CLINICAL OUTCOMES IN PATIENTS WITH PARACETAMOL INGESTION TREATED WITH A TWO-BAG N-ACETYLCYSTEINE REGIMEN IN THE EMERGENCY CENTRE OF KHAYELITSHA HOSPITAL

By Kedibone Mbanga
This study is in partial fulfilment of MMed degree
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Abbreviations

ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
HIV	Human Immunodeficiency Virus
INR	International Normalised Ratio
MMed	Master of Medicine
NAC	N-acetylcysteine
Q1-Q3	25^{th}-75^{th} percentile
SD	Standard Deviation

PART A: MANUSCRIPT IN ARTICLE FORMAT

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Clinical outcomes in patients with paracetamol ingestion treated with a two-bag N-acetylcysteine regimen in the emergency centre of Khayelitsha Hospital.

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Abstract

Introduction: Paracetamol is frequently ingested for intentional self-poisoning. N-acetylcysteine (NAC) is administered to patients at risk of developing hepatotoxicity and was historically administered using a three-bag intravenous regimen. A change towards a two-bag NAC regimen was initiated at Khayelitsha Hospital. The aim of the study was to describe the clinical outcomes in patients with a history of paracetamol ingestion who were treated with the two-bag NAC regimen. A descriptive comparison to a historical cohort of patients treated with the three-bag NAC regimen was also made.

Methods: A retrospective chart review was conducted to assess a 6-month clinical audit. Summary statistics were used to describe all variables.

Results: Overall, 57 patients were included (mean age 26 years, 83% female). The median ingested dose (10 g) was similar between the regimens. An empiric indication occurred more in patients receiving the two-bag regimen (84.0% versus 50.0%). The median paracetamol level (231 umol/L) and the proportion of confirmed paracetamol toxicity (32%) were less in the two-bag regimen. A delay in initiating the first NAC infusion occurred in 22 (38.6%) patients. Forty adverse effects were recorded in 22 (38.6%) patients and a higher proportion occurred in the two-bag regime (44.0% vs. 34.4%). Nausea and vomiting occurred frequently (n=30, 52.7%), which were comparable for both regimens. The prevalence of hepatotoxicity after receiving NAC was 8.8% (n=5).

Conclusion: A large number of patients were empirically started on NAC with a higher incidence of adverse reactions in the two-bag NAC than in the three-bag NAC regimen in contrast to existing evidence. However, there was a reduction in treatment delay in the two-bag NAC regimen compared to the three-bag NAC regimen.

Keywords

Paracetamol, N-acetylcysteine, Adverse drug effects

African relevance

- Paracetamol is frequently the drug of choice for intentional self-poisoning
- A two-bag N-acetylcysteine (NAC) regimen may be easier to administer without additional hepatotoxicity
- Nausea and vomiting remain frequent adverse effects, regardless of the NAC regimen used

Introduction

Paracetamol is globally one of the most frequent toxicology-related ingestions.(1) Morbidity and mortality from paracetamol ingestion occurs mainly from hepatotoxicity,(2–5) with over 40% of patients presenting with acute liver failure after a paracetamol overdose.(6)

The primary management of paracetamol toxicity includes supportive care and the administration of N-acetylcysteine (NAC).(7) The administration of NAC for paracetamol ingestion at a single time point is guided by the Rumack-Matthew Nomogram. This logarithmic graph plots the serum concentration of paracetamol against the time since ingestion in an attempt to predict the development of hepatotoxicity, thus allowing clinicians to decide if treatment with NAC should be initiated.(8) The Rumack-Matthew Nomogram has been in use since 1975.(8)

Changes in the administration of NAC have been mainly related to lowering the treatment threshold for the administration of NAC,(9) with minimal changes to the manner in which NAC is administered. Historically, a three-bag NAC-regimen was used in most countries. The three-bag intravenous regimen was complex and carried a high risk of medication error as it included three separate, weight-related infusions over three different timeframes.(3) The regimen mostly used was NAC 150 mg/kg over 1 hour, followed by 50 mg/kg over 4 hours, and finally 100 mg/kg over 16 hours.(10)

The high initial dose of the three-bag intravenous NAC-regimen also resulted in a high frequency of dose-related adverse reactions.(3) Vomiting occurred in up to 60% of patients, while anaphylactoid reactions caused treatment interruptions and refusals in a further 20%.(11–13) The high frequency of NAC-related adverse events led to an increasing global interest to modify the NAC regimen, primarily to reduce adverse events but also to simplify the regimen.(3,4) A two-bag intravenous NAC regimen was proposed, consisting of 200mg/kg over 4 hours, followed by 100mg/kg over 16hours.(4,14) Subsequent studies indicated that the two-bag regimen (compared to the three-bag regimen) is associated with fewer side effects, a low incidence of hepatotoxicity, and no reports of liver failure or need for liver transplantation.(3–6,14)

Toxicology-related patients often present to emergency centres and place a significant burden on emergency centres. The prevalence of intentional overdose in the resuscitation area of Khayelitsha Hospital, Cape Town, South Africa is approximately 8%, of which a quarter (25%) relates to paracetamol ingestion.(15) A two-bag intravenous NAC regimen (200mg/kg over 4 hours, followed by 100mg/kg over 16hours) for the acute management of paracetamol toxicity was initiated at Khayelitsha Hospital on 1

August 2019, after consultation with the Division of Clinical Pharmacology at Stellenbosch University, the Tygerberg Hospital Poison Information Centre, and the Khayelitsha Hospital Pharmacy. This decision was based on the assumptions that the simplified regimen would be equally effective in managing paracetamol toxicity, be less labour intensive, and be more cost effective than the traditional three-bag regimen (150 mg/kg over 1 hour, then 50 mg/kg over 4 hours, followed by 100 mg/kg over 16 hours).

The aim of the study was to describe the indications, investigations, adverse effects, patient disposition and the frequency of hepatotoxicity in patients who presented with a history of paracetamol ingestion and whom were treated with a two-bag N-acetylcysteine regimen at Khayelitsha Hospital. A secondary objective was to describe the frequency of hepatotoxicity and adverse effects to a historical cohort of patients treated with a three-bag N-acetylcysteine regimen.

Methods

Study design

A retrospective chart review was conducted. The study was approved by the Human Research Ethics Committee of the University of Cape Town (HREC REF: 441/2020) and included a waiver of informed consent.

