A randomized study of coronary artery bypass surgery performed with the Resting Heart™ System utilizing a low vs a standard dosage of heparin

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Abstract

OBJECTIVES: Allogeneic blood transfusion and reoperation for postoperative bleeding after the coronary artery bypass grafting have a negative impact on the patient outcome. This study aimed at evaluating the effects of reduced doses of heparin and protamine on the patient outcome, using a heparin-coated mini-cardiopulmonary bypass (CPB) system.

METHODS: Sixty patients undergoing elective first-time CPB were prospectively randomized either to have a reduced systemic heparinization [activated clotting time (ACT) = 250 s] or to a control group perfused with a full heparin dose (ACT = 420 s). Blood transfusions, ventilation time, early postoperative bleeding, ICU stay, reoperations for bleeding, postoperative cognitive status and the level of mobilization were registered.

RESULTS: Twenty-nine patients were randomized to the control group, 27 patients to the low-dose group and 4 patients were excluded because of protocol violations. Four patients in the control group received a total of 10 units of packed red blood cells, and in the low-dose group, no transfusions were given, \( P = 0.046 \). No patient was reoperated because of bleeding. The ICU stay was significantly shorter in the low-dose group (8.4 vs 13.7 h, \( P = 0.020 \)), less dependent on oxygen on the first postoperative day (78 vs 97%, \( P = 0.034 \)), better mobilized (89 vs 59%, \( P = 0.006 \)) and had less pain (visual analogue scale 2.0 vs 3.5, \( P = 0.019 \)) compared with the control group.

CONCLUSIONS: The use of a mini-CPB system combined with a low dose of heparin reduced the need for blood transfusions and may facilitate the faster mobilization of the patients.

Keywords: Mini cardiopulmonary bypass • Cardiac surgery • Heparin

INTRODUCTION

Cardiac surgery involving coronary artery bypass grafting (CABG) induces inflammatory and haemostatic activation with the potential consequence of increasing haemorrhage and the need for blood transfusions.

Allogeneic blood transfusions and reoperations for postoperative bleeding after CABG have a negative impact on the patient outcome [1] and are associated with an increased risk of morbidity and mortality, extended length of hospital stay and increased cost [1, 2]. The problems have increased with the more aggressive anticoagulant treatment, including not only aspirin (ASA) and low-molecular-weight heparins (LMWHs), but also potent anti-platelet agents, currently applied in unstable angina, e.g. clopidogrel [3]. At present, 60–70% of CABG patients receive allogeneic blood transfusions, and 4–6% undergo reoperations for postoperative bleeding [4]. Consequently, interventions aimed at reducing bleeding and the need for blood transfusions are highly desirable.

Minimized extracorporeal circulation is a promising alternative to conventional cardiopulmonary bypass (cCPB) techniques. The Medtronic Performer™ CPB and Resting Heart® System (RHS) is a compact perfusion system composed of parts (pump, oxygenator, tubing and closed system design) that as isolated units have been shown to have theoretical advantages in terms of inflammatory reactions and red blood cell injury [5]. The entire circuit, including arterial and venous cannula, is heparin coated, i.e. heparin molecules covalently bound to the system surfaces. Surface-bound heparin has been shown to reduce the activation of the complement system and white blood cells [6–8]. Furthermore, heparin-coated surfaces have been proved to reduce thrombosis, allowing reduced systemic heparinization during CPB, which decreases postoperative bleeding, and the need for protamine [9]. Because circulating heparin/protamine complexes act as complement
activators and add to the general inflammatory reaction caused by CPB, a reduced heparin/protamine use will result in reduced inflammation and organ damage [10]. Additionally, the use of procoagulants (platelets, tranexamic acid, desmopressin and recombinant factor VIIa), some of which are expensive, could be reduced [11]. A decrease in postoperative bleeding and blood transfusion makes possible early extubation and earlier mobilization of the patient.

The purpose of this study was to evaluate the effects of reduced doses of heparin and protamine on the patient outcome during CPB with the RHS.

