

Pharmacologic Prophylaxis and Treatment of Venous Thromboembolism after Knee Arthroplasty

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جمال الشوابكة، مالك غنيمات وعمار حجازي

الملخص: الهدف: تقييم فعالية الهيبارين غير المجرأ والوارفيرين والهيبارين ذو الوزن الجزيئي المنخفض. عند استخدامها للوقاية من الانصمام الخثاري الوريدي في جراحة رأب مفصل الركبة. الطريقة: هذه الدراسة الإستباقية (المستقبلية) أجريت على ستين مريضاً خضعوا لجراحة رأب مفصل الركبة الأولى خلال الفترة الممتدة من أغسطس عام 2002 وحتى نوفمبر عام 2004. وتم تقسيمهم إلى ثلاث مجاميع وبأعداد متساوية. كل مجموعة عولجت بنظام معين مختلف عن الآخرين. تم تسجيل حالات الخثار الوريدي العميق العرضي أو الانصمام الرئوي العرضي خلال أول ثلاثين يوماً بعد الجراحة ومن خلال زيارات المتابعة الروتينية. النتائج: أظهرت الدراسة بشكل لافت نقص في حالات الخثار الوريدي العميق و الانصمام الرئوي عند المرضى الذين يستخدمون الوارفيرين والهيبارين ذو الوزن الجزيئي المنخفض بشكل وقائي بالمقارنة مع المرضى الذين يستخدمون الهيبارين غير المجرأ. الخلاصة: يعد الوارفيرين و الهيبارين ذو الوزن الجزيئي المنخفض أكثر فائدة وفعالية من الهيبارين غير المجرأ في حالات الخثار الوريدي العميق والانصمام الرئوي في حالات رأب مفصل الركبة الجراحية.

مفتاح الكلمات: رأب المفصل . الوقاية من الخثار الوريدي العميق . الوقاية . الوارفيرين . الهيبارين ذو الوزن الجزيئي المنخفض.

ABSTRACT Objective: The objective of this study was to evaluate the efficacy of unfractionated heparin, warfarin and low molecular weight heparins (LMWH) used for the prevention of venous thromboembolism in arthroplastic surgery of the knee joint. **Methods:** In this prospective study from August 2002 to November 2004, 60 patients were included and divided into three groups with equal numbers, with each group receiving different treatment protocol. Postoperatively, the occurrence of symptomatic deep vein thrombosis (DVT) or pulmonary embolism (PE) was recorded during the first 30 days after surgery and at a routine follow-up visit. **Results:** A significantly lower prevalence of DVT and PE was found in patients using warfarin and LMWH as prophylaxis in comparison with patients using unfractionated heparin. **Conclusion:** Warfarin and low molecular weight heparins are more beneficial and effective than unfractionated heparin for DVT and PE prophylaxis in arthroplastic knee surgeries.

KeyWords: Arthroplasty, Deep vein thrombosis (DVT), Prophylaxis, Low Molecular Weight Heparin, Warfarin.

Patients having primary or revision total knee arthroplasty have an increased risk of the development of thromboembolism. Without prophylaxis, the overall prevalence of thromboembolism has been reported to range from 40% to 84%, with proximal thrombi in 9% to 24% of patients.¹ Symptomatic pulmonary embolism (PE) has been reported to occur in up to 7% of patients having total knee arthroplasty without prophylaxis, being fatal in 2% of them.² Most surgeons recommend routine prophylaxis against

thromboembolism, but there is controversy about the optimal method.

METHODS

This is a study of three consecutive anti-thromboembolism regimens after total knee arthroplasty conducted in the Farah Royal Rehabilitation Centre, Jordan, during the period August 2002 to November 2004. A total of sixty patients were included in the study. After the purpose of the study and the possible complications

Table 1: Incidence of DVT or PE in Groups A, B & C

Groups	Incidence of Deep Vein Thrombosis (DVT)	Incidence of Pulmonary Embolism (PE)
A	20%	10%
B	5%	0%
C	10%	0%

were explained to the patients, permission was taken. This study has been also authorized by the scientific and research committee of the Royal Jordanian Medical Services.

Three prophylactic methods were used and the patients were classified into three groups, Group A (n=20), who received unfractionated heparin in a fixed dose of 5000 IU, beginning at the night of surgery, twice daily subcutaneous; Group B (n=20), who received warfarin 10 mg daily two days prior to surgery, the dose being titrated according to INR (International Normalized Ratio) level; and Group C (n=20), who received LMWH at the night of surgery in a dose of 20 mg daily one day prior to surgery. All the surgeries were done under general anaesthesia. Patients with a previous history of deep vein thrombosis (DVT), chronic venous insufficiency, stroke, varicose veins, malignancy, renal insufficiency, recent myocardial infarction, heart failure, and those taking oral contraceptives, or steroidal/hormonal/anticoagulant drugs for any medical condition, were excluded from the study.

No mechanical devices were used in DVT prophylaxis in the study. All the patients were mobilized from bed on the first day post-operatively. Post-operative assessment for DVT was done in all patients on both the lower limbs by color Doppler ultrasonography including an examination of bilateral common femoral, superficial femoral, popliteal, anterior tibial, and posterior tibial veins. They were assessed for flow, visualized thrombus, compressibility, and augmentation. A diagnosis of DVT was made where there was visualization of thrombosis, absence of flow, lack of compressibility, or lack of augmentation. A Spiral CT scan was used for the diagnosis of PE.

Patients on LMWH were discharged from the hospital after two weeks with a weekly follow up for two weeks. Those on heparin and warfarin were discharged after PTT (partial thromboplastin time) and INR levels were adjusted and followed up in weekly visits. No complications of the drugs used were encountered.

