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Consequences of acute normovolaemic haemodilution on haemostasis during major orthopaedic surgery

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Acute preoperative normovolaemic haemodilution (NHD) is an accepted tool for reducing allogeneic blood transfusion requirements during surgery. At present, little is known of its impact on haemostasis. We have investigated the consequences of NHD on haemostasis by comparing conventional global tests (prothrombin time (PT), activated partial thromboplastin time (aPTT)) with more specific measures of coagulation (prothrombin fragment 1+2 (F 1+2), thrombin–antithrombin III complex (TAT)) and fibrinolysis (D-dimer (DD), plasmin–α_2-antiplasmin complex (PAP)). Blood samples were collected from two groups (NHD and controls) undergoing elective spinal surgery or pelvic osteotomy until day 3 after operation. The conventional global tests remained within normal limits; there were no significant differences between groups. Although surgery induced significant increases in the more specific measures of coagulation and fibrinolysis, there were no differences between NHD and control patients. Major orthopaedic surgery strongly activates coagulation and fibrinolysis. As the degree of these alterations was similar in haemodiluted and control patients, we suggest that acute preoperative normovolaemic haemodilution itself does not appear to be associated with greater perioperative disturbances in haemostasis.

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Major orthopaedic surgery is associated with large blood loss. Transmission of infectious diseases, haemolytic and non-haemolytic transfusion reactions, immunosuppression and other immunological reactions are serious complications of blood component therapy.[1–3] Normovolaemic haemodilution (NHD) has been suggested as an effective blood saving technique.

Blood loss, haemodilution and surgical trauma are assumed to produce disturbances in the haemostatic system but confirmation that NHD per se causes disturbances in haemostasis is still lacking.[3 4] In most studies, NHD has been reported to have only minor effects on *in vitro* coagulation tests (e.g. prothrombin time (PT), activated partial thromboplastin time (aPTT)). Martin and colleagues[5] found that mild normovolaemic haemodilution (lowest packed cell volume (PCV) 30%) induced significant changes in conventional *in vitro* variables, although both PT and aPTT remained within the normal range. Similar results were published by others.[6 7] In contrast, Bormann and colleagues[8] found a pronounced increase in aPTT after mild normovolaemic haemodilution in patients undergoing liver surgery. No adverse effects of NHD were observed in these studies.

PT and aPTT are known to reflect only global *in vitro* changes in haemostasis. Recently, more specific molecular markers for activation of the haemostatic system have been introduced. They are useful for a more differentiated assessment of haemostatic changes in patients.[9] To the best of our knowledge, no data are available with regard to the time course of these activation markers during and after acute NHD.

To evaluate the consequences of NHD on haemostasis, we have used conventional *in vitro* tests and measured more specific activation markers of coagulation (prothrombin fragment 1+2 (F 1+2), thrombin–antithrombin III complex (TAT)) and fibrinolysis (D-dimer (DD), plasmin–α_2-antiplasmin complex (PAP)) in patients undergoing major orthopaedic surgery.

Patients and methods

The study was approved by the Ethics Committee of the University of Innsbruck. After obtaining written informed

consent, we investigated 40 patients undergoing major orthopaedic surgery. The haemodilution group included 20 patients with a median age of 39 (range 20–64) yr. In the control group (n=20), median age was 40 (range 21–56) yr. There were nine females and 11 males in each group. Thirty patients underwent spinal surgery (15 in each group) and 10 patients underwent pelvic osteotomy (five in each group). The distribution of blood groups was similar between groups (data not shown).

Inclusion criteria were: age >19 yr, major orthopaedic surgery (ventral/dorsal fusion of the spine or pelvic osteotomy) and intraoperative blood salvage (cell saving). Patients who chose not to donate autologous packed red cells within 4 weeks of surgery were recruited to the haemodilution group. Exclusion criteria were contraindications to performing NHD (according to Mathru and Rooney):[10] patients with severe ischaemic heart and cerebrovascular disease, hepatic dysfunction, those treated with beta-adrenergic blockers, patients with pulmonary dysfunction and those with pre-existing anaemia or haemoglobinopathies. In addition, patients with previous haemostatic disorders were excluded.

Anaesthesia was induced in both groups with midazolam 0.05 mg kg^{-1}, thiopental 5 mg kg^{-1} and fentanyl 3 μg kg^{-1}. Tracheal intubation was facilitated with vecuronium 0.1 mg kg^{-1}. Anaesthesia was maintained with ⩽1.0% end-tidal isoflurane and 50% nitrous oxide in oxygen, and additional bolus doses of fentanyl i.v. To maintain normothermia during surgery, a rewarming system (Bair Hugger Augustine Medical Inc., USA) and fluid warmers were used.

