Changes in liver enzymes and bilirubin after coronary artery bypass grafting using acute normovolemic hemodilution

S. H. Akhlagh (*), M. T. M. Vaziri (*), M. H. Nemat (**), and H. Ashraf (***)

Abstract: The aim of this clinical case-control trial was to compare postoperative early jaundice and transient liver damage in patients receiving autologous or homologous blood transfusion in coronary artery bypass grafting (CABG) surgery. In this randomized clinical trial 40 patients scheduled for CABG were randomly allocated to ANH (Acute Normovolemic Hemodilution) group or control group. Both groups were compared in relation to bilirubin (total and direct), alanine transferase (ALT), aspartate transferase (AST) and alkaline phosphatase (ALP) in the first 24 hours. There was a significant difference in bilirubin (total and direct) change between groups (both p < 0.00001). However, there were no changes in ALT, AST and ALP compared with baseline values, and there were no differences in the values between the two study groups. Our randomized, double blinded case control study suggested that patients receiving autologous blood (ANH group) following CABG had significantly lower bilirubin levels compared to patients who received homologous transfusion. However larger studies with more patients are needed to confirm the results.

Key words: CABG surgery ; blood requirement ; autologous ; homologous blood transfusion.

INTRODUCTION

Despite demonstrable advances in all aspects of operative and perioperative management over the last decade, early jaundice and transient liver damage after modern extracorporeal circulation surgery is still occurs frequently (1-4). The appearance of postoperative hyperbilirubinemia as a result of liver dysfunction is associated with serious morbidity and carries a mortality rate of 25% (4, 5). The mortality can reach 85%-90% once the postoperative jaundice progresses to hepatic failure (6, 7). Thus recently, more attention has been paid to the studies of jaundice and liver injuries following CPB and hepatic dysfunction remains a serious postoperative complication with unknown pathogenesis.

Previous studies demonstrated that homologous blood transfusion during and shortly after surgery contributes to the development of jaundice (1, 8). The phenomenal increase in the number of open-heart surgeries done in cardiac centers in the last decade and the proposed beneficial effect of Acute Normovolemic hemodilution (ANH) in terms of reduction in use of homologous blood components (9-11) prompted us to start this prospective study. We aimed to analyze the effect of the ANH combined with autologous transfusion on early postoperative jaundice and transient liver damage following coronary artery bypass grafting (CABG) surgery.

METHODS

Study Design and participants

After obtaining Institutional Review Board approval, we studied forty consecutive patients undergoing coronary artery bypass grafting (CABG) in a randomized prospective design. After written informed consent was obtained, patients were randomized to two groups, ANH group (n = 20, 13 males) and control group (n = 20, 12 males). Patients with deranged liver function tests, severe or unstable angina, recent myocardial infarction, cardiac failure, valvular disease, cerebrovascular disease or hemodynamically significant carotid artery stenosis, hematocrit level less than 35%, and
chronic obstructive pulmonary disease were excluded from the study.

Interventions

In the ANH group, following the induction of anesthesia, and before the initiation of the cardiopulmonary bypass and before heparinization, collection of 15 ml/kg of autologous blood was performed. Collected autologous bloods were stored at room temperature in standard anticoagulant (citrate-phosphate-dextrose). During blood collection three times the amount of the collected blood was replaced by crystalloid fluids (3 mL crystalloid for each 1 mL of blood withdrawn). The need for fluid infusion was based on hemodynamic and electrocardiographic monitoring and was closely monitored by the attending anesthesiologist.

Electrocardiography (ECG) and systemic arterial and central venous pressures were carefully monitored. At the end of operation and after separating the patients from the cardiopulmonary bypass machine, the collected blood was infused to the patients. in the control group, homologous blood was used as needed.

Postoperative homologous blood transfusion was guided by clinical indications, while keeping the hematocrit value above 25%, by the intensive care unit consultant doctor who was blinded to the groups.

The same team performed all the operations using the same operative techniques. All data were registered by an independent investigator.

Operative procedure

All patients underwent on-pump CABG by the same surgeon using primary median sternotomy and routine cardiopulmonary bypass (CPB) with mild hypothermia (32 degrees Celsius) and tepid antegrade blood cardioplegia was used.

Anaesthetic technique

General anesthesia was induced with fentanyl 5 mcg/kg and sodium thiopental 3 mg/kg. Pancuronium 0.1 mg/kg was administered to facilitate tracheal intubation. Isoflurane was used for maintenance of anesthesia.

Cardiopulmonary bypass

Crystalloid priming of CPB circuit was with 1000 ml of Ringer’s lactate. Heparinisation was done (3 mg/kg) with achievement of activated clotting time of more than 450 sec. Cardiopulmonary bypass was instituted with aorto - two stage right atrial cannula using roller pump and membrane oxygenator. All patients were cooled to 32 degree Celsius. Hematocrit concentration was kept between 22-26%. Heparin was fully neutralized with protamine at 1:1 ratio. No extra protamine was given after transfer of the patient to the ICU.

Outcome measures

The cases and controls were matched according to age, sex, preoperative hemoglobin. Both groups were compared in relation to bilirubin (total and direct), alanine transferase (ALT), aspartate transferase (AST) and alkaline phosphatase (ALP) in the first 24 hours.

Statistical analysis

All statistical evaluation was done using Microsoft® SPSS software, version 1 6 (SPSS, Inc., Chicago, IL). Differences within and between groups were analyzed using the two-tailed Independent sample Student’s t-test or Fischer’s exact test as appropriate, when continuous and dichotomized variables were compared. A probability of < 0.05 was taken as the criterion of statistical significance.

