Ringer Acetate versus Ringer Lactate Cardioplegia: A comparative study in Mitral Valve Surgery.

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Abstract

Background: Ringer lactate has long been used in many surgical procedures as one of the isotonic solutions. However, with the development of Ringer acetate, it becomes the crystalloid of choice owing to its main metabolism in muscles unlike lactate which is mainly in liver, also it corrects acidosis more rapidly than lactate and it needs less O2 and produces less CO2. Ringer acetate has also a great utility during cardiovascular surgery with cardiopulmonary bypass. We compared efficacy and safety of Ringer acetate versus lactate in preparing cardioplegic solution during mitral valve surgery. Methods: 42 adult patients undergoing mitral valve replacement using CPB were randomly divided into two groups. Patients in group A received antegrade cold Ringer Acetate cardioplegic solution at a rate of 10 ml/kg followed after 20 minutes by 5ml/kg retrogradely in the coronary sinus. Patients in group B received cold Ringer Lactate cardioplegic solution in a similar regimen to group A. Results: Troponin I level from coronary sinus during reperfusion, was higher in group B than A (4.4±1.6 ng/ml & 3.4±1.49 ng/ml respectively) and after 4 & 24 hours postoperatively there was a significant increase in the serum Troponin I level in group B than in group A (p<0.05). Lactate in the coronary sinus was higher in group B than A during rewarming (2.8±1.9 ng/ml &1.6±1.8 ng/ml respectively). The serum level was always higher in group B than A in the postoperative period (P<0.05). There was no significant difference
between both groups as regards the post–bypass ischemic changes as detected by TEE examination. Also, there were no differences in the duration of inotropic support, ventilation time, intensive care unit or hospital stay in the two groups. **Conclusion:** Both Ringer Acetate & Lactate cardioplegia provide adequate myocardial protection, however the recovery of the heart from ischemia after the Ringer Acetate cardioplegia is better than Ringer Lactate.

**Key Words**

**Introduction**
Effective myocardial protection remains the key element for success in heart surgery. The clinical introduction of cold crystalloid cardioplegic solutions, beginning in the mid-1960s (1,2), may be considered an essential prerequisite for many of the more complex cardiac surgical procedures, which have been developed since that time. In spite of the development of blood cardioplegia in 1990's many institutions around the world still consider cold crystalloid cardioplegia the preferred method of myocardial protection, due to its satisfactory clinical results, institutional experience, and individual surgeon's preference.

Based on the pharmacological mode of action, two types of cold crystalloid cardioplegic solutions may be discriminated: The intracellular and the extracellular solution type. Intracellular type, contain no or low concentrations of sodium & calcium, where as extracellular type solutions contain higher
concentrations of sodium, calcium, and magnesium. Both
contain potassium between 10 & 20 mmol/l, and may have
added osmotically active substances as mannitol & local
anesthetics (Table 1).

**Table 1** Composition of cardioplegic solutions

<table>
<thead>
<tr>
<th></th>
<th>Sodium</th>
<th>Potassium</th>
<th>Magnesium</th>
<th>Calcium</th>
<th>Bicarbonate</th>
<th>Other components</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Custodiol®</strong> (Bretschneider's HTK solution)</td>
<td>15</td>
<td>9</td>
<td>4</td>
<td>0.015</td>
<td>–</td>
<td>Histidin, Tryptophan, Potassium-hydrogen-2-ketoglurat</td>
</tr>
<tr>
<td><strong>Plegisol®</strong> (St. Thomas No. 2)</td>
<td>110</td>
<td>16</td>
<td>16</td>
<td>1.2</td>
<td>10</td>
<td>Lidocaine</td>
</tr>
<tr>
<td>Lactated Ringers (for comparison)</td>
<td>130</td>
<td>24</td>
<td>–</td>
<td>1.5</td>
<td>–</td>
<td>Lactate, chlorine</td>
</tr>
</tbody>
</table>

Example for composition of intracellular (Custodiol®) and extracellular (Plegisol®) cardioplegic solutions. All numbers in mmol/l.