Study setting

Khayelitsha Hospital is a 300-bed district level hospital situated in the township of Khayelitsha, Cape Town. It provides emergency medical services to adults and children as well as inpatient surgical, medical, paediatric and obstetric care to a population of more than 400 000 that is predominantly black African. (16) The emergency centre at Khayelitsha Hospital is larger than that of a standard district hospital emergency centre (17), and has a well-equipped four-bed resuscitation area. The emergency centre manages about 30 000 patients per annum and the prevalence of intentional overdose managed in the resuscitation area of the emergency centre is 8%. (15)

A 6-month clinical audit to assess the implementation of the new two-bag regimen was undertaken from 1 August 2019 to 31 January 2020. Training sessions were held to facilitate the implementation of the new two-bag regimen. The nursing unit manager and professional nurses working in the emergency centre were educated about the new regimen and assisted with the implementation thereof by placing a specially designed clinical audit sheet (appendix 1) in the file of each patient managed for paracetamol ingestion. Nursing staff were also encouraged to verbally remind the doctors of the new regimen. Nurses

were also trained to recognize potential adverse effects related to the NAC infusion. Doctors attended demonstrations on how to correctly complete the audit sheet. Special emphasis was placed on the indications of NAC, the investigations needed and the specific dosage and infusion rates. Emergency physicians further reminded and motivated the staff on a weekly basis to adhere to the two-bag NAC regimen and to complete the audit sheet.

Study population and sampling

All patients that presented to the emergency centre of Khayelitsha Hospital with paracetamol ingestion and treated with a two-bag NAC regimen from 1 August 2019 till 31 January 2020 were included. The historical cohort consisted of patients treated with the three-bag NAC regimen for paracetamol ingestion from 1 January 2018 until 31 July 2019.

Data collection and management

Data were extracted from the clinical audit sheets and from the hospital's electronic patient care records. Data from the historical cohort was obtained from the Khayelitsha Hospital Emergency Centre database - a prospectively collected observational database previously described. (18) Missing and additional data were included by means of a chart review. Electronic data was then coded and stored on a password-protected server. A decoding sheet was stored separately. The database has been registered at the Stellenbosch University Health Research Ethics Committee (Ref: N15/10/107). Participants who ingested paracetamol were first identified using the electronic database. This sample was then cross-checked with the hard-copy drug register to ensure a complete sample. A standardised data collection tool was used. A pilot study of five patient folders for each group (two-bag and three-bag) was completed to adequately train the chart reviewers and to adapt the datasheet if needed. The data from this pilot was included in the study.

Criteria to initiate a NAC infusion included either suspected paracetamol toxicity or confirmed hepatotoxicity. Paracetamol toxicity was defined as an ingested dose of paracetamol ingested of more than 200mg/kg or 10g regardless of the bodyweight in adults; more than or equal to 200mg/kg in children under the age of 6 years (19); and biochemically defined by paracetamol levels above 993umol/L at 4 hours or 132.4 umol/L at 15 hours using the Rumack-Matthew Nomogram.(20) Hepatotoxicity was defined as alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 1000IU regardless of the time of paracetamol ingestion.(2)

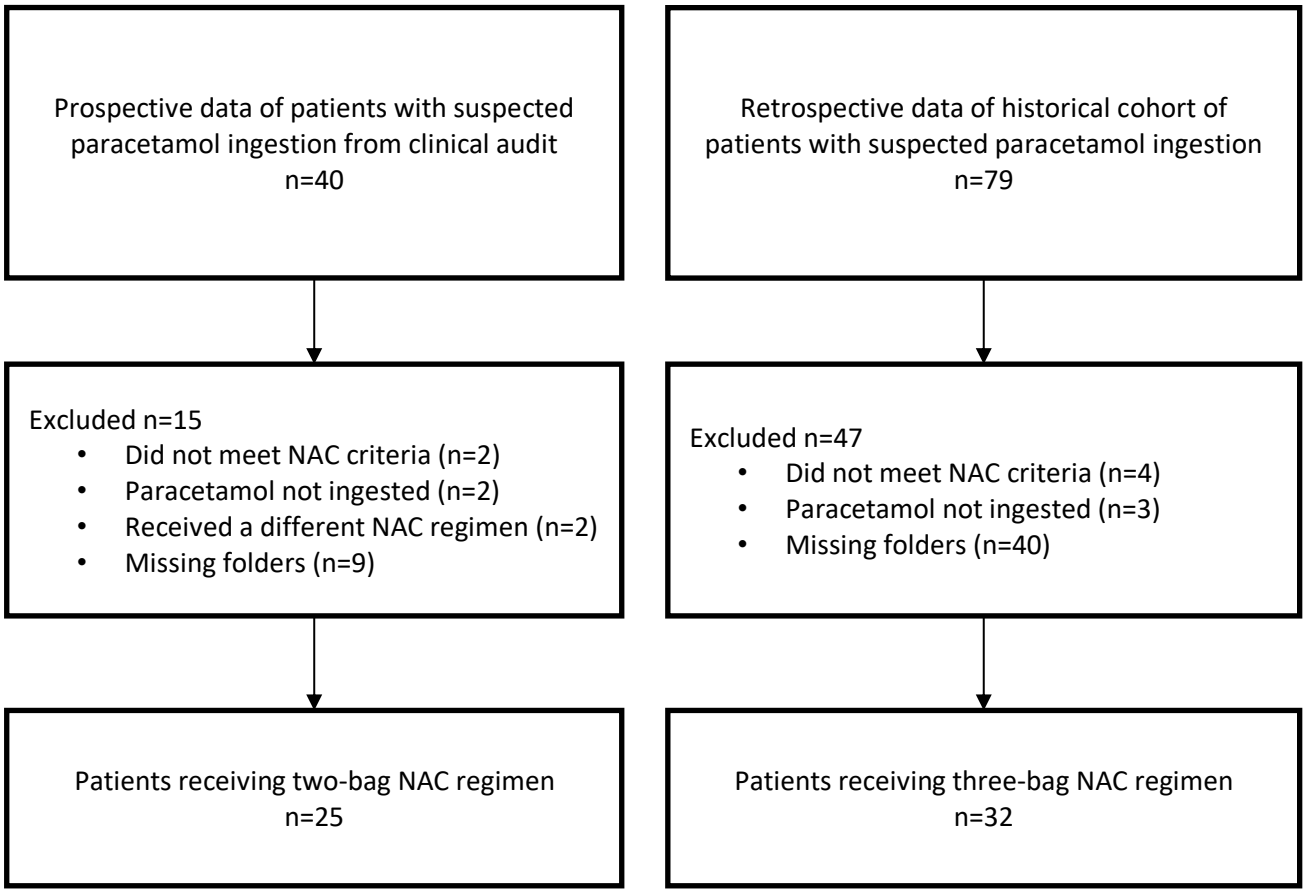
Data collection was performed by a single reviewer. A second reviewer independently recollected data of a 10% random sample. Differences were resolved through discussion and the required corrections were made. Only the second reviewer was blinded to the study's objectives.

