RENOPROTECTIVE EFFECT OF HIGH DOSE N-ACETYLCYSTEINE IN PATIENTS WHO UNDERWENT CARDIAC SURGERY

DR GAN SHEE YIN

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LIST OF SYMBOLS AND ABBREVIATIONS

AKI	Acute kidney injury
AKIN	Acute Kidney Injury Network
BD	Twice a day
CABG	Coronary artery bypass graft
CKD	Chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CPB	Cardiopulmonary bypass
eGFR	Estimated glomerular filtration rate
G	Gram
GFR	Glomerular filtration rate
HUSM	Hospital Universiti Sains Malaysia
IJN	Institute Jantung Negara
IV	Intravenous
JEPeM	Human Research Ethics Committee of Universiti Sains Malaysia
KDIGO	Kidney Disease Improving Global Outcomes
kg	Kilogram
mg	Milligram
NAC	N-acetylcysteine
POD	Postoperative day
RIFLE	Risk, Injury, Failure, Loss of kidney function, End-stage renal failure
RRT	Renal replacement therapy
SPSS	Statistical Package for the Social Sciences

T	Tablet
WHO	World Health Organisation
mmol/L	Millimole per litre
umol/L	Micromole per litre

ABSTRAK

Tajuk: Kesan Renoprotektif Dos Tinggi N-acetylcysteine kepada Pesakit yang Menjalani Pembedahan Jantung.

Latar Belakang: Kesan N-acetylcysteine pada pencegahan kecederaan buah pinggang akut selepas pembedahan jantung masih menjadi kontroversi. Kajian ini direka untuk menilai kesan N-acetylcysteine dos tinggi terhadap fungsi buah pinggang pesakit yang menjalani pembedahan jantung.

Kaedah: Kajian keratan rentas perbandingan yang melibatkan semakan rekod retrospektif (Januari 2017-Disember 2021) telah dijalankan di Hospital Universiti Sains Malaysia. Seratus dua puluh tiga pesakit dewasa menjalani pembedahan jantung dengan pintasan kardiopulmonari dan sekurang-kurangnya 1 daripada berikut adalah: disfungsi buah pinggang sedia ada atau menerima agen kontras kurang daripada 6 minggu dari tarikh pembedahan telah direkrut. Kumpulan kajian (n=40) menerima 600mg BD T N-acetylcysteine sehari sebelum pembedahan dan 10g IV N-acetylcysteine ke dalam mesin pintasan kardiopulmonari manakala kumpulan kawalan (n=83) tidak menerima N-acetylcysteine.

Keputusan: Bagi kumpulan N-acetylcysteine dengan kumpulan kawalan ($p>0.05$), tidak terdapat perbezaan yang signifikan nilai min antara serum kreatinin dengan eGFR semasa pra-pembedahan juga 24 jam dan 48 jam selepas pembedahan. Tidak terdapat perbezaan yang signifikan ke atas kadar buah pinggang akut antara kedua-dua kumpulan [58

(47.2%) vs 37 (44.6%); p=0.41]. Tiada perbezaan diperhatikan bagi keperluan terapi penggantian buah pinggang, tempoh penggunaan mesin bantuan pernafasan, tempoh tinggal di unit rawatan rapi dan tempoh kemasukan ke hospital antara kedua-dua kumpulan (p>0.05).

Kesimpulan: Dalam kajian ini, kami tidak mengesan perlindungan fungsi buah pinggang yang signifikan secara statistik kepada pesakit yang menerima N-acetylcysteine untuk pembedahan jantung. Percubaan rawak terkawal yang lebih selanjut diperlukan dalam bidang ini untuk meminimumkan faktor yang mengelirukan.

Kata Kunci: *N-acetylcysteine, dos tinggi, disfungsi buah pinggang, kecederaan buah pinggang akut, pembedahan jantung*

ABSTRACT

Title: Renoprotective effect of high dose N-acetylcysteine in patients who underwent cardiac surgery

Background: The effect of N-acetylcysteine on the prevention of acute kidney injury post-cardiac surgery remains controversial. This study was designed to evaluate the effect of high-dose N-acetylcysteine on the renal function of patients who underwent cardiac surgery.

