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Research Paper

Efficacy of a two bag acetylcysteine regimen to treat paracetamol overdose (2NAC study)

Anselm Wong[a,b,c,*], Geoff Isbister[d,e], Richard McNulty[f,g], Katherine Isoardi[h,i], Keith Harris[j,k], Angela Chiew[l,m], Shaun Greene[a,b,n,o], Naren Gunja[g,p,q], Nicholas Buckley[r,s], Colin Page[j,k], Andis Graudins[c,t]

[a] *Victorian Poisons Information Centre and Austin Toxicology Unit, Victoria, Australia*
[b] *Centre for Integrated Critical Care, Department of Medicine and Radiology, University of Melbourne, Victoria, Australia*
[c] *Department of Medicine, School of Clinical Sciences at Monash Health, Monash University, Victoria, Australia*
[d] *Clinical Toxicology Research Group, University of Newcastle, NSW, Australia*
[e] *Department of Clinical Toxicology, Calvary Mater Newcastle, NSW, Australia*
[f] *Department of Emergency Medicine, Blacktown Mount Druitt hospitals, Sydney, Australia*
[g] *Western Sydney Toxicology Service, Western Sydney LHD, Sydney, Australia*
[h] *Clinical Toxicology Unit, Princess Alexandra Hospital, Brisbane, Australia*
[i] *Faculty of Medicine, University of Queensland, Brisbane, Australia*
[j] *Clinical Toxicology Unit, Princess Alexandra Hospital, Brisbane, Queensland, Australia*
[k] *School of Medicine, The University of Queensland, Brisbane, Queensland, Australia*
[l] *Clinical Toxicology Unit, Princes of Wales Hospital, Randwick, NSW, Australia*
[m] *Pharmacology, Faculty of Medicine and Health, University of Sydney, Australia*
[n] *Department of Forensic Medicine, Monash University, Victoria, Australia*
[o] *Guy's and St Thomas' NHS Foundation Trust, United Kingdom*
[p] *Department of Emergency Medicine, Westmead Hospital, Sydney, Australia*
[q] *Emergency Medicine, Westmead Clinical School, University of Sydney, Australia*
[r] *Department of Pharmacology, Faculty of Medicine and Health, University of Sydney, Australia*
[s] *NSW Poisons Information Centre, Children's Hospital at Westmead, Westmead, NSW, Australia*
[t] *Monash Toxicology Unit, Dandenong Hospital, Monash Health, Victoria, Australia*

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ABSTRACT

Background: Previous studies of paracetamol overdose treatment show that a 2-bag, 20-h intravenous (IV) acetylcysteine regimen decreased the incidence of non-allergic anaphylactic reactions compared to the 3-bag, 21 h IV regimen, but have not examined efficacy of the 20-h 2 bag regimen.

Methods: This was a multi-centre observational study of paracetamol overdose presentations treated with a 2-bag IV acetylcysteine regimen (200 mg/kg over 4 h, 100 mg/kg over 16 h) compared to a 3-bag regimen, performed from 2009 to 2019. Patients were referred from the emergency department to the inpatient toxicology units for continued management. For the primary non-inferiority analysis: subjects had single, acute ingestions, a serum paracetamol-concentration performed 4 to 8-h post-ingestion. The primary outcome was development of acute liver injury (ALI), defined as peak ALT>150 U/L; and > double admission baseline ALT (for presentations within 24 h post-overdose). Secondary outcomes included adverse reactions to acetylcysteine (cutaneous and systemic).

Finding: Out of 6419 paracetamol overdoses, 2763 received acetylcysteine. For the primary analysis, 1003 received the 2-bag and 783 the 3-bag acetylcysteine regimen. When presentation bloods were performed 4 to 8-h post-overdose, 21 (3.1%) developed ALI with the 2-bag regimen vs 16 (2.9%) with the 3-bag regimen (Difference: 0.2%, 95%CI:-1.6 to 2.2). The incidence of hepatotoxicity was: 1.2% (n = 8) with the two-bag regimen and 1.6% (n = 9) with the three-bag regimen (Difference -0.4%, 95%CI -1.75, 0.91). When presentation bloods were performed 8 to 24-h post-overdose, 70 (21%) developed ALI with the 2-bag regimen vs 46 (23%) with the 3-bag regimen (Difference: -2%, 95%CI -9.12 to 5.36). There were significantly less cutaneous and systemic non-allergic anaphylactic reactions recorded after treatment with the two-bag than the three-bag regimen (1.3% [n = 17] and 7.1% [n = 65], Difference: -5.8%, 95%CI -7.6 to -4.0, $p < 0.0001$), respectively.

Interpretation: A two-bag intravenous acetylcysteine regimen was found to be non-inferior to the three-bag regimen with regards to efficacy in preventing acute liver injury for early presentations of paracetamol

* Corresponding author.
E-mail address: anselm.wong@austin.org.au (A. Wong).

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overdose. No important differences were seen for any other presentations. The two-bag regimen also decreased the incidence of both non-allergic anaphylactic reactions and gastrointestinal adverse events from acetylcysteine treatment.

