OUTCOMES OF CARDIAC SURGERY PATIENTS TREATED WITH AND WITHOUT POSTOPERATIVE IRON THERAPY IN A CARDIAC CENTRE, HOSPITAL SERDANG, MALAYSIA

BY

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DISCLAIMER

I hereby declare that this research has been sent to Universiti Sains Malaysia for the degree of Master of Medicine in Transfusion Medicine. It is not to be sent to any other universities. With that, this research might be used for consultation and can be photocopied as a reference.

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LIST OF ABBREVIATIONS

IV	Intravenous
Hb	Haemoglobin
CPB	Cardiopulmonary bypass
ICU	Intensive Care Unit
PBM	Patient Blood Management
eHIS	Electronic Hospital Information System
LIS	Laboratory Information System
HREC	Human Research Ethics Committee
HUSM	Hospital Universiti Sains Malaysia
NMRR	National Medical Research Register
SD	Standard deviation
SPSS	Statistical Package for the Social Sciences
USM	Universiti Sains Malaysia
WHO	World Health Organization

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ABSTRAK

Pengenalan: Zat besi intravena (IV) adalah pilihan selain transfusi darah merah untuk pesakit anemia. Kajian ini dijalankan untuk menilai hasil klinikal pada pesakit anemia yang menjalani pembedahan jantung yang melibatkan mesin pintasan kardiopulmonari selepas pemberian zat besi IV.

Kaedah: Ini adalah kajian kohort retrospektif melibatkan 158 pesakit anemia selepas menjalani pembedahan jantung menggunakan mesin pintasan kardiopulmonari dari 1 Januari 2018 hingga 31 Disember 2020. Kumpulan zat besi IV (n=79) adalah pesakit yang menerima rawatan standard anemia selepas pembedahan bersama IV sukrosa zat besi dengan maksimum dos 200 mg tidak melebihi tiga kali seminggu dan kumpulan standard (n= 79) adalah pesakit yang menerima rawatan standard dan tidak menerima zat besi IV.

Keputusan: Terdapat kenaikan tahap hemoglobin (Hb) yang signifikan pada kedua-dua kumpulan dari hari 0 hingga ke minggu ke-6 selepas pembedahan ($p < 0.001$). Namun, perbezaan tidak signifikan didapati dalam kenaikan Hb di antara kedua-dua kumpulan pada minggu ke-6 ($p=0.811$) dan dalam bilangan pesakit yang menerima transfusi darah merah di antara kumpulan zat besi IV dan kumpulan standard (51 dan 48, $p=0.622$). Tempoh penginapan di hospital selepas pembedahan adalah lebih lama pada kumpulan zat besi IV berbanding kumpulan standard (12.4 ± 12.3 dan 8.8 ± 4.5 hari, $p=0.016$).

Kesimpulan: Zat besi IV yang diberikan secara dos tetap kepada pesakit anemia selepas pembedahan jantung didapati tidak memberi kesan signifikan dari segi hasil klinkal dan kadar transfusi darah merah. Oleh itu, disarankan pemberian zat besi IV secara khusus kepada individu untuk mencapai kenaikan Hb yang optimum dan menurunkan keperluan transfusi darah merah seterusnya meningkatkan mutu kesihatan pesakit.

Kata kunci: *anemia selepas pembedahan, pembedahan jantung, zat besi intravena, transfusi sel darah merah*

ABSTRACT

Background: Intravenous (IV) iron is an alternative to packed red blood cell (PRBC) transfusion for patients with anaemia. This study aimed to assess the clinical outcomes of postoperative anaemic patients after cardiac surgery using a cardiopulmonary bypass (CPB) machine received IV iron.

Methods: This was a retrospective cohort study that involved 158 patients who acquired postoperative anaemia after CPB-assisted cardiac surgery from 1st January 2018 to 31st December 2020. The IV iron group (n=79) were patients that received standard postoperative anaemia treatment with IV iron sucrose maximum dose of 200 mg not more than three times per week, while the standard group (n=79) received standard postoperative anaemia treatment without IV iron.

Results: There was a significant haemoglobin (Hb) increment for both groups from postoperative day (POD) 0 to six weeks postoperative ($p<0.001$). However, there was no significant difference in Hb increment between both groups at six weeks postoperative ($p=0.811$) and no significant difference between the number of patients that received PRBC transfusions in both groups ($p=0.622$). There was significant longer length of stay (LOS) in the IV iron group as compared to standard group (12.4±12.3 days vs. 8.8±4.5 days respectively, $p = 0.016$).