Methods: A comparative cross-sectional study involving retrospective record review (January 2017-December 2021) was conducted at Hospital Universiti Sains Malaysia. One hundred and twenty-three adult patients underwent cardiac surgery with cardiopulmonary bypass and had at least 1 of the following: pre-existing renal dysfunction or recent contrast less than six weeks from the operation date were recruited. The study group (n=40) received T N-acetylcysteine 600mg BD one-day prior to operation and IV N-acetylcysteine 10g into cardiopulmonary bypass machine, and the control group (n=83) did not receive N-acetylcysteine. We measured the mean serum creatinine level at 24 hours and 48 hours postoperatively and compared the prevalence of acute kidney injury using KDIGO criteria between both groups.

Results: There was no significant difference in comparing the mean values of serum creatinine and estimated glomerular filtration rate (eGFR) across the pre-operation, 24 hours and 48 hours postoperatively between the N-acetylcysteine and control groups

(p>0.05). There was no significant difference in the prevalence of acute kidney injury between the two groups [58 (47.2%) vs 37 (44.6%); p=0.41]. No difference was observed in the two groups' need for renal replacement therapy, duration of ventilation, length of stay in the intensive care unit, and duration of hospitalisation (p>0.05).

Conclusion: In this study, we did not detect statistically significant protection of renal function in patients who received N-acetylcysteine for cardiac surgery. A further randomised controlled trial in this area is needed to minimise confounding factors.

Keywords: *N-acetylcysteine, high dose, renal dysfunction, acute kidney injury, cardiac surgery*

CHAPTER 1: INTRODUCTION

Acute kidney injury is a common and important complication in hospitalised patients, comprising 22-57% of all patients (1). The incidence of acute kidney injury in patients undergoing cardiac surgery ranges from 33-59%, depending on the type of surgery (1,2). It is one of the most important post-operative complications following cardiac surgery and is associated with significant morbidity, mortality, and cost of care in patients who underwent cardiac surgery (2–4).

The development of post-operative renal dysfunction is complex and has a multifactorial aetiology (1,5–7). Factors proposed include exposure to endogenous and exogenous toxins, ischemia-reperfusion injury, embolisation, hemodynamic changes, neurohumoral activation, metabolic factors, systemic inflammation, and oxidative stress (6). Risk factors proposed that can lead to acute kidney injury are advanced age and underlying comorbid such as hypertension, diabetes mellitus, cardiac failure, and pre-existing renal disease (1,5,7–9). In addition, patients on cardiopulmonary bypass during cardiac surgery result in systemic inflammatory response syndrome due to contact of blood and the artificial surfaces of the cardiopulmonary bypass machine (6). Therefore, the use of cardiopulmonary bypass associated with systemic inflammatory response, hypoperfusion and loss of pulsatile perfusion contributes to the development of postoperative renal dysfunction (1,5,7,8). Circulatory failure perioperatively can cause direct toxic effects within renal tubular epithelial cells with depletion of local antioxidants and reactive oxygen species formation (1,5,8).

Various pharmacological and non-pharmacological methods have been evaluated to prevent acute kidney injury in patients undergoing cardiac surgery (6,10). However, no conclusive result is drawn to support the use of any pharmacological drug (dexmedetomidine,

statin, fenoldopam, levosimendan, erythropoietin, N-acetylcysteine, sodium bicarbonate and volatile anaesthetics) in preventing acute kidney injury (6,11).

N-acetylcysteine can be a simple, nontoxic protective measure. It is the N-acetyl derivative of the amino acid L-cysteine, a precursor in the body's formation of the antioxidant glutathione (12). It reduces renal dysfunction in cardiac surgery due to its anti-inflammatory, antioxidant, and reactive oxygen species scavenger properties (8,13–15). In addition, it also acts via the nitric oxide pathway giving antioxidant and vasodilator effects in protecting renal function (8).

Studies have shown that minimal increases in serum creatinine postoperatively are associated with mortality, and acute kidney injury requiring dialysis is an independent risk factor for mortality after cardiac surgery (7,16). Therefore, prevention of acute kidney injury is crucial in patients undergoing cardiac surgery (7,11).

