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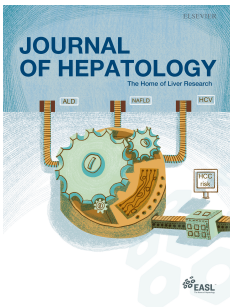

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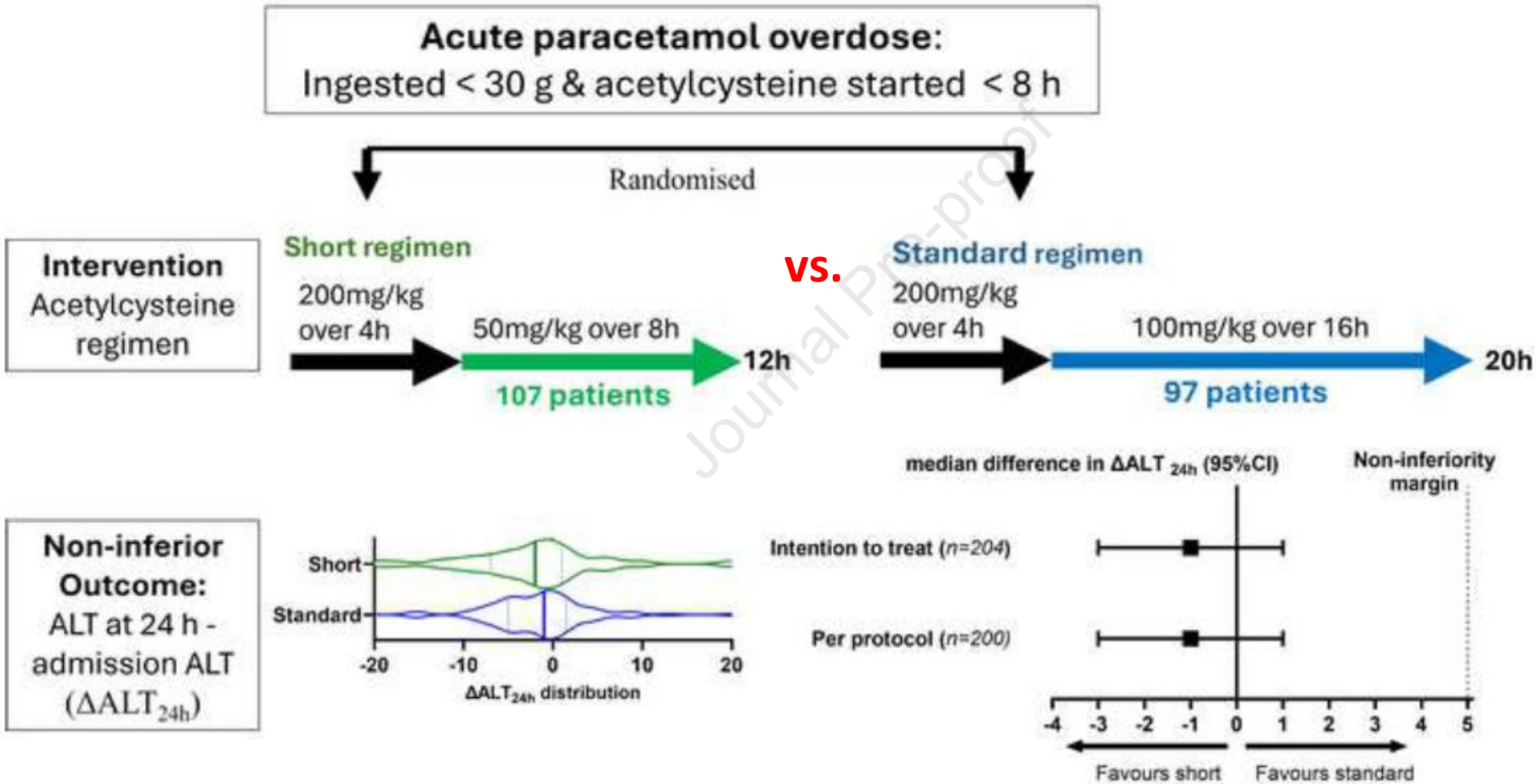

The shorter 12h acetylcysteine regimen had the same effectiveness and safety as the standard 20h regimen

A non-inferiority randomised controlled trial of a Shorter Acetylcysteine Regimen for Paracetamol Overdose – the SARPO trial.

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Short Title: Short acetylcysteine in paracetamol overdose

Declarations

Availability of data and material

All data generated or analysed during this study will be included in the published article (and supplementary information files if required). The dataset used to design this study i.e. sample size calculation, are available from the corresponding author upon reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

CP and GI designed the study and wrote the protocol. NB, AC and KI reviewed the protocol and all authors contributed to the final design of the study. GI, IB, MD, CP, KI and AC recruited patients. GI and NB analysed the data. CP and GI drafted this manuscript. All authors read and approved the final manuscript. GI is guarantor of the paper.

