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To study the adequacy of myocardial protection with cardioplegia solution in patients undergoing cardiac surgery using CPK-MB as biomarker

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Abstract
The use of cardioplegia (pharmacologically induced electromechanical arrest) to achieve the ideal conditions for cardiac surgical operations was introduced over 20 years ago in clinical practice. The goals of myocardial protection during cardiac surgery are not only to facilitate the operation by providing a bloodless field, thereby facilitating the precision of the operation, but also to avoid iatrogenic injury induced by cardiopulmonary bypass itself or by surgically impose ischemia. Cardioplegia plays a very important role in myocardial protection strategies. Acting as perfusion agent, cardioplegia solutions can alter or inhibit ischemic injury by virtue of hypothermia and asystole. In addition, cardioplegia solutions can be used to avoid reperfusion injury. CPK-MB is the most sensitive and the most specific indicator available for the diagnosis of an acute myocardial infarction. This review is designed to investigate the adequacy of cardioplegia solution in coronary artery bypass grafting and its role in protecting the myocardium.

Method: This is a prospective analytical study is going to be conducted in the department of Cardiothoracic and Vascular Surgery, Pushpagiri Medical College Hospital, Thiruvalla. All patients who is willing to participate in the study is briefly explained about the study procedure. Approximately 60-65 patients will be taken into consideration. Blood sample (residual) of 3ml is required which is obtained from the laboratory and CPK-MB level is estimated 6^{th} and 12^{th} hourly after administration of cardioplegic solution. The patients are selected based on inclusion and exclusion criteria. The level of biomarker can be analysed by using semi auto analyzer. The results obtained from the study can be compared with the normal range of CPK MB in blood. Follow up will be conducted during the study period.

Keywords: Coronary artery bypass grafting, Cardioplegia, myocardial protection, ischemia, bloodless field, hypothermia

Introduction

Coronary Artery Bypass Graft (CABG): is a surgical procedure in which one or more blocked coronary arteries are bypassed by a blood vessel graft to restore normal blood flow to the heart. These grafts usually come from the patient's own arteries and veins located in the leg arm or chest.

Cardioplegia: is intentional and temporary cessation of cardiac activity, primarily for cardiac surgery. The word cardioplegia combines the Greek cardio meaning the "heart", and *plegia* "paralysis". Technically, this means arresting or stopping the heart so that surgical procedures can be done in a still and bloodless field. This process protects the myocardium, or heart muscle, from damage during the period of ischemia.

Cardioplegic solution: Cardioplegic Solution is a sterile, non-pyrogenic, essentially isotonic, formulation of electrolytes in Water for Injection, USP. It contains Calcium Chloride Di hydrate, Magnesium Chloride hexa hydrate, Potassium Chloride and Sodium Chloride.

It is a "core solution" intended for use only after addition of sodium bicarbonate to adjust pH prior to administration. After buffering with sodium bicarbonate, it is suitable for cardiac instillation (usually with hypothermia) to induce arrest during open heart surgery. Other agents may be added to the solution prior to instillation.

Cardioplegic solution with added sodium bicarbonate when cooled and instilled into the coronary artery vasculature, causes prompt arrest of cardiac electromechanical activity, combats intracellular ion losses and buffers ischemic acidosis.

When used with hypothermia and ischemia, the action may be characterized as cold ischemic potassium-induced cardioplegia.
Calcium (Ca++) ion in low concentration is included in the solution to maintain integrity of cell membrane to ensure that there is no likelihood of calcium paradox during reperfusion.
Magnesium (Mg++) ion may help stabilize the myocardial membrane by inhibiting a myosin phosphorylase, which protects adenosine triphosphate (ATP) reserves have been shown to be additive.
Potassium (K+) ion concentration is responsible for prompt cessation of mechanical myocardial contractile activity. The immediacy of the arrest thus preserves energy supplies for post ischemic contractile activity in diastole.

CPK- MB: is a cardiac marker used to assist diagnosis of an acute myocardial infarction. CPK-MB test measures the blood levels of CPK-MB, the bound combination of two variants (isoenzymes CKM and CKB) of enzyme phospocreatine kinase. The test detects different isoforms of B subunit specific to myocardium and presence of cardiac related isoenzyme dimmers. Higher levels of CPK-MB indicate the presence of myocardial damage.