PATIENTS AND METHODS

Informed consent was obtained from the subjects prior to any study-specific activity. The study protocol was approved by the Ethics Committee for Clinical Research at Lund University, Sweden. The reporting of this study follows the CONSORT checklist [12, 13].

Patient selection and operation

After written informed consent, patients scheduled for CABG and in spontaneous sinus rhythm were included in the study. In all the patients, the left interior mammary artery was dissected and used as conduit to the left anterior descending (LAD) coronary artery. All the patients received clopidogrel treatment or were eligible for such treatment. None of the patients were operated on an emergency basis and none had preoperative pacemaker, advanced chronic obstructive pulmonary disease (COPD) or cerebrovascular disease. Prior to surgery, the patients were randomized to two groups, one to receive a low-dose heparin regimen and one to a conventional heparin dose regimen.

Preoperative protocol

Patients were admitted on the day before surgery. In all the patients studied, clopidogrel treatment was discontinued at least 5 days before surgery. On admission, haemoglobin (Hb), activated partial thromboplastin time (APTT), prothrombin complex (international normalized ratio, INR), thrombocytes, C-reactive protein (CRP), creatinine and antithrombin-III were analysed. Furthermore, the patients underwent the mini-mental state examination (MMSE) and quality of life assessment by responding to the Short-Form, SF-36 Health Survey Questionnaire [14].

Perioperative protocol

Randomization was performed by an anaesthetist according to a randomization list. The surgical team was not blinded to the study group allocation. All the drugs administered relevant to coagulation and all transfused blood products were recorded. Blood samples for Hb and haematocrit (Hct) analysis were drawn immediately before CPB, 3 min after CPB and thereafter every 20 min to determine the degree of haemodilution. Activated clotting times (ACT) and all heparin and protamine doses were determined with HMS PLUS™ Hemostasis Management System (previously known as Hepcon™; Medtronic, Inc., Minneapolis, MN, USA). A zero residual heparin concentration after protamine was verified. In the conventional heparin dose group, an ACT of >420 s before initiation and during CPB was the aim. In the low heparin dose group, the corresponding ACT was >250 s.

Cardiopulmonary bypass protocol

The Medtronic Performer™ CPB together with the Medtronic RHS (Medtronic, Inc.) is a low-prime, semi-closed loop minimally invasive CPB system, offering minimal air-blood interface with the separation of the pericardial shed blood suction, a centrifugal pump and a reduction in systemic heparinization. The priming volume of the circuit is 800 ml and the membrane surface area for gas exchange is 2.5 m². The primary blood contact surfaces are coated with the Carmeda® BioActive Surface (CBAS®) technique (BioActive Surface, Carmeda, Stockholm, Sweden) throughout to provide thromboresistance and biocompatibility by mimicking critical characteristics of the vascular endothelium. The absence of cardiotomy reservoirs limits the artificial surface-blood contact secondary to aspiration of blood. Accordingly, a separate erythrocyte scavenging device is necessary when using the RHS. One of the key features of this system is the retrograde arterial.

The priming (RAP) procedure that allows for a reduced haemodilution. RAP was performed in all the patients with the intention to avoid a positive CPB balance in excess of 1200. After weaning, final transfusion from the perfusion circuit was performed, including after wash with saline. All the blood shed during operation was collected together with the remaining blood from the CPB circuit, washed in a cell saver and retransfused to the patients. The amounts of retransfused blood and Hb were recorded. The target temperature during perfusion was 37.0°C. Surface heating (Bair Hugger® Therapy, Arizant UK, Ltd, Wakefield, UK) was applied to all the patients before weaning. All infusions were warmed from the start of rewarming on CPB and onwards.

Anaesthesia protocol

The total fluid balance during the procedure—including CPB, all infusions/transfusions and all bleeding/fluid loss—was calculated. One gram of tranexamic acid (Cyklokapron®, Pfizer, Inc.) was given on two occasions during surgery, the first dose just before surgery and the next immediately after the completion of surgery. Anaesthesia was planned to allow for weaning from mechanical ventilation and extubation within 2 h of arrival in the Intensive Care Unit (ICU). Typically, a total dose of between 10 and 15 μg/kg body weight of fentanyl was used for the surgical procedure, and sedation with propofol was established when leaving the operating room.