Results

About sixty two percent of patients were male. The control group was matched with the ANH group regarding sex, age, cardiac function and status, and preoperative hemoglobin. Postoperatively both groups were matched in terms of total heparin and protamine dose, number of conduits, duration of surgery, CPB and aortic cross clamp times. Pre and postoperative values of bilirubin (total and direct), ALT, AST and ALP in the first 24 hours are summarized in Table 1. Low-volume phlebotomy reduced the homologous blood requirements (details are discussed in a coming report). There was significant difference in bilirubin (total and direct) change between ANH and control groups, respectively (both p < 0.00001). The changes in ALT, AST and ALP, however, were not statistically significant compared with baseline values as well as between the two study groups (Table 1). There was also significant difference between preoperative and postoperative bilirubin and ALT levels in each group (all p < 0.00001).
DISCUSSION

It has long been recognized that early jaundice and transient liver damage could occur after extracorporeal circulation surgery. According to earlier studies, overall incidence of postoperative hyperbilirubinemia ranges from about 8.6% to even as high as 40% (1-4).

With improvements in anesthesia, cardiopulmonary bypass, surgical techniques, and postoperative care, the incidence and mortality of postoperative hyperbilirubinemia as a result of liver dysfunction has been significantly reduced but the associated morbidity remains high (4, 5). The immediate occurrence of postoperative hyperbilirubinemia and rapid decline thereafter may reflect the transient damaging effects on the blood and hepatic function following CPB; whereas, steady progressive increase of bilirubin level indicates liver injury and hepatic dysfunction. CPB can lead to a severe and complicated change of pathophysiology of the liver. Operation stress, reperfusion injury, endotoxemia, and inflammatory reaction may lead to the liver injury (12, 13), however, the complex functional and metabolic effects of CPB on hepatocytes require further investigation. Many factors may contribute to the development of jaundice after open heart surgery. The most important contributing factors are preoperative severity of right heart failure (raised right atrial pressure at heart catheterisation) and hyperbilirubinemia, both reflecting the degree of liver congestion, numbers of valves replaced, and hypotension or hypoxemia (1, 8).

Another important factor in the development of hyperbilirubinemia is the number of blood transfusions (1, 8). It is proposed that the use of fresh autologous blood, administered during the operation with citrate anticoagulation, is effective in reducing the need for total and homologous blood (1, 8). On the basis of these assumptions, we tested the hypothesis that acute normovolemic hemodilution combined with retransfusion would be associated with lower rate of postoperative early jaundice and transient liver damage compared with use of homologous blood components. We are not aware of any previous study of this kind. In our patients, there was significant difference in bilirubin (total and direct) between the groups, however there were no difference in ALT, AST and ALP. Low-volume phlebotomy reduced the homologous blood requirements (details are discussed in a coming report), and control group had received significantly more blood transfusions, which would certainly cause an increased bilirubin load to the liver.

There have been conflicting reports regarding the nature of hyperbilirubinemia after open heart surgery. Collins and colleagues (4) and Chu and colleagues (14) attributed it mainly to failure of the canalicular excretion of bilirubin because of an increase in conjugated bilirubin. Klepetko and Micholic (15) proposed that postoperative hyperbilirubinemia after cardiac surgery was mainly from unconjugated bilirubin of hemolytic origin. However, the late appearance of high bilirubin levels with a lower proportion of unconjugated bilirubin reflects a different mechanism at this stage, which may be due to the use of pharmacological and mechanical support, hepatic dysfunction secondary to decreased perioperative hepatic flow, or increased bilirubin load as a result of cardiac failure (16). In the current study, postoperative liver enzymes were unchanged, and postoperative bilirubin levels were higher in both groups, with higher levels in the control group than in the ANH group who have received more homologous blood transfusion.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Billirubin and liver enzymes in the first 24 hours after coronary artery bypass grafting (CABG) surgery</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>ANH Group (n = 20)</td>
</tr>
<tr>
<td></td>
<td>preoperative</td>
</tr>
<tr>
<td>Total billirubin, mg/dl</td>
<td>1.01 ± 0.42</td>
</tr>
<tr>
<td>Direct billirubin, mg/dl</td>
<td>0.39 ± 0.14</td>
</tr>
<tr>
<td>Alanine transferase, mg/dl</td>
<td>25.36 ± 3.73</td>
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<tr>
<td>Aspartate transferase, mg/dl</td>
<td>34.93 ± 4.41</td>
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<tr>
<td>Alkaline phosphatase, mg/dl</td>
<td>209.57 ± 25.33</td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>14.1 ± 0.51</td>
</tr>
</tbody>
</table>

Data are mean ± standard deviation.
ANH : acute normovolemic hemodilution.

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Hemolysis of transfused blood is a major factor in postoperative jaundice (17, 18). It is particularly important in open heart surgery because both the heart lung machine and the prosthesis shorten the survival of transfused blood (19). Though we have not checked the indices of hemolysis, such as serum hepatoglobin and plasma hemoglobin concentrations and red cell survival time, our patients receiving autologous blood (ANH group) had lower bilirubin levels postoperatively compared to those who received homologous blood; there were no changes in ALT, AST and ALP. Larger studies with more patients are needed to confirm the results.

In conclusion, patients receiving autologous blood (ANH group) had significantly more transfused blood. This would certainly cause an increased bilirubin load.

Acknowledgements

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