A randomized controlled clinical trial to study the renoprotective effect of sodium bicarbonate infusion in patients undergoing open heart surgeries

This Dissertation submitted in partial fulfillmemt of the requirement for the M.D. Degree (Branch X) Anaesthesiology Examination of The Tamilnadu Dr.M.G.R. Medical University, Chennai, to be held in March 2011.

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C E R T I F I C A T E

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Signature of the H.O.D

Dr. Sarah Ninan
Professor and Head
Department of Anaesthesia
Christian Medical College,
Vellore - 632004.

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Signature of the guide:

Dr.Manickam Ponniah,
Professor
Department of Anaesthesia
Christian Medical College,
Vellore - 632004.

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I am grateful to **God for His blessings** on this study for its smooth completion

Last,but not the least,I thank all my **patients** for their co-operation in this study.

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AIM of the study

The aim of the study is to test whether perioperative sodium bicarbonate infusion can attenuate post operative increase in serum creatinine in cardiac surgical patients.This is done by studying the

(i) Proportion of patients developing acute renal dysfunction defined as postop increase in serum creatinine >25% of baseline within first 5 postop days.

(ii) Proportion of patients developing blood urea >25% of baseline within first 5 days

(iii) Proportion of patients developing complications like alkalosis, hypokalemia and hypernatremia

INTRODUCTION

Acute renal dysfunction is a common and serious postoperative complication of cardiopulmonary bypass and may affect 25% to 50% of patients.(1-4) Acute renal failure is related to preoperative renal function as well as to the presence of coexisting disease. Cardiopulmonary bypass also may affect renal function adversely because the unphysiologic state of nonpulsatile flow may upset the normal autoregulatory mechanisms of renal blood flow. Acute renal dysfunction also carries significant costs.(5) and is independently associated with increased morbidity and an increase in mortality.(6,7)

Urine acidity may enhance the generation and toxicity of reactive oxygen species induced by cardiopulmonary bypass. Activation of compliment during cardiac surgery may also participate in renal injury. Urine alkalinisation may protect from renal injury induced by oxidant substances, iron mediated free radical pathways ,complement activation and tubular hemoglobin cast formation .

Accordingly we want to study whether urine alkalinisation might protect kidney functions in patients at increased risk of renal dysfunction undergoing cardiopulmonary bypass by sodium bicarbonate infusion .

This study is a randomized controlled trial to see if sodium bicarbonate infusion is helpful in preventing increase in serum creatinine after

cardiopulmonary bypass. A group of 100 patients at increased risk of post operative renal dysfunction are randomized to either 24 hours of iv infusion of sodium bicarbonate or sodium chloride and serial serum creatinine values to be taken for five consecutive days.

The primary outcome is the proportion of patients developing acute renal dysfunction defined as postoperative increase in plasma creatinine >25% of the baseline within the first five post operative days.

We also looked for increase in plasma urea levels >25% of baseline within the first five days .Also for side effects of sodium bicarbonate infusion like hypernatremia, hypokalemia, and metabolic alkalosis .

METHODOLOGY

Design overview: This study was a double blind, single centre, randomized controlled trial. The human research ethics committee, CMC Vellore approved this study. Written informed consent was obtained from each patient.

Setting and participant: Patients were identified in the hospital wards. We enrolled patients at increased risk of postoperative acute renal dysfunction who were scheduled for elective cardiac surgery necessitating the use of cardiopulmonary bypass.

All surgical approaches were by median sternotomy. The cardiopulmonary bypass circuit consisted of a roller pump, tubing, a membrane oxygenator and an arterial filter . The pump priming solution consisted of 700 ml of Ringer lactate, 500 ml of Haesteril with 50 ml of 20% Mannitol. Perioperative bypass management targeted a cardiac output of >2.5 l/min/m^2 and a mean arterial blood pressure of 40-60 mm hg . The use of intraoperative fluid management was left to the discretion of the anaesthetist. Analgesia was achieved with opioids like fentanyl and

morphine with avoidance of nonsteroidal anti-inflammatory drugs. Urine output was maintained at >0.5 ml/kg/hr.

Intervention and Comparator agent: This study deals with comparison of sodium bicarbonate and sodium chloride infusion to prevent the renal dysfunction associated with cardiopulmonary bypass .Anaesthesia practice was not changed or modified for the purpose of the study and followed the same standard protocols. Patients were randomized and one group received 8.4% sodium bicarbonate 0.5 meq/kg/hr for 1 hour followed by 0.15 meq/kg/hr infusion for 23 hours. The control group received 0.9% normal saline same volume and infused at the same rate.

Key inclusion /Exclusion Criteria: Cardiac surgical patients in whom the use of cardio pulmonary bypass was planned and having one/more of the following risk factors for postoperative acute kidney injury

Inclusion Criteria(any one or more of the following factors) : (i) age >60 yrs

(ii) preexisting renal impairment (preop serum creatinine >1.3 mg%)

(iii) NYHA class 3/4 or impaired LVF (LVEF<=45%)

(iv)valvular surgery or concomitant valvular and coronary artery bypass graft surgery

(v)redo cardiac surgery

(vi)type 2 Diabetes Mellitus

Exclusion Criteria:

(i) ESRD (plasma creatinine >3.4 mg/dl)

(ii) Emergency cardiac surgery

(iii) Planned off pump cardiac surgery

(iv) Known blood borne infectious disease

(v) Chronic inflammatory disease on immunosuppression

Method of randomization: Randomisation codes were generated using block randomization method with size of 2, 4 and 6.

Method of allocation concealment: The sequence was generated by the statistician and the allocation codes were serially numbered and sealed in opaque envelopes which were handed over to the anaesthesia technician just before the surgery. He loaded the drugs accordingly .

Blinding and masking: Both participants and the investigators were blinded

Primary outcome: Proportion of patients developing acute renal dysfunction defined as postop increase in serum creatinine >25% of baseline within first 5 postop days.

Secondary Outcomes : (a) Blood urea >25% of baseline within first 5 days

Complications: (b) Hypernatremia >150 meq/l

(c)alkalosis ph >7.5

(d)potassium <3.5 meq/l

Target sample size and rationale: 100with 50 in each limb

Sample size calculation:was calculated based on the formula $n=(4pq)/d^2$ where

P, the expected prevelance

q=100-p

and d, the precision of study

According to the study Sodium bicarbonate to prevent increases in serum creatinine after cardiac surgery : A pilot double-blind ,randomized controlled trial, Critical care Med 2009 Vol 37, No .1, a similar study was done in 100 patients with 50 patients receiving sodium bicarbonate and the other receiving sodium chloride infusion.

1. Aute renal dysfunction in group 1 = 16/50 (p1= 32%)

2. Acute renal dysfunction in group 2 = 26/50 (p2 = 52%)

$$P = \frac{P1 + P2}{2}$$

P=42 , Q=58 (1 –P)

Expected difference between group 1 and 2 taken as 20%

Level of significance = 5% $Z\alpha = 1.96$

Power of the study =80% $Z\beta = 1.282$

Sample size formula $n = \frac{(Z\alpha + Z\beta)^2 \times P \times Q}{d^2}$

Hence n = 90 in each limb .However due to lack of time only 100 patients were enrolled in the study .

Phase of trial:Phase 3

Estimated duration of trial: 6 months

Statistical Analyses:

Data entry was done using Microsoft excel and analysis was done using SPSS (Statistical Package for the Social Sciences) software package version 16 .

Statistical methods used for primary outcome: (i) Descriptive statistics like mean and standard deviation were used for all study variables (ii)comparison of outcomes by Two sample proportion test (iii)odd's ratio with 95% confidence interval also were calculated. Continuous variables were compared using T –test . The study design and methods were approved by the Fluid Research Committee, Christian Medical College ,Vellore .

REVIEW OF LITERATURE

Discussed under the following headings:

1. CARDIOPULMONARY BYPASS
    - -USES
    - -SURGICAL PROCEDURES
    - -DESIGN
    - -COMPLICATIONS - RENAL
        - CAUSES OF RENAL FAILURE WITH CPB
2. RENAL FAILURE
    - -RIFLE SCORE
    - -ACUTE KIDNEY INJURY
    - -PATHOPHYSIOLOGY
3. SODIUM BICARBONATE
4. CONTRAST INDUCED NEPHROPATHY
5. STRATEGIES TO PREVENT RENAL FAILURE

CARDIOPULMONARY BYPASS

Cardiopulmonary bypass (CPB) is a technique that temporarily takes over the function of the heart and lungs during surgery maintaining the circulation of blood and the oxygen content of the body .The CPB pump itself is often referred to as heart –lung machine . Cardiac surgery with cardiopulmonary bypass is one of the common major surgical procedures in the world with more than one million surgeries per year.(8)

USES OF CARDIOPULMONARY BYPASS

Cardiopulmonary bypass is commonly used in heart surgery because of the difficulty of operating on the beating heart. Operations requiring the opening of the chambers of the heart require the use of CPB to support the circulation during that period.CPB can be used for the induction of total body hypothermia, a state in which the body can be maintained for up to 45 minutes without perfusion . .

CPB mechanically circulates and oxygenates blood for the body while bypassing the heart and lungs. It uses a heart-lung machine to maintain perfusion to other body organs and tissues while the surgeon works in a bloodless surgical field. The surgeon places a cannula in right atrium, vena cava, or femoral vein to withdraw blood from the body. The cannula is connected to tubing filled with a priming solution. Venous blood that is removed from the body by the cannula is filtered,

cooled or warmed, oxygenated, and then returned to the body. The cannula used to return oxygenated blood is usually inserted in the ascending aorta, but it may be inserted in the femoral artery. The patient is administered heparin to prevent clotting, and protamine sulphate is given after to reverse effects of heparin. During the procedure, hypothermia is maintained; body temperature is usually kept at 28ºC to 32ºC (82.4-89.6ºF). The blood is cooled during CPB and returned to the body. The cooled blood slows the body's basal metabolic rate, decreasing its demand for oxygen. Cooled blood usually has a higher viscosity, but the crystalloid solution used to prime the bypass tubing dilutes the blood.

SURGICAL PROCEDURES IN WHICH CPB IS USED

1. Coronary artery bypass surgery

2. Cardiac valve repair and/or replacement (aortic valve, mitral valve, tricuspid valve, pulmonary valve)

3. Repair of large septal defects (atrial septal defect, ventricular septal defect, atrioventricular septal defect)

4. Repair and/or palliation of congenital heart defects (Tetralogy of Fallot, transposition of the great vessels)

5. Transplantation (heart transplantation, lung transplantation, heart-

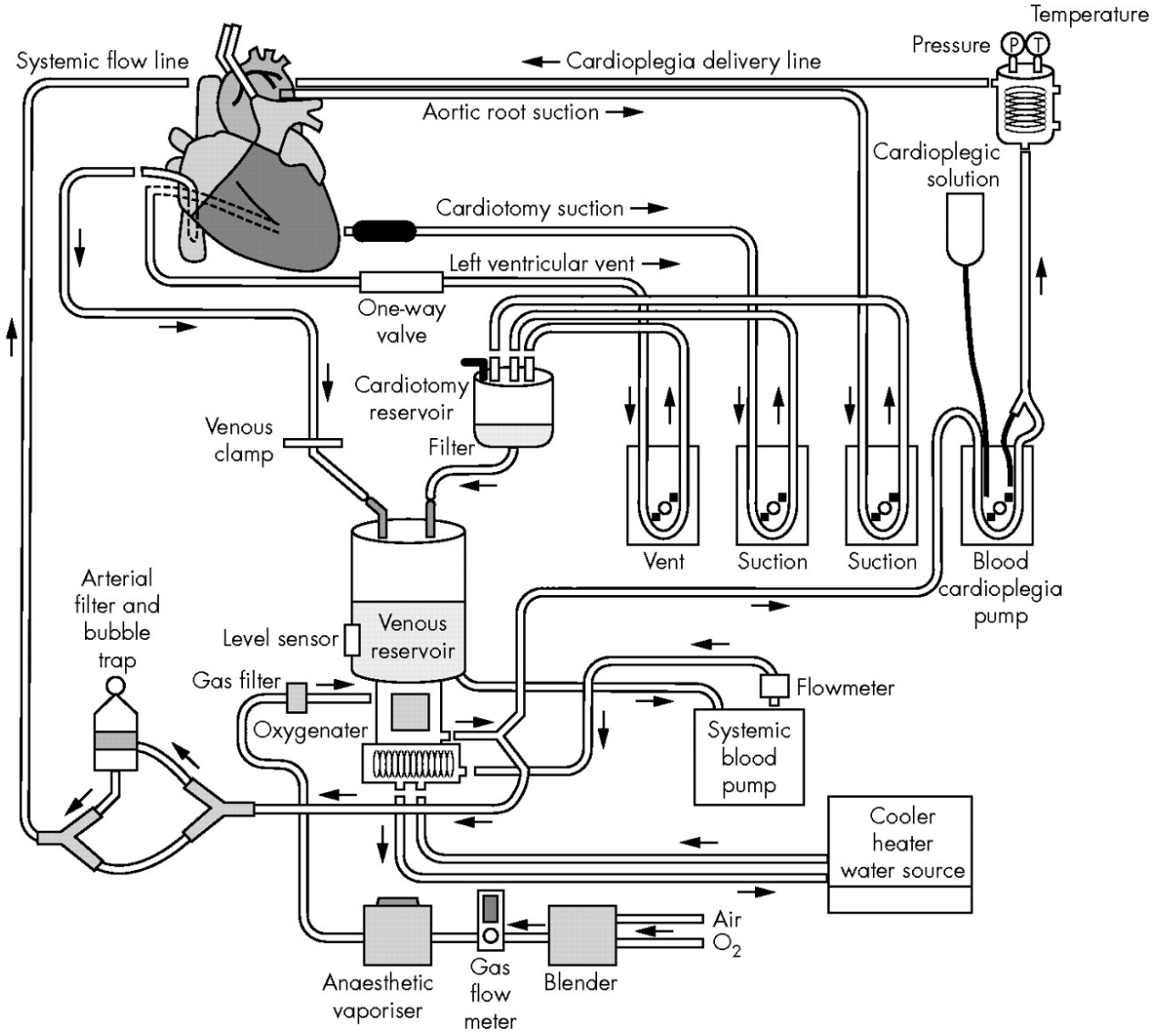
lung transplantation)

6. Repair of some large aneurysms (aortic aneurysms, cerebral aneurysms)

7. Pulmonary thromboendarterectomy

8. Pulmonary thrombectomy

DESIGN OF CPB CIRCUIT



The CPB machine has five basic components:

(i) Reservoir : The reservoir of the CPB machine receives blood from the patient via one or two venous cannulas in the right atrium or the superior and inferior vena cava. Blood flows to the reservoir by gravity drainage. Because venous pressure is normally low, the driving force is directly proportional to the difference in height between the patient and the reservoir but inversely proportional to the resistance of the cannulas and tubing.

