Does the use of Microplegia Significantly Improve Outcomes in Congenital Heart Surgery?

Sharmel Bhika, Geoffrey Candy, Krubin Naidoo

Department of Cardiothoracic Surgery, University of Witwatersrand, Johannesburg, South Africa

Abstract

Objectives: The aim of this prospective randomized study is to compare short term postoperative outcomes of elective congenital cardiac patients undergoing cardiac corrective surgery. A comparison of clinical and biochemical findings would be assessed between two cardiac arresting agents, all-blood Microplegia and crystalloid St Thomas II solution.

Methods: Forty-two patients were prospectively randomized to 2 techniques of myocardial protection; group I tepid (28°C) Microplegia and group II cold (4°C) St Thomas crystalloid cardioplegia. Perioperative data were prospectively collected. Endpoints included serial measurements of Troponin I, haemoglobin/ haematocrit and lactate; time taken for return to normal spontaneous sinus rhythm; and postoperative need for inotropic support.

Results: Surgery resulted in increased immediate post aortic unclamping myocardial lactate and troponin levels in both groups, however, significantly lower lactate (2.36 ± 0.76 vs 4.19 ± 1.09 mmol/l, p=0.000002) and troponin levels (8.18 ± 3.68 vs 22.88 ± 13.39 ng/ml, p<0,0001) were observed in Group I vs Group II. Myocardial contractility; need for transfusion and need for immediate postoperative inotropic support showed superior results in Group I.

Conclusions: Microplegia showed significantly less myocardial injury; haemodilution and reduced need for inotropic support in the first 24 hours post congenital cardiac surgery.

Keywords: myocardial protection; cardioplegia; cardiopulmonary bypass; congenital cardiac surgery

Introduction/ Background

Myocardial protection is critical in the surgical repair of almost all congenital heart surgery requiring cardiopulmonary bypass. The goal of myocardial protection is the minimization of myocardial metabolism during ischaemia thus preserving myocardial function in the relaxed arrested heart, whilst facilitating cardiac repair in a bloodless surgical field. The basic principles of myocardial protection include: rapid diastolic cardiac arrest, hypothermia to decrease myocardial oxygen consumption, and avoidance of myocardial edema[1]. Myocardial preservation techniques have revolutionized cardiac surgery; but continued refinements in myocardial protection are necessary to optimize postsurgical cardiac function. Currently, an almost infinite number of choices can be considered when choosing a myocardial protection strategy. A large variety of solutions have been utilized to arrest the heart and provide myocardial protection from ischaemia and reperfusion.

Most of the available literature and concepts in paediatric myocardial protection today have been borrowed from observations in adults and animal models. The extrapolation of these concepts to the paediatric myocardium is inappropriate as significant differences exist between these two groups in terms of metabolic substrate utilization and subcellular structural and functional organization. Even today, perioperative myocardial injury is the single most common cause of significant morbidity and mortality following open heart surgery for congenital heart disease.

The agent most often utilized to induce cardiac arrest is potassium, most frequently in concentrations ranging from 10 to 40mmol/L. Cardioplegia can be divided into crystalloid and blood cardioplegia. To each of these subtypes a host of additional electrolytes and pharmacological agents can be added in various concentrations. As far as the ingredients are concerned, most European groups use crystalloid cardioplegia, while most North American surgeons use blood cardioplegia to provide

additional oxygen substrate. In a North American Multi-institutional survey, 86% of surgeons used blood-based cardioplegia (of which 5% used microplegia) as their preferred cardioplegia regime in paediatric cardiac surgery, whilst only 14% of surgeons in northern US used crystalloid cardioplegia solutions[2].