Abstract

Background: Paracetamol is a common overdose worldwide. Early acetylcysteine treatment can prevent hepatotoxicity. Multiple intravenous acetylcysteine regimens exist; the commonest recommending 300mg/kg over 20h. We investigated the effectiveness and safety of a shorter regimen in paracetamol overdoses ≤30g.

Methods: In a multicentre non-inferiority randomised controlled trial, 204 patients from three hospitals with acute paracetamol overdose ≤ 30g presenting within 8h, were randomised to standard 20h acetylcysteine (200mg/kg/4h, 100mg/kg/16h) regimen or short 12h acetylcysteine (200mg/kg/4h, 50mg/kg/8h) regimen. The primary outcome was the absolute difference between alanine transaminase (ALT) 24h post-ingestion and admission ALT (ΔALT24). Secondary outcomes included ALT>150U/L at 24h and double admission ALT, systemic hypersensitivity and gastrointestinal adverse effects.

Results: The two groups were similar in age, gender, dose ingested, paracetamol concentration, baseline ALT, hospital, charcoal administration and time until acetylcysteine. The shorter regimen was non-inferior to the standard regimen. ΔALT24 for 107 patients given the shorter regimen was median -2U/L (Interquartile range [IQR]:-7 to 1U/L) compared to 97 given the standard regimen, median -1U/L (IQR:-5 to 1.5U/L); difference in medians of -1U/L; 95% confidence interval:-3 to 1U/L; less than the upper non-inferiority margin of 5). No patient receiving the shorter regimen had a 24h ALT double admission and >150U/L, compared to one receiving the standard regimen. No patient had an ALT>1000U/L. Systemic hypersensitivity reactions were similar between groups [9/107 (8%) for short versus 10/97 (10%) standard regimen]. Gastrointestinal adverse effects occurred in 78/107 patients (73%) receiving the short versus 63/97 (65%) receiving the standard regimen.

Conclusions: The shorter 12h acetylcysteine regimen had the same effectiveness and safety as the standard 20h regimen in acute paracetamol overdoses ≤30g, almost halving the length of treatment required.

Trial Registration: Australian New Zealand Clinical Trials Registry number ACTRN12616001617459.

Keywords: paracetamol, overdose, acetylcysteine, randomised clinical trial

Impact and implications

We aimed to examine a simple and shorter strategy for the antidotal administration of acetylcysteine in low-risk paracetamol overdose. The new shortened protocol of 12 hours duration is safe and effective, and applicable to about one third of acute paracetamol overdoses. The findings will make acetylcysteine treatment easier for treating physicians, with a shortened length of stay. The protocol cannot be extended to high risk paracetamol overdoses, including massive and staggered ingestions, without further study.

Introduction

Paracetamol is one of the commonest medications taken in overdose worldwide and is also the major cause of acute liver failure in the United States and Europe[1-3]. Prior to the introduction of specific antidotes, the rate of severe liver damage was over 50%.[4] The antidote acetylcysteine has been used since the 1970's and now hepatotoxicity and mortality secondary to paracetamol toxicity are rare in those treated within 8 hours of ingestion.[4,5] However, the intravenous acetylcysteine regimen developed in the 1970's by Prescott was never subjected to a randomised controlled trial (RCT) or any dose-ranging studies.[6,7] Recently the intravenous regimen has been simplified from a three-bag regimen to a two-bag regimen in many parts of the world, which has reduced the early very high concentrations and therefore adverse reaction rate.[8] In addition, recommended doses have been increased for 'massive' and modified-release paracetamol overdoses.[9,10]

The rationale for acetylcysteine dosing regimens is to provide sufficient acetylcysteine to restore liver glutathione levels (if depleted) and then maintain them to replace excessive glutathione turnover while paracetamol is still present.[7] Thus ingested paracetamol dose and concentrations are a major factor in determining the amount of acetylcysteine required. Higher ingested doses increases the amount of toxic metabolite N-acetyl-p-benzoquinone imine (NAPQI) and the amount of glutathione required for detoxification. Clinical evidence reinforcing this concept comes from three recent studies of large or massive paracetamol ingestions, which describe hepatotoxicity occurring despite early (<8 hours) administration of standard doses of acetylcysteine.[9-11] It is now accepted that the patient weight-based standard regimen will not be effective for all patients, and an individualised approach to therapy should be based on the amount of paracetamol ingested.[7] This may also mean that patients ingesting smaller doses of paracetamol with normal liver function could be given acetylcysteine for a shorter duration[5].

