Rivaroxaban for the management of Acute DVT and lower limb circumference as an index of prognosis– A Case series

Running title : Rivaroxaban and DVT

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Abstract: Venous thromboembolism (VTE) encompasses deep-venous thrombosis (DVT) and pulmonary embolism (PE) and causes cardiovascular death, chronic disability, and emotional distress. The data about incidence of VTE in India is lacking due to the non-availability of published data. It is well-established that anti-coagulation with Vitamin K antagonist (VKA) is the main-stay of treatment for DVT, after initial treatment with unfractionated heparin (UFH) or low molecular weight heparin (LMWH). A PubMed search of "Deep vein thrombosis + rivaroxaban + India" showed no studies or case reports about the use of rivaroxaban for the management of DVT in the Indian population. In this case series, we report four cases (female)who presented with acute lower limb swelling diagnosed as deep vein thrombosis. Treated with oral rivaroxaban 15 mg BD and monitored by daily serial calf and thigh circumference measurements, irrespective of aetiology. All the four patients responded to the treatment and continued rivaroxaban for three months without the need for tests of coagulation and venous ultrasonography.

Key-words: Deep Vein Thrombosis, Rivaroxaban, Serial calf and thigh circumference measurements.

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Key Messages: Rivaroxaban therapy with bedside serial calf and thigh measurements will be a cost saving approach for the anticoagulation treatment and monitoring response in patients with acute DVT.

Introduction: Venous thromboembolism (VTE) encompasses deep-venous thrombosis (DVT) and pulmonary embolism (PE) and causes cardiovascular death, chronic disability, and emotional distress.[1] The data about incidence of VTE in India is lacking due to the non-availability of published data. A retrospective registry of Indian patients with venous thromboembolism. Kamerkar DR. et al A total of 64% patients had acute DVT, 23% had acute DVT with PE, and 13% had PE. Eighty-seven percent of patients had acute DVT (±PE), and 36% had PE (± acute DVT). findings consistent with a study from North India that reported a 16% incidence of PE in adult medical autopsies. This data showed a significant increase in acute DVT (±PE) from 2006 to 2010.[2] Lee AD, Venous thrombo-embolism in India. Based on their study concluded that VTE is no longer a rarity in India.[3] Another study by Singh S, Kapoor S, Singh B, et al. Real-world data on clinical profile, management and outcomes of venous thromboembolism from a tertiary care centre in India. A majority of patients had unprovoked VTE (76%), which is much higher than that noted by two other Indian studies. The findings are in line with Western data.[4] Patients with symptomatic DVT in India in the PROVE registry had similar baseline characteristics and medical histories to patients enrolled in other countries.[5]

Anticoagulation is the mainstay of treatment for patients with venous thromboembolism (VTE).[6] It is well-established that anti-coagulation with Vitamin K antagonist (VKA) is the main-stay of treatment for DVT, after initial treatment with unfractionated heparin (UFH) or low molecular weight heparin (LMWH). [7] The anticoagulant therapy for DVT has evolved from inpatient administration of intravenous unfractionated heparin (UFH) to outpatient therapy with LMWH, warfarin and non-Vitamin-K antagonist oral anticoagulants (NOACs). The duration of anticoagulant therapy is defined as acute (0-7 days), long term (first 3 months of therapy) and extended therapy (beyond 3 months). Heparin and warfarin need routine monitoring of anticoagulation profile through aPTT and INR respectively, hence limiting their use. Need for frequent laboratory monitoring is a challenge for outpatient management with VKAs especially in India. Therefore, an oral anticoagulant with wide therapeutic window without routine laboratory monitoring would be a good alternative to VKAs in the treatment as well as secondary prevention of DVT. The NOACs offer advantages of predictable pharmacokinetic profile and lesser food and drug interactions compared to warfarin. Moreover, NOACs do not require routine monitoring. The NOACs

