Thrombosis markers in hip versus knee arthroplasty: a pilot study

Olav Reikeras, Torkil Clementsen
Department of Orthopaedics, Rikshospitalet University Clinic, University of Oslo, Norway

ABSTRACT

Purpose. To compare the thrombosis markers for thrombosis and fibrinolysis in patients undergoing hip versus knee arthroplasty.

Methods. Seven women aged 38 to 61 years who underwent total hip arthroplasty (THA) and 7 women aged 57 to 67 years who underwent total knee arthroplasty (TKA) were studied. Thromboprophylaxis was given before and after surgery. In patients undergoing TKA, an automatic pneumatic tourniquet was used. Blood samples were drawn (1) before surgery (control value), (2) at wound closure (immediately before release of the tourniquet in TKA), and (3) 4 hours after surgery. Thrombosis markers (prothrombin fragment 1.2 [F1.2], plasmin/α2-antiplasmin complex [PAP], and D-dimer) of the 2 groups were compared.

Results. The F1.2 level increased significantly at wound closure and remained elevated 4 hours after surgery in the THA group, whereas it was unchanged at wound closure but increased significantly 4 hours after surgery in the TKA group. The PAP level was constant peri- and post-operatively in the THA group, whereas it increased significantly 4 hours after surgery in the TKA group. The D-dimer level increased significantly at wound closure and 4 hours after surgery in the THA group, whereas it was unchanged at wound closure but increased significantly 4 hours after surgery in the TKA group.

Conclusion. Systemic thrombin generation starts perioperatively in THA and after tourniquet deflation in TKA, indicating that wound blood must reach the systemic circulation to activate the relevant mediators.

Key words: arthroplasty, replacement, hip; arthroplasty, replacement, knee; fibrinolysis; venous thrombosis

INTRODUCTION

Venous thrombosis is common in high-risk patients undergoing hip or knee arthroplasty in the absence of thromboprophylaxis.1–4 However, pre- or post-operative prophylactic anticoagulant therapy increases the risk of postoperative bleeding, although evidence suggests that bleeding is not significantly increased.3 In total hip arthroplasty (THA), deep vein thrombosis originates perioperatively and thus preoperative prophylaxis
may optimise antithrombotic effects. In total knee arthroplasty (TKA), a tourniquet is usually used so that blood flow of the operated limb is isolated from the rest of the body. We hypothesised that systemic thrombin generation starts during surgery in THA, and after deflation of the tourniquet in TKA. This may support postoperative thromboprophylaxis for TKA. We therefore compared thrombosis markers for thrombosis and fibrinolysis in patients undergoing THA versus TKA.

MATERIALS AND METHODS

Seven women aged 38 to 61 years who underwent THA and 7 women aged 57 to 67 years who underwent TKA were studied. In all patients, the diagnosis was osteoarthritis; their blood loss ranged from 300 to 1000 ml, and autotransfusion of drained wound blood ranged from 200 to 300 ml. In patients undergoing TKA, an elastic band was applied to exsanguinate the extremity of blood, followed by an automatic pneumatic tourniquet with a pressure of 250 to 300 mm Hg. The median ischaemia time was 100 (range, 78–125) minutes. Anaesthesia was standardised with spinal/epidural injections at the lumbar level with bupivacaine 5 mg/ml preoperatively, and bupivacaine 2.5 mg/ml combined with fentanyl 0.05 mg/ml postoperatively. Thromboprophylaxis was given as subcutaneous injections of low-molecular heparin 5000 IU the evening before surgery and thereafter daily. Prophylactic antibiotic was given as intravenous injections of cefalotin 2 g 3 times for one day.

Blood samples were drawn (1) before surgery (control value), (2) at wound closure (immediately before release of the tourniquet in TKA), and (3) 4 hours after surgery. Plasma was separated by centrifugation at 2500 g for 20 minutes at 18ºC and stored at -80ºC until assayed.

Thrombosis markers of the 2 groups were compared. Prothrombin fragment 1.2 (F1.2) was measured in citrated plasma by enzyme-linked immunosorbent assay (ELISA) using a commercial kit (Enzygnost F1+2 micro; Dade Behring, Marburg, Germany). Plasmin/α2-antiplasmin complex (PAP) was measured in citrated plasma by ELISA using a commercial kit (Enzygnost PAP micro; Dade Behring, Marburg, Germany). D-dimer was measured in citrated plasma using a commercial kit (Sta-Liatest D-Di; Diagnostica Stago, Asnieres-sur-Seine, France).