Data analysis

Summary statistics were used to describe all variables. Patients with missing data were not excluded, instead the specific missing variable was indicated as unknown. Categorical data was summarised using frequency counts or percentages, and distributions of variables are presented as two-way tables or bar charts. The median or mean was used as the measure of central tendency for ordinal and continuous responses and standard deviation (SD) or quartiles as indicators of spread. Data were analysed using SPSS Statistics for Windows, Version 27.0 (IBM Corp. Released 2020. Armonk, NY: IBM Corp.).

Results

A total of 119 patients with suspected paracetamol ingestion were identified. Fifty seven patients were included in the study of which 25 patients received the three-bag NAC regimen and 32 patients received the two-bag NAC regimen (Fig.1).



NAC: N-acetylcysteine

Figure 1. Flow diagram of study population

The demographic and clinical characteristics of patients by regimen received are presented in Table 1. The mean (±SD) age of all patients was 26 (±9) years, and 47 (82.5%) were female. The median weight was slightly higher in patients receiving the two-bag NAC regimen (70 kg versus 65 kg). The most common comorbidity was HIV, affecting 10 (17.5%) patients overall. Twelve patients (21.8%) were substance misusers. This was noted to be more common among patients receiving the three-bag NAC regimen (26.7% versus 16.0%). Fewer patients who received the two-bag NAC regimen were discharged home

from the emergency centre (52.0% versus 78.1%) and were more likely to be admitted to in-hospital specialities or transferred to a higher level of care (36.0% versus 21.9%) (Table 1).

Table 1. Demographics, clinical characteristics and disposition of patients who ingested paracetamol and received N-acetylcysteine

n(%) unless otherwise indicated	**All patients (N=57)**	**Two-bag regimen (n=25)**	**Three-bag regimen (n=32)**
Age (years)			
mean ±SD[a]	26 ± 9	26 ± 11	26 ± 8
Sex			
Male	10 (17.5%)	4 (16.0%)	6 (18.8%)
Female	47 (82.5%)	21 (84.0%)	26 (81.3%)
Weight[b] (kg)			
median (Q1-Q3)[c]	65 (54-80)	70 (57-85)	65 (54-70)
Comorbidities			
HIV[d]positive	10 (17.5%)	4 (16.0%)	6 (18.8%)
Hypertension	3 (5.3%)	2 (8.0%)	1 (3.1%)
Diabetes	2 (3.5%)	2 (8.0%)	0
Renal failure	1 (1.8%)	1 (4.0%)	0
Other	2 (3.5%)	1 (4.0%)	1 (3.1%)
Substance misuse[e]			
Yes	12 (21.8%)	4 (16.0%)	8 (26.7%)
No	43 (78.2%)	21 (84.0%)	22 (73.3%)
Disposition			
Discharged directly home from the emergency centre	38 (66.7%)	13 (52.0%)	25 (78.1%)
Admitted to in-hospital specialities at Khayelitsha Hospital	8 (14.0%)	4 (16.0%)	4(12.5%)
Transferred to higher level of care	8 (14.0%	5 (20.0%)	3 (9.4%)
Refused hospital treatment or absconded	3 (5.3%)	3 (12.0%)	0

[a] Standard deviation, [b] n=53, [c] 25th–75th percentile, [d] Human Immunodeficiency Virus, [e] n=55

An empiric indication for initiating a NAC infusion occurred more in patients receiving the two-bag NAC regimen (84.0% versus 50.0%) (Table 2). Two patients did not have a clearly documented indication. The median ingested dose of paracetamol (10 g) was similar between the NAC regimens, and the median time from ingestion to paracetamol level drawn ranged between 5.5 and 9.4 hours. Paracetamol levels were

drawn later than 4 hours from the time of ingestion in 36 (63.2%) patients. The median paracetamol level (231 umol/L) and the proportion of patients with confirmed paracetamol toxicity (32%) were less in the two-bag regimen (Table 2).

Supplementary table 1 provides data relating paracetamol toxicity to the time paracetamol levels were drawn relative to the time of ingestion. Twenty-three patients (53.5%) in whom paracetamol levels were drawn ≥4 hours from the time of ingestion, exhibited paracetamol toxicity. Toxicity was noted more in the three-bag (17/25, 68.0%) than in the two-bag (6/12, 33.0%) NAC group. Only two patients (both receiving the two-bag NAC regimen) were observed to have paracetamol toxicity amongst those in whom paracetamol levels were drawn less than 4 hours since ingestion (Supplementary table 1).

Table 2. Clinical particulars of patients with suspected paracetamol ingestion receiving N-acetylcysteine

n(%) unless otherwise indicated	**All patients (N=57)**	**Two-bag regimen (n=25)**	**Three-bag regimen (n=32)**
[a]Indications for initiating NAC[b]			
Empiric	36 (65.5%)	21 (84.0%)	15 (50.0%)
Laboratory confirmed toxicity	19 (34.5%)	4 (16.0%)	15 (50.0%)
[c]Paracetamol dose ingested (mg)			
median (Q1-Q3)[d]	10000 (7000-15000)	10000 (7000-14400)	10500 (6350-15000)
Time from ingestion when paracetamol level was drawn			
<4 hours	10 (17.5%)	6 (24.0%)	4 (12.5%)
≥4 hours	36 (63.2%)	15 (60.0%)	21 (65.6%)
Unsure	11 (19.3%)	4 (16.0%)	7 (21.9%)
[e]Median (Q1-Q3)[d]	7.5 (5-16)	5.5(3-12)	9.4(5.1-21.6)
Paracetamol levels (umol/L)			
median (Q1-Q3)[d]	261 (49-724)	231 (66-617)	404 (24-790)
Paracetamol toxicity [1]			
Confirmed	25 (43.9%)	8 (32.0%)	17 (53.1%)
No toxicity	21 (36.8%)	12 (48.0%)	9 (28.1%)
[f]Alanine aminotransferase (ALT) [2]level (IU/L)			
Median (Q1-Q3)[c]	18 (14-35)	15 (14-25)	23 (17-47)
>50 U/L	10 (19.2%)	4 (16.7%)	6 (21.4%)
≤50 U/L	42 (80.8%)	20 (83.3%)	22 (78.6%)
>1000 IU/L	2 (3.8%)	1 (4.2%)	1 (3.6%)
[g] International Normalized Ratio (INR)			

median (Q1-Q3)	1.15 (1.05-1.32)	1.08 (1.05-1.28)	1.31 (1.13-1.43)