1.1 Study Rationale

The incidence of renal dysfunction in patients undergoing cardiac surgery is high (1). This is due to the majority who are scheduled for cardiac surgery comprised of those who are elderly and with multiple comorbid. The use of cardiopulmonary bypass in cardiac surgery is another risk factor (6). Renal dysfunction is associated with the need for renal replacement therapy, higher cost, morbidity, and mortality rate (2–4). Therefore, the ability to prevent renal dysfunction post-operative using pharmacological method is more cost-effective (7).

N-acetylcysteine has been used widely and shown to be effective for contrast-induced nephropathy. However, there have been contradictory findings on different doses of N-

acetylcysteine in the prevention of renal dysfunction in patients undergoing cardiac surgery (8,13,17–25).

Low-dose N-acetylcysteine treatment (2400mg) has been reported to be renoprotective against radiocontrast-induced nephropathy; however, it might be insufficient to counteract the greater oxidative stress for patients undergoing cardiac surgery (13). Recent study by Santana-Santos et al. using high-dose N-acetylcysteine (total intravenous dosage of 200mg/kg) in chronic kidney disease patients undergoing cardiac surgery shows the incidence of kidney injury reduced in the N-acetylcysteine group (23).

The use of high-dose N-acetylcysteine in patients at risk of renal impairment in which patients with raised baseline serum creatinine, had recent contrast angiography and are on cardiopulmonary bypass support could be beneficial. This coincides with Hospital Universiti Sains Malaysia (HUSM) protocol of N-acetylcysteine use, which was incorporated from Institute Jantung Negara (IJN). The protocol administers high-dose N-acetylcysteine to patients at risk of developing post-operative acute kidney injury. Patients will receive oral N-acetylcysteine 600mg BD a day prior to operation and N-acetylcysteine 10g into cardiopulmonary bypass. The dosage is similar to the study done by Santana-Santos et al (23).

To date, neither data nor a study has been conducted in Malaysia on the effectiveness of high-dose N-acetylcysteine in preventing post-operative acute kidney injury among high-risk patients undergoing cardiac surgery. Renoprotective of high-dose N-acetylcysteine among high-risk patients undergoing cardiac surgery remains unclear and should be investigated.

1.2 Literature review

Acute kidney injury is one of the most important post-operative complications following cardiac surgery and is associated with significant morbidity, mortality, and cost of care in patients who underwent cardiac surgery (17,26,27).

There are more than 80% of cardiac surgeries performed with cardiopulmonary bypass (9). Cardiopulmonary bypass serves as a form of extracorporeal circulation that transiently replaces the function of the heart and lungs during surgery (9). However, it is associated with several complications, one of them being acute kidney injury postoperatively (9). The pathophysiology is complex, associated with low-flow, low-pressure non-pulsatile perfusion with hemodilution and hypothermia causing renal hypoperfusion and systemic inflammatory response from the contact of blood with the artificial surface of cardiopulmonary bypass (6,7).

Several studies have found that pre-existing renal insufficiency and contrast use prior to surgery are independent predictors of the need for post-operative renal replacement therapy (6,9,16,28). The incidence of acute kidney injury is highest in patients who underwent contrast angiography and surgery on the same day (16). In addition, even a slight increment in renal function postoperatively is considered as an independent predictor of 30-day mortality after cardiac surgery and the majority of patients requiring dialysis remain dialysis dependent, leading to substantial long-term morbidity and mortality (7,28–30). Therefore, preventing acute kidney injury in patients undergoing cardiac surgery remains the optimal management (11).

The anti-inflammatory property of N-acetylcysteine has been used to counter the inflammatory response to cardiopulmonary bypass in patients undergoing cardiac surgery (6).

In addition, N-acetylcysteine has been used widely and shown to be effective for contrast-induced nephropathy (31,32). Therefore, it has been evaluated for the prevention of acute kidney injury in patients undergoing cardiac surgery (11,16).

