THE EFFECTS OF 5% ALBUMIN AND 4% GELATIN SOLUTION ON RENAL FUNCTION, HAEMODYNAMIC STABILITY AND BLOOD LOSS IN PATIENT UNDERGOING CABG (CORONARY ARTERY BYPASS GRAFTING) IN HUSM

By:

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TABLE OF CONTENT

LIST OF TABLES **PAGE**

LIST OF ABBREVIATION

ACE inhibitor	Angiotensin converting enzyme inhibitor
AKI	Acute Kidney Injury
ANOVA	Analysis of Variance
ASA	American Society of Anaesthesiology
BUSE	Blood Urea and Serum electrolytes
CABG	Coronary Artery Bypass Grafting
CICU	Cardiac Intensive Care Unit
CKD	Chronic Kidney Disease
CPB	Cardiopulmonary Bypass machine
CrCl	Creatinine Clearance
CVP	Central Venous Pressure
FeNa	Fractional Excretion of Sodium
FI02	Fraction of Inhaled Oxygen
FFP	Fresh Frozen Plasma
GFR	Glomerular Filtration Rate
HES	Hydroxyethyl Starch
ICU	Intensive Care Unit
IL	Interleukin

MAP	Mean Arterial Blood Pressure
NYHA	New York Heart Association
OT	Operation Theatre
PCA	Patient Controlled Analgesia
POD1	Postoperative Day 1
POD2	Postoperative Day 2
POD3	Postoperative Day 3
SD	Standard Deviation
TNF	Tumor Necrosis Factor

ABSTRAK

***Tajuk*:** Perbandingan kesan cecair 5% albumin dan 4% gelatin terhadap fungsi ginjal, kestabilan hemodinamik, dan jumlah kehilangan darah bagi pesakit yang menjalani pembedahan pintasan koronari jantung di Hospital Universiti Sains Malaysia.

***Latar Belakang dan Objektif*:** pilihan cecair terbaik untuk digunakan di dalam mesin 'cardiopulmonary bypass' dan juga sewaktu pembedahan masih belum jelas.

***Tatacara Kajian*:** Tiga puluh empat pesakit yang menjalani pembedahan pintasan koronari jantung dikaji. Pesakit tidak akan dimasukkan ke dalam kajian ini sekiranya perlu menjalani pembedahan secara kecemasan, mengambil ubatan yang diketahui mengganggu fungsi ginjal, atau mengalami alahan kepada cecair jenis 'colloid'. Pesakit ditetapkan secara rawak ke dalam salah satu daripada kumpulan cecair 'colloid' samada 5% albumin (n=18) atau 4% gelatin (n=16). Parameter hemodinamik, tahap kepekatan urea, creatinine, natrium di dalam darah dan air kencing di ambil sebelum pembedahan, sebaik sahaja selepas pembedahan, dan di hari pertama sehingga hari ketiga selepas pembedahan. Tahap hemoglobin juga diambil pada hari sebelum pembedahan, sebaik sahaja selepas pembedahan, hari pertama dan kedua selepas pembedahan. Keperluan pesakit kepada ubatan 'cathecholamine' dan 'vasodilator' juga direkodkan sehingga hari kedua selepas pembedahan. 'Glomerular Filtration Rate', 'Fractional Excretion of Sodium', dan jumlah kehilangan darah dikira dan dibandingkan..

***Keputusan*:** Purata perbezaan GFR nyata lebih tinggi di dalam kumpulan 4% Gelatin sepanjang tempoh kajian dijalankan namun FeNa tidak menunjukkan kesimpulan yang serupa. Purata tekanan darah semasa CPB mesin digunakan adalah nyata lebih tinggi di dalam kumpulan 5% Albumin (63.9±3.73mmHg) namun keperluan kepada ubatan 'cathecholamine' dan 'vasodilator' tidak jelas berbeza. Pesakit di dalam kumpulan 4% gelatin(1514.44±697.67mL) kehilangan darah lebih banyak daripada kumpulan 5%

albumin(1425.3±451.81mL) namun perbezaan tersebut tidak signifikan. Sebanyak 22.2% pesakit di dalam kumpulan 5% albumin memerlukan transfuse darah berbanding 43.8% di dalam 4% gelatin.

***Kesimpulan*:** Pemberian cecair 5% albumin dan 4% gelatin ke atas pesakit yang menjalani pembedahan pintasan koronari tidak mempunyai kesan yang berbeza-beza dari segi fungsi ginjal, kestabilan hemodinamik dan kehilangan darah sewaktu pembedahan.

