Management of antithrombotic therapy in venous and arterial thromboembolism
Vink, R.

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**Perioperative Interruption of Anticoagulant Treatment in Patients with Atrial Fibrillation**

Roel Vink, MD*; Renée B.A. van den Brink, MD†; Harry R. Büller, MD*; Marcel Levi, MD‡

From the Departments of Vascular Medicine*, Cardiology† and Internal Medicine‡,
Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands.
ABSTRACT

Background: Patients with atrial fibrillation (AF) should receive long-term treatment with vitamin K antagonists (VKA) to prevent thromboembolic complications. In case of surgery the anticoagulant treatment needs to be interrupted, however the optimal strategy for perioperative anticoagulation is unknown.

Objective: To assess the efficacy and safety of temporary institution of low molecular weight heparin (LMWH) to shorten the period of interruption of anticoagulation in patients with AF who have to undergo non-cardiac surgery.

Methods: Patients with AF were randomised to two different strategies of perioperative interruption. Patients assigned to the interruption strategy stopped the VKA 3 days pre-operatively and resumed the VKA 3 days after surgery. Patients assigned to the LMWH-strategy also stopped the VKA 3 days pre-operatively but received a therapeutic dose of LMWH during the entire period of interruption. The last injection was given the evening before the intervention and was resumed 6 to 8 hours post-operatively. Outcome parameters were the incidence of thromboembolism and bleeding complications.

Results: Three patients were randomised to the LMWH strategy and 9 patients to the interruption strategy. One transient ischemic attack occurred in the interruption group. The three patients in the LMWH group all experienced a bleeding complication (1 major and 2 minor bleedings).

Conclusion: These preliminary data show a high incidence of bleeding complications if LMWH is given in therapeutic dosage to narrow the window of interruption of anticoagulant treatment in patients with AF who undergo surgery. On the other hand, thromboembolic events are a matter of concern as well. Better protective strategies for patients with AF in whom anticoagulant treatment needs to be interrupted are required.
INTRODUCTION

Anticoagulant treatment with vitamin K antagonists (VKA) is essential in patients with atrial fibrillation to prevent arterial thromboembolic complications, in particular ischemic strokes\textsuperscript{1}. However, in case of surgery or other invasive interventions, anticoagulant treatment needs to be interrupted to ensure surgical hemostasis and to prevent excessive perioperative bleeding. Interruption of anticoagulant treatment is usually achieved by discontinuation of anticoagulants preoperatively and reinstitution of the therapy postoperatively. However, the safety of this strategy (in terms of the perioperative prevention of arterial thromboembolism) has been poorly documented. Therefore, an alternative strategy may consist of interruption of VKA treatment and temporary anticoagulation by means of heparin, which can be stopped and subsequently re-started few hours pre- and postoperatively, respectively. This latter strategy is often applied in patients with prosthetic heart valves, who are thought to be at higher risk for thromboembolic events\textsuperscript{2}.

However, the actual perioperative risk of thromboembolism and long-term outcome in patients with atrial fibrillation has never been adequately established. Given the fact that a cerebral thromboembolic event in these group of patients may often be fatal or associated with severe neurological deficit, there is a persuasive argument for a more aggressive approach to prophylaxis against thromboembolic events, including the use of both pre-operative and postoperative heparin\textsuperscript{3}. Recently, low molecular weight heparin (LMWH) has emerged as a potential alternative for unfractionated heparin, because it results in stable anticoagulation without the need for monitoring and dose adjustments. We hypothesize that shortening of the perioperative interruption of anticoagulation (by means of the temporary use of LMWH) may be effective in the prevention of perioperative in patient with atrial fibrillation, although part of the beneficial effect may be offset by an increase in bleeding complications. To test this hypothesis we set out for a prospective randomised study in patients with atrial fibrillation who need to undergo non-cardiac surgery comparing perioperative interruption of VKA with perioperative interruption of VKA and temporary institution of LMWH therapy.

METHODS

Patients

The study was performed in two teaching hospitals in The Netherlands, between October 2001 and December 2003. All patients with atrial fibrillation who used VKA and who were planned to undergo elective surgery in the Academic Medical Center (AMC) or the Onze Lieve Vrouwe Gasthuis (OLVG) were eligible for the study. Only surgery requiring
some form of anesthesia was considered. Exclusion criteria were the necessity for VKA due to other diseases (e.g. prosthetic heart valve or recent venous thromboembolism), the inability to obtain informed consent, the inability to be followed-up, contraindications for LMWH (e.g. presence of heparin-induced thrombocytopenia) and hereditary or acquired coagulation defects.

