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Abstract

The rate of bleeding complications after major orthopedic surgery approximates 2%. It is unclear whether a systematic switch of routine thromboprophylaxis has an impact on the rate of postoperative bleeding complications. We analyzed prospectively recorded postoperative bleeding complications and symptomatic venous thromboembolic events in 8,176 consecutive orthopedic patients at the Schulthess Clinic Zurich during a systematic switch of thromboprophylaxis from nadroparin to enoxaparin in the year 2004. Overall, 3,893 patients received nadroparin in the first nine-month observation period before the switch and 4,283 patients received enoxaparin in the second nine-month observation period after the switch. Overall, 96 (2.5%) patients in the first period and 70 (1.6%) patients in the second period suffered a postoperative bleeding complication requiring surgical revision, puncture, or transfusion (p < 0.01). Five objectively confirmed symptomatic venous thromboembolic events during hospitalization in the first period and three events in the second period were recorded. In conclusion, the switch of thromboprophylaxis in a large orthopedic clinic did not cause an increase of postoperative bleeding complications and therefore was accompanied by high patient safety.
Blood Coagulation, Fibrinolysis and Cellular Haemostasis

Bleeding complications after systematic switch of routine thromboprophylaxis for major orthopaedic surgery

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Summary

The rate of bleeding complications after major orthopedic surgery approximates 2%. It is unclear whether a systematic switch of routine thromboprophylaxis has an impact on the rate of postoperative bleeding complications. We analyzed prospectively recorded postoperative bleeding complications and symptomatic venous thromboembolic events in 8,176 consecutive orthopedic patients at the Schulthess Clinic Zurich during a systematic switch of thromboprophylaxis from nadroparin to enoxaparin in the year 2004. Overall, 3,893 patients received nadroparin in the first nine-month observation period before the switch and 4,283 patients received enoxaparin in the second nine-month observation period after the switch. Overall, 96 (2.5%) patients in the first period and 70 (1.6%) patients in the second period suffered a postoperative bleeding complication requiring surgical revision, puncture, or transfusion (p<0.01). Five objectively confirmed symptomatic venous thromboembolic events during hospitalization in the first period and three events in the second period were recorded. In conclusion, the switch of thromboprophylaxis in a large orthopedic clinic did not cause an increase of postoperative bleeding complications and therefore was accompanied by high patient safety.

Keywords

Thromboprophylaxis, bleeding complications, venous thromboembolism, orthopedic surgery

Introduction

The efficacy and safety of systematic thromboprophylaxis after major orthopedic surgery has been extensively studied within the last 25 years. The incidence of objectively confirmed deep vein thrombosis (DVT) after major orthopedic surgery without prophylaxis ranges between 40 and 60% (1–3). Up to one third of these events are symptomatic proximal DVT with an increased risk of acute pulmonary embolism (PE) (4–6). Randomized controlled trials confirmed that thromboprophylaxis with low-molecular-weight heparins (LMWH) substantially reduces the rate of DVT and PE (7–9). The rate of bleeding complications after major orthopedic surgery with thromboprophylaxis approximates 2% (10). However, because of the different pharmacodynamic properties, LMWH are not interchangeable for the various indications. Unfortunately, no head-to-head comparisons of the various LMWH for efficacy and safety after major orthopedic surgery are available.

Many health-care professionals have direct contact with thromboprophylaxis in daily clinical practice. A systematic change in the routine use of thromboprophylaxis may potentially be associated with an increased risk of thrombotic and bleeding events. In particular, it remains unclear whether a systematic switch of thromboprophylaxis impacts on bleeding complications after major orthopedic surgery.

Methods

Patient population

In 2004, the Schulthess Clinic Zurich, Switzerland, performed a switch of systematic thromboprophylaxis from nadroparin to enoxaparin for major orthopaedic surgery. All patients with major orthopaedic surgery were prospectively evaluated for the occurrence of postoperative bleeding complications and symptomatic venous thromboembolic events during the hospital stay. Data acquisition and entry into the critical incidence reporting system (CIRS) data base using information from patient charts was performed by International Classification of Diseases (ICD) coding officers.

