EFFECTS OF INTRAOPERATIVE HARTMANN'S SOLUTION WITH STEREOFUNDIN IN RENAL TRANSPLANT RECIPIENTS

WAN KAMILAH HANA BT WAN NIK AHMAD MUSTAFA

DISSERTATION SUBMITTED IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTER OF ANAESTHESIOLOGY

DEPARTMENT OF ANAESTHESIOLOGY
UNIVERSITY OF MALAYA
KUALA LUMPUR

2018

UNIVERSITI MALAYA ORIGINAL LITERARY WORK DECLARATION

Name of Candidate : Wan Kamilah Hana Bt wan Nik Ahmad Mustafa

Registration/Matric No: MGE 140018
Name of Degree. : Master of Anaesthesiology
Title of Project Paper/Research Report/Dissertation/Thesis ("this Work"):

Effects of intraoperative Hartmann's Solution versus Stereofundin in renal transplant recipients

Field of Study:

I do solemnly and sincerely declare that:

(1) I am the sole author/writer of this Work;
(2) This Work is original;
(3) Any use of any work in which copyright exists was done by way of fair dealing and for permitted purposes and any excerpt or extract from, or reference to or reproduction of any copyright work has been disclosed expressly and sufficiently and the title of the Work and its authorship have been acknowledged in this Work;
(4) I do not have any actual knowledge nor do I ought reasonably to know that the making of this work constitutes an infringement of any copyright work;
(5) I hereby assign all and every rights in the copyright to this Work to the University of Malaya ("UM"), who henceforth shall be owner of the copyright in this Work and that any reproduction or use in any form or by any means whatsoever is prohibited without the written consent of UM having been first had and obtained;
(6) I am fully aware that if in the course of making this Work I have infringed any copyright whether intentionally or otherwise, I may be subject to legal action or any other action as may be determined by UM.

Candidate's Signature Date

Subscribed and solemnly declared before,

Witness's Signature Date

Name: Designation:

ABSTRACT

Background

Renal transplantation remains as the mainstay treatment for patients who suffer from end stage renal disease. Optimal graft perfusion and function after renal transplantation depends on adequate intravascular volume repletion. The ideal fluid for renal transplantation has not been defined. 0.9% saline has been used commonly in the past during perioperative period. Despite its frequent usage, 0.9% saline is associated with increased risk of hyperchloraemic metabolic acidosis, which also leads to delayed graft function in renal transplant recipients. Balanced crystalloids can substantially decrease the incidence of acidosis. This randomised controlled trial compares the effects of intraoperative Hartmann's solution with stereofundin in renal transplant recipients, in terms of delayed graft function, measured by the need for dialysis at post operative day 7 or failure of serum creatinine to drop by 20% within 72 hours of renal transplant.

Methods

We recruited 11 patients undergoing elective living related renal transplant recipient from April 2018 to December 2018 at the University Malaya Medical Centre, Kuala Lumpur. Patients who refused to participate in this study were excluded. We recorded the serum creatinine at 72 hours post transplant and the need for dialysis at post operative day 7 as the primary outcome. We also compared the acid base status, serum potassium concentration, serum bicarbonate concentration at the end of surgery and post operative day 3, as well as any adverse events from the surgery.

Results

There is reduction plasma pH for both groups in immediate post operative period, but greater in Solution B group (0.071 ± 0.01, $p<0.05$). Solution B group also showed reduction in base excess (-4.6 ± 2.97, $p<0.05$), bicarbonate level (4.14 ± 1.16, $p<0.05$) and higher lactate level (2.26 ± 0.06, $p<0.05$) immediately post operation. Both groups showed reduction is serum creatinine ($p<0.05$) at POD 3, more pronounced with Solution B, despite the increment in lactate seen in this group at POD 3 (0.2 ± 0.06, $p<0.05$). None of the patients needed dialysis at POD 7, but the reduction in creatinine is higher in patients in Solution B group (665.4 ± 169, $p<0.05$). The potassium level in both groups were not statistically significant throughout the study.

Conclusion

There is no difference in occurrence of delayed graft function for both groups, but Solution B showed a lesser reduction in base excess and serum bicarbonate at POD 3. Solution B also showed significant increase in serum lactate at immediate post operative period and POD 3.

ABSTRAK

Latar Belakang

Rawatan pemindahan buah pinggang merupakan pilihan rawatan yang utama bagi pesakit-pesakit yang menghidap sakit buah pinggang peringkat akhir. Fungsi dan perfusi graf yang optimum selepas pesakit-peskit ini menjalani pembedahan pemindahan buah pinggang sangat penting, dan bergantung kepada isipadu intravaskular yang mencukupi. Namun begitu, jenis cecair yang ideal bagi pesakit-pesakit ini masih belum lagi dikaji. Pada masa yang lalu, 0.9% saline telah digunakan di semasa pembedahan bagi pesakit- pesakit ini. Ia telah terbukti untuk mengakibatkan kesan- kesan negatif seperti *hyperchloraemic metabolic acidosis*, yang secara tidak langsung mengakibatkan kelambatan fungsi graf bagi pesakit-pesakit ini. Kajian rawak berkawal ini bertujuan untuk membandingkan kesan cecair yang berlainan, iaitu *Hartmann's solution dan sterofundin,* yang digunakan semasa pembedahan ke atas kejadian kelewatan fungsi graf. Kelewatan fungsi graf dikaji melalui keperluan untuk dialisis pada hari ke tujuh selepas pembedahan, atau pun kegagalan aras kreatinin darah untuk turun sebanyak 20% dari aras asal pada 72 jam selepas pembedahan.

Metodologi

Sebanyak 11 orang pesakit yang menjalani pembedahan pemindahan buah pinggang di Pusat Perubatan Universiti Malaya dari April 2018 hingga Disember 2018 telah direkruit. Pesakit-pesakit yang enggan melibatkan diri dalam kajian ini telah dikecualikan. Kami telah merekodkan aras serum kreatinin pada 72 jam

selepas pembedahan dan keperluan untuk dialisis bagi pesakit-pesakit ini pada hari ketujuh selepas pembedahan. Kami juga telah membandingkan status asid dan bes, aras potassium darah, aras bikarbonat darah pada hari ke tiga selepas pembedahan. Sebarang kemudaratan yang berlaku terhadap pesakit-pesakit ini juga direkodkan.

