METABOLIC ALKALOSIS IN THE PAEDIATRIC CARDIAC INTENSIVE CARE UNIT - A PROSPECTIVE OBSERVATIONAL STUDY

A DISSERTATION SUBMITTED TO

SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY

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BY

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IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR

THE AWARD OF THE DEGREE OF

D.M. CARDIOTHORACIC AND VASCULAR ANAESTHESIOLOGY

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DECLARATION

I hereby declare that this thesis entitled, "***Metabolic alkalosis in the paediatric cardiac intensive care unit – A Prospective Observational Study***" has been prepared by me under the supervision and guidance of **Dr. Suneel P R**, Division of Cardiothoracic and Vascular Anaesthesiology, Department of Anaesthesiology, at Sree Chitra Tirunal Institute for Medical Sciences & Technology, Thiruvananthapuram and **Dr. Baiju S Dharan**, Professor and Head, Division of Cardiothoracic and Vascular Surgery, Sree Chitra Tirunal Institute for Medical Sciences and technology, Thiruvanthapuram.

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- Dr. Diana Thomas

Abbreviations

ABG	Arterial Blood Gas
AG	Anion gap
ALCAPA	Anomalous left coronary artery from pulmonary artery
BE	Base Excess
BE_B	Base Excess of whole blood
BSA	Body Surface Area
CPB	Cardiopulmonary Bypass
ECF	Extracellular fluid
FFP	Fresh frozen plasma
ICU	Intensive Care Unit
IQR	Interquartile range
IVF	Intravenous Fluid
PCICU	Paediatric Cardiac Intensive Care Unit
PDA	Patent Ductus Arteriosus
POD	Postoperative day
RACHS	Risk Adjustment in Congenital Heart Surgery
RV	Right ventricle
SBE	Standard Base Excess
SBE_{Alb}	SBE due to albumin

SBE_{Cl}	SBE due to chloride
SBE_{FW}	SBE due to free water
SD	Standard deviation
SID	Strong Ion Difference
TOF	Tetralogy of Fallot

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1. INTRODUCTION

Metabolic alkalosis is the most common acid base disorder occurring in the paediatric intensive care unit. Post cardiac surgery infants are particularly prone to this condition due to regular use of diuretics in the immediate postoperative period. However data pertaining to metabolic alkalosis after paediatric cardiac surgery is sparse in the existing literature. One of the major studies that looked into metabolic alkalosis in this population of children was by van Thiel et al. in 2005, wherein 186 consecutive cardiac operations in children less than 2 years age, were analysed.[1] Some of the factors that showed significant association with development of metabolic alkalosis were a younger age, preoperative ductal dependency, use of cardiopulmonary bypass and haemodilution.

Arterial blood gas (ABG) analysis in itself has undergone major changes in practice and understanding and multifactorial causation of metabolic alkalosis has been emphasised. The role of chloride and its association with metabolic alkalosis has been increasingly studied. The physiological and organ system effects of metabolic alkalosis, especially in the setting of critically ill post cardiac surgery patients need to be acknowledged. Early diagnosis and treatment of this condition is mandatory.

The method of acid base analysis to be adopted has been a subject matter for great debate since the 1950s. The three approaches used to acid base analysis are the bicarbonate centred approach favoured in North America, the base excess method practised in Europe and the new physicochemical method popularised by Stewart since 1981. The bicarbonate centred approach is useful to determine the primary and secondary acid base changes without quantifying them. The base excess method helps quantifying the non-respiratory or purely metabolic component of the acid base changes. Stewart method emphasises a quantitative approach to acid base chemistry; the Stewart method provides the ability to not only diagnose acid base disorder but also to quantify them.[2] We have used the standard base excess

approach to acid base analysis with further partitioning of the standard base excess as advocated by Berend.[3]

Subsequent studies in this population focussed on the management of metabolic alkalosis with acetazolamide therapy, finding it to be a reliable drug.[4,5] However, the morbidity and mortality associated with metabolic alkalosis remains largely unexplored.

2. AIMS AND OBJECTIVES:

Primary objective:

To study the incidence of metabolic alkalosis in post-surgical infants admitted in the paediatric cardiac intensive care unit (PCICU).

Secondary objectives:

1. To determine the factors associated with development of metabolic alkalosis among post-surgical infants admitted in PCICU
2. To determine the effect of metabolic alkalosis on duration of mechanical ventilation among post-surgical infants admitted in PCICU

3. REVIEW OF LITERATURE

3. 1 *Introduction To Blood Gas Analyses*

Acid base homeostasis and pH regulation form the foundation for normal cell metabolism, physiology and its functioning. Derangements have to be picked up at the earliest, before cellular and organ level manifestations set in, to avoid irreparable damages. When in the 1950s Severinghaus combined methods of measuring oxygen and carbon dioxide partial pressures in blood, into creation of a blood gas analysis apparatus, the medical community welcomed it with much fervour.[6] Being termed the most important laboratory test in patients who are critically ill, arterial blood gas analysis has been vigorously studied over the ages. Acid base disorders have been quantified using one of three major methods namely, the physiological approach, the base excess approach and the physicochemical approach, also known as the Stewart method.[7]

The physiological approach is the most commonly followed method of analysis which is based on the carbonic acid-bicarbonate buffer system, which is fundamentally the acid base interaction between lungs and renal system. Popularised in the 1960s by Relman and Scwartz, this method embraces the Bronsted-Lowry definitions of acids and bases and derives pH as a function of hydrogen ion concentration based on the Henderson–Hasselbalch equation.

At a parallel period, but across the Atlantic, Siggard-Andersen et al. introduced the Van Slyke equation to quantify the role of non-respiratory components in acid base balance and introduced blood base excess (BE) as its index.[8,9] Base Excess of whole blood is defined as the amount of strong acid (millimoles/litre) that when added in vitro to one litre of oxygenated whole blood returns the sample to standard conditions, i.e. pH of 7.40, $PaCO_2$ of 40 mmHg at temperature of 37˚C. BE is, in other words, the difference between the observed

and the normal buffer base concentration. The concept of base excess was criticised because the changes in the respiratory acid-base status affects the value of base excess. That is, the whole blood base excess does not reflect the metabolic component of acid-base balance alone, but could be influenced by the respiratory status. The critics of base excess also pointed out that the base excess of whole blood is not reflective of extracellular (ECF) acid-base state.[10] ECF consists of erythrocytes, plasma and interstitial fluid. ECF is a mobile fluid reservoir that is trapped between the cells. ECF is the carrier fluid that transports nutrients to cells for utilization and waste products for excretion. ECF flows through arteries, veins and lymphatics mixing freely. ECF is the medium in which acid-base changes are regulated and therefore, ECF is the fluid of interest in the study of acid-base changes.[11] The ECF cannot be sampled directly; therefore a hypothetical model of the ECF was created by diluting the arterial blood threefold with its own plasma. The base excess of the ECF is called the Standard Base Excess (SBE). To summarise, the SBE is the base excess calculated for anaemic blood with a haemoglobin concentration of 5 g/dL, that is the titratable hydrogen ion concentration, that is, the amount of acid (HCl) or alkali (NaOH) that needs to be added to an extracellular fluid model to return pH 7.40 when the $PaCO_2$ is 40 mm Hg and the temperature is 37^{o}C. Direct titration may be considered the reference method, but in practice, the concentration of titratable hydrogen ions is based on the knowledge of the titration curve of blood or plasma together with the actual pH. The blood gas machines provide the SBE calculated using the van Slyke equation with the same ease that the blood gas machines report actual bicarbonate.[9]

The physicochemical approach advocated by Stewart in 1981, dismissed the role of serum bicarbonate and hydrogen ions in determining blood pH and questioned the utility of base excess method in differentiating complex acid-base disorders.[12] The physicochemical method embraces the Arrhenius definition of acid-base. According to the Arrhenius

definition, cations such as Na^+, K^+, Mg^{2+} and Ca^{2+} are considered bases as they bring hydroxyl ions of water into solution. Anions such as chloride and lactate are considered acids as they bring hydrogen ions of water into solution. Bicarbonate and pH (or its surrogate, hydrogen ion activity) is not considered the prime movers in any acid base imbalance according to the Stewart model. Bicarbonate and hydrogen ions are considered dependent variables and their concentration is dependent on the concentration of strong ions and non-volatile buffers. In the Stewart method, the acid base status of blood is dependent on three factors, $PaCO_2$, the strong ion difference (SID) and the total concentration of non-volatile weak acid buffer.[12]

SID is defined as the difference between the completely dissociated strong cations and strong anions in plasma, which includes serum electrolytes and a change in this balance is deemed causative of metabolic acid base disorders. A widening of the SID by altered water and electrolyte balance causes metabolic alkalosis. A complete SID equation involves the sum of all cations in plasma such as Na^+, K^+, Mg^{2+} and Ca^{2+} and the sum of all measured anions such as chlorides and lactate. Since plasma must satisfy the laws of electroneutrality, the sum of all positive ions and sum of all negative ions must be equal and the SID should be zero. This is illustrated by drawing “ion-block" histograms, called the Gamblegram[13]. But in life, the sum of all positive ions and negative ions, which is called the SID, approximates 40-44 mEq/L [12] This is because not all negatively charged ions can be measured. The SID so calculated is referred to as “apparent SID”. Non-volatile weak acids are the next important factors that determine acid base equilibrium. Weak acids are partly dissociated acids that act as buffers in plasma, like phosphates and albumin, also are determinants of metabolic acidosis and alkalosis. Albumin is important in critically ill patients. Hyperphosphatemia is an issue only in chronic renal failure. Mechanistically, the role of weak acids is opposite to

that of SID. Increase in weak acids (hyperalbuminemia) causes acidosis whereas hypoalbuminemia causes alkalosis.[14]

Berend advises a three step approach to diagnose an acid-base disorder by incorporating base excess approach and Stewart method.[3] The reference values for analysis are pH 7.40, $PaCO_2$ 40 mmHg and 0±2 mmol/L for standard base excess. The first step is to assess the relation between pH, PCO_2 and base excess, which will reveal the primary acid base disorder. Next step is to evaluate the secondary response, the compensatory changes the body undertakes, to this primary disorder. The third step is to consider the presence of mixed metabolic acid base disorders by evaluating the anion gap or partitioning the base excess, the former being an easier method.

The blood gas machine reports two base excess: the base excess of whole blood which changes with respiratory abnormalities and the Standard base excess which is an exclusive measure of metabolic component. Blood gas machines abbreviate base excess of whole blood as BE_B and standard base excess as BE_{ECF}. We have exclusively used the standard base excess in the analysis of the metabolic component of acid base balance. The National Committee for Clinical Laboratory Standards recommends using devices that calculate standard base excess with a single algorithm and cautions that standard base excess should not be confused with base excess of blood [15]. Another popular term in the literature is standard base deficit, which is the negative version of standard base excess and is calculated as $-1 \times$ SBE. Metabolic alkalosis causes positive standard base excess and metabolic acidosis causes negative standard base excess. In this study we refer to metabolic acidosis as negative standard base excess and not as base deficit. The reason for this nomenclature is historical as well as convenience as blood gas machines report this parameter as positive or negative base excess[3].

Figures 1 and 2 below depict the algorithm proposed by Berend to evaluate acidaemia and alkalemia respectively, following his three step approach.

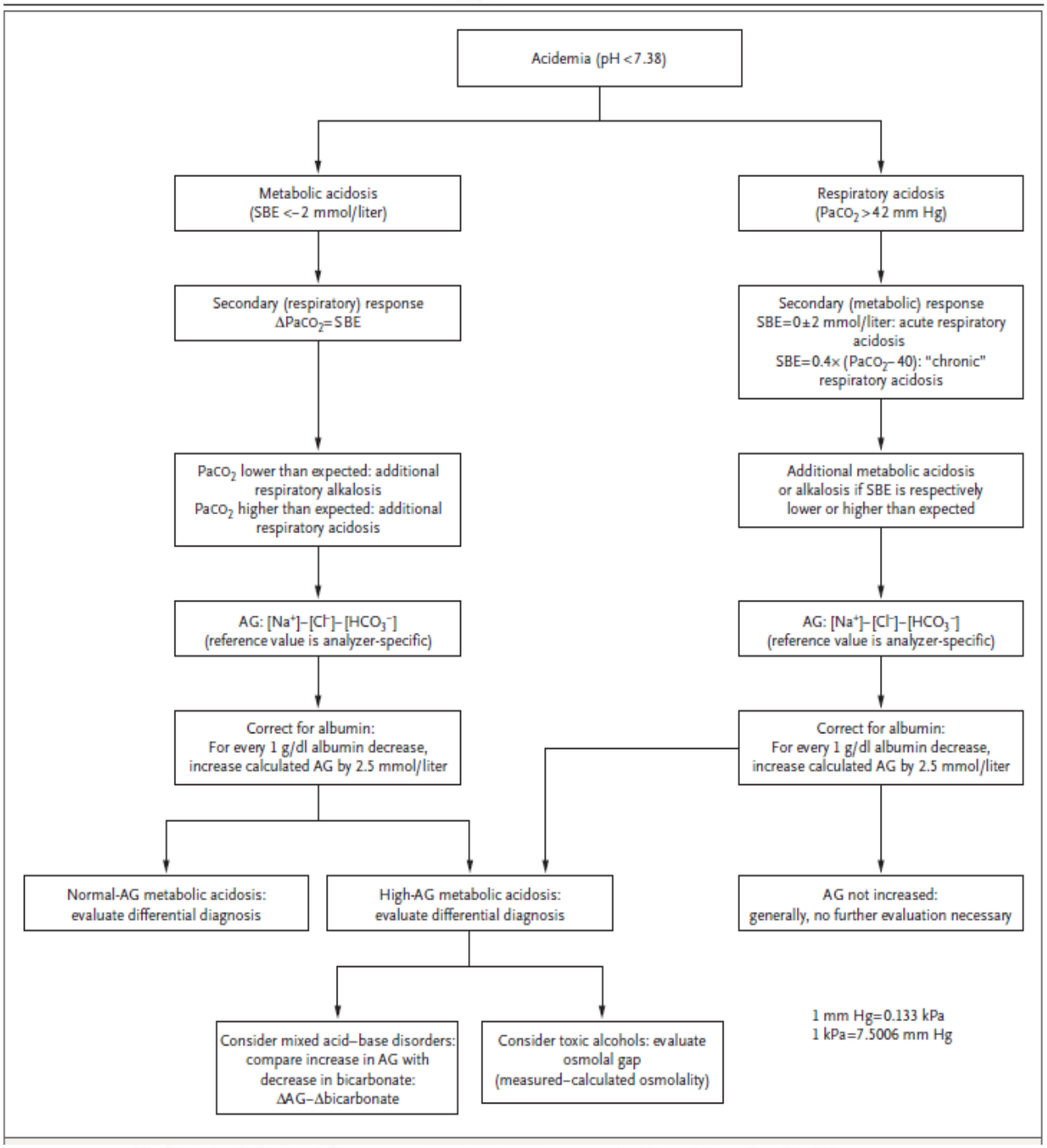

Fig.1. Berend's Algorithm for Evaluating Patients with Acidemia[3]

AG denotes anion gap, the delta symbol "change in," $PaCO_2$ partial pressure of arterial carbon dioxide, and SBE standard base excess.

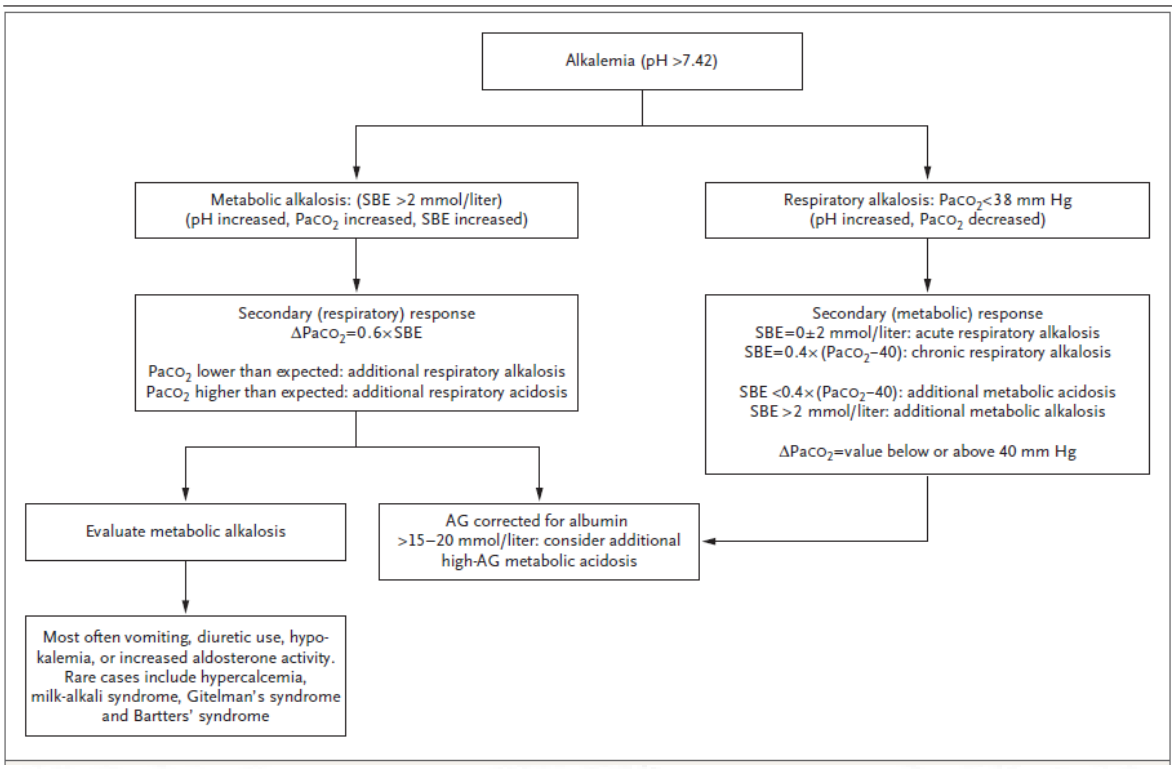

Fig. 2. Berend's Algorithm for Evaluating Patients with Alkalemia [3]
SBE denotes standard base excess; PaCO2, partial pressure of arterial carbon dioxide. AG, anion gap

Nomenclature of standard base excess:

Partitioning base excess into four of its components gives further insight into the acid base disorder and helps identify the causative factor. Assuming that a patient initially has a sodium level of 140 mmol/L, a chloride level of 104 mmol/L, and an albumin level of 4 g/dL, four components of base excess are defined as follows: SBE due to free water (SBE_{FW}), SBE due to chloride (SBE_{Cl}) , SBE due to albumin and SBE due to unmeasured anions.[16] Berend used the following formulae to define these values[3], a slight modification from what was first introduced by Giflix et al.[16]:

Table 1: Partitioning Of Standard Base Excess (SBE)

Componennts	Equation
SBE due to free water (SBE_{FW})	Free water effect (based on sodium) = 0.3 × (Na − 140)
SBE due to chloride (SBE_{Cl})	Chloride effect corrected for sodium = 104 − (Cl × 140 ÷ Na)
SBE due to albumin (SB_{Alb})	Albumin effect (mmol/liter) = (0.148 × pH − 0.818) × (40 − albumin in g/liter)
SBE due to unmeasured anions	Unmeasured anion effect = SBE − SBE_{FW} − SBE_{Cl} − SBEalb

Adapted from Berend's paper on diagnostic uses of base excess.[3, 16]
SBE, serum base excess; Cl, Chloride; Na, sodium

The pathophysiology of metabolic alkalosis is briefly discussed before the practical utility of the above formulae is introduced.

