Brief Report

Rivaroxaban in the Treatment of PICC-associated Upper Extremity Venous Thrombosis

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ABSTRACT

Purpose: Peripherally inserted central catheters (PICCs) are frequently used for prolonged drug administration, but their use is commonly complicated by the development of upper extremity deep venous thrombosis (UEDVT) requiring anticoagulation. Here, we compared the efficacy and safety profile of rivaroxaban (20 mg/d) with low molecular weight (LMW) heparin and vitamin K antagonists in the treatment of PICC-associated UEDVT.

Methods: Patients (N = 84) with PICC-associated UEDVT were studied. All had UEDVT identified by ultrasound scanning. Further ultrasound images were obtained at 1, 2, and 3 months after the start of treatment. Forty-four patients were treated with rivaroxaban and 40 with initial LMW heparin and vitamin K antagonist with continuation of vitamin K antagonists alone once international normalized ratio was therapeutic

Findings: In the rivaroxaban group mean (SD) age was 51 (16) years and 57% were men, whereas in the other group respective values were 50 (16) years and 56%. All patients were receiving treatment for cancer. Resolution of thrombus had occurred in 53.5% at 1 month, 76.1% at 2 months, and 92.6% at 3 months in the rivaroxaban-treated patients. Corresponding values in the LMW heparin/vitamin antagonist–treated patients were 34.2%, 55.5%, and 88.5%, respectively. Differences between groups were significant at 1 month ($P < 0.01$) and 2 months ($P < 0.05$). There were no major bleeds in either group, and cumulative bleeding rates by 3 months were 7.3% in the rivaroxaban group and 11.4% in the LMW heparin/vitamin K antagonist group.

Implications: Rivaroxaban led to faster resolution of PICC-associated UEDVT than LMW/vitamin K antagonists without any increase in bleeding. (*Clin Ther.* 2017;39:1882–1888)

Chemical compounds studied in this article: Rivaroxaban (PubChem CID: 9875401), Warfarin (PubChem: 54678486), Enoxaparin (PubChem: 772).

Key words: bleeding, resolution, rivaroxaban, thrombosis, upper limb, vitamin K antagonists.

INTRODUCTION

Peripherally inserted central catheters (PICCs) are generally placed in arm, subclavian, or jugular veins and terminate in the superior vena cava. They are widely used when drug administration into a peripheral vein would be harmful or when prolonged administration is required. A common indication is the medium term administration of chemotherapeutic agents to patients with cancer. However, a major complication of their placement is the development of thrombosis.[1–3] Central venous catheter (CVC)-associated thrombosis accounts for up to ~70% of all cases

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of secondary upper extremity deep vein thrombosis (UEDVT)[4] with PICC contributing >50% of these. Cancer patients are particularly susceptible to such complications due to the hypercoagulable state often found in the presence of malignancy.[5,6]

The prevalence of PICC-associated thrombosis is underestimated when based on the presence of clinical signs. Thus, prevalence rates of 2% to 11% have been reported for the presence of clinically manifest PICC-related UEDVT.[7,8] In marked contrast, when prospective surveillance is undertaken in all patients, irrespective of the presence or not of clinically apparent thrombosis, prevalence rates of between 35% and 40% have been reported.[9]

The traditional management of DVT and venous thromboembolism (VTE) has been based on the initial use of unfractionated or low molecular weight (LMW) heparin combined with vitamin K antagonists to prevent recurrence.[10,11] Current guidelines recommend similar initial and long-term treatment for UEDVT as for lower limb disease.[12] Such management is hampered by complexity of monitoring and the frequent need for dose adjustment. In recent years alternative management strategies have been possible with the availability of orally active direct thrombin and factor Xa antagonists.[13] Recent trials have indicated that oral agents such as rivaroxaban are cost-effective alternatives to the use of LMW heparin and vitamin K antagonists in lower extremity DVT and VTE. However, the efficacy of novel oral anticoagulants (NOACs) in PICC-associated UEDVT is not established. We report here a single center experience with this strategy.

METHODS

All patients in the study had PICC lines inserted as part of their cancer management. Under ultrasonic guidance, PICC lines were inserted from median basilic or cephalic vein in the forearm to the superior vena cava 2 cm from the entrance of the right atrium. If there were difficulties in access from forearm veins, jugular then subclavian veins were used as alternatives.

Patients were assessed weekly by specialist PICC nurses. These weekly assessments included examination for clinical signs, disinfection of the local site, change of dressing, catheter flushing with saline, and sealing with 10 U/mL heparin during the waiting days for the next period of medical therapy, in the special clinic. Ultrasonic surveillance was undertaken routinely every 2 to 4 weeks unless there were local symptoms or signs in which case ultrasonic imaging was undertaken immediately.

Once thrombus was diagnosed, patients were immediately referred to vascular physicians. Anticoagulation was then commenced immediately. Patients with UEDVT were offered the option of treatment with LMW heparin (enoxaparin) and vitamin K antagonist (warfarin) or with NOAC (rivaroxaban). Patient choice was determined by several factors, including cost of therapy, choice of injection or oral therapy, ease of access to international normalized ratio (INR) monitoring, and so forth. Patients were informed that although no randomized trials results were available comparing these treatment options, trials in other DVT/VTE states had shown equivalence for these therapeutic approaches.

Anticoagulant Therapy

Treatment with rivaroxaban (R) was at 20 mg once per day. Patients undergoing treatment with enoxaparin and warfarin (E+W) received enoxaparin 40000 U every 12 hours a day until INR ≥2 as per current Chinese guidelines. Warfarin dose was subsequently adjusted to maintain INR in the range of 2 to 3, requiring 4.0 (1.5) mg/d. At the 1-month visit 85% had INR in the range or 2 to 3, 10% at 1.5 to 2.0, and 5% >3.

Patient Monitoring

Patients were assessed weekly by an experienced vascular physician. At each visit information was obtained on clinic signs, complications such as bleeding events, blood test results such as prothrombin time-INR, platelets, and so forth. Patients underwent ultrasonic evaluation 2 weeks after anticoagulant and then monthly until 3 months (see below). PICCs were removed once the thrombus had resolved, but anticoagulation was continued for a minimum of 2 weeks with further ultrasound surveillance at that time.

In the rivaroxaban arm 1 patient was lost to follow-up at each of the monthly visits (a cumulative loss of 3 patients over the 3-month evaluation period). In the enoxaparin/warfarin arm 2 patients were lost to follow-up before the first monthly visit, a further 2 before the second-month visits, and 1 before the third-month visit (a cumulative loss of 5 patients).