Conclusion: Clinical outcomes and allogeneic PRBC transfusion did not improved following administration of fixed dose IV iron in patients with postoperative anaemia after cardiac surgery. Therefore, individualized IV iron dose administration is recommended to achieve optimum Hb increment and thus, reducing PRBC transfusion and improving the patients' clinical outcomes.

Keywords: *postoperative anaemia, cardiac surgery, intravenous iron, red blood cell transfusion*

CHAPTER ONE: INTRODUCTION

CHAPTER ONE

INTRODUCTION

1.1 Overview

This chapter provides an outline of the outcomes of cardiac surgery patients treated with and without postoperative intravenous (IV) iron therapy in a cardiac centre, Hospital Serdang, Malaysia. This chapter also highlights the research justifications and research questions.

1.2 Background of study

Anaemia is defined by the World Health Organization (WHO) as having a haemoglobin concentration (Hb) of 12 g/dL or less in adult women who are not pregnant and 13 g/dL or less in adult men (1). Following surgery involving major blood loss, the patient is at risk of developing anaemia during the postoperative period (2).

Postoperative anaemia is common following cardiac surgery, particularly in open heart surgery using a cardiopulmonary bypass (CPB) machine. Peters, et al. in 2018 discovered that 86.2% of 1,265 patients in five intensive care units (ICU) had postoperative anaemia with cardiac surgery accounting for 64% of those cases (3).

The primary function of the CPB machine during cardiac surgery is to deliver oxygenated blood throughout the body while providing the surgeon with a motionless and bloodless operating field (4). Priming of the CPB machine using fluids that is proportional to the patient's blood volume causes mild haemodilution (haematocrit level range of <18% to 30%) that is required to reduce blood viscosity and increase cerebral blood flow during

surgery (5). Haemodilution from IV fluids in addition to intraoperative allogeneic blood transfusion (ABT) further dilutes clotting factors and leads to intraoperative bleeding subsequently causing postoperative anaemia (6).

A study by Rossler, et al. in 2020 shows that patient who had postoperative iron deficiency anaemia (IDA) has a higher increment in 90-day mortality rate (4-14%) as compared to patients without IDA (2-5%) (7). Another study demonstrated that 44% of patients who had coronary artery bypass graft (CABG) surgery had persistent postoperative anaemia for more than 50 days. This persistent postoperative anaemia was associated with an increase in the occurrence of cardiovascular events during the first three months following CABG. Every 1 mg/dL decrease in Hb correlated with a 13% rise in cardiovascular events and a 22% rise in all-cause mortality when Hb was assessed as a continuous variable (8).

In current practice, ABT is the most rapid way to restore Hb levels and replenish iron stores. One unit of packed red blood cell (PRBC) contains an average of 250 mg of iron (9). However, ABT is associated with risks and complications of blood transfusion such as transfusion-transmitted infections and transfusion reactions.

A study on perioperative IDA suggests that PRBC should be restricted to patients with severe IDA, those who are symptomatic or those with poor physiological reserve. PRBC should be used at a minimal rate to stabilize patients clinically, together with pharmacological treatment for anaemia (10). There are also recommendations for clinicians to put in the effort to investigate, diagnose and treat IDA pharmacologically before surgery (11).

Following the patient blood management (PBM) program, medical therapy such as IV iron and recombinant erythropoietin are advisable for anaemia correction (12). Administration of perioperative IV iron was reported to have an effect in the reduction of transfusion requirement, associated with a shorter hospital stay, enhanced iron body stores, and gave a higher mean Hb concentration four weeks after surgery (13). Therefore, IV iron as an iron replacement for correcting postoperative anaemia is recommended to minimize blood transfusion in concordance with PBM strategy (14). Nevertheless, there is limited data available regarding assessment of IV iron effectiveness in our country especially among cardiac patients. Thus, study of postoperative anaemia among cardiac surgery patients treated with IV iron is needed to further assess its effectiveness.

