American Medical Journal 3 (2): 126-129, 2012
ISSN 1949-0070

Rivaroxaban and its Effect on International Normalised Ratio-A Prospective Study of 28 Hip and Knee Arthroplasty Patients

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Abstract: Problem statement: Rivaroxaban is an orally active, competitively reversible antagonist of activated factor Xa. The purpose of this study is to comment on Riveroxaban's effect on INR. **Approach:** At the Queen Elizabeth Hospital, all patients undergoing elective anthroplasty were anticoagulated with 10mg of Rivaroxaban. All patients had INR measurements for 3 days post operatively. Further 16 patients had weekly INR follow follow up for the reminder of their therapy. Measurements between 0.2-1.2 were classified normal, 1.3-1.4 elevated and INR>1.4 high. **Results:** On day 1 after Rivaroxaban was commenced, 67.9% of patients recorded high INR value of >1.4 while 7.1% of patients had normal value of INR value (0.8-1.2). However, the number of patient with normal value of INR increased over next 2 days. On the third day after Rivaroxaban was commenced, 35.7% of the patients recorded a normal INR value while 32.1% of the studied patients had recorded mild elevated INR value. 32.1% of the studied patients had high INR value. All patients had an INR greater than 1.1. In the first 3 days, the maximum INR reached was 3.1. In patients who. All patients with a normal INR on day 1 remined normal throughout their course. 4 patients with an elevated INR on day 1 normalised by day 3. 8 patients had an INR trend upwards from day 1-2. 3 patients had a higher INR at day 3 compared to day 1. Of the 16 pateints followed up till the end of their therapy, 68.8% patients had a normal, 18.8% elevated and 12.5% patients had a high INR. **Conclusion:** Rivaroxaban has been proven as an effective alternate to existing anticoagulats in tehrms of patient compliance, rates of thrombus and bleeding risks. This study successfully demonstrates that Rivaroxaban leads to a trancient increase in INR in the majority of pateints in the first 72 h. Nil litrature exists on the effect of Rivaroxaban on prothrombin time and appropriate reversal and mangemetn of pateints who require further surgical intervention. Further research is required into invistigating the cause and effect of this increase.

Key words: Anticoagulation, rivaroxaban, international normalised ratio, arthroplasty

INTRODUCTION

Anticoagulant agents are vital in the prevention and treatment of venous thrombosis. Several anticoagulants are available for the treatment and prevention of thrombosis, but Vitamin K Antagonists (VKAs) such as warfarin have been the only oral agent available. Although these traditional agents are effective, their use is complex from both the provider's and the patient's perspective, requring regular follow-ups and blood tests.

Activated Factor X (FXa) plays a critical role in the coagulation cascade by linking the intrinsic and extrinsic coagulation pathways and acting as the rate-limiting step in thrombin production. Inhibiting thrombin generation by blocking FXa with selective, direct and indirect FXa inhibitors has been validated as an effective antithrombotic approach. Indirect FXa inhibitors (e.g., fondaparinux, idraparinux) exert their effect via a cofactor (antithrombin), whereas direct inhibitors (e.g., rivaroxaban) block FXa directly. Rivaroxaban is an orally active, competitively reversible antagonist of activated factor Xa. Factor Xa is the active componenet of the prothrombinase complex that catalyses conversion of prothrombin (factor II) to thrimbin (factor IIa). Maximum inhibition of factor Xa occurs 1-4 h after adminstration and lasts for 5-12 h (Kubitza *et al*., 2005a; 2005b; Schenk *et al*., 2009).

The aim of this study is to note the effect of Riveroxaban on INR.

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MATERIALS AND METHODS

At the Queen Elizabeth Hospital (South Australia), all patients underwent elective anthroplasty were anticoagulated with 10 mg of Rivaroxaban daily commenced immediately after surgery and continued for 14 days post surgery for total knee artrhoplasties and 28 days for total hip artrhoplasties. All patients undergoing hip and knee arthroplasty were given 10 mg of riveroxaban daily. The dose was not held or cceased during its course.

Patients with abnormal pre operative liver function tests, coagulation panels and HIV were excluded from the study.

28 consicutive patients undergoing hip and knee arthroplasty were followed up prospectively. All patients had INR measurements for 3 days post operatively. 16 patients had further weekly INR follow follow up for the reminder of their therapy throughout patient basis.