Surgical protocol

Bone wax or other substitutes in the sternum were, for conformity, not used. The left pleural space was always opened in conjunction with the dissection of the mammary artery. Closure of the wound was performed when surgically correctable bleeding had been handled, zero residual heparin concentration was
Postoperative protocol

Timing of extubation of the patients, administration of blood transfusions and fluid administration were performed according to a structured protocol, see Appendix. The need for intensive care was assessed regularly during the stay in the ICU according to a special protocol, and the time point registered when the patients were considered not in need of intensive care anymore was registered. Due to administrative reasons, however, it was not always possible to physically transfer the patient to the ward. Clopidogrel was resumed after the operation in addition to aspirin and LMWH. LMWH was discontinued when the patient was mobilized and Clopidogrel after 1 month. Pain was evaluated daily on a 100 mm visual analogue scale (VAS). Cognitive status (MMSE) and degree of mobilization (activities evaluated as coughing, emptying of a drinking glass, moving from bed, moving to chair and walking indoors classified as Unable, Limited a lot, Limited a little or Not Limited at all) were assessed according to a special protocol. On the fourth postoperative day, MMSE was performed, and Hb, APTT, PK (INR), thrombocytes, CRP, creatinine and U-Hct were analysed.

Statistical analysis

Continuous variables are presented as median, with the 25th and 75th percentiles. Categorical variables are presented as percentage and frequencies. The Wilcoxon, Pearson’s or Fisher’s exact test was used for statistical analysis. Data was analysed using the Hmisc and Design packages of the R software (R Foundation for Statistical Computing, Vienna, Austria), version 2.9.1. The level of significance was set at $P < 0.05$.

RESULTS

Sixty patients were randomized and 56 patients could be evaluated, 29 in the control group and 27 in the low-dose group. Four patients were considered protocol violators. One patient was perioperatively found to require surgery for aortic aneurysm and valve surgery; one had study drug hypersensitivity; one was perioperatively found to require surgery for aortic aneurysm. There were no statistically significant baseline differences between the two groups (Table 1) and no difference in preoperative blood samples. The two groups were comparable with regard to preoperative medication, with the exception of clopidogrel (7% in the control group vs 37% in the low-dose group, $P = 0.006$) and lipid lowering drugs (97% in the control group vs 78% in the low-dose group, $P = 0.034$). Almost all the patients in both groups were on aspirin treatment (97% in the control group vs 93% in the low-dose group).

The patients in the control group received a mean heparin dose of 29 465 (±6483) IU, while the low-dose group received a mean heparin dose of 12 740 (±3490) IU, $P < 0.001$. Similarly, the control group received a mean protamine dose of 188 (±65) mg, while the low-dose group received a mean dose of 98 (±55) mg, $P < 0.001$. Apart from this intended difference, there were no differences in operative procedures between the two groups.

