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Two different dosing regimen of human recombinant erythropoietin beta during preoperative autologous blood donation in patients having hip arthroplasty

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ABSTRACT

Purpose: Aim is to evaluate the effectiveness of two different dosing regimen of human recombinant erythropoietin (rHuEpo) for preoperative autologous blood collection in patients undergoing hip arthroplasty.

Methods: Prospective randomized trial where erythropoietin was administered intravenously;15000IU twice a week or 30000IU once a week (total of 90000IU)), combined with fero II sulfat peroraly and compared to administration of only fero II sulfat.

Results: Although different dosing regimen of the same rHuEpo administration during preoperative autologous blood donation have similar effect on collecting of two units of autologous blood, preoperative haemoglobin level and perioperative allogenic blood transfusion, once weekly dose regimen of rHuEpo was more convenient (although not statistically significant) for patients.

Conclusion: We suggest more practical and comfortable but still very effective therapeutic regimen with single weekly intravenous administration of recombinant human erythropoietin (for patients scheduled for THA).

Key words: autologous blood donation, hip arthroplasty, human recombinant erythropoietin, dose regimen, blood transfusion, erythropoietin

INTRODUCTION

Patients undergoing total hip arthroplasty (THA) with baseline haemoglobin level of ≤ 130 g/L are usually unable to donate sufficient autologous blood volume to satisfy their transfusion requirements during and after the surgery. More than 50% of such patients require additional allogenic blood transfusions [1,2]. The goal of preoperative administration of recombinant human erythropoietin (rHuEpo) is to increase erythropoiesis in patients who are donating blood for autologous use and therefore decrease the need for allogenic transfusions [3,4]. Previous reports found that the pharmacological response to erythropoietin therapy is a function of dose and administration regimen and that repeated administration of rHuEpo is more effective in stimulating reticulocyte response than single-dose administration of the same total amount of rHuEpo[5]. Several studies suggest that if rHuEpo is administered subcutaneously rather than intravenously, a lower dose may be sufficient to maintain the haematocrit at a given level [6]. But, over the last twenty years researches recorded cases where patients developed neutralizing anti-erythropoietin antibodies, a rare complication after usage of rHuEpo to increase red-cell production, in patients with the anaemia because of chronic renal failure. Such antibodies can cause pure red-cell aplasia [7]. The occurrence of antibody-mediated pure red-cell aplasia was mostly related to the subcutaneous administration of human recombinant erythropoietin [8,9]. The optimal dose, interval and route of administration for rHuEpo are yet to be established.

The aim of this study is to evaluate the effectiveness of two different dosing regimen of rHuEpo administered intravenously to avoid all possible complications of subcutaneous administration (15000 IU of rHuEpo intravenously twice a week (total of 90000IU) or 30000 IU of rHuEpo intravenously once a week (total of 90000 IU)), combined with fero II sulfat peroraly and compared to administration of only fero II sulfat peroraly, for collecting of two units of preoperative autologous blood and therefore reducing the need for allogenic blood transfusions after primary THA.

PATIENTS AND METHODS

Patients

The study included 93 patients between 60 and 80 years of age who were scheduled for primary THA due to osteoarthritis. All patients who were able to donate autologous blood preoperatively with haemoglobin level between 105 and 130 g/L were suitable for the study. Patients were enrolled in the study after giving informed consent in accordance with the ethical committee of the hospital. Exclusion criteria were: history of bleeding disorder, history of seizures or uncontrolled hypertension, history of deep vein thrombosis, gastrointestinal

bleeding within 6 month before the surgery, malignancy, acute or chronic infection and consumption of cytostatic or immunosuppressant drugs. Iron was given orally in all patients as ferrous-II sulphate (3x 65 mg elementary iron) during the study, starting one week before the first autologous blood donation. THA in all patients was performed by senior authors using direct lateral approach. The human recombinant erythropoietin beta (Recormon®) used in the study was provided by F Hofmann - La Roche, Basel, Switzerland. For all patients routine premedication included midasolam per os (0,1 mg/kg) 1 hour before the induction of anaesthesia and 500mL of Ringer's solution before they were positioned upright for the induction of spinal anaesthesia at level of either L3/L4 or L2/L3 via midline approach. An isobaric solution of levobupivacain (3,0 – 3,5 mL) were administered with 25 or 27G pencil-point needle.