1.3 Literature review

1.3.1 Postoperative anaemia after cardiac surgery

Postoperative anaemia usually developed after high bleeding risk operations such as intracranial surgery, aortic aneurysm repair, lung resection, hip fracture repair, radical prostatectomy, and cancer resection surgeries. In cardiac surgery, postoperative anaemia was influenced by preoperative Hb levels, haemodilution due to excessive IV fluids, ineffective erythropoiesis, and significant surgical blood loss. The estimated blood loss (EBL) for cardiothoracic procedures is between 300 and 400 mL for surgical valve replacement surgery and between 500 and 600 mL for CABG (15).

Intraoperative blood loss compounded with deleterious effects of surgery-induced inflammation causes erythropoiesis reduction to contribute to the significant incidence of postoperative anaemia after CABG surgery. Post-CABG patients with high inflammatory

cytokines are associated with elevated hepcidin and haptoglobin levels. This will reduce the level of iron exporter ferroportin causing iron sequestration inside macrophages, resulting in functional iron deficiency and impaired iron haemostasis (16).

Functional IDA causes a decrease in iron intake from the gastrointestinal (GI) tract and impaired erythroid response to erythropoietin, resulting in delayed Hb recovery following surgery and subsequently causing postoperative anaemia (17). In postoperative care, Hb concentration is routinely measured in a full blood count (FBC) test. The duration of postoperative anaemia testing is determined by the perioperative bleeding risk associated with the surgery as well as the patient's condition. A nadir in Hb concentration could be identified within the first 3-4 days after surgery in most situations of uncomplicated recovery after surgery (11).

Iron status was not routinely tested postoperatively to diagnose IDA as serum ferritin may falsely be high as an acute phase reactant in response to the postoperative inflammation state. Therefore C reactive protein as an indicator of inflammation with full iron study workup including serum iron, serum ferritin, and transferrin saturation is recommended to identify IDA in a postoperative setting (18).

1.3.2 IV iron sucrose formulation

There are many IV iron formulations in the market such as iron dextran, iron isomaltose, ferumoxytol, ferric carboxymaltose, iron gluconate and iron sucrose. IV iron sucrose with a chemical compound of saccharated iron oxide is the earliest IV iron formulation created in 1930 as documented by Cappel. It was administered to patients with IDA and previous studies had found that it was more suitable than other formulations (19–21). Currently IV

iron sucrose is the most used formulation in the world due to its nearly universal use in chronic kidney disease (CKD) patients with chronic anaemia who are undergoing haemodialysis. To this day, the biggest published literature on iron administered intravenously is with iron sucrose (22,23).

IV iron sucrose had been reported to have a more stable structure and lower toxicity than oral iron formulation (24). The most common side effects of oral iron reported are GI symptoms, such as nausea, vomiting, constipation or diarrhoea, and metallic taste (25,26). IV iron was given to patient who were unable to tolerate oral iron, pregnant women who already has significant nausea and vomiting, patients with malabsorption syndrome and patients with the chronic inflammatory with high hepcidin level that may reduce their oral iron absorption (27).

According to Macdougall, et al., iron gluconate and iron sucrose are associated with twice the amount of labile-free iron release per milligram compared to low molecular weight (LMW) iron dextran. Therefore, these formulations can be administered as a total dose infusion compared to other formulations, hence providing convenience for patients during iron therapy for anaemia treatment (28).

The IV iron sucrose can supply iron at a rate of 300 mg/ 30minutes (29). However, its usage was limited to a maximum dose of not more than 600 mg per week (30). IV iron sucrose has an established safe dosage that is both 200 mg and 300 mg administered over two hours per dosage without any adverse reaction (24,31).

According to Auerbach, et al., the safety of iron sucrose and iron isomaltose 1000 in the trial (FERWON-IDA) was comparable, with a low incidence of hypersensitivity responses and cardiovascular complications (32). A study showed that the majority of reported adverse drug events (ADE) related to IV iron sucrose were mild, such as myalgia, skin rash, metallic taste, dizziness, nausea, and vomiting (33). In contrast, no ADEs were found among patients receiving lower doses (200-300 mg). A study by Chandler G, et al. shows similar findings of 200 and 300 mg doses of IV iron sucrose infused over two hours appear to be safe but if given at higher doses, it caused the patients to develop dizziness, hypotension, and nausea (31).

