A COMPARISON OF SEVOFLURANE VERSUS SEVOFLURANE – PROPOFOL COMBINATION ON RENAL FUNCTION IN PATIENTS UNDERGOING VALVULAR HEART SURGERY
A PROSPECTIVE RANDOMIZED STUDY

PROJECT

BY

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2012-2014

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DECLARATION

I hereby declare that this thesis entitled "**A comparison of sevoflurane versus sevoflurane – propofol combination on renal function in patients undergoing valvular heart surgery – A prospective randomized study**" has been prepared by me under the able guidance of Addl.Prof. Unnikrishnan. K.P, Addl. Prof Suneel P.R, Division Of Cardiothoracic And Vascular Anaesthesia, Department Of Anaesthesiology, at Sree Chitra Tirunal Institute For Medical Sciences & Technology, Thiruvananthapuram.

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ACKNOWLEDGEMENT

Much help came my way in course of preparation of this dissertation. It is my pleasant duty to acknowledge some of these.

At the outset, I owe my deepest gratitude to my guide Dr Unnikrishnan K.P. He was instrumental in framing the idea of the project, inspired me throughout the study and supported me in the preparation of this project.

It is a pleasure to thank my co guide Dr Suneel P.R, for his assistance in finishing this project. He always found time to clarify my doubts and gave valuable insights related to the study.

I express my deep sense of gratitude to Dr Deepa Bhaji and also to Dr Jayakumari, Department of Biochemistry, for their assistance. This thesis would not have been possible without the help and support I received from them.

I express my gratitude and sincere thanks to Prof Shrinivas for his constant motivation and invaluable guidance throughout my tenure as a DM resident.

With a profound sense of gratitude I express my thanks to Prof. Rupa, In- charge, and all other faculty members of the Division of Cardiothoracic and Vascular Anaesthesia, and particularly to Prof. Thomas Koshy, Prof.P.K Dash, Dr Satyajeet and Dr Subin for their valuable advice and constructive criticism and generous help.

I am thankful to my fellow residents for their constant support throughout the study. Dr Amar, Dr. Poornima, Dr Yuvaraj, Dr Jagdeesh and Dr Roshith deserve special mention.

I would like to thank Mr Binu Thomas, Anaesthesiology Technical Assistant who helped me with the paper work for the funding of this project. I would also like to thank all the Anaesthesiology technical assistants, Nursing staff and supporting staff for their active assistance.

I would be failing in my duty if I do not acknowledge my deep gratitude to all those patients who had volunteered for this study.

Last, but not the least, I express my heartiest gratitude and sincere regards to my loving family for their constant encouragement.

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CONTENTS

INTRODUCTION

INTRODUCTION

Acute kidney injury (AKI) is a highly prevalent and prognostically important complication of cardiac surgery. The incidence of AKI is estimated to be up to 30% in cardiac surgery patients.[1]

Cardiac surgery contributes to ischemic kidney injury by inciting a strong inflammatory response. Proinflammatory events during cardiac surgery include operative trauma, contact of blood components with the artificial surface of cardiopulmonary bypass (CPB) circuit, ischemia-reperfusion (I-R) injury and endotoxemia.[2,3] During CPB neutrophils, platelets and vascular endothelium are activated.[4,5] CPB is a potent activator of factor XII which in turn activates the intrinsic coagulation system, kallikrein system and the fibrinolytic system. All these events result in the elaboration of proinflammatory cytokines, oxygen-derived free radicals, proteases, cytokines and chemokines.[6,7] I-R injury results in the production of oxidant agents which leads to the destruction of cell membranes through peroxidation of the lipid and oxygen derived free radicals.[7]

Anaesthetic agents offer some protection against lesions induced by I-R injury. Propofol acts as a scavenger of O_2 free radicals, decreasing lipid peroxidation in the liver, kidney, heart and lung [8]. Volatile anaesthetics protects against I-R injury and reduce myocardial infarct size and offers cardioprotection.[9] The endothelial protection may play a central role in the observed multiorgan protection by volatile anaesthetics. The human endothelial cells exposed to volatile anaesthetics

developed a pronounced resistance against cytokine induced toxicity, consistent with a preconditioning like effect.[10]

Most of the previous studies demonstrate a comparable effect for sevoflurane and propofol on renal function. Since sevoflurane and propofol exert their beneficial effects by different mechanisms, we hypothesized that the combination of sevoflurane and propofol has a better effect on renal function compared to sevoflurane alone.

The goal of our study was to compare the effect of sevoflurane and sevoflurane-propofol combination on renal function in patients undergoing valvular heart surgery.

AIMS AND OBJECTIVES

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The aim of our study is to determine whether the combination of sevoflurane and propofol for induction and maintenance of anaesthesia offered any benefit over sevoflurane anaesthesia alone with regard to

1. Renal function, using NGAL as biomarker
2. The amount of phenylephrine used so as to maintain a mean arterial pressure more than 60mm Hg.
3. The perioperative inotropic requirement.
4. The duration of Intensive Care Unit (ICU) stay and hospital stay

REVIEW OF LITERATURE

REVIEW OF LITERATURE

Acute Kidney Injury

Acute kidney injury (AKI) refers to a clinical syndrome characterized by a rapid decrease in renal excretory function, with the accumulation of products of nitrogen metabolism such as creatinine and urea and other clinically unmeasured waste products.[11] The incidence of AKI in patients undergoing coronary artery bypass graft surgery (CABG) is 2-5% and those undergoing valvular or combined procedure is as high as 30%.[12]

Postoperative AKI is the consequence of interplay of different pathophysiologic mechanisms, with patient-related factors and cardiopulmonary bypass (CPB) as major causes.[12] Kidneys are prone to ischemic damage because of their peculiar blood circulation, in which renal medulla is normally perfused at a low oxygen tension with a limited reserve. Under CPB there is unavoidable alteration of renal blood flow and the causes include ischemia-reperfusion injury, low cardiac output, renal vasoconstriction, haemodilution and loss of pulsatile flow during CPB. All these factors lead to an oxygen supply/demand renal imbalance, with significant cellular injury.[12]

The risk factors for development of AKI after cardiac surgery include female gender, reduced left ventricular function or congestive heart failure, preoperative use of Intra Aortic Balloon Pump (IABP), diabetes mellitus, peripheral vascular disease, chronic obstructive pulmonary disease, need for emergent surgery and an elevated preoperative serum creatinine.[1]

PATHOGENESIS AND CLINICAL PHASES OF ACUTE KIDNEY INJURY

FIGURE 1

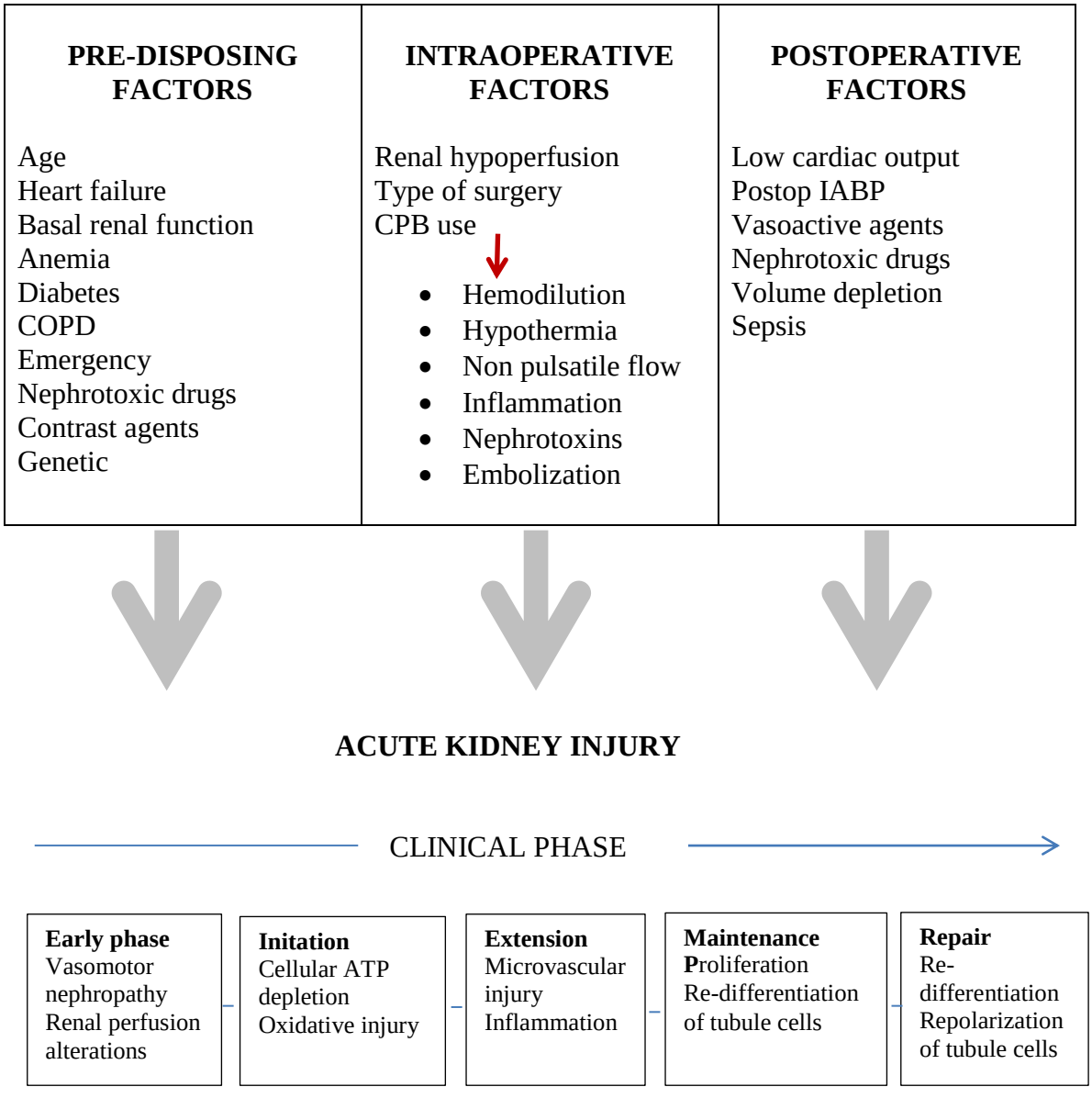


Figure 1. Pathogenesis and clinical phases of acute kidney injury. (ATP -adenosine triphosphate; COPD - chronic obstructive pulmonary disease; CPB - cardiopulmonary bypass; IABP- intraaortic balloon pump; POSTOP - postoperative.)

An important cause of AKI in cardiac surgery is cellular ischemia. This results in tubular epithelial and vascular endothelial injury and activation.[13,14] Cardiac surgery heightens the risk of AKI by several processes. Normally kidney perfusion is autoregulated such that glomerular filtration rate is maintained until the mean arterial blood pressure falls below 80mm Hg. Mean arterial blood pressure during cardiac surgery is often at the lower limits of autoregulation especially during periods of hemodynamic instability. In addition, many cardiac surgery patients have impaired autoregulation due to existing comorbidities, administration of drugs that impact kidney autoregulation or a proinflammatory states. In patients with impaired autoregulation, renal function may deteriorate even when the mean arterial blood pressure is within the normal range.

Cardiac surgery may contribute to ischemic kidney injury by inciting a strong inflammatory response. Proinflammatory events during cardiac surgery include operative trauma, contact of blood components with the artificial surface of CPB circuit, ischemia reperfusion injury and endotoxemia. The generation of free hemoglobin and iron from hemolysis that occurs during CPB, further contributes to ischemic kidney injury.

During CPB, both neutrophils and vascular endothelium are activated with up regulation of adhesion molecules such as CD11b and CD 41. Platelets also undergo activation, degranulation and adherence to vascular endothelium. These lead to the elaboration of cytotoxic oxygen derived free radicals, proteases, cytokines and chemokines. These inflammatory mediators such as interleukins IL-6, IL-8 and tumor necrosis factor (TNF) show considerable rise in serum levels during CPB.[1]

CPB is also a potent activator of factor XII (Hageman factor) to factor XII a. This process initiates the intrinsic coagulation system, the kallikrein system and the fibrinolytic system. The complement proteins are activated through both the classical and alternate pathways. This humoral response amplifies the cellular response that leads to neutrophil, endothelial and monocyte activation and further elaboration of proinflammatory cytokines.[1]

The end result of generalized inflammatory response induced by CPB within kidney is not known. Animal models of renal ischemia reperfusion injury demonstrate the pathologic role of interstitial inflammation and the elaboration of proinflammatory cytokines and reactive oxygen species in production of tubular injury[1].

The RIFLE (an acronym for risk, injury, failure, loss, end-stage kidney disease) criteria and the acute kidney injury network (AKIN) criteria have emerged as diagnostic tools for monitoring the severity and progression of postoperative AKI.[10] These criteria are detailed in table 1 and 2.

Conventional renal biomarkers either do not detect injury in the real time or become abnormal many hours later in the course of injury (S.creatinine or urea) or lack specificity (urine output). Novel biomarkers like Cystatin C, neutrophil gelatinase-associated lipocalin (NGAL), interleukins (IL-6, IL-18), kidney injury molecule-1 (KIM-1), liver-type fatty acid binding protein (L- FABP), and N-Acetyl- β -D Glucosaminidase (NAG) refine the diagnosis and prognosis of AKI.[11]

Classification systems for acute kidney injury

Table 1. RIFLE classification criteria

Class	GFR criteria	Urinary output criteria
Risk	Scr increase x 1.5 or GFR decrease>25%	< 0.5 ml/kg/h x 6 hours
Injury	Scr increase x 2.0 or GFR decrease >50%	< 0.5 ml/kg/h x 12 hours
Failure	Scr increase x 3.0 or GFR decrease >75% or Scr > 4mg/dl with an acute rise >0.5 mg/dl	<0.3 ml/kg/h x 24 hours, or anuria x 12 hours
Loss	Persistent acute renal failure complete loss of kidney function > 4 weeks	
End stage renal disease	End-stage renal disease >3 months	

Table 2. AKIN classification criteria

Classes	Scr criteria	Urinary output criteria
1	Scr increase x 1.5 or Scr increase >0.3 mg/dl from baseline	<0.5 ml/kg/h >6 hours
2	Scr increase x 2 from baseline	<0.5 ml/kg/h >12 hours
3	Scr increase x 3 or Scr increase >4 mg/dl with an acute Increase>0.5 mg/dl	<0.5 ml/kg/h >24 hours, or anuria x 12 hours

NGAL has been investigated extensively and would appear to be one of the most promising early AKI biomarkers. It measures tubular stress and is involved in the ischemic renal injury and repair process. NGAL increases dramatically in response to tubular injury and precedes rises in serum creatinine by more than 24 hours.[12]

Strategies to prevent AKI.

