Safety and preventive effects of rivaroxaban and low-molecular-weight heparin on deep vein thrombosis of lower extremity after total hip arthroplasty

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Deep vein thrombosis (DVT) is a common complication of skeletal surgery, which can cause disability and death in severe cases. Here, we have compared the preventive effects of rivaroxaban and low molecular weight heparin on DVT of lower extremity after total hip arthroplasty and the safety. A total of 310 patients who received total hip arthroplasty from May 2014 to June 2016 were divided into a rivaroxaban group (n=153) and a low molecular weight heparin group (n=157). The rivaroxaban group was orally administered with rivaroxaban (10 mg, qd) 12 h after surgery for 30 consecutive days, and the other group was subcutaneously injected with low molecular weight heparin calcium injection (0.6 mL, ad) for 7 consecutive days. The incidence rate of lower extremity DVT, drainage blood volume, hemoglobin decline, as well as preoperative and postoperative 7-d prothrombin time (PT), activated partial thromboplastin time (APTT), platelet (PLT) count and D-dimer level of the two groups were compared. The two groups had similar incidence rates of lower extremity DVT, drainage blood volumes and extents of hemoglobin decline (P >0.05). There were no significant differences in the preoperative and postoperative 7-d PT, APTT, PLT counts and D-dimer levels between the two groups (P >0.05). Rivaroxaban and low molecular weight heparin show comparable preventive effects on lower extremity DVT after total hip arthroplasty. Results suggest that rivaroxaban is superior than the low molecular weight heparin in terms of convenient use (oral administration), good compliance and absence of dose adjustment.

Keywords: Rivaroxaban, Heparin, Venous thrombosis, Total hip arthroplasty

Deep vein thrombosis (DVT) is a common complication of skeletal surgery, which can cause disability and death in severe cases. The incidence rate of DVT after joint replacement is as high as 45-84%. With the popularization of total hip arthroplasty, postoperative DVT has become a serious issue, with an incidence rate of 40-60%. Low molecular weight heparin calcium which is commonly employed now significantly decreases the incidence rate of DVT after total hip arthroplasty, though with mild adverse reactions. However, its use is limited owing to the need of subcutaneous injection. On the other hand, rivaroxaban is a novel anticoagulant agent that can prevent DVT and pulmonary embolism (PE) in patients receiving hip and knee joint replacements.

In literature, reports on the therapeutic effects of rivaroxaban and low molecular weight heparin on DVT of the lower extremity after total hip arthroplasty are scarce. Hence, here, we compared the preventive effects of rivaroxaban and low molecular weight heparin on lower extremity DVT after total hip arthroplasty and the safety.

Materials and Methods
Baseline clinical data
This study has been approved by the ethics committee of the No. 903 hospital of People's Liberation Army and written informed consent has been obtained from all patients. A total of 310 patients who received total hip arthroplasty in our hospital from May 2014 to June 2016 were divided into a rivaroxaban group (n=153) and a low-molecular-weight heparin group (n=157). The rivaroxaban group consisted of 80 males and 73 females aged 50-75 years old, (58.61±5.72) on average. There were 40 cases of anterior tibial vein thrombosis, 50 cases of posterior tibial vein thrombosis and 63 cases of anterior femoral vein thrombosis. The low-molecular-weight heparin group comprised 83 males and 74 females aged 51-74 years old, with the mean of (58.63±5.46). There were 42 cases of anterior tibial vein thrombosis, 50 cases of posterior tibial vein thrombosis and 63 cases of anterior femoral vein thrombosis. The low-molecular-weight heparin group comprised 83 males and 74 females aged 51-74 years old, with the mean of (58.63±5.46). There were 42 cases of anterior tibial vein thrombosis, 51 cases of posterior tibial vein thrombosis and 64 cases of anterior femoral vein thrombosis. The two groups had comparable baseline clinical data (P >0.05).

Inclusion and exclusion criteria
Inclusion criteria: Patients with femoral neck fracture, hip osteoarthritis and femoral head necrosis who received total hip arthroplasty; 50–75 years old; preoperative colour Doppler ultrasonography disclosed DVT (-) in both lower extremities. Exclusion criteria: Patients with hepatic, renal or coagulation dysfunction; those who had thrombosis; those with active bleeding or high bleeding risk; those who were allergic to the drugs used in this study.