Regarding the cost-effectiveness of IV iron for correcting anaemia, studies had shown that IV iron therapy had significant cost, hospitality and resource savings as compared to blood transfusion (34). A study by Bhandari states that blood is the most expensive option for anaemia treatment that was not including the cost of the crossmatching test which cost GBP£125.00/unit, while IV iron sucrose cost GBP£18.70, LMW iron dextran cost was GBP£15.94 and ferric carboxymaltose cost was GBP£38.20 (35).

1.3.3 Clinical outcomes after IV iron therapy

IV iron has been reported to have significant Hb increment and improve clinical outcomes in the treatment of anaemia. A study by Jeong, et al. showed that Hb levels were increased by 3.2 g/dL in the IV iron group as compared to an increment of 2.5 g/dL in the control group at six months post gastric surgery (36). A study by Madi-Jebara, et al. showed that patients who were administered IV iron, with or without recombinant erythropoietin, had a 1g/dL greater increase in Hb from the postoperative day (POD) 4 to 30 than those who received a placebo (37).

According to Luo, et al. IV iron sucrose administration helped in increasing postoperative Hb levels and decrease intraoperative PRBC transfusion among patients undergoing a second thoracotomy (38). Another study in 2019 by Xu, et al. showed that IV iron sucrose might significantly raise the Hb level >2 g/dL in patients with postoperative functional IDA. However, there was no difference between the placebo group and the IV iron group in terms of the need for blood transfusions or the number of adverse outcomes that occurred after surgery (39).

Another retrospective study by Laso-Morales, et al. on postoperative colorectal cancer surgery anaemic patients showed that postoperative IV iron given to patients with anaemia improved the Hb levels at POD 30, without worsening postoperative complications (40). In contrast, a study by Karkouti, et al. showed that early postoperative IV iron therapy does not enhance early recovery from postoperative anaemia since the drug required 2-4 weeks to increase Hb (41).

In a prospective randomized controlled trial (RCT) conducted by Khalafallah AA comparing IV iron verses placebo in postoperative anaemic patients, 103 patients were supplemented with ferric carboxymaltose, compared to the control group of 98 patients with standard postoperative treatment. At four weeks, mean Hb levels was increased in both groups, ranging from 1.6g/dL (control) to 2.4g/dL (IV iron), with an important difference of 0.8 g/dL favouring the IV iron group. There was no obvious Hb difference between the groups after 12 weeks. Only one patient in the IV iron group received RBC transfusions, compared to five patients in the control group, which had a considerably

higher PC transfusion rate. Additionally, the IV iron group decreased the overall hospital stay by 3.8 days (42).

A study on anaemic patients after postoperative hip surgery revealed that postoperative IV iron lowered transfusion requirements without affecting clinical outcomes. In the IV iron group, the number of blood transfusions was lower (1.7 ±2.7 vs. 1.0 ±1.2 units, $p = 0.002$), and the group also had shorter hospital length of stay (LOS) as compared to the control group (7.6 days vs. 11.8 days) (43). Furthermore, IV iron also had been shown to raise the Hb levels, with or without erythropoietin therapy, and improves patients' quality of life also clinical outcome (28).

Additionally, a study also found that there was no difference in infection rates between patients receiving IV iron plus erythropoietin versus PRBC transfusion for postoperative anaemia (39). Meta-analyses and observational studies also demonstrated that perioperative IV iron did not increase postoperative infection or 30-day mortality in surgical patients (44,45).

A previous study reported that there was no increase in postoperative complications following IV iron administration (30,40). According to Avni, et al., a meta-analysis study of 103 trials involving 19,253 patients concluded that IV iron therapy was not associated with an increased risk of severe adverse events or infection when compared to oral, no iron, or placebo administration (45). A study by Torres, et al. demonstrated that IV iron did not increase the risk of infection as compared to ABT (46).

J. P. Isbister, an Australian haematologist, created the term PBM in 2005 after realising that the focus of transfusion medicine should shift from blood components administration to patients centred. PBM is currently a new standard of care in transfusion medicine (47). According to Goobie, 2022, the WHO recognised PBM in 2010 in supporting the availability of alternatives to transfusions and to urgently incorporate PBM in patient care (48). Among the alternative treatments for anaemia recommended in PBM include IV iron and recombinant erythropoietin administration given perioperatively (12).

In Malaysia, Hospital Serdang is one of the main tertiary centres for cardiac surgery. The Cardiothoracic Department in this hospital has implemented PBM programme since 2018 and IV iron is prescribed for mild to moderate anaemia in stable patients after cardiac surgery. Nevertheless, the outcomes of IV iron treatment in those patients had not been fully assessed and analysed.

