Coagulation monitoring and transfusion in major non-emergency orthopaedic surgery - An observational study

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ABSTRACT

Objective: Perioperative coagulation monitoring and transfusions were evaluated.

Methods: 70 cases were included. Time points: before (PRE), after surgery (POST), day 1, day 3, day 7. Standard and patient near tests were assessed. Groups were: Transfused (TG); Control (CG).

Results: 23 patients were transfused (TG), 47 were not (CG). PRE haemoglobin was reduced, coagulation time (CT) was prolonged in TG. FIBTEM decrease was higher in TG. Leukocytes were elevated in TG. ASPI decreased, TRAP and ADP aggregability increased in both groups.

Conclusion: CT, haemoglobin and fibrinogen were associated with transfusion. TRAP and ADP aggregability increased and could account for thromboembolism.

1. Introduction

Blood loss remains a major concern during major orthopaedic surgery and can induce the need for transfusion, which independently is associated with increased morbidity and mortality.^{1–3} Recently, near-patient coagulation monitoring has been advocated to be effective in reducing transfusion requirements in different settings.^{4–8} Furthermore, especially rotational thromboelastometry has been shown to be able to predict massive transfusion.^{9,10} However, while bleeding complications are primarily concerning during surgery in the postoperative phase, thromboembolic complications become more important.¹¹ In a previously published study by Oberweis and coworkers, it has been shown that levels of single coagulation factors as Factor VIII, FXIII or von Willebrand Factor are affected in the perioperative phase as well as platelet aggregability after spontaneous aggregation or induction by arachidonic acid or collagen.¹²

Especially considering the well known and above-mentioned predictability of massive transfusion by patient near coagulation monitoring (Point of care – POC) in other clinical settings, we aimed to analyze perioperative results of whole blood coagulation analysis in patients undergoing scheduled major orthopaedic surgery. Furthermore, we aimed to complete observation of other induction

pathways of platelet induction to gather information about the influence of major orthopaedic surgery on the coagulation status of the patient.

2. Material and methods

Following IRB approval, this study was conducted in accordance with the Helsinki Declarations and European Unions Convention on Human Rights and Biomedicine. The study was designed as a mono-centric observational study.

2.1. Patients and procedures

Patients scheduled for non-emergency surgery at the DIAKOVERE Annastift-hospital (Hannover, Germany) were screened for following surgical procedures:

- hip arthroplasty exchange, removal or re-implantation
- knee arthroplasty exchange, removal or re-implantation
- spinal fusion (> 2 heights)

Inclusion criteria were adult age ≥ 18 years and no known

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preexisting coagulopathy. Exclusion criteria were pregnancy or patient's refusal. Verbal and written consent was obtained.

Anaesthesia, transfusion and operations were performed to local standard operating procedures and were not affected by the study.

2.2. Measurements and time points

According to local clinical standards laboratory measurements of blood count (including hemoglobin, leukocytes and platelets), aPTT, Quick, TZ, and fibrinogen level were performed. In addition, rotational thromboelastometry (ROTEM, TEM Innovations, Munich, Germany) and multiple electrode platelet aggregometry (MEA, Multiplate®, Roche, Munich, Germany) at following defined time points were assessed.

- immediately preoperative (PRE)
- immediately postoperative (POST)
- in the morning at the first postoperative day (Visit 1 - V1), day 3 (V2), and day 7 (V3)

Furthermore transfusion of blood products (red blood cell concentrate (RBC), fresh frozen plasma (FFP), and platelet concentrates (PC), as well as administration of coagulation factor concentrates (fibrinogen (FIB), prothrombin complex concentrate (PCC)) was documented. The given number of units reflect the units that were transfused in the time period from the measurement point before.

The ROTEM and MEA technique has been described previously elsewhere.^{13,14} All tests were conducted according to the manufacturer's advice using commercially available test solutions (TEM Innovations, Munich, Germany, and Roche, Munich, Germany) and resulting data were stored in a computer.

ROTEM was performed after extrinsically activation (EXTEM-test). Coagulation time (CT [s]) and clot firmness after 10 min (A10 [mm]) was analyzed. Furthermore, fibrin polymerization after 10 min (FIBTEM [mm]) was assessed.