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Research in Context

Evidence before this study

Paracetamol overdose is the most common pharmaceutical poisoning worldwide and can lead to liver injury or acute liver failure. For the last 40 years, a 3 bag intravenous acetylcysteine regimen has been used to treat paracetamol overdose worldwide. However, adverse reactions to acetylcysteine are common and the infusion regimen is complex. Acetylcysteine regimens that have given an initial loading dose over a longer period have shown to decrease these adverse reactions. Specific to this paper, a 2 bag 20 h acetylcysteine regimen has shown to decrease the number of infusion changes and adverse reactions. However, the efficacy of this regimen to prevent liver injury has not been studied.

Added Value of this study

We present evidence from a multi-centre observational study including nine treatment centres. This study shows that a 2 bag intravenous acetylcysteine regimen is as efficacious compared to the traditional 3 bag regimen to treat paracetamol overdose. The study also confirms that a 2 bag regimen reduced the incidence of non-allergic anaphylactic reactions caused by acetylcysteine in a large cohort.

Implications of all the available evidence

The incidence of paracetamol overdose is increasing in many countries and new treatment regimens are needed to simplify treatment and decrease adverse reactions to acetylcysteine. To our knowledge, this is the first large multi-centre study describing the efficacy and safety of the 2 bag 20 h intravenous acetylcysteine regimen to treat paracetamol overdose. This research will have implications of changing national and international treatment guidelines for the management of paracetamol overdose.

1. Introduction

Paracetamol overdose is the most common pharmaceutical poisoning in developed countries and the incidence is increasing in the developing world [1]. It accounts for half of overdoses in the United Kingdom alone (100,000 hospital presentations per annum vs 10,000 in Australia) and is the most frequent call to poisons information centres in Australia [2,3]. A recent study from the United States reported that acute liver failure was the result of paracetamol overdose in 53% of cases (approximately 1000 patients per annum in the US) [4].

After paracetamol overdose, increased production of N-acetyl para-benzoquinoneimine (NAPQI) rapidly depletes hepatic glutathione stores. NAPQI production results in hepatocyte injury. Acetylcysteine (N-acetylcysteine or NAC) is primarily administered to replenish glutathione stores and prevent or mitigate hepatotoxicity after overdose [5]. For the last 40 years, the intravenous (IV) NAC regimen used to treat patients with paracetamol toxicity has been a 20 to 21 h, three-bag infusion regimen [5]. The IV three-bag infusion-dosing regimen used in Australia for many years is 150 mg/kg over one hour, 50 mg/kg over four hours and 100 mg/kg over 16 h [6]. However, prescribing and dispensing errors are common, and often result from dose calculation errors and incorrect infusion rates [7].

The major problem with acetylcysteine treatment is the high proportion of patients developing early adverse reactions to the loading infusion. This appears to be worse with the three-bag regimen [8,9]. The reactions are primarily non-allergic anaphylactic reactions that occur after the loading-dose infusion given over 15-min to one hour. In addition, this can lead to treatment interruption and/or premature cessation of acetylcysteine. Previous studies involving the SNAP (Scottish and Newcastle Antiemetic Pretreatment) regimen [10] and a recent study by Pettie et al. [11] have shown that by infusing the initial loading dose over two hours, it can decrease the number of adverse effects related to acetylcysteine. In addition, recent studies involving hundreds of patients have shown that a two-bag 20 h regimen (200 mg/kg IV loading dose of acetylcysteine infused over four hours, with a further 100 mg/kg infused over 16-h) reduces the incidence and severity of non-allergic anaphylactic reactions, compared to the three-bag regimen administering the same total dose over a similar time-frame [12–15]. Multiple treatment centres in Australia, New Zealand, the US, Vietnam, Sweden and Denmark have adopted the regimen [12–18]. However, there are limited data examining the effectiveness of this two-bag regimen in comparison to the traditional three-bag regimen.

Our aim was to compare the rate of acute liver injury after paracetamol overdose in patients treated with a two-bag acetylcysteine regimen compared to those treated with the three-bag regimen.

2. Methods

2.1. Study design and settings

This was a multi-centre, observational study of patients with paracetamol poisoning requiring acetylcysteine treatment presenting to the Emergency Departments (EDs) of nine Australian metropolitan hospitals. Hospitals included Monash Health (Monash Medical Centre, Dandenong and Casey) and Austin Hospital in Victoria; Calvary Mater Newcastle, Westmead, Blacktown, Prince of Wales Hospitals in New South Wales; and Princess Alexandra Hospital in Queensland. The study was approved by the Monash Health Research and Ethics Committee. This study used the STROBE guidelines for reporting [19].

Use of the two-bag IV acetylcysteine regimen was instituted at the study hospitals from February 2014 with a change in hospital acetylcysteine treatment infusion protocols. Acetylcysteine was commenced based upon the treatment threshold recommendations in the Australian and New Zealand Paracetamol Overdose Management Guidelines [6] and in consultation with the toxicology inpatient units at each site.

For single acute overdoses presenting within 24 h, the modified Rumack-Matthew Nomogram was used with a threshold for treatment based upon a paracetamol concentration greater than 150 mg/L at four hours post-overdose. All paracetamol overdoses were managed by the toxicology units at the respective sites.

Paracetamol overdose patients requiring acetylcysteine were identified on presentation at each toxicology unit and data collected retrospectively from the electronic medical records into a purpose-designed database. The data collected included: type of paracetamol product and formulation; patient age and sex; dose of paracetamol ingested; total acetylcysteine dose; duration of infusion; adverse reactions to acetylcysteine; time from overdose to acetylcysteine; length of stay, mortality; type of paracetamol overdose (deliberate self-poisoning, supra-therapeutic ingestions, accidental); admission paracetamol concentration; time from overdose to paracetamol concentration; peak international normalized ratio (INR), initial and peak alanine transaminase (ALT).