Data were presented as median with 25th and 75th percentiles. Time dependent changes were analysed by a non-parametric test for related samples (Friedman). When significant differences were indicated, the Wilcoxon signed rank test for paired samples (2-sided) was used. Significance of difference between the 2 groups was tested with the Wilcoxon rank sum test for unpaired samples. A p value of <0.05 was considered statistically significant.

RESULTS

The F1.2 level increased significantly at wound closure and remained elevated 4 hours after surgery in the THA group, whereas it was unchanged at wound closure but increased significantly 4 hours after surgery in the TKA group (Table 1). The PAP level was constant peri- and post-operatively in the THA group, whereas it increased significantly 4 hours after surgery in the TKA group (Table 2). The D-dimer level increased significantly at wound closure and 4 hours after surgery in the THA group, whereas it was unchanged at wound closure but increased significantly 4 hours after surgery in the TKA group (Table 3).

DISCUSSION

All these findings suggested that systemic thrombin

<table>
<thead>
<tr>
<th>Blood sample</th>
<th>Median (interquartile range) F1.2 (pmol • mL⁻¹)</th>
<th>p Value (Wilcoxon rank sum test)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hip arthroplasty</td>
<td>Knee arthroplasty</td>
</tr>
<tr>
<td>Before surgery (control)</td>
<td>210 (146–231)</td>
<td>234 (158–365)</td>
</tr>
<tr>
<td>At wound closure or immediately before release of the tourniquet</td>
<td>627 (505–718)*</td>
<td>291 (139–507)</td>
</tr>
<tr>
<td>At 4 hours after surgery</td>
<td>565 (494–1119)*</td>
<td>419 (208–808)*</td>
</tr>
<tr>
<td>p value (Friedman)</td>
<td>0.005</td>
<td>0.001</td>
</tr>
</tbody>
</table>

* p=0.018 (in relation to the control)  
* p=0.05 (in relation to the control)
generation starts perioperatively in THA and after tourniquet deflation in TKA, indicating that wound blood must reach the systemic circulation to activate the relevant mediators.

There is no known side effect caused by autotransfusion of drained wound blood on thrombosis markers. Moreover, in our study, as autotransfusion was started after surgery, intravascular thrombin formation originated during surgery in THA and after tourniquet release in TKA was not influenced by autotransfusion.

The thrombosis markers of F1.2, PAP, and D-dimer are useful for the detection of hypercoagulable states characterised by the risk of thrombosis. Thrombin formation is a key regulatory step in surgical haemostasis. The short half-life of active thrombin precludes direct measurements. However, by conversion of prothrombin to thrombin, the amino terminal of prothrombin is cleaved to generate the inactive F1.2 which is a sensitive marker of prothrombin activation and thrombin generation.

Secondary to thrombin generation, fibrinolysis is activated by plasminogen activator. Plasmin acts on cross-linked fibrin to generate D-dimers, and through its activation, plasmin binds to α2-antiplasmin inhibitor to form the PAP complexes. D-dimer and PAP are indicators of plasmin activity. Fibrinolytic activity is enhanced intra-operatively and shuts down after surgery, owing to a temporarily increase in t-PA inhibitor levels after surgery. In our study, there was no significant increase in PAP or D-dimer before tourniquet release in TKA. This suggests that there was no systemic activation of the clotting cascade during TKA under tourniquet ischaemia.

Changes in thrombosis markers during high-risk surgery are difficult to translate into a recommendation of timing for thromboprophylaxis. Blood clotting involves a multitude of proteins that act in concert in response to vascular injury for the generation of fibrin clotting. Fibrin plug generation is required to arrest excessive bleeding, but unregulated clotting results in the occlusion of the blood vessels and thrombosis. Thus, maintaining the delicate balance between the procoagulant and anticoagulant mechanisms is of importance. Venous thrombosis usually arises in one of the large deep veins of the lower limb and is associated with significant morbidity and mortality. The magnitude of this complication is difficult to assess because many venous thromboses and pulmonary emboli are clinically silent, unlike superficial venous thrombosis, which causes pain.