Advantages of crystalloid cardioplegia are immediate cardiac arrest thereby ensuring minimal depletion of cardiac energy reserves, and because they have no cellular elements of blood, they distribute rapidly and evenly ensuring uniform cooling. Crystalloid cardioplegia has the added benefit of low cost, simplicity of administration, and availability. Bicarbonate or other agents are typically added to provide buffering. Blood cardioplegia offers several theoretical advantages over crystalloid cardioplegia, including the ability to carry oxygen and excellent buffering capacity. Even with the addition of potassium for the initiation and maintenance of cardiac arrest, blood cardioplegia is similar in electrolyte and osmotic composition to blood which routinely perfuses the heart, and in particular the coronary vasculature. Additionally, blood has the potential to scavenge oxygen free radicals and minimize oxidative damage to the heart. Few clinical studies have been published comparing efficacy of Microplegia with other cardioplegia solutions in congenital cardiac surgery.

All-blood, K^+-enriched cardioplegia, called microplegia or miniplegia, was originally described by Menasche et al in 1996 as a safe and effective alternative to blood or crystalloid cadioplegia[3]. Microplegia enables large volumes of blood cardioplegia to be delivered with relatively minimal amounts of crystalloid use. Conventionally blood cardioplegia is composed of ratios of blood:crystalloid (commonly 4:1 or 8:1) including additives, and a potassium-rich solution. Microplegia is a cardioplegia technique that consists of mixing blood from the cardiopulmonary bypass circuit with small quantities of concentrated additives (66:1), including a potassium-rich solution. This technique relies on a precision pump to deliver accurate quantities of additives while minimizing the quantity of crystalloid within the cardioplegia solution. This in turn allows for the delivery of large quantities of cardioplegia without the 'penalty' of large amounts of crystalloid being infused into the patient. Administration of less crystalloid may decrease myocardial oedema and permit more rapid recovery of ventricular function. The detrimental

consequences of haemodilution, volume overload and potential blood transfusions may also be avoided with Microplegia[4]. Velez et al.[5] however, reported endothelial dysfunction with all-blood cardioplegia when compared to the conventional blood cardioplegia group (Blood: Crystalloid= 4:1), possibly due to leucocyte mediated endothelial damage in microplegia. However this phenomenon did not translate into clinically significant differences in infarct size in the canine models studied.[5]

Antegrade cardioplegia (either microplegia or crystalloid) via a cannula placed into the aortic root proximal to the aortic perfusion cannula and crossclamp is administered to arrest the heart and maintenance doses are routinely administered repeatedly at standard 20 minute intervals throughout the procedures. Most cardiac surgeons would probably agree that irreversible ventricular muscle injury occurs with normothermic ischemia of approximately 30 minutes. The observation that the subendocardium[6] and hypertrophied ventricles[7] appear more susceptible to ischemic injury suggests that the imbalance of myocardial energy and oxygen supply relative to myocellular energy and oxygen utilization is the sole mechanism of post-ischemic cardiac dysfunction. Initial protection strategies logically turned to modes of decreasing myocardial oxygen demand.

It is well established that global or regional alterations in the metabolic status of the myocardium occur throughout the cross-clamp ischaemic time and during reperfusion, and that the functional recovery of the myocardium is highly dependent on the metabolic status of the heart during these vulnerable periods[8]. One of the most sensitive markers of inadequate preservation of the myocardium is the development of myocardial tissue acidosis and lactate production[9]. It has been demonstrated that persistent peripheral lactate release during the reperfusion period is an independent predictor of postoperative low cardiac output syndrome[10]. The evaluation of myocardial metabolism during cardiac surgery, therefore, allows the investigator to quantify the degree of physiologic impairment; in particular, direct cannulation of the coronary sinus (venous drainage of the myocardium) for coronary sinus blood sampling post removal of the aortic cross-clamp to measure metabolites or specific biochemical markers of myocardial damage has been shown to be a valid tool to define the degree of such impairment[11-13]. Incomplete myocardial protection is also responsible for blood elevation of troponin I[7,9,13]. Troponin I has been recently shown

to be a specific marker of myocardial damage, with a higher sensitivity and specificity; moreover, recent reports have defined postoperative troponin I as a sensitive marker of the quality of myocardial protection and of prognostic value for cardiovascular events at follow-up[14,15]. Therefore, lactate leakage, as well as the release of troponin I, can define the efficacy of myocardial protection[9].