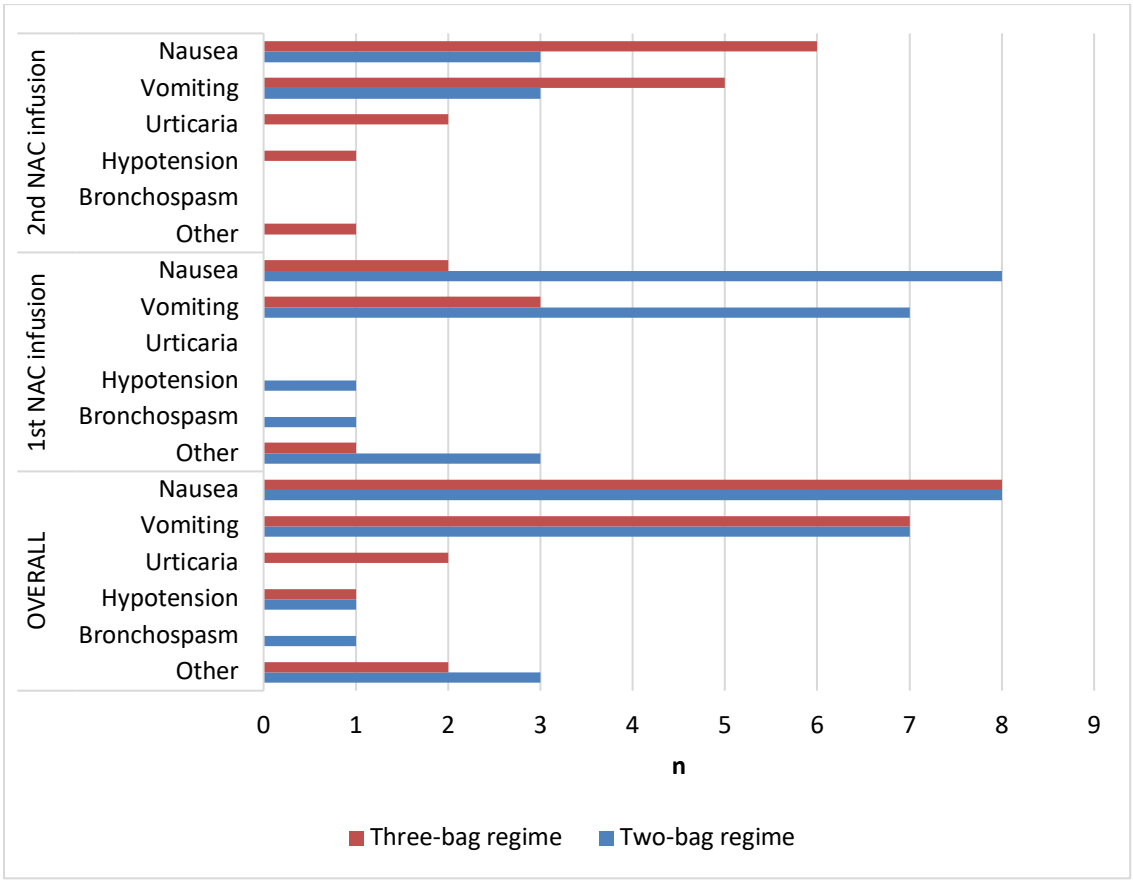
[a] n=55; [b] N-acetylcysteine, [c] n=35; [d] 25th–75th percentile, [e] n=46, [f] n=52, [g] n=26

[1] n=46, confirmed toxicity n=25, not toxic n=21 (criteria for confirmed toxicity : using nomogram, ALT >1000IU anytime from ingestion, >66umol/L paracetamol level unknown time from ingestion). 11 patients did not fall into this category.
[2] n=54 had ALT levels and n=3 did not have ALT levels.

An alanine aminotransferase (ALT) level was requested in 54 patients prior to initiating NAC and the international normalized ratio (INR) requested in 26 patients (Table 2). Four patients (16.7%) who received the two-bag NAC regimen had an ALT level of more than 50 IU/L, compared to 6 (21.4%) of those who received the three-bag NAC regimen. An ALT level of more than 1000 IU/L was measured in only two patients — one in each NAC regimen. Both presented more than 8 hours after ingestion.

Supplementary Table 2 provides data on the delay, interruption, and early termination of the NAC treatment. A delay in initiating the first NAC infusion occurred in 38.6% of patients, in 28.1% for the second NAC infusion, and in 8.8% for the third infusion. The NAC infusion was interrupted 23 times, mostly during the second NAC infusion. The early termination of the NAC regimen occurred in 9 patients of which 5 was in the three-bag NAC group.

Forty adverse effects were recorded in 22 (38.6%) patients while they were being treated with NAC. (Fig. 2). A higher proportion of patients who were treated with the two-bag NAC regimen experienced adverse effects when compared to those treated with the three-bag NAC regimen (44.0% vs. 34.4%). The most frequent adverse effects were nausea and vomiting (n=30, 52.7%), which were equally distributed between the two-bag NAC regimen and the three-bag NAC regimen.



NAC: N-acetylcysteine
Other: other gastro-intestinal tract symptoms or histamine like symptoms related to NAC infusion not specified.

Figure 2. Adverse effects experienced by patients receiving N-acetylcysteine after paracetamol ingestion

Five patients (8.8%) had an ALT level of >1000 IU/L after the NAC regimen was completed, 4 (16.0%) in the two-bag regimen and 1 (3.1%) in the three-bag regimen. The demographic and clinical characteristics of the five patients are presented in Table 3.