The majority of proteins involved in blood

### Table 2

<table>
<thead>
<tr>
<th>Blood sample</th>
<th>Median (interquartile range) PAP (µg • L⁻¹)</th>
<th>p Value (Wilcoxon rank sum test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before surgery (control)</td>
<td>Hip arthroplasty 565 (331–946)</td>
<td>Knee arthroplasty 463 (445–764)</td>
</tr>
<tr>
<td>At wound closure or immediately before release of tourniquet</td>
<td>567 (404–1562)</td>
<td>480 (251–839)</td>
</tr>
<tr>
<td>At 4 hours after surgery</td>
<td>637 (489–1062)</td>
<td>1261 (516–2156)</td>
</tr>
<tr>
<td>p value (Friedman)</td>
<td>0.717</td>
<td>0.013</td>
</tr>
</tbody>
</table>

* p=0.038 (in relation to the control)

### Table 3

<table>
<thead>
<tr>
<th>Blood sample</th>
<th>Median (interquartile range) D-dimer (µg • L⁻¹)</th>
<th>p Value (Wilcoxon rank sum test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before surgery (control)</td>
<td>Hip arthroplasty 0.65 (0.36–1.05)</td>
<td>Knee arthroplasty 0.64 (0.25–2.47)</td>
</tr>
<tr>
<td>At wound closure or immediately before release of tourniquet</td>
<td>1.70 (1.20–3.00)</td>
<td>1.12 (0.37–1.28)</td>
</tr>
<tr>
<td>At 4 hours after surgery</td>
<td>3.76 (2.04–7.08)</td>
<td>5.95 (4.52–8.42)</td>
</tr>
<tr>
<td>p value (Friedman)</td>
<td>0.003</td>
<td>0.039</td>
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* p=0.018 (in relation to the control)
† p=0.046 (in relation to the control)
coagulation circulate as inactive zymogens that require proteolytic activation in order to function. There are 3 contributing factors in the pathogenesis of thrombosis: vessel wall damage, blood flow changes, and alterations in the blood. These factors favour clot formation by disrupting the balance of the opposing coagulative and fibrinolytic systems. At least 2 of these factors in combination are required in the development of a venous thrombi. In a rabbit model, venous stasis alone was insufficient to produce a thrombus. When venous stasis was combined with vessel wall damage, a thrombus may form. Injury to the vessel wall may activate the haemostasis system. Activation products of clotting and fibrinolysis lead to further injury and permeability of the vessel wall. Venous thrombi are composed of fibrin and erythrocytes with variable amounts of interwoven platelets and leukocytes, and increased aggregation of platelets and leucocytes contributes to hypercoagulability. Decreased blood flow secondary to lack of muscle pump action of the limbs also contributes to the pathogenesis of thrombosis. Especially in THA, when the hip and leg is flexed and rotated, the femoral vein is twisted and kinked, and its occlusion may trigger thrombosis intra-operatively. The greatest activation of the clotting cascade in THA is during insertion of the femoral component. This is more pronounced after a cemented rather than a non-cemented stem, because tissue thromboplastin from the bone and bone marrow is forced into the circulation when a cemented stem is impacted. When cement is not used, the less release of tissue thromboplastin ensues. In our study, an uncemented femoral stem was used. If a cemented femoral stem is used, it might be appropriate to give intra-operative heparin at the time of femoral cementing, but in general this has not been accepted.

Under tourniquet application, the operated limb is cut off from the general activation of coagulation. There may be local activation, but to a minor degree as blood is exsanguinated from the extremity before tourniquet application. Using a tourniquet may damage endothelial vessels and create venous stasis of the operated limb, and this may increase coagulation activity. From the viewpoint of coagulation and fibrinolysis, a tourniquet creates a non-physiological state promoting deep vein thrombosis. An increased incidence of deep venous thrombosis has been reported in TKA patients using a tourniquet, and thrombi usually occur in the calf. Although vein occlusion may be a component in the genesis of thrombosis, our results do not suggest that this activity by itself is sufficient to activate systemic thrombogenic and fibrinolytic activities. These activities seem to be triggered when local mediators from the injured limb are released and reach the systemic circulation or vice versa. Nonetheless, divergent observations have also been reported, which may be partly due to differences in study design and approach. For example, the levels of blood coagulation-fibrinolysis markers (PAP and D-dimer) are significantly higher in the group with a tourniquet than without it, and fibrinolytic activity increases in the systemic circulation following the release of tourniquet.

The interval between surgery and first administration of antithrombotic treatment varies between different orthopaedic operations. Further studies should be performed to confirm our results.

REFERENCES