**Design**

The study was a prospective, randomised trial in patients with atrial fibrillation who had to undergo non-cardiac surgery. Patients were randomised to two different strategies of perioperative interruption of anticoagulation. Patients assigned to the interruption strategy were asked to stop the acenocoumarol 3 days preoperatively or their phenprocoumon 7 days preoperatively. One day preoperatively the INR was determined. If the INR was above 1.5 the patient received 10 mg vitamin K orally. Three days after the operation, vitamin K antagonists were resumed. The patients assigned to the LMWH-strategy continued their VKA until two days preoperatively. At one day preoperatively till two days postoperatively, they received 10 mg vitamin K orally. The INR was determined the day before surgery. One day preoperatively subcutaneous LMWH (nadroparin, Fraxiparin®) was started (bodyweight < 50 kg: 3800 IE aXa/2dd, bodyweight 50-70 kg: 5700 IE aXa/2dd, bodyweight > 70 kg: 7600 IE aXa/2dd). The last injection of LMWH was given the evening before the operation. LMWH was resumed 6-8 hrs postoperatively (evening after the operation) and continued until the third postoperative day and when VKA were in the therapeutic range again.

At the start of the study and at 21 days postoperatively, each patient underwent a cerebral CT scan. If clinically indicated, the second CT scan was made earlier. Cerebral infarction was defined as a clearly delineated area of hypodensity with no mass effect or edema in a vascular distribution. Infarcts were classified as either cortical or subcortical. The CT scans were read independently by two radiologists who were unaware of the clinical status and allocated treatment regimen. All infarcts on the postoperative CT-scan that were not seen on the preoperative scan were considered to be new infarcts. Preoperative screening included history and physical examination, ECG, laboratory tests and collecting blood for coagulation tests, echocardiography (in particular atrial and ventricular dimensions, valve disorders, and ventricular function), a short neuropsychological test and CT scan of the brain. Furthermore, hemoglobin and INR was checked on a daily basis up to day 5. For each patient the per- and postoperative transfusion requirements were registered. After discharge patients were followed at 3 months intervals, at which time clinically relevant thromboembolism and bleeding was recorded.
Outcomes
The primary outcome of the study was the composite endpoint of symptomatic cerebral embolism during hospitalisation or at 6-months follow-up and asymptomatic cerebral thromboembolism (as diagnosed by changes in the postoperative CT scan) after 3 weeks. Secondary outcomes were (a) major bleeding during hospitalisation (defined as clinically overt bleeding associated with a fall in Hb > 2 mmol/l, the need for transfusion, or intracerebral, retroperitoneal, or intraarticular bleeding), (b) minor bleeding during hospitalisation (any other clinically overt bleeding), (c) the number of transfusions, (d) any non-cerebral thromboembolic event, (e) all cause mortality (during hospitalisation and follow-up), and (f) duration of hospitalisation.

Statistical analysis
The sample size for the study was based on an estimated incidence of the primary composite outcome event of 10% in the non-heparinized group and a 90% reduction by short-term LMWH administration, resulting in a sample size of 100 patients per treatment strategy ($\alpha$ 0.05, $\beta$ 0.2).

RESULTS

Patients
Twelve patients were enrolled (7 patients in the AMC and 5 patients in the OLVG). Three patients were randomised to the LMWH strategy and 9 patients to the interruption strategy. The mean age at the time of enrolment was 67 years (range 54-82). The patient characteristics, list of procedures, echocardiographic features, perioperative anticoagulation strategies and adverse outcomes are listed in Table I.