The only randomised clinical trial published to date that has examined shorter acetylcysteine regimen compared the traditional three-bag regimen (20.25 h) with a 12 h modified regimen (100 mg/kg over 2 h followed by 200 mg/kg over 10 h; SNAP).[12] The study was primarily designed to examine acetylcysteine adverse effects, which were less with the 12 h regimen. The two regimens had a similar rate of a 50% increase in alanine transaminase (ALT) suggesting similar effectiveness, although this was a

secondary outcome.[12] The authors suggested that patients with no change in their ALT and paracetamol concentrations < 20 mg/L could be discharged at 12 h, but a larger study is required to confirm this. Since this publication, there have been cohort studies supporting the effectiveness of SNAP in widespread use.[13,14] There has also been a small non-randomised cohort study investigating the standard acetylcysteine regimen stopping at 12 h when blood tests are normal, but this has not changed clinical practice in Australia because of the wide confidence intervals around the point estimate of difference in liver injury between arms.[15]

Editorials in both the United Kingdom[16] and Australia[17] have argued for a shorter total duration for patients deemed to be at low risk of hepatotoxicity. The shorter SNAP protocol is now used in across the UK for patients treated within 8 h of ingestion. The acetylcysteine infusion is only stopped at 12 h if paracetamol concentrations are below 20 mg/L, INR 1.3 or less, and ALT < 100 U/L and not more than doubled from admission at the end of a 12 h regimen .[13]

There is a significant clinical advantage in using a shorter acetylcysteine regimen, because it will allow many patients with low-risk paracetamol overdoses to be discharged 12 h post-treatment, shortening length of hospital stay.[14] However, it should be noted that the UK guidelines use a much lower treatment nomogram line and therefore these cohorts include many patients who would not receive any treatment in most countries, including the United States, Europe and Australia.

Our study was designed to examine an even simpler strategy for the majority of patients. We hypothesized that stopping the standard acetylcysteine regimen at 12 h for low-risk patients would provide the same protection as the standard 20 h regimen. We aimed to investigate the effectiveness and safety of this shortened regimen in acute overdoses of ≤ 30 g presenting within 8 h of ingestion.

Methods

Study design and setting

The study design was a multicentre non-inferiority unblinded RCT of a 20 h versus a 12 h regimen of acetylcysteine in patients with low-risk paracetamol overdoses. The primary outcome was the absolute difference between the ALT on admission and the ALT 24 h post-ingestion - ΔALT24. The study was approved by the South Metro Human Research Ethics Committees (HREC/16/QPAH/801), with site-specific approval at the three hospital sites. The study was registered with the Australian New Zealand Clinical Trials Registry, number ACTRN12616001617459. Informed consent was obtained from all patients.

The study was undertaken in three Australian hospitals with dedicated clinical toxicology services. Trained clinical toxicologists treat all poisoned patients presenting to their respective hospitals. The Princess Alexandra Hospital is located in Brisbane, Queensland. Its clinical toxicology unit is based in a tertiary referral adult (>15 years of age) hospital with an emergency department that has approximately 70,000 presentations each year. The Calvary Mater Newcastle (CMN) hospital is located in Newcastle, New South Wales. Its clinical toxicology unit admits all overdoses or poisonings either as primary presentations or hospital referrals (>15 years of age) from a population of over 500,000 people. The Prince of Wales Hospital (POW) is located in Sydney, New South Wales. Its clinical toxicology unit is based within an emergency department that has approximately 60,000 presentations each year. It also admits and takes referrals from nearby hospitals of overdose or poisoned patients.

Study Patients

Patients over 16 years of age were recruited from the 10th July 2017 to the 4th April 2024, if they took an acute single paracetamol overdose, less than or equal to 30 g, presented within 8 h and had an initial paracetamol concentration above but less than twice the nomogram line (paracetamol ratio 1 to 2; Supp Figure 1). The paracetamol ratio is the first paracetamol concentration taken between 4 h and 16 h post ingestion divided by the paracetamol concentration on the 150 mg/L at 4 h standard nomogram line, at the same time point. We excluded any staggered or repeated supratherapeutic ingestions, ingestion of the modified-release formulation, and patients aged 16 years or less.

Treatment Protocol

Patients were identified on admission by nursing or medical staff. All eligible patients with a paracetamol concentration above the nomogram line (Supp Figure 1) were commenced on the 20 h regimen used at the three participating hospitals based on a previous study[8] 200 mg/kg of acetylcysteine over 4 h followed by 100 mg/kg acetylcysteine over 16 h. Once commenced on acetylcysteine and informed consent was obtained, patients were randomised to receive either the full 20 h acetylcysteine (standard treatment arm, 300 mg/kg) or the first 12 h of the 20 h acetylcysteine regimen (experimental treatment arm, 250mg/kg). Randomisation could occur at any time up to the point when the patient has received 12 h of acetylcysteine. Those randomised to receive 12 h of acetylcysteine had their second treatment bag (16 h infusion of acetylcysteine) ceased at 8 h and were then commenced on the equivalent volume of 5% glucose over 8 h.

ALT and paracetamol concentrations were done 12 h after commencement of acetylcysteine (when the infusion was ceased for patients randomised to the experimental arm) and 24 h post ingestion. If the ALT was > 50 IU/L and double the admission value at 12 h post ingestion, the acetylcysteine infusion was continued or restarted for the experimental arm.