Keputusan

Kami mendapati terdapat pengurangan aras pH darah bagi kedua-dua kumpulan ini pada waktu selepas pembedahan. Akan tetapi, pengurang ini lebih besar bagi pesakit-pesakit dalam kumpulan Solusi B (0.071 ± 0.01, $p<0.05$). Kumpulan Solusi B juga telah menunjukkan pengurangan *base excess* (-4.6 ± 2.97, $p<0.05$), aras bikarbonat darah (4.14 ± 1.16, $p<0.05$) dan peningkatan aras laktat darah (2.26 ± 0.06, $p<0.05$) selepas pembedahan. Kedua-dua kumpulan juga telah menunjukkan pengurang aras kreatinin darah ($p<0.05$) pada hari ketiga selepas pembedahan. Namun, pesakit dalam kumpulan Solusi B telah menunjukkan pengurangan yang lebih besar. Tiada pesakit yang memerlukan rawatan dialisis pada hari ketujuh selepas pembedahan, tetapi terdapat penurunan aras kreatinin darah yang lebih besar pada pesakit kumpulan Solusis B (665.4 ± 169, $p<0.05$). Aras potassium darah bagi kedua-dua kumpulan tidak menunjukkan sebarang signifikasi statistik dalam kajian ini.

Konklusi

Tiada sebarang perbezaan dalam kejadian kelewatan fungsi graf bagi kedua-dua kumpulan, tetapi kumpulan Solusi B telah menunjukkan pengurangan *base excess* dan aras bikarbonat darah yang lebih sedikit pada hari ketiga selepas pembedahan. Kumpulan Solusi B juga telah mununjukkan peningkatan aras laktat darah pada waktu selepas pembedahan dan pada hari ketiga selepas pembedahan.

ACKNOWLEDGEMENTS

I would like to extend my highest gratitude to my supervisor Dr Mohamad Fadhil Hadi Bin Jamaluddin for his guidance and assistance in conducting this study, and supervision in this thesis write up.

My appreciation also extends to Miss Wong from the UMMC pharmaceutical department, for her willingness and co-operation in assisting in the blinding process for the participants of this study.

I am also grateful to the participants of this study, for if its wasn't for them, this study would not be able to take place at all. My anaesthetic colleagues, staff nurses, and the academic staff for facilitating in the conduct of this study.

And last but not least, I am indebted to my husband and my parents for their endless support and encouragement in pursuing this path, and to my daughter, for the motivation I lacked but greatly needed for the completion of this study.

Indeed, patients are your best teachers.

TABLE OF CONTENTS

LIST OF FIGURES AND TABLES

LIST OF SYMBOLS AND ABBREVIATIONS

ESKD : End stage kidney disease

NS : Normal Saline

UMMC : University Malaya Medical Centre

IV. : intravenous

SD : Standard deviation

IQR : Interquantile range

BE. : base excess

HCO_3 : bicarbonate

K : potassium

POD3 : pst operative day 3

POD 7 : post operative day 7

LIST OF APPENDICES

CHAPTER 1 : INTRODUCTION

By year 2035, Malaysia is expected to reach the status of ageing population, at which 15 percent of its total population will consist of citizens 60 years old and older [1]. This poses major challenges to our health care systems, as utilisation of healthcare resources are expected to be greater in view of co-morbidities among this ageing population [2]. Prevalence of chronic kidney disease is expected to rise in the future, especially among this population, parallel with the rise of conditions such as obesity, diabetes mellitus and hypertension. Chronic kidney disease is an irreversible and asymptomatic disease, in which if not detected early, may escalate to end stage kidney disease. End stage kidney disease results in the need for renal replacement therapy in the form of dialysis or renal transplant. The incidence of of patients with end stage renal disease who require renal replacement therapy is estimated to be 3.02 per 10 000 population by year 2020, and is forecasted to increase to 3.89 in 2030. This is an astonishing 1.5 fold increase in total number of patients requiring dialysis from 6 985 in 2013 to 10 208 in 2020, with an estimated addition to 14 813 in year 2030, which is a further 1.5 fold. This poses an economic strain to the country finances and resources [3].

Renal transplantation remains as the mainstay treatment for patients who suffer from end stage renal disease. It offers an important chance of survival as compared to dialysis. It is superior in terms of prolonging longevity in these patients, making it the favoured modality of treatment for end stage renal disease [4]. Transplant is also more advantageous considering the rising health care cost in providing treatment for end stage renal disease therapies. This, is however,

bounded by the shortage of feasible donor organs, and hence, the ideal approach is salient to improve short and long term outcomes to fully bestow this limited resources.

A multitude number of complications may arise from renal transplantation , such as haemodynamic instability, acid base imbalance, and electrolyte disturbance due to impaired renal function and acute kidney injury. Long term complications include urologic complications, peritransplant fluid collections, hematomas, lymphocoeles, abscesses and infections, as well as vascular complications [5]. Acute kidney injury may be a manifestation of delayed graft function in the transplanted kidney. The diagnosis of delayed graft function vary, based on its definitions, according to a spectrum of clinical criteria at a specific local transplant centre and region [6-8]. It is universally defined as, the need for dialysis during the first week after kidney transplantation, or failure of serum creatinine to fall by 20% 72 hours after renal transplantation [9]. Delayed graft function has been associated with poorer short and long term outcomes, namely increased allograft immunogenicity, higher transplantation cost, increased risk of acute rejection, prolonged hospitalisation, and decreased five year graft survival [10].