Katakunci: Pintasan koronari, Albumin, Gelatin, Fungsi ginjal, kehilangan darah

ABSTRACT

***Background*:** The most ideal approach on cardiopulmonary bypass (CPB) priming and intravenous fluid choice during Coronary Artery Bypass Grafting (CABG) remains controversial.

***Methods*:** Thirty four patients undergoing elective CABG were studied. Patients were excluded if they scheduled for emergency CABG, on known nephrotoxic drug or have a history of allergy to colloid. Patients were randomly assigned to two groups of 5% albumin (n=18) and 4% gelatin (n=16). Haemodynamic parameters, serum level of urea, creatinine, sodium and urine level of sodium and creatinine was measured preoperatively, immediately after the operation, day 1, 2 and 3 post-operatively. Hemoglobin level was taken preoperatively, immediately post-operation, day 1 and 2 after operation. Cathecolamines and vasodilator requirement was also recorded until day 2 post operation. Glomerular filtration rate (GFR), Fractional Excretion of Sodium (FeNa) was calculated and compared.

***Results*:** mean difference of GFR was significantly higher in 4% gelatin group throughout the study but the FeNa difference was not statistically significant. On the topic of haemodynamic stability, the mean arterial blood pressure (MAP) during cardio pulmonary bypass was significantly higher in 5% albumin group (63.9±3.73 mmHg, *P* value=0.011). Cathecolamines and vasodilator requirement showed no remarkable difference. Intraoperative blood loss was lower in 5% albumin group with mean of 1425.33 (±451.81) mL whereas in 4% gelatin group 1514.44 (±697.67) mL but the difference was not significant(*P value*= 0.658). Intraoperatively, less blood transfusion was required in 5% albumin group(22.2%) compared to 4% gelatin group (43.8%)

***Conclusion*:** Administration of 5% albumin and 4% gelatin in patients undergoing CABG showed no remarkable difference on renal function parameters, haemodynamic stability and blood loss

Keywords: Cardiopulmonary bypass, Albumin, Gelatin, Renal Function, Blood loss

CHAPTER 2: MAIN DOCUMENT

2.1: TITLE PAGE

Comparison on the effects of 5% albumin and 4% gelatin solutions on renal function, haemodynamic stability and blood loss in patients undergoing coronary artery bypass grafting in Hospital Universiti Sains Malaysia

EFFECT OF 5% ALBUMIN AND 4% GELATIN ON RENAL FUNCTION, HAEMODYNAMIC STABILITY AND BLOOD LOSS

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2.2: INTRODUCTION

Coronary artery bypass grafting (CABG) is a major surgery that is associated with significant alteration in the renal function in which the incidence of acute kidney injury (AKI) can be as high as 30% postoperatively with approximately 1% of the patient requires lifelong renal replacement therapy. This in turn is related with considerable morbidity and mortality including prolonged intensive care and hospital stay (1).

It is postulated that the pathogenesis of AKI includes various factors; haemodynamic, inflammatory and nephrotoxic factors that interact with one another causing debilitating kidney function. Among the risk factors related to AKI following cardiac surgery are female gender, patients with pre-existing co-morbidities such as chronic obstructive airway disease (COAD), diabetes, peripheral vascular disease, renal insufficiency, congestive heart failure, left ventricular ejection fraction of less than 35%, emergency surgery, cardiogenic shock needing intra aortic balloon pump (IABP) and those with left main coronary disease (1,2,3).

Apart from that, CABG surgery is also known to encompass haemodynamic instability and also massive blood loss perioperatively though the rate of incidence varies depending on each center and criteria of patient selected for the study.

Multiple factors are said to attribute to all these complications including the use of cardiopulmonary bypass (CPB) machine and the selected intravenous fluid that is utilized during the surgery. Priming fluid can be divided into two types: crystalloids and colloids. Crystalloids which mimic plasma electrolyte concentrations can effectively cause haemodilution but it is lacking in oncotic activity. Colloids, on the other hand,

have the ability to maintain oncotic pressure and prevent tissue oedema but have been linked with higher incidence of allergic reactions and coagulopathy (4).

However, to date, no single approach in the choice of intravenous solutions has proven to be most effective in minimizing the complications of CABG. Hence, the rational of this study is to compare synthetic colloid solution; 4% gelatin (Gelofusine®) with 5% albumin to compare the effect of these two solution on renal parameters as well as haemodynamic stability and blood loss following a CABG surgery.