Recruitment, randomisation and blinding

Emergency department medical staff were informed and educated on the study and the clinical toxicologists on call at the three participating hospitals identified suitable patients. Once identified, patients were enrolled by contacting the investigator at each study site. The treating doctor obtained consent and randomisation was done on a secure online website, using the biased coin design, including minimisation in the algorithm.

Randomisation was minimised by paracetamol ratio (≤1.5 and >1.5, equivalent to ≤ 225 mg/L and > 225 mg/L at 4 h) and by hospital site (PAH, CMN, POW). Minimisation by the paracetamol ratio was required to ensure a similar distribution of paracetamol concentrations in each arm. Site minimisation was to account for any differences in the outcome measure analysis by the three hospital laboratories. Patients could receive activated charcoal but this factor was not included in the minimisation

strategy. The potential impact of activated charcoal was examined in a post-hoc analysis.

To randomise each patient the online website would generate a random number between 0 and 10,000 and allocation to either arm of the study was dependent on whether the generated number was greater than or less than a set-point equal to X_i, where i=1 to 6 based on the six subgroups the patient was in based according to hospital and paracetamol ratio, and was initially 5000. If any of the subgroups were imbalanced then the set-point was decreased or increased to 4000 or 6000 respectively to reduce the chance that the next patient was randomised to the larger group. Adjustments were made by a blinded author (NB).

There was blinded allocation and once randomisation was completed, this was recorded online and could not be changed. Blinding of the patient, treating clinician or investigator to treatment received was not possible. This would have been unlikely to be effective, given the protocol required changes in the duration of regimen based on laboratory results. We thus pre-specified an objective laboratory based primary outcome to reduce the risk of recording or analytical bias.

Data collection

A data collection form was used which recorded study site, basic demographics, paracetamol dose and ingestion time, paracetamol concentration and ratio, activated charcoal use, and acetylcysteine commencement details. Laboratory results: 12 h after acetylcysteine commencement and 24 h post ingestion paracetamol and ALT were also recorded. An acetylcysteine adverse reaction observation table was used to record all adverse effects on the data collection form. This was recorded at regular intervals, including baseline and for the first 12 h, the heart rate, blood pressure, gastrointestinal symptoms (nausea and vomiting), skin reaction (rash, flushing and itch); and respiratory symptoms (shortness of breath and/or wheeze). The acetylcysteine adverse reaction data sheet has been previously used and published.[18] All data were entered into a purpose designed Microsoft Excel™ datasheet and was de-identified. Each patient had a study code designated at randomization, which was stored separately. The study code was used to identify the patient to retrieve missing or additional data.

Adverse events and data monitoring

All adverse events were monitored, recorded and managed by clinical staff, consistent with standard clinical and quality assurance processes. All patients involved had their liver enzymes closely monitored by the respective site investigator and reported to the lead investigator (CP then GI) and to a Data and Safety Monitoring Committee. Any major adverse events were reported to the ethics committee after each review. In the event that the research team and the data monitoring committee felt that the rate of hepatotoxicity in the experimental arm (12 h) was not consistent with a non-inferior treatment, the study could be ceased.

Study outcomes

The primary outcome was the absolute difference between the ALT 24 h post-ingestion and the admission ALT (ΔALT24), a positive number indicating an increase in the ALT and hepatotoxicity. The secondary outcomes were the proportion of patients with a 50% increase in ALT over the admission ALT at 24 h post-ingestion, the proportion of patients with an ALT > 150U/L and double the admission ALT at 24 h, the proportion of patients in each arm with an ALT > 1000IU/L at any time post ingestion, the proportion of patients with systemic hypersensitivity reactions within 12 h of treatment, and the proportion of patients with gastrointestinal adverse effects within 12 h of treatment. A systemic hypersensitivity reaction was defined as either skin only hypersensitivity reaction or non-immune mediated anaphylaxis, if they met NIAID-FAAN consensus criteria.[19]

Analysis

A statistical equivalence boundary (non-inferiority margin) was used for the sample size calculation,[20] and was based on previous data for current acetylcysteine treatment (20 h regimen) effect, that the new alternative treatment is to be compared. The non-inferiority margin or difference between the two treatment effects being compared should be no more than half of the upper limit of the 95% confidence interval of the standard treatment effect.[20]

The ALT data from 121 paracetamol overdoses (single ingestion of < 30 g within 1 h, and treated with the 20 h acetylcysteine regimen within 8 h of ingestion) from the three hospitals participating in the study was collected, prior to the study commencing (Supp Figure 2). The mean difference between admission and 24 h ALT was 0.2 IU/L with a standard deviation of 10.9 and 95% confidence intervals of -21.2 to 21.6 IU/L. Half the

95% confidence interval (21.4) is 10.7 hence the non-inferiority margin had to be 10 or less. An even tighter margin of 5 IU/L was chosen, as we felt clinicians were unlikely to accept any increased risk. Therefore, a mean difference in ALT (between baseline and 24 h post ingestion, ΔALT24) of less than 5.2 (0.2 + 5) in the new treatment arm (12 h regimen) was considered as a non-inferior treatment of acetylcysteine in paracetamol toxicity.