### Table 1: Patient characteristics

|                      | N Control (N = 29) | Low dose (N = 27) | P-value
|----------------------|-------------------|------------------|---------
| Age (years)          | 56 67.0 (61; 73)  | 64.0 (58; 71)    | 0.21*
| Female gender        | 56 10% (3)        | 22% (6)          | 0.29b
| Height (cm)          | 48 175 (171; 180)| 175 (170; 184)   | 0.56*
| Weight (kg)          | 48 84 (77; 93)    | 85 (73; 91)      | 0.84*
| Weight <66 kg        | 56 0% (0)         | 11% (3)          | 0.11b
| Diabetes             | 56 21% (6)        | 19% (5)          | 1b
| Chronic airway disease | 56 3% (1)     | 0% (0)           | 1b
| Prior cerebrovascular disease | 56 0% (0) | 0% (0)     | 1
| Neurological dysfunction | 56 0% (0) | 0% (0)     | 1
| Extracardiac arteriopathy | 56 7% (2) | 7% (2)     | 1b
| Recent myocardial infarction | 56 3% (1) | 4% (1)     | 1b
| Unstable angina      | 56 0% (0)         | 0% (0)          | 1
| LVEF 30–50%           | 56 0% (0)         | 11% (3)         | 0.11b
| Hb (g/l)             | 50 137 (132; 145)| 140 (134; 146)  | 0.53*
| Creatinine (µmol/l)  | 53 79 (68; 86)    | 76 (71; 88)     | 0.85*
| EuroSCORE (points)   | 56 3.0 (1.0; 4.0)| 3.0 (1.0; 3.0)  | 0.64*
| X-clamp duration (min)| 56 42 (36; 51)| 40 (37; 52)     | 0.92*
| ECC duration (min)   | 56 67 (59; 78)    | 66 (58;80)      | 0.85*
| Number of coronary bypasses | 56 3 (3,4) | 3.5 (3, 4) | 0.76*

Median (lower quartile; upper quartile); numbers after percent are frequencies. LVEF: left ventricular ejection fraction; Hb: haemoglobin; N: the number of non-missing values.

*Wilcoxon test.

### Table 2: Postoperative drain loose/bleeding

|                      | N Control (N = 29) | Low dose (N = 27) | P-value*
|----------------------|-------------------|------------------|---------
| Bleeding             |                   |                  |         
| Volume 12 h (ml)     | 56 400 (300; 500)| 340 (218; 528)   | 0.23    
| Volume in res (ml)   | 56 170 (110; 300)| 140 (102; 240)   | 0.35    
| Duration (min)       | 54 210 (170; 280)| 184 (145; 263)   | 0.24    
| Hb in res (g/l)      | 53 70 (56; 87)    | 63 (47; 79)      | 0.15    
| Hb loss (g)          | 52 10.8 (6.6; 22.7)| 7.0 (4.7; 14.9) | 0.13    
| Retransfusion Volume (ml) | 55 345 (243; 380)| 300 (222; 380) | 0.32
| Hb (g/l)             | 55 185 (174; 201)| 188 (175; 202)   | 0.74    

Median (lower quartile; upper quartile); N: number of non-missing values; Hb: haemoglobin.

*Wilcoxon test.
The total number of transfused packed red cells (PRCs) was statistically significantly different between the two treatment groups \((P = 0.046)\). Four patients in the control group received in total 10 PRCs vs none in the low-dose group. Specifically, no patients in either group received transfusions in the operating room, whereas one patient in the control group received PRCs and two patients received platelets in the ICU. Two patients in the low-dose group received plasma transfusions. On the ward, three patients in the control group received PRCs (2, 3 and 4 units, respectively), whereas no transfusions were given in the low-dose group.

As listed in Table 2, patients in the low-dose group had a median bleeding volume of 340 ml compared with 400 ml in the control group. The duration of bleeding was 184 min in the low-dose group, whereas it was 210 min in the control group (median values). Median Hb loss was 7.0 g in the low-dose group, whereas it was 210 min in the control group. The duration of bleeding was 184 min in the low-dose group, whereas it was 210 min in the control group. However, no statistically significant difference was observed between the two groups for any of these variables.

Fewer patients in the low-dose group received oxygen postoperatively, and on the first postoperative day the difference reached statistical significance (97% in the control group compared with 78% in the low-dose group, \(P = 0.034\), Table 3).

Table 3: Number of oxygen-dependent patients

|               | N  | Control \((N = 29)\) | Low dose \((N = 27)\) | P-value* |
|---------------|----|---------------------|----------------------|----------|
| Preoperatively| 56 | 0                    | 0                    |          |
| 3 h postoperatively | 97 (28) | 100 (27) | 0.33 |          |
| Day 1         | 97 (28) | 78 (21) | 0.034 |          |
| Day 2         | 61 (17) | 59 (16) | 0.91  |          |
| Day 3         | 31 (8) | 38 (9)  | 0.62  |          |

*Pearson’s test.

