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Heparin-coated cardiopulmonary bypass circuits and 25% reduction of heparin dose in coronary artery surgery—a clinical study

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ABSTRACT

Cardiopulmonary bypass with systemic heparinization causes trauma to blood cells and coagulation defects. Artificial surfaces could be coated by end-linkage binding of heparin (Carmeda Bioactive Surface, CBAS™). Use of such surfaces during cardiopulmonary bypass in animals resulted in less postoperative blood loss and better preservation of blood cells. In this study heparin-coated circuits were employed during coronary artery grafting in 7 patients (Group HC). Concomitantly, the heparin dose was reduced by 25% and an activated clotting time (ACT) of 300 sec was accepted. Additional 7 patients were operated with standard circuits (Group C), requiring ACT above 400 sec with normal doses of heparin. There were no thromboembolic complications in Group HC. The postoperative bleeding was generally low and without significant intergroup differences. Coagulation parameters displayed significantly lower ACT and anti-Factor Xa during bypass in Group HC. A tendency towards less blood cell trauma was observed with heparin-coated circuits. The protamine dose could be reduced by 50%, which significantly reduced the protamine/heparin quotient.

This study indicates that routine cardiopulmonary bypass could be performed safely with heparin-coated circuits and reduced intravenous doses of heparin and protamine. It is suggested that the use of heparin-coated circuits may lead to less blood cell trauma.

INTRODUCTION

Cardiopulmonary bypass (CPB) has various effects on biologic cascade systems including hemostatic disturbances (3,14). Damage of leukocytes and red blood cells and activation of the complement system are well documented (5,12,15) and may lead to organ

dysfunction (1,9). The negative effects of CPB are partly related to high doses of heparin and protamine as well as to lack of biocompatibility of the CPB circuit itself.

Much effort has been spent to find techniques for coating artificial surfaces with biologically active heparin. CPB circuits with such a surface would permit lower doses of heparin and protamine and might also be more biocompatible. The Carmeda Bioactive Surface (CBAS™, Carmeda, Sweden) is coated by end-linkage binding of heparin molecules to the artificial surface (11). This method binds heparin stable and without loss of its biological activity. The surface inhibits thrombin activation and is also platelet compatible (2,10,16). It has been demonstrated in animal studies that such heparin-coated CPB circuits (CBAS™) reduce the need for systemic heparinization and protamine, thereby reducing postoperative bleeding (18). Platelets, leukocytes and erythrocytes were also better preserved and there was less activation of the complement system (13,18). In vitro studies with coated surfaces have shown reduced granulocyte activation (19).

In this study we have used heparin coated CPB circuits and concomitantly reduced heparin doses by 25% during coronary artery bypass surgery. Standard systems and normal doses of heparin were used in the controls.

MATERIAL AND METHODS

Patients. Fourteen patients, all in functional class III NYHA, with 2 or 3 vessel disease, scheduled for elective coronary artery bypass grafting were included in the study. All patients had normal coagulation parameters. Patients with diabetes, neurologic disease, renal insufficiency or on anticoagulation therapy were not considered. All patients were operated on with the use of left internal mammary artery and vein grafts.

Seven patients (Group HC) were operated on with the use of heparin-coated CPB circuits. These patients were given heparin in a reduced dose (225 IU/kg) and CPB was started when the activated clotting time (ACT) was above 300 sec. Additional heparin was given if the ACT was below 300 sec. The control group also included 7 patients (Group C), who were operated on with non-coated devices. They received a normal dose of heparin (300 IU/kg) and CPB was started when the ACT was above 400 sec. Additional heparin was given if the ACT was below 400 sec.

The study protocol conformed to the rules of the Helsinki declaration and was approved by the Ethical Committee of the Medical Faculty. Informed consent was obtained from patients participating in the study.

Anesthesia. All patients were premedicated with morphine 0.125 mg/kg and scopolamine 0.005 mg/kg one hour before they were taken to the operating theatre. Anesthesia was induced with fentanyl 5 μg/kg and thiopental 2-4 mg/kg. Neuromuscular relaxation was obtained with pancuronium 0.1 mg/kg. The patients were ventilated with 50% nitrous oxide in oxygen until shortly before CPB, when nitrous oxide was discontinued. Anesthesia was maintained with additional doses of fentanyl and isoflurane. Nitroglycerin and additional pancuronium were given when necessary.