(ii) Oxygenator: Blood is drained by gravity from the bottom of the venous reservoir into the oxygenator, which contains a blood – gas interface that allows blood to equilibrate with the gas mixture

(iii) Heat exchanger: Blood from the oxygenator enters the heat exchanger. The blood is then either cooled or warmed, depending on the temperature of the water flowing through the exchanger. Because gas solubility decreases as blood temperature rises, a filter is built into the unit to catch any bubbles that may form during rewarming.

(iv) Main pump:

(a) Roller pump: Roller pumps produce flow by compressing large bore tubing in the main pumping chamber as the heads turn. Subtotal occlusion of the tubing prevents excessive red cell trauma. The constant speed of the rollers pump blood

regardless of the resistance encountered and produces a continuous non pulsatile flow.

(b) Centrifugal pumps: consist of a series of cones in a plastic housing .As the cones spin, the centrifugal forces created propel the blood from the centrally located inlet to the periphery. Because these pumps are nonocclusive, they are less traumatic to blood than roller pumps

(c) Pulsatile flow: is possible with some roller pumps. Pulsatile flow improves tissue perfusion, enhances oxygen extraction, attenuates the release of stress hormones, and results in lower systemic vascular resistance.

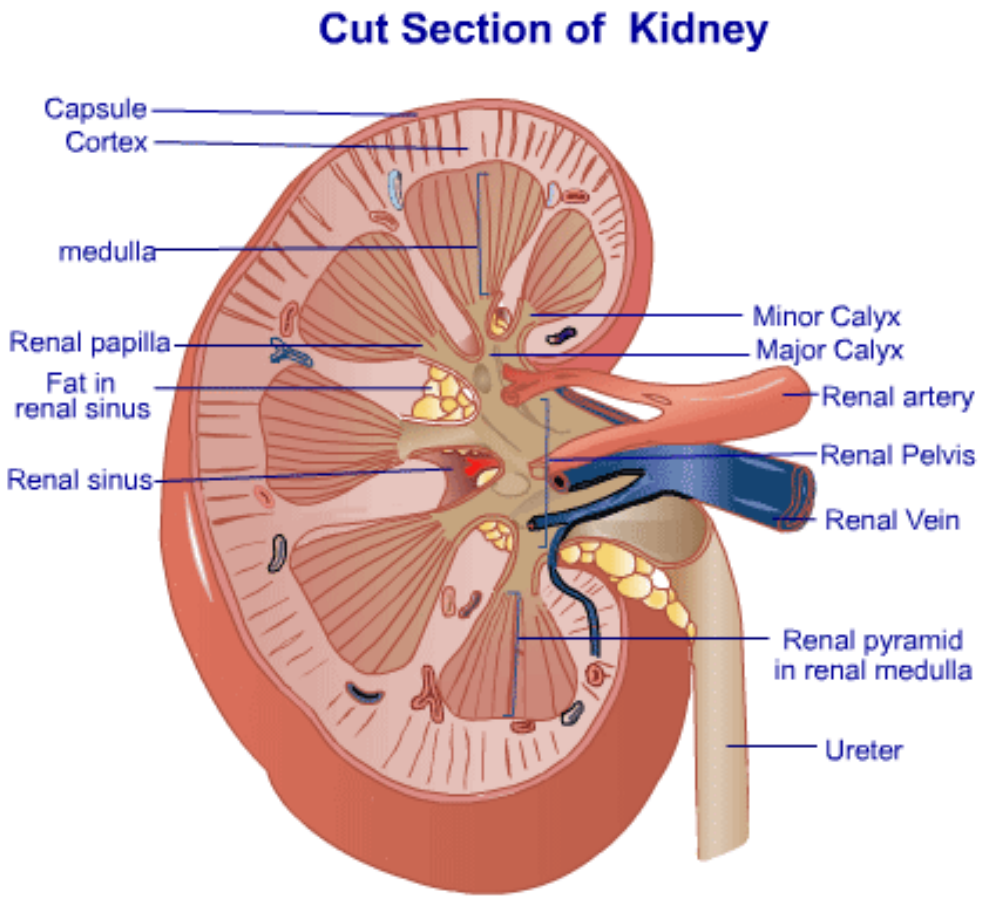
(v)Arterial Filter: is used to prevent particulate matter which enters the CPB circuit from causing systemic embolism.

Other components are Cardiotomy suction, Left ventricular vent, cardioplegia pump and ultrafilter. (9)

COMPLICATIONS OF CPB

CPB is a highly unphysiologic experience that triggers an explosion of adverse events affecting various systems such as cardiovascular, pulmonary, haematologic, renal and neurologic systems.

RENAL COMPLICATIONS



Acute renal dysfunction is a common and serious postoperative complication of cardiopulmonary bypass and may affect 25% to 50% of patients.(1-4) Acute renal failure is related to preoperative renal function as well as to the presence of coexisting disease. CPB also may affect renal function adversely because the unphysiologic state of nonpulsatile flow may upset the normal autoregulatory mechanisms of renal blood flow.

Acute renal dysfunction carries significant costs.(5) and is independently

associated with increased morbidity and an increase in mortality.(6,7) In a prospective study done by Giorgio Zanardo, in Italy, A total of 775 consecutive patients who survived the first 24 hours after cardiac operation were studied to assess the prevalence, mortality rate, and main risk factors for development of new acute renal failure. Normal renal function before operation (serum creatinine level less than 1.5 mg/dl) was registered in 734 (94.7%) patients. Of these, 111 (15.1%) showed a postoperative renal complication including 84 (11.4%) classified as renal dysfunction (serum creatinine level between 1.5 and 2.5 mg/dl) and 27 (3.7%) as acute renal failure (serum creatinine level higher than 2.5 mg/dl). The mortality rate was 0.8% in normal patients, 9.5% in patients with renal dysfunction, and 44.4% when acute renal failure developed. The renal impairment proved to be an independent predictor of mortality . Multivariate analysis identified the following variables as independent risk factors for postoperative renal impairment: use of intraaortic balloon pump ($p < 0.0001$), need for deep hypothermic circulatory arrest ($p < 0.005$), low-output syndrome ($p < 0.005$), advanced age ($p < 0.005$), need for emergency operation ($p < 0.025$), and low urinary output during cardiopulmonary bypass ($p < 0.05$). The 41 patients (5.3%) with preoperative renal failure showed a significantly higher morbidity and mortality rate than those without renal complications before operation. It was concluded that in patients undergoing cardiac operation without

preexisting renal dysfunction the likelihood of severe renal complications is reasonably low (7)

RENAL FAILURE

Acute renal failure (ARF) is characterized by a rapid decline in glomerular filtration rate (GFR) over hours to days. Retention of nitrogenous waste products, oliguria (urine output< 400 ml/d) contributing to extracllular fluid overload), and electrolyte and acid base abnormalities are frequent clinical features. ARF is divided into three major categories (i) pre renal ARF-diseases that cause renal hypoperfusion (ii) intrinsic ARF –diseases that directly involve the renal parenchyma (iii) postrenal ARF – diseases associated with urinary tract obstruction(10).

In recent years the term acute renal failure has been replaced by Acute Kidney Injury(11) to define a more dynamic process of renal dysfunction extending across initiation, maintenance and recovery phases, each of which may be of variable duration and severity.

Another diagnostic classification scheme was developed by the Acute Dialysis Quality Improvement Initiative (ADQI)(3) Renal dysfunction is defined in terms of either a rise in

creatinine or a reduction in urine output, the more severe of the two criteria being selected.

Risk, Injury, Failure, Loss, and End-stage Kidney (RIFLE) classification

Class	Glomerular filtration rate criteria	Urine output criteria
Risk	Serum creatinine × 1.5	< 0.5 ml/kg/hour × 6 hours
Injury	Serum creatinine × 2	< 0.5 ml/kg/hour × 12 hours
Failure	Serum creatinine × 3, or serum creatinine ≥ 4 mg/dl with an acute rise > 0.5 mg/dl	< 0.3 ml/kg/hour × 24 hours, or anuria × 12 hours
Loss	Persistent acute renal failure = complete loss of kidney function > 4 weeks	
End-stage kidney disease	End-stage kidney disease > 3 months	

Diagnostic criteria for acute kidney injury

Emerging evidence suggests that even minor changes in serum creatinine are associated with increased in-patient mortality. ARF has been the focus of extensive clinical and basic research efforts over the last decades. During the last five years, several groups have recognized these limitations and have worked to identify the knowledge gaps and define the necessary steps to correct these deficiencies. These efforts have included consensus conferences and publications from the Acute Dialysis Quality Initiative (ADQI) group the American Society of Nephrology (ASN) ARF Advisory group the International Society of Nephrology (ISN), and the National Kidney Foundation (NKF) and KDIGO (Kidney Disease: Improving Global Outcomes) groups . Recognizing that future clinical and translational research in ARF will require multidisciplinary collaborative networks, the ADQI group and representatives from three nephrology societies (ASN, ISN, and NKF) and the European Society of Intensive Care Medicine met in Vicenza, Italy, in September 2004. They proposed the term acute kidney injury (AKI) to reflect the entire spectrum of ARF .

<u>Diagnostic criteria for acute kidney injury</u>

An abrupt (within 48 hours) reduction in kidney function currently defined as an absolute increase in serum creatinine of more than or equal to 0.3 mg/dl (≥ 26.4

μmol/l), a percentage increase in serum creatinine of more than or equal to 50% (1.5-fold from baseline), or a reduction in urine output (documented oliguria of less than 0.5 ml/kg per hour for more than six hours).

Classification/staging system for acute kidney injury

Stage	Serum creatinine criteria	Urine output criteria
1	Increase in serum creatinine of more than or equal to 0.3 mg/dl (≥ 26.4 μmol/l) or increase to more than or equal to 150% to 200% (1.5- to 2-fold) from baseline	Less than 0.5 ml/kg per hour for more than 6 hours
2	Increase in serum creatinine to more than 200% to 300% (> 2- to 3-fold) from baseline	Less than 0.5 ml/kg per hour for more than 12 hours
3	Increase in serum creatinine to more than 300% (> 3-fold) from baseline (or serum creatinine of more than or equal to 4.0 mg/dl [≥ 354 μmol/l] with an acute increase of at least 0.5 mg/dl [44 μmol/l])	Less than 0.3 ml/kg per hour for 24 hours or anuria for 12 hours

Modified from RIFLE (Risk, Injury, Failure, Loss, and End-stage kidney disease)criteria .The staging system proposed is a highly sensitive interim staging system and is based on recent data indicating that a small change in serum

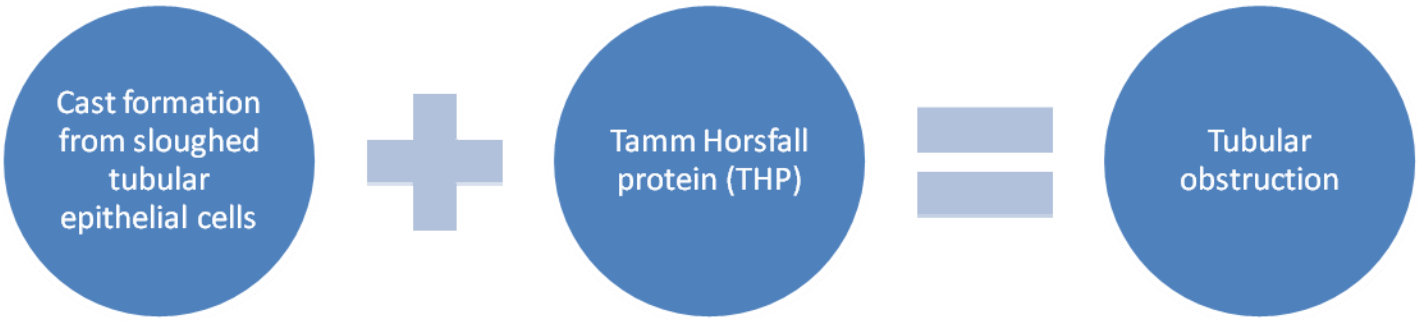
creatinine influences outcome. Only one criterion (creatinine or urine output) has to be fulfilled to qualify for a stage. 200% to 300% increase = 2- to 3-fold increase .Given wide variation in indications and timing of initiation of renal replacement therapy (RRT), individuals who receive RRT are considered to have met the criteria for stage 3 irrespective of the stage they are in at the time of RRT.(12)

PATHOPHYSIOLOGY OF RENAL FAILURE

The effect of renal injury, whether from ischemia or from other causes , is a profound decrease in the GFR. This large decrease in filtration capacity of the kidney often occurs in the absence of overwhelmingly evident damage to the kidney as seen on light microscopy.There are atleast three major classic proposed mechanisms for the fall in GFR :

(i) The first mechanism is a drop in the filtration pressure in the glomerulus.