Hypothermia during cardiopulmonary bypass exerts its protective effect by multiple mechanisms; the most obvious mechanism being the reduction of metabolic rate and oxygen consumption[16]. In most cardiac surgery mild to moderate (mild: 34°C-35°C moderate: 30°C-33°C) systemic hypothermia is used. The optimal temperature for myocardial protection is controversial. Immediate arrest and hypothermia also prevents reperfusion injury (i.e. the prevention of calcium accumulation, prevention of oedema and inhibition of production of oxygen radicals in coronary vascular endothelium).

In comparisons between warm blood cardioplegia (37 degrees Celsius) against tepid blood cardioplegia (29 degrees Celsius) results show that these temperatures were likely to provide similar myocardial protection. Buckberg and colleague's results[17], suggest that the difference in oxygen consumption should be very slight when the temperature falls from 37°C to 29°C. This was confirmed by Hayashida and colleagues[18] who showed that there was no difference in oxygen extraction, lactate or acid production between warm and tepid antegrade Cardioplegia, suggesting that mitochondrial respiration preservation should be equivalent with both techniques.

In neonates, the enhanced tolerance of the immature myocardium to hypoxia is partially explained by the biochemical differences in energy production between immature and mature myocardium. Although the adult heart uses a number of substrates for provision of energy, including lipids, carbohydrates, amino acids and long chain fatty acids (predominant source), the fetal heart relies more on anaerobic metabolism. Neonatal patients will therefore be excluded in this study as the bulk of evidence available at present points to the neonatal myocardium being considerably more resistant to ischaemia than mature myocardium.

The goals of myocardial protection during cardiac surgery are not only to facilitate the procedure by providing a motionless (asystolic heart) bloodless field, thereby

facilitating the precision of the procedure, but also to avoid iatrogenic injury induced by cardiopulmonary bypass itself or by surgically imposed ischaemia. In addition, myocardial protective strategies are geared to preventing reperfusion injury and myocardial oedema which manifests upon the ultimate release of the aortic cross clamp. The aim of this randomised study is to compare patient short-term outcomes using two different compositions of cardioplegia used in our institution each administered at different temperatures during congenital cardiac surgery. Does myocardial protection with microplegia in paediatric congenital open heart surgery significantly reduce the perioperative myocardial damage and improve the postoperative haemodynamic (need for inotropic support) status, the peripheral perfusion, and the resulting ventricular systolic and diastolic function? Does this, in turn, have an impact on duration of ventilation, need for postoperative inotropic support, length of intensive care and even hospital stay? Does the need for blood transfusions and diuresis differ in the postoperative period when using these 2 compositions/regimens of cardioplegia?

Objectives: The aim of this study is to compare short term postoperative outcomes of elective congenital cardiac patients undergoing cardiac corrective surgery. The comparison would be between two cardiac arresting agents, all-blood Microplegia and crystalloid St Thomas II solution.

Hypothesis: In congenital cardiac surgery the use of Microplegia is associated with improved short term outcomes compared with crystalloid Cardioplegia.

Material and Method

Patients and Study design

Study: Once approval from the *Human Research Ethics Committee (MEDICAL) at the University of Witwatersrand, Johannesburg* is obtained and informed consent is obtained from the parents of the patients, methods will be put in place and data will be collected.

During 2016, 80 (40 for each comparative study arm) elective paediatric congenital cardiac patients will be enrolled in a single-centre randomised study comparing outcomes using two different cardioplegia solutions, each administered at different

temperatures. The cardioplegia solutions are both used in our current practice in congenital cardiac surgery at Charlotte Maxeke Johannesburg hospital. The trial will set out to compare 40 patients in each comparative arm (n=80 total). However, an interim analysis would be undertaken after a pilot study of 40 patients (20 in each group of each different cardioplegic composition) to determine any significant benefit of either cardioplegia solution at the given temperatures (Microplegia: 28°C; Crystalloid: 4°C). If so, the remaining 40 patients would be assigned to the better cardioplegia solution. Patients will be randomized to receive either type of Cardioplegia solution.