2.3 STUDY PROTOCOL

Documents submitted for ethical approval, ethical approval letter and amendments to the original study protocol are as attached in the Appendixes

2.3.1 LITERATURE REVIEW

Cardiac surgery with cardiopulmonary bypass (CPB) is known to induce a Systemic Inflammatory Response Syndrome (SIRS) that can cause complications such as generalized edema, Acute Respiratory Distress Syndrome (ARDS), coagulopathy and Acute Kidney Injury (AKI) which may significantly contribute to postoperative morbidity and mortality. This phenomenon is at least partly attributed to the decrease in metabolism due to hypothermia and exclusion from the pulmonary circulation where many of the inflammatory mediators are broken down (1).

The incidence of acute renal failure is common after cardiac operation and is found to be more frequent after a complex cardiac surgery. The incidence of acute kidney injury is rising after a coronary artery bypass (CABG) surgery but the prevalence is unclear in other types of heart surgery (2). Renal injuries are serious

complication of CABG with CPB which can add to morbidity and mortality rate as well as prolonged ICU and hospital stay.

A study done to compare the inflammatory response between crystalloids (Ringer's solution) and colloids (25% albumin and 10% Hydroxyethylstarch (HES)), found that priming the CPB circuit with colloids might exert beneficial effect on inflammatory response by having less tendency for intense inflammatory response evidence by lower serum level of TNFα, IL-1β, IL-6 in 25% Albumin and HES group compared to those primed with Ringer's Solution (3).

Another study done showed that Albumin prime better preserves platelet counts than crystalloid. Albumin also favourably influences colloid oncotic pressure, on-bypass positive fluid balance, postoperative weight gain, and colloid usage. However, the clinical significance of these conclusions needs further study and investigation (4).

Having said that, even though many studies have been conducted to compare various types of CPB machine priming fluid, there is still no conclusive evident on the best type of solution to be used in order to minimise the complications.

Hence, the rational of this study is to compare synthetic colloid solution; 4% gelatin (Gelofusine®) with 5% albumin which is largely extracted from human plasma to see the changes in renal function parameters, haemodynamic stability and blood loss following a CABG surgery.

2.3.2 OBJECTIVES

2.3.2.1 General Objectives

To study and compare the effects of 5% albumin and 4% gelatin solutions on renal function, haemodynamic stability and intraoperative blood loss in patients undergoing Coronary Artery Bypass Grafting (CABG) Surgery in HUSM

2.3.2.2 Specific Objectives

- To compare mean differences of glomerular markers (serum urea, serum creatinine and creatinine clearance, GFR) between 5% albumin and 4% gelatin solution
- To compare mean differences of the tubular markers (Fractional Excretion of Sodium (FeNa) between 5% albumin and 4% gelatin solution
- To compare the haemodynamic stability between 5% albumin and 4% gelatin solution
- To compare the amount of intraoperative blood loss between 5% albumin and 4% gelatin solutions

2.3.3 NULL HYPOTHESIS

- There is no difference between 5% albumin and 4% gelatin on the renal parameter in patients undergoing CABG in HUSM
- There is no difference between 5% albumin and 4% gelatin on haemodynamic stability in patients undergoing CABG in HUSM
- There is no difference between 5%Albumin and 4% gelatin on blood loss in patients undergoing CABG in HUSM

2.3.4 RESEARCH DESIGN

This is a randomized single blinded prospective study.

2.3.5 INCLUSION and EXCLUSION CRITERIA

- **Inclusion Criteria**:
  - ⊡ All patients scheduled for Elective CABG
  - ⊡ Not on any known nephrotoxic drugs
- **Exclusion Criteria**:
  - ⊡ Emergency CABG
  - ⊡ History of hypersensitivity to colloid

2.3.6 SAMPLE SIZE ESTIMATION

- Sample size for two mean independent samples are measure using PS software (Dupont and Plummer, 2010)
  - ⊡ $\alpha = 0.05$
  - ⊡ power = 0.8
  - ⊡ SD of Creatinine Clearance (σ) = 20 ml/min
  - ⊡ Difference in population mean (δ) =20 ml/min
  - ⊡ m =1
- Calculated sample size is 17 for each group
- Total sample size is 34 patients
- To compensate for possible 20% dropouts, the final sample size is 42 (n=21 for each arm)

2.3.7 SAMPLING METHOD

Simple randomization will be done based on computer generated random number using random allocation software in which the allocation probability is not altered as study progress.