Review Articles

1) Faisal A. Mourad *et al* (2016)[1]: conducted study on "Myocardial protection during CABG: Warm blood versus cold crystalloid cardioplegia, is there any difference?" .This study was to compare cold crystalloid cardioplegia and warm blood cardioplegia in patients undergoing CABG. Patients (n =100) undergoing CABG were prospectively randomized into group 1(n= 50) which received antegrade cold crystalloid cardioplegia, group 2 (n = 50) which received antegrade warm blood cardioplegia. Blood samples were collected immediately, 12, and 24 h postoperatively and CK, CKMB, and Cardiac Troponin I were measured and compared between the two groups which were the indicator of myocardial cell injury (the primary end point of this study). Other indicators such as spontaneous defibrillation, use of intra-aortic balloon counter pulsation (IABC), and use of inotropic support were also documented. Preoperative demographic and clinical variables were matched in both groups. However, intraoperatively, the use of inotropic support was significantly higher in Group I compared to Group II (P = 0.032). Postoperative CK, CKMB and Troponin I were significantly higher in group (I) compared to group (II).A significant reduction in the release of cardiac enzymes in patients who received antegrade warm blood cardioplegia suggests better myocardial protection compared to cold crystalloid cardioplegia.
2) Murat Aksun *et al* (2015)[2]: conducted study on "Comparison of intermittent antegrade cardioplegia and antegrade/retrograde continuous cardioplegia in terms of myocardial protection in cardiac surgery". This study was to compare intermittent antegrade cardioplegia and antegrade/retrograde continuous cardioplegia in terms of myocardial protection in cardiac surgery. Hundred six patients who underwent cardiac surgery in our clinic between October 2010 and January 2011 were included in the study. Patients were divided into two groups as patients who received intermittent antegrade cardioplegia (group 1; 18 females, 14 males) and who received antegrade/retrograde continuous cardioplegia (group 2; 16 females, 58 males), and postoperative results were compared. Troponin-I, creatine kinase-myocardial band (CK-MB) levels, durations of cardiopulmonary bypass (CPB) and cross-clamping, total amounts of cardioplegia, and potassium utilization during the process were evaluated. According to the results, mean troponin-I and CK-MB levels were higher in group 1 than group 2. However, this difference was not statistically significant. While troponin-I and CK-MB values were correlated to durations of cross-clamping and CPB in group 1, troponin-I and CK-MB values were not correlated to durations of cross-clamping and CPB in group 2.
3) Helene De Bruyn *et al* (2014)[3]: conducted study on **"**Myocardial Protection during Cardiac Surgery: Warm Blood versus Crystalloid Cardioplegia**".** Prevention of myocardial injury is essential during cardiac surgery. Both crystalloid and blood cardioplegia are popular methods for myocardial protection. Most experimental studies have been in favor of blood cardioplegia. The objective of this study is to determine whether the use of warm blood cardioplegia (BCP) is superior to crystalloid cardioplegia (CCP) by means of myocardial injury markers and clinical outcome parameters. In a consecutive series of 293 patients, the first 150 received crystalloid cardioplegia, whereas the next 143 patients received blood cardioplegia. Postoperative myocardial injury was assessed by CTnI and CK-MB. Perioperative morbidity and mortality and clinical outcome parameters (need for inotropic support, ICU and hospital stay) were recorded. An unpaired student t-test was performed to analyse continuous postoperative variables relating to myocardial damage. The presence of possible confounders influencing the CTnI or CK-MB concentrations was tested using a student t-test for continuous variables, for categorical variables ANOVA was used. A final longitudinal model was created for CTnI and CK-MB. CTnI was analyzed by a mixed model with random intercept and slope. For all tests performed, statistical significance was 5%.Both groups were well matched with respect to preoperative variables. No significant difference could be found in maximum postoperative levels of CTnI (8.8 ± 18.4 µg/l in BCP vs 9.6 ± 16.5 µg/l in CCP, p = 0.6455) or CK-MB (19.2 ± 31.0 µg/l in BCP vs 26.4 ± 41.5 µg/l in CCP, p = 0.1209). Nor was there any significant difference in other postoperative variables. Testing treatment effect over time proved only significant influence of the surgical intervention type on CTnI levels in time ($p < 0.001$).This study could not show significantly higher myocardial injury in the group of patients receiving crystalloid cardioplegia versus warm blood cardioplegia. This suggests that warm blood cardioplegia does not confer superior myocardial protection. Surgical intervention type has an important effect on CTnI concentration in time, while the type of cardioplegia does not.
4) Bjorn Braathen *et al* (2009)[4]: conducted study on "Cold blood cardioplegia reduces the increase in cardiac enzyme levels compared with cold crystalloid cardioplegia in patients undergoing aortic valve replacement for isolated aortic stenosis". Patients were randomized to antegrade cold crystalloid or cold blood cardioplegia. Eighty patients with aortic stenosis undergoing aortic valve replacement without significant

coronary artery stenosis or other significant concomitant heart valve disease were included in the study. They were randomized to either antegrade cold blood or cold crystalloid cardioplegic solution delivered through the coronary ostia every 20 minutes throughout the period of aortic cross clamping. Maximum postoperative creatinekinase isoenzyme MB and troponin-T levels, well-established markers of myocardial damage, were compared between the 2 groups. Both maximum postoperative creatine kinase isoenzyme MB and troponin-T levels were significantly higher by approximately 100% in the cohort of patients receiving crystalloid compared with blood cardioplegia. Only in the group of patients receiving cold crystalloid cardioplegia was there a positive correlation between cardiac enzyme levels and cross clamp time.

