A Systematic review and meta-analysis to compare the effectiveness of shorter 12-hour N-Acetylcysteine (NAC) regimen VS 20-21-hour NAC regimen in management of paracetamol poisoning

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Research Article

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Abstract

Background: Paracetamol poisoning due to unrecommended doses is a leading cause of acute liver failure (ALF) globally, resulting in significant medical consequences. N-Acetylcysteine (NAC) is the standard antidote for paracetamol poisoning, administered through a 20-21 hour 3-bag infusion since 1980. However, this regimen has been associated with adverse reactions, prompting the investigation of shorter NAC regimens like the 12-hour version. A comparison of evidence on the effectiveness and safety between the two interventions is lacking, necessitating this research.

Aims and Objectives: A meta-analysis to compare the effectiveness of a 12-hour NAC regimen with the longer 20-21hour regimen in managing paracetamol poisoning.

Methods: A quantitative systematic review of Randomized Controlled Trials (RCTs) and observational studies was performed, using PICO criteria to search databases Medline, Web of Science, PubMed, Cochrane and Clinical trials.com from 2008 to 2023. The extracted data were analyzed separately for RCTs and observational studies.

Results: Eight studies, including three RCTs and five observational studies involving 10,924 patients, were analyzed. The primary outcome, hepatic injury, showed an insignificant reduction with the 20-21hour NAC regimen (odds ratio= 1.53, 95% CI 0.69-3.40, p=0.29) in RCTs and with the 12-hour NAC regimen (odds ratio= 0.88, 95% CI 0.70-1.11, p=0.29) in observational studies. The secondary outcome, adverse reactions (anaphylactoid reaction), showed a statistically significant reduction with the 12-hour NAC regimen (odds ratio= 0.37, 95% CI 0.20-0.68, p=0.001) in RCTs and (odds ratio= 0.16, 95% CI 0.12-0.22, p=0.00001) in the observational studies.

Conclusions: This study suggests that the 12-hour NAC regimen is as effective as the 20-21hour regimen in managing paracetamol poisoning, but with fewer adverse reactions. However, further research is needed to explore the impact of factors like late presentation and delayed infusion on adverse reactions.

INTRODUCTION

Globally, the trend for aberrant use of over the counter (OTC) drugs and self-medication is on a rise and this poses a critical concern for public health [1]. Paracetamol overdose accounts for 50% of all cases of acute liver failure (hepatotoxicity) in Europe and United states today [2]. Recently, paracetamol poisoning has experienced an increased prevalence rate, especially in developed World. Studies show that paracetamol toxicity is the second most common cause of liver transplantation globally following alcohol-associated liver disease (ALD) [3]. It causes approximately 56,000 visits to emergency department, 2600 hospital admission with 500 mortality incidences yearly in the United State and approximately 90,000 hospital admissions in the United Kingdom [2] [4] [5]. Despite unintentional paracetamol toxicity being common in children, more serious and fatal presentation is often observed in adults with intentional paracetamol ingestion [2] [6].

Paracetamol is one of the most used analgesics for first line treatment of fever and pain due to its superior record of safety when used at therapeutic doses [7] [8]. Paracetamol poisoning occurs when paracetamol is ingested in massive quantities, either intentionally or unintentionally leading to hepatotoxicity [9]. This overdose usage of paracetamol could be attributed to its common availability and perceived safety.

N-Acetylcysteine (NAC) is a 20-21-hour regimen which involves 3 weight-related infusions. The first 150mg/kg is given over 1 hour, second 50mg/kg given over 4 hours and the last 100mg/kg given over 16 hours. This has been

the optimal available therapy since 1980 [10] [11] [12]. However, several evidence shows various adverse effect of this regimen which include anaphylactoid reaction, nausea, vomiting and medication error [13] [14] [15] [16]. In the past decade, different clinical studies have been carried out to propose the adoption of a shorter regimen, the Scottish and Newcastle Antiemetic Pre-treatment (SNAP) 12-hour NAC regimen into clinical practice [4] [17] [18]. Despite the SNAP NAC-12-hour regimen involves giving the same dose of 300mg/kg of NAC, the duration is shorter [17]. It is a two-bag regimen which involves giving 100mg/kg infusion over 2hours, then last 200mg/kg infusion giving over 10hours. [19] in their double-blind RCT trials showed that SNAP 12-hour NAC therapy has a better safety profile and maintained its therapeutic function. The study demonstrates the significance of reduced number of infusions with the shorter 12-hour NAC therapy in minimizing risks of error involved in infusion preparation. However, the cohort study by [20] provides evidence that the 21-hour NAC therapy is effective in preventing hepatotoxicity from massive paracetamol poisoning if received within 8hours of ingestion. Interestingly, the standard 21-hour NAC regimen was also found to cause adverse effects mostly at lower paracetamol concentration or with late presentation of patient to hospital [21]. Several researchers have investigated the effectiveness and adverse effects of these longer and shorter NAC regimens but there has not been a synthesis of primary studies to determine which is more effective with less harm. Thus, the need for this study. This study will focus on comparing the effectiveness and harm of the longer NAC regimens (20-21hours) versus the SNAP 12-hour NAC regimen in the management of paracetamol poisoning. This is necessary to inform standardized guidelines and protocol for the management of paracetamol poisoning

METHODS

Eligibility Criteria

The summary of the eligibility criteria is shown in Table 1. Data was extracted to provide answers to the following research questions.