Study design

Patients were randomly assigned in three groups: 30 patients received 15000 IU (average 200IU/kg) of rHuEpo intravenously twice a week (on 17^{th}, 13^{th}, 10^{th}, 6^{th}, 3^{rd} day preoperatively, and 2nd day postoperatively), and iron peroraly (group I); 31 patient received 30000 IU IU (average 400IU/kg) of rHuEpo intravenously once a week (on 17^{th}, 10^{th} and 3^{rd} day preoperatively), and iron peroraly (group II); 32 patients received only iron peroraly (group III). Donation of 12% of total blood volume was performed at 10^{th} and 3^{rd} preoperative day. The minimum haemoglobin level (Hb) for donation was 110 g/L, according to current European guidelines for preoperative autologous donation[10]. The pre-study evaluation included thorough medical history and physical examination. Pre-study laboratory tests included complete blood count, reticulocyte count, serum chemistry studies, urin analysis, serum iron, TIBC, transferin saturation, and serum ferritin. At the time of each injection of rHuEpo, (17^{th} ,13^{th} ,10^{th} , 6^{th} and 3^{rd} preoperative day, for group I, and 17^{th} , 10^{th} , and 3^{rd} preoperative day, for group II and group III, respectively, vital signs, hematologic values (including reticulocytes) and serum chemistry (potassium) were assessed. If the Hb level was greater than 150 g/L erythropoietin beta was not administered, if the Hb level was less than 110 g/L, autologous blood was not donated. Adverse events, blood loss and transfusion data were collected for all patients by anaesthesiologist. The criteria for perioperative transfusion (both autologous and allogenic) included haemoglobin level ≤80 g/L, and/or clinical symptoms of anaemia (increased heart rate or lower blood pressures despite an intravenous fluid bolus). All patients received the same protocol for deep venous thrombosis prophylaxis with low-molecular-weight heparin, and cefazolin (1g iv) was administered 60min before procedure for perioperative infection prophylaxis. In all patients reinfusion drains were used. The reinfusion drains (for cell salvage) were used in the immediate postoperative period in the

recovery room (first 6 hours), and were later converted to standard Hemovac drains. All drains were removed 48 hours after arthroplasty.

Laboratory studies

Samples were obtained on 17^{th}, 13^{th}, 10^{th}, and 3^{rd} day preoperatively, in group I and II before each injection of rHuEpo, and in group III immediately before donation of autologous blood. Blood was taken on the day of surgery: 2 hours preoperatively and 6 hours postoperatively, and on several postoperative days (1^{st}, 2^{nd}, 3^{rd}, 10^{th}, and 35^{th}) from all patients. Ferro-kinetic studies (serum iron, serum ferritin, TIBC and transferrin saturation) were measured before and at the end of the study. Three groups were similar in terms of male/female ratio, age, height, weight, total blood volume, ASA classification, and baseline haemoglobin level. Group I included 5 male and 25 female patients, with mean age 68.43. Group II included 3 male and 28 female patients with mean age 67.71. Group III included three male and 29 female patients with mean age 66.31. The primary variable which measured efficiency was the percentage of patients in each group requiring allogenic blood and the mean number of units given to each patient who received a transfusion. The secondary variable which measured efficiency was percentage of patients in each group who collected planned two units of autologous blood, the mean number of units collected per patients, and a change in haematological parameters.

Statistical methods

Demographic and analytical values were presented using descriptive statistics and expressed as mean±SD; medians, minimal and maximal observed values or percentage. The paired Student t-test was used to determine the significant differences within the group, and Wilcox test was used for data which values cannot be assumed to be normally distributed. The unpaired Student t-test and MannWhitney test were used to determine the statistical significance between the groups. A p value of less than 0.05 was considered as statistically significant.

RESULTS

Patients in Group I were able to collect 58 of the requested 60 units of autologous blood. Forty-nine of the 58 units were transfused, and nine units were discarded. Patients in Group II were able to collect 61 of the requested 62 units of autologous blood. Forty-three of the 61 unit were transfused, and eighteen units were discarded. Patients in Group III were able to collect 58 of the requested 64 units of autologous blood. Fifty of the 58 units transfused, and eight units were discarded. The effect of erythropoietic activity on haemoglobin level and reticulocytes count over time is shown in Figures 1 and 2. Only one patient in group II had haemoglobin level at

baseline less than, for autologous donation recommended 110 g/L (105. g/L), but because of effective stimulation of erythropoiesis, patient was able to donate one unit of autologous blood (at the time of first autologous blood donation haemoglobin level was 110 g/L). There were no significant differences among groups between postoperative haemoglobin levels. Mean reticulocyte count was not significantly different at initial assessment between all the groups. From 10^{th} preoperative day to the day of surgery, there was significant increase in reticulocyte count in both erythropoietin-treated groups. The reticulocyte count returned to baseline levels 5 weeks after surgery in all three groups. Six hours after surgery, and at the first postoperative day, patients who received erythropoietin (group I and II) had significantly higher values than did those in no-erythropoietin group (III), $p<0.001$, t-test. Difference between reticulocytes count in Group I and II didn't reach significance during study period at any time. Intraoperative blood loss, postoperative reinfusion blood, blood loss in drains, and total blood loss are shown in Figure 3. The perioperative blood loss was similar among all groups.