Computer randomization will be performed and a list generated containing a sequence of either of the two randomly assigned cardioplegia solutions (Ie solution 1 or solution 2). Eighty opaque envelopes will be used (40 initially for the pilot study) arranged in the computer generated random sequence, each containing a note indicating either solution 1 or solution 2. The non-transparent envelopes will be sealed and arranged into a pile which will be labelled numerically according to the randomly generated sequence specified by the computer program. This will be done by an unbiased person who has no involvement or interest in the outcome of the study. On the morning of surgery of the patient enrolled in the study, the next numerical envelope will be opened by the perfusionist preparing the cardiopulmonary bypass machine and cardioplegia solution for the operation and in this way the patient will be assigned that solution for the procedure. One perfusion team will be used (4 members). Only one surgeon and one registrar (the investigator) will operate on these cases, keeping operating technique a constant so as not to introduce a confounding variable. The surgeons will be blinded to the cardioplegia solution used for the operation until such time that they administer the initial dose during the operation. The reason they will then be made aware is that the colours differ between Microplegia (sanguinous) and crystalloid (asanguinous) solutions.

With the exception of the Cardiopulmonary Bypass perfusion technicians, primary surgeon and registrar, all other staff (Anaesthetists, biochemists, cardiologists, nursing staff, intensivists) dealing with the perioperative care, biological sampling, and/or collection and analysis of data will be blinded toward the study.

Patients: Only three of the most commonly seen congenital defects of varying complexity will be included in the study, these being referred electively from surrounding cardiology clinics.

Inclusion criteria: Patients for elective corrective congenital heart surgery with lesions of either Tetralogy of Fallot, ventricular septal defect or atrioventricular septal defects of both genders and of weight 5-20kg.

Exclusion criteria: Interstitial lung disease. Poor preoperative ventricular function EF < 50%, Inherent bleeding disorders (eg Di George Syndrome, Haemophiliacs, Von Willebrands disease), more than 1 Cardiopulmonary bypass run, failure to separate from Cardiopulmonary bypass - ECMO, preoperative liver disease; redo surgery.

Preparation/Composition of Cardioplegia solutions

CRYSTALLOID CARDIOPLEGIA

n=40

St Thomas II cardioplegia will be administered at 4°C

Composition:	KCl:	16mmol/L	Sodium Bicarbonate:	10mmol/L
	MgCl:	16mmol/L	Calcium Chloride:	1,2mmol/L

MICROPLEGIA

n=40

Undiluted substrate-enriched Microplegia will be administered at a tepid temperature of 28°C.

Composition:

KCl:	Induction: 30mEq/L	Maintenance: 15mEq/L
Additives (50ml):	Induction: 15ml/L	Maintenance: 7ml/L
Magnesium Sulphate:	5g/10ml	
2% Lidocaine:	50mg/5ml	
Blood priming solution:	35ml	

The microplegia is delivered to the aortic root with the Quest MPS system (Integrated Myocardial Protection System-2, Quest Medical Inc; Allen TX, US). Ratio blood to crystalloid > 60:1

Operative Technique

Both anaesthesia and surgery will employ routine standard procedures used to correct these defects in all cases. Surgery will be performed through median sternotomy. The standard management of cardiopulmonary bypass (CPB) will be followed - Aorto bi-caval cannulation with antegrade administration of cardioplegia. The cardiopulmonary bypass (CPB) circuit will include a Medtronic phosphorylcholine-coated paediatric/infant custom pack tubing set, Terumo roller pump and a hollow fiber membrane, coated oxygenator, which incorporates a 40 mircon filter. Heparin will be given at a dose of 300IU/kg to achieve a target activated clotting time of 400 seconds or above prior to initiating CPB. For this study the extracorporeal circuit will always be primed with a fresh frozen plasma to leucodepleted homologous packed red cell solution reconstituted in a 1:1 ratio and 100mg/kg IU of heparin. These volumes will be used to calculate the pump balance of fluid input/output at the end of each case. A non-pulsatile CPB flow will be established at 2.4L/min/m^2. The body temperature of the patients whilst the heart is arrested will be cooled to mild-moderate hypothermia at 28-32 °C.