Delayed graft function is a well recognised factor in susceptibility for rejection. Outcomes for renal transplantation are best in living related donor transplantation,

in which delayed graft function has an incidence of 4-10% in these patients [11]. There are many factors that influence the occurrence delayed graft function such as donor type, co-morbidities, ischaemic time and peri-operative fluid status the recipient. An intervention to prevent the damage of delayed graft function is therefore, is of utmost important, and shown to be effective in preventing acute renal failure in this scenario. While it is established that maintaining sufficient amount of peri-operative fluid volume promotes early graft function [12], there is a diverse variety of fluid administered in these patients, depending on transplant units.

To establish optimal graft perfusion, keeping an adequate intravascular volume during kidney transplantation is imperative to maintain its function. There are insufficient evidence regarding this matter specifically concerning renal transplant recipients, however there are many comparable studies regarding fluid management in the critically ill and patients undergoing major surgery. Perioperative fluid management aim to reinstate and maintain intravascular fluid volume to ensure adequate graft function [13]. In experiments with animal models with acute tubular necrosis, renal perfusion has a linear relationship with mean arterial pressure , even in normal pressure ranges. However, paradoxical renal vasoconstriction occurs at low mean arterial pressure [14,15]. In a transplanted kidney, denervation declines hemodynamic autoregulation of the graft, making it susceptible to blood pressure changes. Consequently, renal perfusion is greatly reduced even with mild hypotension, resulting in repeat ischaemia to the transplanted kidney [16-18]. Evidently, any intravascular volume insufficiency

should be corrected to achieve adequate systemic circulation and microcirculation, and must be included in all treatment approaches [19].

There is minimal evidence and studies to recommend the type of fluids to administer in patients at risk of acute renal failure, or should they be differentiated from the critically ill patients [20]. In general, crystalloid solutions are the dominant choice for volume resuscitation and correction of electrolytes in these patients [21]. The ideal fluid for renal transplantation has not been defined, although 0.9% saline was commonly used in the perioperative period in the past [22]. Despite its usage in the last 50 years, 0.9% saline solution is associated with increased risk of hyperchloraemic metabolic acidosis, which may lead to delayed graft function [12,22]. Many perioperative fluid management modalities have been developed in the last decade. These previous meta analyses evaluate, with regards of potential side effects and patient outcomes of different types of crystalloids used during kidney transplantation, as well as comparison between colloids and crystalloids, peri-operatively. Despite the continuous controversy with regards to benefits of different types of crystalloids, the preference of a particular type of fluid in any clinical situation lies on the clinician's perception of the solution's properties and the patient's physiological needs.

These two balanced crystalloids have been recommended in the setting of renal transplantation, as they limit the risk of hyperchloraemic metabolic acidosis and hyperkalemia, contrary to the fact that they are both potassium containing solutions. As there no current recommendation regarding the superior fluids for renal transplant recipients, this study was designed to compare the effects of

Hartmann's solution and sterofundin on delayed graft function in our centre. The primary outcome of this study is delayed graft function, as defined by the need of dialysis within 7 days post transplantation, or failure of serum creatinine to fall by 20% with 72 hours post transplant. Secondary outcomes include acid base status measured by the difference in pH, serum potassium concentration, base excess and serum bicarbonate concentration at post operative day 3 as compared to baseline, and adverse events, if any.

CHAPTER 2 : LITERATURE REVIEW

The kidneys receive approximately 25% of total cardiac output and is responsible in maintaining and adjusting the extracellular volume. One of the challenges with patients with renal failure is a balance of their fluid status, as they tend to fluctuate between states of hypovolemia and hypervolemia. They are also subjected to electrolyte imbalances as a result of hemodialysis and peritoneal dialysis [23].

Fluid and electrolyte substitution in the peri-operative period of major surgeries in these patients aim to preserve sufficient intravascular volume to establish adequate renal perfusion as to not affect graft function. Electrolyte disturbances such as hyperkalaemia should also be prevented in order to avoid any renal insufficiencies and preserve graft function [12, 22]. A vast comprehension of fluid therapy is, therefore, critical in achieving these goals.

Volume resuscitation and correction of electrolyte imbalances are commonly done with the usage of isotonic crystalloid solutions, namely 0.9% saline solution and Hartmann's solution. These crystalloids pose no risk of nephrotoxicity , unlike its contender, the plasma expanders. These crystalloids are distributed promptly to the interstitial compartment , lasting only 20-30 minutes in the intravascular space, and hence, have a considerable constraint on plasma volume expansion. The response on volume expansion does not exceed 20% of the volume administered [19, 23]. Because of this property, crystalloids require four to five

times greater volume as compared to colloids to strive the same volume effect, and by itself, are unable to improve microcirculation in cases of severe haemorrhage [24,25].

Among the different types of available crystalloids, many emphasise on the side effects of using 0.9% saline solution as compared to balanced crystalloid solutions, namely Hartmann's solution and stereofundin. However, many suggest that large volume administration of 0.9% saline may result in hyperchloraemic metabolic acidosis, due to the supraphysiological chloride load and hyperkalaemia due to transcellular movements of ions [26]. Furthermore, interstitial fluid retention and intra-renal microvascular effects are more conspicuous with 0.9% saline infusion, leading to reduction in renal cortical blood flow and oxygen delivery, leading to post-operative renal dysfunction [27]. Patients who received balanced crystalloid solutions, in comparison to 0.9% saline solution, showed less impairment of haemostasis, enhanced gastric perfusion and better preservation of renal function [28].

The above effects can be avoided by using solutions which mimic the ionic composition aqueous fraction of plasma. Prevention of acidosis is possible with inclusion of bicarbonate, or metabolised anions, namely acetate, lactate, malate or citrate, which are found in the balanced crystalloid solutions such as Hartmann's solution, Lactated Ringer's solution, Plasmalyte and sterofundin. Characteristics of these solutions are described in Table 2.1. These solutions has been shown to not increase plasma acidity, did not reduce renal artery and renal cortical perfusion, as compared to 0.9% solution [29] . However, there are limited clinical

studies to compare different types of balanced crystalloid solutions, and their outcomes on renal function in the setting of renal transplantation patients.