Thrombi were classified as proximal if the popliteal or femoral veins were involved and distal if only

the veins of the calf were involved. If the duplex scan showed a calf vein thrombus and the patient was asymptomatic, the prophylaxis was continued and the scan was repeated in one week. In the asymptomatic patient with a popliteal or femoral vein thrombus, the prophylaxis was considered to have failed and anticoagulation was started with LMWH. Oral anticoagulation, with a goal of a prothrombin time of 15 to 18 seconds, was continued for 12 weeks.

The symptomatic patients with a calf thrombus were treated according to the surgeon's judgment, but the symptomatic patients with popliteal or femoral thrombi routinely were given heparin followed by warfarin for 6 months.

RESULTS

Postoperatively, occurrence of symptomatic DVT or PE was recorded during the first 30 days after surgery and at a routine follow-up visit. In Group A, symptomatic DVT was diagnosed in 4 patients (20%) of which two patients had proximal DVT, while PE occurred in two patients (10%). Patients in Group B showed a lower incidence of symptomatic DVT (5%) than those patients in Group C (10%), with no recorded cases of PE in both Groups B and C, as shown in Table 1.

DISCUSSION

Several studies have evaluated the efficacy of LMWH and warfarin for prophylaxis against thromboembolism after total knee arthroplasty.^{3, 4-9} There is no clinically significant difference between warfarin and enoxaparin prophylaxis in terms of efficacy (venographic or clinical events) and safety for hip arthroplasty patients.⁷ There is no significant difference in terms of clinical events between warfarin and LMWH prophylaxis in knee arthroplasty patients.⁹ There are fewer venographic events with LMWH. The safety seems comparable, but LMWH should be started the day after surgery in knee patients.

Warfarin is one of the most commonly used prophylactic agents against thromboembolic disease in

hip arthroplasty patients. For four decades, low-dose warfarin has been used successfully for prophylaxis against deep vein thrombosis following total knee replacement, and its efficacy has been proven both in both studies and well-designed clinical trials.^{16, 17} The reported venographic rates for overall DVT are between 10% and 20% and between 5% and 10% for proximal DVT. Major bleeds occur in 1% to 3% of the cases and minor bleeds in 2% to 5%. Warfarin interferes with vitamin K metabolism in the liver and prevents the formation of functional clotting factors II, VII, IX, and X. It takes at least 36 hours to have a measurable effect, and 4 to 5 days to reach effective anticoagulation. Dose response to warfarin, especially in surgical patients, is highly variable, and prothrombin time (PT) monitoring is necessary. The anticoagulant effect is expressed in the INR value, which corrects for the variability in sensitivity of the different reagents used in various institutions to measure prothrombin time (PT).

High-molecular-weight heparin fractions, however, have a strong affinity for platelets where they inhibit the aggregation. They also inhibit platelet function and vascular smooth-muscle cell proliferation. These fractions delay hypersensitivity reactions and increase the permeability of vessel walls. Finally, they have been implicated in the regulation of angiogenesis

Commercial heparin is a heterogeneous mixture of sulfated polysaccharide chains of molecular weights ranging from 3,000 to 30,000 daltons (mean 15,000). One-third of the heparin, mostly low-molecular-weight fractions, binds to antithrombin III and is responsible for most of the anticoagulant activity at therapeutic levels. At the molecular level, heparin acts on antithrombin III by inducing a conformational change which unmasks an arginine center, which in turn inhibits the active serine center of thrombin and other coagulation enzymes. After doing so, heparin dissociates from antithrombin III and can be reused.

LMWH is not a homogenous drug, but it contains only polysaccharide chains of less than 8000 daltons. There are many commercially available LMWHs which are prepared by various processes. These preparations are pharmacologically different from each other and, therefore, may not be clinically identical. Compared to standard heparin, LMWH fragments have a better bioavailability, a longer half-life, a lesser platelet inhibitory effect.¹⁰

Clinical studies have reported a 60% to 80% overall radiographic DVT risk reduction in hip arthroplasty

patients with LMWH when compared to a placebo. No significant increase in major bleeding complications was found, but a significant increase in minor bleeds (mostly subcutaneous hematomas) has been noted.¹¹ The potential advantages of LMWH compared to unfractionated regular heparin are more predictable dose response, longer half-life and less hemorrhagic effect for a given antithrombotic effect.

Recent studies have demonstrated the efficacy and safety of outpatient treatment of acute proximal DVT using LMWH.^{12,13} In these randomized trials, intravenous heparin was compared with outpatient LMWH, given twice-daily in a weight-adjusted dose regimen. Warfarin therapy was started on the first day of treatment in both study groups. During follow-up, there were no significant differences in the incidence of recurrent venous thromboembolism or bleeding complications.¹⁴ Outpatient treatment of acute DVT is a promising and more versatile approach than conventional, in-hospital treatment and is likely to be more cost-effective. Outpatient treatment of DVT with the combination of LMWH and warfarin should be employed by centres experienced in the treatment of thromboembolic disorders.

An ideal prophylactic regimen has not been identified and the selection of an appropriate agent is usually a balance between efficacy and the risk of bleeding. The most effective prophylactic agents for these patients include low-molecular-weight heparin, warfarin, and fondaparinux,¹⁵ as we found in our study. We suggest the usage of LMWH or warfarin in the prophylaxis of DVT and PE for a thirty day period. More prolonged prophylaxis should be considered following total joint arthroplasties in patients who are at higher risk, including those with a history of venous thromboembolic disease, limited mobilisation, obesity, and cancer.^{18, 19}

CONCLUSION

The usage of LMWH and warfarin is a more beneficial and effective method for the prophylaxis of deep vein thrombosis and pulmonary embolism after knee arthroplasty than unfractionated heparin. This finding corroborates other studies in the literature.

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