The efficacy of myocardial protection by cold crystalloid cardioplegia has been demonstrated in numerous studies (3,4). More recently, the clinical outcome after cold crystalloid cardioplegia has been compared to current techniques of blood cardioplegia in controlled randomized clinical trials (5,6,7,8,9).
Lately, new pharmacological agents, such as free radical scavengers and Na+/H+ exchange inhibitors have been investigated as additives to crystalloid cardioplegic solutions (10,11,12). However, a clear clinical benefit in terms of improved patient outcome remains to be demonstrated for these cardioplegia additives.

Recent studies demonstrated that Ringer's acetate is superior to Ringer's lactate in correcting acidosis more rapidly and needs less O2 and produces less CO2 (13,14).

In this study we compared the safety and efficacy of Ringer acetate versus lactate as a vehicle of cold crystalloid cardioplegia during mitral valve surgery.

**Material & Methods**

After obtaining approval of the Ethics Committee of our department and a written informed consent from every patient enrolled in this study, 42 adult patients scheduled for mitral valve replacement using CPB at the Cairo University Hospitals were included in this double-blinded, randomized prospective trial. Patients included in this study were those with mitral valve stenosis (26 patients) with a varying degree of stenosis from moderate to severe, mitral valve regurge (16 patients) who were all with a severe degree of regurgitation. Exclusion criteria included patients with poor left ventricular function (EF less than 40%), other valvular disease (aortic or tricuspid), patients with atrial fibrillation and those on antidysrhythmic medications. Patients requiring reexploration for bleeding also were excluded, because their myocardial function, their hemodynamic condition and the amount of anesthesia administered to them differed substantially from the others.
Anesthetic and Surgical techniques

Anesthetic technique
Patients were premedicated with 10 mg morphine intramuscularly injected an hour prior to surgery and 0.05 mg/kg midazolam intravenously administered 20 minutes pre-induction.
Anesthesia was induced by 5 microgram/kg body weight fentanyl and 2.5 mg/kg body weight thiopentone sodium. 0.1 mg/kg pancuronium was given to facilitate tracheal intubation. Maintenance of anesthesia was achieved with isoflurane 0.4 to 0.8 in FIO2 0.6 oxygen/air mixture. Mechanical ventilation was maintained at a tidal volume of 6-8 ml/kg and frequency of 10-12 breaths/min, facilitated by 1 mg boluses of pancuronium every hour. Fentanyl infusion at a rate of 2 microgram/kg/hr was used with additional boluses of 50microgram given when needed to maintain adequate analgesia.
Standard monitoring included 2 channels 5 leads ECG with computerized ST segment analysis, continuous invasive arterial blood pressure monitoring, pulse oximetry, end-tidal CO2, nasopharyngeal temperature, urine output, central venous pressure, frequent arterial blood gases and electrolyte analysis, celite-activated clotting time and transesophageal echocardiography was used to assess the mitral valve in the prebypass period where the probe was inserted before anticoagulation. It was also used in the postbypass period to assess the function of the prosthetic valve as well as the wall motion abnormalities.

Surgical technique:
Through a median sternotomy, cardiopulmonary bypass was established with standard aorto-bicaval cannulation. Combined antegrade and retrograde cold crystalloid cardioplegia were used for myocardial protection. Mitral valve was inspected through a left atriotomy or
transatrial incision. Mitral valve replacement was performed with preservation of the posterior mitral valve leaflet & its supporting subvalvular apparatus.

Myocardial protection:
Standard 30 meq/L KCl, 200mg/L lidocaine hydrochloride, 10meq/L sodium bicarbonate and 1g/L of magnesium sulfate were added to both Ringer Acetate & Lactate solutions.

Patients in group A received antegrade Cold (4°C) Ringer Acetate cardioplegic solution at a rate of 10ml/kg body weight followed after 20minutes by 5ml/kg retrogradely in the coronary sinus. Patients in group B received Cold (4°C) Ringer Lactate cardioplegic solution in a similar regimen to group A. In both groups, the heart was perfused with warm blood reperfusion without cardioplegic solution, before aortic declamping, such that on termination of CPB, body temperature in both groups was equal.