Hartmann's solution was first described by Alexis Hartmann, an American paediatrician, by adding the lactate anion in substitute to chloride to overcome the detrimental effects of metabolic acidosis [30]. This solution is thought to be more physiologic with salt composition almost resembling the plasma. Having said that, the sodium concentration in Hartmann's solution is 130mmol/L, which is lower than that in the extracellular fluid (140 mmol/L). This solution is also slightly hypotonic with osmolarity of 273mOsm/L, and further reduced to 255mOsm/L due to incomplete ionisation of lactate salt. This affects the circulating sodium concentration and has the potential to increase brain water content, with a risk of developing cerebral edema [31]. Another component unique to Hartmann's solution is the lactate, acting as the buffer in the solution. Lactate was added to Hartmann's solution to to reduce the chloride load and as a bicarbonate precursor, and hence minimising the risk of hyperchloraemic acidosis. Lactate undergoes gluconeogenesis, leading to increased levels of glucose. Administration of solutions containing lactate might also confound the interpretation of lactate as the marker of tissue perfusion, as its level may be elevated from excessive infusions of this solution [32].

Sterofundin is a balanced isotonic solution very similar to plasma, containing acetate and maleate . In contrast to Hartmann's solution, it is isoosmolar to human plasma with osmolarity of 288mOsm/L, and contains the best electrolyte parameter, closest to extracellular fluid component. Its acetate and maleate

components are widely and rapidly metabolised in all organs and muscles, unlike lactate which is dependant on kidney and liver for its metabolism [29,33].

There are many studies comparing the effects of different crystalloid in the perioperative period, of which majority focus on the different effects of normal saline as compare to the more balanced crystalloid solutions. However, very limited studies compare the effects of different balanced crystalloid solutions, especially in the setting of major surgeries such as renal transplantation. This study aims to find the more superior balanced crystalloid solution, among the two most common balanced crystalloid in UMMC, which are Hartmann's solution and sterofundin. Sterofundin has always been viewed as more superior as compared to Hartmann's solution due to the acetate and maleate content as bicarbonate precursors. Its usage, though, is very limited in our centre in view of its higher cost.

CHAPTER 3 : METHODOLOGY

The study was approved by the University Malaya Medical Ethics Committee (UMREC Number : 201814-5933) and registered with National Medical Research Register (NMRR ID : NMRR-18-2159-42545). We recruited 10 recipients scheduled for elective living related renal transplantation in University Malaya Medical Centre from April 2018 to December 2018. All patients gave their informed, written consent. The inclusion criteria are patients above 18 years old and who are recipient of living related renal transplantation. Exclusion criteria were severe cardiovascular disease, liver dysfunction, cadaveric renal transplantation, and serum potassium more than 5.5 mmol/L.

Patients were randomised into two groups, group of solution A and solution B, using a computer generated randomisation programme. Each solution consisted either Hartmann's solution or sterofundin, based on specific group allocation. After recruitment, the enrolling investigators will randomise the said patient according to the randomisation programme. The study solutions were then prepared and re-labelled into bags of fluids with either solution A or solution B, by the hospital pharmaceutical department. Study participants, trial investigators, attending anaesthetist providing general anaesthesia and outcome assesses were blinded to the type of solution.

All patients were fasted for at least 6 hours prior to surgery. Before induction of anaesthesia, a peripheral intravenous catheter was inserted, with either 20G or 18G IV cannula. After pre-oxygenation, general anaesthesia was conducted as per

anaesthetist in charge. Central venous catheter was inserted after induction of anaesthesia at either left or right internal jugular vein. The patients were monitored using standard monitoring devices according to AAGBI guidelines, which includes non-invasive blood pressure monitoring, capnography, oxygen saturation monitoring, temperature and electrocardiogram, with added central venous pressure monitoring.

IV fluids were administered of about 30-50 mL/kg/hr, with higher proportion of the administration given during the ischaemic phase. The total volume of fluids were recorded. During surgery the temperature was kept at 36˚C and $PaCO_2$ maintained a 30-35mmHg. We provided multimodal analgesia which included intraoperative opioids, intravenous paracetamol, and patient controlled (PCA) fentanyl for post operative analgesia.

At the end of surgery, the study fluid was discontinued, and the patients received dextrose containing solutions in the intensive care unit. Patients extubated prior sending to the intensive care unit, if deemed fit.

Patient's clinical data were recorded at recruitment. Blood gas samples and renal profile including the serum electrolytes were sent for analysis before the start of surgery, at the end of surgery, post operative day 1, post operative day 3, and at post operative day 7. Measurements of of pH, serum bicarbonate, base excess, serum lactate, serum creatinine, serum sodium, potassium, calcium and magnesium were recorded. Figure 3.1 shows the consort diagram illustrating the workflow from recruitment until data analysis.

3.1 Statistical Analysis

Our primary outcome measure was the need for dialysis or the failure of serum creatinine to drop by 20% from baseline at post operative day 3 in renal transplant recipients. Power study was used to determine the sample size of this study. The prevalence of renal transplant in Malaysia is only 8 percent, out of 92% of patients on renal replacement therapy in Malaysia. Since population size is unknown, an appropriate sample size is obtained using the formula. Power analysis at 80% and the 0.05 level of significance showed 11 patients needed in each arm. We aimed to recruit 13 patients in each solution group to account for dropouts, protocol breaches and surgery cancellation. Unfortunately, we did not manage to recruit the targeted sample size due to certain limitations. Hence, this study is a pilot study, and this study is still on going currently, and therefore, the solutions have not been unblinded for continuing research purposes.

Data throughout the study are shown as mean ± SD. Demographic perioperative data were compared using student t-test. All statistical analyses were performed using Statistical Package for Social Sciences (SPSS Inc., Chicago IL, USA) version 23.0. Comparison of data between groups were determined by using Wilxocon Signed Rank Test. For all tests, values were considered to be statistically significant at $p < 0.05$.