3. Inclusion and exclusion groups

We screened all admissions where IV acetylcysteine was administered using the two-bag regimen (200 mg/kg over four hours followed by 100 mg/kg over 16 h) from February 2014 to April 2019. The cohort was compared with a historical cohort of patients with paracetamol overdose treated with the three-bag IV acetylcysteine regimen (150 mg/kg in 200 mL over 1 h, 50 mg/kg over 4 h and 100 mg/kg over 16 h) from October 2009 to May 2015 (overlap between some sites before changeover).

The comparisons were further stratified into groups based on time from ingestion to initial blood tests. Our primary analysis was undertaken on the group with the most common paracetamol overdose presentation: acute single ingestion (initial presentation blood tests taken 4 to 8 h post ingestion) with a secondary analysis performed on other groups. These groups included acute single ingestion (initial blood tests taken 8 to 24 h, combined 4−24 h, and > 24 h), deliberate staggered ingestion (ingestion over more than 2 h) and unknown time of ingestion.

In Australia, those with repeated supratherapeutic ingestions, as defined in the Australian and New Zealand Paracetamol Guideline [6], may receive a shorter treatment course and were therefore excluded from analysis. In addition, those who had sole presentation blood tests performed prior to 4 h post ingestion (e.g. not interpretable in relation to Rumack-Matthew treatment nomogram) or did not receive acetylcysteine were excluded from the analysis.

3.1 Outcome measures

The primary outcome was the incidence of acute liver injury (ALI) (defined as peak ALT>150 U/L during admission; and > double admission baseline ALT (for presentations within 24 h post-overdose)).

Secondary outcomes included incidence of hepatotoxicity (peak ALT>1000 U/L), peak international normalized ratio (INR), length of stay, fulminant hepatic failure and mortality. Non-allergic anaphylactic reactions (or non-IgE mediated allergic reactions) secondary to administration of acetylcysteine were also recorded. These were classified into cutaneous symptoms (flushing, rash, urticaria, itch); and more severe reactions including respiratory symptoms (bronchospasm, wheeze, dyspnea, shortness of breath), angioedema and cardiovascular instability (ie. hypotension). Gastrointestinal symptoms were also recorded, and included nausea, vomiting or both.

3.2 Statistical methods

A previous study, performed by the authors, assessing incidence of adverse reactions with the two-bag acetylcysteine regimen also reported rates of hepatic injury [12]. From an analysis of the study data, there was a 4% rate of ALI in acute single-ingestion paracetamol overdoses with an initial blood test taken within 4 to 8 h of ingestion (primary analysis group), using a treatment nomogram line threshold of 150 mg/L at 4 h. In addition, a similar rate of ALI was reported in a recent study of paracetamol overdose patients treated with a three-bag acetylcysteine regimen [20]. In this study, all sub-groups had rates of ALI of at least 3%, with some sub-groups being much higher.

For the primary analysis group, we aimed to show non-inferiority of the two-bag regimen compared to the three-bag regimen for the outcome of ALI. We calculated that if there was no difference in rates of ALI (4% in each group with initial blood tests taken between 4 and 8 h post-ingestion), we would have 80% power to exclude an absolute difference in favour of the three-bag regimen of more than 3% (one tailed 95% CI of the new regimen would lie within 3% of the rate of the standard group) with 528 patient in each group (Sealed Envelope™, London, UK).

Descriptive data are reported as mean with 95% confidence intervals (CI) or medians and interquartile range (IQR). Continuous variable were compared using the Mann-Whitney U test. Odds ratio (95% CI) and absolute percentage differences were used to compare treatment groups. A negative difference favours the two bag regimen. Statistical analysis was performed using GraphPad Prism V7 (GraphPad software, La Jolla, CA, USA).

4. Results

During the study period there were a total of 6419 paracetamol overdose presentations. The study inclusion criteria were met by 1300 treated with the two-bag regimen and 911 treated with the three-bag regimen (Fig. 1). The median age of patients treated was similar in the two- and three-bag regimens, respectively (27 years [IQR: 19,43] vs 26 [19,38], Table 1). Overdoses were primarily taken by females in both groups (73% vs 80%). The median paracetamol dose reportedly ingested was similar (16 g (10,25) in the two-bag regimen vs 17 g (12,25) in the three-bag regimen). The most common type of presentation was patients with acute single ingestions (n = 2086).

5. Primary group analysis

5.1 Acute single ingestions with initial blood tests performed 4 to 8 h post overdose

Patients having their first paracetamol assay between four- and eight-hours post-ingestion included 668 (41%) vs 557 (49%), in the two- and three-bag groups, respectively (Table 2). ALI was observed in 3.1% (21/668) with the two-bag regimen and 2.9% (16/557) with the three-bag regimen (Difference: 0.2%, 95%CI: −1.6 to 2.2). The incidence of hepatotoxicity was: 1.2% (n = 8) with the two-bag regimen and 1.6% (n = 9) with the three-bag regimen (Difference −0.4%, 95%CI −1.75 to 0.91). The incidence of peak INR >2.0 was 0.9% (n = 6) with the two-bag regimen vs 0.4% (n = 2) with the three-bag regimen (Difference: 0.5%, 95%CI −0.33 to 1.41). The median time from paracetamol ingestion to start of acetylcysteine was six hours (5.5,7) in the two-bag group vs six hours (5,7) in the three-bag group (p = 0.56).