A randomised double-blind study by Fischer et al. comparing the use of N-acetylcysteine and placebo in 40 coronary artery surgery patients concluded that the use of N-acetylcysteine protects renal function in patients subjected to cardiac surgery on cardiopulmonary bypass (14). On the other hand, several meta-analyses and randomised controlled trials show no benefits of N-acetylcysteine in the prevention of acute kidney injury after cardiac surgery (8,17–20,24,33). One meta-analysis has shown the benefit of N-acetylcysteine in cardiothoracic surgery is in atrial fibrillation prevention. However, there were no proven benefits of N-acetylcysteine for reducing other complications (21).

However, the meta-analysis which shows N-acetylcysteine to be ineffective has its limitation. It comprises studies with a heterogenous population and baseline creatinine, wide variability of N-acetylcysteine dosage used ranging from 4-300mg/kg/day, and different routes of administration including oral, intravenous, oral plus intravenous and via cardioplegia solution. These may account for the lack of significance in the N-acetylcysteine effect (24,30).

In addition, a larger sample size might be required to detect possible treatment effects of a single therapy in a multifactorial disease such as perioperative kidney injury (34). As evidenced by several studies that show a statistically non-significant reduction in renal dysfunction individually, however, if a random-effects meta-analysis using perioperative studies of patients with pre-existing renal insufficiency is performed, N-acetylcysteine is associated with a moderate reduction in renal dysfunction that approaches statistical significance (18,19,34).

N-acetylcysteine use in patients with higher preoperative creatinine might be beneficial (30). One of the studies shows no difference in postoperative renal dysfunction between the N-acetylcysteine group and placebo group, but a post-hoc subgroup analysis of patients with baseline serum creatinine more than 120umol/L showed lesser patients experiencing post-operative renal dysfunction in the N-acetylcysteine group (25%) compared with the placebo group (37.1%) (19). In another study, when only patients undergoing cardiac surgery with cardiopulmonary bypass support are considered, NAC-treated patients show a significantly lower incidence of acute kidney injury than controls (40% vs 54%) (25).

Low-dose N-acetylcysteine treatment (2400mg) is reported to be renoprotective against radiocontrast-induced nephropathy; however, it might be insufficient to counteract the greater oxidative stress for patients undergoing cardiac surgery (13). Recent study done by Santana-Santos et al. using high-dose N-acetylcysteine (total intravenous dosage of 200mg/kg) in chronic kidney disease patients undergoing cardiac surgery shows the incidence of kidney injury reduced in the N-acetylcysteine group from 57.1% to 28.6% (23).

1.3 Objective

1.3.1 General Objective

To observe the effect of N-acetylcysteine on renal function in patients who underwent cardiac surgery

1.3.2 Specific objectives

- To compare the mean serum creatinine levels between patients who underwent cardiac surgery receiving N-acetylcysteine and patients not receiving N-acetylcysteine at preoperative, 24 hours post-operative and 48 hours post-operative.
- To compare the prevalence of acute kidney injury between patients who underwent cardiac surgery receiving N-acetylcysteine and patients not receiving N-acetylcysteine.

1.4 Hypothesis

1.4.1 Null Hypotheses

- There is no significant difference between the mean serum creatinine levels between patients who underwent cardiac surgery receiving N-acetylcysteine and patients not receiving N-acetylcysteine at preoperative, 24 hours post-operative and 48 hours post-operative.
- There is no significant difference between the prevalence of acute kidney injury between patients who underwent cardiac surgery receiving N-acetylcysteine and patients not receiving N-acetylcysteine.

1.4.2 Alternate Hypotheses

- There is a significant difference between the mean serum creatinine levels of patients who underwent cardiac surgery receiving N-acetylcysteine and patients not receiving N-acetylcysteine at preoperative, 24 hours post-operative and 48 hours post-operative.

- There is a significant difference between the prevalence of acute kidney injury among patients who underwent cardiac surgery receiving N-acetylcysteine and patients not receiving N-acetylcysteine.

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CHAPTER 2: STUDY PROTOCOL

2.1.1 Research Method and Methodology

Study design: Comparative cross-sectional study involving retrospective record review

Sampling method: Simple random sampling method.

Study area: Hospital Universiti Sains Malaysia (HUSM), Kubang Kerian, Kelantan.