Anticoagulation Protocol:
Prior to aortic cross–clamping heparin was administered at an initial dose of 4mg/kg to achieve an activated clotting time of 480 seconds (Hemocron 8000, International Technique Cor., Edison NJ), or more followed by standard maintenance of the time above that level by heparin top-up boluses. After separation from CPB, reversal of anticoagulation was achieved by administration of protamine sulfate with ratio 1:1 of heparin.

Study Protocol:
Patients were randomly assigned to one of the two groups. Patients in group A received Cold Ringer Acetate cardioplegic solution while
patients in group B received Cold Ringer Lactate cardioplegic solution at a regimen similar to group A.

Preoperative, operative characteristics and demographics for all patients in both groups were recorded. Troponin I levels were measured from the coronary sinus 20 minutes after the 1st dose of cardioplegia, immediately before giving the 2nd one and during rewarming. It was also measured in the serum after 4, 12, 24 and 48 hours postoperatively. Concerning the lactate levels, they were measured in the coronary sinus, also 20 minutes from the 1st dose of cardioplegia and during rewarming. As regards the serum lactate levels, they were measured 4, 12, 24 and 48 hours postoperatively. Additionally, TEE was used to assess the valve function as regards the degree of stenosis or regurge in the prebypass period. Postbypass, TEE was used to assess the function of the prosthetic valve as well as the presence of ischemia.

A number of clinical outcomes were also analyzed including, the postoperative inotropic support, its duration, the postoperative arrhythmias, the duration of ventilation, the ICU stay and the hospital stay.

**Statistical Analysis**

Data were described in terms mean + SD or frequency and percentage when appropriate. Quantitative data were compared using Mann Whitney U test for independent samples. Comparison of categorical data was done using chi squared test. Yates correction equation was used instead when any of expected frequencies was < 5. All statistical tests were done using MS Excel version 7.00 for windows and SPSS statistical program for windows version 13 (SPSS corporation, Chicago, IL-USA). A probability value (P value) < 0.05 was considered statistically significant.
Results
A total of 40 patients were recruited to the study, of whom 21 were in the Lactate group (group B) and 19 in the Acetate group (group A). Two patients who were initially enrolled in group A were excluded from the study due to reopening for postoperative bleeding. The preoperative characteristics of the two groups are summarized in Table 2. No differences were found between group A & group B with regard to CPB and aortic cross clamping time. There were no hospital deaths. Significant postoperative inotropic support (>0.1ug/kg/min. Epinephrine infusion) was required more frequently in group B than group A (57 % versus 36% respectively) and the overall postoperative inotropic duration was longer in group B than in group A without reaching statistical significance. Three patients in group B had supraventricular tachycardia. No differences in ventilation time, ICU stay and the hospital stay were found between the 2 groups, Table 3.

Table 2. Patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>Group A (n=19)</th>
<th>Group B (n=21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>27 (20 to 39)</td>
<td>25 (19 to 37)</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>9/10</td>
<td>11/10</td>
</tr>
<tr>
<td>Body Weight (Kg)</td>
<td>57.6 (45.9 to 80.6)</td>
<td>60.4 (44.3 to 74.2)</td>
</tr>
<tr>
<td>Preoperative Hb (g/dl)</td>
<td>12.2 (11.4 to 12.9)</td>
<td>11.3 (10.4 to 12.8)</td>
</tr>
<tr>
<td>CPB time (min.)</td>
<td>52 (42 to 88)</td>
<td>62 (45 to 91)</td>
</tr>
<tr>
<td>ACC time (min.)</td>
<td>29 (17 to 55)</td>
<td>35 (23 to 56)</td>
</tr>
</tbody>
</table>