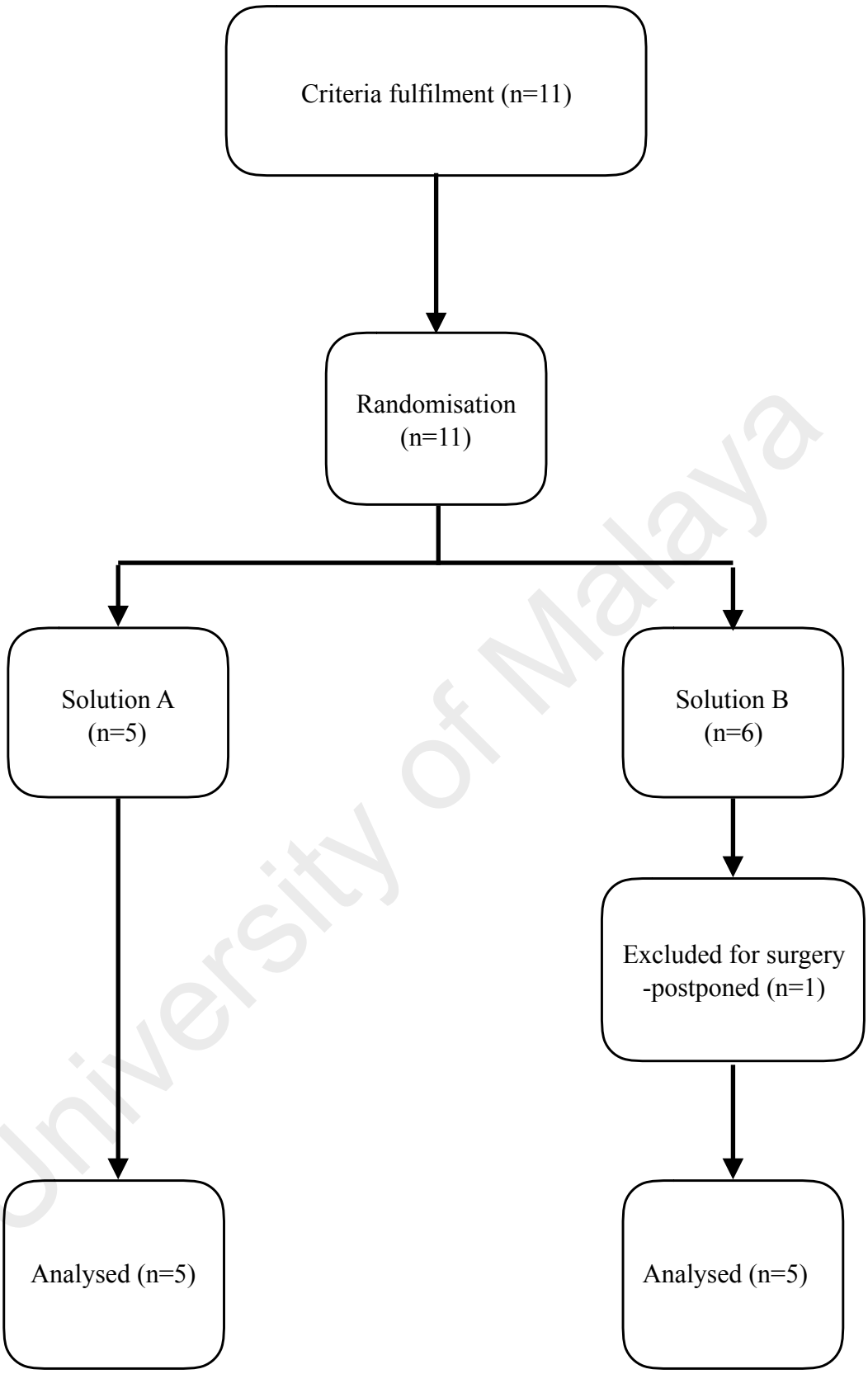

Figure 3.1 : Consort diagram showing study flow

CHAPTER 4 : RESULTS

11 elective renal living related renal transplant recipients were assessed for eligibility for the study and all of the patients consented. They were recruited into the study and were then randomised into 2 arms, with 5 patients in the solution A group and 6 in the solution B group. These solutions were still blinded at the time of this thesis write up , as the study is still on going. The solutions consist of either Hartmann's solution or sterofundin and labelled as Solution A and Solution B, with no knowledge of which arm they fall into. Therefore, these two groups will be referred to as Solution A and Solution B for reference purposes. Out of the 11 patients, 1 patient from the Solution B group dropped out in view of surgery cancellation. In the final analyses, 10 patients were used with 5 patients from each group. Their descriptive statistics are summarised in Table 4.1.

Table 4.1 : Descriptive statistics of patients

Variable	**Solution A (n=5)**	**Solution B (n=5)**
Gender		
Male	1 (20.0)	4 (80.0)
Female	4 (80.0)	1 (20.0)
Median Age (in years)/ IQR	32/12	45/17
Amount of fluids administered (in mls)/ IQR	2500/1850	2000/1350

There were 80% females in group who received solution A and 80% males in the group who received Solution B. Median age of patients who received Solution A was 32, as compared to 45 in Solution B group. Median total of fluid given in Solution A group was 2500, and the median of fluid given in Solution B group was 2500.

Mean serum creatinine at pre-operative period in patients who received Solution A was 614, while the immediate post operative period mean level is 516. There is no significant difference in mean serum creatinine at immediate post operative period as compared to baseline ($p>0.05$) for patients in both groups. For patients who received Solution B, there is only a slight reduction in serum creatinine at immediately post operative period as compared to baseline ($p< 0.05$). These results were taken within one hour of skin closure post operatively.

There is a reduction in plasma pH for both groups in the immediate post operative period compared to baseline. The reduction in plasma pH is greater in patients who received Solution B (0.071 ± 0.01) as compared to Solution A (0.06 ± 0.02, $p<0.05$). However, there is no significant acidosis in both groups (pH <7.25). There is a significant reduction in base excess for patients who received solution B (-4.6 ± 2.97, $p<0.05$) in the immediate post operative period, with no difference seen in base excess in the immediate post operative period in patients who received Solution A (-2.5 ± , 2.92, $p=0.225$). The bicarbonate level is significantly lower immediately post-op in the patients who received Solution B (4.14 ± 1.16, $p< 0.05$). Serum lactate level is also higher in the post -operative

period in patients who received Solution B (2.26 ± 0.06, p< 0.05). There is no significant difference in the base excess level, serum bicarbonate level, serum lactate level, serum creatinine level at immediately post operative period in patients whop received Solution A. Serum potassium level for both groups does not differ at the post -operative period as compared to baseline (p>0.05). These results are shown in Table 4.2.