Cardiopulmonary bypass. A Stöckert heart-lung machine (Germany) with a roller pump was used. The CPB circuit consisted of a membrane oxygenator (Maxima, Medtronic, USA) connected to a collapsible soft venous reservoir (Medtronic, USA) and an arterial filter (40 μm Intercept, Medtronic, USA). The CPB circuit was primed with 2000 ml of Ringer's acetate. There was no venting of the left ventricle or cardiotomy suction. A cell saver was used for suction (Haemonetics, USA). After bypass the remaining blood in the circuit was processed in the cell saver and retransfused.

The pump flow was non-pulsatile and initially 2.2 l/m^2. After body cooling to 30°C in the nasopharynx, pump flow was reduced by 25 %. St Thomas' cardioplegic solution (Plegisol, Abbot, England) was employed. The blood and gas flow through CPB circuit were adjusted at short time intervals according to arterial blood gas results.

Biochemical analyses. ACT was determined by the Hattersly technique (6) including a Hemochron Model 400 analyzer and coagulation test tubes (Celite activated, CA 510). Anti-factor Xa (aFXa), refers to the established method of determination of heparin concentration, expressed in IU (international units) and was assayed amidolytically (according to the manual of Coatest Heparin, Kabi Diagnostica, Sweden). Samples with levels > 0.7 IU/ml were diluted with human normal plasma to a ratio of 1:10 and further analyzed. Platelet count and hematocrit were quantified with an automatic cell counter. Platelet adhesion was determined by glass retention test (7) using Adeplat S columns and an Adeplat pump (Semmelweiss, Italy). Platelet adhesion was expressed as

adhesive platelet count in percent of total platelet count, reference value >72 %. Hemolysis was arbitrarily determined by photometric absorbance at 405 nm (A_{405}) of 75 μl plasma/2.7 ml phosphate-buffered saline (pH 7.4). The platelet count was individually corrected for hemodilution, based on hematocrit, and expressed in percent of the preoperative value. Samples for coagulation parameters were collected after anesthesia, after heparinization, at the start of CPB, after 45 minutes of CPB, at the end of CPB, 15, 60, 120, 180, 240 minutes after protamine reversal and 20 hours postoperatively. Samples for CK-MB were taken preoperatively, 3 hours and 24 hours postoperatively. They were analyzed with respect to activity of CK-isoenzymes following ion exchange fractioning. Samples for creatinine were taken before operation and every second day postoperatively during a week. Serum creatinine was measured kinetically with a Jaffé method. Arterial blood gases were measured at 37°C (ABL 4; Radiometer, Denmark) and were not corrected for temperature.

Respiratory function. The alveolo-arterial oxygen pressure gradient, $PO_2(A-a)$, was measured on 3 occasions. Preoperatively, the patient breathed in a mask supplied with oxygen (FiO_2=40%) during at least 20 minutes. This procedure was repeated 3 hours after bypass, if the patient was extubated. If not, an FiO_2 of 40 % was delivered by the ventilator. The third measurement was made the following morning, when all patients had been extubated. Blood gases were measured and $PO_2(A-a)$ was calculated according to the alveolar gas equation [$PO_2(A-a) = FiO_2 * (P_{atm} - 6.3) - (PCO_2 * 0.8^{-1}) - PO_2$] and with a respiratory quotient of 0.8.

Statistics. Values are given as means±SEM. Statistical analysis of the data was performed by Student's t-test using a data base (MEDLOG™, Information and Analysis Corporations, Calif. USA). $P<0.05$ (*) was considered significant.

RESULTS

Hemostatic and blood cell variables. Hematocrit decreased to about 27% during CPB because of hemodilution, followed by a normalization after CPB. There were no significant intergroup differences.

Group HC received a reduced dose of heparin while Group C received normal dose (Table 1). There were significantly lower peroperative levels of ACT (Fig 1a) and aFXa (Fig 1b) in Group HC.