This is a one-sided test and the alpha level was set at 0.025. With a power of 90% (higher power to minimize the risk of a non-inferior treatment being missed due to chance) and a standard deviation of 10.9 with a non-inferiority limit of 5, the total sample size required was 200 patients - 100 in each arm. Allowing for a 10% margin for failure to adhere to the study protocol, we aimed to recruit 220 patients.

Statistical analysis

The continuous ΔALT24 data was tested for normality by the Kolmogorov-Smirnov test and was found not to be normal, so non-parametric methods were used for the analysis. For the analysis of the primary outcome, non-inferiority was established if the upper limit of the 95% confidence interval of the difference in the medians of the ΔALT24 between the shorter regimen and the standard regimen, was below the pre-defined non inferiority margin of 5. The difference in medians was calculated in PRISM using the Hodges-Lehmann estimate and 95% confidence intervals calculated based on the Hodges-Lehmann method.[21]Secondary outcomes were similarly compared by calculating the 95% confidence intervals in PRISM using the Newcombe/Wilson method with continuity correction.[22] All analysis and graphics will be performed in GraphPad Prism version 10.3.0 for Windows (GraphPad Software, San Diego California USA, www.graphpad.com).

Results

There were 3664 patients with paracetamol poisoning that presented to the three hospitals over the 6 years and 9 month duration of the study. Of these, 204 patient admissions met the inclusion criteria, were recruited to the study and randomised (Figure 1); 190 were recruited once, four were recruited twice and two were recruited three times. No patients were excluded for a paracetamol ratio > 2. One hundred and seven patients were randomised to receive the shorter 12 h regimen, but two of these patients received the standard 20 h regimen and one 17 h of acetylcysteine, so only 104 patients were included in the per-protocol analysis (Figure 1). There were 97 patients randomised to receive the standard 20 h regimen; one patient received a smaller loading dose (50mg/kg over 4h, in error) so was removed from the per protocol analysis.

The two groups were similar in terms of age, sex, dose ingested, paracetamol concentration and paracetamol ratio, baseline ALT, hospital recruited, charcoal administration and time until acetylcysteine commenced (Table 1). One patient in the standard treatment had further acetylcysteine due to ingestion of 35 g (paracetamol ratio < 2) and an increase of the 12 h ALT to 87 U/L from 13 U/L, which decreased at 24 h to 71 U/L. One patient in the shorter regimen took 37 g (paracetamol ratio < 1.5), but their ALT peaked at 11 U/L. Both patients were recruited based on an initial history of less than 30 g being ingested. All other patients received the correct duration of acetylcysteine based on their study allocation and acetylcysteine was not stopped early in any patient.

Outcomes

In an intention to treat analysis, non-inferiority was demonstrated in the difference between the ΔALT24 for 107 patients randomised to the shorter regimen, median of -2 U/L (Interquartile range[IQR]: -7 to 1 U/L) compared to 97 patients randomised to the standard regimen, median -1 U/L (IQR: -5 to 1.5 U/L; difference in medians of -1 U/L; 95% confidence interval [CI] -3 to 1 U/L; less than the upper non-inferiority margin of 5; Figure 2). The per-protocol analysis (104 vs 96 patients) also confirmed non-inferiority on the primary outcome, and no significant differences in any secondary outcomes (Supplementary Table 1). There was no difference between the medians for all subgroups for the primary outcome, including those with a paracetamol ratio > 1.5,

those given activated charcoal, those given acetylcysteine > 6 h post ingestion versus those given it < 6 h, and those ingesting > 20 g (Figure 3, Supplementary Table 2).

No patients receiving the shorter regimen had an ALT at 24 h double the admission value and > 150 U/L, compared to one (1%) patient receiving the standard regimen, and a similar proportion of patients in each group had a 50% increase in ALT over the admission ALT at 24 hours post ingestion (Table 2). No patient had an ALT > 1000U/L. There were five patients with an ALT > 50 IU/L and double the admission value at 12 h after the infusion commenced. One received the shorter regimen, but did not have acetylcysteine recommenced and the ALT decreased 24 h post-ingestion. Four patients received the regular regimen, and in three the ALT decreased 24 h post-ingestion. A further 22 patients had a 12-hour post-infusion ALT > 50 IU/L, but not double their admission ALT (Supplementary Figure 3).

Systemic hypersensitivity reactions were similar between groups 9/107 (8%) for the short regimen versus 10/97 (10%) in the standard regimen (absolute difference, 2%; 95% CI: -7 to 11%; Table 2). Gastrointestinal adverse effects occurred in 78 (73%) of patients receiving the shorter regimen compared to 63 patients (65%) receiving the standard regimen (absolute difference, 8%; 95%CI: -5 to 21%; Table 2).