(ii) The second mechanism is tubular back leakage



(iii) The third mechanism – Tubular Obstruction

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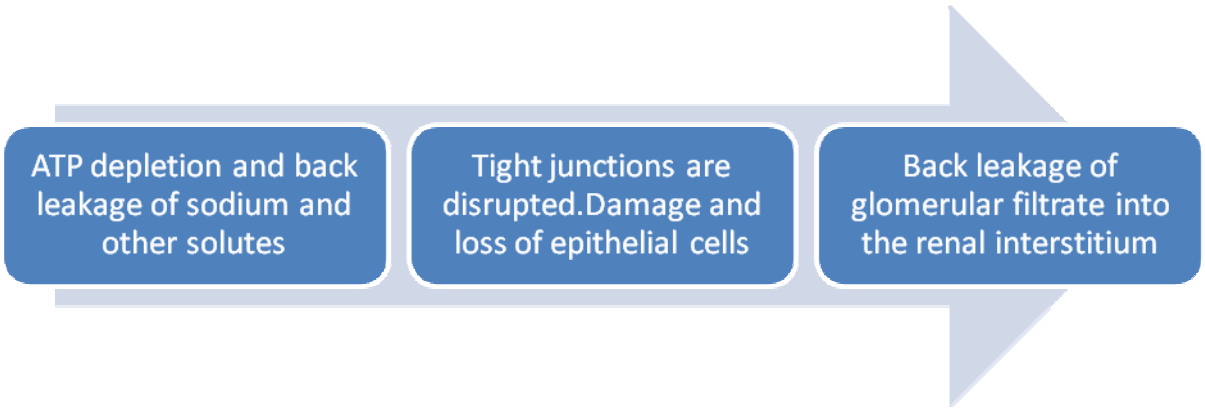


INFLAMMATION:

Inflammation plays a central role in AKI. From initiation to extension through repair, inflammatory cells and soluble mediators are likely major determinants of the outcome from ARF.

MICROVASCULAR INFLAMMATION

The proximal events leading to damage of renal tubular epithelial cells likely start in the microvasculature. The kidney receives 20% to 25% of cardiac output, and most of that blood flow is directed to the renal cortex. Postglomerular vessels, branching from efferent arterioles, eventually become the vessels of the vasa recta. The low flow state in the vasa recta is a critical aspect of the counter current multiplier, allowing for appropriate trafficking of water and solutes. However the low flow state leaves the medulla relatively hypoxic when compared with other regions of the kidney.The partial pressure of oxygen in the outer medulla is only 10 to 20 mm Hg.Hence very slight decreases in the blood flow and oxygen delivery

can lead to anoxic damage. Anoxic injury to local cells, including vascular smooth muscle cells and endothelial cells, leads to depletion of cellular energy stores and resultant disruption of their actin cytoskeleton. The cellular deformities and hypoxia in and around the microvasculature leads to endothelial – erythrocyte interactions and promote sludging of RBCs. Peritubular capillaries also take longer to recover nomal blood flow when compared with other intrarenal vessels. The combination of hypoxic injury, changes in endothelial cell morphology, and heightened interactions between RBC and endothelium leads to the extension of the initial renal injury.

Leukocytes: Early inflammation is classically characterized by margination of neutrophils to vascular endothelium. After the margination , firm adhesion occurs by the interactions of integrins with intercellular adhesion molecule-1.

APOPTOSIS:

Apoptosis plays a major role in the pathophysiology of ARF . IN apoptosis, the cell nucleus and cytoplasm condense and then split off into smaller apoptotic bodies. Cytoplasmic organelles, including the mitochondria, are often intact and are phagocytized by macrophages or other cells, which leads to spillage of cellular contents to cause inflammation.

The signs of apoptosis in the kidney, initially heralded by DNA fragmentation in the cells of the thick ascending limb, can be seen within fifteen minutes of a

hypoxic insult in the kidney. A second peak in the amount of apoptosis in renal tissue occurs days to weeks after the initial insult

THE ENDOTHELIAL CELL

The endothelial cell plays an important role in the development of ARF. When an initial insult damages the endothelium of the renal vessels, the result is an endothelial bed that is ineffective in regulating local blood flow and cell migration into tissues, and preventing coagulation. This vascular dysregulation, as perpetuated by dysfunctional endothelial cells, leads to continued ischemic injury following the initial insult, the extension phase of AKI.(13)

SODIUM BICARBONATE

Sodium bicarbonate or sodium hydrogen carbonate is the chemical compound with the formula $NaHCO_3$. Sodium bicarbonate is a white solid that is crystalline but often appears as a fine powder. It has a slightly salty, alkaline taste resembling that of washing soda(sodium carbonate). The natural mineral form, nahcolite, is found in dissolved form in bile, where it serves to neutralize the acidity of the hydrochloric acid produced by the stomach, and is excreted into the duodenum of the small intestine via the bile duct.

History

The ancient Egyptians used natural deposits of natron, a mixture consisting mostly of sodium carbonate decahydrate and sodium bicarbonate. The natron was used as a cleansing agent like soap.In 1791, a French chemist, Nicolas Leblanc , produced sodium carbonate, also known as soda ash . In 1846 two New York bakers, John Dwight and Austin Church, established the first factory to develop baking soda from sodium carbonate and carbon dioxide .Sodium bicarbonate is an amphoteric compound. Aqueous solutions are mildly alkaline due to the formation of carbonic acid and hydroxide ion:

$$HCO{-}3 + H_2O \rightarrow H_2CO_3 + OH^-$$

Sodium bicarbonate can be used as a wash to remove any acidic impurities from a "crude" liquid, producing a purer sample. Reaction of sodium bicarbonate and an acid to give a salt and carbonic acid, which readily decomposes to carbon dioxide and water:

$$NaHCO_3 + HCl \rightarrow NaCl + H_2CO_3$$

$$H_2CO_3 \rightarrow H_2O + CO_2(g)$$

$$NaHCO_3 + CH_3COOH \rightarrow CH_3COONa + H_2O + CO_2(g)$$

Sodium bicarbonate reacts with bases such as sodium hydroxide to form carbonates

Medical uses

Sodium bicarbonate is used as an antacid taken orally to treat acid peptic disease. It may also be used in an oral form to treat chronic forms of metabolic acidosis such as chronic renal failure and renal tubular acidosis . Metabolic acidosis is usually not treated unless serum bicarbonate concentration falls below15 mmol/L or arterial pH falls below 7.2 .More severe acidosis is corrected by oral or intravenous sodium bicarbonate .Initial rates of replacement are guided by estimates of bicarbonate deficit and adjusted thereafter according to serum levels.

Patients should be monitored for complications of sodium bicarbonate administration such as hypervolemia, hypokalemia.Sodium bicarbonate may also be useful for forced alkaline diuresis in the treatment of acute barbiturate poisoning , aspirin overdosage and uric acid renal stones.(14)It is used as well for treatment of hyperkalemia. 50-100 ml of 8.4% sodium bicarbonate will shift potassium into the cells reducing the serum levels of the same .Sodium bicarbonate has also been used in the treatment of tricyclic antidepressants overdose. It can also be applied topically as a paste, with three parts baking soda to one part water,

to relieve insect bites .Sodium bicarbonate is also used as an ingredient in some mouthwashes. It works as a mechanical cleanser on the teeth and gums, neutralizes the production of acid in the mouth and also as an antiseptic to help prevent infections occurring.

Medical preparation: Sodium bicarbonate is available as two preparations .

(i) 8.4% NaHCO3 which has 1437 mmol/L of Na , 1437 mmol/L of HCO3, 2874 mOsm/L .pH is 8.3 . 8.4% NaHCO3 contains 1 meq of HCO3 per ml

(ii)7.5% NaHCO3 which has 1283 mmol/L of Na ,1283 mmol/L of HCO3 ,2566 mOsm/L .pH 8.3 .7.5% NaHCO3 contains 0.9 meq of HCO3 per ml .

BASE EXCESS : is the difference between the patients normal Buffer Base (BB) and the actual BB .The base excess is a calculated value which estimates the metabolic component of an acid base abnormality. It is an estimate of the amount of strong acid or base needed to correct the metabolic component of an acid base disorder .

Correction =0.3 x body weight x Base excess

Complete correction based on the above calculation is not clinically advisable as the body is in dynamic equilibrium and rapid correction can be deleterious

(paradoxical CSF acidosis, shift of the Hb dissociation curve causing tissue hypoxia) .

CONTRAST INDUCED NEPHROPATHY

A number of preventive measures have been proposed for contrast nephropathy.(15) It is clear that hydration is an effective preventive measure. Other measures that have been proposed include loop diuretics and mannitol, dopamine, fenoldopam, N acetyl cysteine, theophylline , and sodium bicarbonate.(16) Despite favourable experimental data, there is insufficient evidence to support the use of loop diuretics or mannitol to prevent radiocontrast nephropathy or any other cause of ARF. Likewise ,despite its widespread use,dopamine has proved ineffective as a prophylactic agent. Fenoldopam, a dopamine a-1 specific agonist approved for use as a parenteral antihypertensive agent, has been tested in several clinical trials and does not appear to reduce the incidence of contrast nephropathy. Moreover, fenoldopam is associated with significant side effects, including systemic hypotension, and its use as an agent to prevent radiocontrast nephropathy should be discouraged. In contrast, several small randomized control trials have suggested a clinical benefit to the use of N- acetyl cysteine (17), although meta-analyses have been inconclusive.(18). Acetylcysteine is the N-acetyl derivative of the amino acid L-cysteine,and is a precursor in the formation of the antioxidant glutathione in the body. Inhaled acetylcysteine is indicated for mucolytic ("mucus-dissolving")

therapy as an adjuvant in respiratory conditions with excessive and/or thick mucus production which include emphysema, bronchitis, tuberculosis, bronchiectasis, amyloidosis, pneumonia, cystic fibrosis and COPD Chronic Obstructive Pulmonary Disease. It is also used post-operatively, as a diagnostic aid, and in tracheotomy care . Intravenous acetylcysteine is indicated for the treatment of paracetamol (acetaminophen) overdose However, aside from the potential hazards associated with a delay in radiographic imaging,N-acetyl cysteine appears to be safe, and its use in patients at high risk for radiocontrast nephropathy is reasonable, based on its low side effect .profile.(16) Larger RCTs will be required to show definitive benefit.

However a few studies show that hydration with sodium bicarbonate is better than hydration with sodium chloride for prophylaxis of contrast-induced renal failure.(19)

A recent small prospective trial demonstrated that infusion of isotonic sodium bicarbonate was associated with a smaller increase in serum creatinine compared with isotonic saline, suggesting a benefit from alkalinization of the urine. (16)

CAUSES FOR RENAL FAILURE WITH CPB:

Various reasons stated are

(i) Large fluid load typically administered with a crystalline CPB prime solution.

(ii) The potassium usually administered as part of the cardioplegic solution .(20)

(iii) Hypothermia is an independent factor for decrease in renal tubular function

(iv) As there is decrease in global renal blood flow, there is redistribution of blood flow from cortex to outer medulla .

(v) Intravascular hemolysis resulting in hemoglobinuria can cause acute tubular necrosis. It is not clear whether the mechanism is precipitation of pigment in the renal tubules with subsequent blockage of tubular flow/glomerular-tubular injuries caused by red cell stroma and other substances liberated from lysed RBCs .(21)

Multiple other causes of cardiopulmonary bypass-associated acute renal dysfunction have been proposed, including (vi) ischemia-reperfusion, (vii) generation of reactive oxygen species, (viii) hemolysis, and (ix) activation of inflammatory pathways. (22-25)To date, no simple, safe, and effective intervention to prevent cardiopulmonary bypass-associated acute renal dysfunction in a broad patient population has been found .(26-28)

Urinary acidity may enhance the generation and toxicity of reactive oxygen species induced by cardiopulmonary bypass. (25,29)Activation

of complement during cardiac surgery(30) may also participate in renal injury. Urinary alkalinization may protect from renal injury induced by oxidant substances, iron-mediated free radical pathways, complement activation, and tubular hemoglobin cast formation.(24,31,32) Of note, increasing urinary pH—in combination with N-acetylcysteine or without—has recently been reported to attenuate acute renal dysfunction in patients undergoing contrast-media infusion. (19,33,34)

STRATEGIES TO DECREASE THE INCIDENCE OF RENAL FAILURE.

Previous double-blind randomized controlled trials attempting to prevent or attenuate acute renal dysfunction after cardiopulmonary bypass targeting oxidative stress, renal adenosine triphosphate consumption, and improvement of perioperative hemodynamic stability have been found to be ineffective.(26,28,35) , inconclusive or studied in specific cardiac surgical subpopulations(36). To date, no simple, safe, and effective intervention to prevent cardiopulmonary bypass-associated acute renal dysfunction in a broad patient population has been found (26-28).

However a study was done by Dr Michael Haase et al in Austin Hospital , Australia titled “Sodium bicarbonate to prevent increases in serum creatinine after cardiac surgery :A pilot double blinded , randomized controlled trial” (37). Here a cohort of 100 cardiac surgical patients at increased risk of postoperative acute renal dysfunction were selected and randomized to two groups .The study group (n=50) to receive 24 hours of intravenous infusion of sodium bicarbonate (4 mmol/kg) and the control group (n=50) to receive sodium chloride (4 mmol/kg) .The sodium bicarbonate or sodium chloride infusion were given at a dose of 0.5 mmol/kg body weight (bolus) diluted in 250 ml of 5% dextrose water over 1 hour immediately after the induction of anaesthesia followed by continuous intravenous infusion of 0.15 mmol/kg/hr (maintenance) diluted in 1000 ml of 5% dextrose over 23 hours (total dose of 4 mmol/kg over 24 hrs) .

The primary outcome measure was the proportion of patients developing acute renal dysfunction defined as a postoperative increase in plasma creatinine concentration >25% of baseline within the first five postoperative days. Secondary outcomes included changes in plasma creatinine, plasma urea, urinary neutrophil gelatinase-associated lipocalin, and urinary neutrophil gelatinase-associated lipocalin/urinary creatinine ratio. Patients were well balanced for baseline characteristics. According to this study, sodium bicarbonate infusion increased plasma bicarbonate concentration , base excess, plasma pH, and urine pH and was

statistically significant. Fewer patients in the sodium bicarbonate group (16 of 50) developed a postoperative increase in serum creatinine compared with control (26 of 50) with an odds ratio of 0.43 ($p = 0.043$). The increase in plasma creatinine, plasma urea, urinary neutrophil gelatinase-associated lipocalin, and urinary neutrophil gelatinase-associated lipocalin/urinary creatinine ratio was less in patients receiving sodium bicarbonate. There were no significant side effects. Hence the conclusion was that **s**odium bicarbonate loading and continuous infusion was associated with a lower incidence of acute renal dysfunction in cardiac surgical patients undergoing cardiopulmonary pass. This trial was based on the principle that the rise in serum creatinine after cardiopulmonary bypass might be due to a combination of tubular injury induced by reactive oxygen species, complement activation, and free hemoglobin release .