3.2 *Metabolic alkalosis: Pathophysiology*

Metabolic alkalosis is the most common acid base disorder that develops in the intensive care unit, though it is not the most common clinical presentation.[17] This implies the possible contribution of extraneous drugs and infusions in the development of metabolic alkalosis apart from the pathological process within the patient. The pathogenesis of metabolic alkalosis requires the presence of causative factors, i.e. a source of excess alkali/base and in addition, factors that maintain alkalosis by impairing the renal ability to excrete excess bases. The extra bicarbonate can have an exogenous source in the form of sodium or potassium salts, or precursor compounds like lactate, acetate or citrate that

generate bicarbonate. Endogenous sources are the stomach and the kidneys each of which accumulate bicarbonate in response to H+ removal. When bicarbonate accumulates, the kidneys respond by excreting the excess amount in urine, maintaining the acid base balance. However factors like chloride depletion, hypokalaemia, renal impairment, intravascular volume contraction, reduced effective blood volume due to cardiac failure, excess mineralocorticoid activity can interfere with this compensatory response leading to maintenance of metabolic alkalotic state.[18]

The partitioning of SBE aims at delineating the cause of metabolic alkalosis, in the effort to fit the pathogenesis into one of the above abnormalities. In a normal person, the blood sample will have zero base excess. In the presence of acidosis or alkalosis, there is either a base deficit or excess which is measured. On calculating the SBE due to free water, chloride and albumin, we find that the sum of the three equals the measured base excess/deficit. In case the derived sum does not equal the measured value, it indicates the presence of unmeasured basic or acidic elements, as can be calculated using the fourth formula above.[10] In metabolic alkalosis with high SBE, a corresponding high value in any of its three components, (the base excess due to free water, the base excess due to chloride and the base excess due to albumin) attributes the aetiology to the same. However, a high negative value, in the presence of alkalotic pH, indicates the presence of a metabolic acidosis in addition to alkalosis, thus indicating a mixed acid base disorder. The presence of a mixed disorder calls for a different therapeutic approach from that of a solitary metabolic alkalosis.

Alkalemia is often associated with electrolyte disturbances that cause varied effects on organ systems causing consequent dysfunction. This ranges from cardiovascular manifestations like supraventricular and ventricular arrhythmias, neuromuscular derangements causing muscle cramps, weakness and paraesthesia to central nervous system effects like nausea, disorientation and stupor.[18]

3.3 *Metabolic Alkalosis In Postoperative Care*

Postoperative metabolic alkalosis gained interest in the late 1980s and 90s when multiple reports of high incidence of this condition came to be reported in the postoperative intensive care setup. Okusawa et al., in an initial retrospective study on adults undergoing general surgery reported a 35% incidence of metabolic alkalosis in the postoperative period.[19] They followed this up with a prospective study analysing the possible aetiology of this high incidence.[20] While this prospective analysis showed a higher incidence of 50% in a similar group of patients, most of it was attributed to intravenous fluid administration and postoperative fresh frozen plasma (FFP) infusion. Citrate, a significant storage component in FFP, is a known source of alkali in the body after undergoing metabolism. Since a cardiac patient in the postoperative period is exposed to a completely different drug therapy and hemodynamic modulations, the above reasoning may not be transferable to this population.

The etiopathogenesis of metabolic acidosis in open heart surgery and the role of cardiopulmonary bypass in its development have been reported in the past.[21] However development of metabolic alkalosis has seen multiple theoretical evolutions over the years. Krohn et al., in 1968 reported the incidence of metabolic alkalosis in adult patients undergoing heart surgeries.[22] They reported an incidence of 47% among the 49 patients they assessed who had undergone surgery, and were found to be “unusually ill” in the postoperative period. A base excess value more than 2.5 was taken as diagnostic of metabolic alkalosis. They reiterated previous studies that stated metabolic alkalosis to be a result of multiple electrolyte interactions and not solely a consequence of potassium loss. The increased adrenal steroid production in the postoperative period was incriminated as an additive factor to potassium and chloride depletion that already exists in the patient due to prolonged preoperative diuretic therapy. The preoperative acid base status, influenced by the drugs a patient is on, may play a major role in deciding the postoperative outcome of adult

patients due to their prolonged preoperative optimization strategies. This is not the case in paediatric patients, especially infants who undergo surgery with minimal preoperative drug therapy. Since only critically ill patients were studied no comments were made regarding the association of mortality with metabolic alkalosis.

One of the earliest studies focusing on metabolic alkalosis in paediatric cardiac surgery was conducted by Wong et al., in 1993, by retrospective chart review.[23] Fifty six patients were reviewed, in which 52% incidence of metabolic alkalosis was reported. Seventy two percent of infants who underwent surgery developed metabolic alkalosis while the incidence was only 30% in children older than 12 months, indicating a statistically significant propensity of infants in developing this acid base state, a relation to young age which was never reported previously. They defined metabolic alkalosis as a pH > 7.48, with a base excess of ≥5. We have derived our diagnostic blood gas values from this study. Other significant findings they report is a higher furosemide dosing lower serum chloride levels and longer CPB time in children who developed metabolic alkalosis. Serum chloride levels were found to have an independent correlation with the development of metabolic alkalosis. On the other hand furosemide consumption and resultant volume depletion did not show any causative correlation with metabolic alkalosis, indicating presence of an additional non diuretic cause of chloride depletion.

Being retrospective in nature, the study lacks information on chloride monitoring and fluid status assessment. Similar to the previous study on adults, Wong et al. also failed to show any association with mortality or prolonged mechanical ventilation. A significantly lower serum calcium concentration was found in children with metabolic alkalosis, a probable consequence of the alkalotic serum.

A German group conducted another retrospective study with the same diagnostic criteria as Wong et al., on 43 infants and young children undergoing open heart surgery.[24] Following the findings of Wong et al., they focussed only on children with a body surface area <0.5 m^2 and reported a higher incidence, 60%, of metabolic alkalosis in their population. In addition to serum chloride levels and diuretic doses, Schranz et al., recorded the administration of blood products in these patients and hypothesised, albeit without proof, the possible role of citrates in stored blood in contributing to metabolic alkalosis. The presence of additional risk factors in children like an immature hepatic and renal system, surgical factors like longer CPB time and deeper hypothermia were also mentioned. The retrospective nature of this study and the smaller sample size hindered extraction of further practical information in this regard.

It was in 2005 that metabolic alkalosis was last studied in this detail. van Thiel et al. analysed retrospective data on 167 infants younger than 2 years age who underwent cardiothoracic surgery in The Netherlands.[1] Metabolic alkalosis was detected in 49% of the cases, a number in congruence with previous studies. The use of CPB was reported as the most important predictor of development of metabolic alkalosis. Similar to previous studies, a younger age, smaller body surface area and a higher preoperative creatinine were found to be characteristic of the children who developed metabolic alkalosis. Children who underwent arterial switch operation for transposition of great arteries showed a strong association with postoperative metabolic alkalosis, whereas a negative association was found with cases of tetralogy of Fallot (TOF). Causative association of diuretics and chloride depletion with metabolic alkalosis was however not assessed. Like previous studies van Thiel et al., were unable to relate metabolic alkalosis to mortality, cardiac arrhythmias or postoperative ventilation.

Acknowledging that all post cardiotomy patients who undergo surgery on CPB have a general inclination towards metabolic alkalosis, further studies were focussed on management of this condition with an aim to avoid potentiating factors that worsen its physicochemical effects. Drug therapy to reduce alkalemia was also of growing interest as shown by multiple studies. For therapeutic decision making it was important to classify metabolic alkalosis into one of two broad groups, namely: chloride resistant and chloride responsive metabolic alkalosis. High dose diuretic therapy and volume contraction seen in cardiac patients fit into the chloride responsive category. Fluid replacement with chloride containing solutions, potassium replacement or a reduction in diuretic dose are the usual strategy to control metabolic alkalosis in this population.[25]

Moffett et al., in 2007 for the first time described the use of acetazolamide in paediatric patients with hypochloremic metabolic alkalosis.[5] Twenty eight cardiology patients, less than 18 years of age were included for analysis, who had received a three day course of oral or intravenous acetazolamide. Retrospective data regarding serum bicarbonate levels, base excess, pH and chloride levels were retrieved and assessed. A significant reduction in serum bicarbonate levels, base excess and pH were recorded, along with an increase in chloride levels at the end of the three day therapy. There was no change in urine output. Being a retrospective observational study, the evidence was insufficient to advise acetazolamide therapy in similar settings.

In 2015, Bar et al. reported another retrospective study on critically ill, mechanically ventilated children ≤17 years of age with metabolic alkalosis.[26] They studied 61 patients which included 18 cardiac patients recovering from surgery for congenital heart disease and 43 non cardiac patients. They found that serum bicarbonate levels and pH dropped significantly in the non-cardiac group after an 18 hour intravenous acetazolamide therapy,

while no change was found in the cardiac group. They attributed this to the more complex interaction of multiple diuretics and inotropes that cardiac patients received with their altered physiology, fluid status and acid base interaction. Conflicting results with Moffett et al. as well as the retrospective nature of their study on a small cardiac patient group precluded Bar et al., from making a conclusive decision against acetazolamide use in paediatric post cardiac surgery patients.

Bar et al. also introduced the diuretic score to objectively analyse the relationship between diuretic dose and development of metabolic alkalosis. They defined it as the sum of daily furosemide dose (mg/kg) plus one tenth of chlorothiazide dose (mg/kg). We have used a modification of this definition in our study since our second diuretic of choice is metolazone.

Diuretic score = furosemide daily dose (mg/kg) + [10 x metolazone (mg/kg)]

The subsequent year saw Lopez et al., report a retrospective observational study done on critically ill children who had received a minimum 2 day course of enteral acetazolamide for the treatment of metabolic alkalosis.[4] They studied children above 30 days of age and under 16 years admitted in the intensive care unit. A total of 78 treatment courses on 58 children were assessed. Most of these were administered to patients who were recovering after cardiac surgery, while the rest was in children with cardiac failure and primary respiratory disease. They found a significant reduction in serum bicarbonate levels, without a change in chloride levels, in the postoperative patients and children with cardiac failure within 24 hours of acetazolamide administration. The response was milder in the patients with respiratory disease, which was claimed to be due to carbon dioxide retention in these patients due to their primary pathology.

Lopez et al. were the first to demonstrate an increase in diuresis with this drug therapy causing concerns over its administration along with other diuretics in cardiac patients.

Clinical outcome, ventilator dependence and mortality risk still remained areas that were unexplored. Again being a retrospective study posed its own limitation of data.

4. MATERIALS AND METHODS :

4.1 Study Design:

Prospective observational study

4.2 Study Setting:

This study was conducted in the Department of Anaesthesiology, Cardiothoracic and Vascular Anaesthesia Division, *Sree Chitra Tirunal Institute for Medical Sciences and Technology*, Trivandrum, India – A tertiary referral center, University level teaching hospital, operating about 600 paediatric open heart surgeries per year.

4.3 Ethical Considerations:

The study was started after obtaining clearance from the Institutional Ethics Committee, (IEC Regn. No. ECR/189/Inst/KL/2013/RR-16), Sree Chitra Tirunal Institute for Medical Sciences and Technology, Trivandrum, Kerala, India. (IEC certificate No. SCT/IEC/1396/August 2019) (Annexure Page. ii). The background, purpose, procedures involved in the study, measures which were taken to ensure confidentiality of the study participants, the voluntary nature of the study and applicability of findings were explained. The study complied with the revised Helsinki Declaration (2013) and Good Clinical Practice Guidelines.

Informed and written consent (Consent form, Annexure , Pg.v) was sought from the legal guardian/ parent of the participants of the study. They were informed of the purpose and importance of the study in English and Malayalam and their wards were enrolled in the study only if they consented.

4.4 Participant selection

All infants, i.e., children up to 12 months of age, with congenital heart disease (CHD), who had undergone cardiac surgery with cardiopulmonary bypass (CPB) in our institute and requiring postoperative mechanical ventilation for more than 6 hours were prospectively included in the study.

Inclusion criteria

1. Age: new-born to 12 months of age
2. Scheduled for elective cardiac surgery under CPB
3. Postoperative mechanical ventilation for ≥ 6 hours

Exclusion criteria

1. Infants on mechanical ventilation prior to surgery
2. Infants with metabolic alkalosis prior to surgery
3. Cardiac surgeries that require less than 6 hours postoperative ventilation. (Atrial septal defects, patent ductus arteriosus and ventricular septal defects)
4. Non-consent for study participation

Recruitment: Every consecutive patient who fit into the inclusion criteria was recruited into the study. Recruitment was done by the principal investigator.

4.5 Sample size:

Estimated sample size was 96, calculated using OpenEpi v3.01 assuming an alpha (type 1) error of 5%, estimated incidence to be 49 %[1] and absolute precision of 10%. We were able to achieve a sample size of 104 patients.

4.6 Funding:

No extramural or intramural funding was required for the study

4.7 Methodology

Routine preanaesthetic check was conducted on the day before surgery and the eligibility of the patient for the inclusion in the study was determined. Patients were advised to continue on all drugs and premedicated depending on their age and department protocol. Informed consent was obtained from the patients' parent/legal guardian.

On the day of surgery, anaesthesia and surgery were conducted according to routine practice without any changes affected by the study. In our institute, cardiopulmonary bypass was used with a flow rate of 2.0 to 2.4 l/m^2. Alpha-stat pH management was used. Priming volume necessitated stored blood volume administration according to patient size and preoperative haematocrit. Priming additives used were albumin, bicarbonate and mannitol. Hypothermia was set between 28 to 32 degree Celsius depending on the surgery.

The following intraoperative data was collected: type of procedure performed, first haematocrit after induction of anaesthesia, duration of extracorporeal circulation/CPB (min), cross-clamp time (min) and circulatory arrest (min) and the amount of bicarbonate (mmol/kg) and citrate blood (ml/kg) administered during surgery. Patients were scored according to the Risk Adjustment for Congenital Heart Surgery (RACHS-1) method as described by Jenkins.[21]

Postoperatively, the subjects were followed up for three postoperative days or till cessation of mechanical ventilation, whichever occurred earlier. The following postoperative

data was collected: serum creatinine level (mmol/L), maximum amount of inotropes (mg/kg per min) received up to 72 h postoperatively, expressed as inotrope score, total amount of angiotensin converter inhibitor (mg/kg) received up to 72 h postoperatively, potassium supplementation (mg/kg per day) received on the day of operation and up to 72 h postoperatively, urine output (ml/kg per hour) on the day of surgery and up to 72 hours postoperatively, total calcium (mmol/L) and albumin (g/L) levels measured on the first postoperative day, highest and lowest chloride and ionized calcium levels (mmol/L) within 72 hours postoperative, and the time after surgery they were measured (hours), acid– base data to assess the presence of metabolic alkalosis within 72 h postoperatively and blood lactates in the same period.

4.7.1 *ABG analysis:*

Arterial blood gas (ABG) analysis was done every 8 hours as a part of regular postoperative monitoring and care. Blood gas analysis was done immediately after sampling, without any delay, using the ABL800 BASIC^{TM} analyser available in our intensive care unit. The first step in analysis was to assess the relationship between pH, pCO_2 and the standard base excess. Once the primary disorder was identified, compensatory changes in serum bicarbonate levels or pCO_2 levels were analysed. Metabolic alkalosis was diagnosed if 2 consecutive blood gas analyses in a patient fit into one of the following criteria:

- pH >7.48 with a standard base excess > 5mmol/L
- Standard Base excess ≥ 5 mmol/L with pH > 7.42 and $paCO_2$>45 mmHg

For the purpose of analysis, the highest standard base excess (SBE) value in every patient was detected as the maximum deviation from normalcy, considering an SBE of 0 as normal. This was termed as delta SBE.

Once a diagnosis of metabolic alkalosis was made, further assessment was done to detect presence of mixed acid base disorders. Anion gap was calculated as:

$$Anion\ Gap = Na^{+} - (Cl^{-} + HCO_3^{-})$$

A high anion gap more than 12 in the presence of metabolic alkalosis points to the presence of additional metabolic acidosis.