Transfusion

The incidence of blood transfusion is shown in Figure 4. Only two patients in Group II did not receive blood transfusion. There were no patients who received allogenic blood transfusion intraoperatively. The highest proportion of patients who required blood transfusion intraoperatively (autologous) was in Group III, 16 (50%) patients compared with 7 (23,3%) and 4 (13.3%) patients in Group I and II, respectively, III:I,II $p=0.0315$, chi-square test. There was no significant difference in postoperative consumption of autologous blood between groups. There were 34.4% of patients in group III exposed to allogenic blood transfusion postoperatively compared with 13.3% , and 6.4% of patients in Group I and II, respectively, III:I,II $p=0.013$, III:II $p=0<0.001$, chi-square test . The difference in allogenic transfusion rates between Groups I and II (13.3% to 6.4%) did not reach significance ($p=0.09$, chi-square test). The mean number of blood units is shown in Figure 5. The mean number of units of allogenic blood transfused per patient was 0.23±0.49 (0-3), 0.13±0.51 (0-2), and 0.69±1.23 (0-4) in Group I, II and III, respectively, III:I,II $p=0.006$, t-test. The mean number of total transfused units (autologous and allogenic) was 1.87±0.86 (0-5), 1.5±0.78 (0-4), and 2.25±1.24 (0-5), in Group I, II, and III, respectively, III: I, II $p=0.013$, t-test. There was no significant difference among the groups at baseline, as well at the end of study between serum iron, TIBC, ferritin and transferrin saturation. However, serum iron, ferritin and transferitin saturation at the end of study significantly decreased compared with baseline level, $p<0.05$, t-test for paired samples.

The use of erythropoietin in this study was generally well tolerated, with few adverse reactions which were nausea in four (6.5%), pyrexia in four (6.5%) and headache in three (4.9%) patients. The erythropoietin therapy was not discontinued in any patient because of these reactions. Postoperative complications included five wound hematomas (no operative evacuation was needed).

DISCUSSION

This study suggest that two, here compared, regimens of beta human recombinant erythropoietin intravenously (six-dose regimen vs. three-dose regimen, of the same weekly doses) for three weeks enabled collecting of two units of autologous blood and reduced allogenic blood transfusion in patients having THA. These results are in agreement with studies of Green et al. and Rosencher et al. [11,12]. Both, six-dose and three-dose regimen were associated with better haematological parameters on the day of surgery and lower overall requirement for transfusion of allogenic blood, when compared with no-erythropoietin treated group of patients. Previous major, double-blind, placebo controlled trials with daily regimen of rHuEpo for ten preoperative, and five postoperative days have shown benefit from rHuEpo in orthopaedic surgical patients by increasing total red cell mass of patients and reducing perioperative allogenic blood transfusion[13,14]. The trial by Goldberg et al demonstrated that weekly 600 IU/kg dosing regimen of rHuEpo was similar to the daily 300 IU/kg regimen, with respect to safety and the avoidance of allogenic transfusion in patients scheduled to undergo major orthopaedic arthroplasty[15]. After these trial weekly dose regimen was approved as the standard regimen for orthopaedic surgery. Contrary to this study, several trials demonstrated that more frequent administration could be more effective than less frequent one. Cody et al discussed that initial high peak level from high once weekly dose may be wasted as erythropoietin receptors on progenitor cells in bone marrow may become saturated; when these receptor are again free for binding, the level of serum erythropoietin will fall. Frequent administration of small amounts of rHuEpo could maintain a more constant low level, but effective level of serum erythropoietin[16]. Changes of reticulocytes count is one of powerful predictors of responsiveness to rHuEpo treatment[17,18]. In our study the mean reticulocytes count slightly increases, for several days, after the beginning of erythropoietin treatment, compared to baseline level, in both erythropoietin groups, and this results are consistent with the findings of Ramakrishnan et al.[19] They found that, after repeated erythropoietin administration, reticulocytes count steadily starts to rise until the peak level is reached after 200 to 300 hours. Then reticulocytes count starts declining to reach the baseline level. Non-erythropoietin treated patients received postoperatively allogenic blood transfusion at higher rate (34.4%) than patients who had twice weekly regimen

(13.3%), and once weekly regimen (6.4%). Although there was no significant difference between Groups I and II in percentage of allogenic blood transfusions, there was a slightly lower demand for allogenic blood transfusion in Group II (single weekly dose). The average consumption of transfused, overall blood (autologous and allogenic) were significantly higher (2.25±1.24 units/patient) compared with both erythropoietin treated groups. This results were in agreement with previous studies, which demonstrated that preoperative haemoglobin level was one of the strongest predictors of perioperative allogenic blood transfusion in perisurgical setting[20,21].