Sample, n is known in advanced (n=42)

n/2 selected at random and assigned to 4% gelatin and the rest to 5% albumin.

2.3.8 STUDY AREA

Study will be conducted in Cardiac Operation Theatre, Cardiac Intensive Care Unit CICU) and Cardiac High Dependency Ward (HDW) in HUSM Kubang Kerian

2.3.9 RESEARCH TOOL

- Intravenous solutions 4% gelatin (Gelafusine® manufactured by B. Braun Medical) and 5% human albumin (manufactured by Octapharma)
- Standard monitoring devices already available in study area to monitor:
    - ⊡ Blood Pressure and Pulse rate
    - ⊡ Central Venous Pressure
    - ⊡ Oxygen saturation
    - ⊡ Temperature
    - ⊡ Urine output

- Laboratory equipments needed for analysis of serum urea, creatinine and sodium, urine creatinine and sodium
- Medical calculator to calculate the glomerular filtration rate (GFR) (http://nephron.com/cgi-bin/CGSI.cgi)
- Data collection form: Details are as Attached in Appendixes

2.3.10 DATA COLLECTION METHOD

The study was approved by the ethical committee of HUSM. Informed consent was obtained from the patient who met the inclusion criteria listed. Baseline preoperative vital signs, urine and blood tests as listed in the data collection sheet were taken in the ward prior to the scheduled operation

Patients were randomly assigned to either 5% albumin or 4% gelatin solution group based on the computer generated randomisation sequence.

Upon arrival to the operation theatre, pre-induction vital signs (blood pressure, pulse rate, oxygen saturation level will be taken as baseline. Large bore intravenous lines (18G and above), two arterial lines (a 20G in a peripheral artery and another 16G in femoral artery) and a 7F size central venous catheter (CVP) in internal jugular vein will be established.

Patient was given a standardized induction agent of midazolam, propofol, fentanyl and rocuronium based on their bodyweight and sevoflurane will be used as maintenance of anaesthesia. Intubation was done in the usual manner. Intravenous tranexamic acid 2 gram was given as bolus and another 2 gram was added into the priming fluid in all patients. All patients also received calculated dose of prophylactic antibiotics prior to the start of surgical incision.

Weight related dose of heparin was given to patient prior to starting CPB when ordered by the surgeon (300-400unit/kg). Ringer's lactated 1000ml was used to prime the Cardiopulmonary bypass (CPB) machine circuit PLUS 500ml of 10% mannitol PLUS 500ml of either 5% albumin or 4% gelatin. Patients only received either 5% albumin or 4% gelatin as volume replacements intraoperatively to keep the central venous pressure (CVP) of 8 to 14 mmHg.

Mean Arterial Blood Pressure (MAP) was keep within the range of 50 to 80 mmHg by adding cathecolamines when necessary. Cold crystalloids cardioplegia were given in all cases. Blood from the CPB circuit was salvaged with a cell salvaged device and retransfused back to patient after CPB is completed. Packed red blood cells were given when the hematocrit is less than 30% or hemoglobin less than 10 g/dL. Estimation of blood loss during the operation and during postoperative day (POD) 1 and 2 will be estimated based on the difference in haemoglobin level. Urine and blood test were repeated immediately after the operation, first postoperative day (POD1), second postoperative day (POD2) and second day after the operation (POD3).

After the surgery was completed, all patients were transferred to Cardiac Intensive Care Unit (CICU) where mechanical ventilation was continued until the patient was ready to be extubated. To maintain MAP and cardiac index of 2.5 to 3.0 L/min/m^2 adrenaline, noradrenaline or dobutamine were given accordingly whenever indicated. Continuous infusions of either fentanyl or morphine were given as postoperative analgesics and was

converted to Patient Controlled Analgesia (PCA) once patients were extubated

2.3.11 PROPOSED DATA ANALYSIS

The completed research forms will be checked and complied. Statistical analyses will be conducted using SPSS version 22.0 for Windows. Descriptive data analyses will be used to compare the effect of 5% albumin and 4% gelatin with renal function, hemodynamic stability and blood loss. The differences were considered statistically significant when P value < 0.05

2.4 BODY OF MANUSCRIPT

2.4.1 INTRODUCTION

Coronary artery bypass grafting (CABG) is a major surgery that is associated with significant alteration in the renal function in which the incidence of acute kidney injury (AKI) can be as high as 30% postoperatively with approximately 1% of the patient requires lifelong renal replacement therapy (1,6). A retrospective observational study involving over 1200 patients who had undergone CABG in a tertiary public hospital in Malaysia found that the incidence of acute kidney injury was 36.2% with 5.5% of those patient required lifelong renal replacement therapy (7).This in turn is related with considerable morbidity and mortality including prolonged intensive care and hospital stay (1,6).