The SBE was also further segregated by calculating the SBE due to free water (SBE_{FW}) and SBE due to chloride (SBE_{Cl}). The following formulae were used:

$$\boldsymbol{SBE_{FW}} = 0.3 \times (Na - 140)$$

$$\boldsymbol{SBE_{Cl}} = 104 - (Cl \times 140 \div Na)$$

A higher free water contribution to SBE marks a fluid contracted hypernatremic state causing metabolic alkalosis , while a higher SBE_{Cl} points to a hypochloremic alkalosis.

4.7.2 *Diuretic score*:

Exposure to diuretics, its dose and duration of infusion were noted in all patients. The daily dosage of diuretics was calculated and the diuretic score was derived.

Diuretic score *= furosemide daily dose (mg/kg) + [10 x metolazone (mg/kg)]*

Postoperative ventilator parameters, use of inotropes (inotrope score) and other drugs were noted.

4.7.3 *Vasoactive inotrope score:*

Vasoactive-inotrope score formulated by Gaies et al., which was later modified by Koponen et al., to include levosimendan was used in our study.[22, 23] The highest dose of the inotrope a patient received in every 24 h period was used to calculate the score. The formula used was as follows:

> ***Vasoactive inotrope score*** *= Dobutamine (mcg/kg/min) + dopamine (mcg/kg/min) + [noradrenaline (mcg/kg/min) x 100] + [adrenaline (mcg/kg/min) x 100] + [levosimendan (mcg/kg/min) x 50] + [milrinone (mcg/kg/min) x 10] + [vasopressin (mIU/kg/min) x 10000]*

Metabolic alkalosis was treated according to standard department protocol and use of acetazolamide, changes in ventilator parameters were noted. No changes in treatment protocol were implemented as part of the study.

The postoperative outcome, surgical complications, ventilation duration, ICU stay, hospital stay and mortality were noted.

The patients were categorized as follows for further analysis and comparative studies:

- ***Group MA***: subjects who develop metabolic alkalosis
- ***Group No MA***: subjects who did not develop metabolic alkalosis

All data was collected by the principal investigator and stored in data collection proforma.

4.8 Data analysis

Statistical analysis was done using Microsoft for Excel 2019 and IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.

Descriptive analysis was carried out by mean and standard deviation (SD) for quantitative variables; frequency and proportions were used for categorical variables. Non-normally distributed quantitative variables were summarized by median and interquartile range (IQR).

Among the study subjects, incidence of metabolic alkalosis was calculated. Once subjects were divided into one of the two cohort groups, statistical analysis was done to compare the possible risk factors, effects and consequences of development of metabolic alkalosis.

All Quantitative variables were checked for normal distribution within each Category of explanatory variable by using visual inspection of histograms and normality Q-Q plots. Shapiro- Wilk test was also conducted to assess normal distribution. Shapiro Wilk test *P* value of >0.05 was considered as normal distribution.

Categorical outcomes were compared between study groups using Chi square test/Fisher's Exact test. (If the overall sample size was < 20 or if the expected number in any one of the cells is < 5, Fisher's exact test was used.)

For normally distributed Quantitative parameters the mean values were compared between study groups using Independent sample t-test (2 groups) For non-normally distributed Quantitative parameters, Medians and Interquartile range (IQR) were compared between study groups using Mann Whitney u test (2 groups). *P* value < 0.05 was considered statistically significant. IBM SPSS version 22 was used for statistical analysis.

Univariate logistic regression analysis was also done to detect the presence of any association between preoperative, intraoperative and postoperative factors with the incidence of metabolic alkalosis.

5. RESULTS:

In this prospective observational study, 112 consecutive infants posted for elective open heart surgery for congenital heart disease were recruited (Fig.3). Eight children were excluded from analysis due to <6 hours post op mechanical ventilation (n=3) and non-availability of serum chloride values on ABG analysis (n=5). Hence 104 infants were finally included and followed up for analysis, meeting the calculated sample size.

5 .1 *Demographics of the study population*

Our study population included infants up to 12 months of age with a median age of 122 days (29.75, 241.25) (table 2). The youngest was a new-born at 1 day age while the oldest was 12 months old. There were 62.5 % males in our study population. Neonates constituted 26% of our sample population. The children weighed a median of 4.5 kg and a mean body surface area of 0.27 ± 0.07 m^2.

Table 2: Demographics of the study population

Demographic parameters	**Data**
Age (days) Median (IQR)	122 (29.8, 241.3)
Weight (kg) Median (IQR)	4.5 (3.5, 6)
Body surface area (m^2) Mean ± SD	0.27 ± 0.07

Data presented as Median, IQR for non-normally distributed data, Mean ± SD for normally distributed data.
Abbreviations: IQR, interquartile range; SD- standard deviation.

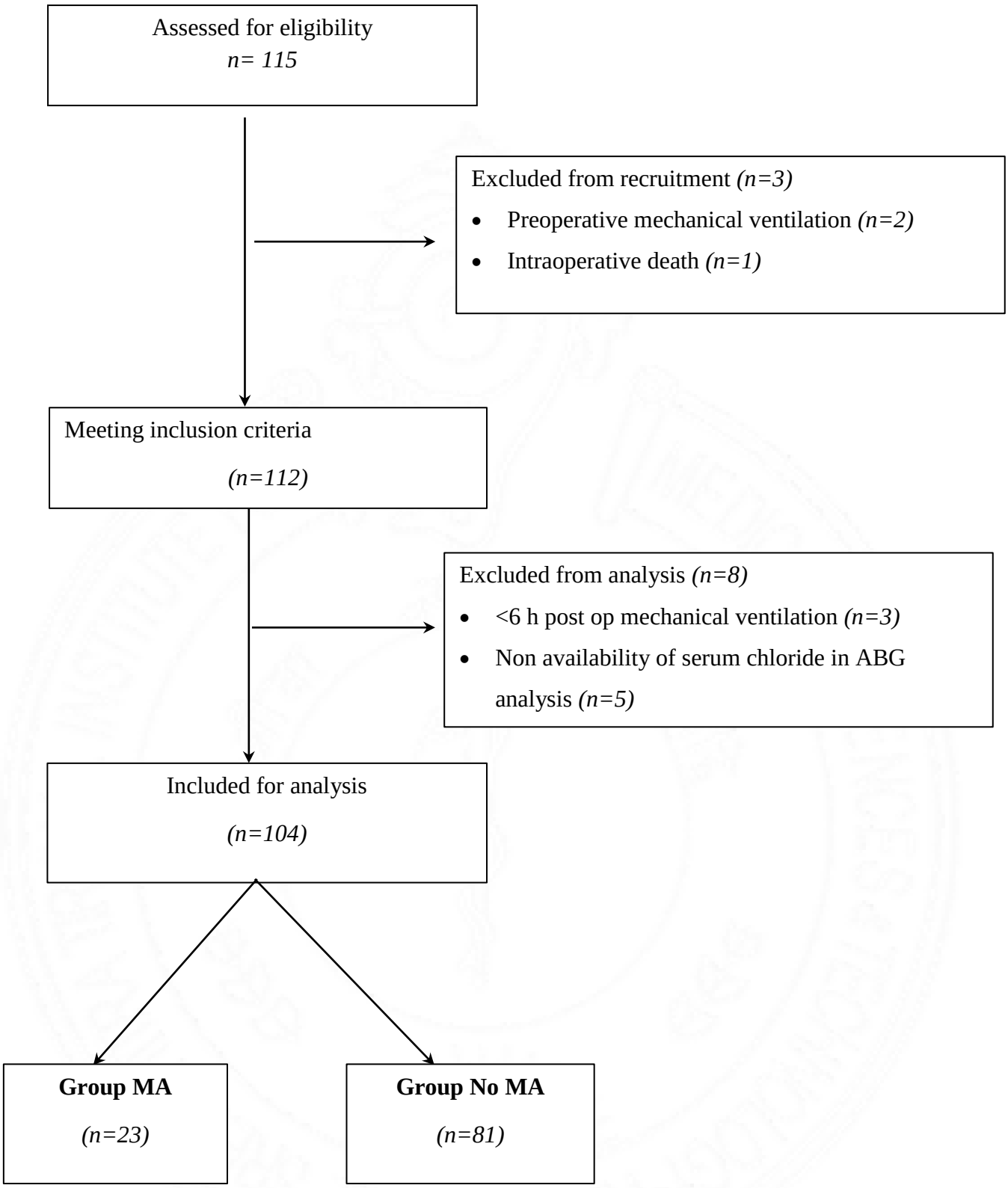

Fig.3. The Study Flow Chart in line with the STROBE statement

Group MA, infants who developed postoperative metabolic alkalosis.
Group No MA, infants who did not develop metabolic alkalosis
STROBE, Strengthening the Reporting of Observational Studies in Epidemiology

5.2 ***Clinical characteristics***

The children were categorised using the Risk Adjustment in Cardiac Surgery-1 scoring system (RACHS-1). Among our subjects, the majority belonged to RACHS-1 category 2, 3 and 4 (table 3). Two patients were grouped as RACHS-1 category 1, while 50 patients belonged to category 2, 24 patients to 3 and 23 patients to category 4. Five patients who had undergone surgery for an anomalous left coronary artery from pulmonary artery (ALCAPA) were considered separately as it was not scored by the RACHS-1 system.

Table 3: Distribution of subjects according to RACHS -1 surgical risk categories

RACHS-1 CATEGORY	Frequency	Percentages (%)
1	2	1.92
2	50	48.08
3	24	23.08
4	23	22.12
Others (ALCAPA)	5	4.81

Distribution of 104 subjects according to RACHS-1: Risk Adjustment in Congenital Heart Surgery-1 scoring system as described by Jenkins[21]
ALCAPA - anomalous left coronary artery from pulmonary artery

Ductal dependent circulation was present in 15.4% of our subjects and 45.2 % were receiving preoperative oral loop diuretics. (Table 4) preoperative serum creatinine level in our subjects was found to have a median of 0.37 (mg/dl). Median haematocrit was 38 %.

Table 4: Preoperative clinical characteristics of the study population

Parameters	Data
Ductal dependency (Frequency, %)	16 (15.4%)
Loop diuretic therapy (Frequency, %)	47 (45.19%)
Serum creatinine (mg/dl) Median (IQR)	0.37 (0.3,0.47)
Hematocrit (%) Median (IQR)	38 (34.2, 44.3)

Categorical data presented as frequency with percentage, non normally distributed data as median, IQR, interquartile range

5.3 *Intraoperative details:*

All 104 of our subjects underwent surgery with cardiopulmonary bypass support. The majority of infants received intravenous fluids in the form of 1% dextrose solution with Ringer Lactate, while 11.54 %, constituted mostly of older infants, received Ringer Lactate alone. A 26 day old neonate was the only subject who received 2% dextrose with Ringer Lactate.

We found a mean CPB time of 156.86 ± 72.64 minutes and a mean cross clamp time of 92.65 ± 53.97 minutes. (Table 5) The volume of intravenous fluid administered in the intraoperative period was a median of 13.9 ml/kg, while blood administered was 52.27 ml/kg. CPB prime was constituted with albumin in all patients, amounting to a median volume of 11.36 ml/kg. Bicarbonate also was added at a mean of 8.65 ± 6.89 ml in the whole group.

Table 5: Description of Intraoperative Characteristics

Intraoperative parameters	Distribution
First Haematocrit (%) Median, IQR	34.80 (31.2,40.2)
CPB Time (Min) Mean ± SD	156.86 ± 72.64
Cross Clamp Time (Min) Mean ± SD	92.65 ± 53.97
Bicarbonate Administered (mEq) Mean ± SD	8.65 ± 6.89
IVF (ml/Kg) Median, IQR	13.9 (11.8, 25.4)
Blood Administered (ml/Kg) Median, IQR	52.3 (36.8, 83.3)
Albumin in prime (ml/Kg) Median, IQR	11.4 (8.3, 14.3)
Modified ultrafiltration (ml/Kg) Median, IQR	47.6 (34.9, 62.5)
Conventional ultrafiltration (ml/Kg) Median, IQR	77.8 (61.4, 108.7)

Intraoperative data presented as Median, IQR for non-normally distributed data, Mean ± SD for normally distributed data. IQR, interquartile range; SD-standard deviation; IVF, intravenous fluids

5.4 *Postoperative details*

On the first postoperative day, serum creatinine and albumin levels were tested. The mean creatinine level was 0.51± 0.25 mg/dL and albumin was 3.87 ± 4.58 g/dL (table 6). The maximum inotrope score recorded in the group was 31, administered to a case of tetralogy of Fallot who had undergone intracardiac repair, following which the child had developed severe right ventricular failure, prolonged ventilator dependence, and disseminated intravascular coagulation, finally succumbing to the same on postoperative day 16. The median highest score in the whole group was 7.5.

Patients were given potassium supplementation in the postoperative period if their blood gas revealed serum potassium less than 3.5 mEq/L. The mean potassium administered in the immediate postoperative period was 0.49 ± 0.47 mEq/Kg, while the overall amount administered over 3 days in the postoperative period was 1.18 ± 1.57 mEq/kg/day.

The highest chloride level recorded among the subjects was 132 mmol/L, 44 hours after surgery in a RACHS-1 category 2 surgical procedure (intracardiac repair for tetralogy) and the child had a further uneventful hospital stay and a favourable surgical outcome. The lowest chloride recorded was 90 mmol/L in a RACHS-1 category 3 surgical procedure, arterial switch operation, done for a case of transposition of great arteries with intact ventricular septum and regressed left ventricle. This child however developed severe left ventricular afterload mismatch, sepsis and necrotising enterocolitis and died on postoperative day 22.

Similarly the highest ionised calcium level recorded in the subjects was 2.5 mmol/L at 46 hours after surgery in a two month old child who underwent repair of total anomalous pulmonary venous connection (RACHS-1 category 2), who developed metabolic alkalosis at approximately 33 to 48 hours after surgery. The child had a further uneventful course and

favourable surgical outcome. The lowest ionised calcium level was found to be 0.52, at 5 hours after surgery in an eight month old infant after atrial septal defect closure (RACHS-1 category 1). Administration of calcium gluconate corrected her hypocalcaemia and the child subsequently had an uneventful hospital stay and outcome.

Table 6: Postoperative Characteristics

Postoperative Parameters	**Data**	**Duration after surgery (days/hours)**
S. Creatinine (mg/dL) Mean ± SD	0.51 ± 0.25	
Albumin on PODd 0 (g/dL) Mean ± SD	3.87 ± 4.58	
Max. Inotrope score upto 72 Hours	31	Post Op day 1
Potassium Supplementation on POD 0 (Meq/Kg) Mean ± SD	0.49 ± 0.47	
Potassium Supplementation up to 72 Hours (Meq/Kg /Day) Mean ± SD	1.18 ± 1.57	
Highest Chloride (mmol/L)	132	44
Lowest Chloride (mmol/L)	90	84
Highest Ionized Ca (mmol/L)	2.5	46
Lowest Ionized Ca (mmol/L)	0.52	5

Postoperative data presented as mean± SD, highest and lowest measured values of calcium and chloride are provided with respect to the number of postoperative hours at which recorded. SD, standard deviation. POD, postoperative day

Almost 60 % of the subjects had their sternum surgically closed before shifting to ICU, while the remaining needed a period of postoperative stabilisation and monitoring before a delayed sternal closure was performed (Fig 4). Of these, 18 % had the procedure done on postoperative day1, while 14 % on day 2. Day 3 and 4 had 5.7 % and 2 % of delayed sternal closures respectively.

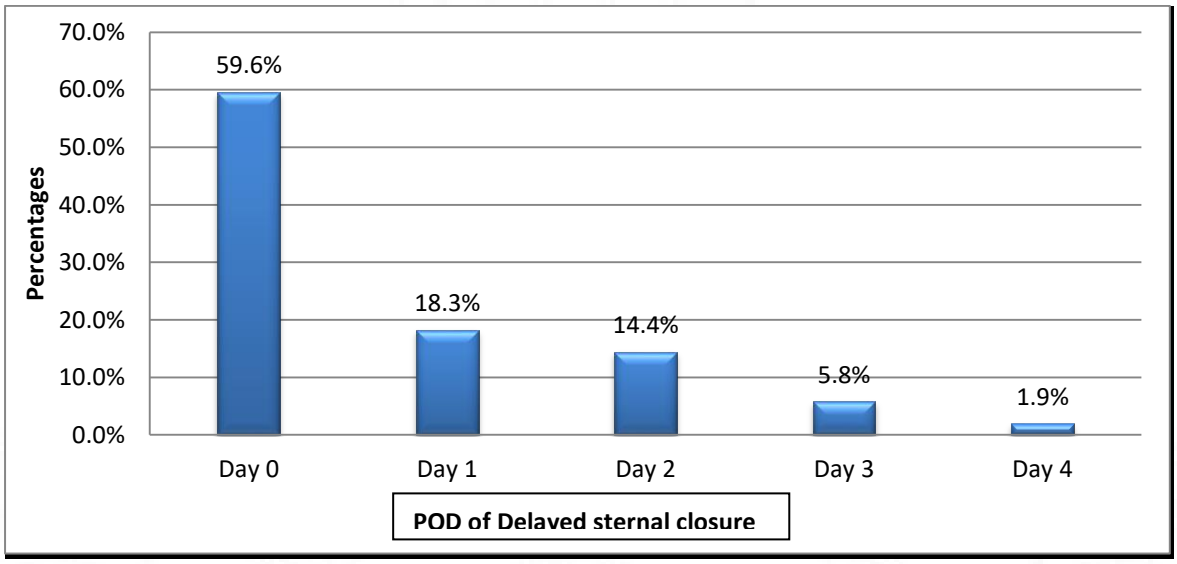

Figure 4: Bar chart depicting frequency of delayed sternal closures on days after surgery in the study population

POD denotes postoperative day

Two out of 104 children (1.9%) received angiotensin receptor inhibitors in the postoperative period, both being cases of anomalous left coronary artery from pulmonary artery (ALCAPA) who are prone to hypertension in the postoperative period. One of them developed metabolic alkalosis in the postoperative period, and had a longer ICU and hospital stay compared to the other child who had a faster recovery. The duration of ventilation was however not affected.