6. Other group analyses

6.1 Acute single ingestions with initial blood tests performed 8 to 24 h post overdose

In the group assessed 8 to 24 h post-overdose, 21% (70/335) developed ALI with the two-bag regimen vs 23% (46/202) with the three-bag regimen (Difference: −2%, 95%CI −9.12 to 5.36). The incidence of hepatotoxicity was 14% (n = 46) with the two-bag regimen and 16% (n = 32) with the three-bag regimen (Difference: −2%, 95% CI

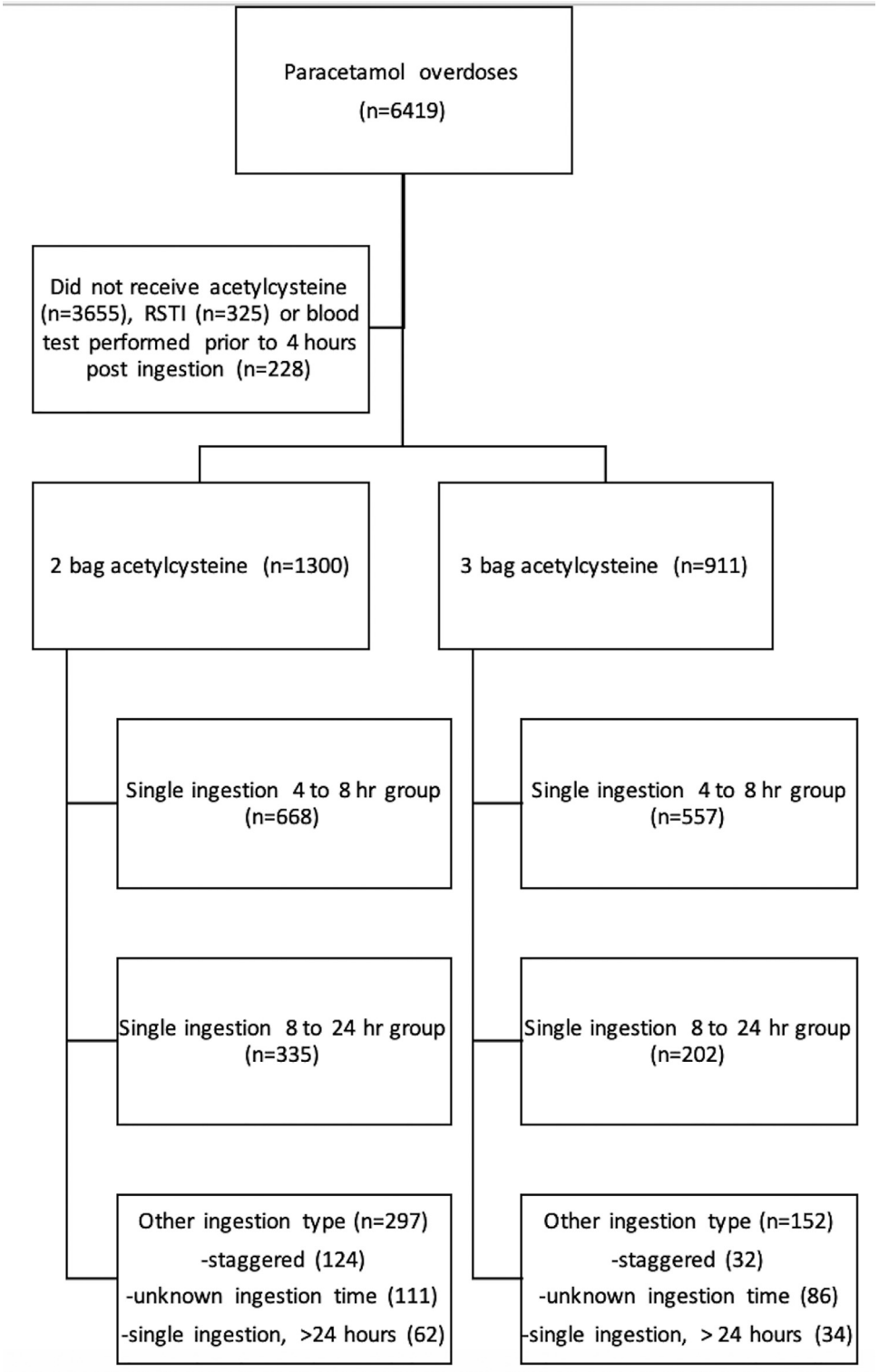

Fig. 1. Paracetamol overdose patients treated with a 2 or 3 bag acetylcysteine regimen. RSTI = repeated supratherapeutic ingestion.

−8.3 to 4.1). The incidence of peak INR >2.0 was 6.9% (n = 23) with the two-bag regimen vs 7.4% (n = 15) with the three-bag regimen (Difference: −0.5, 95% CI −5.1 to 3.9). The median time from paracetamol ingestion to start of acetylcysteine was 14 h (11,18) in the two-bag group vs 13 h (11,17) in the three-bag group (p = 0.1). Fulminant hepatic failure developed in four patients (1.2%) receiving the two-bag regimen and three patients (1.5%) receiving the three-bag regimen (Difference: −0.3, 95% CI −2.3 to 1.7). There was no mortality in patients receiving either acetylcysteine regimen.