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Treatment methods

The two groups were given basic anticoagulant treatment. Surgical operation was as gentle as possible to avoid venous intimal injury. Tourniquet was used in a standard way. The affected limb was elevated after surgery to prevent deep venous return abnormality. Patients were routinely educated regarding venous thrombosis-related information, and required to conduct functional exercises, ambulation activities, deep breath and cough-generating procedure. Besides, they were required to drink sufficient water to avoid dehydration. In addition, they were recommended to change the lifestyle by ceasing smoking and alcohol drinking as well as controlling blood glucose and lipid levels, and also to take physical precautions.

The rivaroxaban group was orally administered with rivaroxaban (10 mg, qd; trade name: Xarelto®, Bayer Pharma AG, Germany; registration number: H20140132) 12 h after surgery for 30 consecutive days, and the other group was subcutaneously injected with low molecular weight heparin calcium injection (0.6 mL; trade name: Clexane; purchased by Aventis Intercontinental (France) and subpackaged by Sanofi-Aventis Pharmaceuticals Beijing Co., Ltd. (China); National Medicine Permit No. J20090095) for 7 consecutive days.

Observation indices

The incidence rate of lower extremity DVT, drainage blood volume, hemoglobin decline, as well as preoperative and postoperative 7-d prothrombin time (PT), activated partial thromboplastin time (APTT), platelet (PLT) count and D-dimer level of the two groups were compared. After treatment, the patients received colour Doppler ultrasonography of both lower extremities by the same sonographer as that of before treatment. Ultrasonographic diagnostic criteria for DVT: (1) Incompressible venous lumen; (2) hypoecho or no echo in the venous lumen; (3) no or only weak blood flow signal in the thrombotic vein segment; and (4) pulsed-wave Doppler ultrasonography shows no blood flow or frequency spectrum does not change along with breathing.

The incidence rates of adverse reactions during treatment were observed. The presence or absence of PE and severe bleeding was observed during medication. Severe bleeding events: Fatal bleeding, bleeding of vital organs (peritoneal, intracranial, intraocular or intraspinal hemorrhage) accompanied by at least a 35 g/L drop in the hemoglobin level, or bleeding of surgical sites which needed transfusion of whole blood or ≤2 units of suspended red blood cells.

Statistical analysis

All data were analyzed by SPSS 19.0 software. The categorical data were represented as mean ± SD and subjected to the ‘t’ test. The numerical data were expressed as percentage and compared by the $\chi^2$ test. $P <0.05$ was considered statistically significant.

Results and Discussion

Postoperative incidence rate of lower extremity DVT, drainage blood volume, hemoglobin decline and blood transfusion volume

The two groups had similar postoperative incidence rates of lower extremity DVT, drainage blood volumes and extents of hemoglobin decline ($P >0.05$). Detailed observations are shown in Table 1.

Preoperative and postoperative 7-d PT, APTT, PLT counts and D-dimer levels

There were no significant differences in the preoperative and postoperative 7-d PT, APTT, PLT counts and D-dimer levels between the two groups ($P >0.05$) (Fig. 1).

Adverse reactions

All patients in the low-molecular-weight heparin group had pain and petechiae at the injection site, accompanied by ecchymoses occasionally. However, there was no hematoma or skin necrosis. Six patients in the rivaroxaban group had slightly elevated levels of alanine aminotransferase and glutamyl transferase which returned to normal three days after drug withdrawal. Besides, three patients suffered from gingival bleeding which was relieved after drug withdrawal. All patients had no subcutaneous hemorrhage or severe hemorrhage of the digestive tract and urinary tract. The reduction of hemoglobin level did not exceed 35 g/L. Also, there were no clinical manifestations of PE, such as chest tightness, dyspnea and jugular vein filling. The discharged

<table>
<thead>
<tr>
<th>Group</th>
<th>No.</th>
<th>DVT</th>
<th>Drainage blood volume (mL)</th>
<th>Hemoglobin decline (g/L)</th>
<th>Blood transfusion volume (mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rivaroxaban</td>
<td>153</td>
<td>3 (1.96)</td>
<td>434.35±8.01</td>
<td>31.14±1.52</td>
<td>522.14±13.42</td>
</tr>
<tr>
<td>Low-molecular-weight heparin</td>
<td>157</td>
<td>4 (2.55)</td>
<td>435.09±7.87</td>
<td>30.99±1.43</td>
<td>522.41±13.53</td>
</tr>
<tr>
<td>$\chi^2$</td>
<td>0.121</td>
<td>0.820</td>
<td>0.895</td>
<td>&gt;0.05</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>$P$</td>
<td>&gt;0.05</td>
<td>&gt;0.05</td>
<td>&gt;0.05</td>
<td>&gt;0.05</td>
<td>&gt;0.05</td>
</tr>
</tbody>
</table>
patients were all cured. Neither DVT nor PE occurred during follow-up for over one year.