Table 3. Demographic and clinical characteristics of patients with alanine aminotransferase (ALT) levels more than 1000 IU/L after receiving N-acetylcysteine

Patient	NAC[a] regimen	Age (years)	Sex	Substance abuser	Paracetamol level (umol/L)	Timing of paracetamol level after ingestion (hours)	Baseline ALT[b] level (IU/L)	Post-NAC ALT[b] level (IU/L)	Post-NAC INR[c]	NAC infusion interrupted	Adverse effects
1	Two-bag	45	F	No	1003	2.17	15	1510	2.73	Yes	Nausea, vomiting
2	Two-bag	16	F	Yes	159	17.58	317	5770	1.73	Yes	Nausea, vomiting
3	Two-bag	22	F	Yes	125	39.5	1213	11412	1.67	Yes	Nausea, vomiting, hypotension
4	Two-bag	16	F	No	55	49	949	10827	1.50	Yes	None
5	Three-bag	16	F	No	73	56.42	389	2365	1.45	No	None

[a] N-acetylcysteine, [b] Alanine aminotransferase, [c] International Normalized Ratio

Discussion

This study described the clinical outcomes of patients with paracetamol ingestion who were treated with a two-bag N-acetylcysteine regimen in the emergency centre of Khayelitsha Hospital. Patients were predominantly women which is consistent with the current literature.(14) The decision to initiate a NAC infusion was made empirically in 66% of patients, but only 44% of all patients had laboratory confirmed toxicity. Delays in initiating NAC infusions occurred frequently and mostly during the first NAC infusion (39%). More than a third of patients experienced adverse effects, with a 10% higher proportion in the two-bag group. Hepatotoxicity occurred in 9% of patients and occurred mainly in the two-bag group.

Serum paracetamol levels are the main screening test performed as part of the diagnostic workup in patients with suspected paracetamol toxicity.(6) The decision to initiate NAC was mainly empirical in this study and is supported by literature which suggests that starting NAC early and empirically in patients with suspected paracetamol toxicity may derive greater benefit than harm to the patient.(21)(22) This is especially relevant in institutions where there are long delays in laboratory turn around times, and where there is limited access to services such as transplant units. In this instance, initiating NAC empirically benefits patient outcomes.(21)

A delay occurred more frequently in initiating the first NAC infusion, and more especially in the initiation of the three-bag regimen. This might be related to the difference in complexity between preparing the two-bag and three-bag regimens, (12) and suggests an advantage to using the two-bag NAC regimen.

Gastrointestinal complaints were common adverse effects and associated with both regimens. Nausea and vomiting (39%) were noted to occur anytime during the NAC infusion. These findings were comparable with the study by Wong et al who also did not exhibit any change in the incidence of nausea and vomiting between regimens in his study. However, another study noted cutaneous adverse effects to be more common than systemic effects (6.2% vs 0.5%). (23) These adverse effects are common during the first five hours of the NAC infusion and are associated with three-bag NAC regimen. This may be attributed to the high loading dose of 150mg/kg given to the patients during the first hour of starting the infusion. (23) There was a higher incidence of adverse effects with the two-bag NAC regimen than the three-bag NAC regimen in our study (44% vs 35%), which is incongruent to current literature. (3,5,14)

Five patients (9%) had hepatotoxicity post NAC infusion, most of whom were young patients and late presenters. NAC is highly effective when given within 8 to 10 hours of paracetamol ingestion and subsequently less effective when given between 16 and 24 hours after paracetamol ingestion (24,25). The

late administration of NAC in our cohort may explain why these patients still demonstrated hepatoxicity post NAC therapy. Notably, there were no reported deaths, and this may support the benefit of giving NAC even to late presenters with paracetamol toxicity.(22)

There were several limitations to the study which may have influenced the results. This was a small single-centred retrospective study that was limited by missing folders and poor documentation by clinicians. Furthermore, the information that was entered on the clinical audit sheet was not double-checked for errors. The data collected was for quantitative analysis only. The audit form designed for the two-bag NAC regimen raised more awareness surrounding NAC administration and capturing of data such as side effects profile, whereas the three-bag NAC regimen did not have any prompting audit form to remind clinicians to constantly document all important data. This could have attributed to a higher incidence of side effects in the two-bag NAC regimen compared to the three-bag NAC regimen and a noted delay in initiating the first NAC infusion that occurred more in the three-bag NAC regimen in our study, therefore, this creates bias when comparing these two regimens. Qualitative methodology will be better suited to study the implementation and administration experiences of health care practitioners in the use of the two-bag NAC regimen. A cost analysis was not done which is imperative in determining potential cost savings with the new regimen. This is an area for future research.

Conclusion

Mostly young female patients were managed with a two-bag NAC regimen. This regimen demonstrated a high incidence of adverse effects such as nausea, vomiting, urticaria, hypotension, and bronchospasm compared to the three-bag NAC regimen which is contrary to the current literature. Nausea and vomiting were the most frequent adverse effects and were comparable in both regimens. Fewer treatment delays were noted with the two-bag regimen compared to the three-bag NAC regimen, however, there was a reduction in hospital length of stay with the three-bag compared to the two-bag which might have been multifactorial. There were few patients with hepatotoxicity post NAC therapy, and no deaths occurred.

Dissemination of results

Results from this study was shared with the management team of the emergency centre at Khayelitsha Hospital.

Authors' contribution

Authors contributed as follow to the conception or design of the work; the acquisition, analysis, or interpretation of data for the work; and drafting the work or revising it critically for important intellectual content:

KM contributed 60%; WK 15%; and DJvH contributed 25%.

All authors approved the version to be published and agreed to be accountable for all aspects of the work.

Declaration of Competing Interest

The authors declared no conflicts of interest.

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SUPPLEMENTARY MATERIAL

Supplementary table 1. Paracetamol toxicity by time paracetamol levels drawn

n(%) unless othewise indicated	≥4 hours			<4 hours		
Paracetamol toxicity	All patients (n=43)	Two-bag regime (n=18)	Three-bag regime (n=25)	All patients (n=3)	Two-bag regime (n=2)	Three-bag regime (n=1)
Yes	23(53.5%)	6 (33%)	17 (68.0%)	2 (66.7%)	2 (100.0%)	0
No	20 (46.5%)	12 (66.7%)	8 (32.0%)	1 (33.3%)	0	1 (100%)