TABLE 1. Heparin-protamine dosages, bleeding and transfused blood products. Group HC= heparin-coated, group C= control. Values are means±SEM. (*= $p<0.05$ & NS= non significant)

Group	HC		C
Heparin, IU/kg bolus	222±1	*	303±2
total	227±5	*	345±2
Protamine, mg/kg	1.75±0.09	*	3.23±0.18
Protamine/heparin	0.78±0.05	*	0.94±0.04
Intraop bloodloss, ml	550±90	NS	620±140
Postop bloodloss, ml/kg			
0- 4 h	5.0±1.9	NS	4.3±0.5
4-16 h	4.9±0.4	NS	4.4±0.8
0-16 h	10.0±2.3	NS	8.7±1.3
Transfused bloodproducts			
Red cells, ml	390±160	NS	600±110
Cell saver, ml	490±70	NS	630±150
Machine blood, ml	290±230	NS	260±90
Stored plasma, ml	840±250	NS	380±260
Albumin, ml	290±230	NS	260±90

Consequently, protamine dose needed to achieve heparin reversal could be decreased (Table 1) in group HC, as reflected by ACT and aFXa. The protamine-heparin ratio (Table 1) was reduced to 0.5 in two patients in Group HC.

Platelets decreased during CPB followed by postoperative restoration. However, correction for the hemodilution revealed a relative increase in platelets of approximately 20% in both groups at the end of CPB and a drop of similar magnitude in Group C after 20 hours (Fig 2a).

Platelet adhesion (Fig 2b) was almost abolished at the start of CPB but returned towards normal levels one hour after protaminization, with no intergroup differences.

Hemolysis (Fig 3) was reduced during CPB and increased postoperatively without significant intergroup differences. Intra- and postoperative bleeding displayed insignificant intergroup differences (Table 1).