To assess different platelet activation pathways following MEA tests were performed: TRAP – activation by thrombin, ADP – activation by adenosine diphosphate, and ASPI – activation by arachidonic acid to assess the platelet's cyclooxygenase pathway. As indicator for platelet function, the area under the aggregation curve (AUC) was determined for each test.

2.3. Group assignment

For further interpretation of the data, patients were posthoc assigned to transfused group (TG – patients that received allogenic blood products), or to control group (CG – patients without transfusions), respectively.

2.4. Statistical analysis

All data are shown as means ($\pm$ standard deviation, SD). After verifying normal distribution by a Kolmogorov-Smirnov test, analysis of variances (two-way ANOVA) with a Tukey posthoc analysis was performed for comparison between groups. When applicable, correlation (Pearson-Test) of data between groups was calculated. Data were analyzed using GraphPad Prism (Version 6.01, GraphPad Software Inc., San Diego, CA., USA). Considering a confidence interval of 95% an α error p of < 0.05 was defined as statistically significant.

3. Results

3.1. Patients and procedures

70 cases (in 24 male/46 female) were identified to meet inclusion criteria and have been included in the study after verbal and written

consent. Average age was 64.8 ± 12.6 years. Operation procedures included $n = 29$ operations after knee arthroplasty (19 exchange, 4 removal and 6 re-implantation), $n = 37$ operations after hip arthroplasty (25 exchange, 5 removal, 7 re-implantation) and $n = 4$ spinal fusion operations.

3.2. Transfusion and administration of coagulation factor concentrates

Transfusion of RBC was greatest intraoperatively and decreased consecutively in the postoperative period. Intraoperatively, 43 units of RBC were transfused ($n = 43$ RBC). In the postoperative phase (V1–V3) transfusion requirement continued to decrease (V1 = 26 RBC, V2 = 11 RBC, V3 = 4 RBC).

The number of patients requiring transfusion also decreased during this process (Intraoperatively $n = 14$, V1 $n = 13$, V2 $n = 7$, V3 $n = 3$).

7 patients received > 3 RBC with $n = 46$ units out of 84 units in total (54.8%).

Transfusion of FFP was low. 10 units were administered during the operation and further 5 units until V1.

Administration of coagulation factor concentrates was highest during the surgical procedure. 23 g fibrinogen concentrate were administered in 9 patients (average 2.6 g per dosing) and 1 patient received 2 g until V1.

3.3. Group assignment

$N = 23$ patients received allogeneic blood products, while $n = 47$ patients did not. Accordingly, they were assigned to the transfused group (TG) and the non-transfused group (control group, CG), respectively.

3.4. Classical laboratory results

Results of classical laboratory tests are displayed in Table 1 and Fig. 1.

3.4.1. Haemoglobin level (Hb)

Hb levels were significantly reduced at POST as compared to PRE (PRE: 10.9 vs POST: 10.0 g/dl, $p = 0.036$). With respect to transfusions Hb values were lower in TG at PRE (10.1 vs. 11.4 g/, $p = 0.0004$) and POST (8.7 vs. 10.7 g/dl, $p = 0.0004$). In the further time course, no significant differences between groups were found.

Table 1

Tabular overall results of classical laboratory tests. Significant changes ($p < 0.05$) to the previous time point are marked bold. Note, that for context reasons platelet count will be listed together with platelet function.

Hemoglobin (g/dl)	PRE	POST	V1	V2	V3	p (ANOVA)
MW	10,9	10,0	9,3	8,6	8,5	$< 0,0001$
SD	1,7	3,0	2,4	1,3	1,2	
Leukocytes ($\cdot 10^9 \cdot L^{-1}$)						
Mean	5,6	10,2	9,6	8,5	7,7	$< 0,0001$
SD	2,3	5,8	3,6	3,3	3,0	
Fibrinogen (mg/dl)						
Mean	291,8	239,0	289,7	424,7	514,8	$< 0,0001$
SD	96,2	89,8	75,6	109,0	131,5	
Quick (%)						
Mean	101,8	91,6	95,7	101,6	109,0	$< 0,0001$
SD	10,5	17,2	11,3	13,1	15,1	
aPTT (sec)						
Mean	29,8	29,4	28,5	27,8	28,5	$< 0,0001$
SD	3,1	4,2	3,0	2,3	2,7	
TT (sec)						
Mean	15,5	16,5	15,5	14,3	14,3	$< 0,0001$
SD	1,3	1,5	1,5	1,2	1,5

Fig. 1. Results of classical laboratory tests with respect to perioperative transfusions. Significant differences between groups ($p < 0.05$) are marked with a *. Note, that for context reasons, platelet count will be listed together with platelet function.