The median diuretic score in this population was 2.2, (Table 7) while the maximum score recorded was 7.3 in a 3 month old child who had undergone ventricular septal defect

closure. This high amount was administered in the immediate postoperative period while the subsequent days the child received doses closer to the median score. Peritoneal dialysis was done in 18.3 % of the subjects, most of whom belonged to RACHS-1 categories 3 and 4.

Table 7: Postoperative Renal parameters

Parameters	Median (IQR)
Mean diuretic score	2.2 (1.4,2.7)
Mean urine output (ml/kg/hr)	3.3 (2.3,4)
Mean fluid balance (ml/kg)	-12.3 (-29.2,0.6)
Peritoneal dialysis n (%)	19 (18.3)

Data presented as median, IQR. IQR denotes interquartile range. Data calculated for a period of three postoperative days or till cessation of mechanical ventilation.

Arterial blood gas analysis revealed the development of metabolic alkalosis in 23 of our subjects amounting to an incidence of 22.1 % among 104 patients. The patients who developed metabolic alkalosis were classified into Group MA and the remaining patients into Group No MA. The detailed ABG analysis will be discussed in the upcoming comparative analysis between these two groups.

About 40 % of the patients received albumin infusion in the postoperative period while on mechanical ventilation to correct hypoalbuminemia or to enhance the intravascular volume. Only 20.2 % of the children received normal saline bolus to correct episodes of acute hypovolemia.

5.5 ***Postoperative outcome***

Seventeen out of 104 patients (16.3%) developed complications in the postoperative period in the form of univentricular or biventricular failure, residual cardiac defect, unbalanced circulation or pulmonary problems (Table 8). The median duration of ventilation in our population was 44 hours. Similarly median duration of ICU stay was 7 days and overall hospital stay was 11 days (Table 8). After extubation, non-invasive ventilation was used in 76 % of the subjects in view of the low age group and the longer mechanical ventilation period in most patients.

Table 8: Markers of postoperative morbidity

Parameter	**Data**
Postoperative complications (n, %)	17 (16.3)
Duration of ventilation (hours) Median (IQR)	44 (21,81.5)
ICU stay (days) Median (IQR)	7 (4,11)
Hospital stay (days) Median (IQR)	11 (7,19)
Non-invasive ventilation (n, %)	79 (75.96)

Postoperative complications included univentricular or biventricular failure, residual cardiac defect, unbalanced circulation or pulmonary complications.
Non invasive ventilation denotes the number of children who required the intervention postoeratively.
Categorical variables expressed as frequency, percentage. IQR-interquartile range.

5.6 ***Mortality*:**

There were 3 postoperative deaths in our study population amounting to a mortality rate of 2.9 %. All three of these occurred after more than 14 days of ICU stay.

5.7 ***Comparative analysis of the 'MA' group vs 'No MA' group***

Twenty three out of 104 patients had at least one episode of metabolic alkalosis and thus were grouped as 'MA' and the remaining 81 were grouped as 'No MA' for comparison of causative factors and outcome. The incidence of metabolic alkalosis in our population was found to be 22.1%.

5.7.1 *Demographic details and clinical status*

Out of 23 infants who developed metabolic alkalosis in our study, 39.1% (9 patients) were neonates, while a smaller proportion of 21% neonates made up group No MA. (Table 9). This was however not found to be a significant difference. Similarly no significant difference was found in the distribution of gender and weight of the infants between the two groups. Comparison of body surface area between the two groups showed that difference between the two groups reached statistical significance, lower mean body surface area of 0.23 ± 0.06 m^2 in the MA group and 0.28 ± 0.07 m^2 in the No MA group. However the values being so numerically low, the clinical significance of this number is contentious.

Table 9: Comparison of preoperative parameters between the two groups (n=104).

Parameters	Study Group		*P* value
	MA (N=23)	No MA (N=81)	
Age			
<30 Days (N=27)	9 (39.1%)	18 (21%)	0.102
≥30 Days (N=77)	14 (60.9%)	63 (79%)	
Sex			
Male	17 (73.91%)	48 (59.26%)	0.200
Female	6 (26.09%)	33 (40.74%)	
Weight (kg) Mean ±SD	3.83 ± 1.43	5.47 ± 4.86	0.114
BSA (m2) Mean ±SD	0.23 ± 0.06	0.28 ± 0.07	0.004*
Ductal dependence			
Present	5 (21.7%)	11 (13.6%)	0.340
Absent	18 (78.3%)	70 (86.4%)	
Loop diuretics			
Present	12 (52.2%)	35 (43.2%)	0.446
Absent	11 (47.8%)	46 (56.8%)	
S. Creatinine (mg/dL) (Median, IQR)	0.4 (0.28,0.49)	0.37 (0.3,0.47)	0.910
Haematocrit (%) (Median, IQR)	39 (36.3,45)	37.2 (33.8,44.6)	0.263

Categorical variables represented as frequency (%), normally distributed continuous data as mean± SD, non normally distributed data as Median, IQR;
Tests of significance used: Chi squared test, Mann Whitney U test, Independent sample t test.
Only BSA showed significant difference between groups.
* $P<0.05$ as significant
Abbreviations: BSA, body surface area; SD, standard deviation; IQR, interquartile range

In group MA, 21.8% patients were ductus arteriosus dependent, while 13.6 % in group No MA were duct dependent. This was not a significant difference (*P*=0.340). In group MA 52% infants were on preoperative loop diuretic therapy against 42% in group No MA (P=0.446). Preoperative serum creatinine and haematocrit were also not significantly different between both groups. The median serum cretinine in group MA was 0.4, vs 0.37 in group No MA (*P*=0.910) (Table 9). Median haematocrit in group MA was 39 as against 37.2 in group No MA (*P*=0.263).

The majority of children in the 'No MA' group belonged to RACHS-1 category 2 (54.3%), while in the MA group they were in category 3 and 4 (table 9).

To compare between the complexity of surgery and morbidity related to the same, we further divided children based on their RACHS-1 category into those belonging to categories 1 and 2, and those belonging to 3 and above, the latter including children not classified in RACHS-1, i.e., 5 patients with ALCAPA in our population. This showed that 73.9 % patients in the MA group belonged to the more morbid surgical risk group, while only 43.2 % belonged to this class in the No MA group (Fig 5). This was found to be of statistical significance with a *P* value of 0.009.

Table 10: Distribution of subjects according to RACHS-1 category between study groups (N=104)

RACHS-1 category	**Study Groups**		***P* value**
	MA (N=23)	**No MA (N=81)**	
1 and 2	6 (26.09%)	46 (56.79%)	0.009*
3 and above*	17 (73.91%)	35 (43.21%)	

*Includes categories 3, 4 and five patients with ALCAPA who were not classified by RACHS-1.
Chi squared test for analysis, **P*<0.05 as significant

5.7.2 *Intra operative details*

All the infants underwent surgery with cardiopulmonary bypass provided as per standard departmental protocol. The first haematocrit after induction of anaesthesia in both groups had a median of 34.8 g/dl, negating any significant difference between the groups in this aspect (Table 11). The duration of cardiopulmonary bypass time and aortic cross clamp time was found to be significantly longer in the MA group (Fig. 6). While the mean CPB time in group metabolic alkalosis was 200.04 ± 83.35 minutes with a mean cross clamp time of 144.59 ± 64.77 minutes, the group No MA had a significantly lower 119.78 ± 63.12 minutes of CPB time and 84.95 ± 48.82 minutes of cross clamp time (table 11).

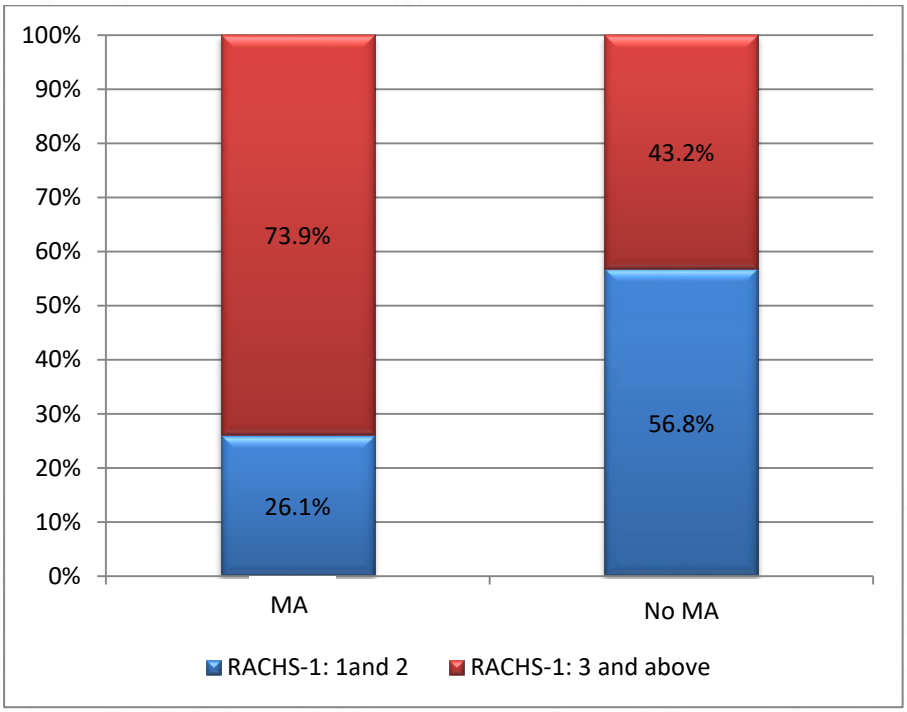

Fig. 5: Comparison of RACHS-1 categories between the two groups
Stacked bar chart depicting data as percentages in each group
RACHS-1, Risk Adjustment for Congenital Heart Surgery-1

The median volume of intravenous fluid administered in the MA group was 12.5 ml/kg, while in the No MA group it was 14.5 ml/kg. In the MA group, blood was administered at a median of 68 ml/kg, while the No MA group received 48.4 ml/kg (Table 11). Both of these components did not show any statistically significant difference between the two groups. Components added to CPB prime such as bicarbonate and albumin were compared. Sodium bicarbonate was added at a median of 5 ml in the MA group, not significantly different from the 8 ml administered in the No MA group. Albumin administration on the other hand showed a significant difference between the groups, with MA group having received more albumin at 14.3 ml/kg compared to the No MA group that received 10.5 ml/kg.

We found that 91.3% of the infants in the MA group had received modified ultrafiltration, compared to 60.5 % in the No MA group, this was found to be statistically significant, P= 0.005 (Table 11). Similar significant difference was seen in the volume of modified ultrafiltrate removed in the population. Group MA had a median 60 ml/kg ultrafiltrate removed by modified ultrafiltration, which was found to be significantly higher than the 44.4 ml/kg removed in the No MA group, $P = 0.003$ (Fig. 7). However no significant difference was seen regarding the application of conventional ultrafiltration. When 95.6 % subjects had received conventional ultrafiltration in the MA group, a similarly high number at 80% had received it in the No MA group. This was reflected in the volume of conventional ultrafiltrate as well, where the difference was 93.1 ml/kg in the MA group and 75 ml/kg in the No MA group, $P = 0.204$ (Fig. 8).

Table 11: Comparison of Intraoperative Parameters Between The Two Groups.

Intra-operative parameters	Study Group		*P* value
	MA (N=23)	No MA (N=81)	
First Hematocrit (%) (Median, IQR)	34.8 (30,39.3)	34.8 (31.1,41.8)	0.661
CPB Time (Min) (Mean ± SD)	200.04 ± 83.35	144.59 ± 64.77	<0.001*
Cross Clamp Time (Min) (Mean ± SD)	119.78 ± 63.12	84.95 ± 48.8	0.006*
Bicarbonate Administered (mEq) (Median, IQR)	5 (5,10)	8 (5,10)	0.297
IVF Administered (ml/Kg) (Median, IQR)	12.5 (11.6,18)	14.55 (12.1,26.5)	0.248
Blood Administered (ml/Kg) (Median, IQR)	68 (40,96.2)	48.39 (34.9,77.3)	0.186
Albumin Administered (ml/Kg) (Median, IQR)	14.29 (11.6,17.9)	10.53 (8.2,13.7)	0.001*
Modified ultrafiltration n (%)	21 (91.3)	49 (60.5)	0.005*
Volume (ml/Kg) (Median, IQR)	60 (44.4,70)	44.44 (32.9,54.3)	0.003*
Conventional ultrafiltration n (%)	22 (95.6)	65 (80)	0.111
Volume (ml/Kg) (Median, IQR)	93.11 (62.3,120)	75 (60.4,103.0)	0.204

Categorical variables presented as frequency (%), normally distributed continuous data as mean± SD, non normally distributed data as Median, IQR;

Tests of significance used: Chi squared test, Mann Whitney U test, Independent sample t test.

CPB time, cross clamp time, volume of albumin administered, application as well as volume of modified ultrafiltration showed statistical significance

* $P<0.05$ as significant difference

Abbreviations: CPB, cardiopulmonary bypass; IVF, intravenous fluid; IQR, interquartile range

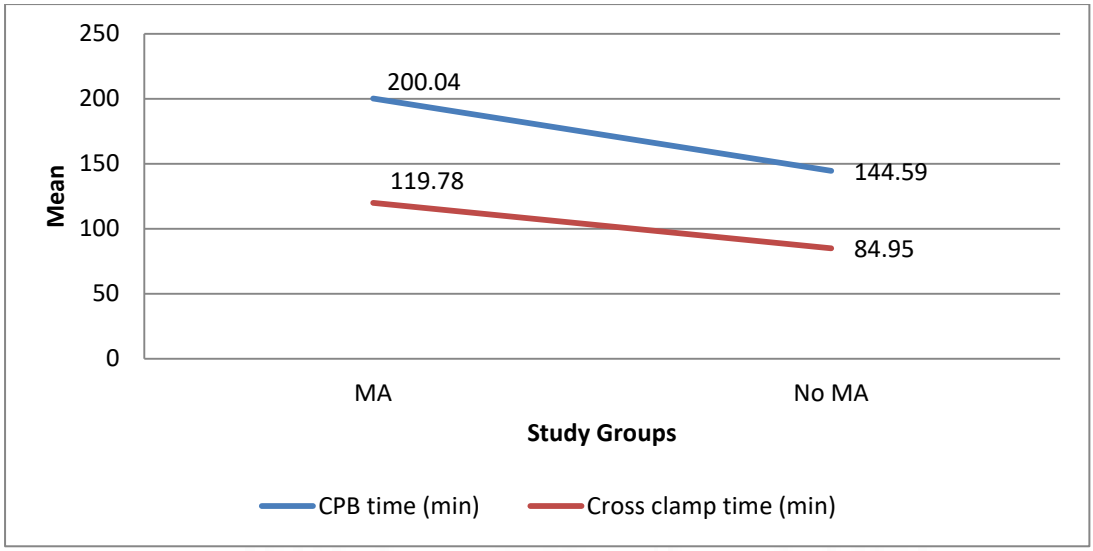

Fig 6: Comparison of mean CPB time and cross clamp time between study groups
Significantly longer CPB time and cross clamp time were noted in the MA group.
Significance tested by Independent sample t test, CPB time *P*=<0.001, cross clamp time *P=0.006.*
CPB- cardiopulmonary bypass. Time expressed in minutes

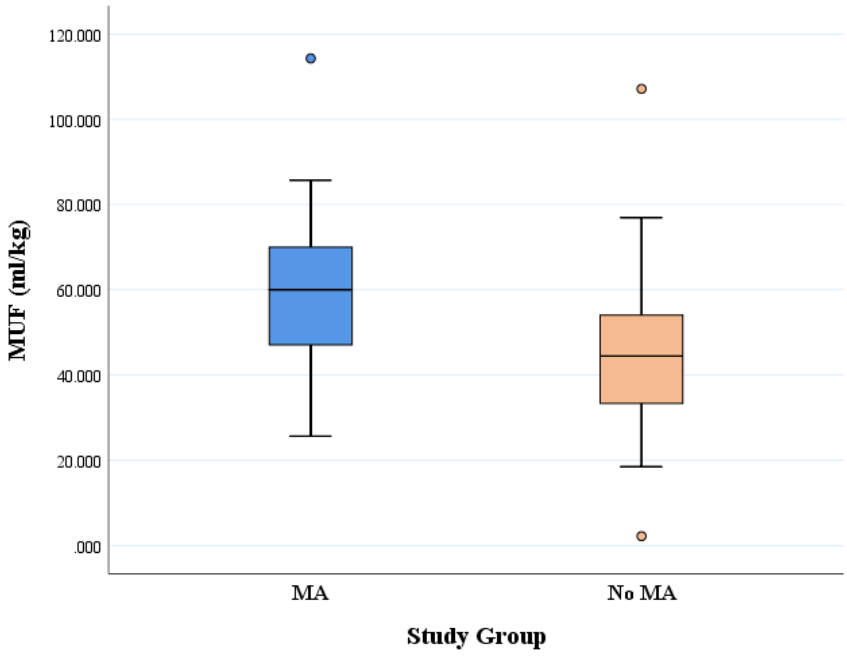

Fig 7: Box plot showing comparison of Modified ultrafiltration between study groups
The central line within each box denotes median in each group, the upper and lower ends of the boxes represent the IQR (interquartile range), the whiskers at either end represent maximum and minimum values. There is one outlier in group MA and 2 in group No MA. MUF, modified ultrafiltration. Statistical significance tested by Mann Whitney U test, *P*=0.003

