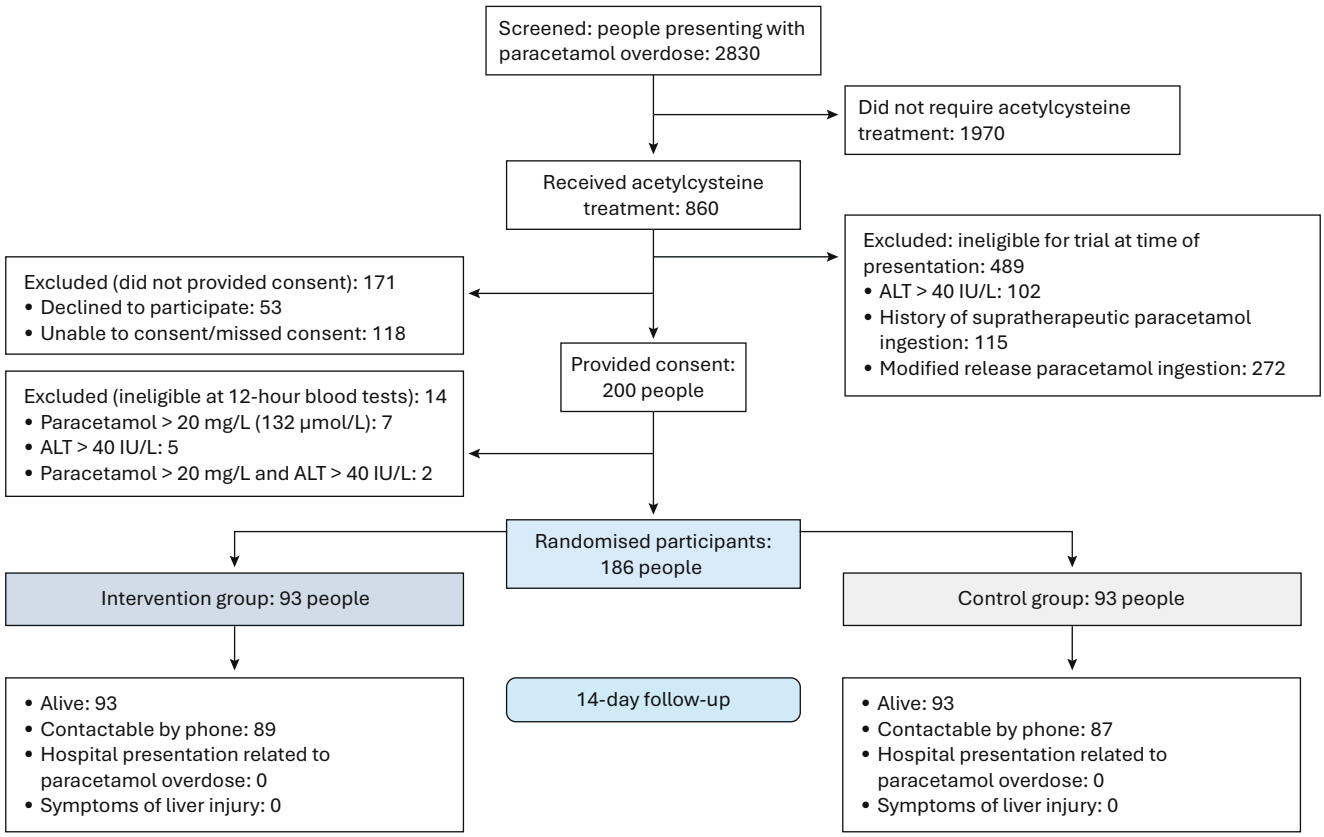

FIGURE 2 | Recruitment and participation of people who presented to six metropolitan hospitals in Sydney and Melbourne with paracetamol overdose, 1 December 2019–31 July 2024, for the NACSTOP 2 trial. ALT, alanine aminotransferase.

