Local and systemic application of tranexamic acid in heart valve surgery: a prospective, randomized, double blind LOST study

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Abstract The study was performed to examine a possible augmentation of systemic administration of tranexamic acid by the additional topical application during heart valve surgery in the post-aprotinin era. One-hundred patients were enrolled in the study and all the patients were given tranexamic acid intravenously. The participants were randomized into two groups (A, $n = 49$; B, $n = 51$), and before commencing the sternal suturing, the study solution (group A: 250 ml of normal saline + tranexamic acid 2.5 g, placebo group B: 250 ml of normal saline) was poured into the pericardial cavity. The cumulative blood loss (geometric means [95% confidence intervals]) 4 h after the surgery was 86.1 [56.1, 132.2] ml in group A, and 135.4 [94.3, 194.4] in group B, test for equality of geometric means $P = 0.107$, test for equality of variances $P = 0.059$. Eight hours after the surgery, the blood loss was 199.4 [153.4, 259.2] ml in group A, 261.7 [205.1, 334.0] ml in group B, $P = 0.130$ and $P = 0.050$, respectively. Twenty-four hours postoperatively the blood loss was 504.2 [436.0, 583.0] ml in group A, 569.7 [476.0, 681.7] ml in group B, $P = 0.293$ and $P = 0.014$, respectively. The proportion of patients transfused postoperatively by fresh frozen plasma differed significantly between the two study groups (group A: $n = 21$, group B: $n = 36$, $P = 0.008$). Our hypothesis is supported by a significant difference in the inter-group variance of blood loss and the proportion of patients requiring fresh frozen plasma; however evident differences in mean postoperative blood loss were not statistically significant.

Keywords Heart valve surgery · Fibrinolysis · Fibrinolytic inhibitors · Tranexamic acid

Introduction

Preventive application of fibrinolytic inhibitors (aprotinin, lysine analogues) in cardiac surgery has been used to reduce postoperative blood loss and transfusion requirements since the 1980s [1, 2]. In 2007 due to the results published by Karkouti et al. [3], Mangano et al. [4] and Fergusson et al. [5] aprotinin has been suspended from the pharmaceutical market. The currently used replacement for aprotinin—tranexamic acid—seems to be rather less effective in blood conservation and its safety profile and correct dosing have been broadly investigated and discussed [6].

Although the systemic (intravenous) application of tranexamic acid is the most common approach, the topical application (into the pericardial cavity) was also reported in the literature [7–11].

This prospective, randomized, double blind study was performed to examine a possible augmentation of systemic administration of tranexamic acid by additional topical application during heart valve surgery (predominantly complex—combined procedures) in the post-aprotinin era. The study focused on postoperative blood loss and the

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primary outcome variable was cumulative blood loss at 24 h postoperatively.

Materials and methods

With the approval of the Medical Faculty Ethics Committee (EK/10/2008) and after obtaining the informed consent of all participants, 100 patients scheduled for valve surgery were enrolled in the study. The criteria for non-enrollment to the study were as follows: isolated coronary artery bypass grafting, previous cardiac surgery and history of hematological disorders. Preoperative treatment with either antiaggregative or anticoagulant drugs (aspirin withdrawal <5 days before surgery, low molecular heparin withdrawal <24 h before surgery, or continuous heparin infusion) were not a contraindication to the inclusion into the study, but the number of medicated patients was monitored. None of the participants were preoperatively under the effective influence of clopidogrel or warfarin (although they were not actively excluded from the study).

Pharmacological protocol and drug administration

All the patients were given tranexamic acid (Exacyl, Sanofi Winthrop, France) 1 g before skin incision and subsequently, continuous infusion 400 mg/h was administered throughout the entire surgical procedure. Another dose of 0.5 g of tranexamic acid was added to the crystalloid pump prime.