6.2 Acute single ingestion with initial blood tests performed 4 to 24 h post overdose

There were 1003 patients who received the two-bag regimen and 759 patients receiving the three-bag regimen with initial blood tests taken between 4- and 24-h post-overdose. There was no difference in the incidence of ALI in patients whose bloods tests were taken between 4 and 24 h post-acute single ingestion of paracetamol: (9.0% [n = 91] for the two-bag regimen and 8.2% [n = 62] for the three-bag

Table 1
Demographics of patients treated with acetylcysteine for paracetamol overdose.

	Single ingestion, initial bloods 4–8 h post ingestion (% total)		Single ingestion, initial bloods 8–24 h post ingestion (% total)		Single ingestion, initial bloods 4–24 h post ingestion (% total)		Single ingestion, initial bloods >24 h post ingestion (% total)		Single ingestion, unknown time (% total)		Deliberate Staggered ingestion (% total)	
	2 bag, *n* = 668 (41)	3 bag, *n* = 557(49)	2 bag, *n* = 335 (20)	3 bag, *n* = 202 (18)	2 bag, *n* = 1003 (61)	3 bag, *n* = 759 (67)	2 bag, *n* = 62 (4)	3 bag, *n* = 34 (3)	2 bag, *n* = 111 (7)	3 bag, *n* = 86 (8)	2 bag, *n* = 124 (7)	3 bag, *n* = 32 (3)
Age, years (IQR)	23 (18,36)	22 (17,34)	24 (18,39)	24 (17,35)	24 (18,37)	22 (17,35)	29 (20,43)	29 (20,40)	39 (26,53)	34 (23,55)	32 (24,48)	32 (19,46)
Female, n (%)	531 (80)	457 (82)	247 (74)	161 (80)	778 (78)	618 (81)	50 (81)	26 (77)	67 (60)	61 (70)	89 (72)	22 (69)
Time to acetylcysteine, hours (IQR)	6 (5.5,7)	6 (5,7)	14 (11,18)	13 (11,17)	7 (6,12)	7 (5,10)	38 (29,50)	39 (30, 48)	–	–	12 (7,19)	12 (7,24)
Dose paracetamol ingested, mg/kg (IQR)	255 (185, 368)	262 (194, 400)	241 (156,352)	231 (167,338)	250 (177,357)	250 (185,380)	238 (146,366)	334 (197,459)	322 (151,1277)	380 (283,3983)	202 (160,384)	373 (186,769)
Median paracetamol concentration on presentation, mg/L (IQR)	163 (120,217)	158 (106,210)	54 (19,105)	76 (30,399)	138 (64, 193)	143 (79,199)	12 (10,37)	21 (1,94)	45 (15,133)	52 (1156)	73 (21,152)	69 (9155)
Median alanine transaminase (ALT) on presentation, U/L (IQR)	20 (14,31)	19 (13,27)	28 (16,63)	26 (16,48)	21 (15,38)	26 (16,48)	174 (32,1018)	390 (20,4446)	39 (19,130)	30 (17,74)	25 (16,69)	32 (20,105)
Median peak INR during admission (IQR)	1.2 (1.1.1.3)	1.2 (1.1,1.3)	1.2 (1.1,1.4)	1.3 (1.1,1.8)	1.2 (1.1,1.4)	1.2 (1.1,1.4)	1.4 (1.2,2.2)	1.4 (1.1,4.4)	1.2 (1.1,1.8)	1.3 (1.1,2)	1.1 (1,1.3)	12 (1,2.2)
Co-ingestant: Ethanol, n (%)	109 (16)	87 (16)	29 (9)	26 (13)	138 (14)	113 (15)	8 (13)	9 (26)	19 (17)	16 (19)	21 (17)	7 (22)
Co-ingestant: opioids, n (%)	100 (15)	111 (20)	72 (21)	27 (13)	172 (17)	138 (18)	12 (19)	6 (18)	29 (26)	23 (27)	38 (30)	7 (22)
Modified release paracetamol preparation, n (%)	76 (11)	40 (7)	46 (14)	18 (9)	122 (12)	58 (8)	6 (10)	4 (12)	10 (9)	3 (4)	6 (5)	2 (6)
Activated charcoal given, n (%)	57 (9)	40 (7)	13 (4)	4 (2)	70 (7)	44 (6)	1 (2)	0	4 (4)	5 (6)	2 (2)	0
Median duration of acetylcysteine, hours (IQR)	20 (20,20)	21 (21,21)	20 (20,36)	21 (21,36)	20 (20,20)	21 (21,21)	20 (20,36)	21 (37,82)	20 (17,21)	21 (21,21)	20 (20,20)	21 (21,21)
Median hospital length of stay, days (IQR)	1 (1,1.2)	1.5 (1,2)	1 (1,2)	1 (1,2)	1 (1,1.5)	1.3 (1,2)	1 (1,3)	1 (1,4)	1 (1,2)	1 (1,2)	1 (1,2)	2 (1,3)

Table 2
Outcome table for primary analysis: single ingestions within initial presentation blood tests taken 4–8 h post overdose. ALT= Alanine transaminase, INR=international normalized ratio. There was no statistically significant difference between outcomes when comparing the treatment regimens.