(93 participants). A total of 162 participants were women (87%); the median age of all participants was 17 years (interquartile range [IQR], 16–23 years). The demographic characteristics of the two groups were similar, as were the median ingested paracetamol doses, initial paracetamol concentrations, initial serum ALT levels, and the proportions who received acetylcysteine treatment within 8 h of paracetamol ingestion. The median time to initial serum paracetamol concentration assessment was 5 h (IQR, 4–8 h) for the intervention group and 4.5 h (IQR, 4–6 h) for the control group (Table 1). The initial paracetamol concentration was less than double the nomogram line concentration (i.e., paracetamol nomogram ratio of 1:2) for 129 participants (70%); for 57 participants (30%), the paracetamol nomogram ratio was > 2 (Figure 3). All participants were admitted to short stay observation units for acetylcysteine treatment, and adherence to the treatment protocol was excellent (i.e., all participants adhered to the study protocols).

3.1 | Primary Outcome

The median change in ALT level between arrival and 20 h after starting intravenous acetylcysteine treatment was similar for the intervention group (−1 IU/L; IQR, −4 to 1 IU/L) and the control group (0 IU/L; IQR, −2 to 2 IU/L) (Figure 4); the difference in median change (−1 IU/L; 95% CI, −2 to 1 IU/L) satisfied our non-inferiority criterion, indicating that the intervention was non-inferior to standard care with respect to this parameter.

3.2 | Secondary Outcomes

The median 20-h ALT level was similar for the intervention (15 IU/L; IQR, 11–23 IU/L) and the control groups (16 IU/L; IQR, 12–21 IU/L). Doubling of ALT level was not measured in any participants; none developed hepatic injury or hepatotoxicity, died, or received liver transplants.

The difference in median 20-h INR was the same for the intervention and control groups (1.2; IQR, 1.1–1.3); peak INR did not exceed 2 for any participants.

The median time from overdose to initiation of acetylcysteine treatment was 7 h (IQR, 6–9 h) in the intervention group and 7 h (IQR, 5–8 h) in the control group. The median duration of acetylcysteine treatment was 13 h (IQR, 13–13 h) in the intervention group and 20 h (IQR, 20–20) for participants who received the full course. No participants required extension of acetylcysteine treatment. The 174 participants who did not require inpatient psychiatric admission were discharged home, with community follow-up planned.

The most frequent adverse reactions to acetylcysteine infusion were gastrointestinal reactions (nausea or vomiting); their incidence was similar for the two study groups (intervention, three people; control, five people). One person in the intervention group and three people in the control group developed rashes. Serious systemic reactions (hypotension, wheeze, angioedema) were not reported in either group.

TABLE 1 | Demographic, paracetamol overdose, and hospital treatment characteristics for 186 participants in the NACSTOP2 trial.

Characteristic	Intervention group	Control group
Participants	93	93
Demographic characteristics		
Age (years), median (IQR)	18 (16–25)	17 (15–21)
Sex (women)	78 (84%)	84 (90%)
Paracetamol overdose characteristics		
Alcohol co-ingested	5 (5%)	1 (1%)
Other drugs co-ingested	40 (43%)	31 (33%)
Opiates	6	5
Antihistamines	1	1
Ingestion type		
Single	87 (94%)	85 (91%)
Staggered	6 (6%)	8 (9%)
Dose ingested paracetamol (g), median (IQR)	15 (10–20)	17 (12–24)
Time from ingestion to treatment less than 8 h	49 (52%)	66 (71%)
Laboratory findings		
Alanine aminotransferase (IU/L), median (IQR)		
Initial	16 (12–21)	15 (12–21)
20 h after acetylcysteine initiation	15 (11–23)	16 (12–21)
Paracetamol serum concentration (mg/L), median (IQR)		
Initial	157 (126–193)	161 (142–201)
12 h after acetylcysteine initiation	5 (4–10)	6 (3–10)
20 h after acetylcysteine initiation	Below limit of detection[a]	Below limit of detection[a]
International normalised ratio (INR), median (IQR)		
20 h after acetylcysteine initiation	1.2 (1.1–1.3)	1.2 (1.1–1.3)
Treatment		
Time from overdose to initial paracetamol assessment (h), median (IQR)	5 (4–8)	4.5 (4–6)
Time from overdose to acetylcysteine treatment initiation (h), median (IQR)	7 (6–9)	7 (5–8)
Acetylcysteine treatment duration (h), median (IQR)	13 (13–13)	20 (20–20)
Hospital stay and disposition		
Length of stay for medical treatment (excluding psychiatric ward admission) (days), median (IQR)	1 (1–1)	1 (1–1)
Disposition after acetylcysteine treatment		
Discharged home	88 (95%)	86 (92%)
Admitted to psychiatric ward	5 (5%)	7 (8%)

Abbreviation: IQR, interquartile range.
[a]Limit of detection: 1 mg/mL.