Several preventive strategies acting at preoperative, intraoperative, and postoperative levels have been proposed for the prevention of AKI. These approaches are often controversial owing to the difficulty in targeting single pathways in the complex AKI pathophysiology.[11]

Nephrotoxic medications or intravenous contrast may lead to tubular damage and subsequent AKI. Delaying cardiac surgery beyond 24 hours of exposure to contrast agent and minimizing its use have significant potential to decrease AKI.[11]

The most relevant preventive strategies have been focussed on deleterious effects related to CPB use, such as hemodilution and nonpulsatile flow. Pulsatile perfusion produces superior renal protection, improving organ perfusion by reducing vasoconstrictive reflexes, optimizing oxygen consumption and reducing acidosis. Poor oxygen availability to the renal medulla during CPB may deteriorate renal function, causing ischemic and inflammatory organ injury. Ranucci and colleagues observed that the lowest haematocrit and oxygen delivery are

independent AKI predictors. Higher risk was observed at haematocrit less than 26% and oxygen delivery less than 272 ml/min/m2, respectively. CPB flow rates of 1.8 to 2.2 l/min/m2 and a mean arterial pressure above 50 to 60 mm Hg are recommended.[1, 11]

Drugs increasing renal blood flow have been extensively tested. Dopamine failed to demonstrate any renoprotective effect. Fenoldopam, increase renal blood flow in a dose dependent manner and has been observed to reduce AKI after cardiac surgery. Atrial and brain natriuretic peptide and urodilatin has been shown to reduce renal dysfunction by improving natriuresis, by increasing GFR and by inhibiting sodium reabsorption by the medullary collecting duct. Diuretics reduce AKI, by preventing tubule obstruction and decreasing oxygen consumption. Neither furosemide nor mannitol was demonstrated to be renoprotective.[11]

Eventhough statins attenuate inflammation and oxidative stress, no renoprotective effects are proven. Similarly, data regarding N-Acetylcysteine for renal protection is inconclusive. There is no role for the use of dexamethasone, aprotinin, or other anti-inflammatory agents, in the prevention of postoperative AKI.[11]

Protective effects of sevoflurane on CPB

Sevoflurane attenuates the pulmonary sequestration of neutrophils and leukocytes and also preserves the pulmonary consumption of cytokines at the time of early pulmonary reperfusion.[13] Sevoflurane before or after ischemia improves

contractile metabolic function while reducing myoplasmic calcium (ca^{2+}) loading in intact hearts.[14] Also it has suppressive effects on cytokine release in human peripheral blood mononuclear cells.[15] Sevoflurane attenuates the systemic inflammation response induced by CPB.[16]

Sevoflurane and renal function

Julier et al's study demonstrated that preconditioning with sevoflurane decreased biochemical markers of myocardial and renal dysfunction. Cystatin C concentrations significantly increased immediately postoperatively and peaked at 48 h after surgery for sevoflurane and placebo group. Cystatin C concentrations were markedly higher for placebo-treated patients than for sevoflurane-treated patients.[9]

Elianna Luccinetti and colleagues studied the effect of sevoflurane inhalation at sedative concentrations to provide endothelial protection against ischemia–reperfusion injury in humans. Their data suggest that human endothelium, a key component of all vital organs, is receptive to protection by sevoflurane in vivo. Peri-ischemic administration of sevoflurane mimics a combination of pharmacologic preconditioning and postconditioning and protects at even low sedative concentrations (< 1 volume %). Inhibition of leukocyte adhesion is likely to be involved in the protection.[17]

Vascular endothelium is critically involved in many steps of tissue damage originating from I-R.[18] Endothelial protection may play a central role in observed

multiorgan protection by volatile anaesthetics.[19] Experimental studies have shown that human endothelial cells exposed to volatile anaesthetics developed a pronounced resistance against cytokine induced toxicity, consistent with a preconditioning like effect.[17] Renal ischemic preconditioning and adenosine mediated renal protection signal via G1 and protein kinase c (PK-C). Shayvit et al showed that isoflurane and halothane significantly attenuated the inflammatory, response associated with multiorgan dysfunction syndrome.[18] Volatile anaesthetics may protect the kidney against I-R injury by reducing necrotic and inflammatory renal cell death.

After I-R injury, proinflamatory cascades are directed to the nucleus via proinflamatory transcription factors such as NF-kB. Lee et al has shown that NF-kB nuclear translocation is significantly reduced in rat kidney after volatile anaesthetic treatment. This may be a component of mechanism for renal protection with volatile anaesthetics. [20]

Laboratory investigations stress the concept that volatile anaesthetics may precondition endothelial and smooth muscle cells implying that anaesthetic preconditioning might beneficially affect a wide variety of tissues including brain, spinal cord, liver and kidneys. [9]

Propofol and organ protection

Propofol is an effective hypnotic agent. Propofol use in cardiac surgery is associated with a decrease in I-R injury in clinically relevant concentration.[21]

Propofol has antioxidant properties. Propofol anaesthesia was directly related to a significant decrease in oxidative activity measured by malondialdehyde levels in plasma and pulmonary lavage. In several investigations, an antioxidant effect of propofol was shown via mechanisms involving decreases in neutrophil infiltration, plasma inflammatory cytokine levels, O_2 free radical production and lipid peroxidation. Infusion of the agent significantly reduced the number of in vitro apoptotic cells. [22,23,24]

Propofol has been proven to ameliorate I-R injury in several organs including the heart, lungs, brain, liver and testicles. Propofol limits oxidative injury in various tissue including the kidneys [22-24]. A study by Wang et al demonstrated that propofol treatment significantly reduced renal dysfunction which was in part mediated by induction of heme oxygenase-1 [25]. The production of free radicals and subsequent lipid peroxidation plays a key role in I-R injury. The antioxidant property is attributed to the phenolic structure of propofol. Propofol appears to inhibit lipid peroxidation either by reacting with lipid peroxyl radicals to form the relatively stable propofolphenoxyl radical or by scavenging peroxynitrate. Propofol can inhibit the activity of neutrophils and Ca^{2+} influx across plasma membranes. [22,23]

Acute kidney injury and renal biomarkers.

Serum creatinine is neither a sensitive biomarker nor an early indicator of renal dysfunction. Since the serum creatinine rise is sluggish in response to the fall in GFR, it is not of use in testing measures for renal protection. Even minimal

increments in serum creatinine are independently associated with an increase in morbidity and mortality. [26]

Markers such as Cystatin C and creatinine accumulate to diagnostic levels because of decreased clearance. The importance of these agents are challenged during the perioperative period because of signal to noise confounders, such as haemodilution, which alter the steady state consumptions and thereby complicate early recognition of AKI. [26]

Most of the biomarkers involve one of the three consequences of AKI: tubular cell damage, tubular cell dysfunction and the adaptive stress response of the kidney. Damaged renal cells leak content directly into urine resulting in increased renal biomarkers like β.N-Acetyl-β-D-glucosaminidase. Markers of kidneys stress response include NGAL, urinary IL-18, cystein rich protein 61 and so on.[27]

Neutrophil gelatinase associated lipocalin.

NGAL is a small covalently bound polypeptide from human neutrophils, which is protease resistant and readily detected in urine and blood.

Serum creatinine is an inadequate marker for AKI because of the following reasons

1. Substantial losses of GFR may occur before an increase in serum creatinine will be measured.
2. Serum creatinine does not accurately depict renal function until a steady state has been reached which may require several days.

NGAL is a renal stress marker. Haase et als study on renal biomarkers after cardiac surgery found a moderate to strong correlation of NGAL concentration and duration and severity of AKI. They found high sensitivity of 73% and specificity of 74% for a serum NGAL concentration >150 ng/ml.[28] The NGAL concentration on arrival in ICU correlated with the length of stay in ICU but not with the length of stay in hospital. The rapid rise and subsequent fall in NGAL (occurring while GFR is being lost) suggests that NGAL is likely to be a marker of cardiac surgery-associated tubular injury.

Hypothermic CPB and its effect on drugs

CPB is frequently conducted at varying degrees of temperature. Hypothermia has anaesthetic properties. The pharmacokinetics of drugs varies during hypothermia. Hypothermia may shift fluid from intravascular to the interstitial space. This alters the volume of distribution by shifting protein-poor fluid from intravascular to the interstitial fluid compartment. Hypothermia causes vasoconstriction, which reduces the rate of reuptake of drugs from peripheral tissue to central compartment. Temperature induced reductions in enzyme mediated biotransformation decrease clearance and increase elimination half times. Changes in organ perfusion alter the drug excretion by kidney as a result of decreased renal perfusion, decreased GFR and decreased tubular secretion. Hypothermia increases solubility of volatile anaesthetics. Hypothermia also alters the clearance of drugs that require enzymatic degradation to terminate their effect.[29]

Acute kidney injury and its biomarkers

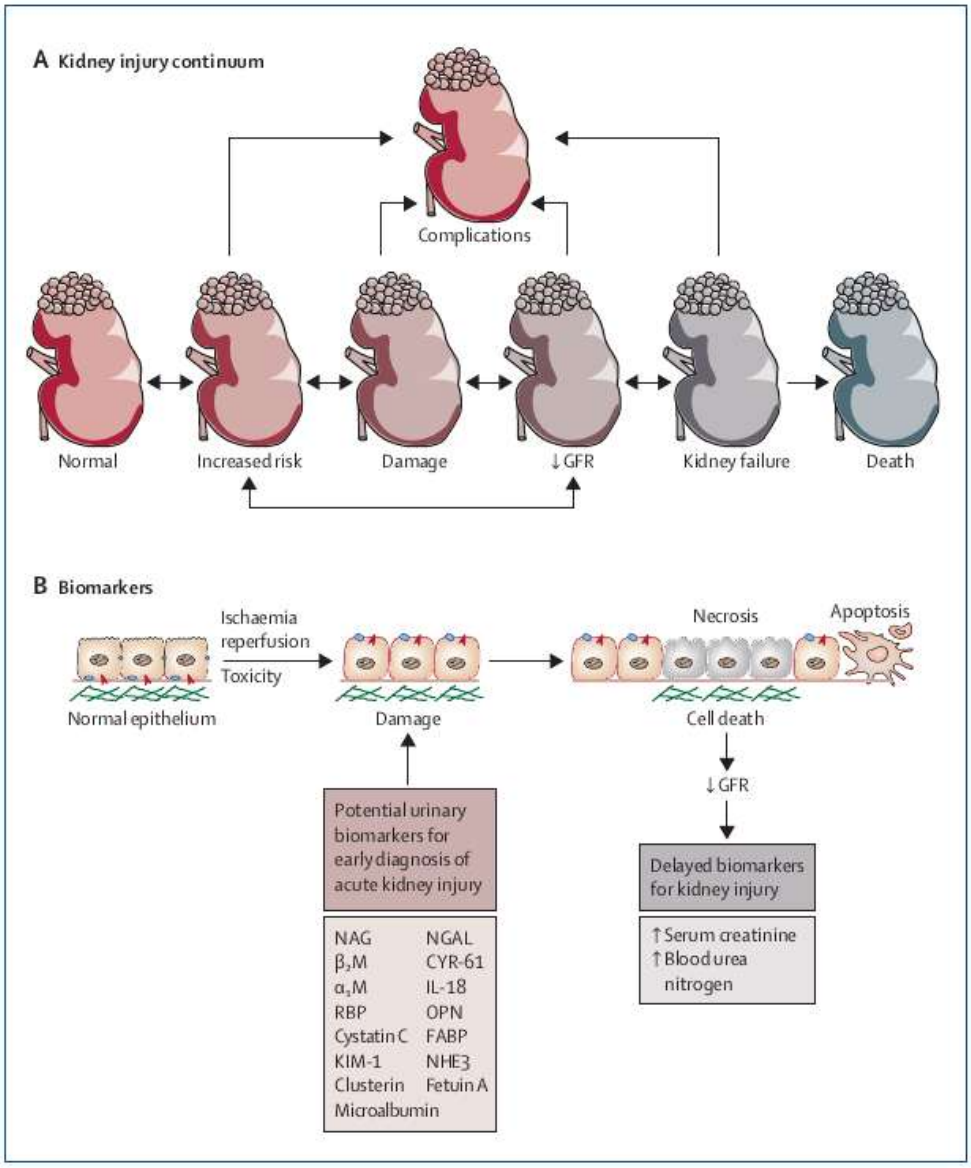


Figure2: acute kidney injury and its biomarkers :nag=n-acetyl-β-glucosaminidase. B2m=β_2-microglobulin. A_1m=α_1-microglobulin. Rbp=retinol-binding protein. Kim-1= kidney injury molecule-1. Ngal=neutrophil gelatinase-associated lipocalin. Cyr-61=cysteine-rich protein. Il-18=interleukin 18, opn=osteopontin. Fabp=fatty-acid-binding protein. Nhe3=sodium/hydrogen exchanger isoform. (a) continuum of acute kidney injury. Process can be divided into various reversible stages depending on severity of insult, starting from increased risk to damage followed by decrease in glomerular filtration rate (gfr), further progressing to kidney failure and death. (b) biomarkers of acute kidney injury. Traditionally used markers, such as blood urea nitrogen and serum creatinine, are insensitive, non-specific, and do not adequately differentiate between different stages of acute kidney injury. Delay in diagnosis prevents timely decisions about management of patients, including administration of putative therapeutic agents. Urinary biomarkers of acute kidney injury will facilitate earlier diagnosis and specific preventive and therapeutic strategies, ultimately resulting in fewer complications and improved outcomes.

Propofol on CPB

Induction of CPB reduced plasma concentration of propofol by hemodilution. Though the total propofol concentration was decreased, the unbound propofol concentration which is responsible for pharmacological activity remained the same.[30] Elimination of the drug is reduced during hypothermic CPB compared to normothermic CPB. [31,32] The clearance of propofol was reduced and the half life was prolonged in cardiac surgery with hypothermic CPB.[32] Schmidlin and colleagues measured the bispectral (BIS) index during hypothermic CPB and found that a propofol infusion rate of 1.6 - 2.4 mg/kg/hr maintained a medium BIS of 41. [33]

Sevoflurane on CPB

Volatile anaesthetics are administered to the oxygenator of CPB to provide anaesthesia and prevent intraoperative awareness.[34,35] During cardiopulmonary bypass the solubility of volatile anaesthetics are affected by hypothermia and crystalloid haemodilution. Hypothermia will increase anaesthetic blood solubility whereas haemodilution will reduce it.

The partition coefficient of sevoflurane in undiluted normothermic blood is 0.65. [36] The same partition coefficient may be assumed during CPB because of counterbalancing effect of hypothermia and haemodilution. Sevoflurane reached a steady state level from the 10^{th} to 20^{th} minute.

Hypothermia decreases anaesthetic requirements in a rectilinear fashion, such that a 10^0c decrease from 38^0c results in approximately 50% decrease in volatile anaesthetic requirement.[37] This is attributed to the increase in solubility of inhaled anaesthetics in the lipid membrane with lower temperature, resulting in larger concentrations of anaesthetics being available at a cellular level. Sevoflurane solubility increased by 5.4% of the solubility at 37^0c for each degree that equilibration temperature was reduced.[37]

Monitoring anaesthetic depth during cardiac surgery

The widely used clinical parameters such as pressure, rate, sweating and tears during the course of anaesthesia, cannot predict episodes of intraoperative awareness.

The EEG (electroencephalogram) can be considered to measure the depth of anaesthesia for several reasons. It represents cortical electrical activity derived from summated excitatory and inhibitory post synaptic activity, which are controlled and paced by subcortical thalamic nuclei. Cerebral blood flow and cerebral metabolism are related to the degree of the EEG activity.

BIS is a dimensionless index from 100 (awake) to 0 (electrical silence). BIS values between 40 and 60 indicate adequate general anaesthesia for surgery. Monitoring the depth of anaesthesia by the bispectral index facilitates the titration of the anaesthetic drugs during operation as well as assist in early recovery.[38]

BIS during cardiac surgery

BIS values always do not coincide with the clinically judged sedative hypnotic state. This could arise from an underlying pathophysiology of EEG cerebral function or because of short comings in the performance and design of the BIS monitors. Since BIS algorithms are based primarily on normothermic patients, the utility of BIS during hypothermic condition is unknown.

Dewandre et al studied BIS in patients undergoing CABG under mild hypothermic (30^{o}c) CPB. They concluded that BIS was a reliable monitor to assess the hypnotic effects of anaesthetics during normothermic or mild hypothermic CPB.[39] BIS was estimated to decrease by 1.12 BIS units for each degree celsius decrease in body temperature. Hypothermia produces a linear decrease in inhaled anaesthetic requirement. [40]

MATERIALS AND METHODS

Materials and methods

Approval was obtained from the institutional ethics committee. This project was funded by the institute. All patients were given information brochure regarding the surgery and anaesthesia and written informed consent was obtained from the patients before the study.

Inclusion criteria

Thirty six patients undergoing mitral valve replacement/repair, aortic valve replacement, double valve replacement/repair (combined mitral with aortic valve replacement or +/- tricuspid valve repair) were recruited for the study.

Exclusion criteria

The patients with the following conditions were excluded.