1. How significantly effective is the shorter NAC-12-hour regimen when compared to longer (20-21hours) NAC regimens in the management of paracetamol poisoning?
2. Which of these treatment regimen has a better safety profile?

Inclusion and Exclusion Criteria

Table 1
Showing the inclusion and exclusion criteria.

Inclusion	Exclusion
• Randomized controlled trials and Observational studies evaluating the effectiveness of longer (20-21hours) NAC treatment and shorter 12-hour NAC treatment	• studies evaluating the effectiveness of NAC treatment in other disease conditions
• Studies evaluating the adverse effects of the regimens	• studies that did not report the effectiveness and adverse effects of the regimens.
• Primary studies between year 2008 and 2023 that are peer-reviewed	• Publications before 2008, non-peer reviewed studies
• Human studies	• Animal studies
• Publications in English Language	• Publications in Foreign language

Systematic Search

The PICO Framework was employed [22], searching the databases Medline, Pubmed, Cinahl, Cochrane, Web of Science and Clinicaltrials.gov spanning from 2008 to 2023. The search utilized keywords such as “paracetamol poisoning,” “N-Acetylcysteine”, “20-hours NAC”, “20.25-hours NAC”, “21-hours NAC” and “adverse effect”. Synonyms of keywords were used, and search outcome expanded using Boolean operator “AND” and “OR”. Reference lists of included studies were also reviewed for additional studies. 217 articles were retrieved and exported to Endnote (version 20) where duplicates were expunged as shown on the PRISMA Flowchart in Fig. 1.

Study Characteristics

Eight studies were selected for the systematic review and meta-analysis. Three were RCTs [4] [23] [24] and five were observational studies [25] [26] [27] [28] [29] as shown in Table 2.

Assessment of Quality and extraction of data

The studies were read independently and jointly by both authors, who then assessed the quality and extracted the Data (as shown in Table 3). The Quality of the RCTs were conducted using Critical Appraisal skills program (CASP tools) as recommended by Cochrane Collaborators [30] while the quality of Observational studies were conducted using the Newcastle-Ottawa Scale (NOS) [31] [32]. The authors employed the use of the Cochrane risk-of-bias tool for RCTs (RoB2) to assess bias in the three RCTs through the structured domains [33]. However, the authors employed the use of the risk-of-bias in non-randomized studies of intervention (ROBINS-I) tool as recommended by Cochrane for the Observational studies [34].

Table 2
Showing Characteristics of studies included RCT (n = 3) Observational studies (n = 5).

Research author, year	Study aim	Location	Study design	Number of participants	Measured outcome
Bateman et al., 2014	To determine reduction in adverse effect of NAC with shorter modified NAC regimen, antiemetic pre-treatment (Ondansetron) or both	United Kingdom	Double blinded factorial RCT	222	Acute liver Injury (ALI) and Adverse reaction
Dear et al., 2021	To compare effect of standard NAC regimen VS 12-hour modified NAC treatment on biomarkers and paracetamol metabolite	United Kingdom	Double blinded factorial RCT	45	Acute liver Injury (ALI)
Wong et al., 2019	To investigate 12-hour treatment regimen for low-risk patient with paracetamol poisoning	Australia	Open-labelled Cluster-control	100	Acute liver Injury (ALI) and Adverse reaction
Pettie et al., 2019	To compare the adverse effect of 12-hour NAC regimen VS standard 21-hour NAC regimen	Edinburg	Prospective Cohort study	3,340	Hepatotoxicity and Adverse reaction.
Humphries et al., 2023	To establish improved hospital length of stay and anaphylactoid reactions	United Kingdom	Retrospective cohort study	294	Adverse reaction.
Alrossies, 2022	To compare efficacy of 12-hour NAC regimen and 21-hour NAC regimen in management of paracetamol poisoning	United Kingdom	Bi-directional cohort study (retrospective and prospective)	4,818	Hepatotoxicity and adverse reaction
Alrossies et al., 2021	To compare efficacy of the 2-bag 12-hour NAC regimen and 3-bag 21-hour NAC regimen in management of paracetamol poisoning	United Kingdom	Prospective cohort study	1,192	Hepatotoxicity
Thanacoody et al., 2018	To evaluate the effectiveness of 12-hour NAC regimen in the management of paracetamol overdose	United Kingdom	Prospective cohort study	913	Hepatotoxicity and Adverse reaction.