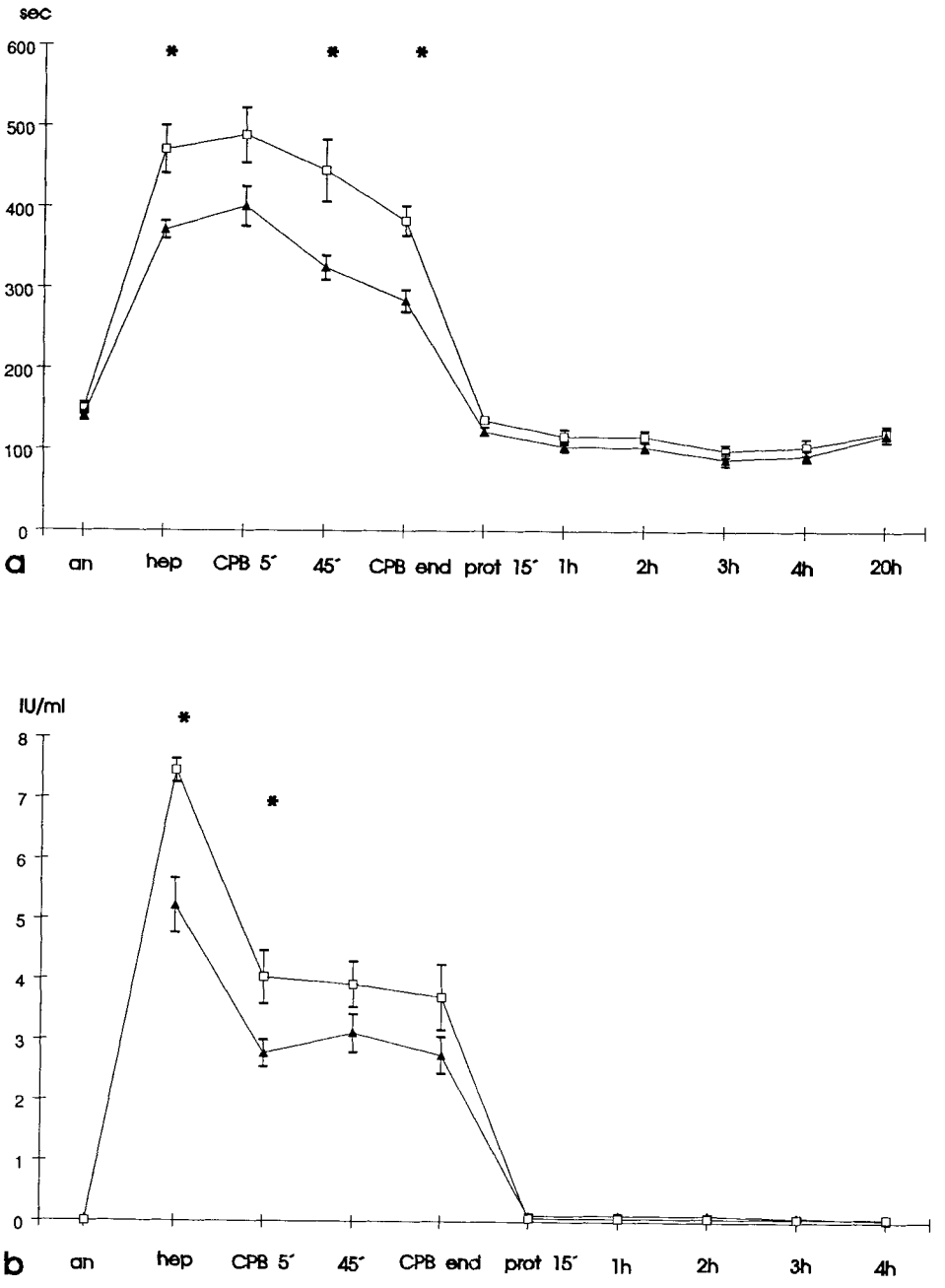

FIGURE 1 a. Active clotting time (ACT) and b. Anti Factor Xa (aFXa) before, during and after CPB.
Groups: -Δ- = heparin-coated, -o- = control.
(* = $p<0.05$).(means±SEM)