1. Patients undergoing emergency surgery.
2. Patients with infective endocarditis or any evidence of infection.
3. Patients on medication like vitamin C or vitamin E within 5 days of surgery.
4. Patient with serum creatinine > 2 mg/dl
5. Concomitant CABG surgery.
6. Patient with hepatic dysfunction.

The techniques of surgery and cardiopulmonary bypass followed existing institutional practice.

Premedication

The patient had oral diazepam 10 mg the night before and the day of surgery. Antihypertensive medications were continued except for ACE (angiotensin converting enzyme) inhibitors and AR (angiotensin receptor) blockers. All oral hypoglycemic medications were omitted on the morning of surgery. Digoxin & diuretics were continued till the day of surgery.

Randomization and allocation of study subjects into group.

The patients were randomly allocated into 2 groups using computerized random allocation table

Sevoflurane group (S-group) n = 18.

Sevoflurane – propofol group or the combination (SP –group) n =18.

Because of haemolysis, 5 patients were excluded from the study. After exclusion, the number of patients in each group was as follows.

S group n = 15

SP group n = 16

Total number of patients in the study = 31

Sevoflurane group (S group)

Anesthesia was induced with 6-8% (3- 4 mac) of sevoflurane with 6 l/min of oxygen. Midazolam 0.05 mg/kg and fentanyl 5 - 10 mcg/kg were supplemented.

Pancuronium 0.2 mg/kg or vecuronium 0.2 mg/kg was used for muscle relaxation. All patients had endotracheal intubation and controlled ventilation to maintain end-tidal carbon dioxide between 35 and 45 mm Hg.

Anaesthesia was maintained using sevoflurane to obtain 2- 3 volume percent (1-1.5 MAC). Morphine infusion was started at 40 mcg /kg/ hr after a bolus dose of 7.5-15 mg. Additional doses of neuromuscular relaxants were used as was necessary. Sevoflurane was titrated to maintain a BIS of less than 60.

Sevoflurane – propofol group

In this group anesthesia was induced with sleep dose of propofol and sevoflurane at 1-2 volume%. Midazolam 0.05 mg/kg and fentanyl at 5-10 mcg were used during induction. Pancuronium or vecuronium at 0.2 mg/kg was used for muscle relaxation. Anaesthesia was maintained using propofol at 50 -200 mcg/kg/hr and sevoflurane at 0.5-1.5 volume%. Morphine infusion was started at 40 mcg /kg/hr after a bolus dose of 7.5 mg-15mg. Propofol infusion and sevoflurane were titrated to maintain a BIS value less than 60.

Monitors

On arrival in the operation theatre preinduction monitors like ECG, pulse oximeter, invasive blood pressure monitoring were secured. Bispectral index electrodes (BIS) were attached before induction of anesthesia. All patients were monitored hemodynamically in accordance with the institutions standard cardiac anaesthetic protocol.

Cardiopulmonary bypass was carried out using a Sarns 9000 (Terumo corporation, Tokyo, Japan) CPB machine and affinity adult (Medtronics) oxygenator. Datex Ohmeda tec 7 vaporizer was used for sevoflurane delivery.

At the end of surgery all patients were transferred to the cardiothoracic intensive care unit. Analgesia, sedation, weaning of artificial ventilation and extubation followed normal institutional practice.

Sample collection

Blood sample for baseline NGAL estimation was drawn as soon as arterial cannula was inserted before anaesthetic induction. Blood sample was drawn for test NGAL estimation 4 hours after CPB. Blood urea nitrogen and serum creatinine values were measured preoperatively and on the 1^{st}, 2^{nd} and 5^{th} day after surgery. The blood samples for NGAL estimation were collected in an EDTA tube. In the biochemistry laboratory, plasma was separated using standard techniques. The prepared clinical specimen was frozen at -20^{0} c.

The NGAL rapid ELISA kit (kit 036 Bioporto diagnostics) was used. The specimen was tested as per the instructions provided in the kit. The kit components included the following.

1. 12 x 8 coated microwells + frame
2. 5 x sample diluent concentration
3. NGAL rapid calibrator 1-6. 0, 0.2, 2, 5, 20 ng/ml
4. 25 x wash solution concentration

5. HRP- conjugated NGAL antibody
6. A color–forming peroxidase substrate containing tetramethyl benzidine TMB substrate.
7. Stop solution
8. Polypropylene U- microwell plate.

Principle of assay

The assay is an ELISA performed in microwells coated with a monoclonal antibody against human NGAL. Bound NGAL is detected with a horse radish peroxidase conjugated monoclonal antibody and the assay is developed by incubation with a color forming substrate. The assay is a rapid 2 step procedure:

Step 1. Aliquots of calibrators, diluted sample and any control are incubated with HRP – conjugated detection antibody in the coated microwells. Only NGAL will bind to both coat and detection antibody. Unbound materials are removed by washing.

Step 2. A chromogenic peroxidase substrate containing tetra methyl benzidine is added to each test well. The HRP linked to the bound detection antibody reacts with the substrate to generate a colored product. The enzymatic reaction is stopped chemically, and the color intensity is read at 450 nm in an ELISA reader. The color intensity is a function of the concentration of NGAL originally added to each well. The results for the calibrators are used to construct a calibration curve from which the concentrations of NGAL in the test specimen are read.

OBSERVATIONS AND RESULTS

OBSERVATIONS AND RESULTS

The total number of patients initially enrolled in our study was 36. Of this 5 patients were excluded because of haemolysis of blood sample. Finally, the number of patients in sevoflurane – propofol group / combination group /SP group was 16 and number of patients in the sevoflurane group /S group was 15.

Total number of patients = 31,

SP group, n = 16,

S group, n = 15.

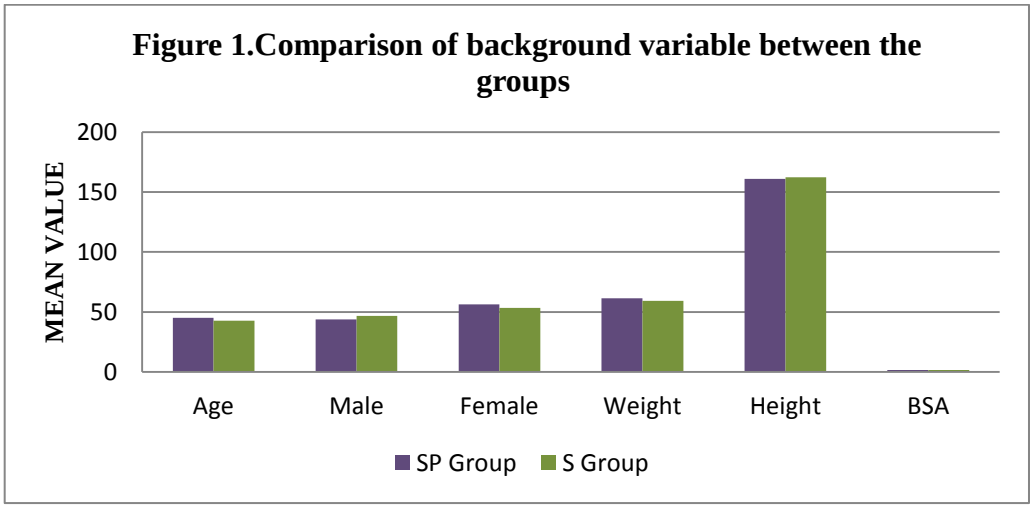
The demographic variables were comparable in both the groups. There were total of 14 male patients and 17 female patients in the study population. There were 7 male patients in both the groups and 9 female patients in the SP group and 8 female patients in the S group.

The mean (± standard deviation) age in years was 45.1 (±12.8) in the SP group and 42.7 (±10.1) in the S group. The height and weight were comparable with a body surface area (BSA) of 1.6 ± 0.2 in both the groups. These are given below.

TABLE 1. *Comparison of background variables between the 2 groups*

Variables		SP group	S group	Total	p value
Age		45.1 ± 12.8	42.7 ± 10.1	44 ± 11.5	0.570
Sex	Male	7 (43.8)	7 (46.7)	14 (45.2)	0.870
	Female	9 (56.3)	8 (53.3)	17 (54.8)	
Weight		61.3 ± 12.3	59.4 ± 9.2	60.4 ± 10.8	0.635
Height		160.8 ± 9	162.3 ± 10.4	161.5 ± 9.5	0.679
BSA		1.6 ± 0.2	1.6 ± 0.2	1.6 ± 0.2	0.841

Figure 1.Comparison of background variable between the groups



In the SP group, total of 6 patients underwent mitral valve replacement (MVR). Of this, 2 patients also underwent tricuspid valve annuloplasty (TVA). Mitral valve repair was done in 2 patients in the SP group. 3 patients had both aortic and mitral valve replacement (DVR) and 5 patients underwent aortic valve replacement (AVR) in the SP group.

In the S group, total of 8 patients underwent MVR. Of this, 1 patient had associated ASD closure and another TVA. 1 patient underwent MV repair in the S group. 4 patients had DVR and of this 1 patient underwent associated TVA. AVR was done in 2 patients in the S group. This is detailed in table 2.

TABLE 2. *Comparison between the groups - based on the procedure undertaken*

SURGERY	SP GROUP	S GROUP
AVR	5	2
MVR	4	6
MVR + ASD CLOSURE	0	1
MVR + TVA	2	1
MV REPAIR	2	1
DVR	3	3
DVR + TVA	0	1

Total of 2 patients were hypertensive in the study population, with 1 each in the SP and S group. 2 patients were diabetic and were in the SP group. 2 patients in the SP group and 4 in the S group were active smokers. Only 1 patient had history of bronchial asthma and was in the SP group. Total of 13 patients were in atrial fibrillation (AF) preoperatively. Of this, 8 patients with AF were in the SP group and 5 in the S group. 9 patients in SP group and 10 patients in the S group were in NYHA class III and 5 patients in the SP group and 7 patients in the S group were in NYHA class II. The ejection fractions were comparable between the groups with a mean (± standard deviation) of 62.3 (±10.2) in the SP group and 64.8 (±11.2) in the S group. The comparison between groups on the basis of preoperative variables is given in table 3.

TABLE 3. *Comparison between groups based on comorbidities*

COMORBIDITY		SP GROUP	S GROUP	TOTAL	P VALUE
HTN	NO	15 (93.8)	14 (93.3)	29 (93.5)	0.962
	YES	1 (6.3)	1 (6.7)	2 (6.5)	
DM	NO	14 (87.5)	15 (100)	29 (93.5)	0.157
	YES	2 (12.5)	0 (0)	2 (6.5)	
LUNG DISEASE	NIL	13 (81.3)	11 (73.3)	24 (77.4)	0.406
	SMOKING	2 (12.5)	4 (26.7)	6 (19.4)	
	ASTHMA	1 (6.3)	0 (0)	1 (3.2)	
AF	NO	8 (50)	10 (66.7)	18 (58.1)	0.347
	YES	8 (50)	5 (33.3)	13 (41.9)	
NYHA	CLASS II	7 (43.8)	5 (33.3)	12 (38.7)	0.552
	CLASS III	9 (56.3)	10 (66.7)	19 (61.3)	
EJECTION FRACTION		62.3 ± 10.2	64.8 ± 11.2	63.5 ± 10.6	0.523

The comparison between the groups based on the preoperative drug use is given below (table 4)

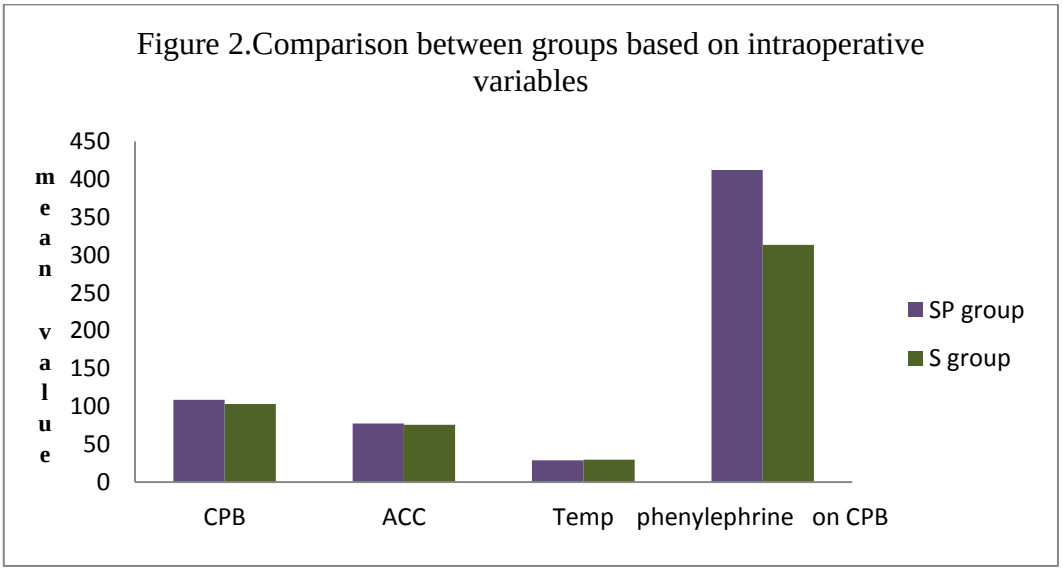
TABLE 4. *Comparison between the groups, based on preoperative drugs used*

Preop Drugs	SP GROUP	S GROUP
Diuretics	12	12
Digoxin	9	3
Beta Blocker	5	6
Calcium channel blocker	3	1
ACE inhibitor	2	0
O H A	1	0
Heparin	8	6
Statins	1	1
Amiodarone	0	2
Thyroxine	1	0
Eptoin	1	0

The cardiopulmonary bypass time and aortic cross clamp time were comparable. The temperature was maintained at 28 – 30^0 c during CPB in both groups. This is shown in table 5 and represented by bar diagram in figure 2.

TABLE 5.*Comparison between groups based on intraoperative variables*

VARIABLES	SP GROUP	S GROUP	TOTAL	P VALUE
CPB	108.8 ± 29.9	103.2 ± 37.8	106.1 ± 33.5	0.653
ACC	77.4 ± 26.8	75.6 ± 31.6	76.5 ± 28.8	0.867
TEMPERATURE	28.7 ± 1.3	29.7 ± 1.9	29.2 ± 1.7	0.080
PHENYLEPHRINE USE ON CPB	412.5 ± 206.2	313.3 ±285	1.12	0.274

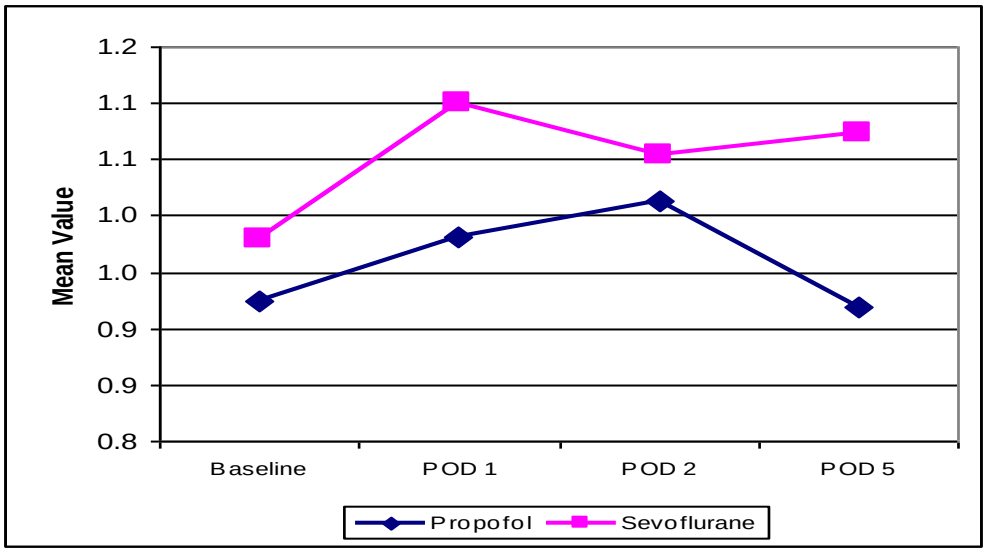


The baseline serum creatinine were 0.9 (± 0.2)mg /dl and 1.0 (±0.3)mg/dl in the SP group and S group respectively. The serum creatinine levels were comparable between the groups on post operative days (POD) 1, 2 and 5. The comparison is given in table 6 and represented by line diagram in figure 3.