It is postulated that the pathogenesis of AKI includes various factors; haemodynamic, inflammatory and nephrotoxic factors that interact with one another causing debilitating kidney function. Among the risk factors related to AKI following cardiac surgery are female gender, patients with pre-existing comorbidities such as chronic obstructive airway disease (COAD), diabetes, peripheral vascular disease, renal insufficiency, congestive heart failure, left ventricular ejection fraction of less than 35%, emergency surgery, cardiogenic shock needing intra aortic balloon pump (IABP) and those with left main coronary disease (1,2).

Apart from that, CABG surgery is also known to encompass haemodynamic instability and also massive blood loss perioperatively though the rate of incidence varies depending on each center and criteria of patient selected for the study. In some centers, perioperative bleeding in on-pump cardiac surgery can consume as high as 10% to15% of the blood supply (8).

Multiple factors are said to attribute to all these complications including the use of cardiopulmonary bypass (CPB) machine and the selected intravenous fluid that is utilized during the surgery due to the fact that surrogate technology in CPB enable it to temporarily replace the physiological function of vital organs such as heart,lungs and kidneys (9).

To prime the CPB circuit, generally a choice of balanced electrolyte solution that consist of normal plasma concentration of major blood ions were chosen (9). These priming fluids can be divided into two types: crystalloids and colloids. Crystalloids which mimic plasma electrolyte concentrations can effectively cause haemodilution but it is lacking in oncotic activity. Colloids, on the other hand, have the ability to maintain oncotic pressure and prevent tissue oedema but have been linked with higher incidence of anaphylactic reactions and coagulopathy (4). Some other benefits of using colloids as priming solution was that it was shown to induce a less intense inflammatory response in post CPB patients undergoing CABG (3).

A meta analysis of randomised controlled trials involving colloids found that tetrastarch (130/0.4) has lesser amount of blood loss when compared to albumin but showed no difference in the need for blood transfusion (11). A study comparing the hemodynamic changes in patients who were on β-blocker between Ringer's lactate and 5% Albumin found that hemodynamic stability was better maintained by 5% Albumin (13).

However, to date, there is no single best approach in the choice of intravenous solutions that could be utilised during CABG surgery either as a priming solution for the CPB circuit or to be given throughout the perioperative period as required by the patient. There is no single choice of solituion that is superior to the other in terms of

having been proven to be most effective in minimizing the complications of CABG. Hence, the rationale of this study is to compare synthetic colloid solution; 4% gelatin (Gelofusine®) with 5% albumin to compare the effect of these two solution on renal parameters as well as haemodynamic stability and blood loss following a CABG surgery.

2.4.2 METHODOLOGY

A randomised control trial, single blinded prospective study was done involving total of 42 patients that was electively scheduled for CABG in HUSM during the study period. They were randomly divided into 2 groups using random allocation software. Patient is excluded from the study if they are on any known nephrotoxic drug or had a history of allergy to colloid or was due for an emergency CABG.

Informed consent was obtained from the patient who met the criteria listed. Baseline preoperative vital signs, urine and blood tests were taken in the ward prior to the scheduled operation. Patients were randomly assigned to either 5% albumin (n=21) or 4% gelatin (n=21) solution group based on the computer generated randomisation sequence. This meant that patient was given either 5% albumin or 4% gelatin as priming solution in the cardiopulmonary bypass (CPB) machine and as intravenous fluid intraoperatively.

In the operation theatre, pre-induction vital signs (blood pressure, pulse rate, oxygen saturation level was taken as baseline. Large bore intravenous lines (18G and above), two arterial lines (a 20G in a peripheral artery and another 16G in femoral artery) and a 7F size central venous catheter (CVP) in internal jugular vein was established. Patient was given intravenous induction agents of midazolam, propofol, fentanyl and rocuronium based on their bodyweight and sevoflurane was used as maintenance of anaesthesia. Intubation was done in the usual manner. Tranexamic acid 2 gram was given as bolus and another 2 gram is added into the priming fluid in all patients. All patients also received calculated dose of prophylactic antibiotics prior to the start of surgical incision. Weight related dose of heparin was given to patient prior to starting CPB when ordered by the surgeon (300-400unit/kg). Mean arterial blood pressure (MAP) was kept within the range of 50 to 80 mmHg and the central venous

pressure (CVP) was kept within the range of 8 to 14 mmHg. Cold crystalloids cardioplegia were given in all cases. Surgical factors were standardized in every case since only one cardiothoracic surgeon was involved in operating all cases.