Medians & ranges are shown for continuous variables. Hb=hemoglobin; CPB=cardiopulmonarybypass; ACC=aortic cross clamp.
<table>
<thead>
<tr>
<th></th>
<th>Group A (n=19)</th>
<th>Group B (n=21)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Postoperative</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>inotropic support</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nil</td>
<td>1</td>
<td>3</td>
<td>0.23</td>
</tr>
<tr>
<td>Minimal</td>
<td>11</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Significant</td>
<td>7</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Inotropic support duration</td>
<td>21 (0 to 107)</td>
<td>25 (0 to 137)</td>
<td>0.5</td>
</tr>
<tr>
<td><strong>Postoperative</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>arrhythmias</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AV block</td>
<td>1</td>
<td>4</td>
<td>0.35</td>
</tr>
<tr>
<td>Pacing</td>
<td>2</td>
<td>5</td>
<td>0.41</td>
</tr>
<tr>
<td>SVT</td>
<td>0</td>
<td>3</td>
<td>0.23</td>
</tr>
<tr>
<td>Ventilation (hours)</td>
<td>8 (2 to 29)</td>
<td>9 (2 to 21)</td>
<td>0.72</td>
</tr>
<tr>
<td>ICU stay (days)</td>
<td>2 (2 to 2)</td>
<td>2 (2 to 4)</td>
<td>0.22</td>
</tr>
<tr>
<td>Hospital Stay (days)</td>
<td>8 (6 to 11)</td>
<td>8 (7 to 10)</td>
<td>0.98</td>
</tr>
</tbody>
</table>

Medians & ranges are shown for continuous variables. AV block=Atrioventricular block. SVT=supraventricular tachycardia. ICU=intensive care unit. Nil=no inotropic support, Minimal=0.05-0.1ug/kg/min Epinephrine, Significant=>0.1 ug/kg/min Epinephrine.
As regards the troponin level from the coronary sinus, there was no significant difference between the 2 groups 20 minutes after the aortic cross clamp where the levels were 4.5±4.16 & 5.1±3.97 ng/ml in groups A & B respectively. However, during rewarming, Troponin level in group B was statistically significant than in group A (P<0.05), the levels of Troponin I were 4.4±1.61 & 3.4±1.49 ng/ml respectively (Figure 1). For the serum troponin level, there was a significant rise in group B than in group A 4, 24 and 48 hours postoperatively (P<0.05) where the levels were 4.10±0.90, 2.10±0.40 & 1.50±0.30 ng/ml in group B in comparison to 2.20±0.3, 1.10±0.3 & 0.75±0.2 in group A (Figure 2).

![Fig. (1): Coronary sinus Troponin I level](image)

* p<0.05
Concerning the coronary sinus lactate level, there was no difference between the 2 groups 20 minutes from the start of the aortic cross clamp, but during rewarming, there was a significant rise in the lactate level in group B than group A (P<0.05) (Table 4). As regards the serum lactate level, there was a significant rise in group B than in group A after 4, 12, 24 & 48 hours in the postoperative period (P<0.05) (Table 5)

**Table 4. Coronary sinus lactate level**

<table>
<thead>
<tr>
<th></th>
<th>Group A (n=19)</th>
<th>Group B (n=21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>After 20min.(ng/ml)</td>
<td>2.51±2.42</td>
<td>2.80±2.20</td>
</tr>
<tr>
<td>Rewarming (ng/ml)</td>
<td>1.60±1.80</td>
<td>2.81±1.90*</td>
</tr>
</tbody>
</table>

Values are presented as mean±SD

*P<0.05
### Table 5. Serum lactate level

<table>
<thead>
<tr>
<th></th>
<th>Group A (n=19)</th>
<th>Group B (n=21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (ng/ml)</td>
<td>1.10±0.21</td>
<td>1.00±0.20</td>
</tr>
<tr>
<td>After 4 hours (ng/ml)</td>
<td>1.60±0.20</td>
<td>2.40±0.30*</td>
</tr>
<tr>
<td>After 12 hours (ng/ml)</td>
<td>1.31±0.25</td>
<td>2.10±0.29*</td>
</tr>
<tr>
<td>After 24 hours (ng/ml)</td>
<td>1.42±0.24</td>
<td>2.25±0.22*</td>
</tr>
<tr>
<td>After 48 hours (ng/ml)</td>
<td>1.45±0.23</td>
<td>2.11±0.26*</td>
</tr>
</tbody>
</table>