After the enrollment in the study, the participants were randomized by an independent pharmacologist (not directly involved in the clinical treatment of randomized patients) into two groups (A, B), the envelope method with random numbers was used. Before the end of surgery, the pharmacologist prepared identical, coded, sterile bottles containing a solution for topical application (group A: 250 ml of normal saline + tranexamic acid 2.5 g, group B: 250 ml of normal saline as a placebo). Both the operating theatre staff and that of the post-operative intensive care unit were blinded in terms of the study solution. The final randomization was as follows: group A: $n = 49$, group B: $n = 51$ patients, respectively.

After surgical hemostasis, and before starting metallic sternal suturing, the study solution was poured into the pericardial cavity and spread over mediastinal tissues. Prior to this, the study solution was pre-heated to body temperature. Two or three chest tubes were used and placed: retrocardially, into the substernal position and in the event of the opening of left pleura (during left internal artery harvesting) into the left pleural space. Continuous drain suction (−20 cm H_2O) was started immediately after chest closure. The recording of the blood loss count was started from the time of the arrival of the patient in the intensive care unit.

Surgical procedures and cardiopulmonary bypass management, anesthetic protocol

Longitudinal medial sternotomy was used in all cases. Cardiopulmonary bypass in a standard setting was established by ascending aortic cannulation and two-stage venous cannulation of the right atrium (for aortic valve surgery) or selective cannulation of superior and inferior vena cava (for mitral valve surgery and tricuspid valve repair). A rheoparin-coated cardiopulmonary bypass system (oxygenator Medos Hilite 7000, Stolberg, Germany) was used. Heparin was given at the initial dose of 300 IU/kg to achieve an activated clotting time of more than 480 s. Normothermic perfusion (2.5 l/m²) with antegrade, intermittent, cold crystalloid cardioplegia (St. Thomas) were used. After the termination of extracorporeal circulation, a full dose of protamine chloride was given to reverse the effect of heparin. Mechanical heart valve prostheses (St. Jude Medical, MN) and bovine pericardial bioprostheses (Sorin, Biomedica, Italy) or porcine valve bioprostheses (St. Jude Medical, MN) were used. In mitral/tricuspid valve plasty anuloplasty rings Uniring (Péters, Bobigny, France) or Carpentier-Edwards Phisio rings (Edwards Lifesciences, Unterschleissheim, Germany) were implanted. MAZE procedures were performed by CryoCath cryoablation system (Cryocath Technologies, Montreal, Canada). Left internal thoracic arteries were harvested in all cases when surgery of heart valves was combined with coronary artery bypass grafting.

General anesthesia with intubation based on midazolam (Dormicum Hoffmann-La Roche, Basel, Switzerland), propofol (Propofol Fresenius, Bad Homburg, Germany), alfentanil (Rapifen, Janssen Pharmaceutica, Beerse, Belgium) and inhaled isofluran (Forane, Abbott, Maidenhead, UK) with an oxygen and air mixture at 1:1 ratio was applied. For muscle relaxation continuous cisatracurium (Nimbex, Glaxo Wellcome Operations, Greenford, UK) was administered. A pulmonary artery catheter was inserted at the start of all procedures in patients scheduled for mitral valve surgery. For all the remaining patients, pulmonary artery catheters were only used in the event of poor left ventricular function, defined as a Left Ventricular Ejection Fraction <30–35%. Preoperative intra-aortic balloon counterpulsation was not utilized in any case.

Transfusion policy, re-exploration criteria

A packed red blood cell transfusion was administered when hemoglobin decreased to less than 8.5 g/dl and/or hematocrit to less than 26 during the procedures, and when

hemoglobin decreased to <9.0 g/dl and/or hematocrit to <30 during the intensive care unit stay, respectively. Fresh frozen plasma was transfused when chest drainage blood levels increased to >150 ml/h or to >100 ml/h for two consecutive hours and according to thromboelastometric (Clot Formation Time >160 s, Maximum Clot Firmness <52 mm) and other laboratory parameters [Prothrombin Time, expressed as the International Normalized Ratio (INR) > 1.5]. If the bleeding continued and the platelet count was below 100×10^9/l then a platelet concentrate was administered. A surgical postoperative re-exploration was based on our standard criteria: chest drainage 300 ml/h for two consecutive hours, or 200 ml/h for 3 h, or clinical signs of cardiac tamponade verified by echocardiography.