Supplementary table 2. Delay, interruption and early termination of N-acetylcysteine in patients suspected to have paracetamol toxicity

n(%)	**All patients (n=57)**	**Two-bag regimen (n=25)**	**Three-bag regimen (n=32)**
Delay in initiating NAC infusion			
Frequency during **first** infusion	22 (38.6)	4 (16%)	18 (56%)
Reasons for delay			
Insufficient stock of NAC	*1 (4.5%)*	*1 (25.0%)*	*0*
Unknown	*21 (95.5%)*	*3 (75.0%)*	*18 (100%)*
Frequency during **second** infusion	*20 (28.1%)*	*8 (32.0%)*	*12 (21.9%)*
Reasons for delay			
Busy staff	*2 (9.1%)*	*2 (25.0%)*	*0*
IV line not functioning	*2 (9.1%)*	*2 (25.0%)*	*0*
Changeover of staff	*1 (4.5%)*	*0*	*1 (5.5%)*
Unknown	*13 (59.1%)*	*4 (100%)*	*9 (50.0%)*
Frequency during **third** infusion	5 (8.8%)	0	5 (15.6 %)
Reasons for delay			
Preparing NAC infusion	*1 (20.0%)*	*0*	*1 (20.0%)*
Patient moved out of resuscitation area	*1 (20.0%)*	*0*	*1 (20.0%)*
Unknown	*3 (60.0%)*	*0*	*3 (60.0%)*
Interruption of NAC infusion			
Frequency during **first** infusion	5 (8.8%)	3 (12.0%)	2 (6.3%)
Reasons for interruption			
Patient transferred to higher level of care	*1 (20.0%)*	*1 (33.3%)*	*0*
Unknown	*4 (80.0%)*	*2 (66.7%)*	*2 (100.0%)*
Frequency during **second** infusion	14 (24.6%)	10 (40.0%)	4 (12.5%)
Reasons for interruption			
IV line not functioning	*3 (21.4%)*	*2 (20.0%)*	*1 (25.0%)*
Patient refused further hospital care	*1 (7.1%)*	*1 (10.0%)*	*0*
Patient transferred to higher level of care	*7 (50.0%)*	*5 (50.0%)*	*2 (50.0%)*
Transient anaphylactoid reaction	*2 (14.3%)*	*1(10.0%)*	*1 (25.0%)*
Unknown	*1(7.1%)*	*1(10.0%)*	*0*
Frequency during **third** infusion	*4 (7.0%)*	*0*	*4 (12.5%)*
Reasons for interruption			
Infusion stopped prematurely	*3 (75.0%)*	*0*	*3 (75.0%)*
Unknown	*1 (25.0%)*	*0*	*1 (25.0%)*
Early termination of NAC			
Frequency during **first** infusion	1 (1.8%)	1 (4.0%)	
Frequency during **second** infusion	8 (14.0%)	5 (20.0%)	3 (9.4%)
Frequency during **third** infusion	2 (3.5%)	0	2 (6.3%)

NAC: N-acetylcystein

PART B: Addenda

ADDENDUM 1: NAC CLINICAL AUDIT SHEET

N-ACETYLCYSTEINE (NAC) - 2 BAG PROTOCOL

Please place patient sticker in NAC register

Attach this document to your clinical notes

Patient sticker
or
Folder nr:_____

Indications for starting NAC:

Emperic treatment ☐ / Laboratory confirmed toxicity ☐

Drug for which NAC indicated: _____

Dose of drug (mg): _____; (Estimated ☐ / Actual ☐)

Date of ingestion: yy / mm / dd; Time of ingestion: _____ (Estimated ☐ / Actual ☐)

Co-ingestions: Y ☐ N ☐ (List below if applicable)

	Name of drug	Dose (mg)	Ingested dose
1			Estimated ☐ / Actual ☐
2			Estimated ☐ / Actual ☐
3			Estimated ☐ / Actual ☐
4			Estimated ☐ / Actual ☐
5			Estimated ☐ / Actual ☐
6			Estimated ☐ / Actual ☐
7			Estimated ☐ / Actual ☐

Comorbidities: Y ☐ N ☐ Please list: _____

_____

Substance abuser: Y ☐ N ☐ Please list: _____

_____

Investigations at admission

Paracetamol level: Time drawn: _____ Time from ingestion: _____

Level: _____

Toxic? Y ☐ / N ☐ **(Stop NAC if non-toxic)**

ALT level: Time drawn: _____ Level: _____

INR level: Time drawn: _____ Level: _____

ECG: _____

NAC regime

Previous significant anaphylactoid reactions: Y ☐ N ☐ (NAC contraindicated if yes)

Pregnancy: Safe to administer NAC if indicated following paracetamol overdose

1] Initial dose:

Adults (≥ 13yrs)	Children <20kg	Children >20kg
200 mg/kg in 500ml 5% dextrose over 4 hours	200 mg/kg in 7ml/kg N/S plus 5% dextrose over 4 hours	200 mg/kg in 250ml N/S plus 5% dextrose over 4 hours

Patient weight: _____kg (Estimated ☐ / Actual ☐)

NAC dose given:_____mg Time infusion started: _____

Delays to initiate NAC: Y ☐ N ☐ Reason(s): _____

Interruptions of NAC: Y ☐ N ☐ Reason(s): _____

Side effects *(tick applicable)*

Nausea		Diarrhoea		Rash		Bronchospasm		Hypotension	
Vomiting		Constipation		Urticaria		Angioedema			
Other:									

2] Second dose:

Adults (≥ 13yrs)	Children <20kg	Children >20kg
100 mg/kg in 1000ml 5% dextrose over 16 hours	100 mg/kg in 14ml/kg N/S plus 5% dextrose over 16 hours	100 mg/kg in 500ml N/S plus 5% dextrose over 16 hours

NAC first dose given:_____mg Time infusion started: _____

Delays to initiate NAC: Y ☐ N ☐ Reason(s): _____

Interruptions of NAC: Y ☐ N ☐ Reason(s): _____

Side effects: *(tick applicable)*

Nausea		Diarrhoea		Rash		Bronchospasm		Hypotension	
Vomiting		Constipation		Urticaria		Angioedema			
Other:									

Investigations after NAC infusion:

ALT: Time drawn: _____ Level: _____

INR: Time drawn: _____ Level: _____

Disposition:

Discharged home ☐ Admitted KDH medicine ☐ Referred to TBH ☐ Other:_____

ADDENDUM 2: AUTHOR GUIDE

https://www.elsevier.com/journals/african-journal-of-emergency-medicine/2211-419X/guide-for-authors

ADDENDUM 3: RESEARCH PROPOSAL

Clinical outcomes in patients with paracetamol ingestion treated with a two-bag N-acetylcysteine regimen in the emergency centre of Khayelitsha Hospital.