3.4.2. Leukocytes

Leukocytes were significantly higher increased in TG as compared to CG at POST (13.3 vs $10.9 \times 10^9 \text{ L}^{-1}$; $p < 0.0001$). The further time course did not show differences between groups.

3.4.3. Classical coagulation tests

While the activated partial thrombin time (aPTT) did not show any significant differences throughout the time course between groups there was a significant lower Quick-value at POST (83.2 vs 96.0% ;

$p = 0.0009$) and a significant longer thrombin time (TT) at POST and V1 (POST: 17.7 vs 15.9s ; $p < 0.0001$; V1: 16.6 vs 15.0s ; $p < 0.0001$).

3.4.4. Fibrinogen level

Fibrinogen level in classical laboratory analysis did not show statistically significant differences between groups in PRE ($p = 0.825$). In the further course, however, groups can be discriminated significantly from each other. Fibrinogen levels in TG were significantly lower at all times: POST $p = 0.009$; V1 $p < 0.001$; V2 $p = 0.003$; V3 $p = 0.014$.

Table 2

Tabular overall ROTEM results. Significant changes ($p < 0.05$) to the previous time point are marked bold.

CT (s)	PRE	POST	V1	V2	V3	p (ANOVA)
Mean	66,2	65,8	65,7	63,5	63,6	$< 0,0001$
SD	9,5	8,3	10,7	10,1	9,2	
A10 (mm)						
Mean	61,6	59,2	61,2	63,9	66,2	$< 0,0001$
SD	6,4	8,0	6,4	5,6	6,2	
FIBTEM (mm)						
Mean	19,6	16,1	19,5	23,6	27,2	$< 0,0001$
SD	9,0	6,3	5,7	5,4	6,6	

In the postoperative period, there is a comparable increase, without equalizing between groups remaining lower over time in TG at any time. However, correlation between groups was very high ($r = 0.99$).

3.5. Results of rotational thromboelastometry (ROTEM)

ROTEM results are displayed in Table 2 and Fig. 2.

3.5.1. Clotting time - CT

On average, CT was within normal range (up to 80s, Fig. 1) at all time points. There were no statistically significant differences between time points. However, in subgroup TG CT was significantly longer at time point PRE ($p = 0.046$). All time points postoperatively showed no further differences.

3.5.2. Clot firmness after 10 min – A10

Both groups showed an almost identical PRE A10 ($p = 0.857$). In the course, however, TG had a reduced A10 at POST ($p = 0.049$) and V2 ($p = 0.036$) while at V1 and at V3 the recorded values tended to be lower, without reaching significant differences (V1: $p = 0.12$; V3: $p = 0.12$).

3.5.3. Fibrin polymerization after 10 min – FIBTEM

FIBTEM results are displayed in Fig. 2. PRE values in TG group are higher, without significant differences ($p = 0.26$). In contrast, POST FIBTEM value is lower in the transfusion group - but again without statistical relevance ($p = 0.52$). However, considering the decrease in fibrin clot strength, clot strength in TG decreased by 6.7 ± 8.6 mm, whereas in the non-transfusion group, a decrease of only 1.8 ± 2.4 mm was detectable. This difference was statistically significant with a $p = 0.011$.

3.6. Platelet count and aggregability

Platelet related results are displayed in Table 3 and Fig. 2.

3.6.1. Platelet count and aggregability

With regard to platelet count (Fig. 2, panel D) and platelet function (Fig. 2, panel E–G), no statistical differences can be identified between groups ($p = 0.0938$). However, overall aggregability after activation by arachidonic acid (ASPI) was significantly decreased in the postoperative phase with a minimum at POST ($p < 0.0001$). In contrast, aggregation after stimulation by ADP ($p = 0.0418$) and TRAP (thrombin; $p < 0.0001$) was increased at POST, while it was at PRE levels in the further time course (V1–3).