TABLE 6. *Comparison of S.creatinine between groups*

S. CREATININE	SP		S		T	P
	MEAN	SD	MEAN	SD		
BASELINE	0.9	0.2	1.0	0.3	0.72	0.475
POD 1	1.0	0.3	1.1	0.3	1.14	0.264
POD 2	1.0	0.3	1.1	0.3	0.37	0.713
POD 5	0.9	0.3	1.1	0.7	0.87	0.392

FIGURE 3.*Comparison of S.creatinine between groups*



According to the AKIN criteria for determination of AKI, renal risk is defined as increase in serum creatinine level more than 0.3 mg/dl above the baseline value. Using this criteria, the number of patients with AKI were 2 (12.5%) and 5 (33.3%)

in the SP group and S group respectively on 1st post operative day. The number of patients with AKI were 4 (25%) in the SP group and 5 in the S group (33%) on postoperative day 2. The number of patients with AKI was less in the SP group, without reaching statistical significance. This is given in table 7.

Table 7. *Number of patients with renal risk based on serum creatinine (criteria - S. Creatinine>0.3mg%) : comparison between groups*

		SP GROUP		S GROUP		P#
		No: of patients	Percent	No: of patients	Percent	
POD1	No renal risk	14	87.5	10	66.7	0.170
	Renal risk	2	12.5	5	33.3	
POD2	No renal risk	12	75.0	10	66.7	0.454
	Renal risk	4	25.0	5	33.3	

: Fisher's Exact Test

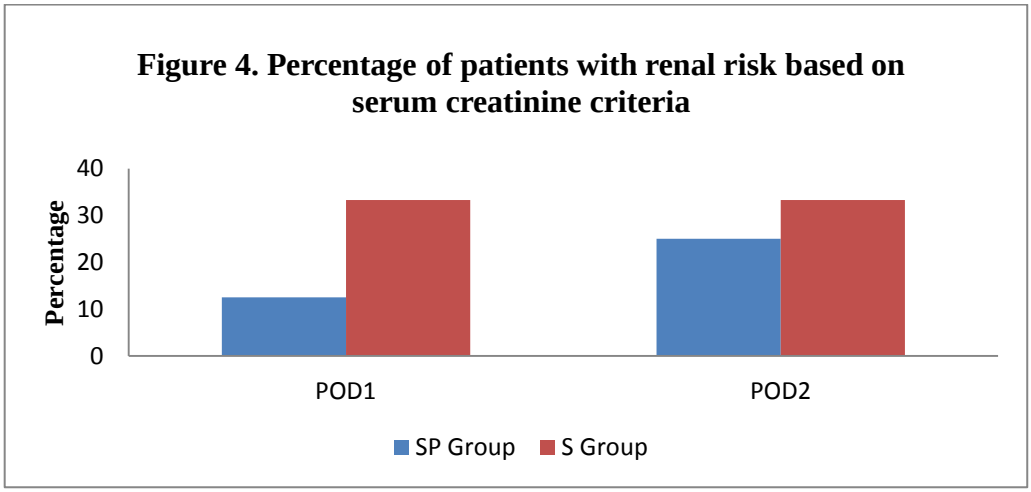
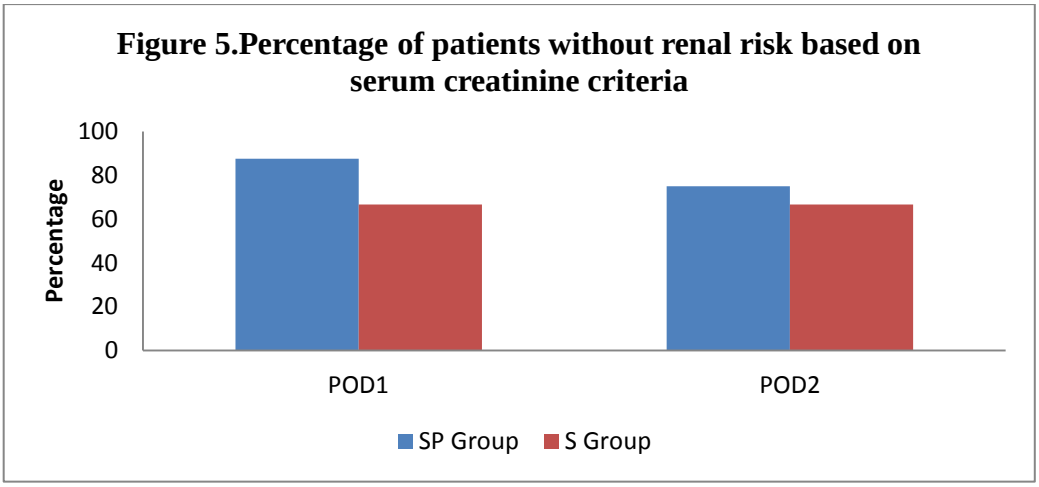


Figure 5.Percentage of patients without renal risk based on serum creatinine criteria



The AKI were also determined using creatinine clearance value. Creatinine clearance was calculated using Cockroft Gault formula.

Creatinine clearance = (140 – age) x s.creatinine / body weight x 72 for males.

The above value is multiplied by 0.85 for the calculation of creatinine clearance in females.

Patients with decrease in creatinine clearance of more than 25% from the baseline value were considered as having AKI. 2 patients in the SP group and 3 in the S group had AKI as per the above mentioned criteria on POD 1. 4 patients each in both the groups had AKI on POD 2 using creatinine clearance criteria. Fischer exact test was used and the values were comparable between the 2 groups. This is given in table 8.

Table 8. *Comparison of renal risk (criteria decrease in creatinine clearance more than 25%) based on group.*

		SP GROUP		S GROUP		P#
		Count	Percent	Count	Percent	
POD1	No renal risk	14	87.5	12	80.0	0.468
	Renal risk	2	12.5	3	20.0	
POD2	No renal risk	12	75.0	11	73.3	0.618
	Renal risk	4	25.0	4	26.7	

: fisher's exact test

There was significant increase in test NGAL value (taken 4 hours after CPB) compared to baseline NGAL value (taken before induction of anaesthesia) in both the groups

TABLE 9. *Change in NGAL from baseline in each group*

Group	Stage	Mean	SD	N	Mean difference	Paired t	p
SP	Baseline	107.7	31.9	16	87.4	5.48**	0.000
	Test	195.1	63.4	16			
S	Baseline	123.4	45.2	15	157.1	4.49**	0.001
	Test	280.5	138.7	15			

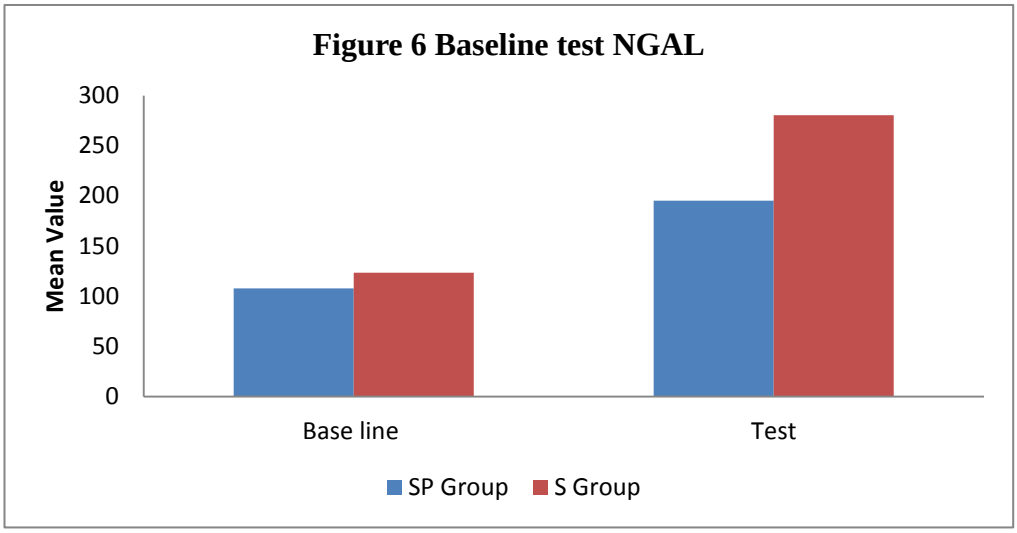
**: - significant at 0.01 level

Although the mean baseline NGAL value was lower in the SP group(107.7 ± 31.9) compared to S group (123.4 ± 45.2), the baseline NGAL values were comparable between the 2 groups as shown in the following table. But, there was a significant difference in the test NGAL values between the 2 groups. The mean NGAL value was 195.1± 63.4 in the SP group compared to 280.5 ± 138.7 in the S group. This is given in table 10 and figure 6.

Table 10. *Comparison between groups based on NGAL*

NGAL	SP		S		t	p
	Mean	SD	Mean	SD		
Baseline	107.7	31.9	123.4	45.2	1.12	0.270
Test	195.1	63.4	280.5	138.7	2.23*	0.034

*: - significant at 0.05 level



The mean of baseline NGAL values in the study population was calculated and 2 standard deviation above this value was taken as significant. We reached at a cut off NGAL value of 200 ng /ml, above which the patients were classified as having AKI. Using this criterion, the number of patients with AKI was determined. The number of patients with AKI was 6 (37.5%) in the SP group and 9 (60%) in the S group. Although the number of patients with AKI was lower in the SP group, it was not reaching statistical significance. This is given in table 11 and represented by bar diagram in figure 7.

Table 11. *Number of patients with renal injury based on NGAL level*

Renal injury	SP		S		χ^2	P
	No: of patients	Percent	No: of patients	Percent		
Baseline	0.0	0.0	1	6.7	1.1	0.294
Test	6.0	37.5	9	60.0	1.57	0.210

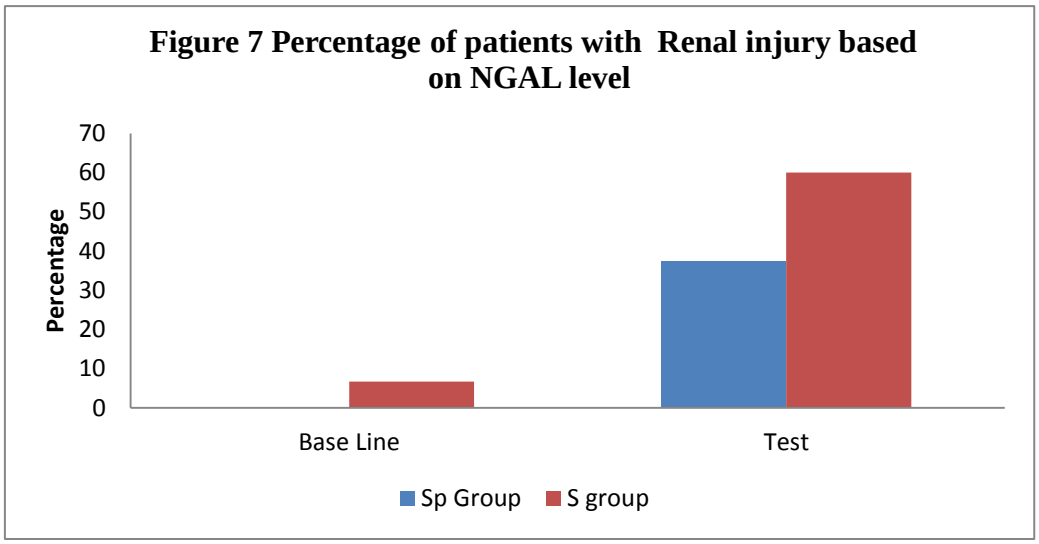


Table 12. *Comparison of renal injury based on NGAL level*

Renal injury	SP		S		χ^2	P
	No: of patients	Percent	No: of patients	Percent		
No renal injury	10	62.5	6	40	1.57	0.210
Renal injury	6	37.5	9	60		

Experimental event rate (EER) is the number of patients with renal injury divided by the total number of patients in the SP group. 37.5% of patients in the SP group had renal injury.

Control event rate (CER) is the number of patients with renal injury divided by the total number of patients in the control group (S group). 60% of patients in the S group had renal injury.

Relative risk or risk ratio is the risk of renal injury occurring in the SP group compared to S group. RR = EER/ CER. The relative risk is 0.63.

Absolute risk reduction is the absolute amount by which the intervention reduces the risk of outcome. ARR= CER –EER. The ARR is 22.5.

Relative risk reduction is the amount by which the risk of outcome is reduced in the SP group compared to S group. RRR= ARR/ CER= 0.38.

Odds ratio is the odds of outcome in the SP group divided by odds of outcome in the S group. An effective treatment will have an odds ratio of <1. In our study SP group had an odds ratio of 0.4.

Number needed to treat (NNT) is the number of patients need to have an intervention in order to prevent one person having the unwanted outcome. NNT = 0.04.

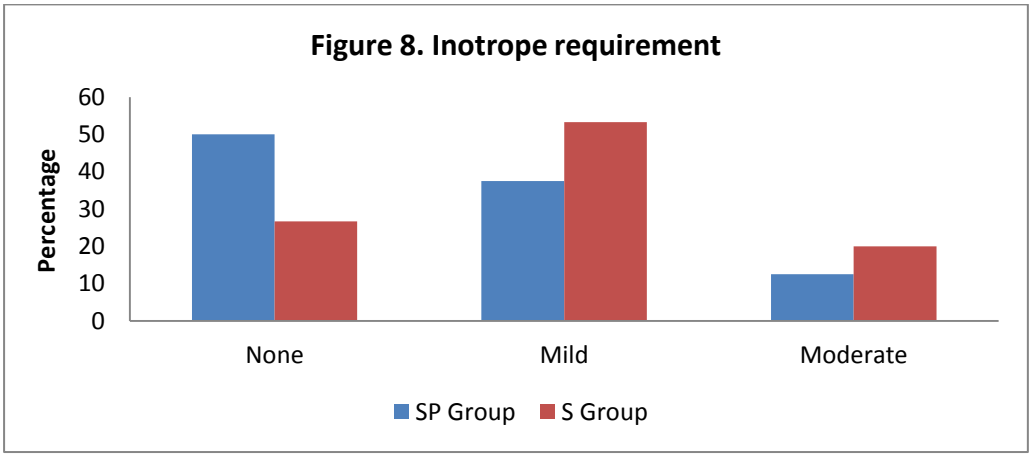
Table 13

EER	37.5
CER	60.0
RR	0.63
ARR	22.5
RRR	0.38
OR	0.40
NNT	0.04

We classified patients into 4 groups based on inotropic requirement – none, mild, moderate and severe. Patients requiring a single inotropic agent at low dose in the postoperative period were classified into the mild group. Patients requiring 2 inotropes or a single inotrope at a higher dose were classified into the moderate group. Patients requiring multiple inotropic supports and / or requiring IABP support for the maintenance of haemodynamic stability were classified into the severe group. 50% of patients in the combination group did not require inotropic support compared with 26.7% in the sevoflurane group. 6 patients in the combination group (SP) and 8 patients in the sevoflurane group required minimal inotropic support. 2 patients in the combination group and 3 in the sevoflurane group received moderate inotropic support. The comparison between the two groups on the basis of inotrope requirement is given in table 14 and figure 8.