Blood from the CPB circuit was salvaged with a cell salvaged device and retransfused back to patient after CPB is completed. Packed red blood cells were given when the hematocrit is less than 30% or hemoglobin less than 10 g/dL. Estimation of blood loss during the operation and during postoperative day (POD) 1 and 2 will be estimated based on the difference in haemoglobin level. If blood transfusion were given intraoperatively, haemoglobin level pre-transfusion was taken. Urine and blood test were repeated immediately after the operation, on the first postoperative day (POD1), second postoperative day (POD2) and second day after the operation (POD3).

After the surgery was completed, all patients were transferred to Cardiac Intensive Care Unit (CICU) where mechanical ventilation was continued until the patient was ready to be extubated. Inotropes were given to maintain MAP and cardiac index of 2.5 to 3.0 L/min/m^2 (adrenaline, noradrenaline, dobutamine or milrinone) accordingly whenever indicated. Continuous infusions of either fentanyl or morphine were given as postoperative analgesics and was converted to patient controlled analgesia (PCA) once patients were extubated.

Patient was extubated when they are stable haemodynamically, axillary temperature was satisfactory (>36.0ºC), had adequate and good spontaneous breathing, not tachypnoeic and arterial blood gas parameters were satisfactory.

Statistical analysis

Results were presented as mean and standard deviation (SD) or count and percentile. The data from the 2 groups were analysed using Independant t-test for numerical data and Chi Square test for categorical data. Along with that, one way and two way analysis of variance with repeated measures (ANOVA) and post hoc Scheffe's test were used to determine the effects of group, time and group-time interaction.

When multiple comparisons were made on a serially measured data (e.g haemodynamic parameter, biochemical data) the Greenhouse-Geisser correction was used. Medical calculation software was used to calculate for creatinine clearance (CrCl) and fractional excretion of Sodium (FeNa). Differences were considered statistically significant when *P* value is <0.05.

2.4.3 RESULTS

Thirty four patients underwent CABG were enrolled in this study. They were divided into 2 groups based on computer generated randomization sequence in which 18 patients received 5% albumin and 16 patients received 4% gelatin solution. In general, majority of the patients were male with 82.4% whereas female patient constituted of 17.6%. Mean age for 5% albumin group was 63.6 (±5.4) years, while in 4% gelatin group was 54.3 (±7.43) years. The mean age difference between the two groups was significant with the *P* value of <0.001 obtained using independent t-test. The other demographic data differences between the two group was not statistically significant as represented in the Table 1.

All of the patients recruited were in American Society of Anesthesiologist (ASA) class III. Regarding New York Heart Association (NYHA) classification, in 5% albumin group 5.6% was in NYHA class 1, 66.7% in NYHA II, 27.8% was NYHA III. In 4% gelatin group, 37.5% was NYHA I, NYHA II class was majority with 56.3% and 6.3% was NYHA III. As regards to coexisting diabetes mellitus (DM) and Hypertension, in 5% albumin group 10 patients (55.6%) and in 4% gelatin group 10 patients (62.5%) had DM while for hypertension; 16 patients (88.9%) in 5% albumin group had it and 13 patients (81.3%) in 4% gelatin group had it. The *P value* for each disease showed no significant difference in its occurrence between both groups with the value of 0.681 and 0.648 for DM and hypertension respectively (Table 1).

Concerning the preoperative renal function parameters; mean serum urea for 5% albumin group was 6.69 (±3.46) mmol and 4% gelatin group showed mean value of 6.03 (±5.85) mmol. The mean difference of serum urea between these two groups was 0.66 (95% CI:-2.65, 3.97) with the *P value* of 0.689 which is not significant (Table 2).

The mean serum creatinine for 5% albumin group was 136.11 (±58.46) umol/L and 148.13 (±151.92) for 4% gelatin group. The mean difference in serum creatinine was-12.01 (95% CI:-90.68, 66.65) with the *P value* of 0.748 which was not significant (Table 3). Mean for the Glomerular Filtration Rate (GFR) preoperatively was 49.22 (±16.26) mL/min for 5% albumin group and 69.79 (±28.39) mL/min for 4% gelatin group. The mean difference in GFR was -20.57 (95% CI:-36.50, -4.64) and the *P value* was 0.013 which was significant (Table 4). Pre-operative Fractional Excretion of Sodium (FeNa) that was within normal range in 5% albumin group was found in 9 patients (50.0%) and 7 patients (43.8%) in 4% gelatin group. The rest of the patients' FeNa was out of normal range (Table 5).