Study population: Adult patients who underwent cardiac surgery in HUSM from 1st January 2017 to 31st December 2021

2.1.2 Subject Criteria

A. Inclusion Criteria

- Patients aged more than 18 years old scheduled for cardiac surgery
- Serum creatinine more than 120 umol/L pre-operatively or had recent contrast for angiography less than six weeks from the operation date
- Received non-pulsatile flow and hemofiltration during cardiopulmonary bypass

B. Exclusion Criteria

- Pregnant
- Known hypersensitivity to N-acetylcysteine
- Use of nephrotoxic drugs
- Patients with a history of renal transplant
- Patients with established chronic kidney disease on dialysis
- Patients on high inotropes before surgery
- Redo cardiac surgery

C. Withdrawal Criteria

- Incomplete data

2.1.3 Sample size estimation

For specific objective 1: To compare the mean serum creatinine levels between patients who received N-acetylcysteine and patients who did not receive N-acetylcysteine underwent cardiac surgery at preoperative, 24 hours postoperatively and 48 hours postoperatively. G-power 3.1 will be used to estimate the sample size for this objective. There are two groups and three measurements, using F-test ANOVA repeated measures, between factors, given α 0.05, power 0.8 and effect size 0.3; the total sample size needed for this study will be 62 (31 for case patients, 31 for control patients). F-test ANOVA repeated measures, within factors, given α 0.05, power 0.8 and effect size 0.25, the total sample size needed for this study will be 28 (14 for case patients, 14 for control patients). F-test ANOVA repeated measures, within-between interaction, given α 0.05, power 0.8, effect size 0.25, the total sample size needed for this study will be 28 (14 for case patients, 14 for control patients). Including the 10% potential dropout rate, the sample size required for this study will be 68 (34 for case patients and 34 for control patients).

For specific objective 2: To compare the prevalence of acute kidney injury between patients who received N-acetylcysteine and patients who did not receive N-acetylcysteine underwent cardiac surgery. Based on previous randomised controlled trial by Santana-Santos et al., the incidence of kidney injury in the N-acetylcysteine group is 28.6%, while the incidence of kidney injury in the non-N-acetylcysteine group is 57.1% (23). G-power 3.1 will be used to estimate the sample size for this objective. Fisher's exact test proportions will be used. We are

planning a study of independent cases and controls with two control(s) per case. Prior data indicated that the probability of exposure among controls is 0.57. If the true probability of exposure among cases is 0.28, we will need to study 37 case patients and 74 control patients to be able to reject the null hypothesis that the exposure rates for cases and controls are equal with probability (power) 0.8. The Type I error probability associated with this test of this null hypothesis is 0.05. Including the 10% potential dropout rate, the sample size needed for this study will be 121 (40 for case patients and 81 for control patients).

The highest sample size calculated based on this study's objectives will be chosen. Thus the sample size needed for this study will be 121 (40 for case patients, 81 for control patients).

2.1.4 Sampling method and subject recruitment

Patient recruitment commences after the study receives Ethical Approval from the Human Research Ethics Committee of Universiti Sains Malaysia Health Campus. The list of patients who underwent cardiac surgery will be traced from the record in the operation theatre. Then their respective case note will be traced from the Unit of Medical Record Hospital Universiti Sains Malaysia. All eligible patients who fulfilled the inclusion and exclusion criteria will be recruited. Patient consent is not required as this is a retrospective medical record review.

2.1.5 Operational Definition

- Acute kidney injury will be diagnosed using Kidney Disease Improving Global Outcomes (KDIGO) criteria, defined by increased serum creatinine level greater than or equal to 1.5 times the baseline or 26.5umol/L within 48hours.

- Estimated glomerular filtration rate (eGFR) will be calculated using Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) Creatinine Equation.

2.1.6 Data Collection Method, Research Tool and Data Analysis

A. Data Collection Method

Data collection shall be done by the primary investigator using a data collection form. Information to be filled in in the data collection form includes patient demographic, preoperative, intraoperative, and postoperative data.