Table 14. *Comparison of Inotrope requirement based on group*

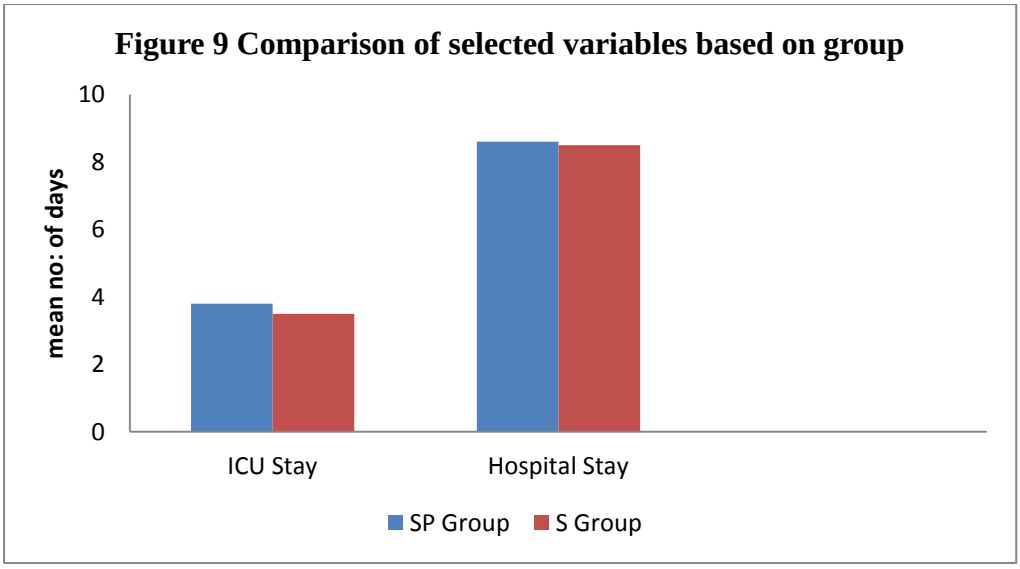
Inotrope requirement	SP group		S group		χ^2	p
	Count	Percent	Count	Percent		
None	8	50.0	4	26.7	1.79	0.409
Mild	6	37.5	8	53.3		
Moderate	2	12.5	3	20.0		



The duration of ICU stay and hospital stay were not significantly different in the 2 groups. This is shown in table 15 and figure 9.

Table 15. *Comparison of selected variables based on group*

	SP			S			t	p
	Mean	SD	N	Mean	SD	N		
ICU stay	3.8	0.8	16	3.5	0.7	15	1.04	0.307
Hospital stay	8.6	1.1	16	8.5	1.2	15	0.07	0.945



2 patients in the SP group and 3 patients in the S group received blood transfusion in the intraoperative period. 1 patient in the S group received transfusion of fresh frozen plasma. See the table below (table 16)

Table 16. *Comparison of IOP- blood transfusion used based on group*

IOP-PRBC	SP group		S group		p#
	Count	Percent	Count	Percent	
No	14	87.5	12	80.0	0.468
Yes	2	12.5	3	20.0	

: Fisher's Exact Test

Table 17.*Comparison of IOP FFP use based on group*

IOP FFP used	SP group		S group		p#
	Count	Percent	Count	Percent	
No	16	100.0	14	93.3	0.484
Yes	0	0.0	1	6.7	

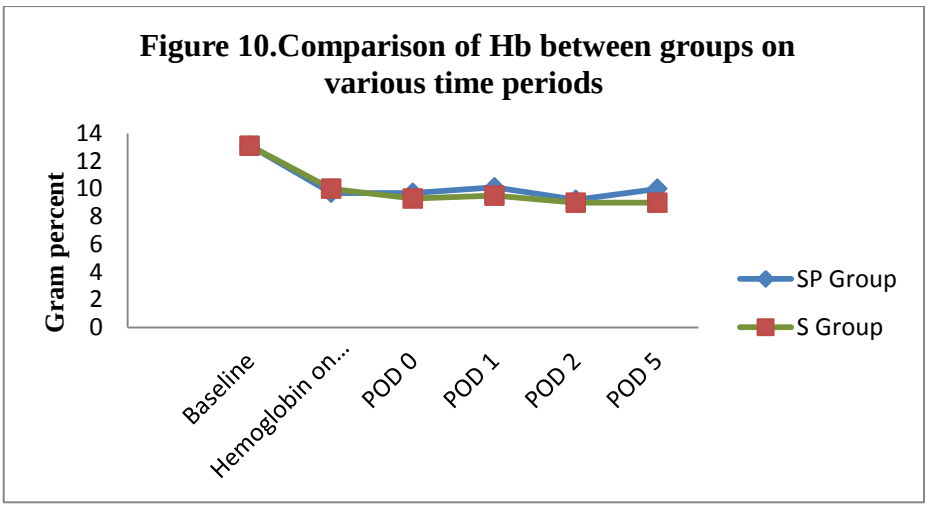
: Fisher's Exact Test

The baseline hemoglobin, lowest hemoglobin on CPB and hemoglobin on 0,1 and 2 post-operative days were comparable between the groups and is given in table 18 and represented by line diagram in figure 10.

Table 18. *Comparison of Hemoglobin (Hb) between groups*

HB	SP group		S group		t	p
	Mean	SD	Mean	SD		
Baseline	13.1	1.6	13.1	1.8	0.1	0.919
Hb on CPB	9.7	1.2	10	1.9	0.49	0.628
POD 0	9.7	1.6	9.3	1.8	0.58	0.564
POD 1	10.1	1.3	9.5	1.2	1.26	0.219
POD 2	9.2	1.0	9.0	1.1	0.58	0.569
POD 5	10.0	1.2	9.0	1.0	2.36*	0.025

*: - Significant at 0.05 level

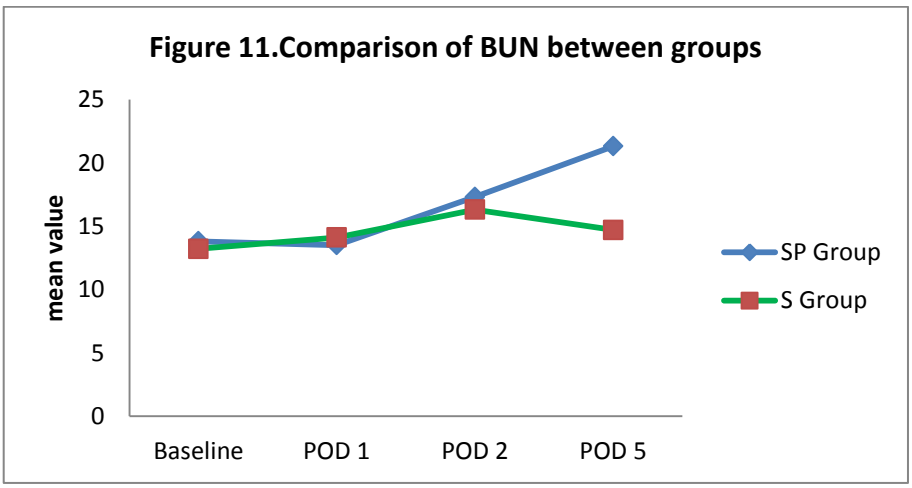


Baseline Blood urea nitrogen values and those on 1st and 2 nd post operative days were comparable. This is shown in table 19 and represented by line diagram in figure 11

Table 19. *Comparison of BUN between groups*

BUN	SP group		S group		t	p
	Mean	SD	Mean	SD		
Baseline	13.8	3.4	13.2	3.6	0.49	0.631
POD 1	13.5	3.6	14.1	3.0	0.48	0.636
POD 2	17.3	5.5	16.3	6.5	0.45	0.653
POD 5	21.3	7.3	14.7	4.8	2.92**	0.007

**: - Significant at 0.01 level



DISCUSSION

DISCUSSION

Acute kidney injury occurs in significant number of patients after cardiac surgery. It may reach up to 30% in patients undergoing valvular heart surgery. The risk factors associated with AKI include emergent surgery, valvular procedures, extended duration of CPB, infection, atrial fibrillation, low cardiac output state, need for inotropic agents, IABP and blood transfusion. Demographic risk factors associated with increased risk of AKI include advanced age, preoperative anemia, hypertension, diabetes, atherosclerotic disease, reduced LV function and COPD.

Inhalational anesthetic agents form an integral part of anesthesia for cardiac surgery, especially with evidence suggesting that they offer significant cardiac protection. Endothelial protection may play a central role in multiorgan protection by volatile anesthetics. It may precondition endothelial and smooth muscle cells with beneficial effect on wide variety of tissues including brain, spinal cord, liver and kidneys [(9)]. In a small experimental study, Lee et al argued that the volatile anesthetic effect mediated renal protection is not by the involvement of K-ATP channels, but by the reduction of necrotic and inflammatory renal cell death. They showed that nuclear transcription factor NF– kB translocation is significantly reduced in rats after volatile anesthetic treatment. They proposed this to be a component of renal protection with volatile anaesthetics.[(20)] Volatile anaesthetics reduces proinflammatory responses after renal ischemia reperfusion (I-R) injury.[20,41)]

Propofol limits oxidative injury in various organ tissues. Propofol reacts with lipid peroxyl radical to stable propofol phenoxyl radicals. It may also exert its antioxidant effect by scavenging peroxynitrate. Propofol acts as a scavenger of oxygen free radicals, decreasing lipid peroxidation in the liver, kidney, heart, and lung.[22] It can also inhibit the activity of neutrophils and calcium influx across plasma membrane. At clinically relevant concentrations, propofol can also suppress neutrophil chemotaxis, phagocytosis, and reactive oxygen species production.[23]

In an experimental animal model, Conde and colleagues compared the ability of propofol and sevoflurane to modulate inflammation and oxidative stress in kidney after aortic cross clamping. They found a lower concentration of myeloperoxidase, TNF alpha, IL-1b, superoxide anion, super oxide dismutase, NF-kB and inducible NOS activity in the propofol group. They came to the conclusion that compared with sevoflurane, propofol administration led to better modulation of markers of inflammation and decreased NF – kB expression.[21]

In another study, the effects of sevoflurane and propofol were compared with regard to the biochemical markers of hepatic and renal dysfunction, in patients undergoing coronary artery surgery. Lorsomradee et al showed that there is no difference between the 2 groups regarding renal biomarkers [42]. Saricaglu and colleagues, in a retrospective study in CABG patents, compared the effects of inhalational agents and propofol infusion on renal function. They could not find any significant difference between the groups.[43]

Our study showed that compared with sevoflurane, sevoflurane– propofol combination, resulted in a significant decrease in the renal biomarker NGAL level after surgery. Although the baseline NGAL values were slightly lower in the combination group (107.7± 31.9) compared to the sevoflurane group, there were no statistically significant difference in the baseline NGAL values between the 2 groups. There was a marked increase in the post-operative NGAL as compared to the baseline values in both the groups. The postoperative NGAL values were significantly lower in the combination group (195.1± 63.4) compared to the sevoflurane group (280.5± 138.7) with a p value of 0.034.

As decided previously, 2 standard deviation above the mean of baseline NGAL values was taken as significant. We reached at a cut off NGAL value of 200 ng/ml, above which the patients were classified as having AKI. In the combination group 37.5% (6/16) of patients had postoperative NGAL values above 200 ng/ml where as in the sevoflurane group 60% (9/15) had renal risk. But the number of patients with NGAL value above 200 ng/ml was not significantly different between the groups.

Julier et al[9] studied the effect of sevoflurane preconditioning in decreasing the biochemical markers for myocardial and renal dysfunction in CABG patients. Seventy two patients who were scheduled for CABG surgery under cardioplegic arrest were randomly assigned to preconditioning during the first 10 minutes of CPB with either placebo or 4 volume % sevoflurane. They concluded that sevoflurane preconditioning preserved renal function compared to placebo group,

as assessed by changes in the Cystatin C. In both the groups, anesthesia was induced with propofol or etomidate and maintained with propofol infusion. Sevoflurane was administered only during the initiation of CPB in their study group. The benefit observed in their study was attributed to the protective effect of sevoflurane on myocardium and kidney. But we know that propofol also exerts its beneficial effect on different organs including kidneys via free radical scavenging properties and anti-inflammatory properties.[9]

In our study, there was significant reduction in the post bypass NGAL level in Sevoflurane - Propofol (SP) combination group as compared to the Sevoflurane (S) group. This could be explained by the enhanced protective effect on renal injury during CPB offered by both sevoflurane and propofol through their distinct organ protective mechanisms. The beneficial effect on renal function in sevoflurane group shown in Julier's study could have been due to the enhanced protective effect offered by both propofol (the placebo in their study) and sevoflurane. Moreover, in our study, 60% of patients in Sevoflurane(S) group developed renal injury based on NGAL criteria as compared to only 37.5% patients in Sevoflurane-Propofol (SP) group. Thus an absolute risk reduction of renal injury of 22.5% was achieved in the SP group.

Our study failed to reveal any significant difference in serum creatinine levels between the groups on 1^{st}, 2^{nd}, and 5^{th} postoperative days. Although not statistically significant, fewer patients developed AKI (increase in serum creatinine >0.3 mg% from baseline) in Sevoflurane-Propofol group (2 out of 16

patients,12.5%) as compared to Sevoflurane group (5 out of 15 patients, 33.3%) on the 1st postoperative day, indicating a promising potential favouring the Sevoflurane-Propofol combination in reducing renal injury.

Our study has some positive strength. We prospectively recruited a homogeneous cohort of adults in whom renal ischaemia-reperfusion injury occured during valvular heart surgery. These patients did not have any difference in terms of comorbid variables such as atherosclerotic disease, diabetes, and nephrotoxin use, all of which can confound and hinder the identification of early biomarkers for ischaemic acute renal injury. All the patients started with normal kidney function and essentially normal concentrations of NGAL in the serum. NGAL is rapidly induced in kidney tubule cells in response to ischemic injury. Though its early appearance in the serum is independent of the glomerular filtration rate, it is highly predictive of a fall in glomerular filtration rate that might happen several days later. Our results indicate that NGAL is a powerful immediate early biomarker for acute renal injury.

The amount of anesthetic agent administered was titrated to maintain a BIS value between 35-60 during surgery. Since propofol is used in combination with sevoflurane we decided to use lower dose of propofol. It was shown that propofol exerts its antioxidant and anti-inflammatory effects even at low doses. Similarly the dosage of sevoflurane used on CPB was lower in the combination (SP) group compared to the sevoflurane (S) group. In the study conducted by Luccinetti and colleagues, they concluded that sevoflurane inhalation even at sedative

concentrations less than 1 volume% can provide endothelial protection against ischemia – reperfusion injury.[17]

Although BIS monitoring has been advocated for guiding anaesthetic requirement during CPB, BIS algorithms are primarily based on normothermic patients. It is unclear if BIS has the same relationship to hypnosis during hypothermic conditions. Dewandre et al studied BIS in patients undergoing CABG under mild hypothermic conditions. BIS was neither affected by surgical stimulation nor by CPB and mild hypothermia. They concluded that BIS was a reliable monitor to assess the hypnotic effects of anaesthetics during normothermic or mild hypothermic CPB.[39] We presume that BIS accurately measured the depth of anaesthesia in these patients.

Basic issues in the management of CPB that relate to the kidney involve the balance between oxygen supply and demand. Perfusion pressure and oxygen carrying capacity determines the supply, while hypothermia helps in modulating renal oxygen demands.[1]

Mean arterial pressures (MAP) were maintained above 60 mm Hg during CPB. This was in accordance with various studies that showed better outcomes with better hemodynamic control. Bolus doses of phenylephrine was used to maintain a MAP more than 60 mmHg. Although the requirement for phenylephrine was slightly higher in the combination group, it was not statistically significant (p value of 0.274).

In our study the temperature was maintained at 28 – 30^0 C during CPB. The base line hemoglobin was similar in both the groups (13.1 gm% in both groups). The hemoglobin on CPB were also comparable, with a hemoglobin value of 9.7gm% in the SP group and 10 gm % in the S group (p value of 0.628). 2 Patients in the combination group and 3 in the sevoflurane group received blood transfusion intraoperatively.