Discussion

We have demonstrated that acetylcysteine given for 12 h is not inferior to the standard 20 h regimen for patients ingesting an acute immediate release overdose of ≤ 30 g, treated within 8 h of ingestion. Outcomes were similar for patients more likely to have toxicity; ingesting doses > 20 g (and/or paracetamol ratios > 1.5), further supporting the similar effectiveness of the shorter 12 h regimen. No patients had an ALT > 1000 U/L and hypersensitivity reactions were similar between groups.

Our study was designed specifically to look at shortening the duration of the acetylcysteine regimen from 20 h to 12 h, which is accompanied by a decrease in the dose. Although this does not include all patients with paracetamol toxicity, such as those with staggered ingestions and presenting to hospital after 8 h, it constitutes between 20% and 35% of patients (Figure 1).

Based on our understanding of the historical evidence behind the original acetylcysteine regimen that was empirically derived to administer a large loading dose (patients thought to be glutathione deplete on presentation) and a 20 h infusion (5 times a theoretical 4h half-life of paracetamol). [4,7] More recent evidence has suggested a "one size fits all" approach is not suitable for all patients.[6] Currently we manage most paracetamol overdoses with a patient weight-based acetylcysteine dose (300 mg/kg) and not based on paracetamol (NAPQI) body burden. In our study we demonstrated that acetylcysteine could be adjusted (250 mg/kg over 12 h vs. 300 mg/kg over 20 h) based on the amount of paracetamol ingested (less than or equal to versus greater than 30 g), if the patient presents within 8 h and the paracetamol ratio is less than 2. This builds on the principle of paracetamol individualising acetylcysteine therapy, as increased doses (400 mg/kg over 20 h) are already recommended for larger ingestions with an paracetamol ratio > 2 and hence more NAPQI.[9] In lower risk patients, selective use of 12 h acetylcysteine regimens will significantly shorten the average patient's length of stay in hospital.[14]

To establish non-inferiority in effectiveness, we used a difference in ALT based on historical data taken from the three toxicology units involved in the study (Supp Fig 1; Figure 2). This has allowed us to choose a very rigorous statistical equivalence boundary, such small changes in ALT are extremely sensitive indicators of liver injury, much less than those that would indicate clinically significant liver toxicity.[23] The trial

was designed to detect an increased risk of even very small increases in ALT. However, the increases in ALT we used as an outcome in this trial were mostly not clinically important or even enough to justify any change in management (e.g. further observation in hospital).

We found a high rate of gastrointestinal adverse effects, which may be due to additional gastrointestinal effects of paracetamol toxicity, but alternatively due to better recording of adverse effects in a prospective clinical trial. A recent systematic review found that gastrointestinal side-effects ranged from <1% to 76%.[24] Higher rates tended to be from prospective studies, whereas lower rates were likely under-reporting in retrospective studies.[24] In the SNAP clinical trial the standard regimen had similar high rates of vomiting of 60-65% to our study, but the experimental SNAP protocol had less with half the loading dose of acetylcysteine.[12] Therefore, the higher rates of gastrointestinal effects may be associated with the acetylcysteine loading dose, which was the same in both arms of our study.

The shorter acetylcysteine regimen of 12 h can be applied to any region or country currently using the standard two bag or three bag acetylcysteine regimen. This includes most of the world except for the United Kingdom where SNAP is the standard treatment. The main difference between many parts of the world is the criteria for the administration of acetylcysteine, with different risk assessment tools, such as lower nomogram lines. However, it is important that the shorter regimen is only applied to the same group included in our study: acute ingestions of immediate release paracetamol < 30 g presenting with 8 h of ingestion.

There are some important limitations to note. We had strict inclusion criteria (Figure 1), and these results cannot necessarily be generalised to the many people who present with unclear timing of the overdose. Nor can acetylcysteine treatment of immediate release overdoses over 30 g or modified-release paracetamol ingestions be treated based on our results. There is a very slight possibility that patients were not included in the study because they had a paracetamol ratio close to 2. This is unlikely because all patients were discussed with the clinical toxicologist and there were only a small number of missed patients, almost always due to late notification to the investigators. Finally, there was an imbalance in the two study arms. This was because attempting to balance allocation for six subgroups using a biased coin randomisation, with a study of 204 patients, lead to an overall imbalance. We opted for randomisation to be balanced

for each subgroup (three hospitals and two paracetamol ratio groups > 1.5 or < 1.5; Table 1), rather than overall.

In conclusion, a shorter 12 h regimen of acetylcysteine had the same effectiveness and safety as the standard 20 h regime in moderate paracetamol overdoses (≤ 30g), almost halving the length of treatment required and therefore hospital admission duration.

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Table 1. Baseline demographics, paracetamol dose and concentration, hospital and treatments.