Thus, this study aims to assess the outcomes of IV iron therapy in the treatment of postoperative anaemia by assessing the Hb increment and clinical outcomes (e.g.: PRBC transfusion requirement, postoperative infection, and duration of the postoperative LOS within six weeks postoperatively. Findings from this study may provide insightful information in for reference on the decision for IV iron usage and blood transfusion in the management of postoperative anaemia in cardiac surgery.

1.4 Research justification

Postoperative anaemia in cardiac patients is linked to a higher risk of morbidity and mortality. However, blood transfusion itself carries many risks and complications for patients. The blood conservation strategy is an important ongoing research in PBM. One

of the important alternatives to blood transfusion is medical therapy such as IV iron therapy.

The outcome of IV iron in postoperative anaemia in cardiac surgery patients is still not well studied among Malaysian patients. Hence its clinical outcomes e.g.: postoperative infection, PRBC transfusion requirement and hospital LOS remained undetermined in this population. Furthermore, an effective dosage of IV iron in correcting postoperative anaemia among cardiac surgery patients remained uncertain.

From this study, we aim to determine IV iron usage and its outcomes for the treatment of postoperative anaemia following cardiac surgery. The outcomes of this study may also provide useful data for reference on the decision for blood transfusion in cardiac surgery patients. Besides, it is also important to investigate the related secondary outcomes of postoperative IV iron such as postoperative infection, PRBC transfusion requirement and postoperative LOS. With these data, the improvement of transfusion service in the cardiothoracic department can be optimized.

1.5 Research questions

1) What is the demographic and clinical characteristic of patients receiving IV iron after cardiac surgery?
2) Is there any significant difference in Hb level and PRBC transfusion among patients who received IV iron with patients who did not receive IV iron postoperatively?
3) Is there any association between postoperative IV iron therapy with PRBC transfusion requirement and clinical outcomes?

CHAPTER TWO: OBJECTIVE

CHAPTER TWO

OBJECTIVE

1.1 General objective

To study the outcome of cardiac surgery patients treated with and without postoperative IV iron therapy.

1.2 Specific objective

1) To determine the demographic and clinical characteristics of patients receiving IV iron after cardiac surgery.
2) To compare Hb level and PRBC transfusion rate among patients treated with and without postoperative IV iron therapy within six weeks.
3) To determine the association between postoperative IV iron therapy with PRBC transfusion requirement and the clinical outcomes.

1.3 Alternative Hypotheses

1) There is a significant increase in Hb level in patients who received IV iron postoperatively.
2) There is a significant reduction in PRBC transfusion rate in patients who received IV iron postoperatively.
3) There are significantly better clinical outcomes among patients who received IV iron postoperatively.

1.4 Null hypotheses

1) There is no significant increase in Hb level in patients who received IV iron postoperatively.
2) There is no significant reduction in PRBC transfusion rate in patients who received IV iron postoperatively.
3) There is no significant improvement in clinical outcomes among patients who received IV iron postoperatively.

CHAPTER THREE: METHODOLOGY

CHAPTER THREE

METHODOLOGY

3.1 Study background

This study focused on the usage and outcomes of IV iron in patients who underwent cardiac surgery in the treatment of postoperative anaemia. This study also evaluated the association between postoperative IV iron therapy with Hb increment, PRBC transfusion requirement and clinical outcomes.

3.2 Study design

This was a retrospective cohort study involving record review of patients that underwent cardiac surgery using a cardiopulmonary bypass machine (CPB) in Serdang Hospital between 1st January 2018 until 31st December 2020. The record reviewed was performed using the electronic Hospital Information System (eHIS), Laboratory Information System (LIS), and from pharmacy dispensable IV iron list.

3.3 Study area

This study was conducted in Serdang Hospital, Kajang, Selangor. The hospital serves as a cardiology and cardiothoracic reference centre in the central region of Peninsula Malaysia. Besides cardiothoracic, this hospital also offers multidisciplinary clinical services. It has 620 beds and about 3000 transfusions were commenced per year. The main study locations were in Cardiothoracic Department and Transfusion Medicine Unit, Pathology Department.