RESULTS

Between march 2010 and july 2010 we randomized 100 patients to receive intravenous sodium bicarbonate A group(n=50) or sodium chloride B group (n=50) .Two sample t test with equal variances were used for statistical analysis .

DEMOGRAPHIC DATA

Table 1 : Age characteristics

	Sample (n)	Mean age(yrs)	Std error	Std dev
Group A	50	49.6	2.147	15.18
Group B	50	48.0	2.012	14.22

Table 2 : Age and sex characteristics

	Sodium Bicarbonate n=50	Sodium Chloride n=50	P value
Age >=6oyrs,mean	13(26%)	14(28%)	0.822
Males ,n	30(60%)	34(68%)	0.405

The mean age in both the study and control groups were comparable Group A being 49.6 and Group B being 48.0 years.There were no differences in both the groups in baseline characteristics like age and sex as seen above in Table 1 and 2 .Out of the 50 in sodium bicarbonate group 13 were >=60 years .Out of the 50 in the placebo group 14 were more than 60 years of age .Out of the 50 in A group 30 were males and out of the 50 patients in B group 34 were females which was again not significant .There were no significant difference in the baseline characteristics like blood urea and serum creatinine .All patients had elective cardiac surgery either a CABG or a valve replacement .

Table 3 : Inclusion criteria

	Group A	Group B	Total	P value
Age >=60 yrs, n (%)	13(26%)	14(28%)	27	0.822
Serum creatinine>=1.3 n%	6(12%)	5(10%)	11	0.749
Left ventricular dysfunction, n (%)	6(12%)	7(14%)	13	0.766
Valvular surgery, n (%)	26(52%)	19(38%)	45	0.218

CABG+ Valve surgery, n(%)	0	3(6%)	3	0.218
Redo cardiac surgery, n(%)	3(6%)	4(8%)	7	0.218
Diabetes Mellitus, n(%)	13(26%)	19(38%)	32	0.198

As seen in the table above all the inclusion criterias were comparable .

Table 4: Preoperative coomorbidities

	Group A	Group B	Total	P value
Systemic hypertension, n(%)	17(34%)	15(30%)	32	0.668
Hypercholestrolemia, n(%)	14(28%)	18(36%)	32	0.391
Atrial fibrillation, n(%)	4(8%)	5(10%)	9	0.727
Recent MI, n(%)	6(12%)	7(14%)	13	0.766

There is no statistically significant difference in preoperative comorbidities in both the study and control groups .

Table 5 : Preoperative medications

	Group A	Group B	Total	P value
ACE inhibitors	15(30%)	20(40%)	35	0.295
B blockers	14(28%)	22(44%)	36	0.096
Nitrates	13(26%)	19(38%)	32	0.198
Antiplatelets	16(32%)	22(44%)	38	0.216

All the preoperative medications are also comparable in both the groups.

PREOPERATIVE MEASURES OF RENAL OUTCOME :

Table 6 : Preoperative plasma urea

	n	mean	Std error	Std dev
GROUP A	50	27.9	1.409	9.96
GROUP B	50	25.62	1.146	8.108

P value is 0.1062

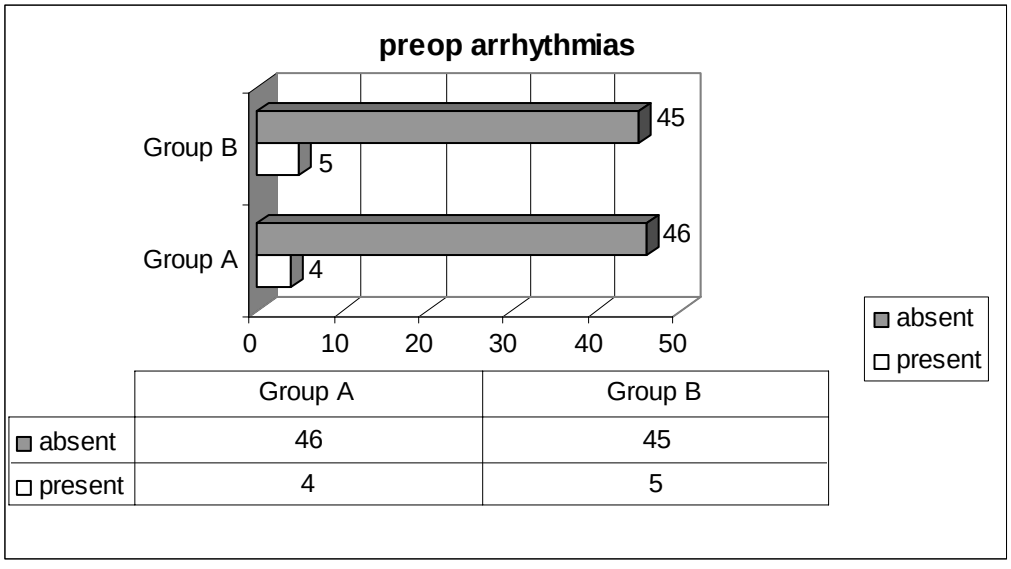
Hence the plasma urea in both the study and control group were relatively the same.

Table 7 : Preoperative serum creatinine

	n	mean	Std error	Std dev
GROUP A	50	1.07	0.033	0.234
GROUP B	50	1.092	0.037	0.265

The baseline serum creatinine values are comparable with a p value of 0.669 .

Fig 1 : Preoperative arrhythmias:



	Group A	Group B
absent	46	45
present	4	5

The frequency of preoperative arrhythmias were almost same in both the study and control groups the p value being 0.727

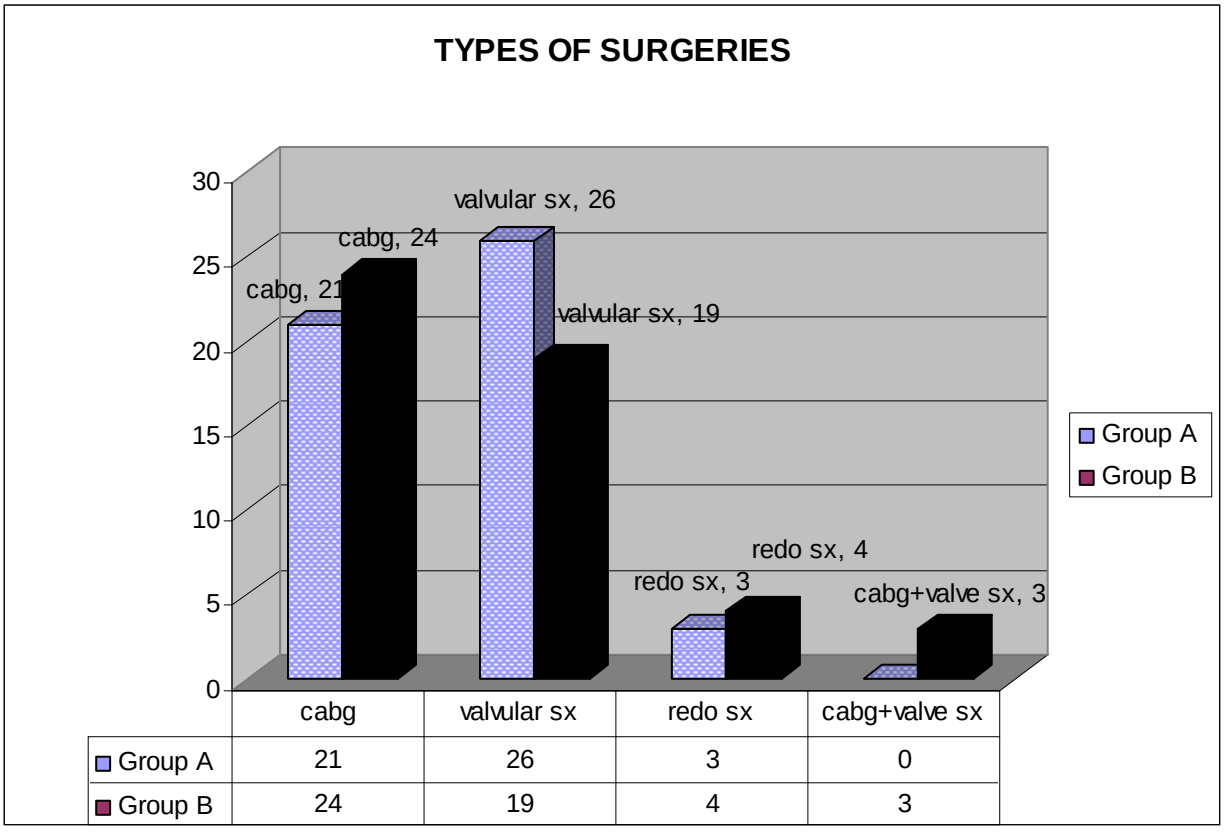
INTRAOPERATIVE FINDINGS :

Table 8: Cardiopulmonary bypass time

	Mean time	Std error	Std dev	95% C I
Group A	78.9	2.83	20	73.2-84.6
Group B	79.2	2.28	16.2	74.5-83.7

There is no significant difference between the study and control groups in terms of cardiopulmonary bypass time which is approximately about 79 minutes ..The p value is 0.9476

Fig 2 : Types of surgeries



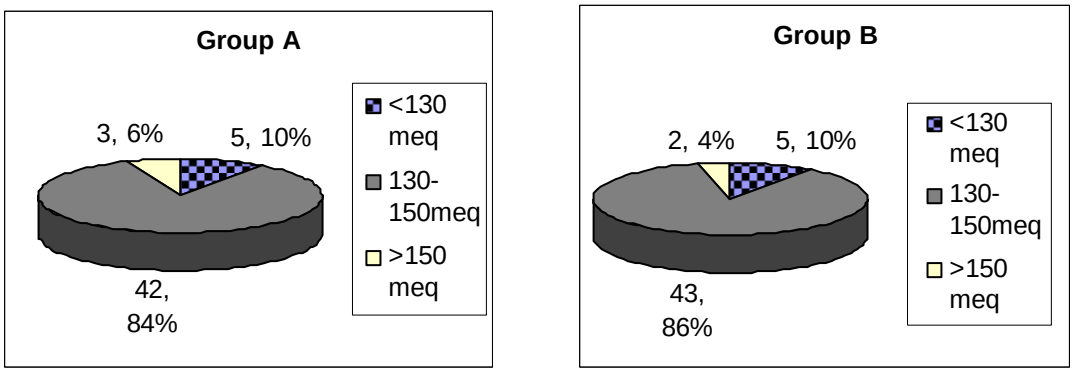
.

The types of surgeries in both the study and control groups are comparable with a p value of 0.218

INTRAOPERATIVE ARTERIAL BLOOD GAS:

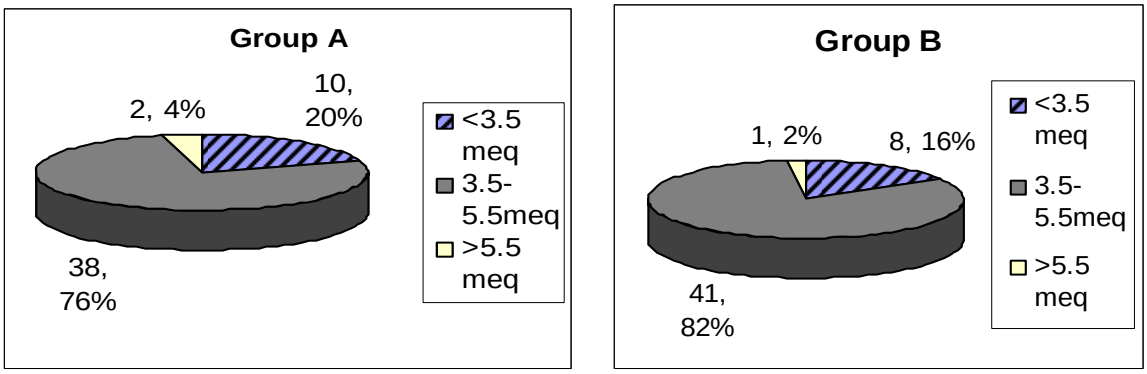
During the surgery three ABGs were done .First (A sample) is a baseline Abg done immediately after intubation and before giving heparin or going on bypass .Second (B sample) was during bypass and third ABG (sample)was after coming off bypass .

Fig 3: A SAMPLE : SODIUM



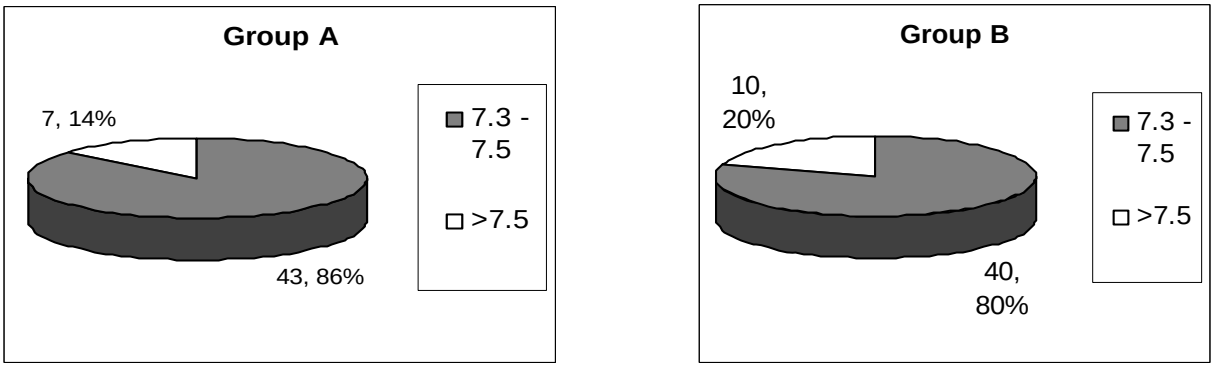
Even though Group A received more sodium as 8.4% NaHCO3 infusion than Group B, there is no statistically significant difference between the two groups in terms of the serum sodium levels in A sample ,the p value being 1.000 .