Cardiac arrest will be accomplished by administration of the hyperkalaemic cardioplegia solutions in an antegrade fashion via a cannula which is placed in the ascending aorta, proximal to both the aortic crossclamp and the aortic arterial cannula which perfuses the rest of the body while the heart is arrested. In this way the cardioplegia is directed into the coronary circulation via the coronary artery ostia at the root of the ascending aorta. Further dispersion of the cardioplegia is prevented by a competent aortic valve proximally and the aortic cross clamp distally.

The cardioplegia will be delivered at a bolus arresting dose of 30ml/kg and maintenance doses of 10ml/kg given repeatedly at 20 minute intervals at an average aortic root pressure of 80-100mmHg. The volume of these doses for both the cardioplegia solutions being compared will be the same, only the compositions and temperatures differ. Topical ice slush will be applied around the heart repeatedly while maintenance doses of cardioplegia are given throughout the procedure.

End points

End points will include:

1. Serial (x5) biochemical measurements: Lactate + Troponin I + Haemoglobin level blood sampling (x5) – In theatre preoperatively (T0); In theatre 10 minutes post removal of aortic crossclamp (T1); 6 hours post cross clamp

removal (T2); 12 hours post cross clamp removal (T3); 24 hours post aortic unclamping (T4).

The lactate and haemoglobin levels will be measured from arterial blood gases and the troponin I levels will be measured with iStat (Point of care) cartridges.

2. Observation of intraoperative spontaneous recovery to normal sinus rhythm after unclamping of the aorta. The perfusionists have timers running from the time of unclamping and observation for sinus rhythm will be made at 60 seconds; 180 seconds; 5 and 8 minutes.

3. Need for inotropic support will be categorized as:

NONE	
LOW	Dobutamine ≤ 2,5ug/kg/min
MEDIUM	Dobutamine > 2,5ug/kg/min ≤ 5ug/kg/min
HIGH	Dobutamine > 5ug/kg/min and/or addition of adrenaline and/or phenylephrine.

It has been noticed that many anaesthetists start inotropic support routinely post unclamping the aorta, irrespective of whether or not the patient requires additional support of cardiac contractility. The study will therefore assess need for inotropic support on admission to ICU (T1) and need for inotropic support at 10am the following morning (T2).

CORONARY SINUS SAMPLING

Coronary sinus blood (venous drainage of the myocardium) sampling will be done through the right atrium (the right atrium is routinely opened during the corrective procedures in this trial). This venous blood will be aspirated 10 minutes after the aorta is unclamped and the heart is allowed to eject, perfusing the coronaries with oxygenated blood while flushing residual Cardioplegia from the coronary system. Aspiration will be done with an Argyle Polyurethane Umbilical catheter size 5Fr and this sample specimen analysed for lactate levels and Troponin I which should reflect metabolic parameters for myocardial injury during the reperfusion state.

Statistics

Data would be recorded in EXCEL (Microsoft) and analysed using Statistica V8. Data would be reported in tables and graphs as frequency (n) and as means (±standard deviation) or median. Frequencies in each group would be compared with a Chi-squared test. Comparison between the groups (Microplegia vs St Thomas crystalloid cardioplegia) would be made using a t-test on normally distributed data. If the data is non-normally distributed differences between groups would be determined with the non-parametric (e.g. length of hospital stay) either a Kruskal-Wallis or Mann Whitney statistical test. Serial measurements would be compared using repeated measures ANOVA or Friedman two way ANOVA. Important predictors of outcome and events would be done using a Kaplan Meier curve and regression analysis. A p-value of <0.05 regarded as being of significant.