Table 3
Showing Data extracted from the outcome measured in the included studies.

Research author, year	Outcome of Study	Intervention group (odds ratio)	Participant in intervention	Control group (odds ratio)	Participant in control group
Bateman et al., 2014	Acute Liver Injury Anaphylactoid reaction	13/112 5/108	112	9/110 31/109	110
Dear et al., 2021	Acute Liver Injury	3/23	26	1/18	19
Wong et al., 2019	Acute Liver Injury Anaphylactoid reaction	1/50 14/36	50	1/50 12/38	50
Pettie et al., 2019	Hepatotoxicity Anaphylactoid reaction	67/1785 37/1815	1852	64/1424 163/1325	1488
Humphries et al., 2023	Anaphylactoid reaction	4/72	76	34/184	218
Alrossies, 2022	Hepatotoxicity Anaphylactoid reaction	74/2872 14/1065	2946	45/1750 25/291	1795
Alrossies et al., 2021	Hepatotoxicity	21/833	854	11/327	338
Thanacoody et al., 2018	Hepatotoxicity Anaphylactoid reaction	18/482 8/492	500	17/396 28/385	413

Statistical Analysis

The use of RevMan (version 5.4) for data analysis was suggested by the Cochrane Collaboration [35]. As this review included 3 RCTs and 5 Observational studies where the presentation of outcome were in numerical quantity, the dichotomous data were entered in RevMan [36]. The individual studies reported results in Odds ratio. Although two of the studies [27] [28] were reported in absolute risk of reduction (ARR). ARR was converted to Odds ratio using MedCalc [37] to maintain the homogeneity of the studies. For both studies, the end of treatment values of the intervention and control groups were used for the analysis. A fixed effect analysis model was used, and the effect measure was odds ratio with 95% confidence interval. Heterogeneity was measured across the studies by I^2 statistic. $I^2 > 50\%$ was subjected to further statistical test (sensitivity test) as this suggests a high variability among studies [38].

RESULTS

212 studies were retrieved and after applying exclusion criteria, 8 studies including 3 RCTs and 5 Observational were used for the meta-analysis. Meta-analysis was conducted separately for the RCT and Observational studies.

Following this, separate meta-analyses were conducted under each of the studies for the outcome, hepatic injury and adverse reaction. First outcome, Hepatic Injury defined as progression to Acute Liver Failure (ALT > 50%) in the RCT (as shown in Fig. 2) and progression to Hepatotoxicity (ALT > 1,000 IU/L) in the Observational studies (as shown in Fig. 3), Second outcome, Adverse reaction defined as anaphylactoid reaction in both studies (as shown in Figs. 4 & 9). The total population is 10,924 having 6,414 in the intervention group (12hour NAC regimen) and 4,433 in the control group (20-21hour NAC regimen). The Meta-analysis was carried out using Revman to statistically analyze the collected data.

Heterogeneity Test

Heterogeneity (I^2) refers to variability in the true effects of included studies. $I^2 > 50\%$ suggests high variability among studies (Higgins, 2003). As suggested by Higgins (2003), a sensitivity analysis is required for a $I^2 > 50\%$. Therefore, the authors conducted a sensitivity analysis for the meta-analysis with 92% heterogeneity using a leave-one-study-out technique (Lin et al., 2016) on Revman 5.4. This is to confirm that the reduction in adverse reaction recorded in these RCT studies is not based on error, but on the true effect of the shorter 12-hour NAC regimen as shown in Fig. 4. This leave-one-study-out approach involves conducting meta-analysis on each subset of the studies by exclusion of a study to determine the effect on the overall estimate (Higgins, 2008). Both fixed effect and random effect model were used for this analysis, but no observed difference was encountered between the two models as shown in Figs. 5,6,7 and 8.

DISCUSSION

Outcome for Hepatic Injury

ALT > 50% and ALT > 1,000IU/L has been used to define hepatic injury. The effectiveness of 12-hour NAC regimen and 20-21hour NAC regimen was compared by prevention of hepatic injury resulting from paracetamol poisoning. The RCT studies show an Odds ratio of 1.53 which is above 1 (the line of null effect). Implication is that reduction in hepatic injury lies on the right side (in favor of 20-21hours NAC regimen) with Confidence interval of 95% ranging from 0.69 to 3.4, having a P-value of 0.29. This implies that the observed reduction in hepatic injury with the longer (20–21) hour NAC regimen is not statistically significant. This suggests that no significant difference exists between the effectiveness of both interventions in terms of preventing hepatic injury. Although the result of comparing the effectiveness of 12-hour NAC regimen and longer (20–21) hour NAC regimen in the Observational studies shows an Odds ratio below 1 (0.88). Implying that the reduction in hepatic injury lies on the left side (in favor of 12-hours NAC regimen). However, the Confidence interval is 95% and it ranges from 0.70 to 1.11 with an overall P-value of 0.29 which is statistically insignificant. This is still suggestive that no significant difference exists between the effectiveness of both interventions in terms of preventing hepatic injury.