As for comparison of these groups at post operative day 3 (POD 3), There is a small reduction in base excess at POD 3 for patients in both groups ; Solution A group (0.92 ± 0.31, p <0.05) and Solution B group (0.58 ± 0.53, p <0.05). Patients in Solution A group show a small increment in serum bicarbonate level (1.0 ± 0.53, p <0.05), while patients in Solution B group showed a decrement in the serum bicarbonate level (0.88 ± 0.99, p<0.05). Despite that, there are no difference in the pH levels at POD3 as compared to baseline in both groups (p >0.05). There is also no significant acidosis seen in both groups at POD 3.

Serum creatinine is significantly lower in patients in both groups, however patients who received Solution B showed more reduction of serum creatinine at POD 3 (649 ± 156, p <0.05). Serum lactate is significantly higher in patients who received Solution B (0.2 ± 0.06, p< 0.05) at POD 3, while no significant difference was seen in patients who received Solution A (p >0.05). Patients in both groups did not show significant difference in serum potassium level at POD 3 as compared to baseline (table 4.3).

Serum creatinine at post operative day 7 (POD 7) showed significant reduction for both groups as compared to baseline. More reduction is seen in patients who

received Solution A (526.8 ± 43.86, $p<0.05$) as compared to patients who received Solution B (665.4 ± 169, $p< 0.05$). Results are shown in Table 4.4.

Table 4. 2 : Changes in pH, base excess (BE), serum bicarbonate (HCO_3), serum lactate (lact), serum creatinine (creat) and serum potassium (K) at immediately post operative period as compared to baseline (base) for solution A and Solution B

d is effect size. Less than 0.2 : small, 0.5 moderate, more than 0.8 is large

Solution A						**Solution B**				
Variable	Base	Post op	Change	P value	d	Base	Post op	Change	P value	d
pH	7.384	7.324	0.06± 0.02	**0.043**	0.06	7.386	7.315	0.071 ±0.01	**0.043**	0.99
BE	0.5	-3.0	2.5±2 .92	0.225	0.79	-0.6	-5.2	-4.6± 2.97	**0.043**	1.06
HCO 3	22.96	21.6	1.36 ±1.76	0.500	0.63	24.12	19.98	4.14± 1.16	**0.043**	1.22
Lact	0.76	2.18	1.42 ±1.08	0.080	1.61	0.84	3.1	2.26± 0.06	**0.043**	1.21
Creat	614.6	516.6	98.6 ±65.9	0.138	0.94	788.0	655.8	132.2 ±34.6 1	**0.043**	0.66
K	3.92	4.44	0.52 ± 0.26	0.080	0.13	4.44	4.00	0.44± 0.06	0.225	0.7

Table 4.3 : Changes in pH, base excess (BE), serum bicarbonate (HCO_3), serum lactate (lact), serum creatinine (creat) and serum potassium (K) at immediately post operative period as compared to baseline (base) for solution A and Solution B

d is effect size. Less than 0.2 : small, 0.5 moderate, more than 0.8 is large

Solution A						**Solution B**				
Variable	Base	POD3	Change	P value	d	Base	POD3	Change	P value	d
pH	7.384	7.379	0.005 ±0.02	0.686	5.0	7.386	7.394	0.008 ±0.04	0.686	0.16
BE	0.5	-0.42	0.92± 0.31	**0.043**	0.2	-0.6	-1.18	0.58± 0.53	**0.043**	0.25
HCO 3	22.96	23.96	1.0± 0.53	**0.043**	0.3	24.12	23.24	0.88± 0.99	**0.042**	0.38
Lact	0.76	0.68	0.08± 0.06	0.257	0.42	0.84	1.040	0.2± 0.06	**0.039**	1.60
Creat	614.6	95.6	519± 43.7	**0.043**	10.38	788.0	139	649± 156	**0.043**	4.10
K	3.92	4.24	0.32 ± 0.18	0.104	0.68	4.44	4.6	0.16± 0.24	0.461	0.29

Table 4.4 : Changes in serum creatinine (creat) level at POD 7 as compared to baseline (base) in patients who received Solution A and B.

d is effect size. Less than 0.2 : small, 0.5 moderate, more than 0.8 is large

Solution A						**Solution B**				
Variable	Base	POD 7	Change	P value	d	Base	POD7	Change	P value	d
Creat	614.6	87.8	526.8± 43.86	**0.043**	10.54	788.0	122.6	665.4± 169	**0.043**	4.27

CHAPTER 5 : DISCUSSION

Renal transplant has a 5-year survival of 70% as compared to end stage renal disease patients on renal dialysis, with only 30% 5 year survival chance [34]. Patients undergoing renal transplantation have multiple comorbidities, which pose an anaesthetic challenge for the perioperative period. Many studies have reported improvement in graft function with large volume of fluids used in the intraoperative period for these patients. Fluid therapy remains a crucial component in management of these patients due to their complexity of their physiological and pathological nature.

From this study, it appears that patient who received Solution B endured bigger changes in pH, base excess, serum bicarbonate level, serum lactate level and more reduction in serum creatinine at the immediate post operative period. Solution B has a mean difference in pH of 0.071 as compared to 0.06 in Solution A group, which are both statistically significant. Patients who received Solution B suffered a more negative base excess, and lower serum bicarbonate level at the immediate post operative period. However, none of these patients had pH of less than 7.25 or needed treatment for metabolic acidosis. Base excess, serum bicarbonate, serum lactate and serum creatinine did not reach statistical significance in Solution A group. Serum potassium did not reach statistical significance in either group.