Fig 4: A SAMPLE - POTASSIUM



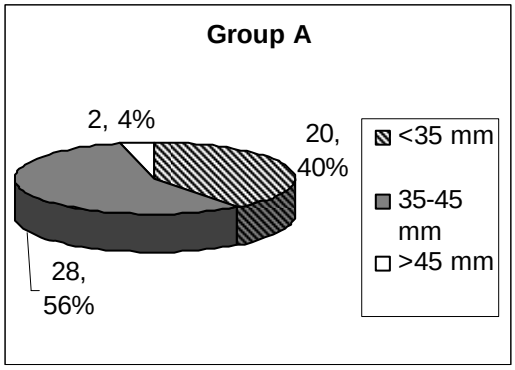
One of the known side effects of sodium bicarbonate is hypokalemia . In our study out of the 50 patients who received sodium bicarbonate infusion10 developed hypokalemia compared to 8 out of 50 who received saline infusion which is not statistically significant with a p value of 0.716 .

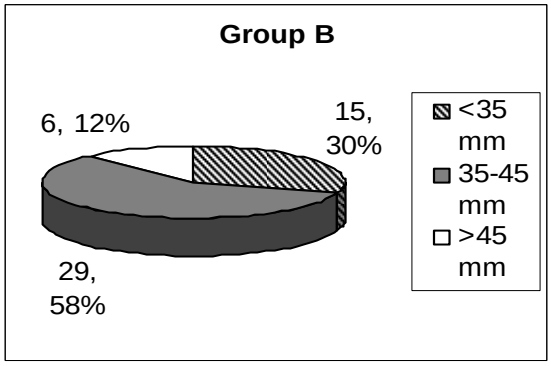
Fig 5: A SAMPLE - PH



Contrary to what was expected , only 7 out of 50 patients of the study group developed ph >7.5 compared to 10 out of 50 patients in the control group .As such the results were not statistically significant .p value 0.424 .

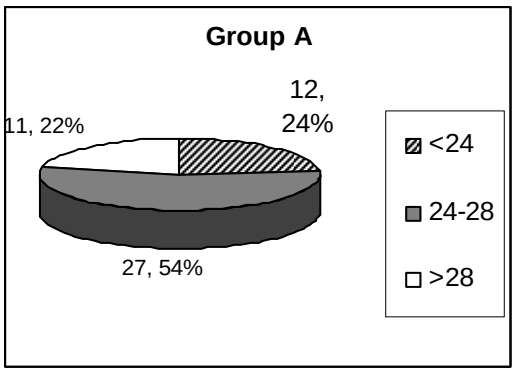
Fig 6: A SAMPLE – PACO2 (mm Hg)

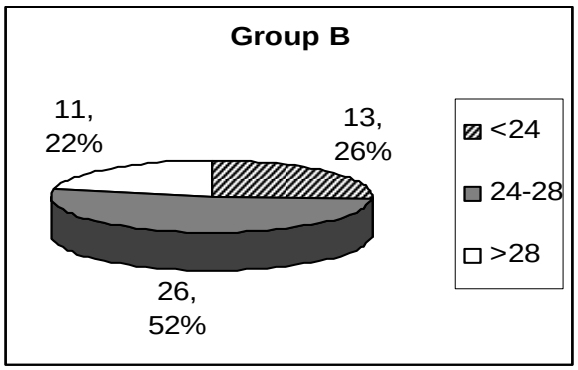




The infusion of sodium bicarbonate in study patients did not cause a significant difference in the PACO2 levels compared to the control group .p value was 0.255

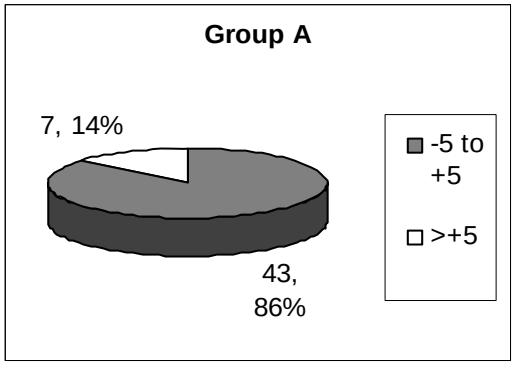
Fig 7: A SAMPLE- BICARBONATE

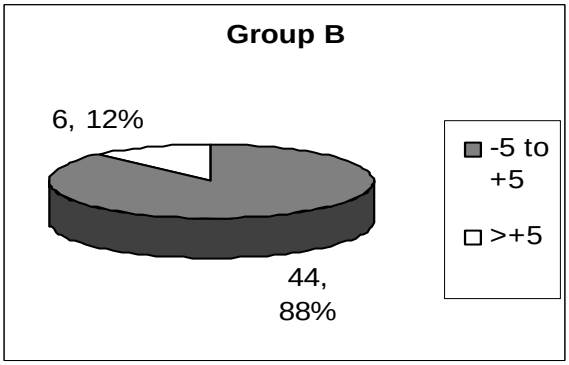




P value is 0.971 .Comparing Group A and Group B there is no statistically significant difference between the 2 groups in regards with raised or lowered bicarbonate levels before going on pump

Fig 8: A SAMPLE – BASE EXCESS

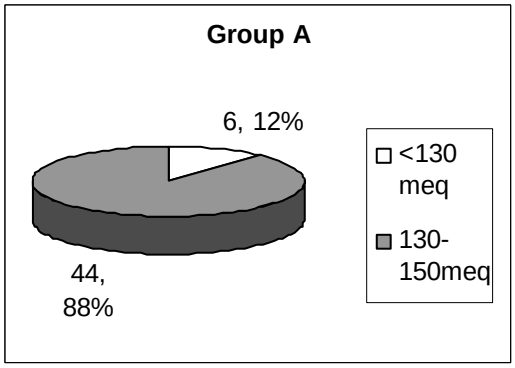


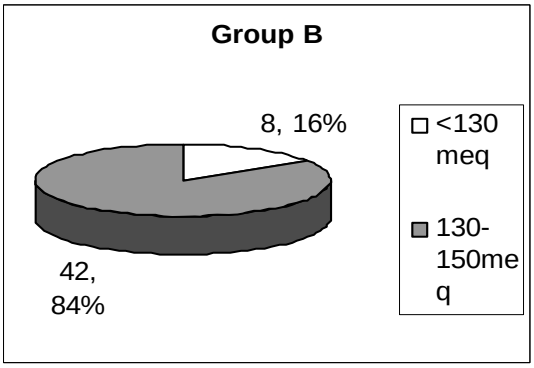


None of the patients developed a base excess of <-5 . 7 out of 50 in study group developed base excess of >5 and 6 out of 50 patients in the control group developed base excess of >5 . p value is 0.766 which is not statistically significant .

B SAMPLE : B sample is the arterial blood sample taken when the patient is on cardiopulmonary bypass .

Fig 9: B SAMPLE- SODIUM

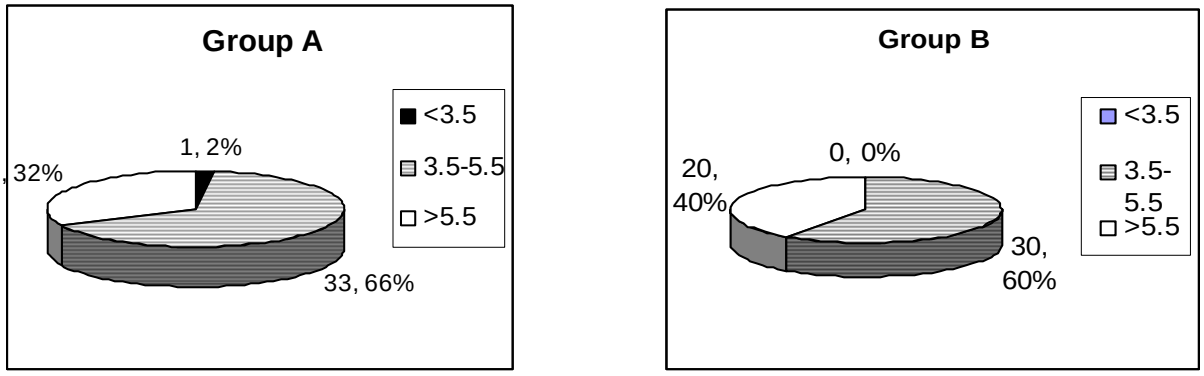




None of the patients in both the study groups had serum sodium levels >150 meq. 6 out of 50 patients in study group had serum sodium <130 meq whereas 8 out of 50 patients in the control group developed serum sodium <130 meq. There is no

statistically significant difference in both the groups when we compared the sodium levels .p value =0.564

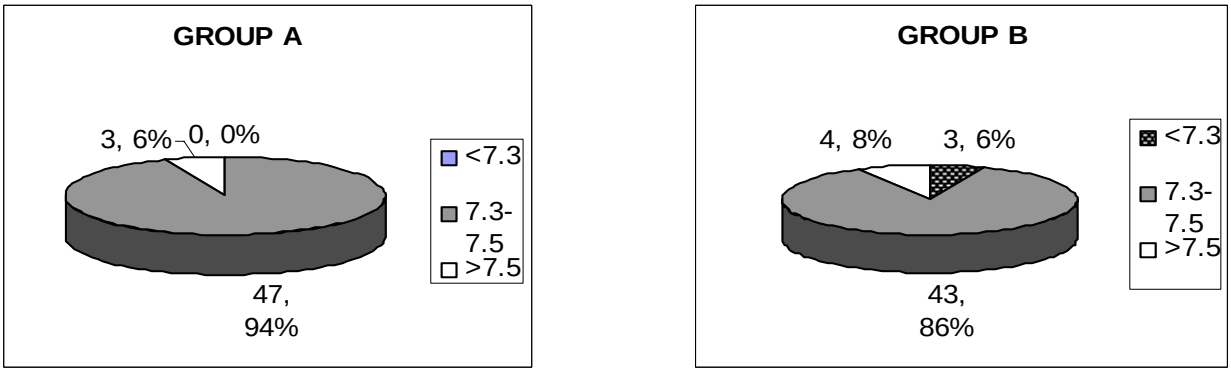
Fig 10: B SAMPLE - POTASSIUM



Study group :Out of 50 patients 1 developed serum K^+ <3.5 meq ,16 had serum K^+ >5.5 meq, and 33 had potassium in the normal range .

Control group :20 patients developed serum K^+ >5.5 and 30 had in the normal range. The p value is 0.452 . Hence the serum potassium values in both the groups are comparable with no significant difference.

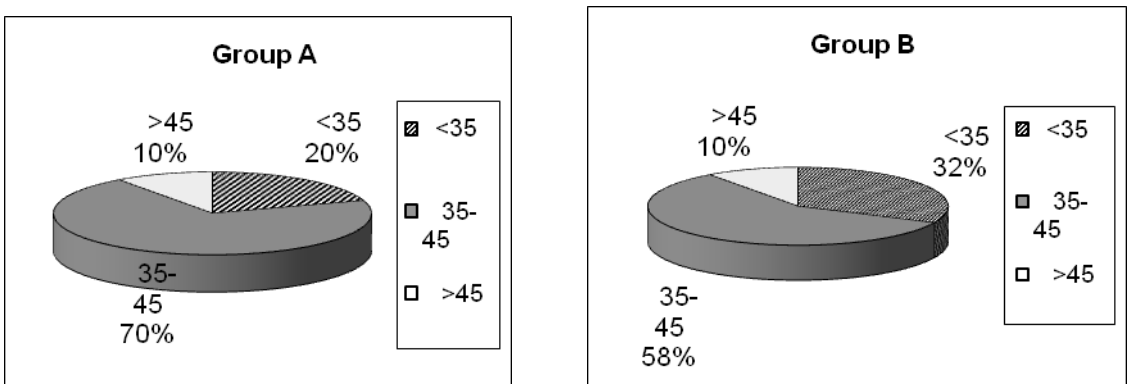
Fig 11: B SAMPLE- PH



Study group :3 out of 50 had pH >7.5 .Rest had ph in the normal range .Control group :4 out of 50 had pH >7.5,3 had pH <7.3 and the remaining had normal pH

P value is 0.190 .There is no statistically significant difference in both the groups with regards to the ph .