INR measurements between 0.2-1.2 were classified as normal, 1.3-1.4 were as considered elevated. INRs greater than 1.4 were termed as high.

RESULTS

Out of the 28 patients, 12 are males and 16 are females. There were 14 total knee replacement, 12 total hip replacement and 2 uni-compartmental knee replacement.

On day 1 after Rivaroxaban was commenced, 67.9% of patients recorded high INR value of >1.4 and 25% of patients had an elevated INR while 7.1% of patients had normal value of INR value (0.8-1.2). On day 2, 17.9% of patients had normal INR, 35.7% elevated INRs and 46.4% of patients had an high INR. On the third day after commencing Rivaroxaban, 35.7% of the patients recorded a normal INR value while 32.1% had elevated INR value. The remaining 32.1% were found to have high INR value.

All studied patients had an INR greater than 1.1. In the first 3 days, the maximum INR recorded was 3.1. All patients with a normal INR on day 1 remined normal throughout their course. 4 patients with an elevated INR on day 1 normalised by day 3. 8 patients had an INR trend upwards from day 1-2. 3 patients had a higher INR at day 3 compared to day 1 (Fig. 1).

Out of the 16 patients whom were followed up till the end of their therapy, 11 patients had a normal, 3 patients elevated and 2 patients had a high INR. All patients with a high INR at the end of their therapy demonstrated an upward trending of INRs. An INR of 2.4 was the highest recorded at the end of the follow up period.

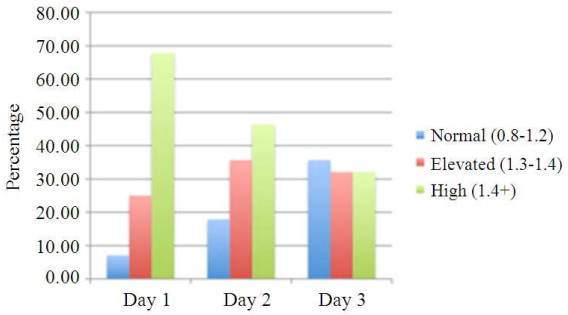

Fig. 1: Percentage of patients with elevated INRs based on days 1, 2, and 3. (X axis- days, Y axis- % of patients)

DISCUSSION

Oral anticoagulants are a new group of drugs used to prevent Venous Thromboembolism (VTE) in orthopaedics surgery. This mainly in joint replacement surgery where risk of VTE is significantly increased post-operatively (Schenk *et al*., 2009). Rivaroxaban is one of the oral anticoagulants that had been commonly used in joints replacement surgery recently. It works by inhibiting activated factor X (Xa). Xa plays a critical role in the coagulation cascade by linking the intrinsic and extrinsic coagulation pathways and acting as the rate-limiting step in thrombin production. Inhibiting thrombin generation by blocking Xa with selective, direct and indirect Xa inhibitors has been validated as an effective antithrombotic approach. Indirect Xa inhibitors exert their effect via a cofactor (antithrombin), whereas direct inhibitors block Xa directly (Gulseth *et al*., 2008; Haake and Berkman, 1989). Rivaroxaban is a derivative of oxazolidone that able to inhibit free factor Xa by attaching to the prothrombinase complex. This inhibition disrupts the intrinsic and extrinsic pathways of coagulation cascade, therefore inhibiting the formation of thrombin and thrombus formation.

Several studies had compared enoxaparin and rivaroxaban as prophylactic agents for VTE post arthroplasty (Lassen *et al*., 2008; Eriksson *et al*., 2008) and found rivaroxaban as a more effective anticagulating agent. Different doses of anticoagulating agents have been trialed at different doses for their effectiveness. For ease of comparison, studies that used Riveroxaban at 10 mg daily and clexane at 40 mg daily doses have been reviewed. VTE and clinically relevant bleeding were used as major study outcomes in those studies. In a study in 2008, Lassen studied 2531 patients who underwent total knee replacement (Lassen