Fourteen days after discharge from the hospital, 176 participants (95%) could be contacted by telephone for follow-up. None reported persisting gastrointestinal symptoms. Review of medical records identified that all 10 people who could not be contacted by phone were alive and that none had re-presented to hospital with symptoms related to the paracetamol overdose or liver injury.

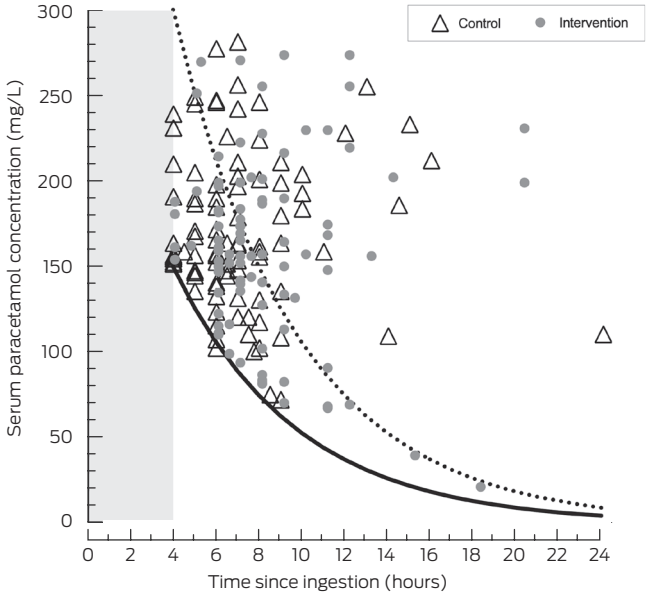

FIGURE 3 | Serum paracetamol concentrations on initial presentation for 186 participants in the NACSTOP2 trial. Shaded area: First 4 h after paracetamol ingestion, during which paracetamol is absorbed, and the nomogram cannot be interpreted. The dark line (150 mg/L at 4 h) marks the paracetamol treatment nomogram; the dotted line indicates levels that are twice the paracetamol treatment line concentrations.

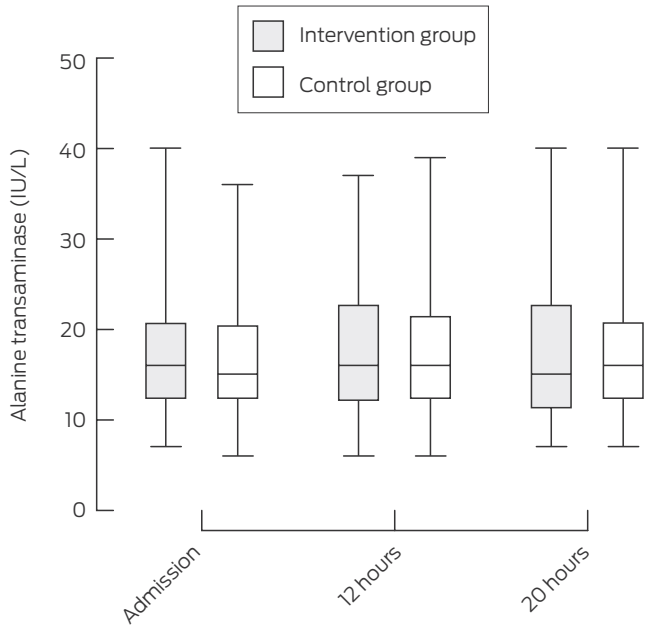

FIGURE 4 | Blood alanine transaminase concentrations for 186 participants in the NACSTOP2 trial, on admission and 12 and 20 h after initiation of acetylcysteine treatment. Depicted are the median values with interquartile ranges (boxes) and overall range of values (whiskers). The admission values are closest in time to the initiation of acetylcysteine treatment.

4 | Discussion

Improvements in risk stratification following paracetamol overdose [9, 15–17] and the wide availability of rapid and accurate paracetamol testing can facilitate individualised acetylcysteine dosing. It has long been recognised that the acetylcysteine treatment threshold is very conservative [8, 18, 19]. In addition, many people are treated within hours of acute overdose and have consistently normal liver function, including paracetamol elimination [15, 17]. This knowledge underpinned the trial described in this article and the NACSTOP pilot trial [12].