Great proportion of authors have shown the superiority of subcutaneous route over intravenous for more sustained serum levels over time (12-18h) and lesser dose requirements[22-24]. But, subcutaneous injection can be painful and also nearly all patients who had antibody-mediated pure red cell aplasia, received erythropoietin administration by the subcutaneous route[25,26]. For this reason, and for short-term administration, Lee et al.[27] think that treatment by intravenous route is better for patients having autologous blood donation as it allows a more reliable serum level to be achieved and maintained. Several clinical studies[28] analysed the relationship between erythropoietin, iron, and the erythropoietic response to anaemia. In our study relative weak response of erythropoiesis to 90 000 IU rHuEpo (approximately 6x200IU/kg or 3x400IU), could be explained with chosen doses of erythropoietin beta, and iron supplementation. Although all baseline iron parameters (including serum iron, TIBC and saturation of transferrin) were within the normal ranges, with no intergroup differences, iron stores are not sufficient, because the iron requirements exceed the available supply, during rHuEpo administration and accelerated erythropoiesis. Approximately 200 mg/d, (which was used in the current study) is a standard regimen of iron supplementation[17].

Conclusion

Although different dosing regimen of the same rHuEpo administration during preoperative autologous blood donation have had similar effect on the collecting of two units of autologous blood, preoperative haemoglobin level and perioperative allogenic blood transfusion, once weekly dose regimen of rHuEpo was more convenient (although not statistically significant), and probably more comfortable for patients. With assumption that for the great proportion of patients it was more inconvenient, costly and psychologically and physically demanding if they had to visit hospital twice a week. For this reason we suggest more practical and comfortable but still very effective therapeutic regimen with single weekly intravenous administration of recombinant human erythropoietin (for patients scheduled for THA).

The authors declare that they have no conflict of interest.

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Figure 1. Haemoglobin values (means) during the study.

Figure 2. Change in mean reticulocyte count from baseline during the study.

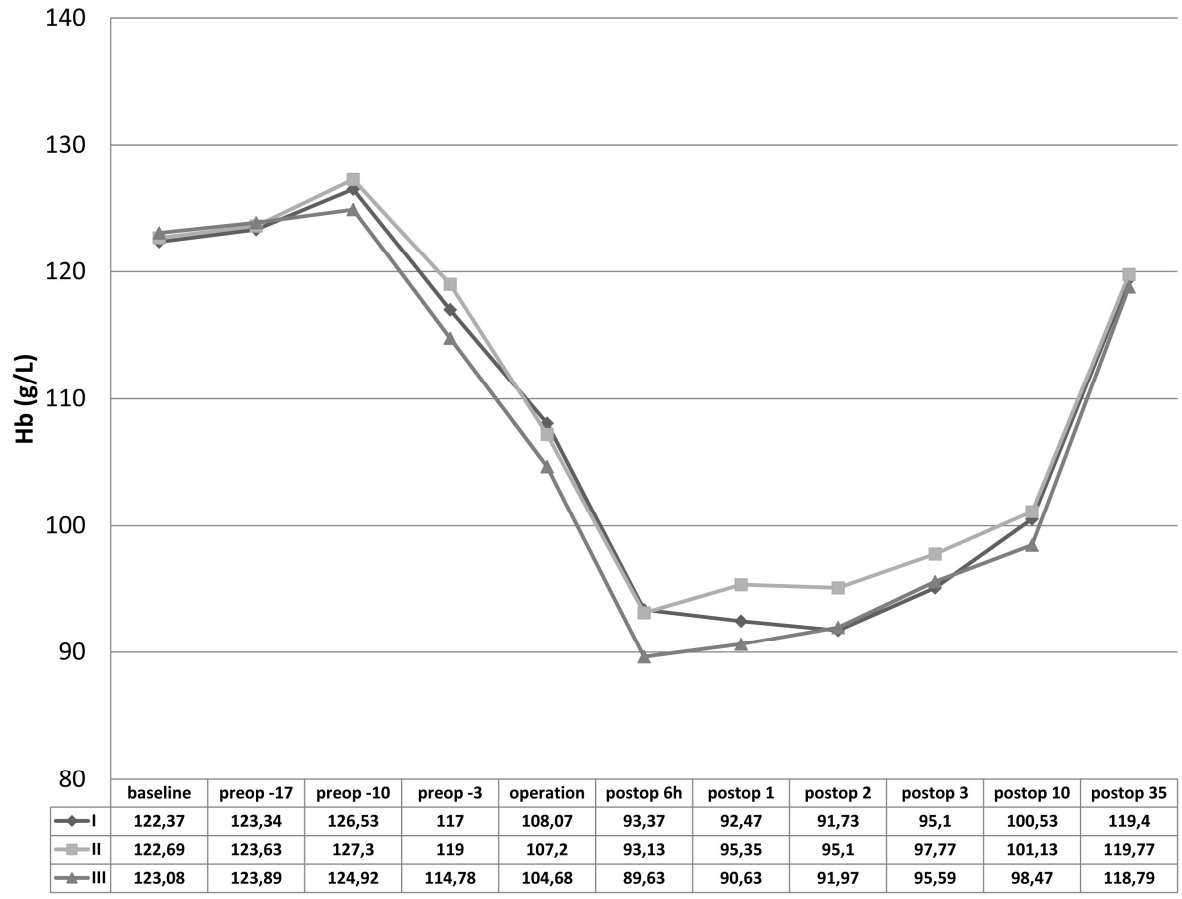
Figure 3. Perioperative blood loss.