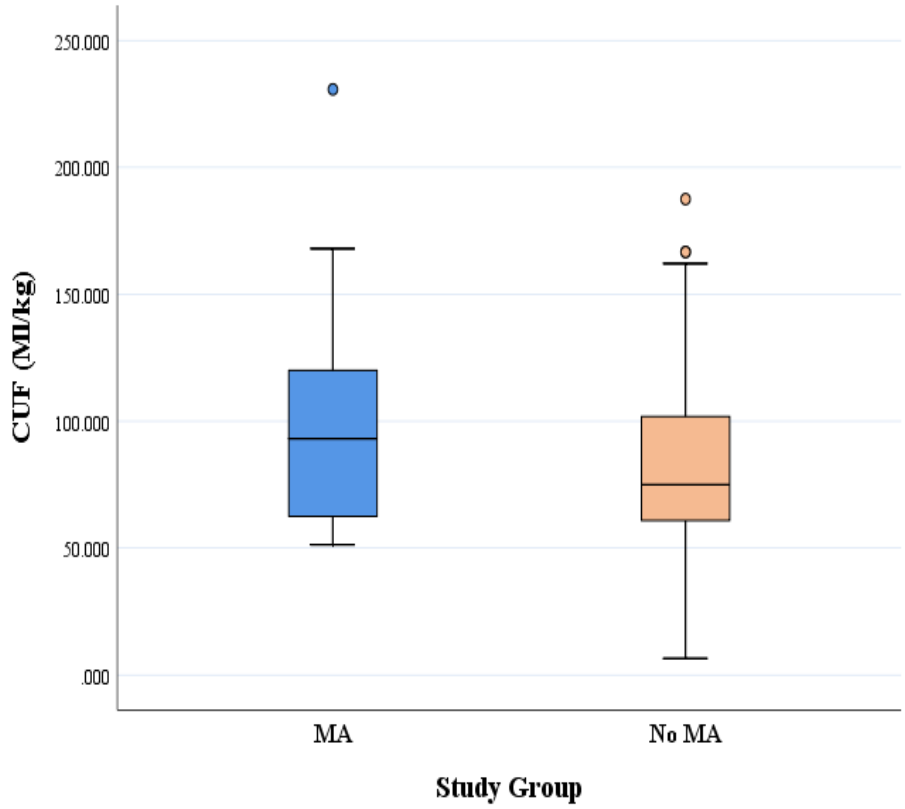

Fig 8: Box plot showing comparison of Conventional ultrafiltration between study groups

The central line within each box denotes median in each group, the upper and lower ends of the boxes represent the IQR (interquartile range), the whiskers at either end represent maximum and minimum values. There is one outlier in group MA and 2 in group No MA. CUF, conventional ultrafiltration. Statistical significance tested by Mann Whitney U test, **P**=0.204

5.7.3 *Postoperative details*

Serum creatinine levels were assessed on the first postoperative day. The MA group had a mean creatinine level of 0.65 ± 0.32 mg/dl which was found to be significantly higher than the No MA group, 0.47± 0.21 mg/dl, *P* =0.002 (Table 12). Serum albumin level was however not significantly different between the groups.

Table 12: Comparison of Postoperative Parameters between the Two Groups.

Postoperative Parameters	Study Group		*P* value
	MA (N=23)	No MA (N=81)	
Serum Creatinine (mg/dL) Mean ± SD	0.65 ± 0.32	0.47 ± 0.21	0.002*
Albumin on POD 0 (g/dL) Mean ± SD	3.37 ± 0.27	4.02 ± 5.19	0.552
Max. Inotrope score upto 72 Hours Mean ± SD	11.89 ± 6.04	10.11 ± 5.55	0.186
Potassium Supplementation up to 72 Hours (Meq/Kg /Day) Median, IQR	1 (0.7,1.6)	0.7 (0.3,1.12)	0.014*
Highest chloride (mmol/l)	115.35 ± 4.67	114.16 ± 4.86	0.300
Lowest chloride (mmol/l)	103.26 ± 4.46	104.62 ± 6.18	0.329
Highest ionized Ca^{2+} (mmol/l)	1.46 ± 0.3	1.4 ± 0.21	0.244
Lowest ionized Ca^{2+} (mmol/l)	0.97 ± 0.11	1.05 ± 0.14	0.007*
Mean Lactate (mmol/L)	1.94 ± 0.94	1.55 ± 0.62	0.0193*

Normally distributed continuous data presented as mean± SD, non normally distributed data as Median, IQR;

Tests of significance used: Independent sample t test, Mann Whitney U test

Serum creatinine, potassium supplementation, lowest ionized calcium levels and mean lactate levels showed statistically significant difference between groups.

* $P<0.05$ as significant

Abbreviations: SD, standard deviation; IQR, interquartile range POD 0, postoperative day zero.

The maximum inotrope score in the metabolic alkalosis group was found to be 28 in an 8 month old child who had undergone left ventricle to aorta rerouting and pulmonary root translocation (RACHS-1 category 3) for subaortic ventricular septal defect with severe pulmonary stenosis. The child had a prolonged ICU stay due to postoperative biventricular failure and diaphragm palsy for which he underwent diaphragm plication. He developed metabolic alkalosis after 56 hours of ICU stay. After a prolonged hospital stay of 36 days, he was discharged home. In the No MA group the maximum score was 31, who as discussed previously had postoperative right ventricular failure following intracardiac repair for tetralogy of Fallot and disseminated intravascular coagulation and succumbed to necrotising enterocolitis after 15 days. A comparison of the mean maximum inotrope scores between the groups was made, which did not show any statistical significance. Table 12 shows that the MA group had a mean score of 11.89 ± 6.04, which is comparable against 10.11 ± 5.55 in the No MA group.

Potassium supplementation was required in most of the patients with the MA group receiving a median of 1 mEq/kg/day in the postoperative period, in comparison to 0.7 mEq/kg/day in the No MA group. This was found to be a statistically significant difference, $P = 0.014$.

The overall highest postoperative chloride level was found in the No MA group, the value being 132 mmol/L (table 13). This was found in a child who had undergone intracardiac repair for TOF (RACHS-1 category 2) and had an otherwise uneventful hospital stay and outcome. The highest chloride in the MA group was 128 mmol/L, found in a child with atrial septal defect and mitral valve prolapse, who had undergone closure of the defect and mitral valve repair (RACHS-1 category 3). Neither of these children had received any volume bolus with chloride containing solutions before their blood samples were drawn for

ABG analysis. A comparison of mean chloride levels were made between the two groups for the highest and lowest values. No significant difference was found (Table 12).

Table 13: A Comparison of Serum Electrolytes between The Groups

Post-op Parameter	Study Group	
	MA (N=23)	No MA (N=81)
Highest Chloride (mmol/L)	128	132
Hours after surgery	28	44
Lowest Chloride (mmol/L)	93	90
Hours after surgery	43	84
Highest Ionized Ca^{2+} (mmol/L)	2.5	2.1
Hours after surgery	46	0
Lowest Ionized Ca^{2+} (mmol/L)	0.76	0.52
Hours after surgery	22	5

The highest and lowest serum chloride and ionised calcium levels noted in each group are displayed along with the number of hours after surgery that this was recorded.

Similarly ionised calcium levels were also analysed between the groups. In group MA, the highest calcium level detected was 2.5 mmol/L (table 13), 46 hours after surgery in a 2 month old who had undergone repair of total anomalous pulmonary venous connection and had a normal postoperative course. The highest calcium level noted in the No MA group was 2.1 mmol/L in the immediate postoperative period of a 11 months old child after intracardiac repair for tetralogy of Fallot (RACHS-1 Category 2). The lowest calcium level noted in the MA group was 0.76 mmol/L in a 13 day old neonate who had undergone arterial switch operation for transposed great arteries. The lowest calcium in No MA group was 0.52 mmol/L which was also the lowest in the whole population, detected in an 8 month old child after atrial septal defect closure (RACHS-1 category 1). The child had a good postoperative

recovery and early discharge from hospital. A comparison of overall values between the groups was done. Though the highest calcium levels were not significantly different between the groups, the lowest calcium levels showed a mean lower level in the MA group in relation to the No MA group, *P*=0.007 (Table 12).

Serum lactate levels were significantly higher in group MA which showed a mean lactate level of 1.94 ± 0.94 mmol/L, compared to group No MA which had 1.55 ± 0.62 mmol/L, *P*=0.019. (Table 12)

Delayed sternal closure was done in 56.5 % of the infants belonging to group MA, while only 35.8 % in the No MA group required the same (Table 14). However this did not yield any statistical significance.

Table 14: Comparison of Sternal Closure and Fluid Management Between The Groups

Parameters	Study groups		*P* value
	MA	No MA	
Delayed sternal closure n (%)	13 (56.5)	29 (35.8)	0.0739
Mean diuretic score (N=103) (Median, IQR)	2.33 (1.75,3)	2.2 (1.14,2.7)	0.218
Mean urine output (ml/kg/hr) (Median, IQR)	3.94 (3.3,4.73)	3.03 (2.24,3.85)	0.007*
Mean fluid balance (ml/kg) (Median, IQR)	-18.7 (-47.2,-9.8)	-7.6 (-27.4,1)	0.025*
Peritoneal dialysis	4 (17.39%)	15 (18.52%)	1.000

Categorical variables presented as frequency (%), non normally distributed data as Median, IQR;
Tests of significance used: Chi square test, Mann Whitney U test
Mean urine output and fluid balance showed statistically significant difference between groups.
* *P*<0.05 as significant
Abbreviations: IQR, interquartile range.

The median diuretic score in group MA was 2.33, which was comparable to the score 2.15 in group No MA, *P* =0.218 (Table 14). Although the diuretic scores were not significantly different between the groups, the urine output and mean fluid balance were statistically varied. The MA group had a median urine output of 3.94 ml/kg/hour as against 3.03 ml/kg/hour in the No MA group, *P* =0.007 (Table 14). While the infants in group MA were in a higher fluid negative state at -18.7ml/kg, the No MA group was slightly less volume constricted at -7.6 ml/kg, *P* =0.025. Peritoneal dialysis was done in 17.4 % of the patients in the MA group, which was comparable to the 18.5 % in the No MA group (Table 14).

Fluid management also included transfusion of albumin and normal saline boluses in periods of acute hypotension. In group metabolic alkalosis, albumin was administered in 60.9 % of patients, which was not significantly different from the 44.4 % infants who received it in group No MA, *P* =0.164. On the other hand, normal saline infusion to combat hypotension was used meagrely but in comparable numbers in both groups. Group MA had 30.4% of patients receiving saline bolus while the number was 17.3 % in the No MA group, *P* =0.237.

5.7.4 *ABG analysis*

Twenty three infants developed metabolic alkalosis in the postoperative period, when monitored up to 84 hours after surgery. Majority of them developed metabolic alkalosis within 12 hours after surgery (Fig. 9). The subsequent peak occurred after 24 hours, when 7 more patients developed metabolic alkalosis. There was a progressive decrease in incidence of metabolic alkalosis after 36 hours of postoperative period. Out of the 23, nine infants had a second subsequent episode of metabolic alkalosis on ABG analysis after a period ranging from 8 to 26 hours.

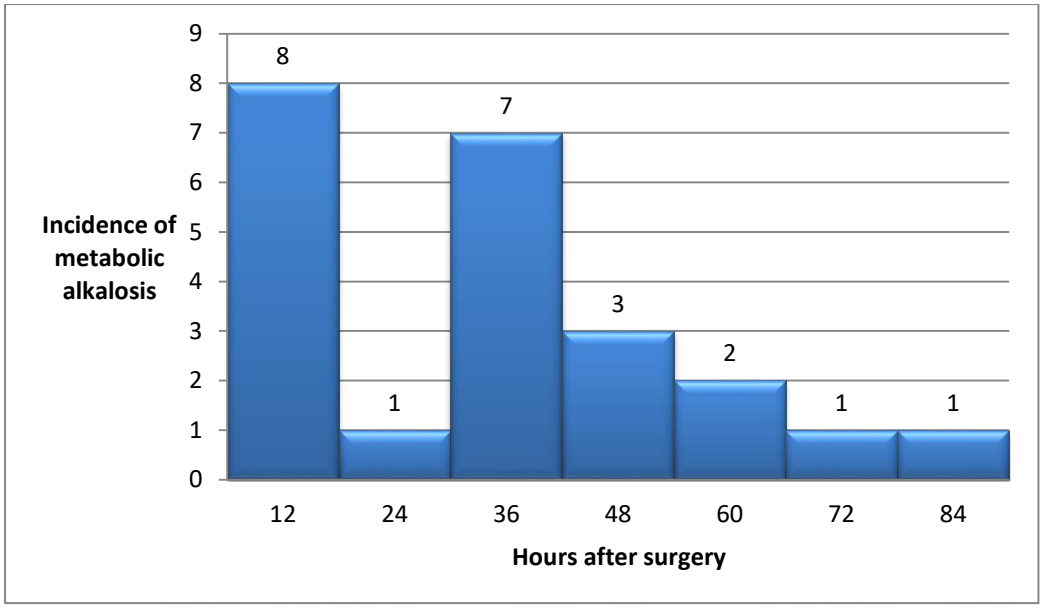

Fig 9: Histogram depicting incidence of metabolic alkalosis with progressive duration after surgery (n=23)

The highest number of infants, 8 out of 23, developed metabolic alkalosis within 12 hours of surgery , the period in which maximum fluid shifts occur postoperatively, the next peak was seen in the 24 to 36 hour period where 7 more infants developed metabolic alkalosis;, the subsequent periods showed a lower incidence

Metabolic alkalosis occurred at a median time of 30 hours after surgery. The earliest detected episode was at 0 hours after surgery while the last to occur was 80 hours after surgery.

Only one child was treated with oral acetazolamide when persistent metabolic alkalosis was present for more than 24 hours after first detection at 33 hours after surgery. Subsequent ABGs showed an improvement in pH and base excess. This was a case of truncus arteriosus in a 4 month old who underwent truncus repair (RACHS-1 category 4) and was in a relatively positively fluid balanced state in the initial 24 hours. Subsequent increase in diuretic therapy resulted in a fluid negative state and development of metabolic alkalosis.

Metabolic alkalosis was diagnosed based on the pH, the standard base excess and secondary pCO_2 changes detected on ABG. Table 14 shows the mean pH and the difference in pH from baseline seen across the two groups. Delta pH is the difference of the highest pH in every patient over the whole period of study from the normal pH of 7.44. On comparing the means of these parameters between the groups, a statistically significant difference was established. When group MA showed a mean pH of 7.44 ± 0.04 and a delta pH of 0.08 ± 0.04, in group No MA the mean pH was 7.39 ± 0.04 and the mean delta pH was 0.02 ± 0.11; p,0.001 and *P* =0.006 respectively. The mean SBE in group MA was found to be significantly more at 2.58 ± 1.82 as against -0.92 ± 1.79 in group No MA, *P* <0.001 (Table 15). Comparison of delta base excess revealed a mean delta SBE of 7.33 ± 1.56 in group MA, a significantly higher value compared to 1.84 ± 2.29 in group No MA, *P*<0.001.

Table15: Comparison of ABG Variables Between Study Groups (N=104)

Parameters	Study Group (Mean± SD)		*P* value
	MA (N=23)	No MA (N=81)	
Mean pH	7.44 ± 0.04	7.39 ± 0.04	<0.001*
Delta pH	0.08 ± 0.04	0.02 ± 0.11	0.006*
Delta SBE	7.33 ± 1.56	1.84 ± 2.29	<0.001*
Mean SBE	2.58 ± 1.82	-0.92 ± 1.79	<0.001*
SBE_{FW}	-8.65 ± 8.86	-19.22 ± 13.18	<0.001*
SBE_{CL}	-5.28 ± 4.23	-4.43 ± 5.93	0.522

Delta pH is the difference of the maximum pH from 7.44; delta SBE is the highest SBE recorded considering SBE of 0 to be normal

Data represented as mean± SD, Test of significance used: Independent sample t test.

Statistically significant difference was found in most of the presented parameters

* *P*<0.05 as significant difference

Abbreviations: SBE, standard base excess; SBE_{FW}, standard base excess due to free water; SBE_{CL}, standard base excess due to chloride; SD, standard deviation

Further segregation of SBE was done which showed a significant difference in Base Excess from free water (SBE_{FW}) between the groups, with group MA having a mean SBE_{FW} of -8.65 ± 8.86 compared to -19.22 ± 13.18 in group No MA, $P<0.001$. The mean Base Excess from chloride (SBE_{CL}) in group MA was -5.28 ± 4.23 which was not significantly different from -4.43 ± 5.93 found in group No MA, $P = 0.522$.

In further analysis of the ABG to detect presence of mixed acid base disorders anion gap was assessed. The median anion gap in group MA was 9.56, as against 6.39 in group No MA (Table 16). This difference was found to be statistically significant, $P = 0.009$. The delta anion gap did not show any significant difference (Table 16).

Table 16: Analysis of Anion Gap

Parameters	Study Group (Median (IQR))		*P* value
	MA (N=23)	No MA (N=81)	
Mean Anion Gap	9.56 (6.09,12.35)	6.39 (3.12,9.06)	0.009*
Delta anion gap	2.1 (-1.9,4.9)	0.4 (-3.5,2.9)	0.091

Delta anion gap is the difference of the maximum anion gap from normal gap considered as 12
Data represented as median, IQR, Test of significance used: Mann Whitney U test.
Statistically significant difference was found in mean anion gap
* $P<0.05$ as significant difference
Abbreviations: IQR, interquartile range

5.7.5 *Postoperative outcome*

Six out of 23 infants (26.1%) in the MA group developed postoperative complications, while 11 out of 81 (13.6%) in group No MA faced complications (Table 17). In either group complications were related to their preoperative cardiac status and morbidity of the surgery

with patients developing univentricular or biventricular failure and the consequences of the same. There was no significant difference in this number between the two groups.