Baseline characteristic	Standard (97)	Short (107)
Age (years)	25 (21 - 32)	24 (19 - 38)
Female	85 (87%)	93 (87%)
Dose (g)*	15 (12 – 20; 8.5 – 35)	15 (13 – 20; 5 – 37)
Paracetamol concentration (mg/L)	182 (148 – 219)	179 (152 – 228)
Paracetamol ratio	1.3 (1.1-1.5)	1.3 (1.1 - 1.5)
Paracetamol ratio > 1.5	26 (27%)	32 (30%)
Baseline alanine transaminase (U/L)*	18 (13 – 24;5 – 108)	22 (15 – 35; 5 – 169)
Hospital		
Princess Alexandra	66 (68%)	74 (69%)
Calvary Mater Newcastle	26 (27%)	29 (27%)
Prince of Wales	5 (5%)	4 (4%)
Activated Charcoal	13 (13%)	17 (16%)
Time to acetylcysteine (hours)	6.2 (5.5 – 6.8)	6.2 (5.7 – 7.2)

NB: Data shown are median (interquartile range [IQR]) or n (%) except * median (IQR; range).

Table 2. Primary and secondary outcomes for the standard versus short regimens for the intention to treat analysis, with medians (primary outcome) or proportions (secondary outcomes) and 95% confidence intervals in parentheses.

Outcome	Standard (N=97)	Short (N=107)	Difference
ΔALT24	-1 (-5 to 1.8)	-2 (-7 to 1.8)	-1 (-3 to 1)
ΔALT24 > 50%	8 (8.2%)	8 (7.5%)	0.8% (-8 to 9%)
ALT24 > 150 U/L and double ALT_0	1 (1%)	0	1% (-4 to 5%)
Peak ALT > 1000 U/L	0	0	-
Adverse Effects			
Systemic hypersensitivity	10 (10%)	9 (8%)	2% (-7 to 11%)
Gastrointestinal effects	61 (63%)	77 (72%)	9% (-4% to 22%)

ALT – alanine transaminase; ΔALT24 – delta ALT24, difference between the ALT at 24 h and the ALT on admission.

Figure Legends

Figure 1. Flow diagram and patients with paracetamol poisoning, those eligible for the study and exclusions, randomised patients and three trial violations.

Figure 2. Frequency histogram of the delta ALT (24 h ALT – admission ALT) for patients given the short regimen (12 h; green) versus patients given the standard regimen (20 h; blue)

Figure 3. Forest plot of the difference between the median (with 95% confidence intervals) for the primary outcome of absolute difference between the ALT on admission and the ALT 24 h post-ingestion, in those having the standard regimen (20 h) versus those having the shorter regimen (12 h).

Figure 1

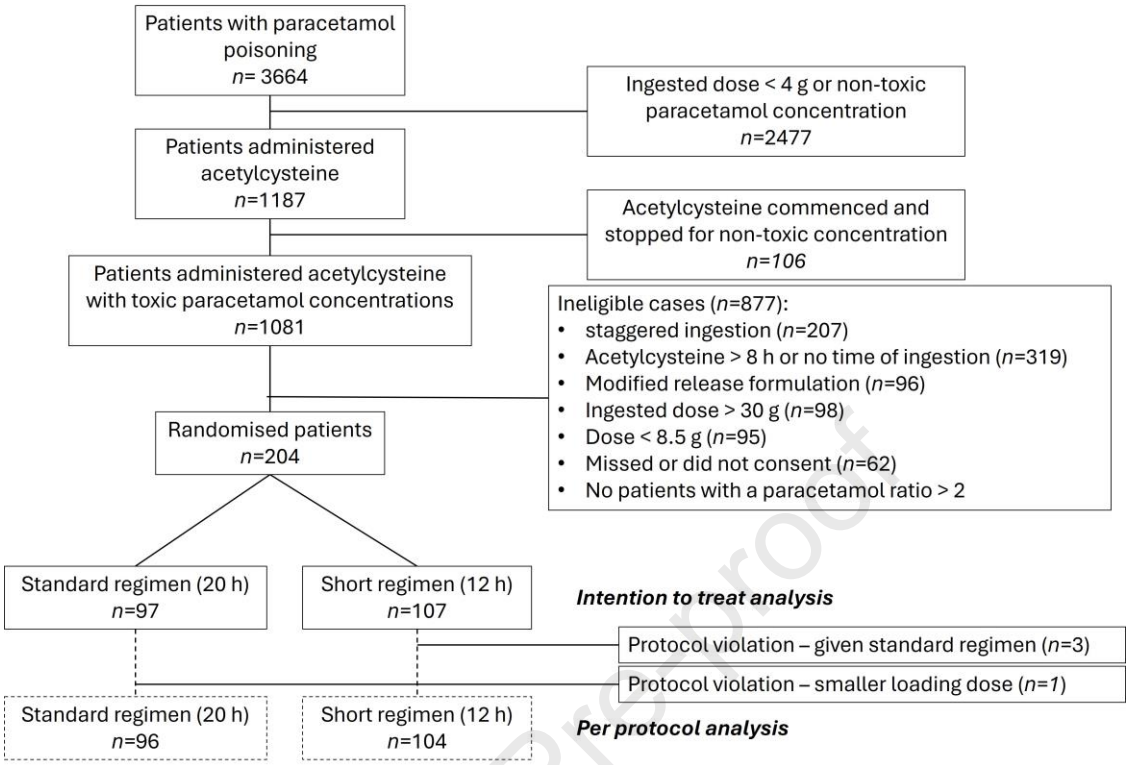


Figure 2.