Nadroparin (Fraxiparine®) was routinely used until April 30, 2004 and the switch date was May 1, 2004 when enoxaparin...
(Clexane®) was introduced for routine thromboprophylaxis. In the first nine-month observation period prior to the switch (June 1, 2003 to February 28, 2004), 3,893 patients were treated with nadroparin. In the second nine-month observation period after the switch (June 1, 2004 to February 28, 2005), 4,283 patients were treated with enoxaparin. The dosing regimens of both drugs are shown in Table 1. Nadroparin was administered in a weight-adjusted dose, and enoxaparin was administered in a fixed dose of 40 mg per day. The enoxaparin dose was reduced to 20 mg per day in patients with a body weight of less than 50 kg, in patients with severe renal dysfunction (creatinin-clearance < 30 ml/min), and in patients who underwent surgical procedures that increased the risk of bleeding complications according to the orthopaedic surgeon in charge. The weight-adjusted dose of nadroparin was reduced during the first three postoperative days. The timing of the first postoperative dose of thromboprophylaxis was not earlier than eight hours after surgery in the second observation period. Patients without thromboprophylaxis or those with thromboprophylaxis medications other than nadroparin or enoxaparin were excluded from the analysis. There were no differences in surgical techniques or transfusion regulations between the two observation periods.

Clinical endpoints
We analyzed in-hospital events of postoperative bleeding complications and symptomatic venous thromboembolism using the CIRS database of the Schulthess Clinic Zurich. The following two predefined bleeding complications were captured: i) local haematoma requiring surgical revision or puncture or anemia necessitating transfusion of at least one unit of packed red blood cells; ii) local haematomas not requiring revision were not included. Symptomatic thromboembolic events including DVT and PE were evaluated if the diagnosis was objectively confirmed by an imaging test.

Statistical analysis
Sample size calculation was based on the following assumptions: an overall rate of bleeding complications of 2% (10); an increase or decrease in bleeding complications of 1% within the two observation periods was defined as non-inferiority margin. With an alpha of 5% and a power of 90%, the sample size was then calculated at 3,358 patients prior to the switch date of thromboprophylaxis and 3,358 patients after the switch date. The number of orthopaedic surgical procedures and the number of bleeding complications in the two observation periods were compared with the Fisher’s exact test, respectively. The level of significance was adjusted using Bonferroni’s correction for multiple comparisons (11). The effect of the enoxaparin dose on the rate of bleeding complications was analyzed using the chi2-test. All analyses were performed with the statistical software SPSS V15.01. The study was approved by the local ethics committee.

Results
In both observation periods, the average mean age was 56 years. Knee surgery, shoulder surgery, and hip surgery were performed
similarly often in both observation periods (Table 2). However, the number of patients receiving thromboprophylaxis after spinal surgery and upper extremity operations was lower in the second observation period. The mean length of hospitalization was 8.3 ± 0.2 days in the first observation period and 8.3 ± 0.1 days in the second observation period.

Overall, there were 166 (2%) postoperative bleeding complications in the two observation periods during the hospital stay: 96 (2.5%) patients in the first and 70 (1.6%) patients in the second observation period suffered a bleeding complication (p<0.01, Fig. 1). The number of bleeding complications according to the type of surgery is shown in Table 3. In the second observation period, there appeared to be fewer bleeding complications after hip and knee surgery. The numbers of bleeding complications according to drug doses are summarized in Table 4. There was no difference in bleeding complications for patients having received the 20-mg or the 40-mg enoxaparin dose. In patients with postoperative bleeding complications from the first observation period, the mean time between the end of surgery and the first postoperative thromboprophylaxis dose was four hours, and it was eight hours in patients with bleeding complications from the second observation period.

Four in-hospital events of symptomatic DVT and one event of acute PE were diagnosed in the first observation period; three events of symptomatic DVT and no events of PE were detected in the second observation period.

Discussion

Our analysis of 8,176 patients confirmed that the switch of routine thromboprophylaxis for major orthopaedic surgery at the Schulthess Clinic Zurich did not cause an increase in bleeding complications and therefore was associated with high patient safety.

The overall bleeding rate of 2% after major orthopaedic surgery is comparable with the clinical outcome of large randomized trials (10). The rate of symptomatic DVT and PE during the hospitalization was even lower than expected, confirming the high efficacy of thromboprophylaxis with LMWH in daily clinical practice.

As expected, bleeding complications occurred more often after hip (4.2%) or knee arthroplasty (5.1%) than with the other orthopaedic surgery types (Table 3). Although the number of patients with thromboprophylaxis after spine and upper extremity operations was lower in the second observation period, it probably did not affect the validity of the results because the rates of bleeding complications after these procedures were similar in both observation periods.