In our study, clinical and biochemical outcomes for participants with normal serum ALT values at the start of and after 12 h of acetylcysteine treatment, and for whom serum paracetamol concentrations fell to the therapeutic range within 12 h of treatment initiation, were similar with the abbreviated and the complete two-bag acetylcysteine regimen. This finding also applied to the considerable proportion of participants with initial paracetamol concentrations more than double the treatment nomogram level. In addition, there were no differences between the treatment groups in secondary outcomes, including doubling of serum ALT value, peak INR or hepatic injury.

As the median interval from overdose to acetylcysteine treatment initiation was 7 h, ALT measurements 20 h after its initiation were undertaken more than 24 h after the paracetamol overdose. All 20-h ALT measurements were normal; the ALT level has normally risen by this time point in patients who develop hepatic injury [17]. Clinical practice guidelines recommend monitoring transaminase levels for 20 h after the initiation of acetylcysteine treatment and ceasing it if they are within the normal range [13, 19]. This monitoring was performed for both groups in this trial, and participants were followed up by phone 14 days after discharge from hospital.

Abbreviated paracetamol treatment regimens with different protocols have been reported [20, 21]. A randomised clinical trial [21] of 300 mg/kg acetylcysteine over 12 h (Scottish Newcastle Acetylcysteine Protocol) reported the reduced incidence of adverse reactions; the protocol required a third acetylcysteine bag if further treatment was indicated. Conversely, the protocol in our study foresaw continuing acetylcysteine treatment without needing an infusion change if the serum ALT level started to rise or the serum paracetamol concentration was still high after 12 h of treatment. In addition, the larger loading dose provided by our regimen (200 mg/kg) maintains normal protocol dosing, which can be useful after massive paracetamol ingestions [22]. Other examples of abbreviated dosing include a retrospective review of outcomes for people after supratherapeutic paracetamol ingestions treated according to an 8-h acetylcysteine regimen; none of the 46 patients in whom the ALT level was below 50 IU/L on presentation developed liver injury [10]. NACSTOP2 also expands and supports the findings of the NACSTOP pilot trial [12].

A recent Australian study [11] found that a 12-h acetylcysteine treatment regimen for people at low risk of hepatic injury (people with single acute ingestions of less than 30 g paracetamol who presented to hospital within 8 h of overdose) was non-inferior to the standard two-bag 20-h regimen, supporting the findings of our study. In addition, the NACSTOP and NACSTOP 2 trials also found that outcomes were also good for people who presented late (more than 8 h after paracetamol overdose), with staggered ingestions, or with initial serum paracetamol concentrations

more than double the nomogram treatment threshold if they had met the acetylcysteine treatment cessation criteria.

In practice, about half the people who require acetylcysteine treatment in Australia could be eligible for the abbreviated NACSTOP2 regimen (Figure 1). Eligibility would be greater in countries with lower treatment thresholds [23], particularly in countries in which all paracetamol overdoses are treated, regardless of serum paracetamol concentration [24].

The benefits of reduced duration of medical treatment for people with paracetamol overdoses include the earlier opportunity for mental health assessment and interventions, and fewer hospitalisations. In addition, it may allow treatment of more patients in busy hospitals and emergency departments by reducing bed occupancy duration, increasingly important as crowded emergency departments and hospital access block are major problems [25, 26].

Our findings confirmed the very low rate of non-IgE-mediated anaphylactoid reactions when modifying initial loading to 200 mg/kg acetylcysteine infused over 4 h. Several other studies have also reported lower adverse event rates during acetylcysteine treatment using this administration regimen [6, 7, 27, 28]; however, some studies have reported higher rates of gastrointestinal reactions during acetylcysteine treatment [6, 21]. One reason for the low gastrointestinal reaction rate in our study could be that in a large proportion of participants, the initial paracetamol concentrations were high, which is associated with lower rates of adverse reactions to acetylcysteine treatment [5].