Thromboembolic and hemorrhagic complications
One thromboembolic complication occurred in the interruption group. A patient with multiple risk factors for thromboembolism had a transient ischemic attack 4 days after nephrectomy. The VKA had not been resumed at the time of the event. Three patients had a bleeding complication, all of which occurred in the LMWH group. One patient developed a pocket hematoma after replacement of a pacemaker. Nadroparin was administered preoperatively according to the protocol. There was 1300 cc bloodloss in the postoperative period. Surgical re-exploration and transfusion of 5 packed cells was necessary to stop the bleeding. The patient recovered without any sequelae. The second patient reported a local hematoma after replacement of a pacemaker. Despite careful instructions, the patient received two injections of nadroparine 7600 IE with a 5 hours interval, instead of the usual 12 hours interval. The last injection was administered
<table>
<thead>
<tr>
<th>Patient</th>
<th>Age, sex</th>
<th>Type of surgery</th>
<th>Cardiovascular comorbidity</th>
<th>Perioperative strategy</th>
<th>Bleeding / thromboembolism</th>
<th>Other complication</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>65, m</td>
<td>pancreaticoduodenectomy</td>
<td>hypertension</td>
<td>interruption</td>
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<tr>
<td>2</td>
<td>81, f</td>
<td>nephrectomy</td>
<td>TIA, diabetes, CHF, hypertension, MI</td>
<td>interruption</td>
<td>TIA 4 days p.o.</td>
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<tr>
<td>3</td>
<td>74, m</td>
<td>prostatectomy</td>
<td>no</td>
<td>interruption</td>
<td>no</td>
<td>Septic shock, transfer to intensive care unit</td>
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<td>57, m</td>
<td>arthroscopy</td>
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<td>interruption</td>
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<td></td>
</tr>
<tr>
<td>5</td>
<td>68, f</td>
<td>total knee replacement</td>
<td>no</td>
<td>interruption</td>
<td>no</td>
<td></td>
</tr>
<tr>
<td>6</td>
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<td>total hip replacement</td>
<td>no</td>
<td>interruption</td>
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<tr>
<td>7</td>
<td>59, m</td>
<td>inguinal hernia repair</td>
<td>MI, mitral regurgitation hypertension</td>
<td>bridging with LMWH</td>
<td>Drain production 1300cc in first hours; re-exploraration</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>74, m</td>
<td>pacemaker replacement</td>
<td>hypertension</td>
<td>bridging with LMWH</td>
<td>Local hematoma</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>80, m</td>
<td>inguinal hernia repair</td>
<td>history of stroke</td>
<td>bridging with LMWH</td>
<td>Local hematoma</td>
<td></td>
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<td>10</td>
<td>73, m</td>
<td>endovascular repair of aneurysm</td>
<td>no</td>
<td>interruption</td>
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<td></td>
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<tr>
<td>11</td>
<td>76, f</td>
<td>pacemaker replacement</td>
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<td>bridging with LMWH</td>
<td>Local hematoma</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>83, m</td>
<td>circumcision</td>
<td>congestive heart failure</td>
<td>interruption</td>
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<td></td>
</tr>
</tbody>
</table>

LMWH = low molecular weight heparin; TIA = transient ischemic attack; CHF = congestive heart failure; MI = myocardial infarction; m = male; f = female
12 hours prior to the intervention. The estimated bloodloss after surgery was 10 cc. Nadroparin was not re-started after the intervention. The third bleeding complication occurred after an inguinal hernia repair. This patient received two preoperative injections of nadroparine 7600 IE with an 8 hour interval. The last injection was given 10 hours before surgery. The nadroparin was restarted 8 hours after surgery, according to the protocol. A local hematoma at the incision site in the left inguinal region developed 1 day after surgery. The nadroparin was not discontinued and VKA was reinstitituted after 3 days.

Patient recruitment was prematurely stopped, as recommended by the Medical Ethical Committee because of an increased incidence of bleeding complications among participants receiving LMWH as perioperative anticoagulation.

**DISCUSSION**

The main goal of this study was to establish the efficacy and safety of the temporary institution of LMWH therapy, to shorten the period of interruption of anticoagulation in patients with atrial fibrillation during non-cardiac surgery. We hypothesized that perioperative anticoagulation would reduce the incidence of ischemic strokes with only minimal increase in bleeding complications. The high rate of bleeding complications in the LMWH-group led to a preliminary termination of the study. The Medical Ethic Committee advised that the incidence of the adverse events was a sufficient argument to discontinue the trial, because the original hypothesis that LMWH therapy would be beneficial was unlikely.