3.4 Study population

3.4.1 Reference population

Patients who received treatment at Hospital Serdang.

3.4.2 Target population

Patients underwent cardiac surgery with CPB.

3.4.3 Source population/sampling pool

Patients who underwent cardiac surgery with CPB from 1st January 2018 to 31st December 2020.

3.4.4 Sampling frame

Patients who developed anaemia after cardiac surgery with a CPB machine.

3.5 Subject criteria

3.5.1. Inclusion criteria

1) Patients who underwent cardiac surgery using CPB and developed postoperative anaemia.
2) Patients aged 18 years and above.

3.5.2. Exclusion criteria

1) Reopened surgery after 24 hours
2) Haemodynamically unstable postoperative
3) Patients with inherited bleeding disorders
4) Patients with haematological malignancy
5) Patients with haemoglobinopathy
6) Incomplete/Missing data (10% missing data is acceptable)
7) Defaulted treatment or follow-up.

3.6 Sample size

Specific Objective 1

To determine demographic and clinical characteristics of patients receiving IV iron after cardiac surgery

To estimate the demographic and clinical characteristics of patients receiving IV iron after cardiac surgery, single proportion formula as the following was used to calculate the sample size$= \left(\frac{z}{\Delta}\right)^2 (\mathrm{P}(1-\mathrm{P}))$

where n = sample size

z = the value to estimate the 95% confidence interval (1.96)

P = true population proportion

Δ= precision or detectable difference between expected population proportion and true population proportion (in the proportion of one; if 5%, Δ = 0.05 = 0.1)

A randomized control trial of 60 patients who underwent cardiac surgery, demonstrated that received 17 from 30 patients (0.56%) received IV iron (49). Thus, the sample size required with dropouts was:

n= $(1.96/0.1)^2$ x 0.56(1-0.56)

= 384.16 x 0.56(0.44)

= 384.16 x 0.2464

= 94.66 + 9.47 (10% dropout)

= 104

Hence, the sample size required for objective 1= **104 patients**

Specific Objective 2

To compare Hb level and PRBC transfusion rate among patients treated with and without postoperative IV iron therapy within 6 weeks.

Two means formula was used to calculate the sample size to compare Hb level and PRBC transfusion requirement among patients treated with and without postoperative IV iron therapy within 6 weeks:

$$n= 2\sigma^2/ \Delta^2 (z_\alpha+z_\beta)^2$$

Where n = sample size

σ= standard deviation (SD)

Δ= precision (2/3) SD

z_α= 1.96 for α= 0.05 (two tailed)

z_β= 0.84 for 80% power

A study by Madi Jebara, et al. showed that the patients who were randomized into group that received IV iron had Hb level of 8.71 ±0.93 (mean ± SD) at day five postoperatively (37).

$N= 2(0.93^2)/(0.62^2)x (1.96+0.84)^2$

$= 2(0.8649)/0.3844 \times 7.84$

$= 1.7298/0.3844$

$= 35.28$ (one arm)

Sample size = 35.28 x2

= 70 + 7 (10% dropout)

= 77

Hence, the sample size required for objective 2 was = **77 patients**

Specific Objective 3

To determine the association between postoperative IV iron therapy with PRBC transfusion requirement and clinical outcomes.

Two proportion formula was used to calculate the sample size required for the association between postoperative IV iron therapy, PRBC transfusion requirement and clinical outcomes:

$$n = \frac{P_1(1 - P_1) + P_2(1 - P_2)}{(P_1 - P_2)^2} (Z_\alpha + Z_\beta)^2$$

Where

P_1 = proportion of blood transfusion requirement among IV iron recipients

P_2 = proportion of blood transfusion requirement among non-IV iron recipients

Z_α= Level of significance, 2.58 for α= 0.01 (two-tailed)

Z_β= Power of study to demonstrate association if one does exist, 1.28 for 90% power

A study by Yoo (50) involved 74 patients with preoperative anaemia given pre and post-IV iron + recombinant human erythropoietin (rHUEPO). The patients were randomised into two groups; group I: control= 37 patients and group II: IV iron + rHUEPO= 37 patients. 22 patients receiving IV iron required blood transfusion (22/37= 59%) while 32 non-IV iron recipients required blood transfusion (32/37 = 86%). Using a significance level of 0.01 and a power of 90%, the minimum required sample size to determine the association between postoperative IV iron therapy, blood transfusion requirement and clinical outcomes:

$$n = \frac{0.59(1 - 0.59) + 0.86(1 - 0.86)}{(0.59 - 0.86)^2} \times (2.58 + 1.28)^2$$

$$= \frac{0.59(0.41) + 0.86(0.14)}{(0.27)^2} \times (3.83)^2$$

$$= \frac{(0.2419 + 0.1204)}{0.0729} \times 14.66$$

$= 4.96 \times 14.66$

$= 72$ (one arm) $\times 2$

$= 144 + 14$ (10 % dropout)

$=$ **158**

Hence, the sample size required for objective 3=**158** patients.