Fig 12: B SAMPLE : PACO2 (mm Hg)

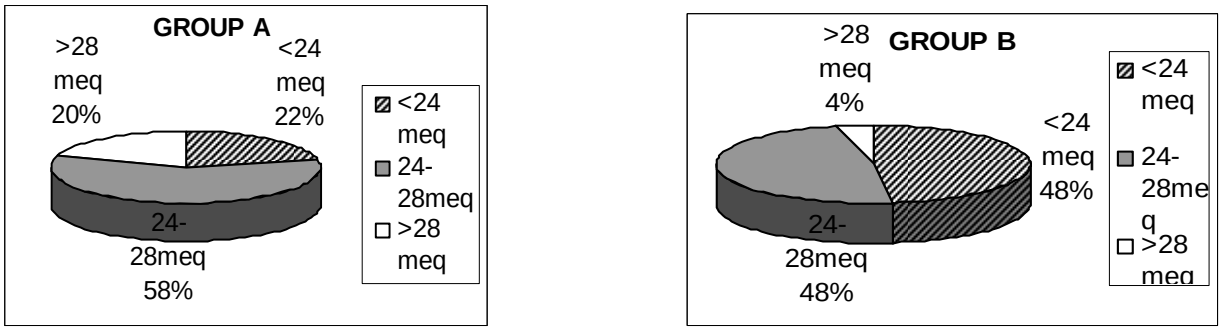


Study group :Out of 50 patients 5 had PACO2 >45 ,35 in the normal range and 10 in the group with PACO2<35 mm Hg

Control group :Out of 50 patients 5 had PACO2 >45,29 in the normal range and 16 with PACO2 of <35 mmHg

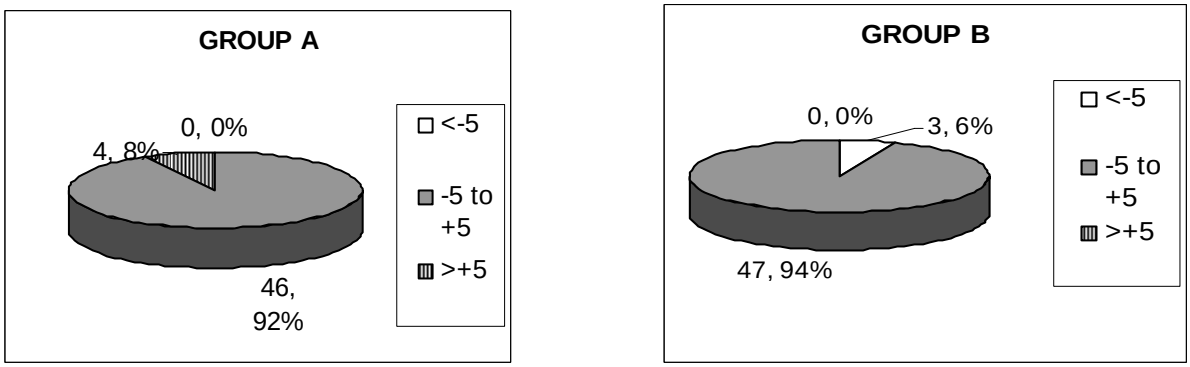
P value is 0.378 .Comparing Group A and Group B there is no statistically significant difference between the 2 groups with regards to raised or lowered PACO2 levels after going on pump .

Fig 13: B SAMPLE - BICARBONATE (meq)



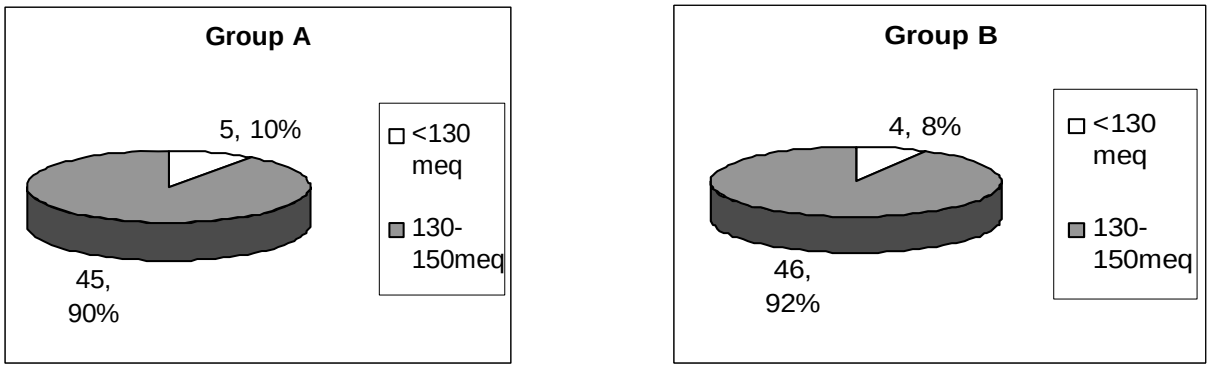
Out of 50 patients in the control group 24 patients had bicarbonate levels <24 .Out of the 50 patients in the study group only 11 developed serum bicarbonate levels <24 with a p value of 0.005 which is statistically significant .Out of 50 in the control group only 2 developed serum bicarbonate levels > 28 and in the study group 10 out of 50 developed alkalosis which is again significant .

Fig 14: B SAMPLE -BASE EXCESS



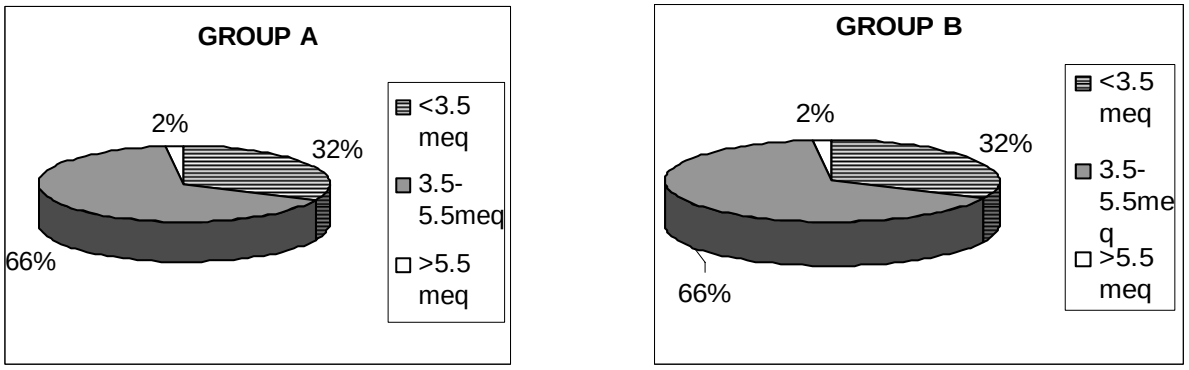
None of the patients in the study group developed base excess <-5and none in the control group developed base excess > +5 .However the base excesses values are comparable in both groups without any statistical significance p value = 0.039

Fig 15: C SAMPLE - SODIUM



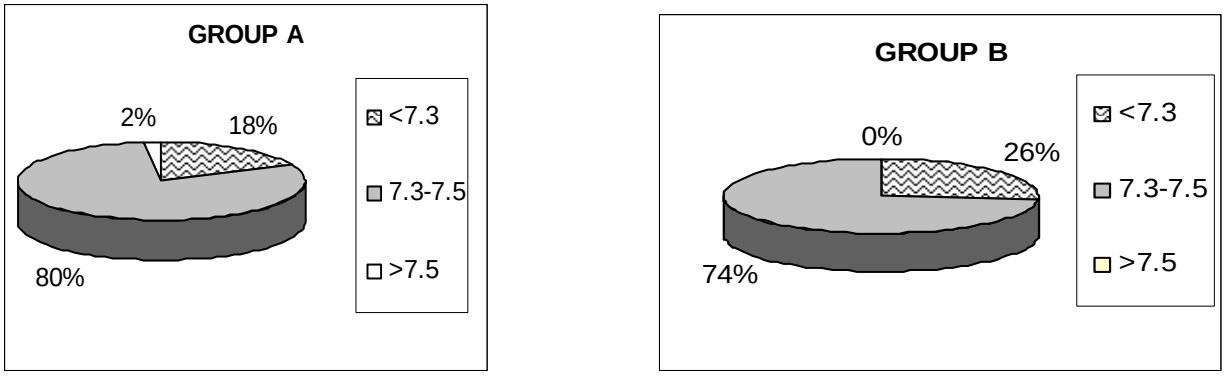
In both the study and the control groups none of the patients developed serum sodium >150 meq .Otherwise the serum sodium levels are comparable in both the groups with a p value of 0.727.

Fig 16: C SAMPLE-POTASSIUM



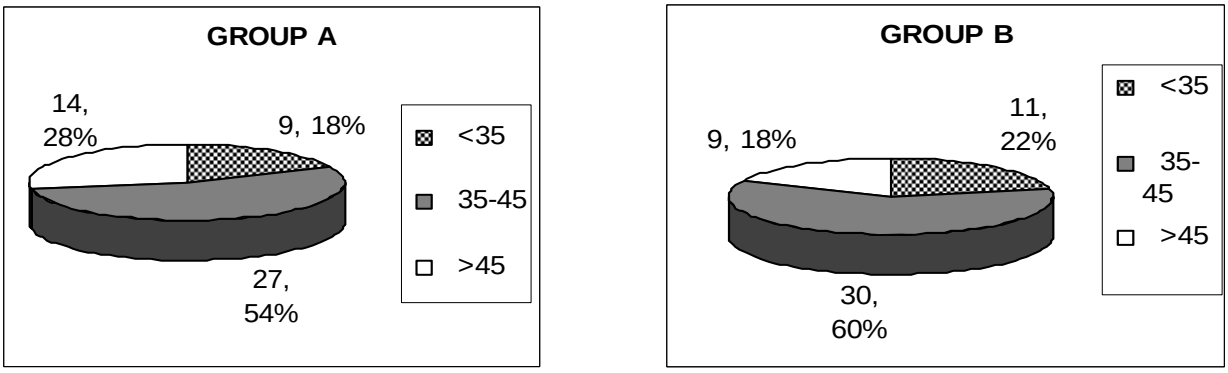
The potassium values are exactly same in both the study and control groups with a p value of 1.000

Fig 17: C SAMPLE - PH



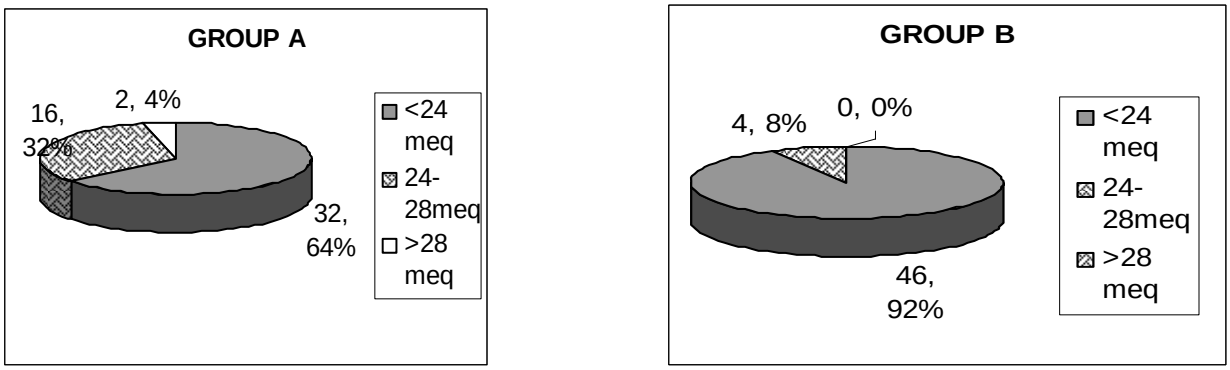
P value is0.228 .There is no statistically significant difference in both the groups in regards to the ph .

Fig 18: C SAMPLE -PACO2



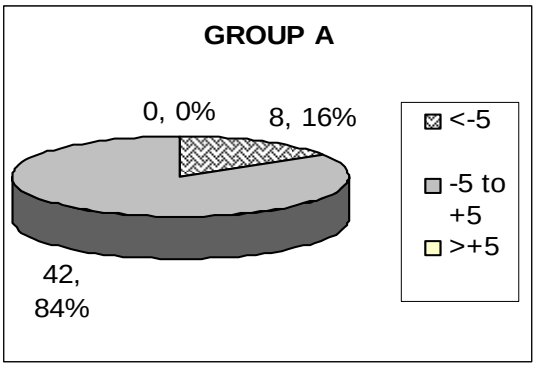
P value is 0.486 .Comparing Group A and Group B there is no statistically significant difference between the 2 groups with regards to raised or lowered PACO2 levels after coming off pump .

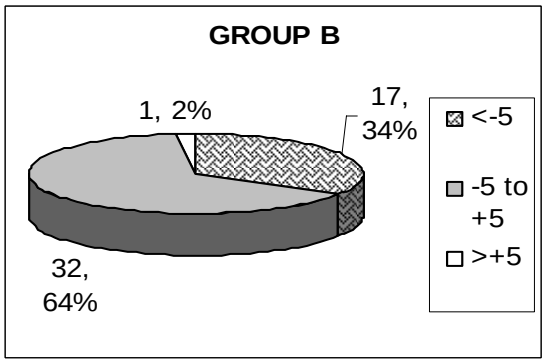
Fig 19: C SAMPLE - BICARBONATE (HCO3)



Out of the 50 patients who received sodium bicarbonate infusion ,32 patients had bicarbonate value <24 meq compared to 46 patients out of the 50 patients who received sodium chloride infusion. This was statistically significant with a p value of 0.003 which means that sodium bicarbonate infusion can actually reduce the metabolic acidosis which can occur otherwise .

Fig 20: C SAMPLE - BASE EXCESS





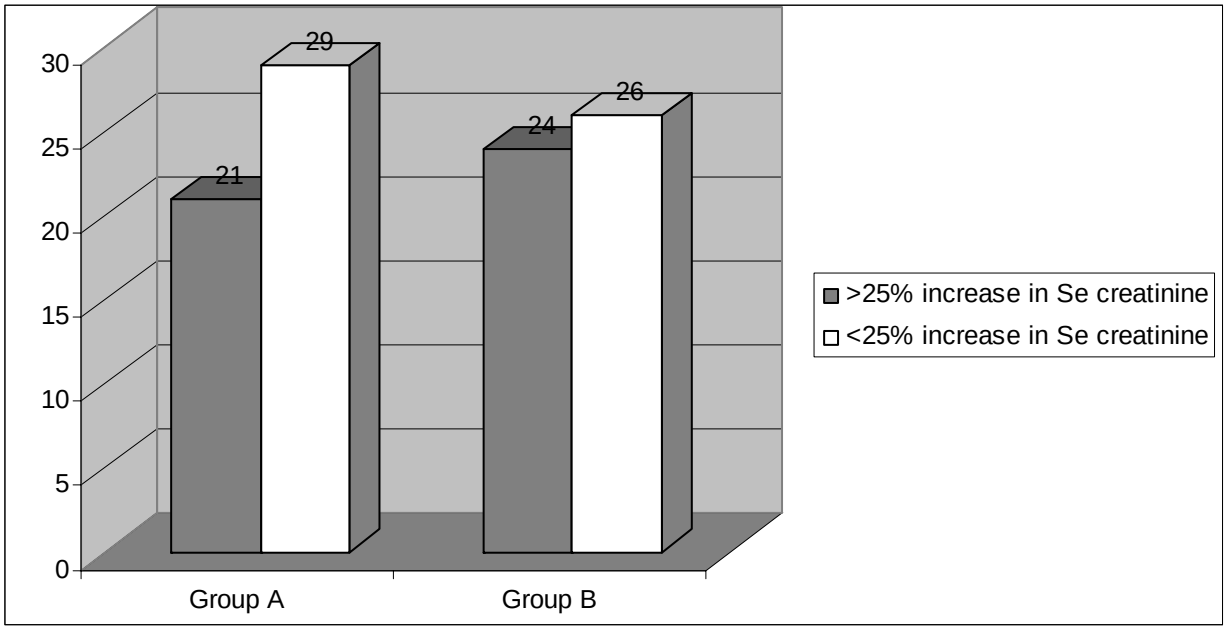
P value is 0.061 which means that there is no statistically significant difference between the two study groups in terms of base excess .