Funding

Cossni Medical Pty Ltd (Distributors of Quest Medical MPS) has sponsored the Argyle Polyurethane Umbilical size 5Fr catheters for sampling of coronary sinus blood. We have received stock of these catheters for the maximum number of patients to be enrolled in this study.

Cossni Medical Pty Ltd has also assisted with the design and sponsored printing of new perfusion record-keeping charts for the study and the Cardiothoracic service at Charlotte Maxeke Johannesburg Academic Hospital. The company has also sponsored us with a photocopying/scanning machine for the duration of the study to aid in data capturing.

iStat machines, printer, printing paper and cartridges for troponin level measurements are available for the study in our ICU and theatre. We currently have stock for 50 patients (5 troponin measurements each) and may have to order more if the study would need to continue after the Pilot Study phase.

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Informed Consent: The parents / legal guardians of the patients for surgery will be told of the study concomitantly with the preoperative counseling concerning the operative procedure, potential complications and postoperative events in detail before the surgery. A documented explanation of the aims and risks vs benefits of the study will be included in the consent template (Appendix A) which is to be dated and signed.

Study Authorization and Ethics

Permission and support in conducting the study has been obtained from Charlotte Maxeke Johannesburg Academic Hospital management (Department of Surgery and CEO's office) as well as the Department of Cardiothoracic Surgery. The Human Research Ethics Committee (Medical) has reviewed the protocol application in a closed meeting on 1st April 2016.

Protocol No.: **M160384**

The Ethics committee approved the protocol for the study subject to changes made and submitted.

PARENT/ GUARDIAN CONSENT FORM Appendix A

Study title: Does the use of Microplegia significantly improve outcomes in Congenital Heart Surgery?

Dear Parent/ Guardian

We, the surgeons of the Congenital Cardiac Surgery Department at Charlotte Maxeke Johannesburg Academic Hospital are doing research on protection of the heart during heart operations. Research is the way we find better ways to do the operations and in so doing, improve our patient's recovery/outcomes. In this study we want to perform a few extra blood tests in addition to the normal tests that we would routinely perform during and after the operation. In this way, we could learn if a different way of protecting the heart during the operation would benefit your child and perhaps other children coming for heart operations.

Invitation to participate: We are asking for your permission to include your child in this research study

What is involved in the study
Your child will be one of many in this study. The operation being performed will still be the routine operation done to correct the heart defect.
During these operations, the heart needs to be stopped routinely. There are many ways of stopping the heart in order for us to perform the correct operation safely, adequately and for the best recovery of the heart. We would like to test two of these methods. Both are safe and have been already used on many heart operations worldwide and by us in this hospital.
In this study, the only additional procedures that we will perform is to take two blood samples during the operation (each half a teaspoon) and a further three blood samples during the recovery stage in ICU.

Risks: There are **no** additional risks besides that of the heart operation routinely being performed on your child and that has already been explained to you

Benefits: We are continually trying to improve the way we perform cardiac surgery, in order to benefit your child and children to come.

Participation is voluntary. Refusal to participate will involve no penalty or loss of benefits to which your child is otherwise entitled. You may remove your child from the study at any time without penalty or loss of benefits to which the participant is otherwise entitled.

The results of this research may be made available to other medical professionals through academic publications.

Name and Surname	Signature	Date

Doctor Name, Surname and Signature Date

Witness Name, Surname and Signature Date

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Contact details of researcher/s:
Primary investigator: Dr Sharmel Bhika Tel: 011 717 2536
sharmel.bhika@wits.ac.za
Clincal Supervisor: Dr Krubin Naidoo Tel: 011 717 2536

Contact details of REC administrator:
Ms Zanele Ndlovu Tel. 011 717 1234/1252/2700
zanele.ndlovu@wits.ac.za

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