However, duration of postoperative mechanical ventilation (hours) and total ICU stay (number of days) were significantly longer in the MA group compared to the other. The median duration of postoperative ventilation in the MA group was 67 hours against 25 hours in the No MA group, P =0.003 (Table 17). When total ICU stay in group MA was 9 days, it was a shorter 6 days in the No MA group, P =0.008 (Fig 10). This did not however transfer to an increase in total duration of hospital stay in group MA, which showed a median stay of 14 days, compared to 9 days in the No MA group, P =0.055 (Table 17).

Table 17: Markers Of Postoperative Morbidity

Parameter	Study Groups		*P* value
	MA (n=23)	No MA (n=81)	
Postoperative complications	6 (26.1%)	11 (13.6%)	0.200
Duration of ventilation (hours) (Median (IQR)	67 (44,93)	25 (19.25,71.5)	0.003*
ICU stay (days) (Median (IQR)	9 (7,14)	6 (4,10)	0.008*
Hospital stay (days) (Median (IQR)	14 (9,19)	9 (7,19)	0.055

Categorical variables presented as frequency (%), non normally distributed continuous data as Median, IQR;
Tests of significance used: Chi squared test, Mann Whitney U test
A significantly longer duration of ventilation and ICU stay was found in group MA.
* P<0.05 as significant
Abbreviations: ICU, intensive care unit; IQR, interquartile range

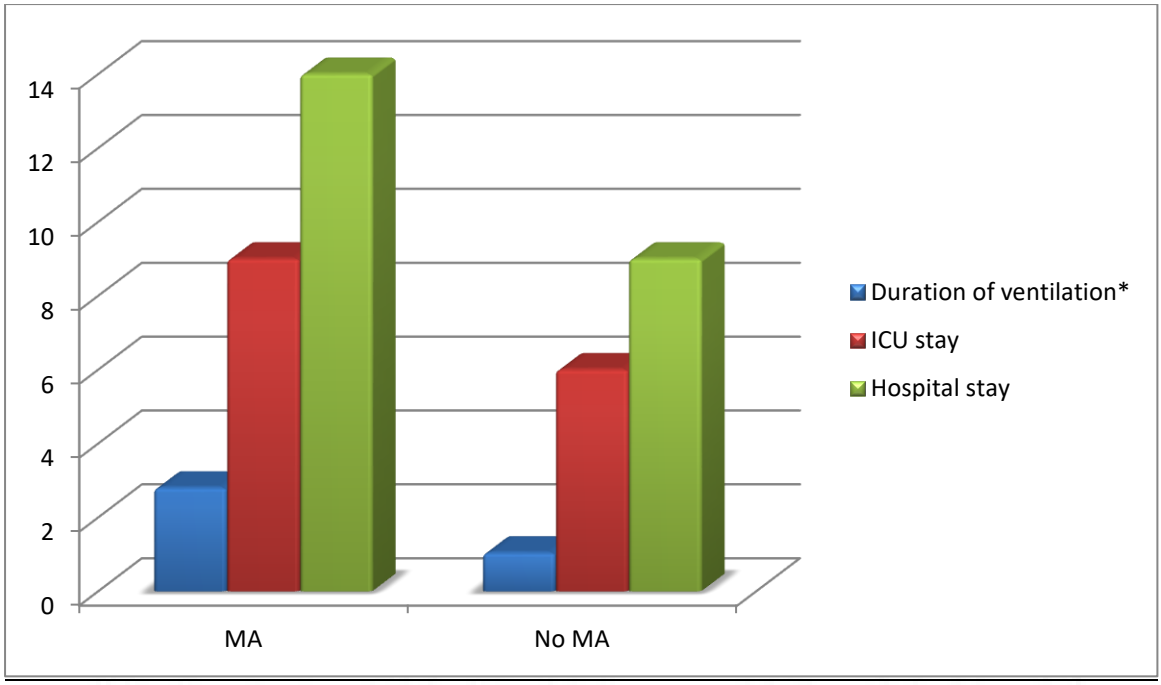

Fig 10: Cluster Bar Graph Depicting Morbidity Markers Between the Two Groups.
Y- axis displays number of postoperative days.
*duration of ventilation equated to number of days
A significantly longer duration of ventilation and ICU stay was found in group MA.

5.7.6 *Mortality*:

There were no deaths in the MA group, while the mortality in group No MA was 3.7 % (3 out of 81) which is translated as the mortality in the entire study population. First of these was a 25 day old neonate with ventricular septal defect, interrupted arch and PDA dependent circulation who underwent arch advancement and pulmonary artery banding (RACHS-1 category 4). The child had a turbulent postoperative ICU stay with delayed sternal closure being done on day 6 after surgery. He further developed necrotising enterocolitis after 29 days followed by sepsis and cardiac arrest on day 41 after surgery.

The second child was 3.5 months old with transposition of great arteries, intact ventricular septum and regressed left ventricle who underwent arterial switch operation

(RACHS-1 category 3). The cardiac anomaly predisposed her to postoperative left ventricular afterload mismatch, superseded with sepsis and necrotising enterocolitis, ultimately leading to death on postoperative day 22.

The last case of mortality was in an 8 month old infant with tetralogy of Fallot who underwent intracardiac repair with mono-cusp reconstruction of pulmonary valve (RACHS-1 Category 2). He succumbed to severe RV failure and disseminated intravascular coagulation on day 15 after surgery.

5.8 ***Determinants of metabolic alkalosis***

To analyse the presence of risk factors for development of metabolic alkalosis, logistic regression analysis of the various demographic, clinical and intraoperative parameters were done in association with metabolic alkalosis as the dependent variable (Table 18, 19).

Table 18: Logistic Regression Analysis Of Preoperative Factors Associated With Metabolic Alkalosis In Study Population (N=104)

Preoperative factors	Adjusted odds ratio	95% C.I. for adjusted odds ratio		*P* value
		Lower	Upper	
RACHS-1 score (Baseline = 3 & more)	0.269	0.096	0.752	0.012*
Loop diuretic use	1.434	0.566	3.629	0.447
Serum creatinine (mg/dL)	1.248	0.330	4.724	0.744
Haematocrit	1.020	0.964	1.079	0.497

Univariate logistic regression analysis showed RACHS-1 score 3 and above to have a significant association with development of metabolic alkalosis. Although the odds ratio was only 0.269

*P value was found significant

Abbreviations: to RACHS-1: Risk Adjustment in Congenital Heart Surgery-1; CI, confidence interval

Table 19: Logistic Regression Analysis of Intraoperative Factors Associated With Metabolic Alkalosis In Study Population (N=104)

Intraoperative factors	Adjusted odds ratio	95% C.I. for adjusted odds ratio		*P* value
		Lower	Upper	
IVF (ml/Kg)	0.981	0.939	1.024	0.377
Blood administration (ml/Kg)	1.007	0.994	1.020	0.306
Albumin (ml/Kg)	1.176	1.053	1.314	0.004*
CPB time (mins)	1.010	1.003	1.017	0.003*
Cross clamp time (mins)	1.011	1.003	1.020	0.011*
Modified ultrafiltration (ml/Kg)	1.044	1.02	1.08	0.007*
Conventional ultrafiltration (ml/Kg)	1.008	0.996	1.019	0.193
Bicarbonate administered (mEq)	0.947	0.842	1.065	0.361

Univariate logistic regression analysis showed administration of albumin, duration of CPB time, cross clamp time and volume of modified ultrafiltration to have a significant association with development of metabolic alkalosis.

*P<0.05 considered statistically significant

Abbreviations: IVF, intravenous fluid; CPB, cardiopulmonary bypass; CI, confidence interval

After adjusting for the effect of other variables in the equation only two parameters had shown statistically significant association with occurrence of metabolic alkalosis in the study. The strongest association was found with preoperative loops diuretics (odds ratio=1.434, 95% CI 0.566 to 3.629, P value 0.447). The odds of metabolic alkalosis were 0.269 times (95% CI 0.096 to 0.752, *P* value =0.012) less with RACHS score of 1 & 2, as compared to 3 and more. In relation to age, the odds ratio was close to one implying no impact of increasing age on incidence of metabolic alkalosis. Table 19 shows the significance of intraoperative factors in determining risk of metabolic alkalosis. Albumin administration, CPB time, cross clamp time and modified ultrafiltration were found to slightly increase the odds of postoperative metabolic alkalosis. However the odds ratios of all four of these

parameters were very close to 1, implying almost no association with the incidence of metabolic alkalosis.

Table 20 shows logistic regression analysis of postoperative factors. Significant association was found between an increasing serum creatinine level with development of metabolic alkalosis, raising the odds by 17 times for each unit increase in creatinine. No association was found between the inotrope score, diuretic score, mean urine output or mean fluid balance with metabolic alkalosis.

Table 20: Logistic Regression Analysis of Postoperative Factors Associated With Metabolic Alkalosis In Study Population (N=104)

Postoperative factors	Adjusted odds ratio	95% C.I. for adjusted odds ratio		*P* value
		Lower	Upper	
Serum Creatinine (mg/dL)	17.738	2.200	143.031	0.007*
Albumin (g/dL)	0.623	0.190	2.040	0.434
Max Inotrope up to 72 hours	1.053	0.975	1.138	0.189
Potassium supplementation up to 72 hours of ventilation (mEq)	1.208	0.928	1.573	0.160
Peritoneal dialysis	1.080	0.320	3.639	0.902
Lowest Chloride (mmol/L)	0.961	0.887	1.041	0.326
Albumin infusion	1.944	0.756	5.003	0.168
Normal saline Bolus	2.094	0.726	6.035	0.171
Mean Inotrope score	1.076	0.970	1.195	0.168
Mean diuretic score	1.009	0.783	1.301	0.944
Mean urine output (ml/kg/day)	1.051	0.912	1.211	0.490
Mean fluid balance (ml/kg)	0.995	0.990	1.001	0.096

Univariate logistic regression analysis showed postoperative serum creatinine to have the highest association with development of metabolic alkalosis. Odds ratio-17.7

*P <0.05 considered statistically significant

Abbreviations: CI, confidence interval

5.9 ***Surgical risk as a determinant of postoperative morbidity***

A significantly increased duration of ventilation and ICU stay were found in group MA (table 17). An increased number of infants belonging to RACHS-1 category 3 and above were found in group MA as well (Table 10). Hence, a comparison of morbidity parameters was made between the low and high surgical risk group.

The median duration of ventilation in infants with RACHS-1 category 1 & 2 and 3 & above were the same, 58.5 hours in group MA (table 21). The median duration of ICU stay was 8 days in RACHS-1 1 and 2, compared to 9 days in the higher categories. The median duration of hospital stay was 12.5 days in the low risk RACHS group, compared to 14 days in the higher risk group. There was no statistically significant difference in any of these parameters between the two groups

Table 21: Comparison of outcomes between low and high risk surgeries classified according to RACHS-1 categories, in group MA

Parameter	RACHS-1 category		*P* value
	1 & 2 (N=6)	3 & more (N=17)	
Duration of ventilation (hours)	58.50 (35, 76.50)	58.50 (35, 76.50)	0.310
ICU stay (days)	8 (5.50, 11.75)	9 (7.50, 14.50)	0.325
Hospital stay (days)	12.50 (7.75, 24)	14 (10.50, 18.50)	0.674

Data presented as median, IQR. Test of significance-Mann Whitney U test.
No significant difference in above parameters were found between infants belonging to higher and lower RACHS-1 category in group MA; n=23
P <0.05 considered statistically significant
Abbreviations: to RACHS-1: Risk Adjustment in Congenital Heart Surgery-1; ICU, intensive care unit; IQR, interquartile range

The median duration of ventilation in RACHS-1 categories 1 and 2 in No MA group was 20.25 hours (IQR 17 to 25.375) compared to 73 hours (IQR 45 to 116) in the higher surgical risk group (Table 22). This was found to be statistically significant. A similar increase in duration of ICU stay and overall hospital stay were found in children belonging to RACHS-1 categories 3 or above.

Table 22: Comparison of outcomes between low and high risk surgeries classified according to RACHS-1 categories, in group No MA

Parameter	RACHS-1 category		*P* value
	1 and 2 (n=46)	3 and above (n=35)	
Duration of ventilation (hours)	20.25 (17, 25.375)	73 (45, 116)	<0.001*
ICU stay (days)	4 (4, 6)	10 (6, 15)	<0.001*
Hospital stay (days)	8 (6, 11)	18 (9, 25)	<0.001*

Data presented as median, IQR. Test of significance-Mann Whitney U test.
A significantly longer duration of ventilation, ICU stay and hospital stay was found in children belonging to the higher RACHS-1 category of 3 and above compared to RACHS-1 categories 1 and 2 in group No MA; n=81
**P* <0.05 considered statistically significant
Abbreviations: to RACHS-1: Risk Adjustment in Congenital Heart Surgery-1; ICU, intensive care unit; IQR, interquartile range

DISCUSSION

The best method of acid base analysis eludes consensus. Clinicians employ one of three methods, the bicarbonate - $PaCO_2$ "rules of thumb", the base excess method or the physicochemical method. The Boston school developed the bicarbonate-$PaCO_2$ "rules of thumb" from data derived from volunteers. These rules work throughout the working range of $PaCO_2$ and therefore, are carbon dioxide invariant. But the measure of metabolic acidosis provided by this method is not stoichiometric: the Boston method does not provide the amount of acid or base required to correct the metabolic derangements either in vitro or in vivo. Standard base excess offers a stoichiometric measure of acid base derangement and is carbon dioxide invariant.[29,30] The further partitioning of standard base excess was advocated by Berend et al.[7] The advantage of partitioning the standard base excess is to find the contribution of strong ions and hidden anions in the generation of metabolic acidosis. Using standard base excess alone ignores the contribution of strong ions to the causation of metabolic acid base balance. To our knowledge such an approach has not been attempted before in the assessment of metabolic alkalosis after paediatric cardiac surgery. The utility of standard base excess has been demonstrated in a manner that serum bicarbonate has failed to achieve. Multiple studies attest to the utility of standard base excess to predict transfusion requirements, renal failure, acute respiratory distress syndrome, intensive care stay and mortality.[31, 32] This is a feature that bicarbonate based calculations lack. As stated by physicochemical principle, the serum hydrogen ions and bicarbonate ions are not independent variables that cause acid base imbalance. The acid base changes depend upon the $PaCO_2$, strong ion concentration and total amount of weak acids. Therefore we have relied on standard base excess and not serum bicarbonate to make all calculations on acid base abnormalities.

The study done by van Thiel et al. and published in 2005 remains the latest study on metabolic alkalosis in paediatric cardiac surgery. They reported a 49 % incidence of metabolic alkalosis in children after undergoing cardiac surgery, we report a lower incidence of 22.1 % in our population within three postoperative days after cardiac surgery in infants. Others have reported metabolic alkalosis at an incidence ranging from 45 to 60 % in paediatric and adult post cardiotomy population[1,22–24]. A lower age and use of CPB during surgery were reported as independent predictors of post-operative metabolic alkalosis by van Thiel et al.[1] However this study had some limitations. It was retrospective in nature, lactate and chloride values were not reported. In our study there is no statistical difference in the occurrence of metabolic alkalosis between neonates and in those between one and twelve months of age. Earlier studies showed strong association between the occurrence of metabolic alkalosis and lower age and body surface area. This association with body weight was not seen in our study because we principally focused on a homogeneous group: infants; and our children in the study belonged to an almost similar age group and a low body weight category (median body weight of 4.5 Kg). Investigations that reported an age dependent development of metabolic alkalosis were carried out in a study population that had a wider age-range. The study by van Thiel et al. was done in those under two years of age.[1] Though our study showed that children with lower body surface area had higher incidence of metabolic alkalosis (Table 9) reaching statistical significance, the difference between the groups in body surface area is not clinically significant (mean of body surface between MA vs no MA being 0.23 ± 0.06 versus 0.28 ± 0.7).

The metabolic derangements due to CPB are closely monitored and controlled to a considerable extent by use of miniaturised circuits, regular intraoperative ABG analysis, alpha-stat management and ultrafiltration methods. Although an association between CPB and development of metabolic alkalosis has been shown in the past, the duration of CPB was

not implicated[1]. We found a significantly longer duration of CPB (200±83.35 in MA versus 144.59±64.77 in no MA) and cross clamp time (119.78±63.12 in MA versus 84.95±48.8 in no MA) to be present in the infants who developed metabolic alkalosis (Table 11). Similarly children who underwent modified ultrafiltration were also found to have significantly higher chance of developing metabolic alkalosis than those who did not (21 in MA verus 49 patients in no MA). The volume of ultrafiltrate removed by this method also showed a significant association with incidence of metabolic alkalosis. The infants who developed metabolic alkalosis were found to have a larger intravascular fluid volume removed by modified ultrafiltration (60 ml/Kg in MA versus 44.4 ml/Kg in no MA). Modified ultrafiltration is electively utilised in our Institute for cases that are to undergo delayed sternal closure. Such patients belong to category 3 and 4 of RACHS-1 scoring system. Such cases require more CPB and aortic cross clamp times. Conventional ultrafiltration is employed intraoperatively in these patients with a view to reducing fluid load. Modified ultrafiltration is instituted after separation from CPB with a view to reducing myocardial oedema, improving blood viscosity and facilitating early sternal closure. These are the patients that are prescribed diuretics in addition to peritoneal dialysis postoperatively. Clinicians should therefore anticipate the occurrence of metabolic alkalosis in these patients and should take measures to prevent and treat metabolic alkalosis.

A positive association of metabolic alkalosis with arterial switch surgeries (RACHS-1 category 3) was shown by van Thiel et al. and a negative association was shown with cases of tetralogy of Fallot (RACHS-1 category 2).[1] We report similar findings, with a higher incidence of metabolic alkalosis in children belonging to category 3 and 4 of RACHS-1 scoring system (Table 10).