Perioperative deep venous thrombosis prophylaxis was started in the evening before surgery with standard heparin 5000 u., s.c. Heparinization was continued on the first postoperative day using enoxaparin s.c.

Perioperative monitoring until collection time E (until the patient's discharge from the intermediate care unit to the ward) included continuous arterial pressure measurement (radial artery), ECG, pulse oximetry, central venous pressure, urine output, arterial lactate concentration, arterial blood-gas analysis, calculation of arterial oxygen content and measurement of haemoglobin concentration and PCV, in addition to conventional measures of haemostasis (PT, aPTT). On the ward, the following variables were measured: non-invasive arterial pressure, venous lactate concentration, arterial blood-gas analysis, urine output, haemoglobin concentration, and PT and aPTT.

Acute preoperative normovolaemic haemodilution

Acute preoperative normovolaemic haemodilution was performed after induction of anaesthesia but before the start of surgery. To determine the patient's blood volume to be withdrawn before operation, we used the original equation of Gross[11]:

$$V_L = EBV \times \frac{PCV_0 - PCV_F}{PCV_{AV}}$$

where V_L=blood volume (ml) to be withdrawn, EBV=estimated total blood volume of the patient (ml) (EBV=70 ml/kg body weight), PCV_0=initial PCV (%), PCV_F=patient's minimal allowable PCV (%) and PCV_{AV}=average of PCV_0 and PCV_F.

After venepuncture, calculated blood volume was withdrawn and stored at room temperature. According to the equation of Gross, the volume of blood collected was dependent on the preoperative PCV value. The target PCV after preoperative normovolaemic haemodilution was 25%. Simultaneously, the volume of shed blood was replaced with gelatin solution (Gelofusin, Braun, Melsungen, Germany) in a normovolaemic manner (1:1). Intraoperative blood loss, which was collected with a cell saving system (Haemonetics GmbH, Germany), was replaced with gelatin solution (Gelofusin) and Ringer's lactate solution (Ringer-Lactat 'Leopold', Leopold Pharma Gmbh Graz, Austria). During surgery we used a PCV of 20% as the 'transfusion trigger'. After reaching the trigger PCV autologous blood (collected blood before surgical procedure and collected intraoperative blood loss) was re-infused. Additional allogeneic blood components (buffy coat depleted packed red cells (PRC), fresh frozen plasma (FFP)) were transfused when necessary.

Control group

Patients included in the control group donated 1–3 units of packed red cells within 4 weeks before surgery. As an 'optimal control group' (i.e. maintaining preoperative PCV values) is not acceptable from a medico–legal point of view, intraoperative mild haemodilution was allowed. Thus the 'transfusion trigger' in the controls was a PCV value of 20%, similar to that in the preoperative haemodiluted patients. Intraoperative blood loss was collected with a cell saving system (Haemonetics GmbH, Germany). Additional autologous and allogeneic blood components (PRC and FFP) were transfused when necessary.

Blood sampling

In the haemodiluted patients, serial venous blood samples were collected from a central venous catheter immediately after induction of anaesthesia (A), immediately after normovolaemic haemodilution (B), before re-transfusion of blood components (autologous blood and allogeneic PRC and FFP) (C), 3 h after the end of surgery (D), and in the morning of the first (E) and third (F) postoperative days. In controls, blood samples were collected at corresponding times. The first syringe of 10 ml was used for determination of variables other than coagulation and fibrinolysis. In the second syringe, 9 ml of blood were added to 1 ml of sodium citrate-containing tubes (c=sodium citrate 0.106 mol $litre^{-1}$; Sarstedt, Numbrecht, Germany). PT and aPTT were measured in plasma within 1 h after withdrawal. Blood was centrifuged immediately in a refrigerated centrifuge at 2000×g for 30 min after withdrawal. Multiple aliquots of plasma were frozen and stored below –20°C until further analysis.