Figure 4. The incidence of blood transfusion.

Figure 5. The mean units collected/patient and transfused/patients.

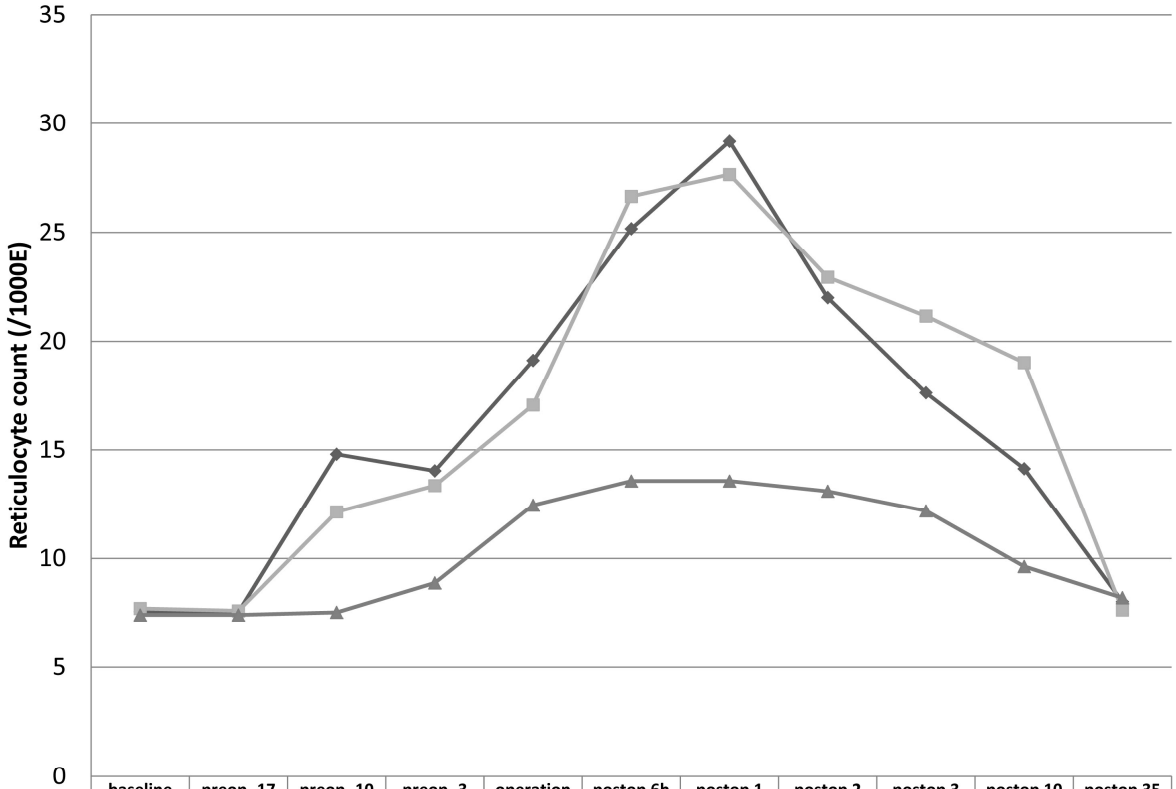
Table 1. The ferrokinetic studies.