MORTALITY: There were 2 deaths which occurred during the study .One was a 50 yr old lady(study group) who underwent a redo MVR who went into low cardiac output syndrome immediately post op . she was started on high inotropic support .Due to clots in the pericardium she was taken up for a reexploration . Postoperatively she went into acute renal failure not responding to diuretics .She received repetitive dialysis, eventually went into liver failure and expired after 10 days .

The second case was that of a 69 year old gentle man (control group) who underwent a CABG .He developed worsening of renal functions postoperatively .He also had mesenteric ischemia . Laporotomy was done after 6 days .There was further worsening of renal functions and eventually he died after 3 days .

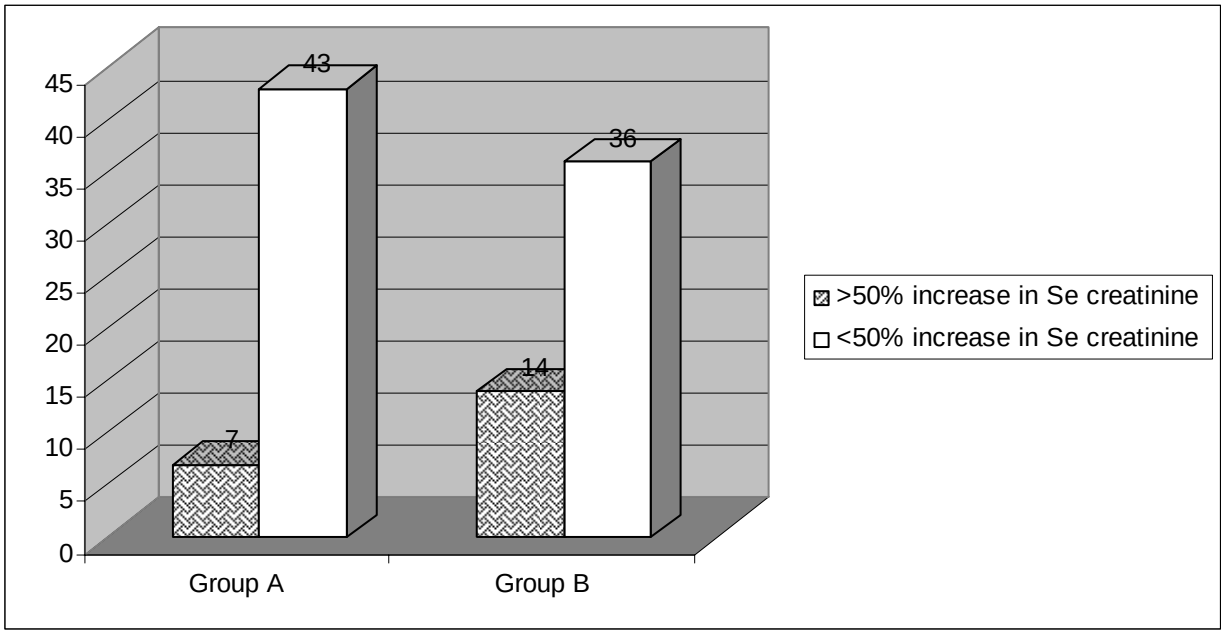
PRIMARY OUTCOME :

Fig 21:Proportion of patients developing acute renal dysfunction defined as postoperative increase in serum creatinine >25% of baseline within first 5 postop days.



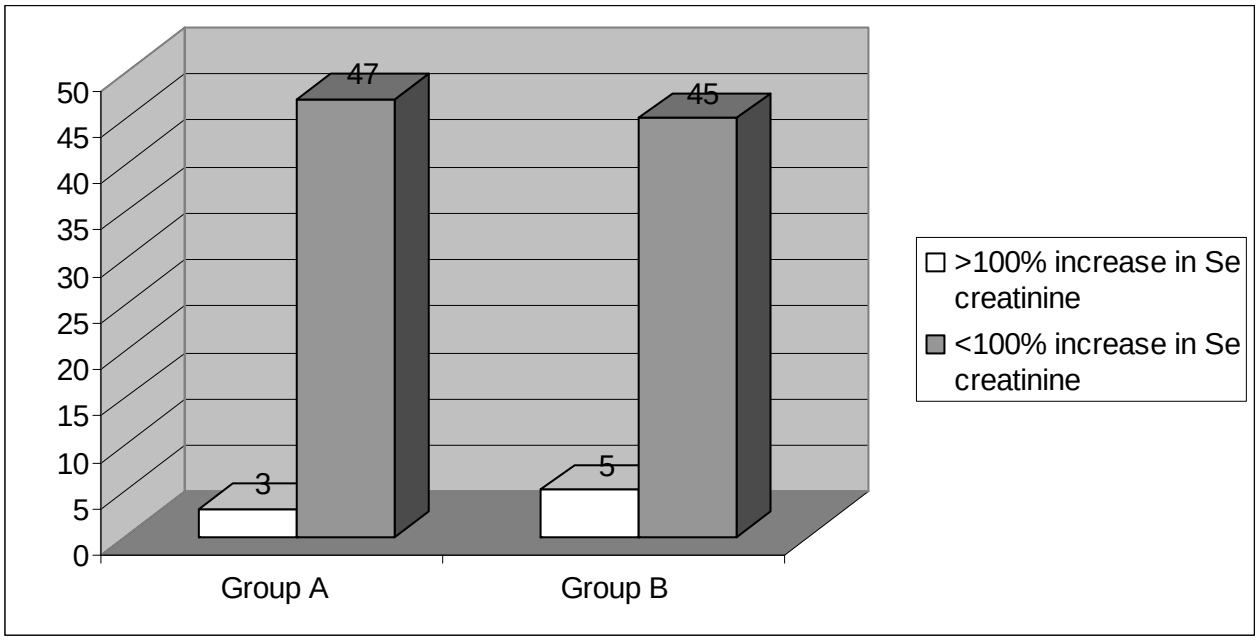
The p value is 0.546 which means that there is no significant statistical difference between the study group and control group in terms of post operative increase in Serum creatinine >25% from the baseline within the first five postoperative days .

Fig 22: Proportion of patients developing acute renal dysfunction defined as post operative increase in se creatinine>50% from the baseline



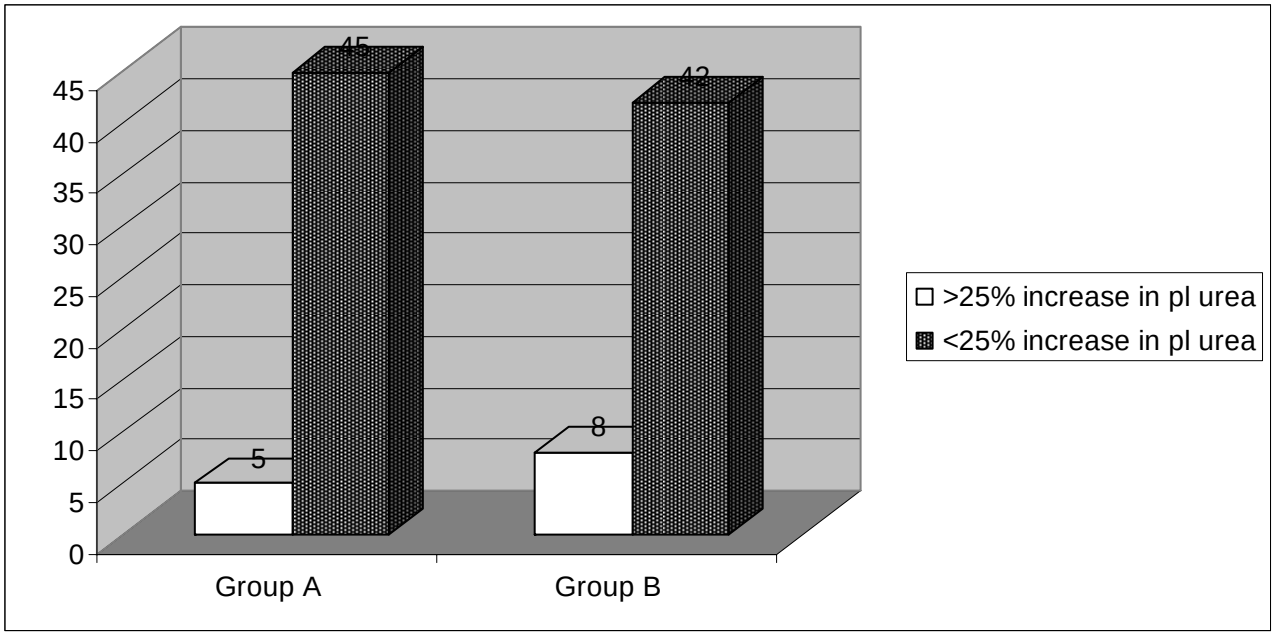
The p value is 0.086 which means that there is no significant statistical difference between the study group and control group in terms of post operative increase in Serum creatinine >50% from the baseline within the first five postoperative days .

Fig 23: Postoperative increase in serum creatinine >100% from the baseline



The p value is 0.461 which means that there is no significant statistical difference between the study group and control group in terms of post operative increase in Serum creatinine >100% from the baseline within the first five postoperative days .

Fig 24: Postoperative 25% increase in plasma urea from the baseline



There is no statistical difference between the study group and control group in terms of increase in plasma urea from the baseline .The p value being 0.198

Fig 25: GRAPH SHOWING TREND OF SERUM CREATININE IN BOTH THE STUDY AND CONTROL GROUP

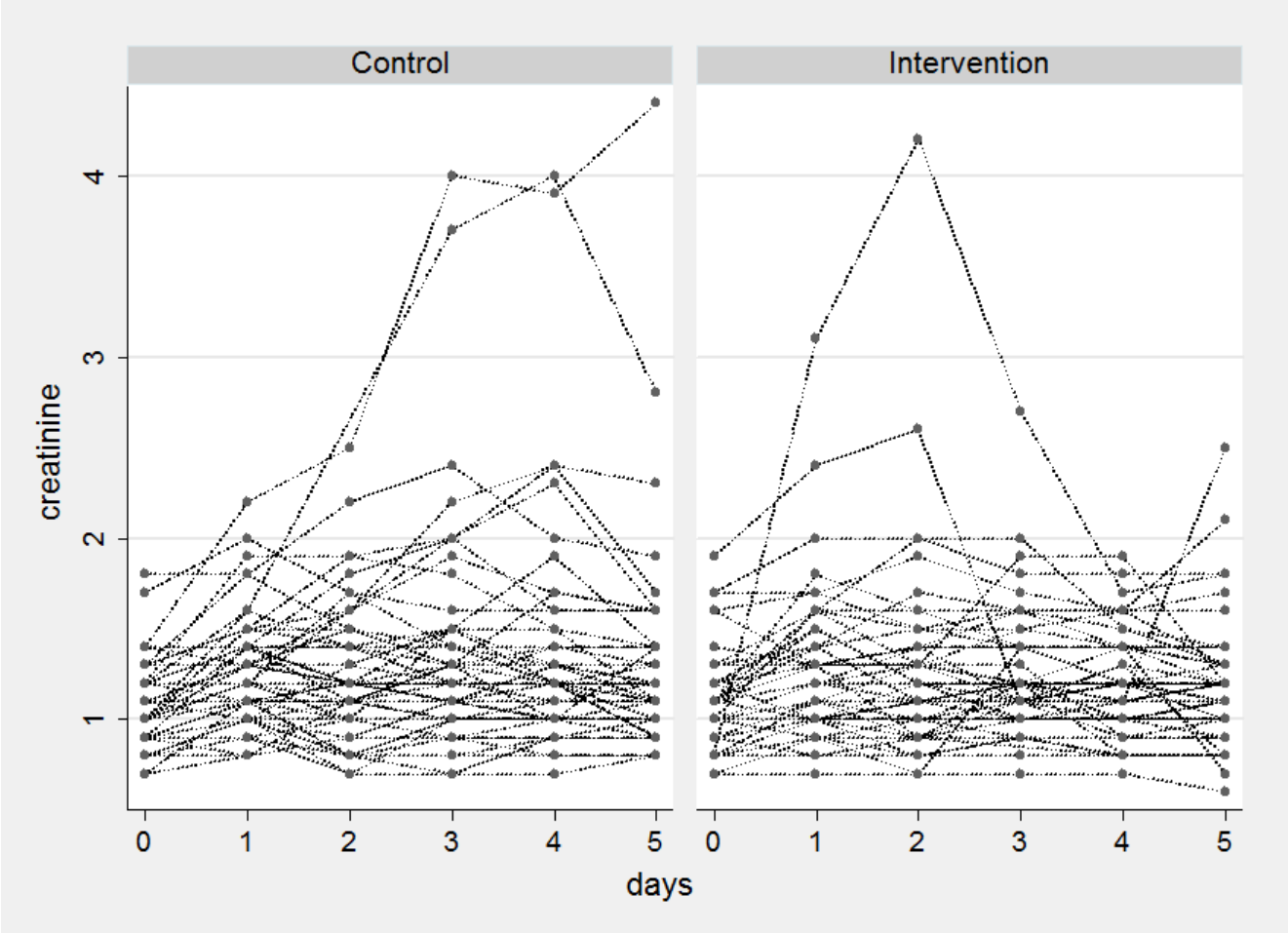
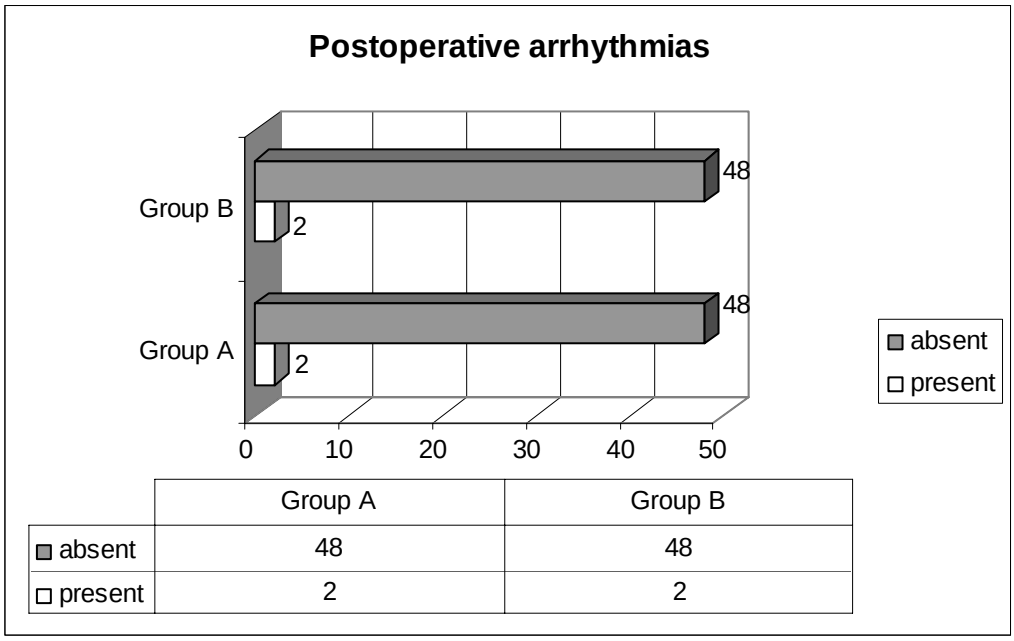