Outcome for Adverse Reaction

Comparing the adverse reaction resulting from treatment with 12-hour NAC regimen and 20-21hour NAC regimen in the RCT studies shows an Odds ratio of 0.37. This is below 1 (the line of null effect) and it implies that the reduction in adverse reaction lies on the left side (in favor of 12-hour NAC regimen). The Confidence interval is 95% and it ranges from 0.20 to 0.68, which shows a more precise estimate. It shows an overall P-value of 0.001 which is statistically significant. Similarly, the result in the Observational studies shows an Odds ratio of 0.16. This is also below 1 (the line of null effect) and implies that the reduction in adverse reaction lies on the left side (in favor of 12-hour NAC regimen). The observed reduction in adverse reaction with the 12-hour NAC regimen in both studies are

statistically significant, which suggests that a significant difference exists in adverse reaction experienced by patients treated with 20-21hour NAC regimen compared to 12-hour NAC regimen.

The outcome of this study is in congruent with a formal factorial RCT study by Bateman [39] which shows that the 12-hour NAC regimen was associated with a significantly reduced anaphylactoid reaction when compared with the 20.25-hour NAC regimen. This study was conducted in Europe and had a 2% drop-out rate of 47 participants. The study concluded that 12-hour NAC regimen is associated with simpler infusion, less adverse reaction and shorter hospital stay. Similarly, [40] conducted a prospective study to assess 12-hour NAC regimen as standard of care for paracetamol poisoning in pediatric patients as against the 21-hour NAC regimen. The study concluded that the 12-hour NAC regimen demonstrated reduced anaphylactoid reaction with no observed difference in the rate of liver injury when compared to the 21-hour NAC regimen.

Independently, these studies were insufficient to confidently inform clinical practice. However, this review combines data from both RCT and observational studies to compare the safety and efficacy of the shorter 12hour NAC regimen and the longer (20–21) hour NAC regimen. The outcome of this study reveals that 12-hour NAC regimen is effective in the management of paracetamol poisoning, causing less harm. By the application of Evidence-Based Medicine (EBM) model, this meta-analysis can be seen to provide valuable evidence supporting the 12-hour NAC regimen as a more effective approach in managing paracetamol poisoning. This presents a strong basis for recommending the 12-hour NAC regimen in clinical guidelines and practice. Thus, promoting evidence-based decision-making in healthcare. The clinical implication of this result is that 12-hour NAC regimen can be adopted into the guideline and procedures for the management of paracetamol poisoning. This will enhance short hospital stay and less adverse reactions.

Strength and Limitation

The author adopted several techniques to demonstrate methodological and statistical rigor. Further analysis was conducted to test for heterogeneity using the leave-one-study-out approach. Also, recent evidence was used for this review, and it is believed that this meta-analysis reflects which regimen is most effective in managing paracetamol poisoning. However, some limitations were inevitable. First, the exclusion of non-English published studies could have hindered the chances of obtaining some good studies that could inform evidence for meta-analysis. Second, this is a systematic review and meta-analysis with a combination of RCTs and Observational studies. Observational studies may be subject to biases from unmeasured confounding variables.

Recommendation for Clinical practice

The simplicity and the safe profile of 12-hour NAC regimen is a justification for its use in clinical practice. By this research, additional evidence has been provided to justify the continuous use of 12-hour NAC regimen as standard of care in the management of paracetamol poisoning.

Recommendation for further research

Further research is required to examine how the 12-hour NAC regimen will perform in patients with late presentation and variations in overdose (staggered or acute). Likewise, delayed infusion of regimens on the effectiveness and adverse reactions from these regimens as suggested by [41] [42].

Conclusion

This study was able to provide evidence of effectiveness and less harm in favor of the SNAP 12-hour NAC regimen. In response to the first research question, no significant difference exists in effectiveness between the shorter 12-hour NAC regimen and the longer (20–21) hour NAC regimen in the management of paracetamol poisoning. However, regarding adverse reactions, the 12-hour NAC regimen showed a statistically significant lesser harm than the 20-21-hour NAC regimen. This provides an answer to the second research question. The robustness of this study will inform clinical decision-making. This will reduce the adverse reactions experienced with the longer (20–21) hour NAC regimen by using the shorter 12-hour NAC regimen in the management of paracetamol poisoning. Also, the 12-hour NAC regimen may translate to shorter stay of patients and rapid turnaround of available bed spaces for other patients in the hospital.

Declarations

I affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted. The Corresponding Author has the right to grant on behalf of all authors and does grant on behalf of all authors, an exclusive licence (or non-exclusive for government employees) on a worldwide basis to the BMC Publishing Group Ltd to permit this article (if accepted) to be published in BMC editions and any other BMC affiliates and sublicences such use and exploit all subsidiary rights, as set out in our licence.