Values are presented as mean±SD

*P<0.05

For the TEE, all valves were functioning well & ischemic changes which were detected as hypokinesia, occurred only in 1 patient in group A & 2 patients in group B. These ischemic changes improved markedly in all patients shortly after CPB.

### Discussion

There is a magnitude of technical modification for protecting the heart during ischemic arrest, such as different temperature (cold, tepid, warm) (15,16), different route of administration (antegrade, retrograde and combination of both) (17,18), additive, substrates or drugs (19,20-23). The large amount of laboratory studies, most of them indicating the benefit of blood cardioplegia (19,24), do not really help the clinician to evaluate the effects on the most relevant patient outcome variables, particularly because of the lack of larger prospectively randomized patient studies. In a study by Ovrum et al (25) comparing different cardioplegic solutions in CABG patients, there were some disappointment after realizing that no overall clinical benefits were seen when comparing blood cardioplegia and crystalloid cardioplegia. Even
more, no beneficial effects could be shown in groups of patients at higher operative risk, such as those with unstable angina, redo operations, lower ejection fraction, female sex, diabetes or older age. The results of Ovrum et al (25) were similar to those of other randomized series (26-28) in which no difference between cold blood and cold crystalloid cardioplegia could be seen, where as others suggested improved myocardial protection with blood cardioplegia (24,29,30).

Ringer's solution (sodium chloride=147.3 mmol/liter, potassium=4.02 mmol/liter and calcium chloride =2.25 mmol/liter) to which was added 24 mmol/liter of potassium chloride to effect and total dose of 28 mmol/liter, 7g/liter of glucose and 0.8 ml of THAM (31), has been used for a long time as a cardioplegic solution during myocardial protection. The classic St. Thomas differed by having a lower concentration of potassium chloride, 19.59 mmol/liter, and added 15.9 mmol/liter of magnesium chloride and 1 mmol/liter of procaine hydrochloride. Ringer's Acetate differs from Ringer's Lactate in the fact that the bicarbonate content is present as Acetate instead of Lactate. Many studies have proven that Ringer's Acetate solution is the most balanced electrolyte solution (32) owing to its main metabolism in muscles unlike Lactate which is mainly in liver (33). Additionally, other studies had demonstrated that Acetate is superior than Lactate in the fact that it corrects acidosis more rapidly and needs less O2 and produces less CO2 (13,14).

In our study, we have compared the 2 crystalloid solutions, Ringer Acetate & Ringer Lactate as 2 cold crystalloid cardioplegic solutions. To our knowledge these two solutions have not been compared in cardioplegic solution preparation. We demonstrated that the use of Ringer Acetate has been associated with less ischemic insults than use of Ringer Lactate. This has been clear from the coronary sinus & serum levels of both Troponin I & Lactate. The coronary sinus level of Troponin I in
acetate group was statistically significant than in the Lactate one during rewarming. In addition, the serum Troponin I level in the acetate group was also higher than in the Lactate group after 4, 24 & 48 hours in the postoperative period. Concerning the lactate level, it was significantly higher in the Lactate group than in the Acetate one, also during rewarming and in the immediate post operative period.

However, there may be some limitation about this study owing to the limited number of patients studied which may necessitate further investigations and research. Also studies may be extended to other patient groups including CABG and those with poor ventricular function

Conclusion
Ringer Acetate cardioplegia may be superior to Lactate one as regards the ischemic insult & the recovery of the heart after ischemia during mitral valve replacement.

References


21- Hynninen M, Borger MA, Rao V, Weisel RD, Christakis GT, Carroll Cheng DC. The effect of insulin cardioplegia on atrial fibrillation after