	2 bag regimen, *n* = 668	3 bag regimen, *n* = 557	Absolute difference% (95%CI)
Peak ALT >150 U/L and double baseline, n (%)	21 (3.1)	16 (2.9)	0.2 (−1.6,2.2)
ALT > 1000 U/L, n (%)	8 (1.2)	9 (1.6)	−0.4 (−1.8,0.9)
Peak INR > 2, n (%)	6 (0.9)	2 (0.4)	0.5 (−0.3,1.4)
Fulminant hepatic failure, n (%)	1 (0.15)	1 (0.18)	−0.03 (−0.49,0.43)
Mortality, n	0	0	0

regimen (Difference: 0.8%, 95% CI −1.7 to 3.5%). In addition, the incidence of hepatotoxicity was also similar (5.38% [*n* = 54] with the two-bag regimen and 5.4% [*n* = 41] with the three-bag regimen (Difference: −0.02%, 95%CI −2.1 to 2.2). Stratification by nomogram group depending upon paracetamol concentration is shown in Table 3*a*+3b.

7. Other ingestion types

There were no differences in incidence of ALI, hepatotoxicity or INR >2 when comparing the two-bag and three-bag regimens in the single ingestion with initial blood tests performed >24 h, unknown time of ingestion and deliberate staggered ingestion groups (Table 4).

8. All groups analysis

Overall, there was no difference in the incidence of ALI, hepatotoxicity, peak INR >2.0 or mortality when using the two- or three-bag regimens (Table 5).

There was no difference in the overall incidence of ALI (183/1300 [14%] vs 115/911 [13%], Difference: 1% 95% CI −1.4 to 4.3, p = 0.4) or hepatotoxicity (96 [7.4%] vs 76 [8.3%], Difference: −0.9% 95% CI −3.3 to 1.3, p = 0.41) comparing the two-bag and three-bag regimens, respectively (Fig. 2). There were two transfers to a liver transplant unit, one in each group, with both patients surviving. There was one death in each group related to fulminant hepatic failure. There was one death from an intracranial haemorrhage as a complication of thrombolytic therapy to treat a massive pulmonary embolism in a patient treated with the two-bag regimen.

Table 3
Incidence of (a) acute liver injury (ALI) and (b) hepatotoxicity after paracetamol overdose from presentation tests with paracetamol concentration taken 4 to 24 h post-ingestion.These concentrations refer to the back-extrapolation of the paracetamol concentration on the nomogram to the 4 h mark assuming a 4 h paracetamol elimination half-life. ALT=alanine transaminase.

a) ALI	2 bag regimen			3 bag regimen			P value	Absolute difference% (95%CI)
Nomogram group	total (n)	ALI (n)	%	total (n)	ALI (n)	%		
150–199	82	6	7.3	58	5	8.6	0.47	−1.3 (−10.5, 7.9)
200–299	313	18	5.8	179	10	5.6	0.49	0.2 (−4.1,4.4)
300–499	296	21	7.1	220	15	6.8	0.48	0.3 (−4.2,4.7)
>=500	126	28	22.2	110	25	22.7	0.48	−0.5 (−11.2, 10.2)
b) Hepatotoxicity	2 bag regimen			3 bag regimen			P value	Absolute difference% (95%CI)
Nomogram group	total (n)	ALT>1000 (n)	%	total (n)	ALT>1000 (n)	%		
150–199	82	1	1.2	58	4	6.9	0.16	−5.7 (−1.3,12.6)
200–299	313	4	1.3	179	7	3.9	0.11	−2.6 (−0.5,5.7)
300–499	296	9	3.0	220	5	2.3	0.78	0.77 (−2.0,3.5)
>=500	126	22	17.5	110	15	13.6	0.47	4.9 (−3.9, 13.9)

Table 4
Comparison of other presentation types in paracetamol overdose treated with a two- or three-bag regimen.

Presentation and initial blood tests >24 h post single ingestion		2 bag regimen, *n* = 62	3 bag regimen, *n* = 34	Absolute difference % (95% CI)
	Peak ALT >150 U/L, n (%)	37 (60)	20 (59)	1 (−19.7,21.4)
	ALT > 1000 U/L, n (%)	21 (34)	16 (47)	−13 (−33.7, 7.3)
	Peak INR > 2, n (%)	14 (23)	8 (24)	−1 (−18.6,16.7)
	Fulminant hepatic failure, n (%)	5 (8)	4 (12)	−4 (−16.5, 9.1)
	Mortality, n	2 (3)	1 (3)	0.3 (−6.9,7.5)
Unknown Time of Ingestion		2 bag regimen, *n* = 111	3 bag regimen, *n* = 86	Absolute difference% (95% CI)
	Peak ALT >150 U/L, n (%)	25 (23)	19 (22)	0.4 (−11.3,12.2)
	ALT > 1000 U/L, n (%)	16 (14)	14 (16)	−2 (−12.0,8.3)
	Peak INR > 2, n (%)	13 (12)	7 (8)	4 (−4.8,11.9)
	Fulminant hepatic failure, n (%)	1 (0.9)	1 (1.2)	−0.3 (−3.1,2.6)
	Mortality, n	0	0	0
Staggered ingestions		2 bag regimen, *n* = 124	3 bag regimen, *n* = 32	
	Peak ALT >150 U/L, n (%)	21 (17)	8 (25)	−8 (−24.5,8.3)
	ALT > 1000 U/L, n (%)	8 (6)	4 (12.5)	−6 (−18.3, 6.2)
	Peak INR > 2, n (%)	3 (2.4)	4 (12.5)	−10.1 (−21.9,1.7)
	Fulminant hepatic failure, n (%)	1 (0.8)	1 (3.1)	−2.3 (−8.5, 3.9)
	Mortality, n	0	0	0

Table 5
Outcome Table for all paracetamol overdose ingestion types. ALT= Alanine transaminase, INR=international normalized ratio. There was no significant difference between outcomes when comparing the treatment regimens.