Regarding of intra-operative data, mean duration of anesthesia in 5% albumin group was 301.4 (±74.97) minutes while in 4% gelatin group 328.9 (±42.17) minute. Mean duration of time patient was on cardiopulmonary bypass (CPB) in 5% albumin group was 114.6 (±25.25) minutes and 126.7 (±27.89) minutes. The mean duration of aortic cross clamp was 92.3 (±39.19) minutes in 5% albumin group and 93.9 (±20.14) minutes in 4% gelatin group. The average mean arterial blood pressure (MAP) was higher in 5% albumin group with the value of 63.9 (±3.73)mmHg while in 4% gelatin group was 60.0 (±4.72)mmHg and the difference was statistically significant (*P value* = 0.011) (Table 6).

Concerning the cumulative intravenous fluid (colloid) intake and urine output (Table 7), in average, intraoperative fluid requirement for 5% albumin group was 791.67(±334.86) mL and 4% gelatin group was 1390.63 (±353.18) mL . The difference of mean volume of colloid requirement intraoperatively between these two groups was significant with the *P value* of <0.001 in which the 5% albumin group required smaller

volume. However, postoperative fluid requirement on day 1 and day 2 showed no significant difference between both groups with the *P value* of 0.615 and 0.630 respectively. Average intraoperative urine output for 5% albumin group was 842.94 (±402.86) mL and 905.31 (±638.68) mL with the *P value* of 0.738. Nevertheless, on subsequent Day 1 and 2 after the operation, 5% albumin group showed average of 1719.41 (±714.53) mL and 2054.53 (±666.60) mL respectively while 4% gelatin group produced average of 1588.25 (±701.97) mL and 2050.63 (±1031.55) mL urine output for day 1 and 2 respectively (Table 7).

With reference to GFR and FeNa value that was taken: mean difference in GFR values that was sampled immediately after the operation and on day 1 till day 3 postoperatively showed significant differences with *P* value of 0.018, 0.019,0.009 and 0.005 with respect to the time of sampling mentioned earlier. However, the mean difference in GFR value on preoperative day and day 3 postoperatively was not statistically remarkable with *P* value of 0.125 (mean difference -9.43(-21.62,2.76)) using independent t-test (Table 8) . The mean difference in FeNa immediately post operation till day 3 post operation was statistically not significant between the two groups (Table 5).

Regarding the requirement of cathecolamines and vasodilators, descriptive statistics was used to compare the two groups. In 5% albumin group (Table 9), all 18 patients required norepinephrine infusion since the beginning of the operation, 7 (38.8%) of them required norepinephrine only till day 1 after the operation and 6 (33.3%) patients till second postoperative day. In total, 14 patients (87.5%) from the 4% gelatin group required norepinephrine throughout the operation, 2 of those patients were

free from the infusion on day 1 and 8 of them on day 2 post operatively. The remaining patients required support more than two days post-operatively (Table 10).

Glyceryl trinitrate (GTN) was required in majority for both groups; 16 patients (88.9%) and 15 patients (93.8%) in 5% albumin group and 4% gelatin group respectively. For epinephrine infusion, in 5% albumin group 6 patients (33.3%) required it and 4 patients (25.0%) in 4% gelatin group needed it. 9 patients (50.0%) and 4 patients (25.0%) necessitate the use of dobutamine infusion in 5% albumin group and 4% gelatin group respectively. Milrinone infusion was required by 5 patients (27.8%) in 5% albumin group (Table 9) and by 2 patients (12.5%) in 4% gelatin group (Table 10). The rest of the patient needed haemodynamic support for more than two days after the operation.

On the topic of intraoperative blood loss, 5% albumin group showed mean of 1425.33 (±451.81) mL whereas in 4% gelatin group 1514.44 (±697.67) mL (Table 11). The mean difference for the intraoperative was -89.16 mL (95% CI: -495.21, 316.89) with the *P value* of 0.658 which signified no remarkable difference. Throughout the operation, 4 patients (22.2%) did not require blood transfusion in 5% albumin group while in 4% gelatin group, 7 patients (43.8%) was blood transfusion free. The mean difference of pre-operative and postoperative haemoglobin level was not significant (*P* value=0.128) being 4.75 (±1.84) g/dL in 5% albumin group and 3.84 (±1.52) g/dL in 4% gelatin group (Table 12).