Table 1 Perioperative blood turnover and blood transfusions in the haemodilution (NHD) and control groups (mean (SEM)). There were no significant differences between groups. PRC = Buffy coat depleted packed red cells, FFP = fresh frozen plasma

	NHD	Controls
Blood volume withdrawn (ml)	855 (60) (range 350–1500)	
Collected blood (cell saver) (ml)	3177 (555) (range 200–11 890)	2391 (395) (range 683–6565)
Re-transfused blood (cell saver) (ml)	1108 (81) (range 200–3565)	776 (155) (range 100–2700)
PRC (autologous/homologous) (u.)	2.5 (0.5)	3.9 (0.4)
FFP (autologous/homologous) (u.;1 u. ≅ 230 ml)	1.3 (0.4)	1.4 (0.4)
Perioperative colloids (ml)	2600 (300)	2500 (300)

Analytical procedures

PT and aPTT were measured immediately after blood sampling by standard methods (Amelung Coagulometer, Baxter, UK). Fibrinogen antigen was measured by immunoturbidimetry with an antiserum to human fibrinogen (Turbiquant Fibrinogen, Behringwerke AG, Marburg, Germany). Heparin cofactor activity of antithrombin III was determined using the coamate antithrombin test (Chromogenix, Molndal, Sweden). TAT was measured with an enzyme immunoassay (Behringwerke AG, Marburg, Germany). Intra- and inter-assay coefficients of variation were 4.2% and 3.5%, respectively.[12]

Prothrombin F 1+2, a split product of prothrombin, was measured using an enzyme immunoassay (Behringwerke AG, Marburg, Germany). Intra- and inter-assay coefficients of variance were less than 7.5% and 13%, respectively.[13] The cross-linked fibrin degradation product DD was measured with an enzyme immunoassay (Behringwerke AG, Marburg, Germany). Coefficients of variation from day to day were 4–18%; coefficients in the series were 6–13%.[14]

Tissue-type plasminogen activator antigen (t-PA) was measured with a solid phase enzyme immunoassay (Chromogenix, Molndal, Sweden). The assay is highly specific for one- and two-chain forms of t-PA and does not interfere in the presence of plasminogen activator inhibitor-1 (PAI-1). Intra- and inter-assay coefficients of variation were $<7\%$.[15]

PAI-1 was measured using a solid phase enzyme immunoassay (Chromogenix, Molndal, Sweden). The assay is specific for total PAI-1, including free and complexed forms. Intra- and inter-assay coefficients of variations are $<7.3\%$.[16] PAP was determined with an ELISA (Behringwerke AG, Marburg, Germany). The coefficient of variation from day to day was 5–10%; the coefficient of variation in the series was 4–9%.[17]

PCV was measured in duplicate using a microhaematocrit centrifuge (Heraeus, Germany). Haemoglobin concentration and platelet count were measured by standard methods (Haemoglobinometer SPKS Coulter, UK). An oesophageal probe was used to estimate blood temperature (YSI Reusable Temperature Probe, Yellow Springs Instrument Co, Inc., USA).

Statistical analysis

The distribution of all variables was tested for normality using the one-sample Komolgorov–Smirnov test. Differences between and within groups over time were analysed by ANOVA for repeated measures. The Student's paired *t* test was used for comparing variables within each group. Baseline characteristics and differences between groups were compared using an independent *t* test or Mann–Whithney test, as appropriate. $P<0.05$ was considered significant. In addition, a Bonferroni–Holm correction for multiple comparison was performed for all *P* values. Results are expressed as mean (SEM).

Results

There was no significant difference between groups in age, type of surgery or perioperative bleeding.

Mean operation time was 366 (SEM 20) min (range 210–600 min) in the NHD and 371 (13) (270–540) min in the control group (ns). In the haemodiluted patients, the volume of blood withdrawn before operation was 870 (59) ml. Blood turnover is shown in Table 1. The volume of colloid and crystalloid solution administered was not statistically significant between groups. Blood temperature did not decrease to less than 35.1°C.

Before re-transfusion of blood components, haemoglobin concentration decreased to 73 (2.6) (range 56–94) g litre^{-1} in the haemodilution group and to 85 (4) (57–124) g litre^{-1} in the control group. Corresponding changes in PCV are shown in Figure 1. PCV at times B and C were significantly lower in the preoperative haemodilution group compared with the control group.

Changes in haemostasis

Changes in PT, aPTT, fibrinogen, antithrombin III (AT III) and platelets are shown in Table 2. PT activity was reduced significantly after NHD until the first postoperative day. Similar changes were observed in the control group (ns, NHD *vs* controls). With the exception of a significant increase in aPTT at time C, there were no significant changes in the NHD group. In contrast, aPTT was reduced significantly at times D and F in the control group (ns, NHD *vs* controls). Fibrinogen decreased during surgery in

both groups, recovered quickly thereafter and increased further until time F. AT III activity decreased significantly in both groups and reached a minimum at collection time C (ns, NHD *vs* controls). Thereafter, AT III normalized slowly until time F. During surgery, platelet count decreased significantly in the NHD and control groups and was still reduced on day 3 after surgery (ns, NHD *vs* controls).