5) Venugopal *et al* (2009)[5]: conducted study on "Remote ischaemic preconditioning reduces myocardial injury in patients undergoing cardiac surgery with cold-blood cardioplegia: a randomised controlled trial". Remote ischaemic preconditioning (RIPC) induced by brief ischaemia and reperfusion of the arm reduces myocardial injury in coronary artery bypass (CABG) surgery patients receiving predominantly cross-clamp fibrillation for myocardial protection. However, cold-blood cardioplegia is the more commonly used method worldwide. Adults patients (18–80 years) undergoing elective CABG surgery with or without concomitant aortic valve surgery with cold-blood cardioplegia. Patients with diabetes, renal failure (serum creatinine >130 mmol/l), hepatic or pulmonary disease, unstable angina or myocardial infarction within the past 4 weeks were excluded. Interventions: Patients were randomised to receive either RIPC (n=23) or control (n=22) after anaesthesia. RIPC comprised three 5 min cycles of right forearm ischaemia, induced by inflating a blood pressure cuff on the upper arm to 200 mm Hg, with an intervening 5 min reperfusion. The control group had a deflated cuff placed on the upper arm for 30 min. Main outcome measures: Serum troponin T was measured preoperatively and at 6, 12, 24, 48 and 72 h after surgery and the area under the curve (AUC at 72 h) calculated. Results: RIPC reduced absolute serum troponin T release by 42.4% (mean (SD) AUC at 72 h: 31.53 (24.04) µg/l.72 h in controls vs 18.16 (6.67) µg/l.72 h in RIPC; 95% CI 2.4 to 24.3; p=0.019).Remote ischaemic preconditioning induced by brief ischaemia and reperfusion of the arm reduces myocardial injury in CABG surgery patients undergoing cold-blood cardioplegia, making this non-invasive cardioprotective technique widely applicable clinically.

6) Michael Carrier *et al* (2000)[6]: conducted study on "Troponin levels in patients with myocardial infarction after coronary artery bypass grafting". The objective of this study was to evaluate serum cardiac troponin T and I levels in patients in whom electrocardiogram, myocardial scan, and serum CK-MB levels of the MB isoenzyme of creatine kinase indicated perioperative myocardial infarction (MI) after coronary artery bypass grafting (CABG).We studied 590 patients who underwent CABG at the Montreal Heart Institute between 1992 and 1996. Postoperative cardiac troponin T levels (493 patients), troponin I levels (97 patients), and activity of the MB isoenzyme of creatine kinase, electrocardiograms, clinical data, and clinical events were recorded prospectively. The diagnosis of perioperative PMI was defined by a new Q wave on the electrocardiogram, by serum levels of the MB isoenzyme of creatine kinase higher than 100 IU/L within 48 hours after operation, or both.Results. After CABG, 22 patients in whom troponin T levels (22/493, 4.5%) and 6 patients in whom troponin I levels (6/97, 6.2%) were measured had sustained a perioperative MI according to current diagnostic criteria. In these patients, troponin T levels higher than 3.4 µg/L 48 hours after CABG best detected the presence of perioperative MI, with an area under the receiver operating characteristic curve of 0.95, a sensitivity of 90%, a specificity of 94%, a positive predictive value of 41%, a negative predictive value of 99%, and a likelihood ratio of 15. Serum troponin I levels higher than 3.9 µg/L 24 hours after CABG confirmed the perioperative MI with an area under the receiver operating curve of 0.86, a sensitivity of 80%, a specificity of 85%, a positive predictive value of 24%, a negative predictive value of 99%, and a likelihood ratio of 5. Serum troponin T levels higher than 3.4 µg/L 48 hours after CABG correlated best with the diagnosis of perioperative MI. Serum troponin T levels greater than 3.9 µg/L 24 hours after CABG also correlated with the diagnosis of perioperative MI, although a larger experience is needed to confirm the validity of the chosen cutoff value.

7) Van Lente F *et al* (1987)[7]: conducted study on "Changes in serum CK-MB mass after coronary artery bypass surgery", assessed the release of creatine kinase MB as both mass and activity during the postoperative period following cardiac surgery**.** CK-MB mass was determined by enzyme immunoassay using reagents obtained from Hybritech. CK-MB activity was determined both by agarose electrophoresis and by an immunochemical method. Fifty-five patients who underwent coronary artery bypass surgery and 52 control subjects who had orthopedic surgery were selected for study. Serial serum samples were collected following surgery and total LD, CK, AST, LD-1, CK-MB mass, and CK-MB activity determined. Results were compared to each other and to surgical parameters. All patients exhibited significant CK-MB mass and activity after surgery and peak serum levels were 6-94 micrograms/L and 12-84 U/L, respectively. CK-MB mass correlated with CK-MB activity on paired samples (r = 0.94). Total AST and CK activities correlated with CK-MB mass (r = 0.60, and 0.63, respectively). Peak levels of CK-MB mass correlated significantly with peak MB activity (r = 0.88), peak LD-1 (r = 0.62), peak AST (r = 0.71), and time on pump (r = 0.54). Similar correlations were also seen between peak CK-MB activity and these parameters. No relationship could be identified between extent of CK-MB mass release and number of grafts, degree of hypothermia, or minimum PaO2. The time course of CK-MB mass release exhibited 85% concordance with CK-MB activity.

Conclusion

Controlled ischaemic cardiac arrest induced temporarily by cold blood cardioplegia during CABG surgery reduces myocardial injury, making these cardio-protective techniques widely applicable clinically.

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