	2 bag regimen, n = 1300	3 bag regimen, n = 911	Absolute difference% (95% CI)
Peak ALT >150 U/L, n (%)	183 (14)	115 (13)	1 (−1.4,4.3)
ALT > 1000 U/L, n(%)	96 (7.4)	76 (8.3)	−0.9 (−1.3,3.3)
Peak INR > 2, n (%)	63 (4.8)	40 (4.4)	0.4 (−1.3,2.2)
Fulminant hepatic failure, n (%)	12 (0.9)	11 (1.2)	−0.3 (−1.2,0.6)
Mortality, n (%)	2 (0.1)	1 (0.1)	0.04 (−0.3,0.4)

9. Adverse reactions to acetylcysteine

There were significantly less cutaneous and systemic non-allergic anaphylactic reactions recorded after treatment with the two-bag than the three-bag regimen (1.3% [n = 17] and 7.1% [n = 65], Difference: −5.8%, 95%CI −7.6 to −4.0, $p < 0.0001$), respectively. The two-bag regimen resulted in three episodes of severe non-allergic anaphylactic reactions (dyspnea [2] and angioedema [1]) and 14 skin reactions. The three-bag regimen resulted in 15 episodes of severe non-allergic anaphylactic reactions (dyspnea [7], angioedema [5], chest tightness [2], bronchospasm [1]) and 58 episodes of skin reactions. There were significantly less gastrointestinal reactions (nausea and/or vomiting) recorded with the two-bag regimen compared to the three-bag regimen (19% [n = 245] vs 31% [n = 279], $p < 0.0001$).

10. Discussion

Acetylcysteine is the mainstay of treatment for paracetamol poisoning. The traditional intravenous three-bag acetylcysteine regimen developed four decades ago was designed as a “one size fits all” approach to management and has a significant risk of adverse reactions [21, 22]. Previous studies have reported that the two-bag acetylcysteine regimen, described in the current study, is associated with a lower incidence of adverse reactions. This has been validated in a number of centres around the world [12–15]. Importantly, the current study demonstrates similar efficacy of the two regimens for prevention of liver injury after paracetamol overdose.

We found that the incidence of acute liver injury and hepatotoxicity was not significantly different with the two treatment regimens. In addition, as seen with previous studies of the 20-h acetylcysteine regimen, mortality was very low for both infusion regimens [23]. Further, we found similar or lower incidences of ALI treated with the two-bag regimen in the two largest sub-groups (4–8 h and 8–24 h groups), than those reported in the literature for the three bag regimen [20]. More specifically, we demonstrated non-inferiority between the two regimens in the largest paracetamol overdose group (4–8 h).

However, in the staggered ingestion subgroup there was an increased proportion of patients with ALI and hepatotoxicity treated with the three-bag acetylcysteine regimen. One reason for this could be the higher dose of paracetamol ingested in those treated with the three-bag acetylcysteine regimen (373 mg/kg IQR 86,769 vs. 202 mg/kg IQR 160,384) in this subgroup. Another reason could relate to the small number of patients in this subgroup as this was not a statistically significant difference.

The combination of the first two infusions of the traditional three-bag acetylcysteine regimen into a single bag delivering 200 mg/kg over four hours results in a lower peak but more sustained concentration of acetylcysteine over time. From pharmacokinetic modelling [24], the two-bag regimen provides a more constant delivery of