B. Research Tool and Data Analysis

Data will be recorded and analysed using SPSS version 26. Numerical data will be described in mean ± standard deviation upon normality checking, while categorical data will be presented in frequency with percentage. Categorical data will be analysed using the Chi-square test. The power of the study is 0.8, and P-value < 0.05 is deemed significant for statistical tests in this study. Serum creatinine levels and eGFR between two groups pre-operatively, POD1 and POD2, will be analysed using repeated measures ANOVA. A comparison of the prevalence of acute kidney injury between the two groups will be analysed using the Chi-square test.

2.1.7 Ethical Consideration

A. Subject Vulnerability

Vulnerability issue is not applicable in this study as this study involved a retrospective medical record review.

B. Declaration of conflict of interest

There is no conflict of interest in this study.

C. Privacy and Confidentiality

All information obtained in this study is confidential per applicable laws and regulations. All patients will be assigned an identification number, and electronic data will be numbered accordingly without patient information. Confidentiality shall only be broken if the study subject is suspected of having been harmed directly or indirectly by the study.

D. Community Sensitivities and Benefits

Study drugs have been provided at no cost to the patients involved. The potential benefit of the study to the community includes clarifying the renoprotective effect of high-dose N-acetylcysteine among the population undergoing cardiac surgery. If proven effective, this will reduce the prevalence of acute kidney injury, morbidity and mortality of patients undergoing cardiac surgery.

E. Honorarium and Incentives

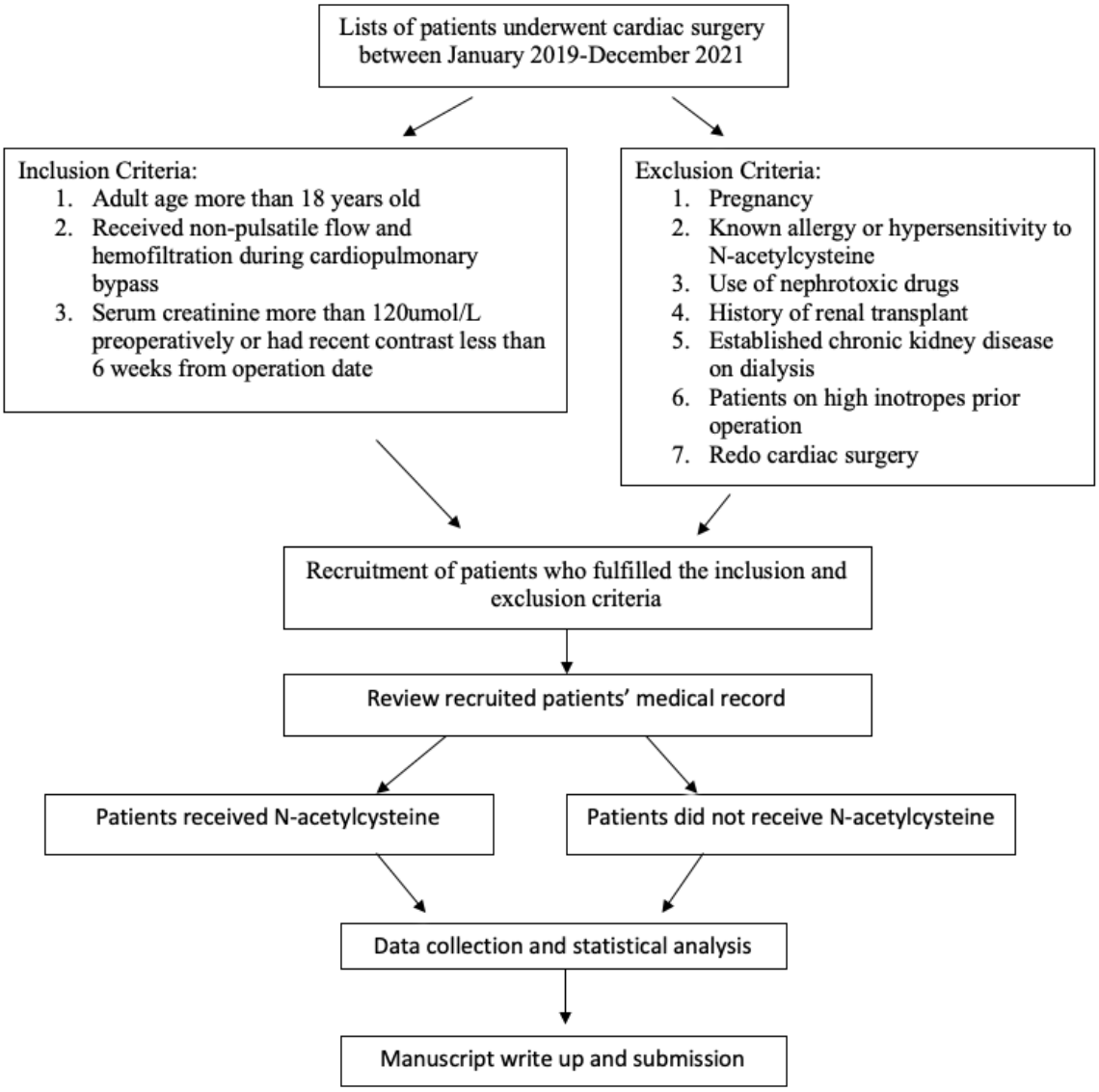
This is a study involving a retrospective medical record review. No honorarium will be given to the subjects involved in this study.