In contrast to the immediate post operative period, patients who received Solution A had bigger changes in terms of base excess and serum bicarbonate as compared to patients who received Solution B, at POD 3. Patients who received

Solution A, had mean difference in base excess of 0.92, and mean difference of serum bicarbonate of 1.0, as compared to patients who received Solution B, who had mean differences of only 0.58 in base excess, and 0.88 in serum bicarbonate level at POD 3, of which are statistically significant in both groups. Having said that, patients in both groups did not reach statistical significance in pH difference. Despite the fact that these balanced crystalloids contain bicarbonate precursors, metabolic alkalosis was not seen in any of the patients in both groups thus far. Metabolic alkalosis has been linked to poorer outcome [35].

Serum creatinine at POD 3, are significantly lower in both groups, with mean difference of 519 for patients who received Solution A and 649 for patients who received Solution B, of which are both statistically significant. Therefore, solution B showed a greater reduction in serum creatinine at POD 3 as compared to baseline. Both these groups showed a mean reduction of greater than 20% compared to mean baseline serum creatinine. As mentioned previously, the primary objective of this study is to compare the effects of these solutions on delayed graft function, which is defined as the need of dialysis at POD 7, or failure of serum creatinine to reduce by 20% at POD 3. The results of this study thus far, showed that both of these fluids did not have any effect on delayed graft function at POD 3. Serum lactate, however, showed an increment in patients who received Solution B at POD 3, which is statistically significant. Again, serum potassium did not reach statical significance in both groups at POD 3, similar to immediate post operative period. Despite the fact that both these fluids contain potassium, none of the patients recruited in this study from either group suffered from hyperkalemia (potassium >6 mEq/L), or received treatment for

hyperkalemia. This is similar to findings of a meta analysis which showed that potassium difference between Ringer's Lactate and normal saline infused in patients undergoing renal transplantation was not significant, despite the potassium content in Ringer's lactate [36].

None of these patients needed dialysis post operatively, therefore the need for dialysis at POD 7 was not included in this analysis. Serum creatinine, however, markedly dropped for patients in both groups, with a bigger reduction is seen in patients who received Solution B. These findings are statistically significant in both groups. Evidently from this study, none of the patients recruited suffered from delayed graft function, as none of these patients fulfilled the definition of delayed graft function stated in the study protocol.

There are a few limitations in this study. Firstly, this study did not achieve its target number of patients, and hence, the sample size is considerably small for analysis and may not reflect its true findings. Nonetheless, this study is still on going and the findings of this data may, if anything at all, pose as an interim analysis for further continuation of this study. Secondly, the fluids in question was only used during the intraoperative period, and was not continued into the post operative/ intensive care stay. Therefore, the post operative data may be affected by the different fluids used in the post operative period. Thirdly, this study only collects data up to post operative day 7. Any electrolyte or acid base disturbances due to the fluids used may be missed. Lastly, as this study objectively looks into delayed graft function, it does not take into consideration other confounding factor

that my affect delayed graft function, such as cold ischaemia time, donor age, recipient age, presence of diabetes and HLA compatibility [37].

Overall, these findings showed no significant effect on delayed graft function, but has minor effects in acid base status, mainly at POD3, favouring Solution B with lesser reduction on base excess and serum bicarbonate level. Having said that, Solution B also showed increment in serum lactate both at immediate post operative period and POD 3. Even though, Solution B has a lower median of fluid used as compared to Solution A, these differences are still seen markedly. Since these fluids are still blinded at the time of this thesis write up, premature determination of the fluids based on the results is difficult, as there are no prominent differences in the data between the two groups. However, it is likely that Solution B consists of Hartmann's solution, as the changes in lactate in this group is more pronounced as compared to Solution A, and is statistically significant.

CHAPTER 6 : CONCLUSION

This study shows no difference in intraoperative usage of Solution A or Solution B in living related renal transplantation, in terms of occurrence of delayed graft function, which is defined as the need of dialysis at post operative day 7 or failure of serum creatinine to drop by 20% at 72 hours post-operatively. However, Solution B does show a lesser reduction in base excess and serum bicarbonate at POD 3, which may suggest that Solution B has a better acid base profile for these patients as compared to Solution A, but may be offset by the slight increase in lactate seen in these patients. Given that the sample size of this study is small, further continuation of this research needs to be done to clarify the effects of these fluids on renal transplant recipients.

REFERENCES

1. Department of Statistics, Malaysia. Population Quick Info, Department of Statistics. http://pqi.stat.gov.my/searchBit.php

2. M. A Bujang, A.M. Abdul Hamid, N.A. Zolkepali, N.M. Hamedon, S. S. Mat Lazim, J. Haniff. Mortality rates by specific age group and gender in Malaysia; trend of 16 years, 1995-2010. Journal of Health Informatics in Developing Countries ; 2012; 6(2);521-529

3. M.A. Bujang, T. A. Adnan, N. H HAshim, K. Mohan, A. K. Liong, G. Ahmad, G.B. Leong, S. Bavanandan, J. Haniff. Forecasting incidence and prevalence of patients with end stage renal disease in Malaysia up to year 2040. Int Jour of Nephrology, 2017;1-5

4. Port FK, Wolfe RA, Mauger RA, Berling DP, Jiang K; Comparison of survival probability fir dialysis patients versus cadaveric renal transplant recipients. JAMA 1993;270:1339-1343

5. Syed A Akbar,S. ZAfar, M. A. Amendola, B.L. Madrozo, R. Salem, K. G. Bis. Complications of renal transplantation radiographics. 2005;25:1335-1356

6. Akkina SK, Connaire JJ, ISrani AK, Snyder JJ, MAtas AJ, Kasiske BL. Similar outcomes with different rates of delayed graft function may reflect centre practice, not centre performance. Am J Transplant. 2009;9(16):1460-1466

7. Tapiawala SN, Tinckam KJ, CArdella CJ, Schiff J, CAttian DC, Dole EH, et al. Delayed great function and the risk of death with a functioning graft. J Am Soc Nephrol. 2010;21(1):153-161