Fig 26: POSTOPERATIVE ARRHYTHMIAS



	Group A	Group B
absent	48	48
present	2	2

The incidence of post operative arrhythmias was same in both the study and control groups with p value of 1.000

DISCUSSION

We conducted a double-blind, randomized controlled clinical trial from march 2010 to june 2010 in the Department of Anaesthesia CMC Vellore .The aim was to investigate whether sodium bicarbonate infusion with preoperative intravenous loading to achieve urinary alkalinization could attenuate the creatinine rise associated with cardiopulmonary bypass in cardiac surgical patients at increased risk. We randomized 100 patients to receive either sodium bicarbonate infusion(study group) or sodium chloride infusion (control group) .All patients were Indians most of them from West Bengal and the other group mainly from Tamilnadu . All patients had elective cardiac surgery- either a CABG or a valve replacement .We enrolled patients with a variety of cardiac surgeries so that our results may have implications for a wide variety of cardiac cases .The internal validity of our results was strengthened by double blinding and central randomization .

This study was conducted based on another study done by Dr Michael Haase et al in Austin Hospital , Australia titled “Sodium bicarbonate to prevent increases in serum creatinine after cardiac surgery :A pilot double blinded , randomized controlled trial” .Here a cohort of 100 cardiac surgical patients at increased risk of postoperative acute renal dysfunction were selected and randomized to two groups

.The study group (n=50) to receive 24 hours of intravenous infusion of sodium bicarbonate (4 mmol/kg) and the control group (n=50) to receive sodium chloride (4 mmol/kg) .The sodium bicarbonate or sodium chloride infusion were given at a dose of 0.5 mmol/kg body weight (bolus) diluted in 250 ml of 5% dextrose water over 1 hour immediately after the induction of anaesthesia followed by continuous intravenous infusion of 0.15 mmol/kg/hr (maintenance) diluted in 1000 ml of 5% dextrose over 23 hours (total dose of 4 mmol/kg over 24 hrs) .

The primary outcome measure was the proportion of patients developing acute renal dysfunction defined as a postoperative increase in plasma creatinine concentration >25% of baseline within the first five postoperative days. Secondary outcomes included changes in plasma creatinine, plasma urea, urinary neutrophil gelatinase-associated lipocalin, and urinary neutrophil gelatinase-associated lipocalin/urinary creatinine ratio. Patients were well balanced for baseline characteristics. According to this study, sodium bicarbonate infusion increased plasma bicarbonate concentration , base excess, plasma pH, and urine pH and was statistically significant. Fewer patients in the sodium bicarbonate group (16 of 50) developed a postoperative increase in serum creatinine compared with control (26 of 50) with an odds ratio of 0.43 ($p = 0.043$). The increase in plasma creatinine, plasma urea, urinary neutrophil gelatinase-associated lipocalin, and urinary neutrophil gelatinase-associated lipocalin/urinary creatinine ratio was less in

patients receiving sodium bicarbonate. There were no significant side effects. Hence the conclusion was that sodium bicarbonate loading and continuous infusion was associated with a lower incidence of acute renal dysfunction in cardiac surgical patients undergoing cardiopulmonary pass. This trial was based on the principle that the rise in serum creatinine after cardiopulmonary bypass might be due to a combination of tubular injury induced by reactive oxygen species, complement activation, and free hemoglobin release .Hence the first study done was successful in establishing these facts .

Similar to this study, we also measured the proportion of patients developing acute renal dysfunction defined as postoperative increase in serum creatinine >25% of baseline within first 5 postoperative days (primary outcome). In the control group out of 50 patients 24 developed acute renal dysfunction and out of the study group only 21 out of 50 patients developed renal dysfunction .However these findings were not statistically significant (p value =0.546).Hence we concluded that sodium bicarbonate infusion did not cause any risk reduction for acute renal dysfunction in cardiac surgical patients .

Also in previous RCTs, urine alkalinisation with sodium bicarbonate infusion for patients undergoing contrast media infusion (another condition where free oxygen radical generation is involved) has been found to attenuate acute kidney injury .

In our study, there was no significant difference between both the groups in baseline characteristics such as age ,sex ,baseline serum creatinine and plasma urea. We included patients who are at a high risk for renal dysfunction in this study which included age >60 yrs, preexisting renal impairment (preop serum creatinine >1.3 mg%),NYHA class 3/4 or impaired LVF (LVEF<=45%) , valvular surgery or concomitant valvular and coronary artery bypass graft surgery, redo cardiac surgery, type 2 Diabetes Mellitus .All the inclusion criteria characteristics were also comparable .

Preoperative comorbidities like systemic hypertension, hypercholesterolemia, atrial fibrillation and recent MI were also comparable in both the groups . Preoperative medications were also similar in both the groups .

Intraoperatively, the cardiopulmonary bypass time was approximately 78 minutes in both the groups .

RENAL OUTCOME

As mentioned in the literature review ,the latest diagnostic criteria for acute kidney injury is classified into stage (i) increase in serum creatinine 1.5-2 times from baseline ,stage (ii) increase in serum creatinine 2-2.5 times,stage (iii)increase in serum creatinine >3 fold. Accordingly we measured the primary outcome of acute renal dysfunction as postoperative increase in serum creatinine >25% of baseline within

first 5 postop days .Secondary outcomes measured included (a) post operative increase in serum creatinine>50% from the baseline (b) post operative increase in serum creatinine >100% from the baseline and (c)post operative increase in plasma urea >25% from the baseline .Although less number of patients from the study group developed acute renal dysfunction, the results were not statistically significant .

OTHER OUTCOMES

During the surgery, 3 Arterial Blood Gas estimations were done .There was significant metabolic acidosis in patients in the control group compared to the study group in terms of serum bicarbonate. Hence we can infer that sodium bicarbonate was useful intraoperatively to decrease the incidence of acidosis .

SAFETY

We checked for side effects of sodium bicarbonate infusion like hypernatremia, hypokalemia, any peri operative arrhythmias .None of the patients in the study group developed any of the above mentioned complications which was statistically significant .

COMPARISON OF THE TWO STUDIES :

Both the studies were done in a similar way but had contradicting results .Both the studies were similar in most aspects except for the population group. The first study

mainly had a population from Australia .Our study involved a mixed Indian population .

The first study measured other parameters like urinary neutrophil gelatinase-associated lipocalin (NGAL) concentration and urinary NGAL/urinary creatinine ratio within the first 24 hours after commencement of cardiopulmonary bypass.(38) .Neutrophil gelatinase-associated lipocalin (NGAL) is expressed and secreted by immune cells, hepatocytes, and renal tubular cells in various pathologic states. NGAL acts as a growth and differentiation factor in multiple cell types, including developing and mature renal epithelia, and some of this activity is enhanced in the presence of siderophore:iron complexes. NGAL is massively upregulated after renal tubular injury and may participate in limiting kidney damage.(39, 40) Hence it is a very sensitive marker for acute kidney damage .However we could not use NGAL due to nonavailability and high costs of the same .

Our interest in sodium bicarbonate to prevent renal dysfunction came up after reviewing a few other studies also . Merten et al in 2004 studied the effect of sodium bicarbonate infusion on contrast induced nephropathy. A prospective, single-center, randomized trial conducted by them on 119 patients with stable serum creatinine levels of at least 1.1 mg/dL who were randomized to receive a 154-mEq/L infusion of either sodium chloride (n = 59) or sodium bicarbonate (n = 60) before and after iopamidol administration (370 mg iodine/mL). Serum

creatinine levels were measured at baseline and 1 and 2 days after contrast. Contrast-induced nephropathy was defined as an increase of 25% or more in serum creatinine within 2 days of contrast. The primary end point of contrast-induced nephropathy occurred in 8 patients infused with sodium chloride but in only 1 of those receiving sodium bicarbonate; Hydration with sodium bicarbonate before contrast exposure is more effective than hydration with sodium chloride for prophylaxis of contrast-induced renal failure.(19)

Wong et al studied the use of various therapies in contrast induced nephropathy(CIN).CIN is usually defined as an increase in serum creatinine of 44 μmol litre^{-1} (0.5 mg dl^{-1}) or a 25% increase from the baseline value 48 h after intravascular injection of contrast media. It is a common and potentially serious complication of the use of iodinated contrast media in patients at risk of acute renal injury .Impact of CIN on clinical outcomes has been evaluated most extensively in patients undergoing percutaneous coronary intervention where it is associated with increased mortality both in hospital and at 1 year after the intervention. This trial demonstrated that infusion of isotonic sodium bicarbonate was associated with a smaller increase in serum creatinine compared with isotonic saline, suggesting a benefit from alkalinization of the urine. (16).

However we found that sodium bicarbonate was not efficacious to prevent increases in serum creatinine after cardiac surgery . The only benefit of sodium bicarbonate infusion revealed in this study was that metabolic acidosis(incurred by CPB period) can be avoided or the incidence can be kept low. The other important finding in this study is that there is a significant40-50% incidence of high risk of patients developing renal dysfunction after CPB .The results of this study may have been different if we had been more strict in the inclusion criteria and included only those patients with preexisting renal dysfunction as depicted by elevated serum creatinine .These findings need to be confirmed or refuted by further clinical investigations in other geographic and institutional settings .

LIMITATIONS

1. The recommended target of sample size could not be achieved during the time period of the study .This could have influenced the outcomes of the study .
2. The results of this study may have been different if we had been more strict in the inclusion criteria and included only those patients with preexisting renal dysfunction as depicted by elevated serum creatinine
3. We could not use highly sensitive markers of renal dysfunction like NGAL due to high costs involved and non availability.

CONCLUSIONS

1. There is a significant 40-50% incidence of patients developing acute renal dysfunction after cardiopulmonary bypass in the high risk group.
2. Sodium bicarbonate infusion did not cause any decrease in incidence of renal dysfunction in cardiac surgical patients .
3. Sodium bicarbonate infusion was useful intraoperatively to decrease the incidence of metabolic acidosis otherwise associated with cardiopulmonary bypass .
4. None of the patients developed side effects like hypernatremia, hypokalemia, and perioperative arrhythmias which was statistically significant .

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ANNEXURE I

PATIENT INFORMATION SHEET

Patients who need to undergo a cardiac surgery often need to undergo cardiopulmonary bypass.This means that the heart and lung work will be taken care of by a machine (heart lung machine)during the operation. However it's been proved that patients on cardiopulmonary bypass have increased chance of kidney damage .This study is an attempt to see if infusion of sodium bicarbonate for 24 hours (low dose)can decrease the incidence of this complication.This is not a new drug. It is used very often during routine cardiac surgeries.During this surgery there is chance of body sodium and bicarbonate levels going up.But these are routinely monitored and treatment can be given promptly.

For this study you will be randomly chosen to get a low dose of either sodium bicarbonate or normal saline infusion for 24 hours . Blood samples will be taken during and after surgery to check sodium , potassium , acid base status and tests to know the kidney functions .These tests are routinely done after any cardiac surgery.

However volunteering for this study is optional and the care that you receive in this hospital will not be affected by your decision

ANNEXURE II

INFORMED CONSENT

I _____, Hosp no :_____
have been explained in detail about the study .I am willing to volunteer at my own free will and am aware that I can withdraw at any time without it affecting my medical care in this hospital.

Doctor's name:
Signature: Signature of the patient

ANNEXURE III

DATA ENTRY PROFORMA

Serial no:

Date:

Name of the patient:

Name of the surgery:

Hospital no: Age: Weight:

INTAROPERATIVE VALUES:

	A	B	C
Serum sodium			
Serum potassium			
ph			

POST OPERATIVE VALUES:

Post op	Day 1	Day 2	Day 3	Day 4	Day 5
Serum creatinine					

Post op	Day 1	Day 2	Day 3
Blood urea			
Serum sodium			
Serum potassium			
ph			

MASTER SHEET