High preoperative creatinine was reported to increase the risk of postoperative metabolic alkalosis by van Thiel et al; we did not find any correlation for the same. Although preoperative creatinine levels were not associated with the development of metabolic alkalosis in our study, postoperative creatinine levels on day 1 after surgery were found to be significantly higher in infants who developed metabolic alkalosis eventually. Though the comparison of postoperative creatinine levels reached statistical significance in group MA, 0.65±0.32 mg/dl versus 0.47±0.21 mg/dl) the values of serum creatinine were within normal clinical range (table 14).

Albumin levels as an institute protocol was assessed only on post-operative day 1 after surgery and repeated only if deemed clinically necessary. Post-operative day 1 levels of serum albumin (3.37±0.27 versus 4.02±5.19) were of comparable levels in either group (Table 12). Daily effect of serum albumin on anion gap could not be assessed due to this.

The postoperative ICU management in these infants included stringent management of intravascular volume to optimize haemodynamics (table 14). The diuretic score was comparable between the two groups (2.33 in MA versus 2.15 in no MA). However, urine output was found to be significantly higher in group MA (3.94 ml/Kg/hr versus 3.03 ml/Kg/hr) leading to a more negative fluid balance state in the same group (-18.7ml/kg versus -7.6ml/kg). Hence, we had a group of children, who had a higher RACHS-1 score, who had undergone conventional ultrafiltration, a higher volume of modified ultrafiltration intra-operatively, who further had an increased urine output in the postoperative period and a more fluid depleted state leading on to metabolic alkalosis. The association of these factors have not been studied previously.

Analysis of arterial blood gas

Berend's three step approach was used for analysing each ABG as discussed in the section on review of literature (Figures 1 and 2).[3] The criteria we used to detect metabolic alkalosis in our study was the presence of (i) pH >7.48 and a standard base excess > 5mmol/L or (ii) standard Base excess ≥ 5 mmol/L with pH > 7.42 and PaCO2>45 mmHg. This definition of metabolic alkalosis is derived from the study of Wong et al.[23] and Schranz et al.[24] Once a primary metabolic alkalosis was diagnosed, anion gap was calculated to assess presence of concomitant metabolic acidosis. Although the mean anion gap in infants who developed metabolic alkalosis was significantly higher than those who did not, the number was within the normal range in both groups (Table 16). The mean delta SBE in group MA was 7.33 ± 1.56 which is comparable to the 8.7 reported by van Thiel et al. Delta SBE is the maximum SBE recorded in each patient, which is considered as the maximum increase in SBE from a baseline value of 0 (considered normal), signifying the metabolic impact of this variation.

The segregation of standard base excess is a relatively newer method to differentiate the cause of metabolic acid base disturbances. This method has been primarily utilised to study metabolic acidosis and find the 'hidden anions'. The standard base excess (SBE), is partitioned into four components, SBE due to free water (SBE_{FW}), SBE due to chloride (SBE_{Cl}), the partition into SBE due to albumin change (SBE_{Alb}) and the fourth partition the subtraction of the sum of the above three parts from the machine reported SBE to find out the hidden anions. We have analysed the partitions of SBE_{FW} and SBE_{Cl}. Since serum albumin was not measured on a daily basis, the anion gap was not corrected for serum albumin and the standard base excess was not partitioned for serum albumin and hidden anions.

The equation of SBE_{FW} is designed in a way to pick up relative changes in Na ions with respect to the extracellular fluid, a method that will reveal the contribution of volume status to the generation of acid base changes. A positive value for SBE_{FW} indicates that there is an increase in serum Na, suggesting ECF constriction and alkalosis; and a negative value indicates a decrease in Na ions and dilutional acidosis. In our study, we found a significant difference in mean SBE_{FW} between the groups. However both groups had a negative SBE_{FW} showing that free water constriction was not the major contributor to SBE and instead there was presence of significant quantities of acidifying ions in either group. The higher negative value in group No MA indicates presence of more acidifying components in no MA group than group MA.

The second component of SBE is $SBE_{Cl..}$ The SBE_{Cl} equation is designed to find out the contribution of the chloride ions with respect to changes in Na ions and therefore, free water. A positive value for SBE_{Cl} indicates a decrease in chloride ions or increase in Na ions, both indicative of alkalosis from volume constriction. Negative value of SBE_{Cl} indicates an increase in chloride or decrease in Na ions, both indicative of acidosis from hemodilution. In our study we had a negative SBE_{Cl} with a mean of -5.28 in the alkalotic children (Table 15), indicating the presence of acidifying influences. SBE_{CL} levels were however comparable between the two groups, signifying that chloride depletion was not the primary cause of metabolic alkalosis, also supported by a lack of significant hypochloraemia in the same group (Table 12). The third and fourth components were not assessed in our study as daily albumin levels were not monitored in these children. One significant finding from our study is the absence of hypochloremia in patients with metabolic alkalosis. The lowest chloride in the MA group was 93 mmol/L, not significantly different from the “no MA group”. Our finding is against the conventional wisdom that metabolic alkalosis is caused and perpetuated by

hypochloraemia in the postoperative period. Earlier studies by Wong et al. report hypochloraemia in association with metabolic alkalosis after cardiac surgery in children[23].

Wong and Chundu in their study published in 1994 pointed out the causative association of depleted chloride levels in metabolic alkalosis.[17] However, diuretic therapy, which is the most common cause of chloride depletion in their study, did not show any association with development of metabolic alkalosis in their subjects. This led to their conclusion that chloride depletion could be multifactorial in origin. Chloride depletion was however not found among our patients (table 12). Both groups had comparable levels of serum chloride. This is because we have used normal saline boluses and albumin infusion in our patients to treat hypovolemia. On the other hand a significantly higher potassium chloride supplementation was administered in the metabolic alkalotic children (Table 12). Hypokalemia is an associated electrolyte anomaly seen with the use of loop diuretics and associated with alkalosis, hence explaining the higher requirement for supplementation in this group. Potassium chloride is the formulation used to supplement the same, and therefore, serves as an additional source of chloride; this provides another explanation for the absence of hypochloraemia in our patients.

An important factor that deserves comment is the normal value of serum chloride and the relevance of dyschloraemia in the critically ill. Chloride is the major extracellular anion and is vital to the maintenance of acid base balance. The normal serum chloride values have not been properly defined. For the age range between one to seventeen years, the normal chloride values ranges anywhere between 102-112 mmol/L and for the age group > 18 years the normal serum chloride is between 98-107mmol/L.[33] Normal range of serum chloride values in the neonatal and infant groups are not described. Serum chloride not within normal range is called dyschloraemia. Hypochloraemia is defined as serum chloride levels below 96-101mmol/L while hyperchloraemia normally is defined as serum chloride greater than 106-

111mmol/L. Temporary hyperchloraemia is known to occur in up to 75% of intensive care patients in the first twenty-four hours. Dyschloraemia is known to cause serious morbidity in intensive care patients.[34]

The method of detection of chloride ions, which is the ion of interest in metabolic alkalosis deserves comment, especially in the manner in which it is measured. Discrepancies have been noted in the measurement of serum chloride values when a comparison was made between laboratory derived values and point of care instruments. Morimatsu et al. simultaneously measured plasma sodium, potassium and chloride concentrations on the point of care blood gas machines and the central hospital biochemistry laboratory analyser. They found significant differences in the measurement of sodium and chloride but not potassium.[35] Potential inaccuracies in chloride have been noted in severe metabolic acidosis (pH of < 7.2) with central laboratory analyser and a point of care blood gas analyser. They found that the central laboratory analysers underestimated chloride values in metabolic acidosis and overestimated chloride in metabolic alkalosis. The point of care blood gas machine (ABL800FLEX) did not show this error.[36] Other negatively charged ions like bromide, salicylate or lithium present in the sample are known to artifactually increase the serum chloride.[37, 38] These ions which are known to confound the results of serum chloride do not arise in the paediatric cardiac postoperative patient. The blood gas machine used in the study (ABL800 BASIC^{TM} analysers) was frequently calibrated and routinely relied upon in all patients for assessment of electrolyte and acid base balance. We have therefore placed reliance on the chloride values as provided by our point-of-care blood gas analyser and accepted the reference range of normal chloride to be between 110-112 mmol/L.[33]

We have found that lactate levels were significantly higher in group MA than in non MA infants, however the mean lactates levels were not clinically significant in either group (Table 12). The presence of lactates will have the influence of decreasing the SBE i.e. if not

for the presence of these lactates, the SBE and pH would have been higher (more alkalotic) in the metabolic alkalosis group than that was detected.

From this ABG analyses we conclude that metabolic alkalosis occurs in one fifth of infants undergoing cardiac surgery on CPB in our practice but the metabolic alkalosis is not associated with hypochloraemia. The derangement is not a single entity but associated with the presence of metabolic acidosis.

Determinants of Metabolic Alkalosis Using Univariate Logistic Regression

Univariate logistic regression analysis of preoperative, intraoperative and postoperative factors was done to determine risk factors of metabolic alkalosis.

Among the preoperative factors, the odds ratio of RACHS-1 score more than 3 posing a risk for metabolic alkalosis had a *P* value < 0.05 (table 18). Treatment with preoperative diuretic had an odds ratio of 1.434 but the *P* value was 0.447, showing no significant association with development of metabolic alkalosis. Wong and Chundu found a conclusive role of chloride depletion with pathogenesis of metabolic alkalosis, on the other hand diuretic therapy was incriminated by van Thiel et al. In our study we did not find a correlation, using univariate regression, between diuretic therapy (using diuretic score, Table 20) or a depleted chloride level in the development of metabolic alkalosis.

We found that intraoperative factors had the highest association with incidence of metabolic alkalosis. Cross clamp time, CPB time and volume of modified ultrafiltration show an increased risk of causing metabolic alkalosis postoperatively (Table 19). Van Thiel et al. also had shown a similar association with the use of circulatory arrest and CPB. However the role of modified ultrafiltration has not been studied before. Priming of CPB circuit with

albumin was also found to increase the odds of developing metabolic alkalosis. The group MA received a mean of 14 ml/Kg of albumin on CPB versus 10 ml/Kg in the no MA group. Albumin is an acidifying influence and hypoalbuminemia masks the presence of acidosis. Therefore anion gap is always corrected for hypoalbuminemia. In our study, the finding of increased albumin administration in group MA counters its role in metabolic acidosis. The levels of postoperative albumin levels in both groups, MA and no MA were similar.

The only postoperative factor that showed significant association was an increasing serum creatinine level. The odds were raised 17 times for every unit increase in creatinine. However none of the patients had a 'unit' increase in creatinine and the change was merely in fractions, the overall value always remaining within the normal levels. Hence the clinical significance of serum creatinine as a solitary predictor of metabolic alkalosis is uncertain, especially in infants who have physiologically low creatinine levels.[39] The concentration of this molecule is also dependent on the muscle mass of the patient, which is usually reduced in infants with congenital heart disease, added on by perioperative morbidity.

Postoperative outcome

There was no mortality associated with metabolic alkalosis in our population. There were 3 mortalities in the non-alkalotic group, all of which occurred 14 days after surgery, primarily due to ventricular failure, necrotising enterocolitis and sepsis.

We found a statistically significant prolongation in duration of ventilation and ICU stay in children with metabolic alkalosis. The overall hospital stay was also increased, but did not strictly meet statistical significance (P=0.055). Since the alkalotic children largely belonged to category 3 and above of RACHS-1 scoring system, we investigated for a

probable increase in morbidity due to the high surgical risk alone. We found a significant increase in these parameters in the higher surgical risk infants among those who did not develop metabolic alkalosis, implying that surgical risk does independently increase duration of ventilation, ICU stay and hospital stay. However in the infants with metabolic alkalosis, no significant difference was found between the low and high surgical risk groups. This implies that metabolic alkalosis does increase postoperative morbidity and hospital stay in. our study.

As we found that metabolic alkalosis was not a solitary entity in our subjects, the additive effects of metabolic acidosis could have contributed to electrochemical derangements. An alkalotic pH is known to disturb ionic balances and influence normal enzyme function, decreasing myocardial contractility and oxygen delivery. All of these factors may have contributed to the elevated morbidity in this group of patients.

LIMITATIONS OF THE STUDY

1. The lower incidence of metabolic alkalosis in our patients, precluded reliable conclusions from logistic regression models regarding determinants of metabolic alkalosis.
2. Since albumin levels were not monitored daily in our patients and therefore anion gap was not corrected for albumin and SBE_{alb} could not be assessed. The fourth part of SBE, which is the contribution of unmeasured anions towards SBE, calculated as the difference of the sum of SBE due to free water, chloride and albumin from the total SBE measured in the blood gas analysis, was also not measurable.
3. A preoperative baseline ABG could not be used for comparison due to the age group of our subjects.
4. An accurate preoperative loop diuretic dose could not be calculated as they received oral furosemide syrup formulations and consumption and bioavailability of the same is not reliable.
5. Acetazolamide therapy is sparingly used in our institute and therefore the role of acetazolamide in the management of metabolic alkalosis could not be assessed.
6. Post cardiac surgery patients receive multiple drugs in the form of infusions constituted with normal saline or Ringer's lactate. An understanding of the specific fluids received in the postoperative period and its volume will further help in understanding the role of ionic currents in acid base balance.

CONCLUSION:

In this prospective observational study, the overall incidence of metabolic alkalosis in infants undergoing cardiac surgery on cardiopulmonary bypass was found to be 22.1 %. We have analysed arterial blood gases using Berend's three step method and further inculcated a lesser known 'partitioning' of base excess, to find that metabolic alkalosis was not of solitary occurrence, but associated with metabolic acidosis simultaneously. In contrast to previous studies, diuretic therapy did not show any association with metabolic alkalosis, however a significantly higher postoperative urine output and a more negative fluid balance state were found in children who developed metabolic alkalosis. We found that a surgical risk score of 3 and above according to RACHS-1, marginally raised the odds of developing metabolic alkalosis. Significant association was found with intraoperative factors such as cross clamp time, CPB time and modified ultrafiltration, which has not been reported before. The role of albumin in affecting base excess and thus metabolic alkalosis could not be assessed in our study. Further exploration of albumin's role in metabolic alkalosis will shed more light onto this area of research.

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ANNEXURES

TAC approval

Technical Advisory Committee (Clinical Studies)

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

TAC Registration No: SCT-/S/2019/932 **Date: 14.06.2019**

Project title: METABOLIC ALKALOSIS IN THE PAEDIATRIC CARDIAC INTENSIVE CARE UNIT – A PROSPECTIVE OBSERVATIONAL STUDY

Principal Investigator:
Dr. Diana Thomas, Senior resident, (Cardiothoracic & Vascular Anesthesia), Division of Cardiac Anesthesia, SCTIMST Degree: MD
Co-Principal Investigator(s)
Dr. Suneel P. R, Professor, Division of Cardiac Anesthesia, SCTIMST Degree: MD, PDCC
Co- Investigator(s)
Dr. Baiju S Dharan, Professor, Department of cardiovascular and thoracic surgery, SCTIMST Degree: MS, MCh

Members who participated in the TAC meeting on 01/06/2019
Dr. Rupa Sreedhar (Chairperson)
Dr. Sankara Sarma P
Dr. Prasantakumar Dash
Dr. Sylaja. P.N
Dr. Ashalatha
Dr. Krishna Kumar K
Dr. Sanjay G
Dr. Bijulal S
Dr. Syam K
Dr. Jayadevan ER
Dr. K. Shivakumar (Member Secretary)

Dr. Jayadevan ER, Dr. Sylaja. P.N, Dr. Bijulal S, Dr. Ashalatha, Dr. Rupa Sreedhar, Dr. Prasantakumar Dash and Dr. Sanjay G stayed away from the proceedings when the projects in which they are involved as investigator were discussed (#921, 925, 929, 934, 937, 938, 942, 943, 945, 948).

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

The PI may 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).

IEC Approval

श्री चित्रा तिरुनाल आयुर्विज्ञान और प्रौद्योगिकी संस्थान, त्रिवेन्द्रम
तिरुवनन्तपुरम - ६९५०११, केरल, इंडिया
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Institutional Ethics Committee
(IEC Regn No. ECR/189/Inst/KL/2013/RR-16)

SCT/IEC/1396 /AUGUST-2019

07.09.2019

Dr. Diana Thomas
Senior Resident, Department of Anaesthesiology
SCTIMST, Thiruvananthapuram

Dear Dr. Diana Thomas,

The Institutional Ethics Committee reviewed and discussed your application to conduct the study entitled "METABOLIC ALKALOSIS IN THE PAEDIATRIC CARDIAC INTENSIVE CARE UNIT – A PROSPECTIVE OBSERVATIONAL STUDY (IEC/1396)" on 17th August, 2019.