are broadly classified into two major categories: direct thrombin (factor IIa) inhibitors and direct Factor Xa inhibitors. The NOACs have been extensively studied in the treatment of acute VTE and prevention of VTE. Dabigatran, rivoroxaban, apixaban and edoxaban have shown to be effective and at least comparable in safety with the conventional treatment of acute VTE. [8] Among various DOACs, dabigatran and edoxaban have been evaluated after initial treatment (nearly 7–9 days) with a parenteral agent, whereas apixaban and rivaroxaban have been evaluated by the single-drug approach.[9] Major bleeding, fatal bleeding, intracranial bleeding, and clinically relevant nonmajor bleeding were found to be significantly lower in DOAC-treated patients. Treatment with a DOAC significantly reduced the risk of major bleeding. In parallel, intracranial bleeding, fatal bleeding, and clinically relevant nonmajor bleeding occurred significantly less in DOAC recipients. [10] DOACs should be considered as first-line agents in the treatment of DVT. If safety is a major concern, apixaban can be considered over other DOACs. [11] The ESC recommends Venous ultrasonography (VUS) as first-line imaging for DVT. [9]

Case History:

Case1: A 50-year-old female presented with of swelling of left lower limb for 20 days, which is insidious in onset, gradually progressive from ankle to hip associated with mild dull aching pain and the patient also had a history of breathlessness for the past 15 days which is insidious in onset, aggravated on exertion and relieved on rest. There was no history of palpitations, chest pain, cough, decreased urine output, abdominal distension, drug usage. but there was a significant history of immobility in recent days due to mild trauma. There was no past history of diabetes or hypertension, nor any recent travel. There was no history of similar complaints in the past or in the family. General physical examination revealed that patient was conscious and coherent. The entire left lower limb was swollen. Local rise of temperature and mild tenderness were present associated with pitting pedal oedema. Neurological examination was normal. A probable diagnosis of acute DVT of lower limb was suspected. Modified Wells score was 3. The VUS of left lower limb was done immediately and it showed significant loss of compressibility and thrombosis of common femoral vein, superficial femoral vein and Computerized tomographic pulmonary angiogram showed multiple micro thrombi in right main pulmonary trunk. It was classified as a major VTE - Acute DVT with pulmonary thromboembolism. Patient was admitted and relevant laboratory investigations were done and were within normal limits and started on rivaroxaban 15mg per oral twice a day and daily serial leg

measurements were recorded. After 48hrs there was significant symptomatic improvement in the form of decreased dyspnoea, reduced tightness of thigh, redness and pain which correlated with reduced circumference of thigh and calf. Patient was discharged on 4rth day with advice to continue daily serial leg measurements. VUS after one week showed normal flow in femoral veins and with resolution of pain and swelling in the entire lower limb. Oral rivaroxaban was continued for 3weeks and changed to 20mg once a day for three months.

Case2: A 30-year-old female presented with complaints of swelling of left lower limb below Knee which is insidious in onset, gradually progressive over 25 days from ankle to Knee joint associated with mild pitting type of oedema, pain, redness and local raise of temperature. there was no history of breathlessness, palpitations, chest pain. There was no history of drug usage, trauma. There was no history of immobility. There was no past history of diabetes, hypertension, thyroid disorder and there was no history of similar complaints in the past or in the family. Her Modified Wells score was 4. VUS of left lower limb showed significant loss of compressibility of popliteal vein and thrombosis, suggestive of DVT of popliteal vein. Patient was admitted and relevant laboratory investigations done and found to be normal except for anaemia. Her haemoglobin was 6gm/dL and started on rivaroxaban 15mg per oral twice a day and daily serial calf measurements were recorded. After 48hrs there was significant symptomatic improvement in the form of reduced tightness of calf, redness and pain which correlated with reduced circumference of calf. Patient was discharged on 3rd day. VUS after one week showed normal flow in the popliteal vein and with resolution of pain and swelling in the lower limb. Oral rivaroxaban was continued for 3weeks and changed to 20mg once a day for three months.