CONSENT FOR PUBLICATION

Not Applicable

AVAILABILITY OF DATA AND MATERIALS

Data are available in Table 2 and 3.

ETHICAL APPROVAL AND CONSENT TO PARTICIPATE

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist. All authors have completed the unified competing interest form and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work.

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AUTHORS CONTRIBUTIONS

This work was carried out in collaboration between the two Authors. Both Authors (Author A- Olawunmi Oluwakemi Oyedjei & Author B- Emmanuel Ojeabuo Oisakede) equally contributed to all chapters of this work and are both first authors. Both Authors read and approved the final Manuscript.

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Figures

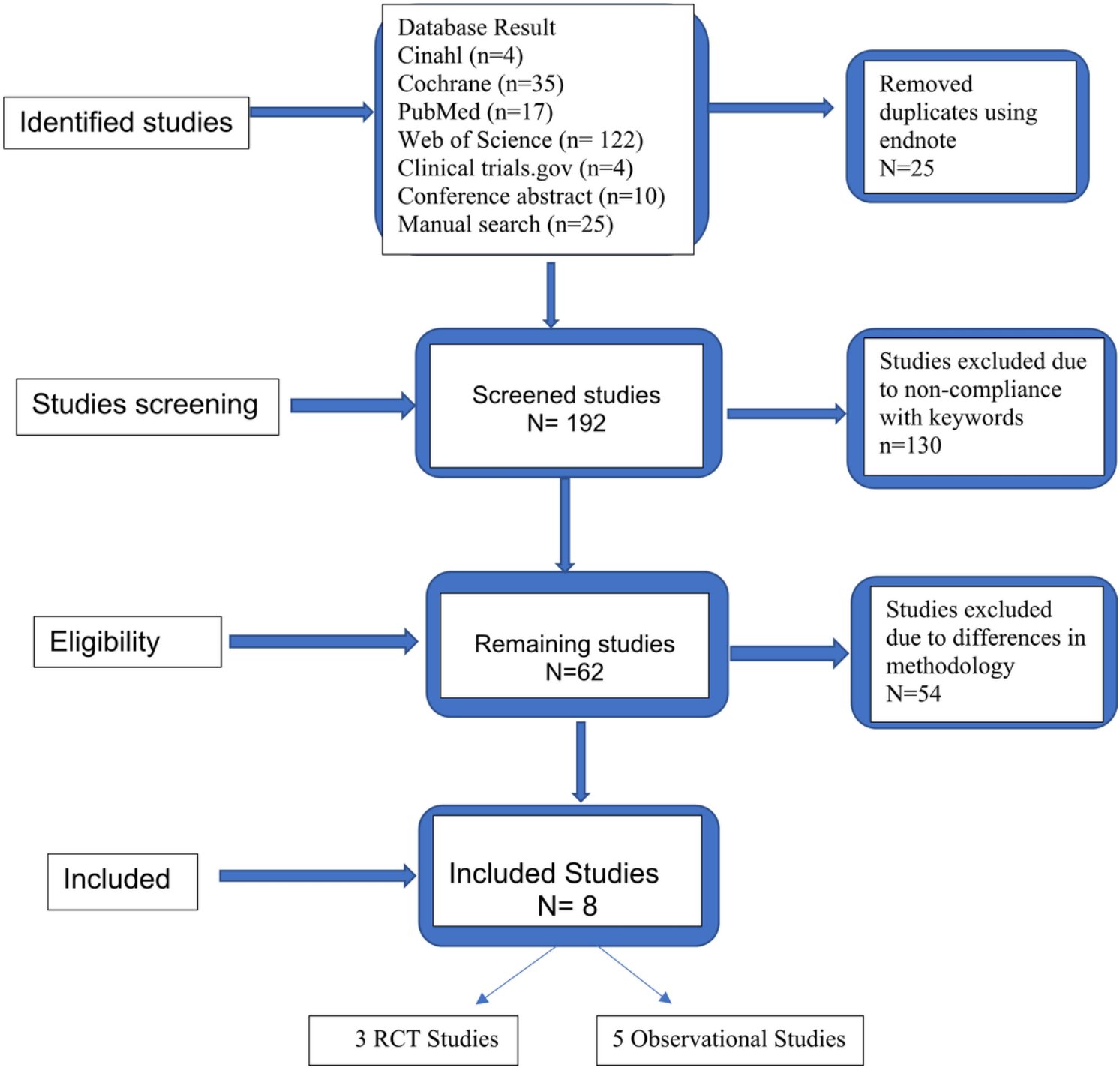

Figure 1

PRISMA flowchart which illustrates the selection process of the included RCTs and observational studies