As regards to the length of hospitalization, patients in 5% albumin group stayed in Cardiac intensive care unit CICU) for an average of 6.33 (±9.43) days compared to 4% gelatin group which was 3.75(±2.83) days. The average total hospital stay day was 13.41 (±14.09) days for 5% albumin group and 8.38 (±2.83) days for 4% gelatin group.

P value for both was not significant being 0.268 and 0.167 for CICU and total hospital stay respectively (Table 7).

2.4.4 DISCUSSION

The aim of this study was to compare the effect that 5% albumin and 4% gelatin that were used as priming solution and as intravenous fluid during CABG surgery on renal function, hemodynamic stability and blood loss. Since CABG is a major surgery and is known to cause renal impairment to a certain extent, exhibit haemodynamic instability and major blood loss in some centres all over the world (5). In this study, the demographic difference between the two groups was not significant except for the mean age in which the patients in 4% gelatin were significantly younger with the mean age of 54.3 years compared to 63.6 years for those in 5% albumin group (*P value* < 0.001). However, this outcome was inevitable in view of a computerised randomisation was done to allocate the study subject.

In this study, we found that there was no significant different on the values of Serum urea and creatinine of the patients in both groups. However, mean difference in GFR was higher in 4% gelatin since before the operation till POD3 and those values were also statistically significant. This could be postulated that since renal insult during and post CABG was bound to occur though to a different degree, and since the pre-operative mean GFR in 4% gelatin group was better, their values continue to be better post-operatively compared to 5% albumin group.

A study was conducted involving 60 patients that aimed to investigate the effects of 5% albumin and 6% HES 130/0.4 as priming solutions in on pump CABG on renal function and their association with coagulation, postoperative blood loss and renal function (5). It was found that GFR differences were statistically lower in Albumin

group at 24, 48 and 72 hours after the operation compared to 6% HES 130/40 group (5). This findings was not parallel to our study, partly could be attributed to the fact that pre-operative GFR value was significantly lower in the 5% albumin group compared to 4% gelatin as proposed earlier.

A meta-analysis of randomised trials done by on the effect of HES on bleeding after CPB suggested that compared with albumin which is a natural type of colloid, HES increased amount of bleeding, increased the rate of resternotomy to secure hemostasis, and transfusion of blood and blood product after cardiopulmonary bypass (4). This finding is similar to ours in which our synthethic colloid 4% gelatin showed greater amount of bleeding though the figure was not statistically significant. We also discovered that blood transfusion requirement in patients that received 5% albumin were lower compared to the other group. On the other hand, another study done discovered no difference between 4%gelatin and 5% albumin on their effect on coagulation profile, blood transfusion requirement and volume of blood loss in patients undergoing open heart surgery (10). Various measures and technique have been adopted in order to minimize the amount of blood loss including withholding Clopidogrel a few days prior to surgery (14) and application of topical tranexamic acid which was shown to reduce mediastinal bleeding and blood transfusion requirement after CABG (23).

On the topic of haemodynamic stability, average MAP during CPB was higher in 5% albumin group however, in terms of inotropic usage and vasodilator requirement between the two groups no significant difference was found. Findings from studies that was previously done discovered that hemodynamic stability was better with the usage of 5% Albumin (12,13). Having said that, there were some limitations that were associated with this study. Firstly, the desired calculated sample size which was 42 patient (n=21

in each arm) was not able to be met due to limited time frame and sampling population during the course of the study. In future, bigger sample size in a longer duration of study should be undertaken. Secondly, patients with pre-existing renal impairment were not excluded from this study and this could greatly influence the results. Other than known nephrotoxic drugs, there are other drugs that was known to exert some degree of alteration in the parameters of renal function that was not studied for example ACE inhibitors, aminoglycosides, macrolides and diuretics and these data were not considered in the exclusion criteria.

Despite all the possible complications that could arise following a CABG surgery, a cross sectional descriptive study done involving 69 patients showed that their quality of life was good after the operation (24).

2.4.5 CONCLUSION

This study concluded that 5% albumin and 4% gelatin had no significant influence on renal function markers, hemodynamic stability and degree of blood loss in patients undergoing coronary artery bypass grafting surgery in HUSM.

2.4.6 REFERENCES

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