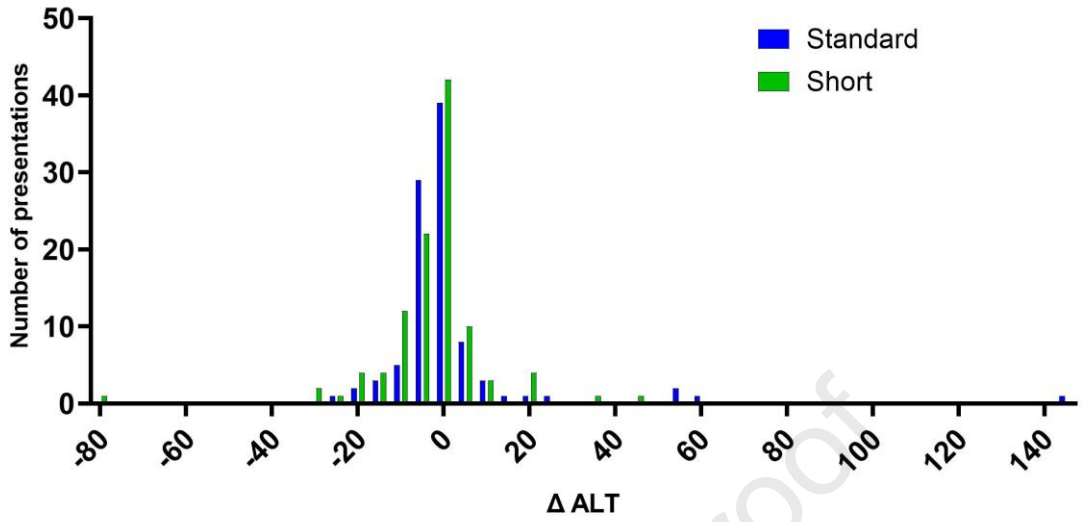
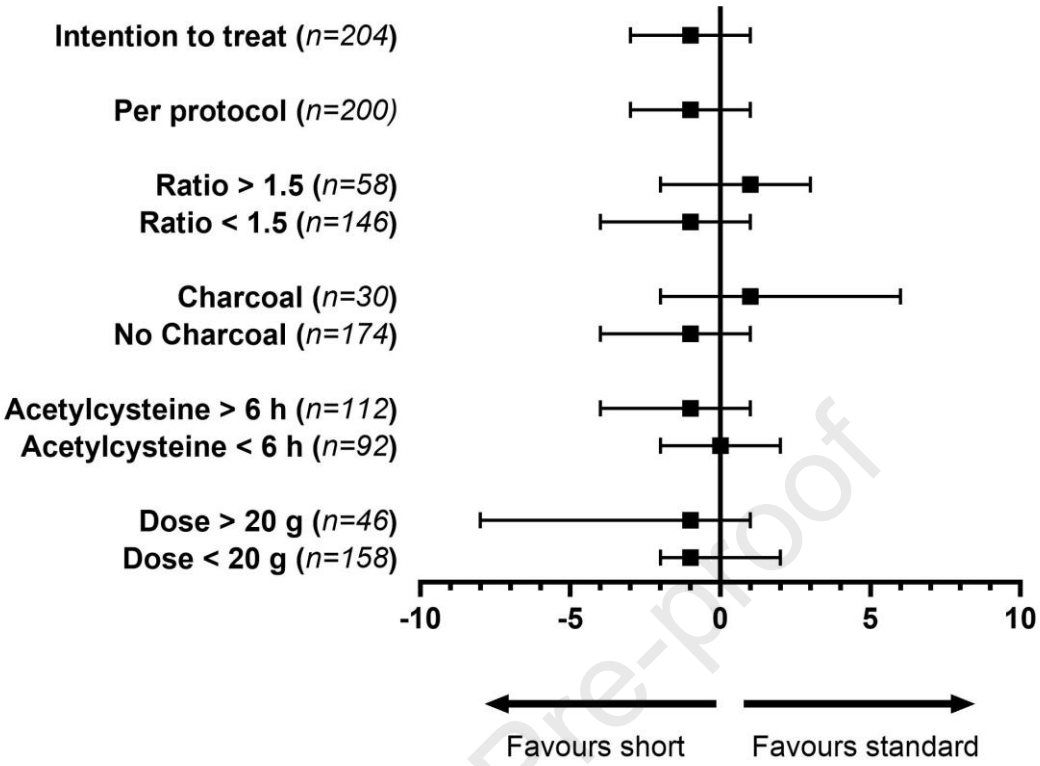


Figure 3.



Highlights

- A shorter 12h acetylcysteine regimen was as effective as the standard 20 h regimen in <30g paracetamol overdoses.
- The shorter regimen was safe with similar adverse effects.
- The 12 hour regimen almost halved the length of treatment.