Even though the number of patients with inotropic requirement was less in the combination group, it was not significantly different. We classified patients into 4 groups based on inotropic requirement – none, mild, moderate and severe. Patients requiring a single inotropic agent at low dose (dobutamine at < 5mcg/kg/min, adrenaline at < 0.05 mcg/kg/min or noradrenaline at < 0.05mcg/kg/min) in the postoperative period were classified into the mild group. Patients requiring 2 inotropes or a single inotrope at a higher dose were classified into the moderate group. Patients requiring multiple inotropic supports and / or requiring IABP support for the maintenance of haemodynamic stability were classified into the severe group. 50% of patients in the combination group did not require inotropic support compared with 26.7% in the sevoflurane group. 6 patients in the combination group and 8 patients in the sevoflurane group required minimal inotropic support. 2 patients in the combination group and 3 in the sevoflurane group received moderate inotropic support.

In our study we found that the duration of ICU stay and hospital stay was not influenced by the choice of anesthetic agents.

We observed that there is 30-60% incidence of AKI in patients undergoing valvular heart surgery as shown by the rise in serum NGAL levels in post bypass period. There was significant reduction in the rise of post bypass NGAL levels in patients anesthetized with combination of sevoflurane and propofol combination as compared to sevoflurane alone in immediate post-operative period (4 hours after CPB). But there was no statistical difference in terms of number of patients developing AKI, AKI according to creatinine levels in 1^{st}, 2^{nd}, and 5^{th} postoperative days. So further studies with a larger sample size may be needed to validate or refute our findings.

LIMITATIONS

LIMITATIONS

An important limitation of our study was that it was performed in patients at a comparatively low risk of postoperative renal dysfunction, as patients with preoperative creatinine greater than 2 mg% were excluded. Consequently this is not an outcome study, as the incidence of hemodialysis was zero, as expected.

Another limitation was that this was a pilot study for which no exact power analysis concerning the main variable (serum NGAL) was possible. Moreover, only a single time point (4hrs after CPB) post bypass NGAL level was measured to determine the incidence of AKI. Serial levels at different time points would have been revealed the precise extent of NGAL level after CPB.

Although we could elicit a significant decrease in renal dysfunction in the post-operative period in the SP group by NGAL level, but the number of patients with renal injury based on NGAL criteria was not significantly different between the two groups. It could be because of the smaller sample size, that we were not able to obtain a significant reduction in the number of patients with renal injury in the SP group. Larger studies may be required to delineate the difference between the groups.

We observed a comparable effect of sevoflurane and propofol on renal function in previous studies. In our study, we compared the renal protective effect between sevoflurane - propofol group and sevoflurane group. There was no control group for propofol.

CONCLUSION

CONCLUSION

1. There was significant reduction in the rise of post bypass NGAL levels in patients anesthetized with combination of sevoflurane and propofol as compared to sevoflurane alone in immediate post-operative period (4 hours after CPB). This could be because of the enhanced protective effect on renal injury during CPB offered by both sevoflurane and propofol through their distinct organ protective mechanisms. Further studies with a larger sample size may be needed to validate or refute our findings.

2. Mean arterial pressures were maintained above 60 mm Hg in all patients in our study population. Phenylephrine was used to maintain mean arterial pressures above 60 mm Hg. Even though the total amount of phenylephrine used was more in the combination group, it was comparable statistically.

3. Even though our primary focus was on renal function, we also looked into the number of patients with inotropic requirement. Inotropic requirement was less in the combination (sevoflurane propofol) group, but it was comparable.

4. The duration of ICU stay and hospital stay was not influenced by the choice of anesthetic agents.

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ANNEXURES

CONSENT FORM

Title of the study:

COMPARISON OF THE EFFECT OF SEVOFLURANE VERSUS SEVOFLURANE PROPOFOL COMBINATION ON RENAL FUNCTION IN PATIENTS UNDERGOING VALVULAR HEART SURGERY : A PROSPECTIVE RANDOMIZED STUDY.

Study number:

You are being requested to participate in a study to evaluate the effects of the anaesthetic agents - sevoflurane and sevoflurane propofol combination on function of the kidneys with serum NGAL as a biomarker. We hope to include about 60 people from this hospital in this study.

What is valvular heart surgery?

You are going to have a surgery on your heart to replace the diseased valve in the body to make the blood flow forward and uninterrupted.

Why is sevoflurane and propofol used for anaesthesia?

Anaesthesia is administered during all surgical procedures so that

- You are asleep during the procedure,
- You are unaware of the procedure, and
- You remain pain free during the surgery

Sevoflurane is a anaesthetic vapour administered along with oxygen during surgery so that you remain asleep, unaware and pain free.

Propofol is an anesthetic agent that is administered through your veins during surgery.

After the procedure, these anesthetic agents are discontinued and you will become awake slowly.

Why are we doing the study?

One of the complications of valve surgery is kidney dysfunction.Sevoflurane and propofol are drugs routinely used in anesthetic practice. In addition to being anesthetic agents they exert a beneficial effect on most of the organs including kidneys. This study is undertaken to determine whether the combination of sevoflurane and propofol as anesthetic agents provide more beneficial effect on kidneys

than sevoflurane alone.

How are these Drugs titrated ?

These drugs are titrated with the help of bispestral index monitor with electrodes attached to the forehead. This monitor gives us an idea about the depth of anesthesia. Depth of anesthesia will be maintained between 40 -60 to maintain an adequate level.

Is propofol and sevoflurane safe to be used for valvular surgery ?

The anaesthetic agents propofol and sevoflurane are routinely used during anaesthesia for valvular surgery and are considered safe agents, Although they cause minimal depression of the blood pressure they are helpful in controlling the cardiovascular reflex responses during surgical stress.

How is renal dysfunction detected ?

Renal dysfunction will be detected with the help of a biomarker present in blood known as NGAL. Blood will be withdrawn from you at the time of insertion of intravenous cannula. This is kept as baseline sample. Another sample will be withdrawn 6 hours after surgery .

Can you withdraw from this study after it starts?

Your participation in this study is entirely voluntary and you are also free to decide to withdraw permission to participate in this study. If you do so, this will not affect your usual treatment at this hospital in any way.

What will happen if you develop any study related injury?

We do not expect any injury to happen to you but if you do develop any side effects or problems due to the study, these will be treated at no cost to you. We are unable to provide any monetary compensation, however.

Will you have to pay for the study?

No.

Will your personal details be kept confidential?

The results of this study will be published as thesis and in a medical journal but you will not be identified by name in any publication or presentation of results. However, your medical notes may be reviewed by people associated with the study, without your additional permission, should you decide to participate in this study.

If you have any further questions, please ask

Dr Reshmi Liza Jose TEL:9048265566

Dr Unnikrishnan K P - Additional Professor, Department of Anaesthesia

Ph: 9446177521

DECLARATION

I , _____ ,

Participant's name: Date of Birth / Age (in years)

son/daughter of _____ (Please tick boxes) •

Declare that I have read the above information provide to me regarding the study:

A comparison of sevoflurane versus sevoflurane propofol combination on renal function in patients undergoing valvular heart surgery - A Prospective Randomized study.

and have clarified any doubts that I had. [ ]

• I also understand that my participation in this study is entirely voluntary and that I am free to withdraw permission to continue to participate at any time without affecting my usual treatment or my legal rights [ ]

• I also understand that neither I, nor my doctors, will have any choice of whether I will get Sevoflurane or sevoflurane propofol combination during the conduct of the study. [ ]

• I understand that the study staff and institutional ethics committee members will not need my permission to look at my health records

even if I withdraw from the trial. I agree to this access [ ]

• I understand that my identity will not be revealed in any information released to third parties or published [ ]

• I voluntarily agree to take part in this study [ ]

• I received a copy of this signed consent form [ ]

Name:
Signature:
Date:

Name of witness:
Relation to participant:

Date:

(Person Obtaining Consent)

I attest that the requirements for informed consent for the medical research project described in this form have been satisfied. I have discussed the research project with the participant and explained to him or her in nontechnical terms all of the information contained in this informed consent form,including any risks and adverse reactions that may reasonably be expected to occur. I further certify that I encouraged the participant to ask questions and that all questions asked were answered.

Dr Reshmi Liza Jose (PI):
Dr Unnikrishnan K.P (Co – PI):

_____ _____
Name and Signature of Person Obtaining Consent

സമ്മതപത്രം

പഠന പദ്ധതിയുടെ പേര്?

ഹൃദയത്തിന്റെ വാൽവുകൾക്ക് തകരാർ വന്നിട്ടുള്ള രോഗികളിൽ ഹൃദയ വാൽവ് മാറ്റിവയ്ക്കൽ ശസ്ത്രക്രിയ ചെയ്യുമ്പോൾ അവരുടെ വൃക്കയുടെ പ്രവർത്തനങ്ങളിൽ സെവോഫ്ളൂറേൻ എന്ന മരുന്നും സെവോഫ്ളൂറേൻ -പ്രോപോഫോൾ എന്നീ മരുന്നുകൾ ഒരുമിച്ചുപയോഗിക്കുമ്പോൾ ഉണ്ടാകുന്ന പ്രതിഫലനങ്ങളുടെ താരതമ്യ പഠനം.

പഠനത്തിന് വിധേയമാക്കപ്പെടുന്നവരുടെ എണ്ണം

ഈ പ്രത്യേക ഹൃദയശസ്ത്രക്രിയ സമയത്ത് മയക്കം നൽകുന്നതിന് ആവശ്യമായ സെവോഫ്ളൂറേൻ എന്ന മരുന്നും സെവേഫ്ളൂറേൻ പ്രോപോഫോൾ എന്നീ മരുന്നുകളുടെ ഒരുമിച്ചുള്ള ഉപയോഗം വൃക്കകളുടെ പ്രവർത്തനങ്ങളിൽ വരുത്തുന്ന ഗുണപരമായ വ്യതിയാനങ്ങളുടെ ഒരു താരതമ്യ പഠനം നടത്തുവാൻ ഞങ്ങൾ ഉദ്ദേശിക്കുന്നു. ഈ പാഠ്യപദ്ധതിയിൽ പങ്കാളിയാകുവാൻ നിങ്ങളോട് വിനീതമായി അഭ്യർത്ഥിക്കുകയാണ്. ഈ ആശുപത്രിയിൽ നിന്നും 60 രോഗികളെ ഉൾപ്പെടുത്തിക്കൊണ്ടുള്ള ഒരു പഠനം നടത്തുവാൻ ഞങ്ങൾ ആഗ്രഹിക്കുന്നു.

വാൽവ് ശസ്ത്രക്രിയ എന്താണ്?

താങ്കളുടെ ഹൃദയത്തിന്റെ വാൽവുകൾക്ക് കേടുപാടുകൾ സംഭവിച്ചിരിക്കുന്നതിനാൽ ഈ വാൽവുകൾ മാറ്റിവയ്ക്കേണ്ടത് രക്തചംക്രമണം സാധാരണ നിലയിൽ ആകുവാൻ ആവശ്യമാണ്.

സെവോഫ്ളൂറേൻ, പ്രോപോഫോൾ എന്നീ മരുന്നുകൾ മയക്കം നൽകുന്നതിന് ഉപയോഗിക്കുന്നത് എന്തുകൊണ്ടാണ്?

എല്ലാ ശസ്ത്രക്രിയകൾക്കും മരുന്നു നല്കി രോഗികളെ ബോധം കെടുത്താറുണ്ട്. ഇവയുടെ ഉപയോഗം മൂലം.

- ശസ്ത്രക്രിയ സമയത്ത് നിങ്ങൾ ഉറക്കമായിരിക്കും
- എന്താണ് സംഭവിക്കുന്നത് എന്നതിനെപ്പറ്റി നിങ്ങൾ ബോധവാനായിരിക്കുകയില്ല
- ശസ്ത്രക്രിയ സമയത്ത് നിങ്ങൾക്ക് വേദന അനുഭവപ്പെടില്ല.

വാതകരൂപത്തിലുള്ള സെവോഫ്ളൂറേൻ എന്ന മരുന്ന് ഓക്സിജൻ കലർത്തി നിങ്ങളുടെ ശ്വാസകോശത്തിൽ കടത്തിവിടുമ്പോൾ നിങ്ങൾ ഉറങ്ങുകയും, വേദന

അനുഭവപ്പെടാതിരിക്കുകയും, ചുറ്റുപാടുകളെപ്പറ്റി ബോധവാനല്ലാതാവുകയും ചെയ്യുന്നു.

പ്രോഫോഫോൾ എന്ന മരുന്ന് നിങ്ങളുടെ അശുദ്ധ രക്തം വഹിക്കുന്ന രക്തധമനികളിൽ കൂടി നിങ്ങളുടെ ശരീരത്തിലേയ്ക്ക് കടത്തിവിടുകയും അതിന്റെ പ്രവർത്തനഫലമായി നിങ്ങൾ ഉറങ്ങുകയും ചെയ്യുന്നു. ശസ്ത്രക്രിയയ്ക്ക് ശേഷം ഈ മരുന്നുകളുടെ ഉപയോഗം നിറുത്തുമ്പോൾ പതുക്കെ നിങ്ങൾ ബോധവാനാകുന്നു.

ഈ പഠനം എന്തിനുവേണ്ടിയാണ് നമ്മൾ നടത്തുന്നത്?

വൃക്കകളുടെ അപര്യാപ്തമായ പ്രവർത്തനം ഹൃദയശസ്ത്രക്രിയയുടെ ഒരു പാർശ്വഫലമാണ്. സെവോഫ്ളൂറേൻ, പ്രോപോഫോൾ എന്നീ മരുന്നുകൾ മയക്കം നൽകുന്നതിനായി സാധാരണമായി ഉപയോഗിക്കുന്നതാണ്. മയക്കം നൽകുന്നതിന് പുറമേ ഈ മരുന്നുകൾ നമ്മുടെ വൃക്കകളുടെയും മറ്റ് അവയവങ്ങളുടെയും പ്രവർത്തനങ്ങളിൽ ഗുണകരമായ ഒരു ഫലമുണ്ടാക്കുന്നതായി പഠനങ്ങൾ സാക്ഷ്യപ്പെടുത്തുന്നു. സെവോഫ്ളൂറേൻ - പ്രോപോഫോൾ എന്നീ മരുന്നുകൾ ഒരുമിച്ചുപയോഗിക്കുമ്പോൾ വൃക്കകളുടെ പ്രവർത്തനങ്ങളെ അവ എത്രമേൽ മെച്ചമായി സ്വാധീനിക്കുന്നു എന്ന് അറിയുവാനുള്ള പഠനമാണിത്.

ഈ മരുന്നുകളുടെ അളവ് എങ്ങനെയാണ് നിശ്ചയിക്കപ്പെടുന്നത്?

നെറ്റിയിൽ പതിപ്പിക്കുന്ന ഇലക്ട്രോഡുകൾ ഉപയോഗിച്ചുള്ള ബൈസപെക്ട്രൽ ഇൻഡക്സ് മോണിറ്റർ എന്ന ഉപകരണത്തിന്റെ സഹായത്തോടുകൂടിയാണ് ഈ മരുന്നുകളുടെ തോത് നിർണ്ണയിക്കുന്നത്. ഈ മോണിറ്റർ നമ്മൾക്ക് മയക്കത്തിന്റെ അളവിനെക്കുറിച്ച് ഒരു ധാരണ നൽകും.

സെവോഫ്ളൂറേൻ, പ്രോപോഫോൾ എന്നീ മരുന്നുകൾ ഈ ശസ്ത്രക്രിയയ്ക്ക് സുരക്ഷിതമായി ഉപയോഗിക്കുവാൻ സാധിക്കുന്നവയാണോ?

സെവോഫ്ളൂറേൻ, പ്രോപോഫോൾ എന്നീ മരുന്നുകൾ ഹൃദയശസ്ത്രക്രിയയ്ക്ക് പതിവായി ഉപയോഗിക്കുന്നതും, സുരക്ഷിതമാണെന്ന് കണ്ടിട്ടുള്ളതുമാണ്. ഈ മരുന്നുകൾ രക്തസമ്മർദ്ദത്തിൽ നേരിയ കുറവ് ഉണ്ടാക്കാൻ സാധ്യതയുണ്ടെങ്കിലും ശസ്ത്രക്രിയ മൂലം ഉണ്ടാകുന്ന കാർഡിയോ വാസ്കുലർ സ്ട്രസ്സ് റെസ്പോൺസസിനെ നിയന്ത്രിക്കാൻ വളരെ സഹായിക്കുന്നു.