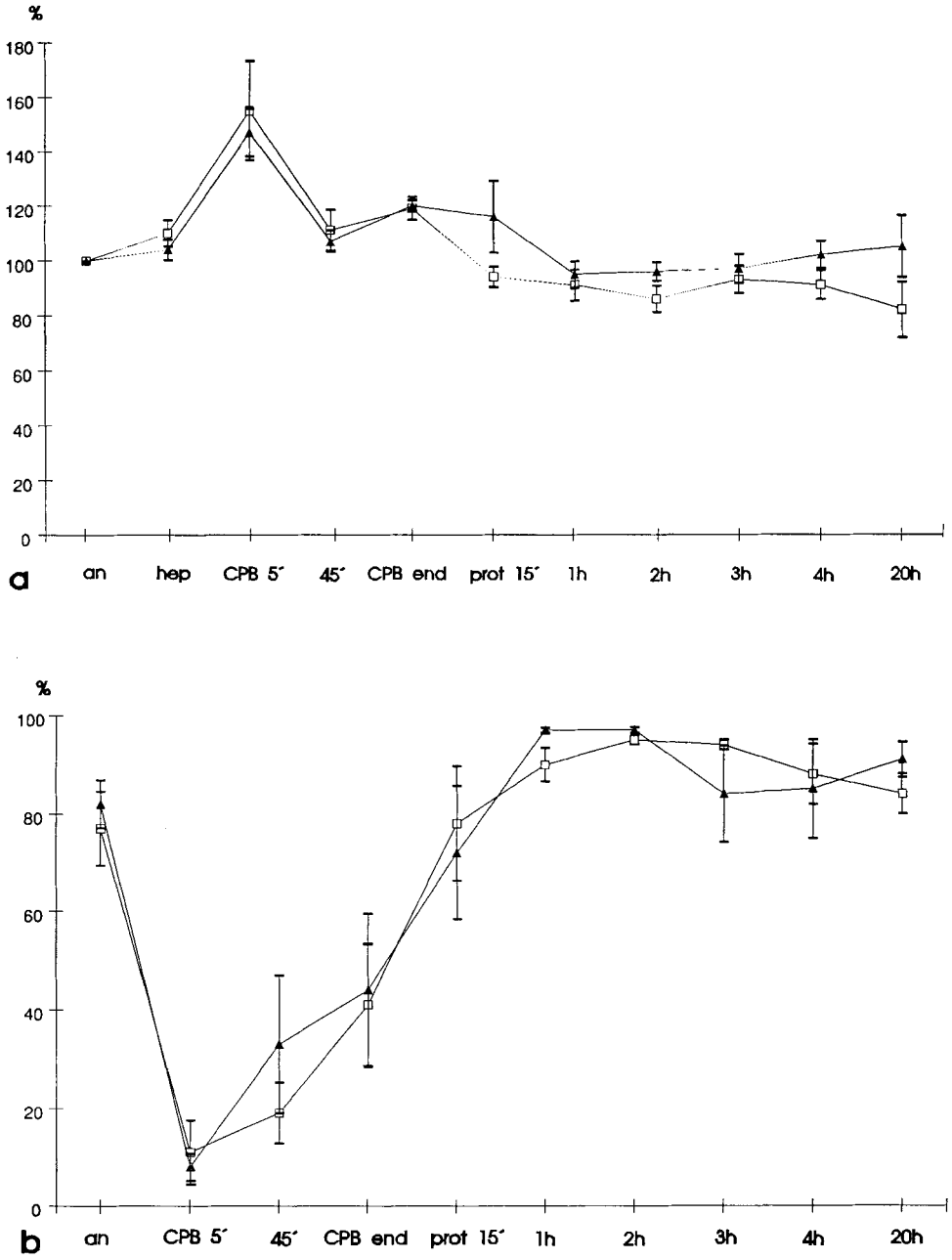

FIGURE 2. a. Platelets (in % of the preoperative value and corrected for hematocrit) b. Platelet adhesion before, during and after CPB. Groups as in Fig 1. (means±SEM)

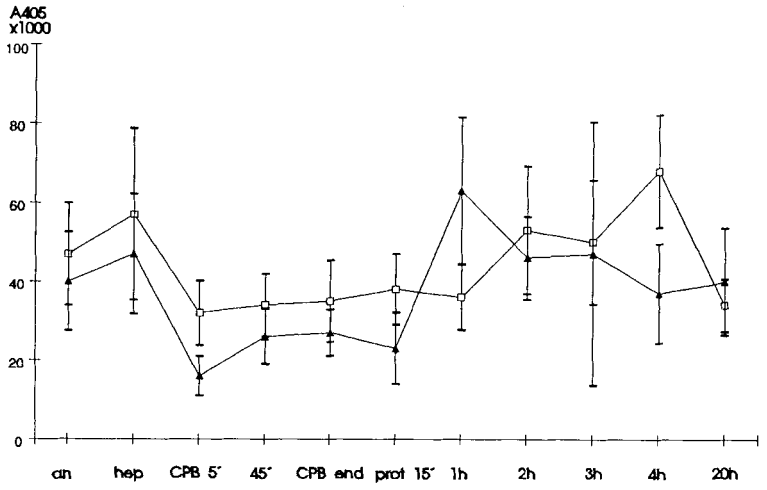

FIGURE 3. Hemolysis before, during and after CPB. Groups as in Fig 1. (means±SEM.)

TABLE 2. Arterial blood gases, alveolo-arterial oxygen pressure gradient PO_2(A-a), CK-MB and creatinine levels as markers of respiratory, myocardial and renal damage. Groups as in table 1. Values are means±SEM. (*= $p<0.05$ & NS= non significant)

Group	HC		C
Blood gases at CPB end			
PO_2, kPa	23.3±3.8	NS	29.4±4.6
PCO_2, kPa	4.4±0.2	NS	4.3±0.2
pH	7.46±0.01	NS	7.46±0.02
Arterial saturation, %	98.9±0.4	NS	99.4±0.2
PO_2(A-a), kPa			
preop	10.5±1.6	NS	9.7±2.7
postop 3 h	16.6±0.8	NS	17.1±1.5
postop 24 h	18.3±1.3	NS	16.4±1.4
CK-MB, μkat/l			
preop	0.16±0.03	NS	0.18±0.02
postop 3 h	0.61±0.17	NS	0.41±0.04
postop 24 h	0.40±0.05	NS	0.52±0.18
Creatinine, μmol/l			
preop	97±6	NS	100±5
max postop	104±4	NS	109±6

Biochemical variables. Blood gases during CPB were within normal limits and without significant differences between the groups (Table 2). There were no significant differences between groups in regards to gas and blood flow in heart-lung machine. The alveolo-arterial oxygen pressure gradient, $pO_2(A-a)$, showed a slight increase after CPB in both groups (Table 2). There were no significant differences in CK-MB postoperatively after CPB (Table 2). Both groups displayed a small increase in creatinine levels after CPB (Table 2).