Data have shown as mean ±SD, and (minimal and maximal values)



	baseline	preop -17	preop -10	preop -3	operation	postop 6h	postop 1	postop 2	postop 3	postop 10	postop 35
I	122,37	123,34	126,53	117	108,07	93,37	92,47	91,73	95,1	100,53	119,4
II	122,69	123,63	127,3	119	107,2	93,13	95,35	95,1	97,77	101,13	119,77
III	123,08	123,89	124,92	114,78	104,68	89,63	90,63	91,97	95,59	98,47	118,79

Fig1



	baseline	preop -17	preop -10	preop -3	operation	postop 6h	postop 1	postop 2	postop 3	postop 10	postop 35
I	7,57	7,55	14,8	14,03	19,13	25,17	29,17	22	17,63	14,13	8,02
II	7,71	7,6	12,13	13,35	17,07	26,65	27,65	22,94	21,16	19,03	7,64
III	7,41	7,41	7,53	8,88	12,44	13,56	13,56	13,09	12,18	9,63	8,2

Fig2

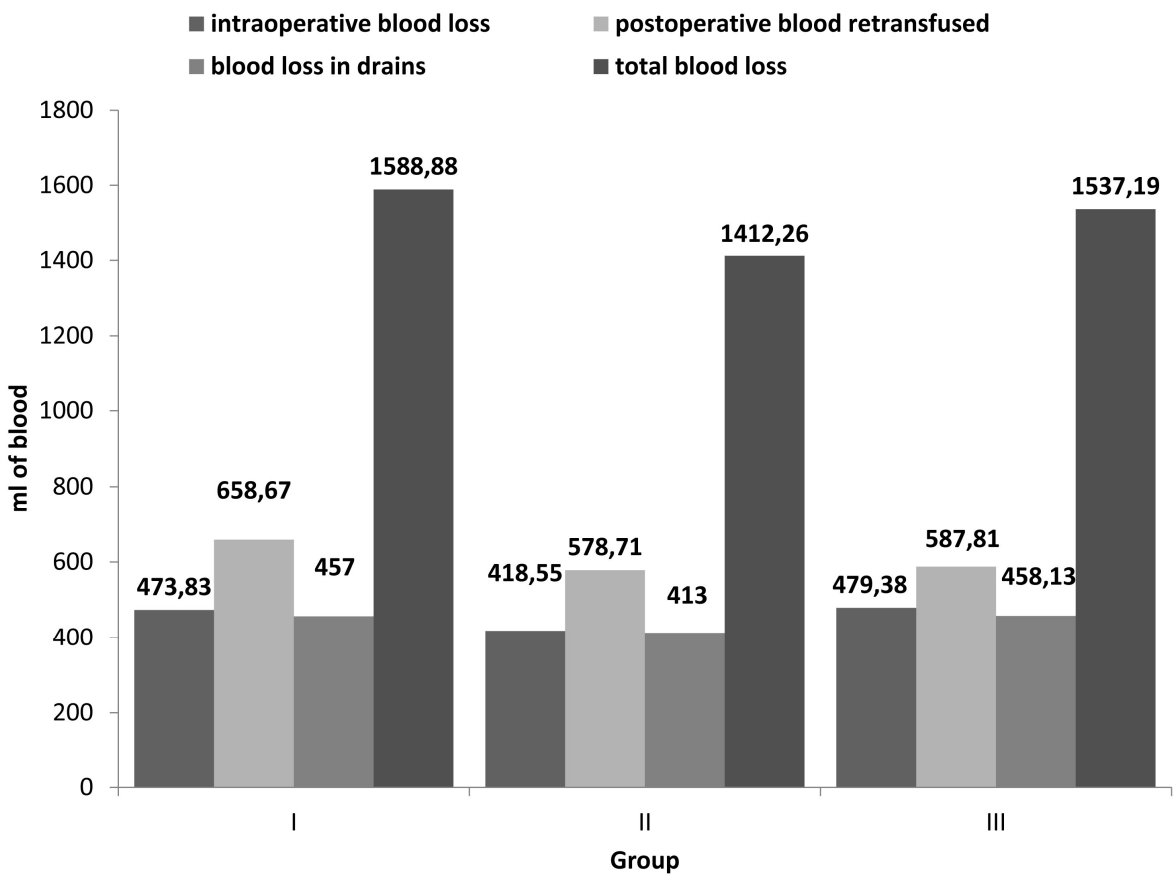

intraoperative blood loss
postoperative blood retransfused
blood loss in drains
total blood loss
1800
1600
1400
1200
1000
800
600
400
200
0
ml of blood
473,83
658,67
457
1588,88
418,55
578,71
413
1412,26
479,38
587,81
458,13
1537,19
I
II
III
Group