4. Discussion

In the perioperative period in major non-emergency orthopaedic surgery, the coagulation system is affected with respect to both, the plasmatic coagulation system as well as platelet function. While bleeding mostly occurred during surgery, our study shows that patients

that needed transfusion had a significant longer CT before the operation, even it was within the upper normal range (< 80 s). This confirms findings of previously published studies indicating that a prolonged CT correlates with a higher risk of transfusion necessity.¹⁰ On the other hand, PRE findings in standard coagulation tests did not show differences between groups consolidating findings of low prediction possibilities of these tests as stated before elsewhere.¹⁵ However, at POST findings in extrinsically activated standard parameters (PT and Quick) were significantly affected in TG while intrinsically activated aPTT did not show differences between groups.

Point of care systems, such as thrombelastography or -metry, are advocated to exceed standard tests.^{10,16} Consumptive and dilutional coagulopathy are initially characterized by fibrinogen value derangements.¹⁶ Fibrin polymerization is directly impaired by decreasing fibrinogen levels and moreover by interaction with artificial colloids like hydroxyethyl starch preparations.¹⁶ In our cohort, neither fibrinogen levels nor FIBTEM values showed differences between groups before the operation (at PRE). This, however, indicates that in these non-emergency patients, initial fibrinogen levels did not play a crucial role for transfusion in first line. On the other side fibrinogen levels were lower in TG at POST and the decrease of FIBTEM values were higher in TG as well - indicating that fibrinogen is significantly affected during operation most likely due to dilutional effects as described above.

Postoperative fibrinogen levels and polymerization markers (FIBTEM) were reduced in TG, most likely due to dilutional effects. In face of acute blood loss, compensation with infusion solutions and blood products induces dilution of plasma coagulation factors.¹⁶ Considering substitution of blood loss by blood components (mostly RBC) and coagulation factors (mostly fibrinogen concentrate) during the operation, it is of interest that TG fibrinogen levels and FIBTEM values were below CG. Considering fibrinogen substitution was performed in TG but not in CG, this indicates that substitution did not lead to elevated fibrinogen levels with a potential of an increased risk for thromboembolic complications. However, at V1 in both groups levels were comparable to PREOP while in the further time course results were even higher than PREOP - most likely due to induction of the acute phase.

With view on coagulation therapy there is paradigm shift in recent literature.¹⁷ While therapy of coagulopathy was primarily based on fresh frozen plasma for long times recent recommendations and guidelines suggest goal directed coagulation factor application and include first line interventions with such concentrates even without knowledge of laboratory results.^{18,19} In our cohort, this is mirrored by the low rate of FFP transfusion in relation to used RBC and the intraoperative use of fibrinogen concentrates instead.

However, since our study is of observational nature, there still is a need to evaluate a goal-directed therapy in this population. In other clinical settings, such treatment led to reduced transfusion rates.^{7,8,20}

Even with starting haemoglobin levels above a potential transfusion trigger, our data show that TG started with significant lower Hb levels into the operation. Correlation of low Hb levels and transfusion necessity is addressed in modern patient blood management (PBM), which aims to normalize Hb levels before elective surgery.²¹

However, in our cohort average, Hb in some TG patients was below the required minimum preoperative Hb level as proposed by PBM. $N = 4$ (17%) patients had a Hb below 8 g/L while $n = 11$ (48%) were below 10 g/L. Since our cohort includes surgical procedures, needed to be performed within days rather than within weeks or even months, a normalization of Hb levels before the operation was not possible in all cases. However, in this context, a preoperative normalization seems very reasonable and necessary whenever possible and a postponement of elective surgery should be considered as option until the patient is optimally prepared and discussed individually with the patient and the medical team. Any preventable RBC transfusion during operation should be avoided, and a reasonable preoperative preparation should be achieved.

Fig. 2. ROTEM (panels A-C) and platelet related results (panels D-G) with respect to perioperative transfusions. Significant differences between groups ($p < 0.05$) are marked with a *. Note, that platelet related results did not show significant differences between groups throughout the study.