et al., 2008) and found the rate of major and clinically relevant VTE were lower in patients who were started on Rivaroxaban (1.0 and 0.7%) as compared to Enoxaparin (Clexane) (2.6 and 2.0%). There were no statistically significant differences in bleeding rate. In a similar study in 2008, Eriksson studied 4541 patients who underwent total hip replacement and again found the rate of major VTE to be significantly lower in patients on Rivaroxaban at 0.2% compared to 2.0% for Enoxaparin (Eriksson *et al*., 2008). 0.3% of patients on Rivaroxaban had clinically relevant VTE as opposed to 0.5% of patients on Enoxaparin. Similar to total knee replacements, Eriksson showed no statistically significant differences in major and minor bleeding rate between Rivaroxaban and Enoxaparin in total hip arthroplasty. The major bleeding rate with Rivaroxaban was 0.3% compared to 0.1% with Enoxaparin while minor bleeding rate with Rivaroxaban was 3.2 and 2.5% with Enoxaparin.

Since Rivaroxaban is a relatively new drug, minimal data exists in regards to its interactions with other drugs (Kubitza *et al*., 2006; Escolar, 2006). From an anticoagulation point of view, Rivaroxaban was not been shown to have the anti-platelet effects of aspirin, clopidogrel, or abciximab in primates (Hoppensteadt *et al*., 2005). The most commonly reported adverse effects of Rivaroxaban were bleeding and elevated liver function tests. At dose of 10 mg daily, the frequency of major bleeding ranged from below 0.1-0.7% as compared to <0.1-1.9% with Enoxaparin (Eriksson *et al*., 2006; Anderson *et al*., 1993; Kakkar *et al*., 2008; Lassen *et al*., 2008). Rivaroxaban had been shown to cause elevated Alanine Transaminase (ALT) and Aspartate Transaminase (AST). Elevated ALT and AST levels were reported as 1.6-3.8% in patients taking Rivaroxaban while patients receiving Enoxaparin were 1.6-7.1% (Turpie *et al*., 2005). Eventhrough the differences in bleeding rates and increases in serum transaminases were not statistically significant, we have decided to exclude patients with elevated LFTs.

From data thusfar, riveroxaban has increased INR in patients who pre operatively had normal coagulation profiles and liver function studies. The effect of INR on surgical outcomes in joint arthroplasties has been studied. Intraoperatively, the INR level has been found to closely correlate blood loss. Increased intra-operative blood loss can cause decrease in level of clotting factors and can lead to further elevation in post-op INR (Lenzini *et al*., 2007). This could inflate patients INR level and leads to oversensitive to Warfarin in post-operative patients (Rahman *et al*., 2006). Meanwhile, high post-operative INR level has also been showed to increase risk of post-operative surgical effects, most notably infection after a Total Knee Arthroplasty (TKR) (Minnema *et al*., 2004). An INR level of 3 or more will significantly increase rate of surgical site infection. However, there were minimal data available on the effects of prolonged INR in arthroplasty surgery. Authors have speculated that prologned high INR could cause increased bleeding, haematoma formation and eventually wound site infection (Francis *et al*., 2003). At therapeutic levels (INR 2-3), treatment had been to have significantly reduced risk of venous throboembolism events after a knee joint arthroplasty surgery (Leclerc *et al*., 1998). All the patients in this study had a normal coagulation profile pre and intra operatively. By day 2, 3 patients had an INR greater than 2 and 1 patient with an INR greater than 3. By day 3, only 1 patient had an INR greater than 2.

To minimise intraoperative blood loss and comlpications, elective surgery is avoided in patients with an INR greater than 1.4. After commencement of rivaroxaban, 19 patients had an INR greater than 1.4. This correlates to 67.9% of patients at increased risk of bleeding if taken immediately to theater. To optamise patient outcome, one suggestion would be to review the post op imaging prior to commencement of anticoagulation.

The efficacy and long-tem safety of rivaroxaban are being evaluated in ongoing clinical trials to observe the drug's effects in managing acute PE, preventing stroke in patients with atrial fibrillation and managing acute coronary syndromes.

CONCLUSION

Rivaroxaban is an effective new agent in preventing venous thromboebolism despite several side effects as mentioned. It has similar to better efficacy compared with enoxaparin and is safe to use in VTE prophylaxis in orthopaedics surgery. It also has a greater ease of use compared to other anticagulating agents. Its effect on INR is concerning and further research is necessary to understand the impact of the elevated INR on patient outcome. One suggestion is to commence Rivaroxaban after review of post operative imaging to avoid anticoagulating patents who may require immediate revision of their surgery.

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