വൃക്കകളുടെ അപര്യാപ്തമായ പ്രവർത്തനം കണ്ടുപിടിക്കുന്നതിനായി എന്തു പരിശോധനയാണ് നടത്തുക?

വൃക്കകളുടെ അപര്യാപ്തമായ പ്രവർത്തനം കണ്ടുപിടിക്കുന്നതിനായി രക്തത്തിലുള്ള NGAL എന്ന രാസവസ്തുവിന്റെ അളവ് നിർണ്ണയിക്കപ്പെടുന്നു.

ശസ്ത്രിക്രിയയ്ക്ക് മുമ്പായി രക്തധമനികളിൽ ഇടുന്ന ഇൻട്രാവീനസ് കാനുലയിൽ നിന്ന് രക്തം (2ml) ശേഖരിക്കുന്നു. ശസ്ത്രക്രിയയ്ക്ക് ആറു മണിക്കൂർ ശേഷം പരിശോധനയ്ക്കായി വീണ്ടും രക്തം ശേഖരിക്കുന്നു.

ഈ പഠനം തുടങ്ങിയതിനുശേഷം ഇതിൽ നിന്നും പിന്മാറുവാൻ നിങ്ങൾക്ക് സാധിക്കുമോ?

നിങ്ങളുടെ തീർത്തും സ്വമേധയാലുള്ള തീരുമാനത്തിലൂടെയാണ് ഈ പഠനത്തിൽ പങ്കുചേരുന്നതും, അതുപോലെ തന്നെ ഇതിൽ താൽപര്യമില്ലെങ്കിൽ നിങ്ങൾക്ക് പിന്മാറാവുന്നതുമാണ്. പിന്മാറിയാലും ഈ ആശുപത്രിയിലെ നിങ്ങളുടെ പതിവുപോലെയുള്ള ചികിത്സയെ അത് ഒരു വിധത്തിലും ബാധിക്കുകയില്ല.

ഈ പഠനം മൂലം നിങ്ങളുടെ ആരോഗ്യത്തിന് ദോഷകരമായ ഫലങ്ങൾ ഉണ്ടാവുകയാണെങ്കിൽ എന്തുചെയ്യും?

ഈ പഠനം മൂലം നിങ്ങളുടെ ആരോഗ്യത്തിന് യാതൊരു ദോഷഫലങ്ങളും ഉണ്ടാകുമെന്ന് പ്രതീക്ഷിക്കുന്നില്ല. എന്നിരുന്നാലും എന്തെങ്കിലും പാർശ്വഫലങ്ങൾ ഉണ്ടായാൽ അതിനുള്ള ചികിത്സ നിങ്ങൾക്ക് ചിലവുകളൊന്നുമില്ലാതെ തന്നെ ഇവിടെ നൽകുന്നതാണ്. ധനസഹായങ്ങളൊന്നും നൽകാൻ സാധിക്കുകയില്ല.

ഈ പഠനത്തിന് നിങ്ങൾക്ക് എന്തെങ്കിലും ചിലവുകൾ വഹിക്കേണ്ടിവരുമോ?

ഇല്ല

നിങ്ങളുടെ സ്വകാര്യ വിവരങ്ങൾ രഹസ്യമായി സൂക്ഷിക്കുമോ?

ഈ പഠനഫലമായി കിട്ടുന്ന അന്തിമ വിവരങ്ങൾ ഒരു പ്രബന്ധമായിട്ടും, അതുപോലെ മെഡിക്കൽ ജേർണലുകളിലും പ്രസിദ്ധീകരിക്കും. എന്നാൽ നിങ്ങളുടെ പേരു വിവരങ്ങളും മറ്റും രഹസ്യമായി തന്നെ സൂക്ഷിക്കും. എങ്കിലും ഈ പഠനവുമായി ബന്ധപ്പെട്ട ആളുകൾക്ക്, നിങ്ങളുടെ രോഗവിവരങ്ങൾ, ഇനി ഒരു സമ്മതം കൂടാതെ തന്നെ പുന:പരിശോധന നടത്താവുന്നതാണ്.

പുതിയതായി നിങ്ങൾക്ക് എന്തെങ്കിലും ചോദിക്കുവാനുണ്ടെങ്കിൽ, താഴെ പറയുന്ന ഡോക്ടർമാരെ സമീപിക്കാവുന്നതാണ്.

ഡോക്ടർ രശ്മി ലിസ ജോസ് (ഫോൺ: 9048265566)

ഡോക്ടർ ഉണ്ണിക്കൃഷ്ണൻ. കെ.പി., അനസ്തേഷ്യ വിഭാഗം അഡീഷണൽ പ്രൊഫസർ. ശ്രീചിത്തിര തിരുനാൾ ഇൻസ്റ്റിറ്റ്യൂട്ട് ഓഫ് മെഡിക്കൽ സയൻസസ് ആന്റ് ടെക്നോളജി (ഫോൺ: 9446177521)

അല്ലെങ്കിൽ ഇ-മെയിൽ അഡ്രസ്സ് - ഹശ്വമഷീലെ@രെശോേെ.മേര.ശി

പ്രഖ്യാപനം

ഞാൻ . . . .(രോഗിയുടെ പേര്) . . . . . .(ജനന തീയതി) . . . . . .(വയസ്സ് വർഷങ്ങളിൽ) . . . . . യുടെ പുത്രൻ/പുത്രി

(താഴെ കാണുന്ന ബ്രാക്കറ്റുകളിൽ □അടയാളം ഇടുക)

ഈ പ്രത്യേക പഠനത്തെക്കുറിച്ച് മുകളിൽ പറഞ്ഞിരിക്കുന്ന വിശദവിവരങ്ങൾ വായിച്ച് മനസ്സിലാക്കിയയതായി പ്രഖ്യാപിക്കുന്നു.

ഹൃദയത്തിന്റെ വാൽവുകൾക്ക് തകരാറ് വന്നിട്ടുള്ള രോഗികളിൽ ഹൃദയ വാൽവ് മാറ്റിവയ്ക്കൽ ശസ്ത്രക്രിയ ചെയ്യുമ്പോൾ അവരുടെ വൃക്കയുടെ പ്രവർത്തനങ്ങളിൽ സെവോഫ്ളൂറേൻ എന്ന മരുന്നും സെവോഫ്ളൂറേൻ -പ്രോപോഫോൾ എന്നീ മരുന്നുകൾ ഒരുമിച്ചുപയോഗിക്കുമ്പോൾ ഉണ്ടാകുന്ന പ്രതിഫലനങ്ങളുടെ താരതമ്യ പഠനം.

- എനിക്കുണ്ടായിരുന്ന എല്ലാ സംശയങ്ങളും ചോദിച്ചു മനസ്സിലാക്കിയിട്ടുണ്ട് ( )
- ഈ പഠനത്തിലുള്ള എന്റെ പങ്കാളിത്തം തികച്ചും എന്റെ സ്വമനസ്സാലെയുള്ള തീരുമാനമാണെന്നും, എന്റെ ചികിത്സയെ പ്രതികൂലമായി ബാധിക്കാതെയും, എന്റെ നിയമപരമായ ആവശ്യങ്ങൾക്ക് കോട്ടം തട്ടാതെയും, എപ്പോൾ വേണമെങ്കിലും എനിക്ക് ഇതിൽ നിന്നും പിന്മാറാൻ സാധിക്കുമെന്നും ഞാൻ മനസ്സിലാക്കുന്നു.
  ( )
- ഈ പഠനം നടക്കുന്ന സമയത്ത് എനിക്ക് സെവോഫ്ളൂറേൻ എന്ന മരുന്നാണോ അതോ സെവോഫ്ളൂറേൻ പ്രൊപോഫോൾ എന്നീ മരുന്നുകൾ ഒരുമിച്ച് ഉപയോഗിക്കുകയാണോ ചെയ്യുന്നത് എന്ന് തിരഞ്ഞെടുക്കുവാനുള്ള അവകാശം, എനിക്കോ എന്റെ ഡോക്ടർമാർക്കോ ഇല്ല എന്നുള്ളതും ഞാൻ മനസ്സിലാക്കുന്നു.
  ( )

- ഈ പാഠ്യപദ്ധതിയിൽ നിന്ന് പിന്മാറിയാലും, എന്റെ അനുവാദമില്ലാതെ തന്നെ ഈ പഠനം നടത്തുന്ന ഡോക്ടർമാർക്കും, ഈ സ്ഥാപനത്തിലെ എത്തിക്കൽ കമ്മിറ്റി അംഗങ്ങൾക്കും എന്റെ രോഗവിവരരേഖകൾ പരിശോധിക്കാവുന്നതാണെന്ന് ഞാൻ മനസ്സിലാക്കുന്നു. ഇതിന് എനിക്ക് സമ്മതമാണ്. ( )
- എന്നെക്കുറിച്ചുള്ള വിശദവിവരങ്ങൾ പരസ്യപ്പെടുത്തുകയോ, മൂന്നാമതൊരാളിന് കൈമാറുകയോ ചെയ്യുന്നില്ലെന്നുള്ള വസ്തുതയും ഞാൻ മനസ്സിലാക്കുന്നു. ( )
- ഈ പാഠ്യപദ്ധതിയിൽ പങ്കുചേരുന്നതിന് ഞാൻ സ്വമനസ്സാലെ സമ്മതിച്ചിരിക്കുന്നു.
  ( )
- ഈ സമ്മതപത്രത്തിന്റെ കയ്യൊപ്പുള്ള ഒരു പകർപ്പ് ഞാൻ കൈപ്പറ്റിയിരിക്കുന്നു.
  ( )

പേര് :

ഒപ്പ് :

തീയതി :

സാക്ഷി :

രോഗിയുമായുള്ള ബന്ധം

തീയതി :

(സമ്മതം വാങ്ങുന്ന വ്യക്തി)

ഈ പ്രത്യേക വൈദ്യശാസ്ത്രപഠന പദ്ധതിക്കുവേണ്ടിയുള്ള സമ്മതപത്രത്തിന് ആവശ്യമായ എല്ലാ വിവരങ്ങളും വളരെ തൃപ്തികരമായ രീതിയിൽ ഇതിൽ അടങ്ങിയിട്ടുണ്ടെന്ന് ഞാൻ സാക്ഷ്യപ്പെടുത്തിക്കൊള്ളുന്നു. ഇതിൽ പങ്കാളികളായ രോഗികളോട് ഈ പഠനത്തെപ്പറ്റി വിശദമായി സംസാരിക്കുകയും, ഈ സമ്മതപത്രത്തിൽ അടങ്ങിയിരിക്കുന്ന വിവരങ്ങൾ സാധാരണ സംസാര ഭാഷയിൽ തന്നെ പറഞ്ഞു മനസ്സിലാക്കുകയും ചെയ്തിട്ടുണ്ട്. ഇതിനിടയിൽ ഉണ്ടായേക്കാവുന്ന അപകട സാധ്യതകളെയും, പ്രതികൂല ഫലങ്ങളെയും കുറിച്ച് വിശദമായി പറഞ്ഞ് മനസ്സിലാക്കിയിട്ടുണ്ട്. ഇതിനെപ്പറ്റിയുള്ള കൂടുതൽ വിവരങ്ങൾ ചോദിക്കുവാൻ ഈ രോഗികളെ പ്രോത്സാഹിപ്പിക്കുകയും, എല്ലാ ചോദ്യങ്ങൾക്കും വ്യക്തമായ മറുപടി നൽകുകയും ചെയ്തിട്ടുണ്ടെന്ന് ഇതിനാൽ ബോധയപ്പെടുത്തുന്നു.

സമ്മതം വാങ്ങുന്ന വ്യക്തിയുടെ

പേര് :

ഒപ്പ് :

A comparison of sevoflurane versus sevoflura combination on renal function in patients under heart surgery –

A prospective Randomized study-

Name of the patient:
Age:
Sex:
(kg/cm2)
Hospital number:
Diagnosis and surgery:
Date of surgery:

Weight(kg):
Height (cm):
body surface area:

RISK FACTORS

HYPERTENSION		
DIABETES MELLITUS		
COPD/LUNG DISEASE		
ATRIAL FIBRILLATION		
NYHA		
EJECTION FRACTION		
PREOPERATIVE	Hb	
	BLOOD URIA	
	S. CREATININE	

INTRAOP DRUGS	
DIURETICS	
DIGOXIN	
BETA BLOCKER	
CCB	
HEPARIN	
OTHERS	

INTRAOPERATIVE DATA

CARDIOPULMONARY BYPASS TIME	
CROSS CLAMP TIME	
MINIMAL CORE TEMPERATURE CPB	
CARDIOPLEGIA	
PHENYL EPHRINE USE	
USE OF LASIX	
Hb ON CPB	
USE OF ULTRAFILTRATION	
IABP	

INOTROPES

DRUG	ADRENALINE	NORADREN	DOBUTAMINE	
DOSE				
DURATION				

URINE OUTPUT

ON CPB				
POST CPB				48 HRS

POST OP HB	O DAY	IST DAY	2^{ND} DAY

BASE LINE NGAL	TEST NGAL

BASE LINE	BUN	S. CREATININE	CREATININE CL
1^{ST} POST OP DAY			
2^{ND} POST OP DAY			
5^{TH} POST OP DAY			

Ho	RBS	TB/DB
PCV	BUN	T. protein
TC	S. Cr	Albumin
ESR	S. K/Na/Cl	Globuline
Platelet count		ALP
INR		SGOT /SGPT

Chest X-ray	
ECG	
Echo	

CPB

Perfusion pressure	
Av. Flow /comp. flow	
Blood transfusion	
Hemoglobin	
Temperature	
Use of phenylephrine	
Use of inotropes	

O POD

Hemoglobin	
Blood transfusion	
Reexploration	
Extubation time	
Inotropes	
Atrial fibrillation	

1ST POD

Hemoglobin	
Blood urea	
S. Creatinine	
Blood transfusion	
Reexploration	
Inotropes	
A f	

2ND POD

Hemoglobin	
Blood urea	
S. Creatinine	
Blood transfusion	
Inotropes	
A F	

5TH POD

Hemoglobin	
Blood urea	
S. Criatinine	
A F	

ICU STAY

HOSPITAL STAY

SIGNATURE

Technical Advisory Committee (Clinical Studies)

SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCE & TECHNOLOGY
THIRUVANANTHAPURAM – 695011, INDIA

TAC Registration No: SCT-/S/2012/152 **Date: 25.01.2013**

Project title: A comparison of sevoflurane versus sevoflurane–propofol combination on renal function in patients undergoing valvular heart surgery

Principal Investigator:
Name: Dr. RESHMI LIZA JOSE, DM Cardiothoracic and Vascular Anesthesia Resident, Department of Anaesthesiology, SCTIMST Degree: MBBS, MD(ANAESTHESIOLOGY),PDCC
Co-Principal Investigator(s)
(1)Name : Dr. UNNIKRISHNAN K.P, Additional professor, Department of Anaesthesiology, Cardiothoracic and vascular division, SCTIMST Degree: MBBS, MD (Anesthesiology), Dip NBE
Co- Investigator
NAME: Dr. SUNEEL P. R, Additional professor, Department of Anaesthesiology, Cardiothoracic and vascular division, SCTIMST Degree: MBBS, MD (Anesthesiology), PDCC

Members who participated in TAC meeting on 14/01/2013

Dr. V. Mohan Kumar (Chairman)
Dr. R. Sankar Kumar
Dr. T. V. Kumary
Dr. C. Kesavadas
Dr. Narayanan Namboodiri
Dr. Thomas Koshy
Dr. Rathore Chaturbhuj Gopalsingh
Dr. K. Shivakumar (Member Secretary)

Risk Classification of the project (Minimum/ Moderate/ High): Minimum

Requirement of DSMB: No

Recommended members of DSMB: Not applicable

Recommendations of TAC:

Recommended for consideration of IEC in the light of the responses received from the investigator. Please note that there can be no additions / alterations in the documents approved by TAC when they are submitted to the IEC.