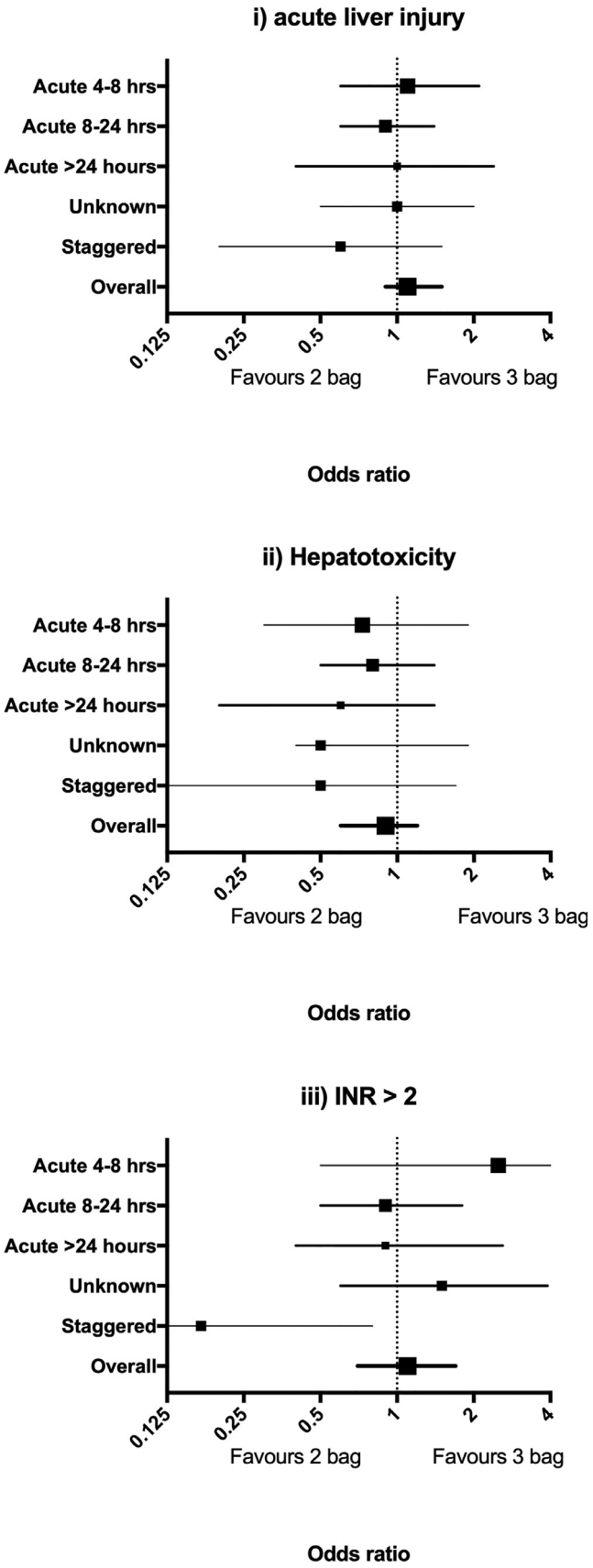

Fig. 2. Forest plot of odds ratio (95% CI) for (i) acute liver injury, (ii) hepatotoxicity and (iii) INR >2 stratified by time and type post ingestion of paracetamol.

glutathione substrate during the initial stage of poisoning, when paracetamol concentration is at its highest. Given that paracetamol metabolism is continuous, a lower peak but sustained acetylcysteine concentration within the first few hours of treatment, in addition to individual endogenous liver glutathione stores, may be the reason there is no difference in preventing liver injury as an initial transient peak in concentration.

We found a decreased incidence in non-allergic anaphylactic reactions with the two-bag regimen compared to the three-bag regimen. This included gastrointestinal, cutaneous and systemic reactions. Similarly, the SNAP regimen studies which decreased the infusion rate of the loading-dose over the first hour have shown similar findings [10,11]. Some previous studies assessing safety of the two-bag regimen did not find a difference in the incidence of gastrointestinal reactions [12,13], but in this larger efficacy study, these were significantly less frequent that with the three-bag regimen. The lower incidence of adverse reactions with the newer regimen is significant from a clinical perspective. Adverse drug reactions often result in treatment interruptions or cessation of infusions. Delaying acetylcysteine treatment has the potential to increase the risk of liver injury. In addition, the two-bag regimen simplifies treatment. This has the potential to reduce the risk of prescribing and dispensing errors. It also removes an intravenous bag change from the therapy, thereby reducing nursing time.

11. Limitations

There are a number of limitations that must be considered regarding this study. This large multicentre study retrospectively compared treatment with the two-bag regimen to a historical control three-bag regimen group, but was not a randomised controlled trial. Acute liver injury may not lead to the rare but important outcomes of fulminant hepatic failure or death. However, it is highly unlikely for patients to develop hepatic failure without first developing ALI and hepatotoxicity.

Notably, the key outcomes were objective laboratory studies (ie. ALT, INR), which were recorded electronically. In both groups, the search for adverse reactions was retrospective, from hospital clinical records. It is possible that some reactions were not recorded in the medical or nursing notes in both cohorts. Hence, the adverse reaction incidence may be greater than recorded.

In addition, other confounding factors such as acetylcysteine and paracetamol contribution to elevations in INR must be taken into account. Larger studies are required to determine whether important differences exist in uncommon outcomes (e.g. mortality or fulminant hepatic failure) or sub-groups (e.g. very late presentations or massive ingestions). With the adoption of this two-bag acetylcysteine regimen in multiple centres and several countries, it will be important to validate the findings of this study in larger cohorts and the other subgroups for which this study was not powered to assess. Importantly, this study was appropriately powered to support the hypothesis that the two-bag regimen is non-inferior with reference to incidence of liver injury in the most common presentation group, single ingestions with initial bloods taken 4 to 8 h post ingestion.

Further study focused on treatment regimens addressing the treatment of specific paracetamol poisoning scenarios (e.g. low risk patients) may lead to reduced hospital length of stay, and treatment related morbidity [25,26].

12. Conclusions

A two-bag intravenous acetylcysteine regimen was found to be non-inferior to the traditional three-bag regimen with regards to efficacy in preventing acute liver injury for early presentations of paracetamol overdose. No important differences were seen for any other presentations. This regimen also decreased the incidence of both non-allergic anaphylactic reactions and gastrointestinal adverse events from acetylcysteine treatment. This regimen simplifies administration of acetylcysteine, reduces bag changes, and has the potential to influence the incidence of both prescribing and dispensing errors.

Declarations of competing interest

Nil to declare

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Supplementary materials

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