Table 3

Tabular overall platelet related results. Significant changes ($p < 0.05$) to the previous time point are marked bold.

Platelet Count ($\times 10^9 \text{L}^{-1}$)	PRE	POST	V1	V2	V3	p (ANOVA)
Mean	231,1	218,8	195,7	178,9	188,4	$< 0,0001$
SD	72,0	77,3	70,6	56,7	62,5	
TRAP (units)						
Mean	117,7	145,8	126,8	111,8	116,5	$< 0,0001$
SD	23,0	35,9	34,3	34,3	34,3	
ASPI (units)						
Mean	78,7	47,5	59,0	57,3	59,8	$< 0,0001$
SD	31,9	39,0	38,6	36,8	39,0	
ADP (units)						
Mean	74,6	91,7	83,7	79,8	84,0	$< 0,0001$
SD	26,1	33,2	27,8	25,6	28,4	

In this context, the effect of transfusion on leukocyte levels is of great interest. Leukocytes levels in TG were significantly increased but not in CG at POST indicating an immune response to performed transfusions. However, even considering the known effects of transfusion on the immune system and potential infections associated to transfusions²² recent meta-analysis studies in different clinical settings including orthopaedic surgery did not find differences in outcome between a restrictive and a liberal transfusion regime²³ but state that there is more evidence on long-term outcome data after transfusion needed and transfusion triggers remain a matter of discussion in literature.²⁴ However, taking into account that possible side effects or even human factor associated mistakes in transfusion lead to severe health issues²⁵ indication for transfusions should be made with appropriate care.

A previously published study by Oberweis and coworkers showed in orthopaedic patients during surgery a decrease in platelet aggregability with and without stimulation of arachidonic acid.¹² We were able to confirm these findings, that platelet function in ASPI was lower at POST. However, when considering other pathways, that have not been evaluated by Oberweis, naming TRAP and ADP, platelet aggregability was elevated at POST which stands in complete contrast to the Oberweis findings. In the discussion section, they state that interference with aspirin or other non-steroid antiphlogistic drugs (NSAID) could be responsible for their findings. Effects of NSAID medication on the arachidonic pathway as stated by Oberweis seem reasonable. While in our setting during surgery pain therapy was performed by morphine agonist (Fentanyl or Remifentanyl) medication for postoperative pain care was given before end of surgery – Paracetamol, Metamizole, or Ibuprofen which are cyclooxygenase inhibitors and can contribute to the observed effects in ASPI. On the other hand, the exact mechanism for the increase of aggregability in TRAP and ADP can only be a matter of speculation and needs further research, especially when considering that thrombin (as used in TRAP) is the most potent platelet activator and works irrespectively of a blockade of other pathways. However, a possible contra regulation of other induction pathways as reaction to an arachidonic blockade seems at least conceivable. Since there was no difference between groups in platelet function and platelet count, thrombocytes seem to play a less important role during operation in terms of transfusion. However, a possible connection to postoperative thromboembolic events could be possible and should be addressed in further studies. Furthermore, since in the clinical setting, mostly platelet count rather than platelet function is analyzed it seems reasonable that aggregability as a parameter of platelet function should be considered more often.

Our study has a few limitations. The study was designed as prospective observational study. We do not know if changes in platelet activity transfer into risks of thromboembolic or bleeding events due to insufficient power according to the sample size in our study. Furthermore, even with tests that are performed in whole blood instead of plasma only, the complex coagulation system can be displayed in

parts only. Clinical decisions should be taken with appropriate care. Further research should analyze larger cohorts to give useful information about a possible connection of elevated platelet function and postoperative complications and in second-line should address interventions to reduce risks.

Due to the observational character of our study, we are not able to make out effects of POC monitoring as compared to standard coagulation monitoring for treatment guiding. In other clinical settings, POC usage has been shown to be advantageous,^{7,8,20} and further research should address this question in major non-emergency orthopaedic surgery.

One issue in our study is the observed connection of low preoperative Hb and transfusion. In our cohort, we were not able to establish accurate preoperative Hb levels in all cases. However, whenever possible, a necessary reaction to preoperative existing low Hb levels should be addressed as stated in modern PBM concepts.

CRedit author statement

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Declaration of competing interest

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