There was less pain experienced by patients in the low-dose group compared with the control group (Fig. 1), reaching statistical significance on first postoperative day \((P = 0.019, \text{Table 4})\). On the fourth postoperative day, the median pain score was the same in the two groups.

Grade of activity was preoperatively comparable, i.e. none of the patients were limited in any of the activities evaluated (i.e. coughing, emptying of a drinking glass, moving from bed, moving to chair and walking indoors). Postoperatively, no statistically significant difference was observed 3 h after surgery, whereas on the first postoperative day, patients in the low-dose group had a significantly better ability to move to chair compared with the control group \((41\% \text{ in the control group vs } 11\% \text{ in the low-dose group, } P = 0.006)\). No other difference in mobilization was observed at any time point. The MMSE performed on the fourth postoperative day was likewise comparable between the treatment groups.

Postoperative complications and postoperative blood samples were not significantly different between the two treatment groups. A need for a shorter ICU stay was found in the low-dose group, i.e. 8.4 h in the low-dose group compared with 13.7 h in the control group \((P = 0.02)\).

**DISCUSSION**

The use of minimized CPB systems in CABG surgery has been demonstrated to contribute clinical advantages compared with cCPB [15]. Heparinized circuits hold the potential to reduce the need for systemic heparin administration during CABG, which might further minimize the adverse effects associated with the surgical procedure. This study was undertaken to evaluate the effects of reduced doses of heparin and protamine on the patient outcome during CPB with the RHS.

In the study, a significant reduction in blood transfusions was seen in the low-dose group receiving approximately half the amount of heparin and protamine as the conventional group. This finding is consistent with what has been reported previously [16, 17]. In addition, the minimized CPB system has been shown to reduce haemodilution and donor blood usage in CABG patients when compared with cCPB circuits [18].

Few postoperative complications were observed in the present study in either of the treatment groups. Recently, Prasser et al. [19] demonstrated an improvement in liver function by the use of minimized CPB system compared with a conventional system.
In support of this, liver function parameters—as well as laboratory data—were within the normal range in the present investigation. Less organ damage and inflammation have furthermore been suggested as beneficial effects of the miniaturized system [19, 20]. Time to extubation in the present study was shorter compared with department average for cCPB, but not further improved by the use of low doses of heparin. Kofidis et al. [20] presented an improved postoperative FEV1 and a trend for a shorter time on ventilator. The faster mobilization observed in this group (mobile to chair) combined with the need for shorter ICU stay could, however, suggest that the reduced amount of heparin promotes early extubation and faster postoperative recovery.

Neurocognitive dysfunction is a well-recognized complication following CPB. Cerebral hypoperfusion and gaseous microembolization have been suggested to be among the causative factors. The use of a mini-bypass system has recently been suggested to improve neurocognitive performance compared with conventional bypass as evaluated at discharge from hospital as well as 3 months postoperatively [21]. In the present study, no difference in cognitive performance was observed between the two treatment groups; thus, a low dose of heparin did not seem to attenuate neurocognitive outcome. Anastasiadis et al. considered 3 months after the most optimal time for neurocognitive evaluation to be discharged when pain and limitation of physical activity had resolved. In this study, MMSE was performed 4 days after surgery, which might influence the result.

Interestingly, the patients in the low-dose group reported less pain. This is a unique finding, which requires further investigation.

Concerns have been raised regarding the safety with a low-dose regimen. However, in this study, no adverse effects were recorded in either group. The same conclusion was reached in a recent study comprising nearly 6000 patients undergoing CABG, where the use of heparin-coated equipment and reduced systemic heparinization has been suggested to be among the causative factors. In support of this, liver function parameters—such as aspartate aminotransferase, alanine aminotransferase, and bilirubin—were within the normal range in the present investigation. Less organ damage and inflammation have furthermore been suggested as beneficial effects of the mini-extracorporeal circulation system (Medtronic resting heart system). Interact CardioVasc Thorac Surg 2006;5:680–2.