Laboratory analyses

Blood samples for evaluation of hematological parameters were taken and processed routinely. Additionally, in the first 80 consecutive patients a thromboelastometric analysis was performed by ROTEM® System (Pentapharm, Munich, Germany). The blood sampled from the arterial lines was processed immediately with the use of heparinase for heparin removal and ex-TEM® including thromboplastin for the extrinsic pathway activation. The sampling time points were as follows: preoperatively, at the termination of cardiopulmonary bypass and 2 h post completion of the surgery.

Statistical analysis

The trial was designed to have an 80% power to detect 1.5-fold between-groups difference in geometric means of 24 h postoperative blood loss as statistically significant. This expectation corresponds to the results found by Baric et al. [9] and reviewed in Ngaage and Bland [6]. Since the data of these authors show substantial differences in variability between groups, comparisons of both characteristics of location and variability were planned.

Values of continuous variables are given as arithmetic or geometric means (for normally or log-normally distributed data, respectively) and their variability is characterized by 95% confidence intervals. The comparison of means between groups was based on the Student's two-sample t-test with possibly unequal variances. Based on the result of Shapiro–Wilk test for normality the data were log-transformed in particular cases. Non-parametrical comparison was undertaken by Mann–Whitney test. Brown and Forsythe modification of Levene's robust test based on an ordinary one-way analysis of variance applied to the absolute deviations of observations from the median was used to test the equality of variances of blood loss between groups. Dubey/Armitage-Parmar procedure (as described in [12]) which takes into account correlational structure of the variables was used to adjust for multiple testing in case of blood loss measured at different time points. For categorical data, the differences in proportions between groups were analyzed using Fisher's exact test and its generalization. All statistical tests were evaluated at a significance level of 0.05. Statistical analysis was performed by statistical software Stata, release 9.2 (Stata Corp LP, College Station, TX).

Results

The basic demographic data of patients are listed in Table 1, no differences between study groups were found. The surgical procedures performed are listed in Table 2, valvular surgery combined with coronary artery bypass grafting was performed in 38 patients on the whole (group A: $n = 19$ (38.8%), group B: $n = 19$ (37.3%), $P = 1.000$). Hematological parameters at the end of extracorporeal circulation, 2 and 24 h postoperatively are presented in Table 3, no significant differences were observed.

Thirteen (26.5%) patients from study group A were under the influence of aspirin, while in group B the number of patients was 18 (35.3%), which was not statistically different ($P = 0.392$). Low molecular heparin withdrawal <24 h before surgery was in 9 (18.3%) patients from group A and in 5 (9.8%) patients from group B ($P = 0.258$). Continuous heparin was preoperatively administered to few patients only [group A: $n = 4$ (8.2%), group B: $n = 2$ (3.9%), $P = 0.432$].

According to the above mentioned criteria, 12 (12%) patients required postoperative surgical revision [group A: $n = 4$ (8.2%), group B: $n = 8$ (15.6%), $P = 0.358$]. The major or minor surgical sources of bleeding were found in nine cases (the sources of bleeding were identified as follows: three from the aortic suture line, two from the right atrial suture, two from the left internal thoracic grafts and one each from the suture of the left atrium and the sternum). In two patients [group A: $n = 1$ (2.0%), group B: $n = 1$ (2.0%)] evident surgical causes of bleeding were not confirmed, and in one patient from group B clinical and echocardiographic suspicion of cardiac tamponade was false. The postoperative incidence of neurological complications was 4 (8.2%) in group A and 1 (2.0%) in group B ($P = 0.200$). These transient neurological attacks disappeared in the early postoperative period in all patients. In total, 4 (4%) patients died [group A: $n = 2$ (4.1%), group B: $n = 2$ (3.9%)] due to generally complicated postoperative course, leading to multi-organ failure. In the other patients the geometric mean of intensive care unit stay was 36 h in group A and 48 h in group B. Patients from group A were discharged from the hospital after 8.7 days and from group B after 8.9 days, on average.