Student: K Mbanga

Division of Emergency Medicine

University of Cape Town

Supervisors W Khan

Division of Emergency Medicine

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Daniël J van Hoving

Division of Emergency Medicine

University of Stellenbosch

This study is in partial fulfilment of the MMed degree

Abstract

Background

Paracetamol toxicity is frequently seen in Emergency Centres. The treatment has historically been a three-bag intravenous N-acetylcysteine(NAC) regimen, but the regimen was complex and frequently resulted in adverse reactions. A new intravenous two-bag NAC regimen was implemented at Khayelitsha Hospital on 1 August 2019 after consultation with the Division of Clinical Pharmacology at Stellenbosch University. A purposefully-designed clinical audit sheet was used to monitor its implementation. The aim of this study is to describe the clinical outcomes in patients with paracetamol ingestion treated with the two-bag NAC regimen at Khayelitsha Hospital. A secondary objective is to describe the clinical outcomes of a historical cohort of patients with paracetamol ingestion treated with the three-bag NAC regime.

Methods

A chart review will be perfomed retrospectively. All patients that were managed with the two-bag NAC regimen between 1 August 2019 and 31 January 2020 will be included in this study. The historical cohort of patients treated with the three-bag NAC regimen will consist of patients with paracetamol ingestion from the electronic Khayelitsha Hospital Emergency Centre database (1 January 2018 and 31 July 2019). This database is a prospectively collected observational database that is registered with the Stellenbosch University Health Research Ethics Committee (Ref: N15/10/107). Variables will be described using appropriate summary statistics. This is a purely descriptive study and no statistical comparisons will be made between the two groups (two-bag versus three-bag). Inter-rater reliability will be assessed on 10% of the charts reviewed.

Conclusion

We expect the simplified two-bag regimen to have similar clinical outcomes, that could prove to be less labour intensive and be more cost effective.

Introduction

Paracetamol is globally one of the most frequent toxicology-related ingestions.(1) Morbidity and mortality from paracetamol ingestion occurs mainly from hepatotoxicity (2–5), with over 40% of patients presenting with acute liver failure after a paracetamol overdose.(6)

The primary management of paracetamol toxicity includes supportive care and the administration of N-acetylcysteine (NAC).(7) The administration of NAC for paracetamol ingestion at a single time point is guided by the Rumack-Matthew Nomogram. This logarithmic graph plots the serum concentration of paracetamol against the time since ingestion in an attempt to predict the development of hepatotoxicity, allowing clinicians to decide if treatment with NAC should be initiated.(8) The Rumack-Matthew Nomogram has been in use since 1975,(8) and changes in the administration of NAC have mainly related to lowering the treatment threshold for the administration of NAC,(9) with minimal changes to the manner in which NAC is administered. Historically, a three-bag NAC-regimen was used in most countries. The three-bag intravenous regimen was complex and carried a high risk of medication error as it included three separate, weight-related infusions over three different timeframes.(3) The regime mostly used was NAC 150 mg/kg over 1 hour, followed by 50 mg/kg over 4 hours, and then finally at 100 mg/kg over 16 hours.(10)

The high initial dose of the three-bag intravenous NAC-regimen resulted in a high frequency of dose-related adverse reactions.(3) Vomiting occurred in up to 60% of patients, while anaphylactoid reactions caused treatment interruption and refusal in a further 20%.(11–13) The high frequency of NAC-related adverse events led to an increasing global interest to modify the NAC regime; primarily to reduce adverse events but also to simplify the regimen.(3,4) A two-bag intravenous NAC regimen was proposed, consisting of 200mg/kg over 4 hours, followed by 100mg/kg over 16hours.(4,14) Subsequent studies indicated that the two-bag regimen (compared to the three-bag regimen) is associated with fewer side effects, a low incidence of hepatotoxicity, and no reports of liver failure or need of a liver transplantation.(3–6,14)

Motivation

Toxicology-related patients often present to emergency centres. The prevalence of intentional overdose in the resuscitation area of Khayelitsha Hospital is approximately 8%, of which a quarter (25%) relates to paracetamol ingestion.(15) A two-bag intravenous NAC regimen (200mg/kg over 4 hours, followed by 100mg/kg over 16hours) for the acute management of paracetamol toxicity was initiated at Khayelitsha Hospital on 1 August 2019, after consultation with the Division of Clinical Pharmacology at Stellenbosch University, the Tygerberg Hospital Poisoning Information Centre, and

the Khayelitsha Hospital Pharmacy. This decision was based on the assumptions that the simplified regimen would be equally effective in managing paracetamol toxicity, be less labour intensive, and be more cost effective than the traditional three-bag regimen (150 mg/kg over 1 hour, then 50 mg/kg over 4 hours, followed by 100 mg/kg over 16 hours). A clinical audit sheet was designed in order to monitor the implementation of this new regimen (Appendix 1).

Aim

This study's aim is to describe the clinical outcomes in patients with paracetamol ingestion treated with the two-bag N-acetylcysteine regimen at Khayelitsha Hospital.

Objectives

The objectives are:

i. To describe the indications for starting the two-bag N-acetylcysteine regimen in patients with paracetamol ingestion
ii. To describe the investigations done in patients with paracetamol ingestion treated with the two-bag N-acetylcysteine regimen
iii. To describe the adverse effects in patients with paracetamol ingestion treated with the two-bag N-acetylcysteine regimen.
iv. To describe the disposition of patients with paracetamol ingestion treated with the two-bag N-acetylcysteine regimen.
v. To describe the clinical outcomes (indications, investigations, adverse effects, disposition) of a historical cohort of patients with paracetamol ingestion treated with a three-bag N-acetylcysteine regimen.

Methods

Study design

A retrospective chart review will be conducted within the emergency centre of Khayelitsha Hospital.

Study setting

Khayelitsha Hospital is a 300-bed district level hospital situated in the township of Khayelitsha, Cape Town, which serves a predominantly black African population of more than 400 000. Services rendered are both adult and paediatric emergency related as well as inpatient services such as surgical, medical, paediatric and obstetrics.(16,17) The emergency centre at Khayelitsha Hospital is

larger than that of a standard district hospital emergency centre (17), and has a well-equipped four-bed resuscitation area. The emergency centre manages about 30 000 patients per annum and the prevalence of intentional overdose managed in the resuscitation area of the emergency centre is 8%.(15)

Study population and sampling

A clinical audit to assess the implementation of the new two-bag NAC regimen was undertaken at the request of Division of Clinical Pharmacology at Stellenbosch University, Tygerberg Hospital Poisoning Information Centre and Khayelitsha Hospital Pharmacy from 1 August 2019 to 31 January 2020 in patients with paracetamol ingestion presenting to the emergency centre of Khayelitsha Hospital. Training sessions were held to facilitate the implementation of the new two-bag regimen. The nursing unit manager and all the professional nurses working in the emergency centre were educated about the new regime and agreed to help implementation thereof by placing an audit sheet (appendix 1) in the medical file of each patient managed for paracetamol ingestion. The audit sheets were kept in a red file next to the drug cupboard in the resuscitation area. Nursing staff were encouraged to verbally remind the doctors of the new regime. Nurses were also trained to recognize potential adverse effects relating to the NAC infusion. Doctors attended demonstrations on how to correctly complete the audit sheet. Special emphasis were placed on the indications of NAC, the investigations needed and the dosage regime. Emergency Centre consultants further reminded and motivated the staff on a weekly basis to adhere to the two-bag NAC regime and to continue completing the audit sheet. For the purpose of this study, convenience sampling will be used and will include all patients that formed part of the clinical audit; we expect the sample size to be ±40 patients.