Changes in F 1+2 and TAT are shown in Table 3. F 1+2 increased during surgery in both groups, reaching a maximum 3 h after surgery (D). It was still increased on day 3 after operation. TAT remained unchanged in the NHD group and was increased significantly only at D in controls (ns, NHD *vs* controls).

Changes in DD, t-PA, PAI-1 and PAP are shown in Table 4. DD increased significantly and reached maximum concentrations at time D (ns, NHD *vs* controls). t-PA increased significantly three-fold in the NHD group and 2.2-fold in controls. t-PA normalized in both groups until time F. PAI-1 increased significantly, peaked at time D and returned to baseline at time F in the NHD and control groups, respectively (ns). Similar changes were found for PAP: in both groups, maximum concentrations were observed 3 h after operation, and concentrations remained increased until day 3 after operation ($P=0.049$, NHD *vs* controls).

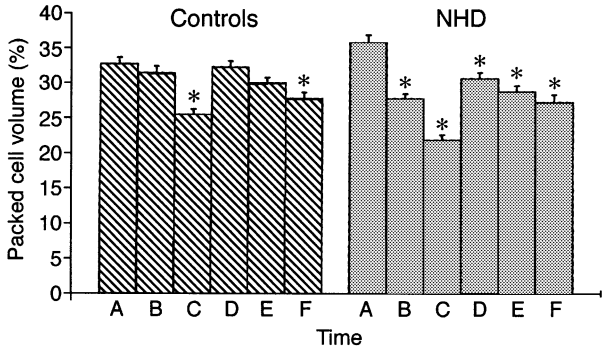

Fig 1 Perioperative changes in packed cell volume in the haemodilution (NHD) and control groups. Data are mean (SEM). Blood samples were collected after induction of anaesthesia (A), immediately after normovolaemic haemodilution (B), before re-transfusion of blood components (autologous blood and allogeneic PRC and FFP) (C), 3 h after the end of surgery (D) and in the morning of the first (E) and third (F) postoperative days (F). *$P<0.05$, A *vs* B–F.

Discussion

Acute normovolaemic haemodilution (NHD) is recommended as a technique for reducing allogeneic blood transfusion requirements during surgery. Whether acute preoperative normovolaemic haemodilution per se is associated with major haemostatic disorders is still a matter of debate. In our study, we observed only small changes in PT and aPTT in the NHD and control groups. In contrast, we found increased concentrations of the activation markers for coagulation (F 1+2, TAT) and fibrinolysis (DD, PAP) in both groups, with no significant differences between groups.

Table 2 Time course of perioperative changes in routine variables of haemostasis in the haemodilution (NHD) and control groups. Blood was collected after induction of anaesthesia (A), after normovolaemic haemodilution (B), immediately before transfusion of blood components (C), 3 h after termination of the operation (D), and in the morning of the first (E) and the third (F) days after surgery. Data are mean (SEM). There were no significant differences between groups. *$P<0.05$ compared with baseline values (A)

		Time					
		A	**B**	**C**	**D**	**E**	**F**
PT (%)	NHD	104 (1.5)	71 (2.5)*	57 (2.4)*	71 (3.8)*	70 (3.0)*	93 (2.6)
	Controls	89.9 (2.7)	88.6 (2.6)	75.5 (2.3)*	81.4 (3.9)	76.8 (3.9)*	93.2 (3.2)
aPTT (s)	NHD	32 (0.9)	34.9 (0.9)	38.2 (1.4)*	29.7 (1.1)	33.2 (0.9)	30.7 (0.9)
	Controls	31.8 (0.6)	32.6 (0.7)	33.1 (1.1)	27.5 (1.3)*	29.9 (1.0)	29.3 (0.9)*
Fibrinogen (g litre^{-1})	NHD	222 (14)	155 (7.4)*	106 (9.9)*	140 (9.8)*	297 (18)	550 (34)*
	Controls	230 (13)	224 (13)	153 (12)*	180 (15)*	330 (16)*	551 (37)*
AT III (%)	NHD	84.3 (2.8)	60.6 (1.9)*	48.4 (2.6)*	62.2 (3.1)*	68.9 (3.1)*	75.9 (2.1)*
	Controls	84.4 (2.1)	82.5 (2.2)	59.9 (2.2)*	70.6 (3.1)*	73.6 (2.1)*	78.8 (1.9)
Platelets ($\times10^9$ litre^{-1})	NHD	223 (12)	180 (11)*	157 (9)*	150 (11)*	157 (11)*	156 (11)*
	Controls	231 (13)	208 (16)*	195 (15)*	175 (13)*	162 (9)*	168 (10)*