Table 1 Basic demographic, preoperative hematological, and intraoperative characteristics

		Group A ($n = 49$)	Group B ($n = 51$)	P value
Age (years)	Arithm.	71.1 (68.7,73.4)	71.1 (68.7,73.5)	0.983
Gender (male/female) (no. of pts, percentage)		28 (57.1%)/21	26 (51.0%)/25	0.554
Weight (kg)	Arithm.	81.7 (77.4,85.9)	80.0 (75.1,84.8)	0.594
Additive EuroSCORE	Arithm.	6.47 (5.73,7.21)	6.08 (5.47,6.69)	0.412
Logistic EuroSCORE	Geom.	5.90 (4.72,7.36)	5.27 (4.37,6.36)	0.440
Left ventricular ejection fraction	Arithm.	52.3 (48.7,55.8)	55.0 (51.9,58.0)	0.247
Hematocrit	Arithm.	41.44 (40.37,42.51)	40.40 (39.15,41.66)	0.210
Hemoglobin (g/dl)	Geom.	13.63 (13.26,14.02)	13.38 (12.95,13.83)	0.394
Platelet count (10^9/l)	Geom.	216.1 (197.4,236.6)	217.2 (202.0,233.6)	0.930
Fibrinogen (g/l)	Geom.	4.25 (3.98,4.53)	3.93 (3.68,4.19)	0.090
aPTT (s)	Geom.	36.41 (35.03,37.85)	35.93 (34.98,36.90)	0.564
INR	Geom.	1.11 (1.08,1.14)	1.10 (1.08,1.13)	0.671
D-dimers (ng/ml)	Geom.	549.8 (455.6,663.5)	515.9 (388.0,686.0)	0.706
Operating time (min)	Geom.	234.2 (212.4,258.1)	247.4 (227.5,268.9)	0.392
Duration of cardiopulmonary bypass (min)	Geom.	84.9 (73.7,98.0)	86.2 (76.4,97.4)	0.870
Aortic cross-clamp time (min)	Geom.	64.9 (56.4,74.6)	65.9 (58.8,73.9)	0.863

Data are presented as arithmetic means (arithm.) or geometric means (geom.) and 95% confidence intervals, unless otherwise specified

Table 2 List of surgical procedures

Procedure	Group A ($n = 49$)	Group B ($n = 51$)	Total
AVR	11	10	21
Bentall operation	1	4	5
AVR + CABG	8	13	21
AVR + MVR (MVP) + TVP	2	3	5
AVR + MVR (MVP) + TVP + CABG	4	0	4
MVR (MVP)	3	4	7
MVR (MVP) + TVP	10	8	18
MVR (MVP) + CABG	4	4	8
MVR (MVP) + TVP + MAZE	3	3	6
MVR (MVP) + TVP + MAZE + CABG	3	2	5

AVR Aortic valve replacement, *CABG* coronary artery bypass grafting, *MAZE* CryoMAZE procedure, *MVP* mitral valve plasty, *MVR* mitral valve replacement, *TVP* tricuspid valve plasty

Intraoperative and postoperative blood loss

No statistically significant differences between groups were found in the mean intraoperative blood loss (geometric means [95% confidence intervals]—group A: 471.2 [409.2, 542.6] ml, group B: 527.1 [457.2, 607.7] ml, ($P = 0.264$).

Cumulative blood loss at the time points of 4, 8, and 24 h postoperatively is represented in Table 4. A continuous tendency towards lower blood loss is apparent in group A; however no statistical significance in the mean blood loss was reached at any time points. Figure 1 suggests that in group B greater variability in blood loss exists at all postoperative time points, leading to a statistically significant difference of variances 24 h postoperatively ($P = 0.014$). This difference remained significant after applying Dubey/Armitage-Parmar correction to comparisons in columns of Table 4 and Fig. 1 ($P = 0.020$).