The historical cohort of patients treated with the three-bag NAC regimen (objective v) will be assembled by selecting all patients with paracetamol ingestion from the electronic Khayelitsha Hospital Emergency Centre database (1 January 2018 and 31 July 2019). The capturing of observational data for all the patients managed within the resuscitation area since the 1st of November has been collected prospectively and stored in the database. This electronically captured data, are coded and stored onto a password protected server. A decoding sheet is separately stored. The database has been registered at the Stellenbosch University Health Research Ethics Committee (Ref: N15/10/107). Convenience sampling will be used to include all patients that received the three-bag NAC treatment regimen, we expect the sample size to be ±100 patients.

Data collection

Data will be collected by the lead investigator on site at Khayelitsha Hospital. Data will be abstracted from the clinical audit sheets and from the hospital electronic clinical record directly onto a standardised Excel spreadsheet (Appendix 2).

Briefly, the following data points will be collected

- Age and gender
- Body weight
- Indications for starting NAC
- Paracetamol ingestion dosage and timing
- Co-ingestions dosage and timing

A pilot study will be completed using five patient folders for each group (two-bag and three-bag) and will be used to adequately train the chart reviewers and to adapt the datasheet if needed; data will be included if of adequate quality. Interrater reliability of the data will be assessed. A minimum of 10% of participants' folders will be re-abstracted by a second reviewer blinded to the results from the initial reviewer. None of the reviewers will be blinded to the study's objectives.

A personal computer will be used to capture and store data within a password protected account. Patient folder numbers, which is the main identifier used, will be removed once data capture is completed for each patient. Each will then be assigned a unique number linked to the patient folder number. A decoding sheet will be separately stored with access privileges limited to the lead investigator.

Data back-up will occur biweekly on a university server. Upon study completion, two copies of the de-identified electronic database will be backed-up for long term storage on an external hard drive, the University server, and one hard copy will be kept secure in a locked cabinet in the offices of the Division of Emergency Medicine. Data will be stored for at least five years after which it will be destroyed.

Data analysis

Data points that are incomplete will be excluded from analysis for each outcome variable, however, participants with missing data will be reported and will (where possible) not be excluded. This is a purely descriptive study and no statistical comparisons will be made between the two groups (two-

bag versus three-bag). Reproducibility of 10% of the study sample will be measured using κ statistics with 95% confidence intervals. The κ statistics will be interpreted as previously described.(18)

Summary statistics will be used to describe all variables. Categorical data will be summarised using frequency counts or percentages, and distributions of variables will be presented as two-way tables or bar charts. Medians or means will be used as the measures of central tendency for ordinal and continuous responses and standard deviations or quartiles as indicators of spread.

A STROBE checklist will be used to structure the final report.(19)

Projected time

	Apr 2020	May 2020	Jun 2020	Jul 2020	Aug 2020	Sep 2020	Oct 2020	Nov 2020	Dec 2020	Jan 2021
HREC approval	X									
WCG health approval			X							
Data collection				X	X					
Data analysis						X	X			
Write up								X	X	X

Ethical considerations

The study will be conducted according to the guidelines for research involving human subjects as reported by the Declaration of Helsinki 2017.

Facility approval for the study will be sought via the National Health Research Database once ethical approval has been obtained.

Risks and benefits

The two-bag NAC regime is used internationally and has been implemented after consultation with the Division of Clinical Pharmacology at Stellenbosch University, the Tygerberg Hospital Poison Information Centre, and the Khayelitsha Hospital pharmacy. As this study is observational and retrospective, risk to participants is likely minimal. A potential risk is possible if there is unauthorised access to patient data. Patient de-identification will occur to mitigate this risk after data collection is completed. The retrospective analysis in itself offers no direct benefit to participants, however, potential of indirect benefit to similar future patients exists.

Informed consent process

Data will be obtained from a clinical audit that was instituted as part of quality assurance at Khayelitsha Hospital. Furthermore, the database from which the comparative group's data will be drawn is registered with the Stellenbosch University Health Research Ethics Committee (Ref: N15/10/107). The information obtained from the database will be supplemented from the patient record. As this will be retrospective, taking individual consent will be near impossible. The registered database also includes a formal waiver of informed consent. We thus request a waiver of informed consent for participants drawn from both the clinical audit and the registered database.

Privacy and confidentiality

As described earlier, the study will make use of a combination of safeguards to ensure anonymity of study subjects. This will include on-site data management using a password protected electronic platform containing the data sample, and coding data immediately after data collection is completed.

Limitations

This is a retrospective analysis with inherent risks of error as well as missing information. Missing data allow for selection bias by allowing preference for study participants with complete data. Safeguards were in place during the clinical audit to limit missing data. The study participants with missing data will be reported on, where possible, and not be excluded from analysis. Incomplete data points will be excluded.

The short study period might result in a very small sample size. As this study is purely descriptive, the effect of a small sample size will be minimal. In any case, care will be taken to not over-interpret the results.

As this study is a retrospective chart review, we have no means to determine whether the variables of interest were completed and to what extent it reflects the truth.

Reporting & implementation of results

Publication as an original article is anticipated, in a peer reviewed journal is anticipated. The study results will also be distributed to the management team of Khayelitsha Hospital Emergency Centre and hospital administration.

Resources

Non-clinical resources will be utilised. This will include use of an existing personal computer. Khayelitsha Hospital clerks will not be utilised to access hard copy folders as most patient information

will be electronically available,. The investigators will conduct the study oiut of work hours. The study will be self-funded.

Budget

Consumables	**Cost**
Stationery/papers	R300
Internet	R300
Travel to research site *Twenty visits @ R74.10 (R1.30 /km ; Return distance between UCT and Khayelitsha Hospital = 57km)*	R1482
Total	**R2082**

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