The RHS closed circuit has previously been demonstrated to suppress thrombin formation [23]. However, a reduction in systemic heparinization has been observed to be associated with increased thrombin formation [24, 25], although in the latter study, no evidence of hyper fibrinolysis or thromboembolic complications was observed. In our setting, no clinical signs of increased thromboembolism were seen.

The strengths of this study are the randomized design and the uniformity of treatment groups. Only three surgeons performed all the operations, and the patients in the two treatment arms were evenly distributed among the surgeons in order to exclude any bias attributed to the individual surgeon technique. The small number of patients in each group and the single-institution design limit the results of this study; however, despite the less number of patients, clinical advantages of the low-dose regimen were demonstrated.

In conclusion, the use of minimized CPB circuits combined with a low-dose regimen for heparin was shown to reduce the need for allogeneic blood transfusions compared with conventional heparin dosage. In addition, patients in the low-dose group were less oxygen-dependent and experienced less pain, which might in turn lead to faster mobilization as suggested by the improved mobility to chair. Further studies involving more patients are needed to confirm these preliminary results. However, the minimal extracorporeal circulation seems to be a promising technique for future CABG procedures.

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Patients should be on clopidogrel or suitable to such treatment. LIMA is going to be dissected and planned to use as conduit to the LAD. Written consent to participate in spontaneous sinus rhythm is scheduled for CABG.

APPENDIX I: DEFINITIONS AND PROTOCOLS

Inclusion criteria

- Scheduled for CABG
- In spontaneous sinus rhythm
- Written consent to participate
- LIMA is going to be dissected and planned to use as conduit to the LAD
- Patients should be on clopidogrel or suitable to such treatment

Exclusion criteria

- Emergency operation
- Redo operation

Patients in dialysis

- Patients with preoperative pacemaker
- Patients on warfarin medication
- Patient considered unsuited to fit the transfusion criteria due to
  - advanced COPD
  - cerebrovascular disease
  - Transfusion need: A point reached in a normovolemic patient where Hb <75 g/l for patients <70 years, or Hb <85 g/l for patients >70 years. N.B. Transfusion with PRC should not be performed in patients with Hb >95.
  - Total amount of lost Hb during early postoperative bleeding. The volume of shed mediastinal bleeding multiplied with the Hb concentration when the recorded volume per hour is <50 ml for two consecutive hours.
  - Time point when early bleeding end. When total amount of lost Hb during early postoperative is measured.
  - Total postoperative shed volume loss. The volume of shed mediastinal bleeding 12 h after active drainage begins.

Ventilation time. Time between arrival in the ICU and extubation.

- Exxtubation protocol. When the following criteria are fulfilled this should lead to extubation of the patient:
  - The ventilator set to FiO2 = 0.4 and PEEP 2 cm H2O
  - Fully awake, RLS 1-2
  - Regained muscular tone (being able to move extremities and lift head)
  - SpO2 >95%
  - ScvO2 ≥55%
  - Body temperature ≥35.8°C
  - Fulfilling bleeding criteria as defined below.

Bleeding regulations allowing for extubation

- <70 ml during the first hour after arrival in ICU and <200 in total volume (including shed bleeding from the OR)
- <200 ml in the first 2 h with bleeding during the second hour < first hour
- <400 ml after 3 h if the bleeding during the third hour <100 ml
- <70 ml 2 h in a row

Patients bleeding in excess of the above-mentioned, but less than what is considered an indication for a reoperation should be treated according to the present ICU protocol.

Reoperation. The following circumstances in a bleeding patient should suggest that he/she be reoperated: ACT in the ICU normalized (ACT <140 s, measured with the ACT analysis in ICU).

- Postoperative bleeding occurs after arrival in the ICU at a rate of >250 ml for two hours in a row or 500 ml in one hour.
- Shed volume exceeds 1000 ml in less than 5 h.
- If the patient shows sign of circulatory instability and this is clinically assessed by responsible surgeon and anaesthetists, as reason to operate, none of the criteria above have to be fulfilled.

SpO2. Measured with pulsoximetry

EtCO2. End tidal CO2 measured with portable capnometer