Conclusion

The largest sample was chosen hence the total sample size required was **158** patients.

3.7 Sampling Method and subject recruitment

This was a retrospective cohort study. Universal sampling was used as a sampling method for the population sample during the study period which was from 1st June 2021 until 31st May 2023.

Postoperative anaemia patients after cardiac surgery who met the inclusion and exclusion criteria from 1st January 2018 until 31st December 2020 at Hospital Serdang were chosen as the study subjects. All data collection was done till six weeks postoperative.

3.8 Research tool

The data were collected using the Patient's PROFORMA. The data was obtained from the pharmacy dispensable intravenous iron list/ Operation theatre (OT) list/ PPDK5 form/

LIS and eHIS:

i. Patient demographic characteristics that were assessed include:

- Age
- Weight
- Comorbid
- Date of admission
- Date of discharge or date of death (if applicable)
- Treatment

ii. Disease characteristics were assessed from eHIS:

- Diagnosis and date of diagnosis
- Date and type of surgery
- Single or multiple procedures
- CPB time
- Intraoperative and postoperative bleeding
- Intraoperative and postoperative transfusion

iii. Medication characteristics were assessed from the pharmacy dispensable IV iron list and eHIS:

- IV iron dose
- IV iron frequency
- IV iron duration

iv. Laboratory data was extracted from LIS:

- Hb level (g/dL) (preoperative and postoperative)

v. Blood bank data was extracted from blood bank records at Serdang Hospital and from LIS:

- Numbers of PRBC transfused
- Numbers of patients required PRBC transfusion
- Date of PRBC transfusion

3.9 Data collection method

The collection of data was done anonymously. Informed consent was not required as data was retrieved from the records of the patients and not directly involving the patients.

The data of 158 postoperative anaemic patients were extracted and analysed based on inclusion and exclusion criteria. They were divided into two groups which were the IV iron group that received IV iron and the standard group that did not receive IV iron.

Standard group received standard current practice for postoperative anaemia which include ABT and/or oral iron or received no treatment. For the IV iron group, the subjects received standard current practice with additional IV iron that usually would be given within the first week postoperative. Patient demographics and clinical outcomes such as Hb increment, postoperative PRBC transfusion requirement, postoperative infection and hospital LOS were studied in both group of patients during the postoperative period up to six weeks.

The timing of six weeks postoperative was chosen due to patients were routinely given appointment for postoperative clinical and laboratory assessment by the surgeon at 4 to 6 weeks postoperatively. Earlier appointment was given to patient that developed complications during or after surgery. Basic laboratory investigations were taken during appointment such as FBC, renal profile (RP), liver function test (LFT) and coagulation

profile. Hb level was collected from the FBC result and recorded into PROFORMA. Furthermore, IV iron takes up 3-4 weeks for Hb increment as stated by few studies hence timing of 6 weeks postoperative was selected (40).

3.10 Statistical analysis

All data including the patient characteristics, anaemia status, diagnosis of heart disease and number of PRBC transfusion was analyzed using Statistical Package for Social Sciences (SPSS) software version 25.0.

Types of statistical analysis based on specific objectives:

1) To determine demographic and clinical characteristics of patients receiving IV iron after cardiac surgery: Descriptive statistic of categorical data using number and percentage and numerical data using mean and standard deviation.
2) To compare Hb level and PRBC transfusion rate among patients treated with and without postoperative IV iron therapy within 6 weeks: independent t-test and paired t test.
3) To determine the association between postoperative IV iron therapy with PRBC transfusion requirement and clinical outcomes: categorical data in Chi-square, numerical data in independent t-test.

3.11 List of variables

i) Independent variables:

1) Age
2) Gender
3) Comorbidities