The following documents were reviewed:

Original documents

1. *Covering Letter addressed to the Chairman, IEC, SCTIMST dated 28.06.2019 with checklist*
2. *TAC Approval Letter*
3. *IEC Application Form*
4. *Project Proposal*
5. *Proforma*
6. *Patient Information Sheet and Consent Form in English and Malayalam*
7. *Forwarding Letter from the HOD*
8. *CV of Principal Investigator and Co-Principal Investigators*

Revised documents

1. *Covering Letter addressed to the Chairman, IEC, SCTIMST dated 31.08.2019 with checklist*
2. *TAC Approval Letter*
3. *IEC Application Form*
4. *Project Proposal*
5. *Proforma*
6. *Patient Information Sheet and Consent Form in English and Malayalam*
7. *Forwarding Letter from the HOD*
8. *CV of Principal Investigator and Co-Principal Investigators*

The following members of the Ethics Committee were present at the meeting held on 17th August, 2019 at G. Parthasarathi Board Room, AMCHSS, SCTIMST

SL. No.	Member Name	Highest Degree	Gender	Scientific /Non Scientific	Affiliation w Institution(s
1.	Dr. R V G Menon	M Tech, PhD	Male	Lay Person (Chairman)	No
2.	Dr. Rema M. N	MD	Female	Basic Medical Scientist	No
3.	Dr. Kala Kesavan. P	MBBS, MD	Female	Basic Medical Scientist	No
4.	Dr. K R S Krishnan	M.E., Ph.D.	Male	Medical Technology	Yes
5.	Dr. Harikrishna Varma PR	Ph.D(Materials Science)	Male	Medical Technology	Yes
6.	Dr. S S Giri Sankar	LL.M. Ph.D.	Male	Legal Expert	No
7.	Dr. Anand Kumar A	MD, DM	Male	Clinician	No
8.	Dr. V. Raman Kutty	M D, M Phil, M P H	Male	Health Sciences Expert/Clinician	Yes
9.	Dr. Aneesh V Pillai	BA. LLB (Hons.), LLM, Ph. D, SET (Law)	Male	Legal Expert	No
10.	Smt. Sathi Nair	MA (English Literature)	Female	Lay Person	No
11.	Dr. P. Manickam	BSMS, MSc (Epid).,PhD	Male	Health Science Expert/ Social Scientist	No
12.	Dr. Harikrishnan S	MD, DM (Cardiology) DNB (Cardiology)	Male	Clinician	Yes
13.	Mr. Satheesh Chandran	MSW, PGDPM	Male	Lay person/ NGO/ Social Scientist	No
14.	Dr. Mala Ramanathan	PhD	Female	Social Scientist (Member Secretary)	Yes

IEC Decision

The IEC approved the conduct of the study in the 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).

Sincerely,

Mala Ramanathan
Member Secretary, IEC

PATIENT INFORMATION SHEET

Title of study: Metabolic alkalosis in the paediatric cardiac intensive care unit – A Prospective Observational Study

Aim of the study (why we are doing this study):

Children after heart surgery are prone to certain metabolic derangements in their blood. This has varying effects on their clinical status and outcome. We aim to study how often this type of derangements occur in children, who are more prone to this and what factors could be contributing to this. Finding this can help us in avoiding such conditions in future.

Risks and side-effects for your child for participating in this study:

As part of the study, we will not be modifying the treatment of your child at any stage. After surgery, your child will be monitored in the Intensive Care Unit (ICU) round the clock and blood investigations will be done regularly as part of regular postoperative intensive care. We will be assessing these blood reports for our study. There will not be any extra injections or blood sampling done for the purpose of the study. Therefore there will not be any additional risks or side effects due to the study per se.

Can you withdraw your child from this study after it starts?

Your consent for allowing the participation of your child in this study is entirely voluntary and your will be free to decide to withdraw permission for your child to participate in this study, should you feel so. If you do so, this will not affect your child's usual treatment in this hospital in any way.

What will happen if your child develops any study related injury?

We do not expect any injury to happen to your child as a result of this study. As mentioned earlier, this study will only analyse the results of blood samples done as a part of regular postoperative intensive care

Will you have to pay for the study?

This study does not require you to pay any additional charges over and above what you will have to bear for the routine expenditure for the operation for your child.

Will your child's personal details be kept confidential?

Your child's personal details will be kept confidential. The result of this study will be sent for publication in a medical journal upon its completion, but your child will not be identified by name or any other form of identification in such a publication or any presentation anywhere.

If you have any further questions, please ask any of the study investigators listed below:

1. Dr. Diana Thomas, Senior Resident, Department of Cardiothoracic and Vascular Anaesthesia (Ph No: 9791064353) Email : dianapensive@gmail.com
2. Dr.Suneel P.R, Professor, Department of Cardiothoracic and Vascular Anaesthesia.
3. Dr. Baiju S. Dharan, Professor, Department of cardiovascular and thoracic surgery
4. Dr. Mala Ramanathan, Member Secretary IEC, SCTIMST (Ph No-0471-2524234) Email: iec.mem.sec@sctimst.ac.in

DECLARATION

I give consent for my child _____ (Participant's name) _____Date of Birth / Age _____(in months/years), son/daughter/of _____ (Father/Mother's name) to participate in this study titled "Metabolic alkalosis in the paediatric cardiac intensive care unit – A Prospective Observational Study"

Please tick the relevant boxes

- My doubts have been clarified. [ ]
- I also understand that my child's participation in this study is entirely voluntary and that I am free to withdraw permission for my child to continue to participate at any time without affecting his/her usual treatment or legal rights [ ]
- I understand that the study staff and institutional ethics committee members will not need my permission to look at my child's health records even if I withdraw permission for my child to participate in this trial. I agree to this access [ ]
- I understand that my child's identity will not be revealed in any information released to third parties or published in future [ ]
- I voluntarily agree for my child to take part in this study [ ]
- I have 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's guardian and explained to him/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's guardian to ask questions and that all questions asked were answered by me.

Name and Signature of Person Obtaining Consent

Patient Information Sheet - *Malayalam*

കാര്യവിവരണപത്രം

പഠനശീർഷകം

ഹീഡിയാട്രിക് കാർഡിയാക് തീവ്രപരിചരണവിഭാഗത്തിലെ മെറ്റബോളിക് ആൽക്കലോസിസ് – ഭാവി കാലപ്രാപ്യമായ ഒരു നിരീക്ഷണ പഠനം

പഠനത്തിന്റെ ലക്ഷ്യം (ഞങ്ങൾ എന്തുകൊണ്ട് ഈ പഠനം നടത്തുന്നു)

ഹൃദയശസ്ത്രക്രിയയ്ക്കുശേഷം കുട്ടികളുടെ രക്തത്തിൽ ചില മെറ്റബോളിക് താളം തെറ്റലുകളുടെ പ്രവമതയുണ്ട്. അവരുടെ രോഗനിലവാരത്തിലും ചികിത്സാഫലത്തിലും ഇതിന് വിവിധ രപ്രഭാവ ങ്ങളുണ്ടാകുന്നു. കുട്ടികളിൽ എപ്പോഴൊക്കെ ഇത്തരം താളം തെറ്റലുകൾ ഉണ്ടാകുന്നു, ആർക്കാണ് അതിനുള്ള പ്രവണത കൂടുതൽ, അതിനു സഹായിക്കുന്ന ഘടകങ്ങൾ ഏതെല്ലാം എന്നിവ പഠിക്കാ നാണ് ഞങ്ങൾ ലക്ഷ്യമിടുന്നത്. ഇവ കണ്ടെത്തുന്നത് ഭാവിയിൽ ഇത്തരം സാഹചര്യങ്ങൾ ഒഴിവാക്കാൻ ഞങ്ങളെ സഹായിക്കും.

ഈ പഠനത്തിൽ പങ്കെടുക്കുന്നതുകൊണ്ട് നിങ്ങളുടെ കുട്ടിക്കുണ്ടാവാനിടയുള്ള അപായവും പാർശ്വഫ ലങ്ങളും?

പഠനത്തിനുവേണ്ടി നിങ്ങളുടെ കുട്ടിയുടെ ചികിത്സയിൽ ഞങ്ങൾ ഒരു പരിഷ്കരണവും വരുത്തുന്നി ല്ല. ശസ്ത്രക്രിയയ്ക്കു ശേഷം,താങ്കളുടെ കുട്ടിയെ മുഴുവൻസമയവും ശസ്ത്രക്രിയാനന്തര തീവ്രപരിച രണത്തിന്റെ ഭാഗമായി തീവ്രപരിചരണ വിഭാഗത്തിൽ (ഐസിയു) നിരീക്ഷിക്കുകയും ഇടവിട്ട് രക്തപരി ശോധന നടത്തുകയും ചെയ്യും. ഈ രക്തപരിശോധനകൾ പഠനത്തിനായി ഞങ്ങൾ വിലയിരുത്തും. പഠനത്തിനായി അധികമായ കുത്തിവയ്പ്പുകളോ രക്തപരിശഓധനകളോ ഇല്ല. ആകയാൽ പഠനവു മായി ബന്ധപ്പെട്ട് കൂടുതൽ അപായങ്ങളോ പാർശ്വഫലങ്ങളോ ഇല്ല.

പഠനമാരംഭിച്ചശേഷം താങ്കളുടെ കുട്ടിയെ പഠനത്തിൽ നിന്നും പിൻവലിക്കാനാകുമോ?

താങ്കളുടെ കുട്ടിയെ ഈ പഠനത്തിൽ പങ്കെടുപ്പിക്കുന്നത് തികച്ചും സ്വമേധയായാണ്, താങ്കൾക്ക് തോന്നുകയാണെങ്കിൽ ഈ പഠനത്തിൽ നിന്നും കുട്ടിയെ പിൻവലിക്കാനും താങ്കൾക്കവകാശമുണ്ട്. അങ്ങിനെ ചെയ്യുന്നതുകൊണ്ട് ഈ ആശുപത്രിയിലെ താങ്കളുടെ കുട്ടിയുടെ ചികിത്സയെ ഒരു വിധത്തിലും ബാധിക്കില്ല.

പഠനസംബന്ധമായി താങ്കളുടെ കുട്ടിക്ക് വരുക്കുണ്ടായാലെന്തുസംഭവിക്കും.

ഈ പഠനഫലമായി താങ്കളുടെ കുട്ടിക്ക് വരുക്കൊന്നുമുണ്ടാവുമെന്ന് ഞങ്ങൾ പ്രതീക്ഷിക്കുന്നില്ല. ശസ്ത്രക്രിയയ്ക്കുശേഷമുള്ള തീവ്രപരിചരണത്തിലെ പതിവ് രക്തപരിശോധനയുടെ ഫലങ്ങൾ വിശക ലനം ചെയ്യുകമാത്രമാണ് ഞങ്ങൾ ചെയ്യുന്നത്.

പഠനത്തിന് താങ്കൾ പണം മുടക്കണോ?

താങ്കളുടെ കുട്ടിയുടെ ശസ്ത്രക്രിയാചിലവുകൾക്കപ്പുറം പഠനത്തിനായി താങ്കൾ അധികമായി പണം മുടക്കേണ്ടതില്ല.

താങ്കളുടെ കുട്ടിയുടെ വ്യക്തി വിവരങ്ങൾ രഹസ്യമായി സൂക്ഷിക്കുമോ?

ഈ പഠനത്തിന്റെ ഫലങ്ങൾ ഒരു വൈദ്യശാസ്ത്ര ജേർണലിൽ പ്രസിദ്ധീകരിക്കുമെങ്കിലും താങ്കളുടെ കുട്ടിയെ പേരുകൊണ്ടോ മറ്റു രീതികളിലോ പ്രസിദ്ധീകരണത്തിലോ പ്രദർശനങ്ങളിലോ തിരിച്ചറിയാനാവില്ല.

താങ്കൾക്ക് കൂടുതലെന്തെങ്കിലും ചോദ്യങ്ങളുണ്ടെങ്കിൽ താഴെപ്പറയുന്നവരോട് ദയവായി ചോദിക്കുക.

1. ഡോ. ഡയാന തോമസ്, സീനിയർ റെസിഡന്റ്, കാർഡിയോ തൊറാസിക് ആന്റ് വാസ്ക്കുലാർ അനസ്തീഷ്യ ഡിപ്പാർട്ട്മെന്റ്, SCTIMST, ഫോൺ. 9791064353) ഇമെയിൽ. dianapensive@gmail.com
2. ഡോ. സുനീൽ പി ആർ, പ്രൊഫസർ, കാർഡിയോ തൊറാസിക് ആന്റ് വാസ്ക്കുലാർ അനസ്തീഷ്യ ഡിപ്പാർട്ട്മെന്റ്.
3. ഡോ. ബൈജു എസ് ധരൻ, പ്രൊഫസർ, കാർഡിയോ വാസ്ക്കുലാർ ആന്റ് തൊറാസിക് സർജറി

പഠനത്തിന്റെ നൈതീക അനുവാദവുമായി ബന്ധപ്പെട്ട ഏത് വിശദീകരണത്തിനും ബന്ധപ്പെടുക.
ഡോ. മാല രാമനാഥൻ
മെമ്പർസെക്രട്ടറി, SCTIMST-IEC (ഫോൺ. 0471 2524234) ഇമെയിൽ iec.mem.sec@sctimst.ac.in

ഡോ. ഡയാന തോമസ്
പ്രധാന ഗവേഷകൻ

DECLARATION – *Malayalam*

സമ്മതപത്രം

എന്റെ കുട്ടി (പങ്കെടുക്കുന്നകുട്ടിയുടെ പേര്).....ക്കുവേണ്ടിയുള്ള സമ്മതം ഞാൻ നൽകുന്നു.

ജനനതിയത്/വയസ്സ് (മാസത്തിൽ/വർഷത്തിൽ)_____ പുത്രൻ/പുത്രി

_____ (പിതാവിന്റെ/മാതാവിന്റെ പേര്)

പഠനശീർഷകം :

ഹിഡിയാട്രിക് കാർഡിയാക് തീവ്രപരിചരണവിഭാഗത്തിലെ മെറ്റബോളിക് ആൽക്കലോസിസ് - ഭാവി കാലപ്രാപ്യമായ ഒരു നിരീക്ഷണ പഠനം

..... (ദയവായി കോളങ്ങളിൽ ശരിയടയാളപ്പെടുത്തുക)

- മുകളിൽ പറഞ്ഞ പഠന സംബന്ധിയായി എനിക്കു നൽകിയ വിവരങ്ങൾ വായിച്ചു എന്നു പ്രസ്താവിക്കുന്നു.[ ]
- എന്റെ എല്ലാ സംശയങ്ങളും പരിഹരിച്ചു.[ ]
- എന്റെ കുട്ടിയുടെ ഈ പഠനത്തിലുള്ള പങ്കാളിത്തം പൂർണ്ണമായും സ്വതന്ത്രയായും ആണെന്നും അനുവാദം എനിക്ക് ഏതുസമയത്തും എന്റെ കുട്ടിയുടെ ചികിത്സയെയോ നിയമപരമായ അവകാശങ്ങളെയോ ബാധിക്കാതെ പിൻവലിക്കാൻ അവകാശമുണ്ടെന്നും ഞാൻ മനസ്സിലാക്കുന്നു. [ ]
- എന്റെ കുട്ടി ഈ പഠനത്തിൽ നിന്നും പിൻമാറിയാലും പഠനം നടത്തുന്നവർക്കും സ്ഥാപനത്തിലെ നൈതിക കമ്മിറ്റി അംഗങ്ങൾക്കും എന്റെ കുട്ടിയുടെ ആരോഗ്യരേഖകൾ പരിശോധിക്കുന്നതിന് എന്റെ അനുവാദം ആവശ്യമില്ലെന്ന്ഞാൻ മനസ്സിലാക്കുന്നു. അതിനോട് ഞാൻ യോജിക്കുന്നു. [ ]
- എന്റെ കുട്ടിയെ തിരിച്ചറിയാനുതകുന്ന വിവരങ്ങൾ ഒന്നും മൂന്നാം കക്ഷികൾക്കു നൽകുകയോ പ്രസിദ്ധീകരിക്കുകയോ ചെയ്യില്ലെന്ന് ഞാൻ മനസ്സിലാക്കുന്നു. [ ]
- എന്റെ കുട്ടിയെ സ്വതന്ത്രയായ പഠനത്തിൽ പങ്കെടുക്കാൻ സമ്മതിക്കുന്നു. [ ]
- സമ്മതപത്രത്തിന്റെ ഒപ്പിട്ട ഒരു കോപ്പി എനിക്കു കിട്ടി [ ]

പങ്കെടുക്കുന്നയാളുടെ പേര്

ഒപ്പ്

തീയതി

സാക്ഷിയുടെ പേര്

ഒപ്പ്

പങ്കെടുക്കുന്ന ആളുമായുള്ള ബന്ധം

തീയതി

(സമ്മതം വാങ്ങുന്നയാൾ)

Data collection proforma

Table 1: Demographic details

Patient Number		Sex (M/F)		Age (months)	
Weight (in kg)		Body surface area (m^2)		Date of surgery	
Preop diagnosis				Ductal dependency	

Table 2: Preoperative data

Loop diuretics (Y/N)		S. creatinine		Hematocrit	

Table 3: Intraoperative data

Type of procedure				IVF used (type/quantity)	
First hematocrit after induction		Citrate blood administered		Albumin use during cpb	
CPB time (min)		Cross-clamp time (min)		Circulatory arrest (min)	
MUF (Y/N)		CUF (Y/N)		Bicarbonate administered	

Table 4: postoperative data

Serum creatnine		Albumin on POD 0		DSC (Y/N) Date	
Max. inotrope upto 72 hrs (mg/kg/min)		Total ACE inhibitor upto 72 hrs (mg/kg)		NIV (Y/N)	
Potassium supplement day of surgery (mg/kg/d)		Upto 72 hrs (mg/kg/d)		PD (Y/N)	
Chloride (in 72 hrs) Highest (mmol/l) Lowest		Hrs after surgery	**Ionized calcium** Highest (mmol/l) Lowest		Hrs after surgery

Surgical outcome and complications: ICU stay: Hospital stay:

	POD - 0			POD - 1				POD - 2				POD - 3			
hrs after surgery															
pH															
pO2															
pCO2															
HCO3															
Base excess															
K															
Na															
Ca															
Cl															
Lactate															
Analysis															
Total fluid intake															
Total urine output															
Urine (ml/kg/hr)															
Fluid balance															
Diuretic : total Mg/kg/day															
Acetazolamide															
Diuretic score															
Inotrope (mc/kg/h)															
Inotrope score															
Corrective measures															
Mode															
Tidal volume															
Rate															
Minute ventilation															
Extubation															

Metabolic alkalosis (Y/N): No. of episodes of MA: Group: Time/ day of extubation: Ventilation duration:

PLAGIARISM REPORT

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Document Information

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