Clinical variables. There were no signs of clotting in the CPB-line including the oxygenator, arterial filter and venous reservoir. No patients had focal neurological symptoms postoperatively.

There were no significant differences in CPB-time between group HC and C (87±7 min vs 101±7 min). No perioperative infarcts and postoperative mortality were noted. Two patients in Group HC and three patients in Group C needed inotropic support after CPB.

DISCUSSION

Cardiopulmonary bypass is an unphysiologic environment for the organism. The blood is subjected to abnormal conditions regarding contact surfaces, temperature, anticoagulants and anticoagulant reversal agents. Excessive bleeding following CPB is a reality and has multifactorial pathogenesis (8). The damage of blood components may also lead to organ dysfunction, sometimes recognized as "postperfusion syndrome". One possible way to diminish the risk of these complications would be to reduce the thrombogenicity and to improve the biocompatibility of the artificial surfaces by using heparin-coated extracorporeal circuits.

In this study the CBAS™ coated systems were used during routine heart surgery. The most important finding was that coated circuits could be used safely without any identified thromboembolic complications. There were no signs of pulmonary, myocardial or renal damage (Table 2) and no neurologic defect was observed on clinical examination. This indicates that perfusion with heparin-coated circuits during heart surgery could be performed without any major impairments in organ perfusion.

The CBAS™ has a coating factor of 2 $\mu g/cm^2$, rendering about 6000 IU of active heparin in the circuit itself. Consequently, to compare the effects of a coated surface versus a non-coated one,

patients receiving a coated circuit were given less heparin intravenously. Thus, both groups were exposed to approximately the same amount of active heparin. Anti-Factor Xa reflects the plasma concentration of heparin. Both aFXa and ACT levels verified the lower systemic dose of heparin which had been given to Group HC. These results also indicate that there was no important release of heparin from the coated surface. Along with the decreased amount of intravenous heparin the following protamine could be reduced to 50%. It was our clinical impression that heparin reversal was quicker as well as more efficient in Group HC and this was further indicated by the somewhat shorter ACT levels in this group after protamine administration.

The coagulation parameters did not show any significant postoperative differences between the groups. However, the tendencies were similar to our earlier results from animal experiments (18). Postoperative bleeding in the present study was generally low and without significant differences between the groups. A further reduction of intravenous heparin may result in reduced postoperative blood loss.

Platelet adhesion reflects the ability of platelets to adhere to foreign surfaces and to damaged endothelium, representing the first step of platelet activation. Both groups in this study displayed a more rapid recovery in platelet adhesion than seen previously and the same tendency towards rapid recovery was seen in number of platelets and hemolysis (14). These indicate that a circuit with a hollow fiber membrane oxygenator and a collapsible venous reservoir, in itself is less harmful than previously used CPB systems. The exclusion of cardiotomy suction may also have been beneficial to blood cell preservation. Such a device may trigger thrombus formation during periods of low or no blood flow and by mixing of air and blood. Venting of the left ventricle was not applied since this could also cause clotting, by periods of low or no flow in the venting line. We did not experience any technical difficulties in performing surgery under these circumstances.

In order to achieve normal blood gases during CPB both groups needed gas flow of the same level to the oxygenators. This indicates that the gas flux over the hollow fiber membranes is unaffected by the coating process.

The CBAS™ coating has been used clinically for long lasting perfusions with varying doses of systemic heparinization (4,17). In

the majority of such perfusions clotting has not been a problem as long as there has been a high pump flow.

In summary, standard CPB perfusions for coronary artery surgery were performed with heparin coated circuits and a 25% reduction in systemic heparinization. There were no signs of clotting or embolic events. A tendency towards less blood cell trauma was observed when heparin-coated circuits were used, although not verified statistically. This may partly be explained by the small number of patients involved in the study. A further reduction of the systemic heparin dose may result in even less postoperative bleeding and blood cell trauma. Controlled clinical trials are needed.

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