Venous thromboembolism, including DVT and PE, is the third most common cardiovascular disease following ischemic heart disease and stroke\textsuperscript{12}. About 1\% of hospitalized patients die of PE, with 90\% originating from lower extremity veins. Four-fifths of patients have no clinical symptoms at the onset of PE, and 2/3 of them die within 2 h\textsuperscript{13}. Patients receiving major orthopedic surgeries such as total hip arthroplasty are prone to DVT which leads to loss of functions of lower extremities or disability and PE or even death in severe cases, which have been effectively treated through thromboprophylaxis\textsuperscript{14}.

The secondary risk factors for DVT include age, trauma, fracture, severe infection, central venous catheterization, chronic venous insufficiency, chronic respiratory disease, congestive heart failure and artificial prosthesis placement. The American Academy of Orthopedic Surgeons recommends that patients receiving major orthopedic surgeries should be given antithrombotic agents for 10-14 d\textsuperscript{15}. For patients receiving major orthopedic surgeries, the Chinese Orthopedic Association recommends that\textsuperscript{16}: routine thromboprophylaxis is not required for patients without risk factors; for patients with other risk factors, heparin prophylaxis using low molecular weight heparin, fondaparinux sodium, dabigatran, apixaban and rivaroxaban alone, or prevention using physical methods such as inflation and compression of lower extremities should be performed; patients with multiple risk factors should use intermittent inflation and compression devices during hospitalization; patients with high bleeding risk should use intermittent inflation and compression devices or be left untreated. In clinical practice, DVT is mainly prevented by elastic bandaging, massage, active and passive function exercises of lower limbs in combination with anticoagulants\textsuperscript{17}.

Heparins mainly act on coagulation factor Xa, and those with lower molecular weights exhibit higher anticoagulant activities. Therefore, one third of low molecular weight heparins has strong anticoagulant effects, whereas high molecular weight ones easily cause hemorrhage, thrombocytopenia and other adverse reactions\textsuperscript{18}. Low molecular weight heparin cannot be readily neutralized by platelet factor IV, thereby enhancing anticoagulation and fibrinolysis. Meanwhile, the antiplatelet and bleeding inducing effects are markedly attenuated, and the half-life is 2-3 times longer than those of unfractionated heparins\textsuperscript{19}. In clinical practice, low molecular weight heparin has been used to effectively prevent DVT for over 10 years. Although low molecular weight heparin at a routine dose is safe for preventing DVT after major orthopedic surgery\textsuperscript{20}, it is injected subcutaneously, resulting in pain and hematoma at the injection site. In the meantime, complicated operation leads to poor compliance during hospitalization and limitations after discharge.

As a new and selective oral anticoagulant agent, rivaroxaban directly suppresses coagulation factor Xa. The selectivity of rivaroxaban to activated Xa is 10,000 times more than those of other serine proteases, thereby inhibiting thrombin generation and thromboembolism. Moreover, its bioavailability and safety surpass those of low molecular weight heparin, without needing monitoring to adjust dosage or causing cross resistance. Meanwhile, rivaroxaban induces mild adverse reactions. Hence, this drug can be well accepted and tolerated by patients\textsuperscript{21}. Based on lower risks of global bleeding and other adverse reactions, Treceño-Lobato\textit{et al.}\textsuperscript{22} also verified that rivaroxaban was a safe anticoagulant agent.

In this study, the two groups had similar incidence rates of postoperative lower extremity DVT, drainage blood volumes, extents of hemoglobin decline, blood transfusion volumes and coagulation functions 7 days after surgery, without severe bleeding events. Accordingly, rivaroxaban and low molecular weight heparin exerted comparable preventive effects on postoperative DVT.
Conclusion

Rivaroxaban and low molecular weight heparin exert comparable preventive effects on lower extremity DVT after total hip arthroplasty. Nevertheless, rivaroxaban has been shown to be superior owing to convenient use (oral administration) and better compliance. Studies with larger sample sizes are ongoing in our group to further validate the above findings.

Conflict of interest

Authors declare no competing interests.

References