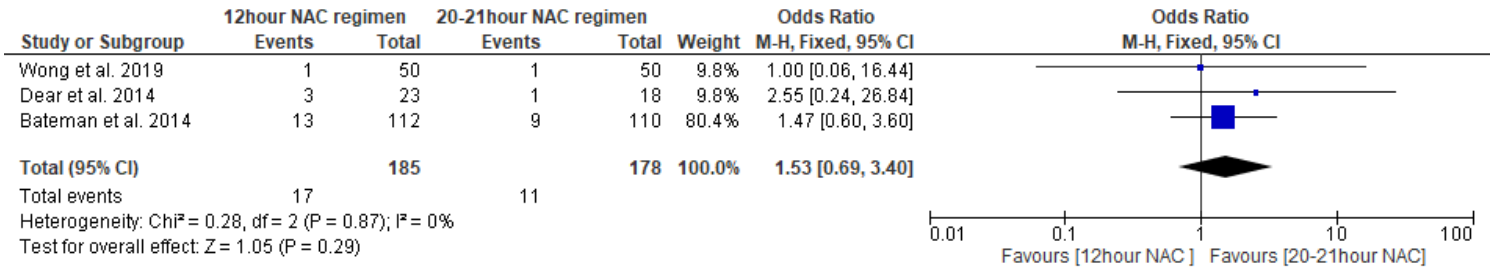

Figure 2

showing forest plot of hepatic injury in RCT. (The result shows decreased rate of hepatic injury with the longer (20-21) hours NAC regimen more than in the 12-hour NAC regimen. The overall pooled effect size of 1.05 at 95% Confidence Interval (C.I = 0.69 to 3.40) crosses the line of null effect. Implication is that the reduction of hepatic injury with longer (20-21) hours NAC regimen group is not statistically significant having P-Value of 0.29 and heterogeneity is 0%).

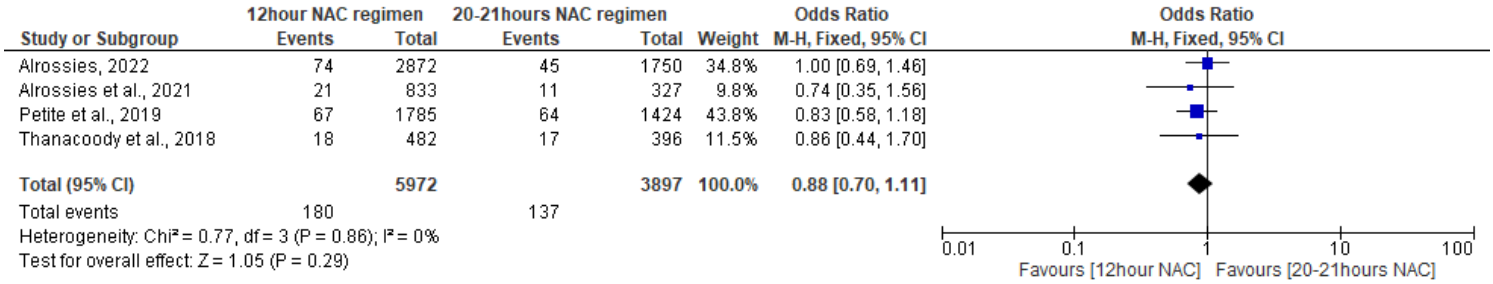

Figure 3

showing forest plot of hepatic injury in Observational Studies. (The result shows a reduction in hepatic injury with the 12-hour NAC regimen more than in the 20–21hour NAC regimen. The overall pooled effect size is 1.05 at 95% Confidence Interval (C.I = 0.70 to 1.11). This observed reduction with 12-hours NAC regimen group is not statistically significant having P-Value of 0.29, heterogeneity is 0%).

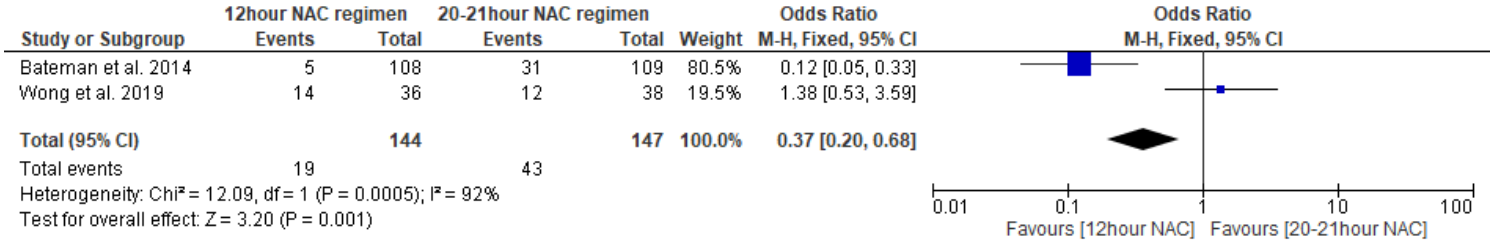

Figure 4

showing forest plot of adverse reaction in RCTs. (12-hour NAC regimen was found to have less adverse reaction than longer (20-21) hour NAC regimen. The overall pooled effect size is 3.20 at 95% Confidence Interval (C.I = 0.20 to 0.68) which lies on the left side, not crossing the line of null effect. This indicates that the lesser adverse effect in 12-hours NAC regimen group is statistically significant having P-Value of 0.001 and heterogeneity is 92%, warranting further statistical testing).