Transfusion requirements

During the procedures 67 (67%) patients did not require transfusion of packed red blood cells. The rest of the patients [group A: $n = 14$ (28.6%), group B: $n = 19$ (37.3%), $P = 0.400$] received on average (geometric means) 546.4 ml of red blood cells in group A, and 584.2 ml in group B ($P = 0.246$).

Postoperative transfusion requirements are summarized in Table 5.

Only 27 (27%) patients were not transfused by any packed red blood cells postoperatively. Among the transfused patients, the geometric mean volume of red blood cells was 662.2 ml in group A and 670.5 ml in group B, $P = 0.882$.

Forty-three (43%) patients didn't receive any fresh frozen plasma postoperatively, the remaining transfused patients (57%) were more likely to belong to group B (group A: $n = 21$, group B: $n = 36$, $P = 0.008$). However, the geometric mean of fresh frozen plasma in transfused patients was similar in both groups (group A: 948.4 ml, group B: 838.3 ml, $P = 0.376$).

Less than one quarter (23%) of patients were transfused by platelet concentrate postoperatively. The proportion of

Table 3 Hematological parameters at the end of extracorporeal circulation, 2 and 24 h postoperatively

		Group A ($n = 49$)	Group B ($n = 51$)	P value
End of extracorporeal circulation				
Hematocrit	Arithm.	27.93 (26.80,29.08)	27.51 (26.48,28.54)	0.578
Hemoglobin (g/dl)	Geom.	9.19 (8.85,9.54)	9.12 (8.78,9.47)	0.777
Platelet count (10^9/l)	Geom.	133.4 (116.7,152.5)	135.6 (120.5,152.6)	0.852
Fibrinogen (g/l)	Geom.	2.44 (2.25,2.65)	2.37 (2.20,2.55)	0.584
aPTT (s)	Geom.	234.9 (215.8,255.8)	232.0 (213.0,252.7)	0.835
INR	Geom.	2.56 (2.32,2.81)	2.56 (2.30,2.83)	0.999
D-dimers (ng/ml)	Geom.	466.4 (388.9,559.3)	422.8 (324.0,551.7)	0.549
2 h postoperatively				
Hematocrit	Arithm.	30.52 (29.33,31.71)	31.06 (29.09,33.03)	0.644
Hemoglobin (g/dl)	Geom.	10.04 (9.66,10.44)	10.15 (9.76,10.56)	0.695
Platelet count (10^9/l)	Geom.	140.4 (126.6,155.6)	136.7 (124.3,150.3)	0.703
Fibrinogen (g/l)	Geom.	2.78 (2.59,2.99)	2.68 (2.48,2.90)	0.500
aPTT (s)	Geom.	38.3 (35.2,41.5)	36.7 (35.4,38.0)	0.344
INR	Geom.	1.52 (1.45,1.59)	1.53 (1.45,1.61)	0.856
24 h postoperatively				
Hematocrit	Arithm.	31.32 (30.30,32.35)	30.91 (30.05,31.77)	0.534
Hemoglobin (g/dl)	Geom.	10.34 (10.01,10.69)	10.23 (9.96,10.51)	0.620
Platelet count (10^9/l)	Geom.	120.1 (108.9,132.5)	119.8 (110.1,130.3)	0.964
Fibrinogen (g/l)	Geom.	3.92 (3.69,4.17)	4.07 (3.80,4.35)	0.432
aPTT (s)	Geom.	42.2 (40.2,44.4)	45.3 (41.8,49.2)	0.143
INR	Geom.	1.32 (1.29,1.36)	1.27 (1.15,1.39)	0.387
D-dimers (ng/ml)	Geom.	474.6 (397.3,567.0)	570.5 (460.3,707.0)	0.187

Data are presented as arithmetic means (arithm.) or geometric means (geom.) and 95% confidence intervals