There was an excess of bleeding complications in the study. This excess could be attributed to 1 major and 2 minor bleeding episodes in 3 consecutive patients assigned to the LMWH strategy. But these three bleeding complications cannot definitively be attributed to the administration of LMWH. Two patients assigned to the LMWH-strategy developed a pocket hematoma after replacement of a pacemaker. However, a randomised trial comparing unfractionated heparin initiation 6 hours or 24 hours after pacemaker implantation showed that the formation of a pocket hematoma is a frequently occurring complication\(^4\). In both groups, approximately 20% of the patients developed this complication. Evacuation was necessary in 4% of these patients. One patient in the LMWH group developed a hematoma 1 day after hernia repair. Hence, this complication was not necessarily due to a failure of the LMWH-strategy since an incidence of 25% of hematomas after open repair of an inguinal hernia has been reported\(^5\).

Several studies showed that LMWH is at least as effective and safe as unfractionated heparin in the treatment and prevention of thromboembolism. The incidence of major bleeding complications in patient treated for venous
thromboembolism using LMWH is only 1.1%. In addition, pharmacokinetic studies have shown that following a therapeutic dose of nadroparin the aXa levels are < 0.2 after 12 hours and < 0.1 after 16 hours. Based on this data, a last dose of nadroparin with an interval of 12 hours before the start of surgery is unlikely to result in bleeding. However, 2 patients with a bleeding complication received 2 injections LMWH within a time interval of 5 hrs and 8 hrs respectively, presumably resulting in higher aXa levels. This might have contributed to the bleeding complication.

The periprocedural use of LMWH has been evaluated by several groups of investigators. Spandorfer and colleagues studied 20 patients receiving chronic anticoagulation for atrial fibrillation, mechanical heart valves and deep vein thrombosis. Enoxaparin at 1 mg/kg every 12 hours was started approximately 36 hours after VKA was stopped. Enoxaparin was stopped 12-18 hours prior to surgery and reinitiated an average of 13 hours after the procedure. Three patients developed postprocedure bleeding complications, all soft tissue bleeding. One patient had a major bleeding at the incision site three days after inguinal hernia repair. This patient started enoxaparin 30 hours after surgery. Two other patients had minor bleeding episodes. Tinmouth et al. studied 24 patients with atrial fibrillation, mechanical heart valves or recent thromboembolic disease who underwent 26 procedures. A therapeutic dose dalteparin (200 IE/kg) was given until two days prior to surgery. The final preoperative dose of dalteparin was given at least 24 hours prior to surgery and recommenced on the morning following surgery. Two patients had a minor bleeding complication after a biopsy and one patient reported having a transient ischemic attack. Kovacs reported on a registry of 216 patients (108 with atrial fibrillation and 108 with prosthetic heart valves) who received dalteparin as perioperative anticoagulation regime. VKA was discontinued five days preoperatively. A dose of 200 IE/kg dalteparin once daily starting 2 days before the procedure. The day prior to the intervention, a dose of 100 IE/kg was given. No dalteparin was given on the day of the procedure. Dalteparin was re instituted the next day or as soon as adequate hemostasis had been achieved. There were 15 major bleeds (6.8%), of which 8 occurred intraoperatively or in the first 2 hours post-surgery before dalteparin was administered. There were a total of 8 (3.7%) thromboembolic events: five were myocardial infarctions and two were cerebral thromboembolic events.

Perioperative management of the anticoagulation in patients with mechanical heart valves is a complex problem as well. Data on the incidence of perioperative thromboembolic and bleeding events are equally scarce. Only a few uncontrolled observational studies addressed the perioperative anticoagulant management for patients with mechanical heart valves requiring non-cardiac surgery and therefore decisions should be made based on quantification of thromboembolic and bleeding risk. The strategy of complete coverage with intravenous heparin during the period
of interruption of the VKA is frequently used in this group of patients. As described above, LMWH as alternative agent the perioperative period in patients with mechanical heart valves is now subject of prospective trials.

In conclusion, these preliminary data show a high incidence of bleeding complications if LMWH is given in therapeutic doses to narrow the window of interruption of anticoagulant treatment in patients with atrial fibrillation who undergo surgery. On the other hand, thromboembolic events are a matter of concern as well. Better protective strategies for patients with atrial fibrillation in whom anticoagulant treatment needs to be interrupted are required.

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REFERENCE LIST

or high risk atrial fibrillation. Presented at the 44th annual meeting of the American Society of Hematology, Philadelphia, 6 Dec 2002