The present analysis has several limitations. The study was conducted in only one center, thus, the results may not necessarily be applicable to other institutions. Although data were captured systematically and prospectively, the analysis was retrospective, and no adjudication of the bleeding complications and thromboembolic events was possible. We were not able to directly compare the results of our study with other clinical practices because we did not collect data about patient comorbidities.

According to international consensus guidelines, a predefined time interval of eight hours was introduced for the first postoperative thromboprophylaxis dose in the second observation period (12). However, the timing of the first postoperative dose of thromboprophylaxis was not pre-specified for the first observation period, and we observed a mean time of four hours after surgery in patients who suffered a bleeding complication in the first observation period. The latter point could in part explain the higher bleeding rate seen in the first observation period. Since the time interval between the end of surgery and the first postoperative dose in patients without a bleeding complication from the first observation period was not available, we were not able to further investigate the effect of the timing of the first dose on the occurrence of bleeding complications. In addition, the enoxaparin dose was reduced to 20 mg per day in 16.3% of patients, including those patients who underwent surgical procedures with increased risk of bleeding. However, there was no difference in bleeding complications between the patients who received the 20-mg and the 40-mg enoxaparin dose. No such dosing precautions were recommended during the first observation period for nadroparin, and this could also have contributed to a

<table>
<thead>
<tr>
<th>Substance Operation Bleeding</th>
<th>1. Period</th>
<th>2. Period</th>
<th>1.+2. Period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enoxaparin 40 mg 3587 083.7 61 01.7*</td>
<td>2.0</td>
<td>1.6</td>
<td>2.0</td>
</tr>
<tr>
<td>Enoxaparin 20 mg 0696 016.3 09 01.3*</td>
<td>2.0</td>
<td>1.6</td>
<td>2.0</td>
</tr>
<tr>
<td>Nadroparin 1.0 ml 0142 01.4 2 0.1</td>
<td>2.0</td>
<td>1.6</td>
<td>2.0</td>
</tr>
<tr>
<td>Nadroparin 0.8 ml 0121 029.8 15 1.3</td>
<td>2.0</td>
<td>1.6</td>
<td>2.0</td>
</tr>
<tr>
<td>Nadroparin 0.6 ml 0813 020.9 22 2.7</td>
<td>2.0</td>
<td>1.6</td>
<td>2.0</td>
</tr>
<tr>
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<td>1.6</td>
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</tr>
<tr>
<td>Nadroparin 0.3 ml 1160 029.8 15 1.3</td>
<td>2.0</td>
<td>1.6</td>
<td>2.0</td>
</tr>
<tr>
<td>Nadroparin 0.2 ml 0100 026.3 5 5.0</td>
<td>2.0</td>
<td>1.6</td>
<td>2.0</td>
</tr>
<tr>
<td>Total Nadroparin 3893 100.0 96 2.5</td>
<td>2.0</td>
<td>1.6</td>
<td>2.0</td>
</tr>
</tbody>
</table>

*P-value for dose dependence of the observed bleeding rate: P = 0.438.
higher bleeding rate in the first observation period. It is important to note that not only the drug choice but also other factors may affect the efficacy and safety of thromboprophylaxis. The switch of thromboprophylaxis in the Schulthess Clinic Zurich was accompanied by hospital-specific guidelines and training of the involved health care professionals. These additional factors may have contributed to the low bleeding rate seen in the second observation period. Another limitation is that bleeding complications without puncture or surgical revision but with potential prolongation of the patient rehabilitation were not recorded. This was the subjective perception of the surgeons in charge during the second observation period, which, however, was not reflected by the number of severe bleeding complications.

In the present study, only symptomatic venous thromboembolic events were recorded for the index hospital stay. However, postoperative DVT or PE may occur up to 90 days post surgery, and therefore, we probably have missed several thrombotic events that the patients experienced after discharge and that could reasonably be attributed to their previous orthopaedic surgery (1, 13). This may explain the substantially lower rate of venous thromboembolism in comparison to event rates from randomized controlled trials with longer follow-up. Because of the continuing risk of venous thromboembolism, thromboprophylaxis for major orthopaedic surgery, especially for hip or knee replacement surgery, should be extended beyond the hospital stay up to 35 days post surgery (1). In contrast, postoperative bleeding complications usually occur in the first few days after surgery and therefore were captured completely in our analysis, owing to the systematic and prospective recording of all in-hospital bleeding complications that necessitated intervention or blood transfusion.

In summary, the systematic switch of thromboprophylaxis driven by consensus guidelines and supported by staff training in a large orthopaedic clinic was not associated with an increase in postoperative bleeding complications.

References