4.1 | Limitations

Although the study was open-label, the primary endpoint was a biochemical test result, and consequently unlikely to be subject to bias. However, the nurses who recorded adverse reactions to acetylcysteine treatment were not blinded to study allocation. As we could not follow-up all people by phone, we checked the hospital medical records of those we could not contact and found no subsequent presentations related to paracetamol toxicity; however, presentations to hospitals not involved in the study were possible.

4.2 | Conclusion

An abbreviated acetylcysteine treatment regimen was non-inferior to the standard 20-h two-bag regimen for people with paracetamol overdose at low risk of hepatic failure, confirming that acetylcysteine treatment can be safely stopped early in these cases.

Author Contributions

Anselm Wong: study design/conception, investigation, data curation/analysis, writing (first draft). **Richard McNulty:** study design/conception, enrolment, data curation, writing (revision). **Sarah E. Hodgson:** study design/conception, investigation, writing (revision). **Naren Gunja:** study design/conception, data analysis, writing (revision). **Andis Graudins:** study design/conception, investigation, data analysis, writing (revision).

Acknowledgements

We thank our colleagues in the treating hospitals who assisted with recruitment.

Funding

Anselm Wong was supported by National Health and Medical Research Council Research Fellowship (1159907) and Australasian College for Emergency Medicine (ACEM) Foundation.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The de-identified data set for this investigation is available upon request, from the date of article publication, from the corresponding author (Anselm Wong).

References

1. P. Hey, T. Hanrahan, M. Sinclair, et al., "Epidemiology and Outcomes of Acute Liver Failure in Australia," *World Journal of Hepatology* 11 (2019): 586–595.

2. D. N. Bateman, R. Carroll, J. Pettie, et al., "Effect of the UK's Revised Paracetamol Poisoning Management Guidelines on Admissions, Adverse Reactions and Costs of Treatment," *British Journal of Clinical Pharmacology* 78 (2014): 610–618.

3. Austin Health, "Victorian Poisons Control Centre: Annual Report 2018," Austin Health, https://www.austin.org.au/Assets/Files/VPICAnnualReport2018.pdf.

4. L. F. Prescott, J. Park, A. Ballantyne, P. Adriaenssens, and A. T. Proudfoot, "Treatment of Paracetamol (Acetaminophen) Poisoning With N-Acetylcysteine," *Lancet* 2 (1977): 432–434.

5. E. A. Sandilands and D. N. Bateman, "Adverse Reactions Associated With Acetylcysteine," *Clinical Toxicology (Philadelphia, Pa.)* 47 (2009): 81–88.

6. A. Wong and A. Graudins, "Simplification of the Standard Three-Bag Intravenous Acetylcysteine Regimen for Paracetamol Poisoning Results in a Lower Incidence of Adverse Drug Reactions," *Clinical Toxicology (Philadelphia, Pa.)* 54 (2016): 115–119.

7. A. Wong, G. Isbister, R. McNulty, et al., "Efficacy of a Two Bag Acetylcysteine Regimen to Treat Paracetamol Overdose (2NAC Study)," *EClinicalMedicine* 20 (2020): 100288.

8. B. H. Rumack, "Acetaminophen Hepatotoxicity: The First 35 Years," *Journal of Toxicology. Clinical Toxicology* 40 (2002): 3–20.

9. A. Wong and A. Graudins, "Risk Prediction of Hepatotoxicity in Paracetamol Poisoning," *Clinical Toxicology (Philadelphia, Pa.)* 55 (2017): 879–892.

10. A. Wong, N. Gunja, R. McNulty, and A. Graudins, "Analysis of an 8-Hour Acetylcysteine Infusion Protocol for Repeated Supratherapeutic Ingestion (RSTI) of Paracetamol," *Clinical Toxicology (Philadelphia, Pa.)* 56 (2018): 199–203.

11. G. Isbister, A. Chiew, N. Buckley, et al., "A Non-Inferiority Randomised Controlled Trial of a Shorter Acetylcysteine Regimen for Paracetamol Overdose: The SARPO Trial," *Journal of Hepatology* 83 (2025): 881–887.

12. A. Wong, R. McNulty, D. Taylor, et al., "The NACSTOP Trial: A Multicenter, Cluster-Controlled Trial of Early Cessation of Acetylcysteine in Acetaminophen Overdose," *Hepatology* 69 (2019): 774–784.