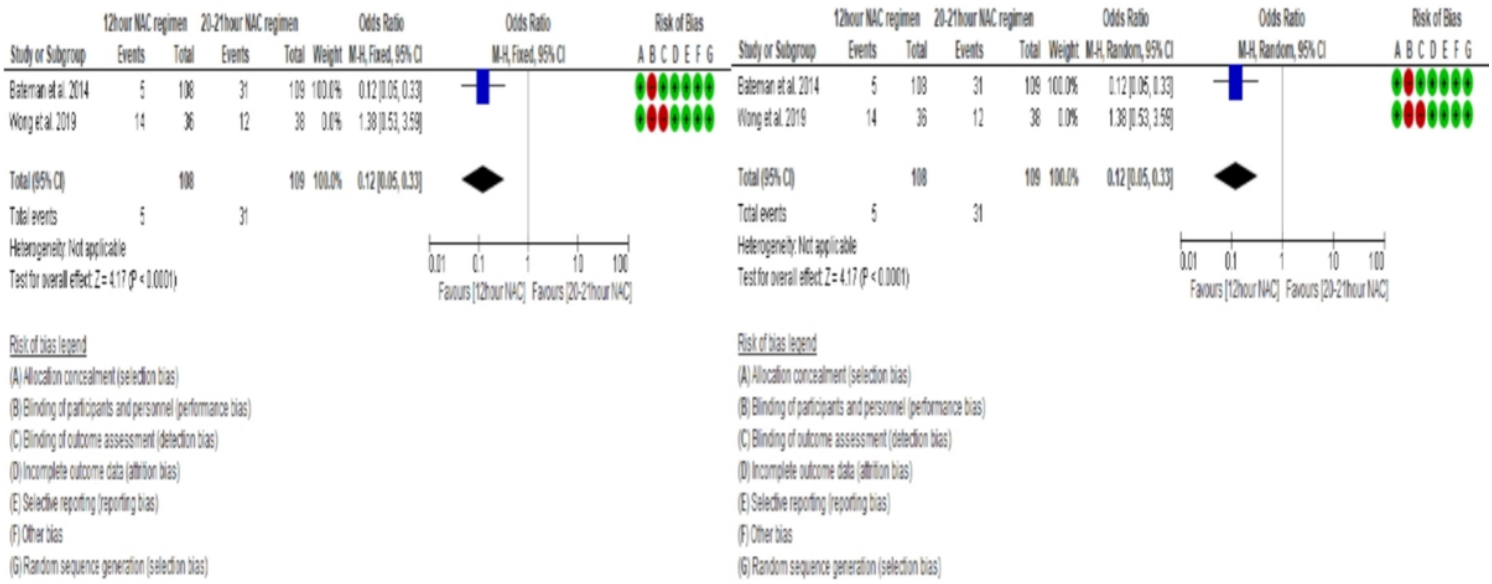

Figure 5

Figures 5 & 6: showing forest plot of the changes of I^2 due to leaving out a study using Fixed effect and Random effect model respectively