Fig3

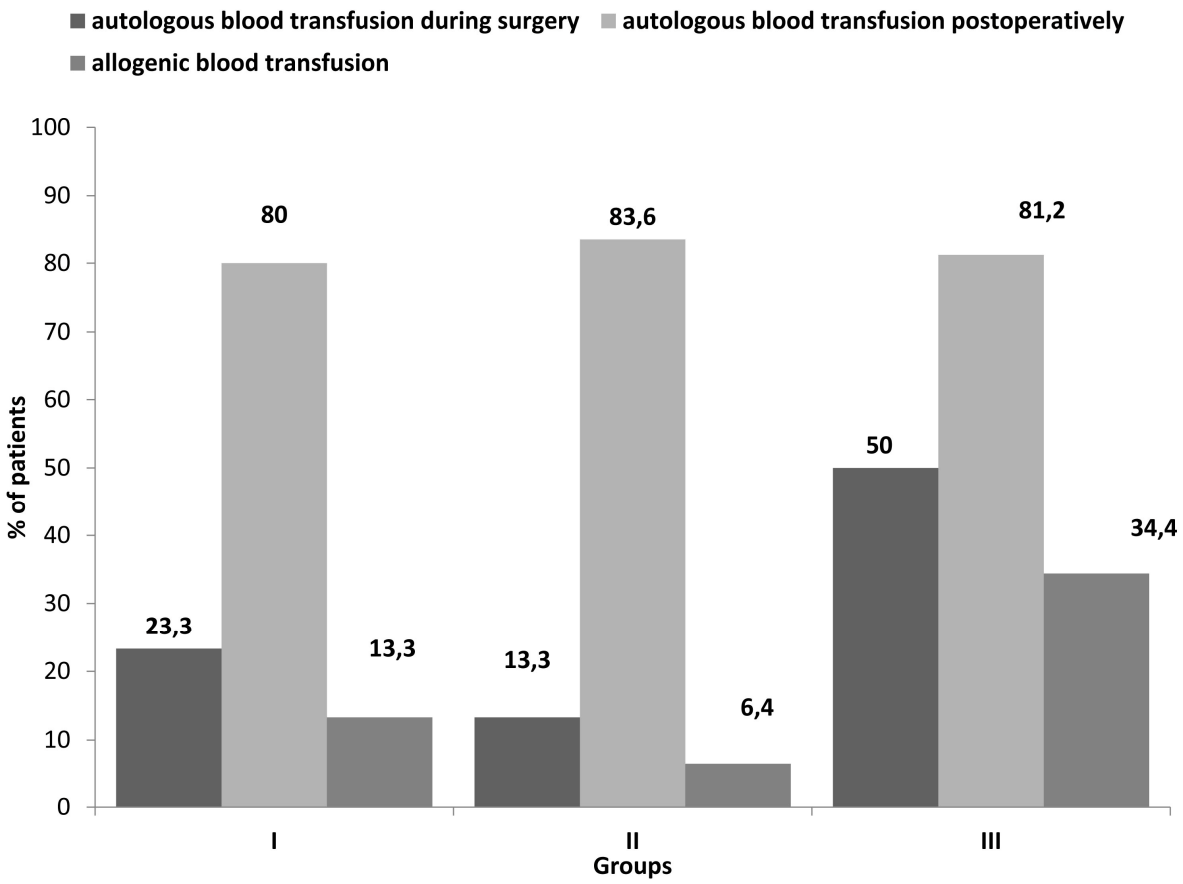

autologous blood transfusion during surgery
autologous blood transfusion postoperatively
allogenic blood transfusion
100
90
80
70
60
50
40
30
20
10
0
% of patients
80
83,6
81,2
50
34,4
23,3
13,3
13,3
6,4
I
II
III
Groups