13. S. Hopewell, A. W. Chan, G. S. Collins, et al., "CONSORT 2025 Statement: Updated Guideline for Reporting Randomised Trials," *BMJ* 388 (2025): e081123.

14. A. L. Chiew, D. Reith, A. Pomerleau, et al., "Updated Guidelines for the Management of Paracetamol Poisoning in Australia and New Zealand," *Medical Journal of Australia* 212 (2020): 175–183.

15. M. L. Sivilotti, M. C. Yarema, D. N. Juurlink, A. M. Good, and D. W. Johnson, "A Risk Quantification Instrument for Acute Acetaminophen Overdose Patients Treated With *N*-Acetylcysteine," *Annals of Emergency Medicine* 46 (2005): 272–274.

16. A. Wong, M. L. A. Sivilotti, P. I. Dargan, D. M. Wood, and S. L. Greene, "External Validation of the Paracetamol-Aminotransferase Multiplication Product to Predict Hepatotoxicity From Paracetamol Overdose," *Clinical Toxicology (Philadelphia, Pa.)* 53 (2015): 807–814.

17. T. J. Green, M. L. A. Sivilotti, C. Langmann, et al., "When Do the Aminotransferases Rise After Acute Acetaminophen Overdose?," *Clinical Toxicology (Philadelphia, Pa.)* 48 (2010): 787–792.

18. N. Buckley and M. Eddleston, "Paracetamol (Acetaminophen) Poisoning," *BMJ Clinical Evidence* 2007 (2007): 2101.

19. R. C. Dart and B. H. Rumack, "Patient-Tailored Acetylcysteine Administration," *Annals of Emergency Medicine* 50 (2007): 280–281.

20. J. M. Pettie, T. M. Caparrotta, R. W. Hunter, et al., "Safety and Efficacy of the SNAP 12-Hour Acetylcysteine Regimen for the Treatment of Paracetamol Overdose," *EClinicalMedicine* 11 (2019): 11–17.

21. D. N. Bateman, J. W. Dear, H. K. Thanacoody, et al., "Reduction of Adverse Effects From Intravenous Acetylcysteine Treatment for Paracetamol Poisoning: A Randomised Controlled Trial," *Lancet* 383 (2014): 697–704.

22. A. L. Chiew, G. K. Isbister, K. A. Kirby, C. B. Page, B. S. H. Chan, and N. A. Buckley, "Massive Paracetamol Overdose: An Observational Study of the Effect of Activated Charcoal and Increased Acetylcysteine Dose (ATOM-2)," *Clinical Toxicology (Philadelphia, Pa.)* 55 (2017): 1055–1065.

23. D. J. McQuade, P. I. Dargan, J. Keep, and D. M. Wood, "Paracetamol Toxicity: What Would Be the Implications of a Change in UK Treatment Guidelines?," *European Journal of Clinical Pharmacology* 68 (2012): 1541–1547.

24. L. E. Schmidt, "Identification of Patients at Risk of Anaphylactoid Reactions to N-Acetylcysteine in the Treatment of Paracetamol Overdose," *Clinical Toxicology (Philadelphia, Pa.)* 51 (2013): 467–472.

25. P. C. Sprivulis, J. A. Da Silva, I. G. Jacobs, A. R. L. Frazer, and G. A. Jelinek, "The Association Between Hospital Overcrowding and Mortality Among Patients Admitted via Western Australian Emergency Departments," *Medical Journal of Australia* 184 (2006): 208–212.

26. M. L. McCarthy, "Overcrowding in Emergency Departments and Adverse Outcomes," *BMJ* 342 (2011): d2830.

27. R. McNulty, J. M. E. Lim, P. Chandru, and N. Gunja, "Fewer Adverse Effects With a Modified Two-Bag Acetylcysteine Protocol in Paracetamol Overdose," *Clinical Toxicology (Philadelphia, Pa.)* 56 (2018): 618–621.

28. L. E. Schmidt, D. N. Rasmussen, T. S. Petersen, et al., "Fewer Adverse Effects Associated With a Modified Two-Bag Intravenous Acetylcysteine Protocol Compared to Traditional Three-Bag Regimen in Paracetamol Overdose," *Clinical Toxicology (Philadelphia, Pa.)* 56 (2018): 1128–1134.

Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Data S1:** mja270114-sup-0001-DataS1.pdf.