Table 3 Time course of perioperative changes in markers for the activated coagulation system in the haemodilution (NHD) and control groups (times as in Table 2). Data are mean (SEM). There were no significant differences between groups. *$P<0.05$ compared with baseline values (A)

		Time					
		A	**B**	**C**	**D**	**E**	**F**
F 1+2 (nmol litre^{-1})	NHD	1.4 (0.1)	1.4 (0.1)	2.3 (0.3)*	5.9 (0.4)*	2.3 (0.5)*	2.5 (0.3)*
	Controls	1.5 (0.1)	1.7 (0.1)	3.7 (0.5)*	7.7 (0.7)*	2.7 (0.5)	4.3 (0.9)*
TAT (μg litre^{-1})	NHD	32.7 (7)	23.8 (4.3)	23.6 (4.4)	40.2 (4.5)	21.7 (4.2)	21.1 (3.6)
	Controls	28.8 (4)	20 (3)	25.6 (4.5)	64.6 (8)*	37 (6.7)	25.8 (7.5)

Table 4 Perioperative changes in markers of fibrinolysis in the haemodilution (NHD) and control groups (times as in Table 2). Data are mean (SEM). *$P<0.05$ compared with baseline values (A)

		Time					
		A	**B**	**C**	**D**	**E**	**F**
DD (μg litre^{-1})	NHD	15 (2.5)	12 (1.5)	67 (13)*	508 (68)*	398 (66)*	252 (47)*
	Controls	20 (2.1)	31 (6.9)	107 (17)*	706 (67)*	552 (69)*	333 (42)*
t-PA (μg litre^{-1})	NHD	4.8 (0.5)	4.2 (0.4)	4.3 (0.5)	14.4 (1.4)	8.9 (1)*	4.2 (0.5)
	Controls	5.9 (0.8)	5.3 (0.7)	5.5 (0.7)	13 (1.6)*	8.3 (0.9)*	5.1 (0.6)
PAI-1 (μg litre^{-1})	NHD	29 (2.5)	25.9 (3)	45 (4)*	98 (11)*	79 (9.4)*	25.3 (2)
	Controls	59.5 (11)	45.9 (7.6)	70 (8.8)	105 (17)*	83.2 (9.4)	48.9 (8)
PAP (μg litre^{-1})	NHD	419 (77)	402 (88)	281 (48)*	616 (76)	278 (69)	615 (65)
	Controls	296 (32)	365 (44)	362 (40)	1231 (24)*	351 (47)	690 (67)*

Haemodilution with i.v. fluids decreases the concentration of each component in the haemostatic system. Thus, depending on the degree of haemodilution, one would expect changes in the results of *in vitro* coagulation tests. In addition, perioperative blood loss and increased activation of coagulation and fibrinolysis with concomitant consumption of coagulation factors and inhibitors may be responsible for changes in *in vitro* coagulation tests.

Remarkably, despite different study designs (e.g. different degrees of haemodilution, inhomogeneous inclusion criteria, different methods for cell salvage), in most studies, including our investigation, only small changes in PT and aPTT after normovolaemic haemodilution were observed. For example, Olsfanger and colleagues[6] did not detect significant changes in PT and aPTT in the perioperative period in patients undergoing total knee replacement. Similar results were found in 31 haemodiluted patients undergoing elective major surgery after haemodilution to a PCV of approximately 30%[5]. Bormann and colleagues[8] compared the haemostatic status of haemodiluted and non-diluted patients undergoing major abdominal intervention (e.g. liver surgery). In contrast with PT, which remained within the normal range, aPTT was prolonged two-fold in the haemodilution group on the day of surgery. In our study, acute preoperative normovolaemic haemodilution in combination with a more pronounced normovolaemic haemodilution during surgery (minimum PCV 17%) did not alter markedly PT or aPTT. With the exception of an abnormal PT in the haemodilution group during surgery, PT and aPTT remained within the normal range in both groups. Thus acute normovolaemic haemodilution as such had no major effects on PT or aPTT.