Case3: A 65-year-old female presented with swelling of left lower limb for 28 days, which is insidious in onset, gradually progressive from ankle to hip associated with mild dull aching and burning pain. There was no history of dyspnoea, palpitations, chest pain, cough, decreased urine output, abdominal distension, drug usage, trauma, there was a no significant history of immobility in recent days. There was no past history of diabetes or hypertension, nor any recent travel. There was no history of similar complaints in the past or in the family. General physical examination revealed that patient was conscious and coherent. The entire left lower limb was swollen associated with local rise of temperature and mild tenderness were present associated with nonpitting pedal oedema. A probable diagnosis of acute deep vein thrombosis of lower limb was suspected. Her

Modified Wells score was 4. The VUS of left lower limb showed significant loss of compressibility and thrombosis of common femoral vein, superficial femoral vein, left popliteal, ant tibial, post tibial veins. It was classified as a major VTE - Acute Deep Vein Thrombosis. Patient was admitted and relevant laboratory investigations were done and were within normal limits except for Protein c, s and homocysteine levels were abnormal. She was started on rivaroxaban 15mg per oral twice a day and daily serial calf and thigh measurements were recorded. After 48hrs there was significant symptomatic improvement in the form of reduced tightness of thigh, redness and pain which correlated with reduced circumference of thigh and calf. Patient was discharged on 4rth day with advice to continue daily serial leg measurements and anti-oedema measures. VUS after one week showed normal flow in femoral veins only, after four weeks showed normal flow in femoral, popliteal veins, after 8 weeks there was normal flow in all the left lower limb veins with resolution of pain and swelling of the thigh. After 9 weeks there was still lower limb oedema below knee. Oral rivaroxaban was continued for 3weeks and changed to 20mg once a day for three months along with anti-oedema measures.

Case4: A 62-year-old female presented with complaints of swelling of right lower limb which is insidious in onset, gradually progressive over 15 days from ankle to Knee joint associated with mild pitting type of oedema, pain and local raise of temperature. There was no history of breathlessness, palpitations, chest pain. There was no history of drug usage, trauma. There was no history of immobility. There was no past history of diabetes, hypertension, thyroid disorder and there was no history of similar complaints in the past or in the family. Her Modified Wells score was 3. VUS of left lower limb showed significant loss of compressibility and partial thrombosis of right common femoral vein, suggestive of DVT. Patient was admitted and relevant laboratory investigations done and found to be normal and started on rivaroxaban 15mg per oral twice a day and daily serial calf measurements were recorded. After 48hrs there was significant symptomatic improvement in the form of reduced tightness of calf and pain which correlated with reduced circumference of calf. Patient was discharged on 3rd day. VUS after one week showed normal flow and with resolution of pain and swelling in the lower limb. Oral rivaroxaban was continued for 3weeks and changed to 20mg once a day for three months.

OBSERVATIONS: We observed that oral rivaroxaban alone was effective in the management of acute DVT irrespective of aetiology of dvt when the modified wells score was below 5 and there was a significant response in the form of

symptomatic improvement followed later by decreased serial measurements of leg. whereas radiological resolution of thrombus was ranged from one week to nine weeks. No need for regular monitoring of coagulation is needed and there were no adverse side effects and life-threatening effects to stop the treatment.

Discussion: All the four patients were treated with rivaroxaban irrespective of the cause of dvt and daily serial calf and thigh measurements were recorded. Heydari AK et al. in their study concluded that Daily measurement of lower limb circumference was an accurate and cost-effective technique for early diagnosis of DVT [18]. In a study conducted by Swarczinski C et al. [19], described the three criteria for clinical diagnosis of DVT taking serial leg measurements. But monitoring response to treatment by serial leg measurements was not found in the literature. This bedside monitoring will help to treat dvt without any economic burden in a resource limited setting. Yang L in their study concluded that rivaroxaban was a cost-saving treatment strategy.[20] Further research is needed to compare the cost-effectiveness of rivaroxaban therapy with serial calf and thigh measurements and when compared with serial lower limb VUS.

Conclusion: Rivaroxaban therapy with a bedside serial calf and thigh measurements will be a cost saving for the anticoagulation treatment and monitoring response in patients with acute DVT. Our study was only in Indian female patients. Similar large-scale studies in Indian male patients are necessary to apply the same.

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21. .

List of Abbreviations:

Abbreviation	Definition
DVT	Deep Vein Thrombosis

VTE	Venous thromboembolism
LMWH	low molecular weight heparin
UFH	unfractionated heparin
NOACs	non-Vitamin-K antagonist oral anticoagulants
DOACs	Direct oral anticoagulants
aPTT	activated partial thromboplastin time
INR	international normalized ratio
PROVE	Prospective Registry On Venous thromboembolic Events
VUS	Venous ultrasonography

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Design	✓	✓	✓		
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