Fig4

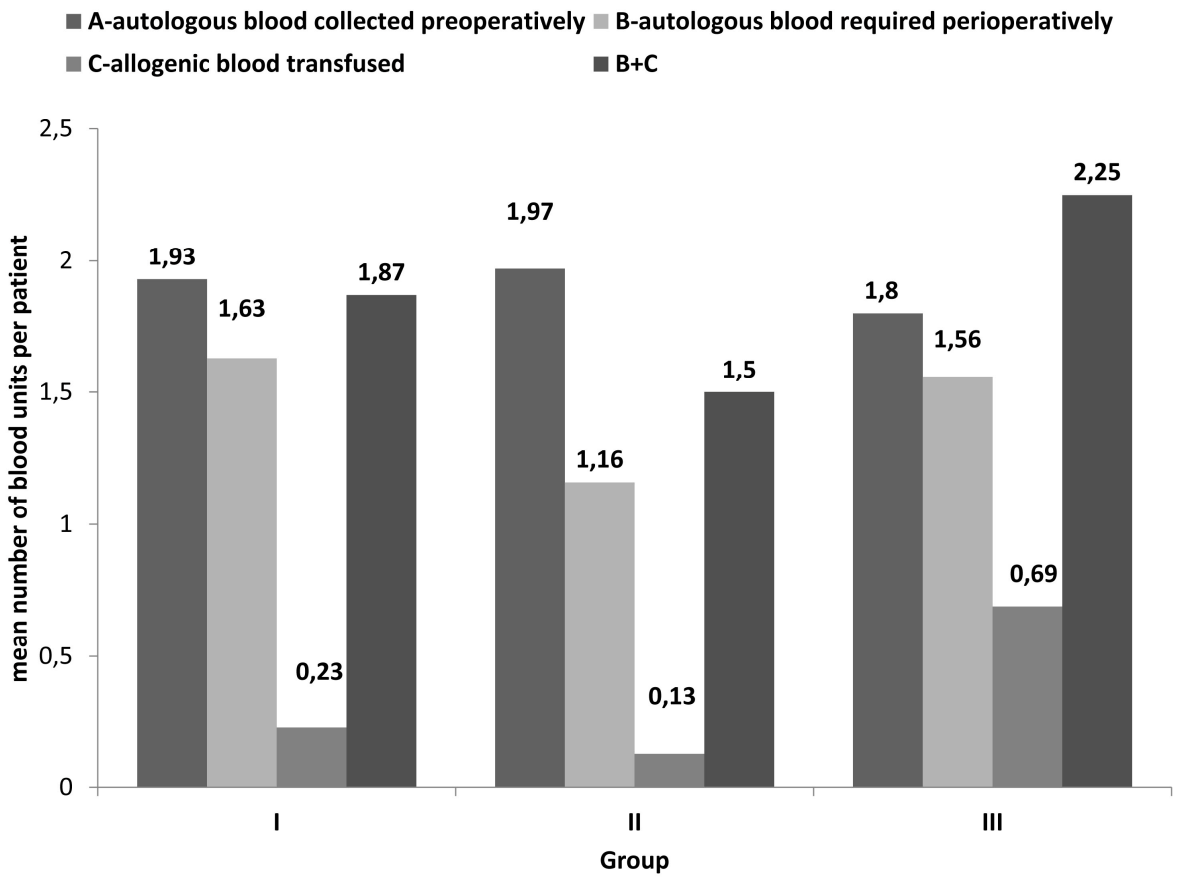

A-autologous blood collected preoperatively
B-autologous blood required perioperatively
C-allogenic blood transfused
B+C
mean number of blood units per patient
2,5
2
1,5
1
0,5
0
1,93
1,63
0,23
1,87
1,97
1,16
0,13
1,5
1,8
1,56
0,69
2,25
I
II
III
Group

Fig5

		Group I	Group II	Group III	p
Fe (µg/L)	**baseline**	13.72±3.54 (8.00-23.00)	15.29±4.04 (7.80-23.50)	14.27±3.95 (7.00-25.90)	0,276
	at the end of the study	12.09±4.72 (7.60-32.00)	12.71±4.17 (8.64-31.00)	11.37±2.58 (7.32-28.00)	0,4
TIBC (µg/L)	**baseline**	53.81±6.16 (40.20-67.00)	56.41±8.22 (44.60-78.00)	56.44±4.26 (49.00-66.00)	0,189
	at the end of the study	52.53±8.39 (40.10-87)	54.15±5.59 (46.50-72.00)	55.42±5.11 (45.60-65.00)	0,22
Feritin (ng/mL)	**baseline**	78.56±12.6 (45.3-136.8)	81.25±9.8 (52.0-141.80)	76.21±10.2 (50.0-130.6)	0,326
	at the end of the study	62.7±10.2 (40.6-124.8)	58.7±12.8 (46.4-130.80)	70.7±10.8 (59.7-131.8)	0,354
Transferin saturation (%)	**baseline**	25.72±5.49 (15.00-42.80)	26.94±6.64 (14.90-39.60)	24.96±6.39 (12.10-43.00)	0,5
	at the end of the study	21.72±11.41 (10.90-77.00)	20.17±6.44 (13.30-33.90)	20.53±4.49 (11.60-32.20)	0,239

Table 1