AT III, a serine protease inhibitor, decreased significantly in the perioperative period with no significant differences between groups. The lowest activity was found during surgery with a tendency to recover thereafter. The reduction in AT III activity may be a result of blood loss and plasma dilution. The same mechanism may account for the decrease in fibrinogen concentration during surgery. Fibrinogen increased rapidly after surgery, which is in accordance with its increased synthesis in the liver as an acute phase protein.

The surgical procedure itself can activate the coagulation and fibrinolytic systems by mobilization of fat and bone debris and by releasing proinflammatory mediators, for example.[18–23] This activation is not easily detectable with common laboratory tests such as PT and aPTT. Consequently, in our study, we used recently introduced molecular markers to assess distinct disturbances in coagulation and fibrinolysis.[9] F 1+2 and TAT are known to be specific markers for intravascular thrombin formation. Increased concentrations of F 1+2 and TAT are found after trauma and major surgery, especially when combined with large wound areas, and in patients with disseminated intravascular coagulopathy (DIC).[19 21 22 24] In our study, F 1+2 was increased significantly during surgery and remained increased for 3 days after surgery in both groups. In contrast, TAT increased significantly only at 3 h after surgery in the control group with no significant increase in the haemodiluted patients. As there were no differences in F 1+2 and TAT between the haemodilution and control groups, we conclude that acute preoperative normovolaemic haemodilution with intraoperative normovolaemic haemodilution did not modify the degree of prothrombin and thrombin formation in the perioperative period. Concerning TAT formation, a similar time course was reported during and after total hip arthroplasty by Jorgensen and colleagues[25] and Menges and colleagues.[7] Intraoperative prothrombin activation and thrombin formation, as measured by F 1+2 and TAT, were less in our orthopaedic patients than observed in those during hepatic or gastric resection[18] and during cardiac surgery,[26] respectively. Whether the use of heparinized autotransfusion systems, as in our study, may influence F 1+2 and TAT formation is at present unclear.

DD is known to be a specific marker for reactive degradation of cross-linked fibrin.[27 28] Its measurement reflects the degree of secondary fibrinolysis caused by previously activated coagulation. Increased concentrations of DD are common in the perioperative period in orthopaedic patients,[25 28 29] whereas absolute changes exhibit great variability. In our study DD increased markedly in the perioperative period (maximum 3 h after surgery: 34-fold increase in the haemodilution group and 35-fold in controls)

which is greater than that found after total hip or knee arthroplasty.[25 28] Even 3 days after surgery, DD was increased significantly in our patients, indicating a long lasting secondary fibrinolysis. As no significant difference was observed between groups, it would appear that acute preoperative normovolaemic haemodilution did not influence the degree of secondary fibrinolysis.

The most important plasminogen activator *in vivo* is t-PA, released from endothelial cells by various stimuli (e.g. shear stress, catecholamines, endothelial damage). Even moderate local mechanical stimulation activates endothelial cells and releases t-PA, thus activating fibrinolysis.[29] t-PA forms a complex with fibrin whereby the enzymatic effect is catalysed. In our study, t-PA increased significantly in both groups 3 h after surgery (three-fold in haemodiluted patients and 2.2-fold in controls) and returned to normal by day 3 after operation. The endogenous inhibitor of t-PA is PAI-1, released mainly from endothelial cells and platelets. Similar to t-PA, PAI-1 is released mainly by endothelial cells and by platelets, and is reported to be increased after surgery.[30 31] In our study, changes in PAI-1 paralleled changes in t-PA, with maximum concentrations occurring 3 h after surgery and returning to normal within 3 days after operation. There were no differences between the haemodilution and control groups.

Released plasmin is bound rapidly by α_2-antiplasmin in blood by forming PAP complexes. PAP measurements are suggested to reflect the amount of generated plasmin in the circulation. In both groups, the time course of changes in PAP complexes was similar, with the highest concentrations after surgery. The lower maximum values in the diluted patients could be a consequence of haemodilution.

In summary, our data indicated that major orthopaedic surgery strongly activates coagulation and fibrinolysis, as measured by specific markers. In both haemodiluted patients and controls, this activation was not reflected by changes in conventional *in vitro* tests (PT, aPTT). As the degree in addition to the perioperative time course of changes in haemostasis were similar in the haemodiluted and control groups, acute normovolaemic haemodilution does not seem to be associated with additional perioperative disturbances in haemostasis.

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