GANTT CHART

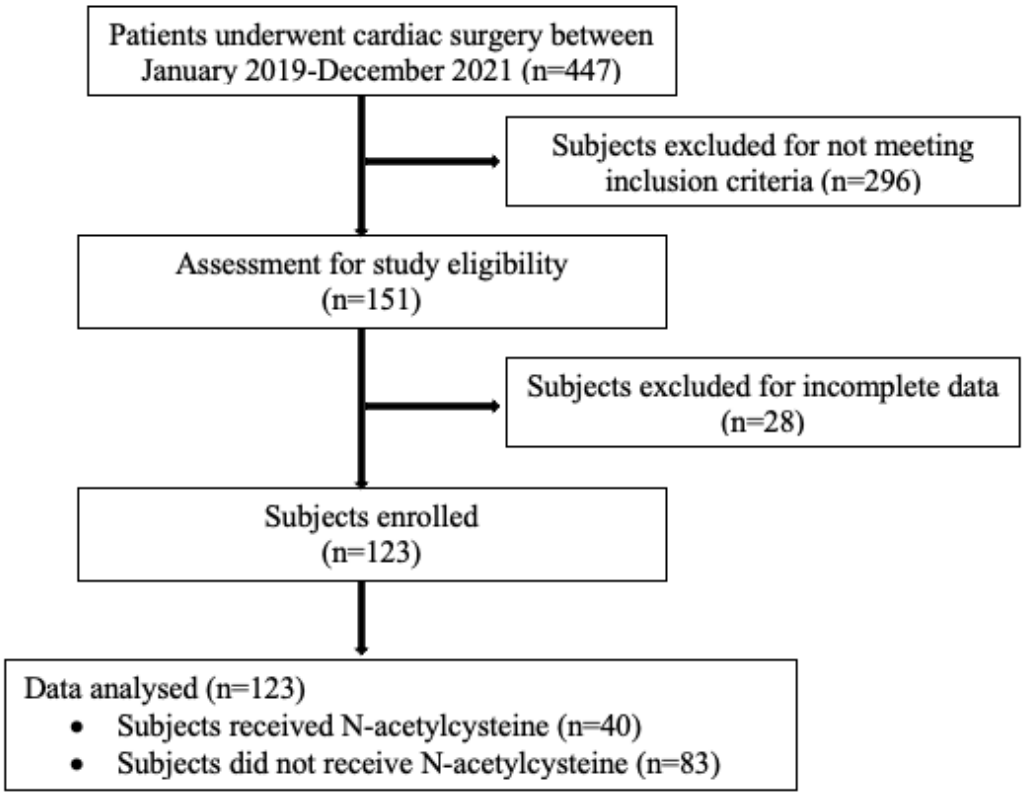
Table 4: Projected chronological progress of the study