Table 4 Cumulative blood loss 4, 8 and 24 h postoperatively

Postoperative time (h)	Group A ($n = 49$)	Group B ($n = 51$)	P value[a]	P value[b]
4	86.1 (56.1,132.2)	135.4 (94.3,194.4)	0.107	0.059
8	199.4 (153.4,259.2)	261.7 (205.1,334.0)	0.130	0.050
24	504.2 (436.0,583.0)	569.7 (476.0,681.7)	0.293	0.014

Data are presented as geometric means and 95% confidence intervals

[a] Test for equality of geometric means

[b] Test for equality of variances

transfused patients was insignificantly lower in group A [$n = 9$ (18.4%)] as compared to group B [$n = 14$ (27.5%)], $P = 0.345$. No other hemostatic medication (e.g. cryoprecipitate, fibrinogen, clotting factor concentrates, rFVIIa) were used.

Thromboelastometry

No significant differences between the study groups were found in parameters monitored by thromboelastometry (Coagulation Time, Clot Formation Time, Maximum Clot Firmness, α-Angle, Maximum Lysis, Lysis Index at 30, 45, and 60 min, respectively). At the termination of extracorporeal circulation Maximum Lysis (arithmetic means) was 9.6% in group A and 9.4% in group B ($P = 0.829$). Two hours postoperatively mean Maximum Lysis was 10.4% in group A and 10.9% in group B ($P = 0.576$) and mean Lysis Index at the time of 60 min of measurement was 96.9% in both groups ($P = 0.964$).

Discussion

During cardiac surgery, fibrinolytic activity is initiated by the release of tissue plasminogen activator; this starts with the skin incision and sternotomy and continues throughout
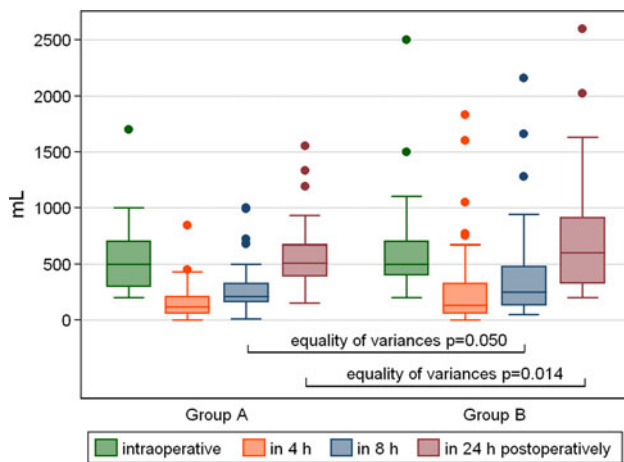
Fig. 1 Intraoperative and cumulative postoperative blood loss at the time points of 4, 8 and 24 h. Borderline inter-group difference in data variability at the time point of 8 h postoperatively was found, and at the time point 24 h postoperatively the variance of blood loss was significantly greater in group B in comparison with group A. No statistically significant differences in characteristics of location between groups were proven

the surgical tissue manipulation. In operations where cardiopulmonary bypass is used, activation of coagulation (only partially suppressed by heparin) occurs related to the contact of blood with foreign, non-endothelial surfaces and consequent activation of the fibrinolytic system is described [13–16]. Re-infusion of the suctioned fluids from the surgical field thereafter enhances these pathological processes [17].

Formerly, in accordance with our protocol, aprotinin was administered for the prevention of increased bleeding in heart valve surgery with possible prolonged duration of cardiopulmonary bypass. Since the withdrawal of this drug from the market we have been routinely using systemic (intravenous) application of tranexamic acid in this type of surgery. Tranexamic acid is an important part of blood saving strategies in other centres [18], although aprotinin seemed to be about twice as effective as tranexamic acid in reducing total postoperative blood loss [19].