8. Chang SH, Russ GR, Chadban SJ, Campbell SB, McDonald SP. Trends in kidney transplantation in Australia and New Zealand 1993-2004. Transplantation. 2007;84(5);611-618

9. Yarlagadda SG, Coca SG, GArg AX,Doshi M, Poggio E, Marcus RJ, et al. Marked variation in the definition and diagnosis of delayed graft function, a systematic review. Nephrol Dial Transplant. 2008; 23(9):2995-3003

10. Yarlagadda SG, Cica SG, Formica RN Jr, Poggioe E, PArikh CR. Association between delayed graft function and allograft and patient survival: a systematic review and meta analysis. Nephrol Dial Transplant. 2009;24(3):1039-1047

11. Perico N, Catianto D, Sayegh MH, Remuzzi G. Delayed graft function in kidney transplantation. Lancet. 2004;364(9447):1814-1827

12. Schnuelle P, Johannes VDWF. Perioperative fluid management in renal transplantation: a narrative review of the literature. Transplant Int. 2006;19(12): 947-959

13. Tockall C, Amante AJ, KAhan BD, Jasttrzebski J, Keown PA. Renal transplantation. 1999:241-267

14. Adams PL, Adams FF, Bell PD, Navar LG. Impaired renal blood flow auto regulation in ischaemic acute renal failure. Kidney Int. 10980:18:6-8

15. Conger JD, Robinette JB, Schner RW. Smooth muscle calcium and endothelium0derived relaxing factor in the abnormal vascular responses of acute renal failure. J Clin Inves.1988:82:532

16. Morita K, Seki T, Nonomura K, Koyonagi T, Yashioka M, Saito H. Changes in renal blood flow in response to sympathomimetics in the rat transplanted and denervated kidney. Int Jour Urol. 1999;6:24

17. Shannon JL, Headlan R, Maclver AG, Ferryman SR, Barber PC, Howie AJ. Studies on the innervation of human renal allografts. J Pathol. 1998;186:109

18. Thomas MC, Mathew TH, Russ GR, Rao MM, Moran J. Perioperative blood pressure control, delayed graft function and acute rejection after renal transplantation. Transplantation.2003;75:1989

19. Kreimeier U, Peter K. Strategies of volume therapy in sepsis and systemic inflammatory response syndrome. Kidney Int 1998;53:575

20. Metha RL, Clark WC, Schetz M. Techniques for assessing and achieving fluid balance in acute renal failure. Curr Opin Crit Care 2002;8:535

21. Ragaller MRJ, Theilen H, Koch T. Volume replacement in critical ill patients with acute renal failure. J Am Soc Nephrol 2001;12:533

22. Kim My, Jeon NY, Hyn SK, et al. The effects of normal saline versus Hartmann's solution in the acid base and electrolytes status and renal function after kidney transplantation. J Korean Soc Transplant 2015;29:194-199

23. Yee J., Parasuraman R, Narins RG,. Selective review of key perioperative renal - electrolyte disturbances in chronic renal failure patients. Chest 1999;115(5):149S-57S

24. Wang P., Ayala A, Dean RE, et al. Adequate crystalloid resuscitation restores but fails to maintain the active hepatocellular function following hemorrhagic shock. J Trauma 1991;31:601.

25. Kreimeier U, Ruiz-Morales M, Messmer K. Comparison of the effects of volume resuscitation with dextran 60 vs Ringer's lactate on central

hemodynamics, regional blood flow, pulmonary function and blood composition during hyperdynamic endotoxaemia. Circ Shock 1993;39:89

26. Ding X, Cheng Z, et al. Intravenous fluids and acute kidney injury , Blood Purif 2017;43:163-172

27. Wan S., Roberts MA, Mont P. Normal saline versus lower chloride solutions for kidney transplantation (Review). The Cochrane Collabration 2016.

28. Wilkes NJ, Woolf R, Mutch M, et al. The effects of balanced versus saline based hexastarch and crystalloid solutions on acid base and electrolyte status and gastric mucosal perfusion in elderly surgical patients. Anaesth Analg 2001;93:811

29. Guidet B, N. Soni, G.D Rocca, S. Kozek, B. Vallet, D Cannane, M. James. A balanced view of balanced solutions. Critical Care 2010;14:325

30. Skellet S, Mayer A, Tibby SM, Murdoch IA. Chasing the base deficit: hyperchloraemic acidosis following 0.9% saline fluid resuscitation. Arch Dis Child 2000;83:514-516

31. Maristella Santi, Sebastiano A. G Lava, Pietro Camozzi, Oliver Gianini. The great fluid debate : saline or so called “balanced” salt solutions?. Ital J Pediatr 2015;41:47

32. Lobo DN, Awad S. Should chloride-rich crystalloids remain the mainstay of fluid resuscitation to prevent ‘pre renal’ acute kidney injury?. Kidney Int 2014;86:1090-105

33. Hangy JM, Soni N,. Physiological effects of Hyperchloraemic and acidosis. Br J Anaesth 2008;101:141-150.

34. Wolfe RA< Ashby VB, Milford EL, Ojo AO, Ettenger RE, Agodoa LY, et al. Comparison of mortality in patients on dialysis, patients on dialysis awaiting transplantation, and recip[ients of first cadaveric transplant. N Engl J Med 1999;341:1725-30

35. Tripathy S. Extreme metabolic alkalosis in intensive care. Indian Journal of Critical Care Medicine: Peer-reviewed, Official Publication of Indian Society of Critical Care Medicine 2009;13(4):217-220

36. Trujilio-Zea JA, Aristizabal-Henao N, Fonseca-Ruiz N. Lactated Ringer’s versus normal saline solution for renal transplantation : Systemic review and meta analysis 2015;43:194-203

37. Ojo, Akinlolu O,Wolfe, Robert A, Held, Philip J, Port, Friedrich K, et al. Delayed graft function: Risk factors and implications for renal allograft survival. Transplantation 1997;63(7):968-974