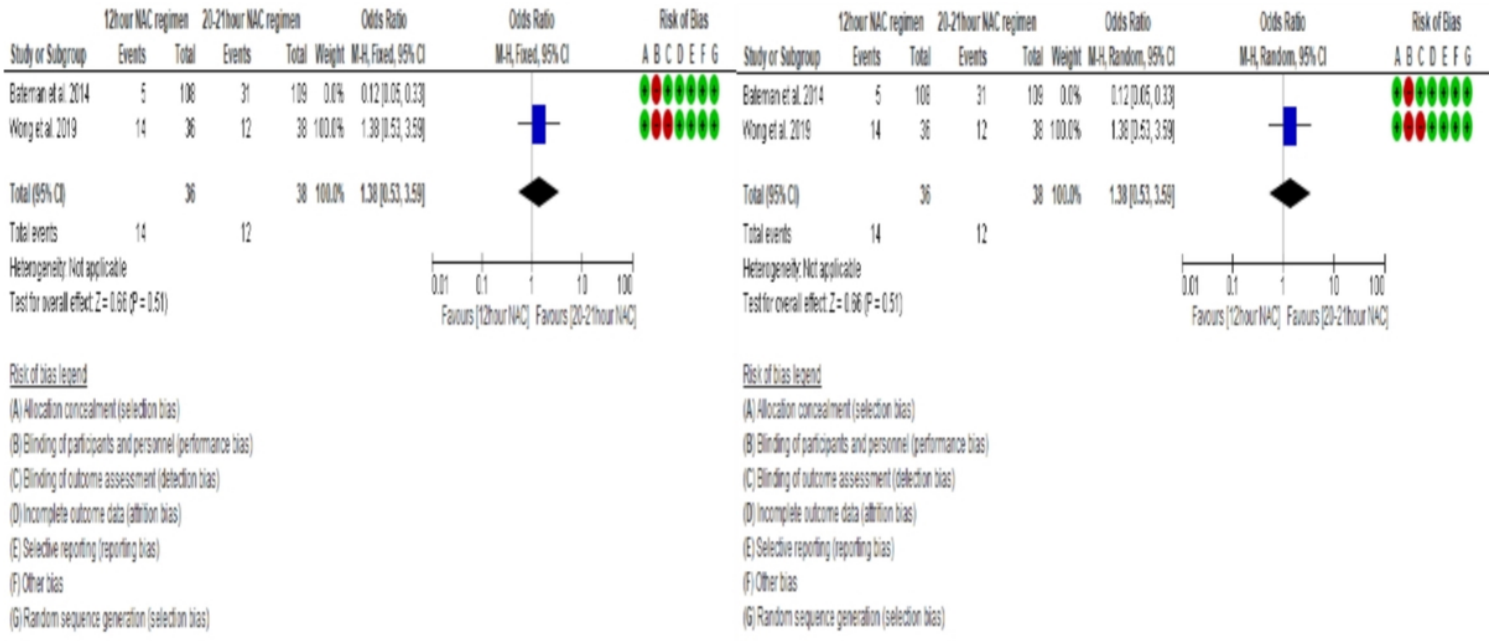

Figure 6

Figures 7 & 8: showing forest plot of the changes of I^2 due to leaving out a study using Fixed effect and Random effect model respectively

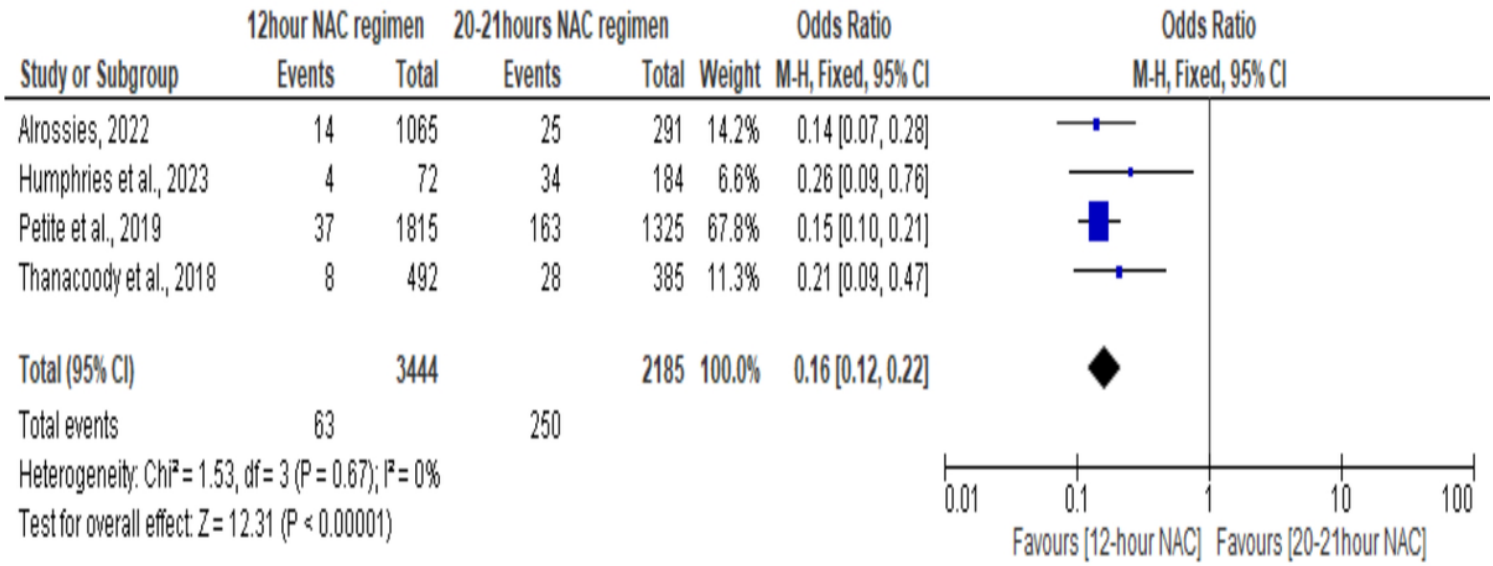

Figure 7

Figure 9: showing Forest Plot for Adverse reaction in Observational studies.(12-hour NAC regimen was observed to have less adverse reaction than 20-21hour NAC regimen. The overall pooled effect size (diamond shape) of 12.31 at 95% Confidence Interval (C.I = 0.12 to 0.22) lies on the left side, far away from the line of null effect. This implies that the lesser adverse effect with 12-hours NAC regimen group is statistically significant having P-Value of 0.000001 and heterogeneity is 0%).