In our study a statistically significant difference in the inter-group variance of blood loss 24 h postoperatively and the proportion of patients requiring fresh frozen plasma after the surgery are well documented. Moreover, our hypothesis of positive augmenting effect of the additional topical application of tranexamic acid to the systemic application is supported by observed shifts in mean postoperative blood loss, but without statistical significance. To the best of our knowledge, this is the first study on combined use (systemic and topical) of tranexamic acid in cardiac surgery. The rationale for both systemic and topical application of fibrinolytic inhibitor is based on findings of Tabuchi et al. [20] and Khalil et al. [21] that the local fibrinolytic activity in the pericardial cavity exceeded that in the systemic circulation. Looking at our data we might speculate that this topical addition of tranexamic acid could prevent the occurrence of excessive blood loss, but recommendation for the routine use of this method requires further clinical trials. At the time point of 24 h postoperatively, chest tube drainage is often serosanguinous and theoretically volume differences should be caused rather by anti-inflammatory than prohemostatic influence of tranexamic acid [22, 23]. Anti-inflammatory effects of tranexamic acid were not investigated in this study.

According to literature, varying systemic doses of tranexamic acid were used (loading intravenous dose ranged from 1 to 10 g, 500–2500 mg of tranexamic acid was added to the content of the cardiopulmonary bypass circuit prime, continuous infusion ranged from 200 to 1000 mg/h) [6]. For the topical administration different dosages varying from 1 g [7, 10] to 2.5 g [9] were also applied. There

Table 5 Postoperative transfusion requirements

	Group A (n = 49)	Group B (n = 51)	P value
Packed red blood cells			
Number (%) of transfused patients	37 (75.5%)	36 (70.6%)	0.655
Median—all patients—(25th–75th percentile) [maximum]	540 (325–600) [1680]	560 (0–610) [1470]	0.783
Geometric mean (95% CI)—transfused patients	662.2 (584.7,749.9)	670.5 (598.0,751.8)	0.882
Fresh frozen plasma			
Number (%) of transfused patients	21 (42.9%)	36 (70.6%)	0.008
Median—all patients—(25th–75th percentile) [maximum]	0 (0–900) [2310]	520 (0–1000) [1890]	0.045
Geometric mean (95% CI)—transfused patients	948.4 (744.4,1208.4)	838.3 (710.8,988.6)	0.376
Platelet concentrate			
Number (%) of transfused patients	9 (18.4%)	14 (27.5%)	0.345
Median—all patients—(25th–75th percentile) [maximum]	0 (0–0) [420]	0 (0–170) [730]	0.244
Geometric mean (95% CI)—transfused patients	212.7 (172.6,262.2)	243.4 (192.5,307.7)	0.393

Data are presented in ml, unless otherwise specified

was no individual case of fibrinolysis being detected by thromboelastometry in our study, and D-dimers levels remained postoperatively stable and at relatively low levels. Bearing in mind the results of our previous work clearly demonstrating fibrinolytic activity during markedly shorter non-coated cardiopulmonary bypass when no fibrinolytic inhibitors were used [24, 25], we suggest that systemic application of tranexamic acid in used dosage is sufficient for satisfactory inhibition of fibrinolytic activity.

We are quite aware of the fact that our proportion of patients who required early postoperative surgical revision (12%) is apparently high compared with standard published data (2–6%) [26], but on the other hand most of the operations were complex procedures on a relatively old patient population with an expected higher rate of re-exploration [27]. Furthermore Karthik et al. [28] and Choong et al. [29] convincingly demonstrated that delaying postoperative surgical revision results in a worse outcome.

Study limitations

Our study is a real life one with only minimal limitations of inclusion criteria. Patients in daily practice referred for valve surgery were quite inhomogeneous in preoperative treatment with antiaggregative/anticoagulant drugs, cardiac diagnosis and performed procedures. Theoretically cardiac disease per se can affect a tendency for postoperative bleeding (varying degrees of chronic low cardiac output, acquired von Willebrand's disease in aortic stenosis, renal and liver dysfunction in mitral and tricuspid disease etc.). Practically it is difficult to eliminate this bias from the heterogeneous study population. From our opinion the real impact of topical addition to the systemic application will be necessary to verify on a larger group of more uniform patients.

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