Signature of the Member Secretary, TAC (Clinical Studies)

Note for IEC

Copy of the investigator's responses to questions/suggestions from TAC is attached (Appendix-1).

श्री चित्रा तिरुनाल आयुर्विज्ञान और प्रौद्योगिकी संस्थान
तिरुवनन्तपुरम- 695 011, केरल, इंडिया
SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY
THIRUVANANTHAPURAM - 695 011, INDIA
(An Institute of National Importance under Govt. of India)

Institutional Ethics Committee (IEC)

SCT / IEC-455/APRIL-2013 27-05-2013

Dr.Reshmi Liza Jose
DM Cardiothoracic and Vascular Anaesthesia Resident
SCTIMST
Trivandrum.

Dear Dr. Reshmi Liza Jose,

The Institutional Ethics Committee reviewed and discussed your application to conduct the clinical trial titled ""A Comparison of Sevoflurane Versus Sevoflurane-Propofol Combination on Renal Function in Patients Undergoing Valvular Heart Surgery" (IEC- 455).

The following documents were reviewed:

1. *Covering letter dated nil.*
2. *IEC Application form.*
3. *TAC Approval letter.*
4. *Consent form- English and Malayalam.*
5. *Declaration form.*
6. *Study proposal.*
7. *Covering letter & Application for TAC.*

तार : चित्रमेट फोन फाक्स ई-मेइल
Grams : Chitramet Phone : 2443152 Fax : (91) 471 - 2446433 2550728 E-mail : sct.@sctimst.ker.nic.in

8. *Observation chart.*
9. *CV of Investigators.*
10. *Letter dated 24/05/13 addressed to the Chairperson, Institutional Ethics Committee, SCTIMST from Dr. Reshmi Liza Jose, DM Resident, Division of Cardiothoracic and Vascular Anaesthesia, SCTIMST submitting the modified consent form and clarifications to the queries raised in the IEC meeting held on 20 April, 2013.*
11. *Modified consent form in English and Malayalam.*

The following members of the Ethics Committee were present at the meeting held on 20th April, 2013 at Director's Conference Hall.

Sl. No	Member Name	Highest Degree	Gender	Scientific / Non-scientific	Affiliation with Institution (s)
1.	Justice M.R. Hariharan Nair.	MA BL	Male	Legal Expert (Chairperson)	No
2.	Prof. K. Radhakrishnan	MD	Male	Clinician (Neurologist)	Yes
3.	Dr. C. P. Sharma	PhD	Male	Basic Scientist (Biomaterials)	Yes
4.	Smt. Lalithambika IAS	MBA	Female	Lay Person (Administrator)	No
5.	Dr. Rema M. N	MD	Female	Pharmacologist	No
6.	Dr. K. A. Kumar	MD	Male	Clinician (Psychiatrist)	No
7.	Dr. Meenu Hariharan	DM	Female	Clinician (Gastro Enterologist)	No

8.	Dr. S. N. Pal	PhD	Male	Basic Scientist (Biomaterials Expert)	No
9.	Dr. R.V.G. Menon	PhD	Male	Lay Person	No
10.	Dr. P. G. Prameela	MD	Female	Clinician (Paediatrician)	No
11.	Dr. Anoopkumar Thekkuveettil	PhD	Male	Basic Scientist (Molecular Biology) /Ethicist (Member Secretary)	Yes

IEC Decision

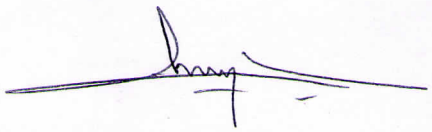
IEC approved the study to be conducted in its present form.

Remarks:

The Institutional Ethics Committee expects to be informed about the progress of the study, any SAE occurring in the course of the study, any changes in the protocol and patient information/informed consent and asks to be provided a copy of the final report.

There was no member of the study team who participated in voting / decision making process. The ethics committee is organized and operated according to the requirements of Good Clinical Practice and the requirements of the Indian Council of Medical Research (ICMR).

Yours Sincerely



Dr. Anoopkumar Thekkuveettil
Member Secretary, Ethics Committee.

LIST OF ABBREVIATIONS

AF	- Atrical Fibrillation
AKI	- Acute Kidney Injury
AKIN	- Acute Kidney Injury Network
BIS	- Bispectral Index
CABG	- Coronary Artery Bypass Graft
COPD	- Chronic Obstructive Pulmonary Disease
CPB	- Cardio Pulmonary Bypass
GFR	- Glomerular Filtration Rate
IABP	- Intra Aortic Balloon Pump
I-R injury	- Ischemia Reperfusion injury
MAP	- Mean Arterial Pressures
NGAL	- Neutrophil Gelatinase Associated Lipocalin
RIFLE	- Risk, Injury, Failure, Loss of function, End stage renal disease
TNF	- Tumor Necrosis Factor

MASTER CHART

SEVOFLURANE - PROPOFOL

SL	Age	Sex	Surgery	Wt	Ht	BSA	HTN	DM	Lung disea	AF	NYHA	EF	CPB	ACC	Temp	CP	CUF
1	21	M	DVR	36.5	165	1.29	0	0	0	0	3	40	137	104	28	4.root	1
2	36	F	AVR	57	158	1.58	0	0	0	0	2	58	136	91	30	3.ostial	0
3	43	F	AVR	53.5	155.5	1.52	0	0	0	0	3	72	113	76	30	2.ostial	0
4	61	F	MVR,TVA	70.5	154	1.73	0	1	0	1	2	48	133	73	28	3.root	0
5	42	M	AVR	64	165	1.71	0	0	0	0	2	63	107	74	28	3.RG&ostial	0
6	51	F	AVR	72	156	1.76	1	0	0	0	2	75	89	72	30	1.RG&ostial,1.RG,1.Ostial	0
7	49	F	DVR	61.8	154.5	1.62	0	1	ASTHMA	1	3	75	186	150	27	1.RG,1.Ostial	0
8	24	M	AVR	78	174	1.94	0	0	0	0	2	60	116	96	28	1.RG&ostial,1.RG,1.Ostial	0
9	42	F	MVR	68.5	161	1.75	0	0	0	0	3	59	100	70	28	2.root	0
10	54	F	MVR	50	150	1.44	0	0	0	1	3	62	80	50	32	2.ostial	0
11	39	M	MVR	85	180	2.06	0	0	Smoker	1	2	65	96	66	28	1.root,1RG	0
12	60	M	MVR	60	164	1.65	0	0	0	1	3	80	82	44	30	1.root,1RG	0
13	66	F	MVR	65	149	1.64	0	0	0	1	3	55	104	69	28	2.root	0
14	33	M	MVR	45	159	1.41	0	0	smoker	1	3	57	119	102	28	1.RG&ostial,2.Ostial	0
15	45	F	MVR	53	154.5	1.5	0	0	0	1	2	62	64	45	28	2.root	0
16	56	M	MV Repair	60.5	174	1.71	0	0	0	0	3	66	78	56	28	2.root	0

SEVOFLURANE - PROPOFOL

SL	B.Hb	0.Hb	1.Hb	2.Hb	5.Hb	B.BUN	1.BUN	2.BUN	5.BUN	B.S.Cr	1.S.Cr	2.S.Cr	5.S.Cr	B.Cr.Cl	1.cr.cl	2.Cr.Cl	5.Cr.Cl	B.NGAL	T.NGAL
1	11.3	8.8	8.3	7.9	9.1	19	24	34	34	1	1.8	1.6	1.2	60.33	33.51	37.704	50.27	36.9	201.5
2	12.5	8.2	11	8.7	11.8	11	12	13	17	0.7	0.8	0.9	0.8	99.97	87.48	77.76	87.48	126.2	138.9
3	11.3	8.9	10.6	9.7	10.4	16	15	20	33	0.9	0.9	1	1	68.07	68.07	61.26	61.26	125.5	245.8
4	12.3	8.9	8.2	8.5	9.2	14	9	21	19	0.9	0.5	1.2	0.8	73.06	131.5	54.79	82.19	159.4	188.2
5	15.2	11.5	10.4		11.2	11	12	14	15	1	1.1	0.9	0.6	87.11	79.19	96.79	145.19	106	135.8
6	12.4	9.7	9	8.4	10.5	15	8	11	14	0.9	0.7	0.5	0.9	84.06	108.07	151.3	84.06	82.6	180.8
7	13.3	9	8.2	7.6	8.2	17	15	15	14	0.9	0.8	0.5	0.5	73.77	82.99	132.78	132.78	142.6	327
8	16	13	11.1	9.7	9.3	13	12	14	17	0.9	1	0.9	0.9	139.63	125.67	139.63	139.63	53.1	154.3
9	11.6	8.6	8.4	9.5	10.1	16	13	13	12	0.9	0.7	0.7	0.6	88.06	113.22	113.22	132.08	91.5	208.1
10	11	8.4	11.1	11.1	11.8	18	16	17	25	0.8	0.9	0.9	0.9	63.45	56.4	56.4	56.4	108.5	156.5
11	15.9	10.9	11.5	10.3	9.4	5	13	22	16	0.8	1	1.2	0.9	149.05	119.24	99.36	132.48	106.3	135.1
12	13.8	10.9	11.2	9.5	8.6	14	15	15	28	1.4	1.5	1.4	1.6	47.62	44.44	47.62	41.67	101.9	332.9
13	13.1	11.3	11.9	10.6	10.3	15	12	16	29	0.8	0.8	1	0.9	70.98	70.98	56.78	63.09	132.1	217.7
14	12.4	11.3	9.7	8.8	9.4	14	14	15	18	1.1	1	1.1	0.8	60.8	66.88	60.8	83.59	132.6	196.3
15	14.7	7.2	10.5	9.1	11.3	11	15	21	29	0.9	1.3	1.3	1.3	66.05	45.72	45.72	45.72	126.3	191.6
16	12.1	8.6	9.9	8.5	8.6	12	11	15	20	0.9	0.9	1.1	1	78.43	78.43	64.17	70.58	91.6	111.6

SEVOFLURANE - PROPOFOL

SL	I	Blood	FFP	PC	CRYO	
1	S		1	0	0	0
2	S		1	0	0	0
3	S		1	0	0	0
4	S		1	0	0	0
5	S		0	0	0	0
6	S		0	0	0	0
7	S		0	0	0	0
8	S		0	0	0	0
9	S		3	0	0	0
10	S		2	0	0	0
11	S		0	0	0	0
12	S		0	0	0	0
13	S		0	0	0	0
14	S		0	0	0	0
15	S		1	0	0	0
16	S		1	0	0	0

SL	age	sex	surgery	wt	ht	BSA	HTN	DM	SEVOFLURANE Lung disea	AF	NYHA	EF	CPB	ACC	Temp	CP	CUF
1	37	M	DVR,TVA	55	170	1.61	0	0	0	Y	3	45	175	130	28	4. Ostial	1
2	53	F	MVR	62.8	149	1.61	0	0	0	N	2	60	87	50	31	2.root	0
3	36	M	MVR,ASD closre	57	176	1.66	0	0	0	N	3	60	153	115	28	4.root	0
4	42	M	AVR	69	178	1.84	0	0	0	N	2	88	86	62	28	2.RG, ost	0
5	52	F	MVR	41	152	1.32	0	0	0	Y	3	75	60	41	32	1.root	0
6	43	M	AVR	65.5	169	1.75	0	0	Smoker	N	2	67	87	66	32	2RG,1RG ,ostial	0
7	48	F	MVR	53	155	1.51	0	0	0	N	3	72	76	56	32	1.root,RG, 1.root	0
8	33	M	MVR,TVA	75	177	1.92	0	0	Smoker	N	2	55	137	99	28	1.root,RG, 2.root	0
9	61	F	MV repair	64	160	1.68	1	0	0	N	3	62	108	82	28	3.root	0
10	29	F	MVR	60	153	1.59	0	0	0	Y	3	67	55	33	32	1.root	0
11	61	M	DVR	46	157.5	1.41	0	0	Smoker	Y	3	55	130	105	29	3.ostial	0
12	35	F	MVR	63	168	1.71	0	0	0	N	3	69	76	50	32	1root,2.RG	0
13	37	M	MVR	55	152	1.55	0	0	Smoker	Y	2	80	120	97	28	2.RG,ostial, 1.RG	0
14	39	F	DVR	54	150.5	1.5	0	0	0	N	3	65	142	110	28	2RG&ostial,1.RG	0
15	35	F	MVR	70.5	167.5	1.81	0	0	0	N	3	52	56	38	30	1.root	0

SEVOFLURANE

SL	NO	b.Hb	0.Hb	1.Hb	2.Hb	5.Hb	B.BUN	1.BUN	2.BUN	5.BUN	B.S.Cr	1.S.Cr	2.S.Cr	5.S.Cr	B.Cr.Cl	1.Cr.Cl	2.Cr.Cl	5.Cr.Cl	B.NGAL	T.NGAL
1	S1	15.1	7.5	9.7	8.6	9	14	17	33	23	1.3	1.4	1.6	1.2	60.52	56.2	49.18	65.57	111.4	575.1
2	S13	14.9	9.3	9.2	7.2	10.1	15	11	9	10	0.8	1.1	0.6	0.8	80.63	58.64	107.5	80.63	208.2	404.5
3	S16	13.6	11.3	8.3	7.9	9	7	9	15	14	0.8	1	1.2	1	102.92	82.33	68.61	82.33	170.5	172.7
4	S17	16.1	8.5	9.1	8.7	9.1	16	16	15	17	1.4	1.5	1.3	1.2	67.08	62.61	72.24	78.26	100.4	104
5	S18	11.6	8.5	11.6	10	10.6	14	18	27	15	0.6	1	1.3	0.7	70.99	42.59	32.76	60.85	146.1	163.8
6	S20	12.5	9.5	8	7.7	8	11	16	14	11	1.1	1.4	1	0.8	80.22	63.03	88.24	110.3	91.5	236.2
7	S21	11	7.6	10.1	9.5	8.6	10	17	16	11	1	0.9	0.7	0.8	57.56	63.96	82.23	71.95	89.3	169.8
8	S22	16.3	14.5	11.7	11.4	9.9	16	14	19	26	1.2	1.2	1.3	1.2	92.88	92.88	85.74	92.88	185.3	324.8
9	S23	11.3	7.6	8.7	9	9.3	13	11	15	11	0.7	0.7	0.8	0.7	85.27	85.27	74.61	85.27	102.6	183.8
10	S24	12.8	8.5	10.7	9.9	8.9	9	12	9	15	0.8	1.2	0.8	3.3	98.28	65.52	98.28	23.83	98.9	253.9
11	S25	13.6	9.5	8.6	9.4	8.4	19	14	11	12	1	0.8	0.7	0.8	50.47	63.09	72.1	63.09	181.6	443.7
12	S26	11.1	8.8	7.4	8.2	6.8	12	13	10	10	0.7	0.7	0.7	0.6	111.56	111.56	111.56	130.16	54.6	217.1
13	S27	13.7	9.2	10.2	9.9	8.1	20	18	16	11	1.4	1.3	1.2	0.9	47.77	51.44	55.73	74.31	70.1	414.9
14	S34	11.5	10.9	9.9	9.2	9	10	10	19	16	0.9	1.2	1.2	0.8	71.54	53.66	53.66	80.48	121.6	137.9
15	S35	11.7	9	9.2	8	10.6	12	15	16	19	1	1.1	1.4	1.3	87.39	79.45	62.42	67.22	119	405.4

SEVOFLURANE

SL	NO	BLOOD	FFP	PC	CRYO
1	S1	2	2	2	2
2	S5	1	0	0	0
3	S16	1	1	0	2
4	S17	0	0	0	0
5	S18	0	0	0	0
6	S20	1	0	0	0
7	S21	1	1	0	0
8	S22	0	0	0	0
9	S23	2	0	0	0
10	S24	1	0	0	0
11	S25	1	0	1	1
12	S26	2	0	0	0
13	S27	0	0	0	0
14	S34	1	0	0	0
15	S35	0	0	0	0