	2020		2021												2022									
Project activities	N	D	J	F	M	A	M	J	J	A	S	O	N	D	J	F	M	A	M	J	J	A	S	O
Research proposal planning																								
Proposal presentation at department level																								
Ethics board presentation and ethical clearance																								
Data collection																								
Data entry and analysis																								
Thesis write-up																								
Thesis submission																								

Study Flow Chart



Study Flow Chart according to STROBE guideline



Ethics Approval Letter

Jawatankuasa Etika
Penyelidikan Manusia USM (JEPeM)

Human Research Ethics Committee USM (HREC)

Universiti Sains Malaysia
Kampus Kesihatan
16150 Kubang Kerian, Kelantan, Malaysia.
Tel. : +609 - 767 3000/2354/2362
Fax. : +609 - 767 2351
Email : jepem@usm.my
Laman Web : www.jepem.kk.usm.my
www.usm.my

3rd February 2022

Dr. Gan Shee Yin
Department of Anesthesiology
School of Medical Sciences
Universiti Sains Malaysia
16150 Kubang Kerian, Kelantan.

JEPeM Code : USM/JEPeM/21070525
Protocol Title: Renoprotective Effect of High Dose N-Acetylcysteine in Patients Underwent Cardiac Surgery.

Dear Dr.,

We wish to inform you that your study protocol has been reviewed and is hereby granted approval for implementation by the Jawatankuasa Etika Penyelidikan Manusia Universiti Sains Malaysia (JEPeM-USM). Your study has been assigned study protocol code **USM/JEPeM/21070525**, which should be used for all communications to JEPeM-USM in relation to this study. This ethical approval is valid from **3rd February 2022** until **2nd February 2023.**

Study Site: Hospital Universiti Sains Malaysia.

The following researchers are also involved in this study:
1. Assoc. Prof. Dr. Saedah Ali
2. Dr. Huda Zainal Abidin
3. Dr. Chong Soon Eu
4. Dr. Ariffin Marzuki Mokhtar

The following documents have been approved for use in the study.
1. Research Proposal

In addition to the abovementioned documents, the following technical documents were included in the review on which this approval was based:
1. Data Collection Form (Proforma)

The list of JEPeM-USM members present during the full board meeting reviewing your protocol is attached.

While the study is in progress, we request you to submit to us the following documents:
1. Application for renewal of ethical approval 60 days before the expiration date of this approval through submission of **JEPeM-USM FORM 3(B) 2019: Continuing Review Application Form.**
2. Any changes in the protocol, especially those that may adversely affect the safety of the participants during the conduct of the trial including changes in personnel, must be submitted or reported using **JEPeM-USM FORM 3(A) 2019: Study Protocol Amendment Submission Form.**
3. Revisions in the informed consent form using the **JEPeM-USM FORM 3(A) 2019: Study Protocol Amendment Submission Form.**
4. Reports of adverse events including from other study sites (national, international) using the **JEPeM-USM FORM 3(G) 2019: Adverse Events Report.**
5. Notice of early termination of the study and reasons for such using **JEPeM-USM FORM 3(E) 2019.**

6. Any event which may have ethical significance.
7. Any information which is needed by the JEPeM-USM to do ongoing review.
8. Notice of time of completion of the study using **JEPeM-USM FORM 3(C) 2019: Final Report Form.**

Please note that forms may be downloaded from the JEPeM-USM website: **www.jepem.kk.usm.my**

JEPeM-USM is in compliance with the Declaration of Helsinki, International Conference on Harmonization (ICH) Guidelines, Good Clinical Practice (GCP) Standards, Council for International Organizations of Medical Sciences (CIOMS) Guidelines, World Health Organization (WHO) Standards and Operational Guidance for Ethics Review of Health-Related Research and Surveying and Evaluating Ethical Review Practices, EC/IRB Standard Operating Procedures (SOPs), and Local Regulations and Standards in Ethical Review.

Thank you.

"WAWASAN KEMAKMURAN BERSAMA 2030"

"BERKHIDMAT UNTUK NEGARA"

Sincerely,

ASSOC. PROF. DR. AZLAN HUSIN
Chairperson
Jawatankuasa Etika Penyelidikan (Manusia) JEPeM
Universiti Sains Malaysia