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A REVIEW ON NOVEL ORAL ANTICOAGULANTS ROLE IN PREVENTION AND TREATMENT OF VENOUS THROMBOEMBOLISM COMPLICATIONS IN CLINICAL SETTINGS

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ABSTRACT

Venous thromboembolism (VTE) which consists principally of deep vein thrombosis (DVT) and pulmonary embolism (PE) is a common cause of morbidity and mortality. Venous thromboembolism (VTE), which includes DVT and pulmonary embolism (PE), affects 1 per 1,000 people and contributes to 60,000–100,000 deaths annually. Normal blood physiology depends on a delicate balance between pro- and anti-coagulant factors. Virchow's Triad distills the multitude of risk factors for DVT into three basic elements favoring thrombus formation includes venous stasis, vascular injury, and hypercoagulability. Clinical, biochemical, and radiological examinations are used to detect the incidence of deep vein thrombosis in the community. Deep venous thrombosis is a life threatening condition. Administration of oral anticoagulants can lower the future occurrence of disease complications. Early assessment of an individual patient's risk factors, clinical history, interacting medications, can enhance the therapeutic outcomes of individuals. Novel drugs for the treatment of deep vein thrombosis include the direct factor Xa inhibitors, rivaroxaban, apixaban can prevent the future occurrence of deep vein thrombosis complications in the society.

KEYWORDS: Venous thromboembolism, pulmonary embolism, venous stasis, vascular injury, anti-coagulants.

INTRODUCTION

Deep vein thrombosis is a major preventable cause of morbidity and mortality worldwide. The incidence of VTE is estimated to be 1 per 1,000 people annually and approximately two-

thirds of the patients affected by these events. Pulmonary embolism (PE) is a horrible complication of DVT, occurs in up to one-third of cases and is the primary contributor to mortality. The morbidity of DVT results from the development of post-thrombotic syndrome, which occurs in up to 50% of patients within 2 years of DVT and presented with leg pain, swelling, and in severe cases, venous ulcers. Anticoagulation is the mainstay of therapy for DVT, with the goal of preventing progression to PE and recurrence of thrombosis. The 30-day mortality rate exceeds 3% in patients with DVT who are not anticoagulated, and this mortality risk increases 10-fold in patients who develop PE.[1-3] The advent of direct oral anticoagulants has generated a need to compare these newer agents with the more conventional vitamin K-antagonists for the treatment of DVT. Venous thromboembolism is the third most frequent cardiovascular disease after myocardial infarction and stroke. The estimated incidence rate of VTE is around one case per 1000 person-years.[4-7] The most frequent site of VTE is deep vein thrombosis (DVT) of the legs. For several years, the standard of care treatment of acute VTE was the subcutaneous application of low molecular weight heparin (LMWH) or fondaparinux, followed in time by the oral intake of a vitamin K antagonist. It is highly effective for the prevention of recurrent VTE.

Epidemiology

DVT is a major cause of death worldwide. It affects approximately 0.1% of persons per every year. The overall average age- and sex-adjusted annual incidence of venous thromboembolism is 117 per 100,000 (DVT, 48 per 100,000; PE, 69 per 100,000), with higher age-adjusted rates among males than females (130 vs 110 per 100,000, respectively). Both sexes are equally to develop deep vein thrombosis, men having a higher risk of recurrent thrombosis as compared to females. DVT is predominantly a disease of the elderly with an incidence that rises markedly with age. The recurrence of Caucasians is lower than that of African-Americans and Hispanics. The incidence of VTE is low in children.[8-10] Annual incidences of 0.07 to 0.14 per 10,000 children and 5.3 per 10,000 hospital admissions have been reported in Caucasian research studies. The highest incidence in childhood is during the neonatal period. The incidence rate is comparatively high in adolescent females because of pregnancy and use of oral contraceptive agents. Pregnant women have a much higher risk of VTE than non-pregnant women of similar age and the risk has been shown to be higher after cesarian section than after vaginal delivery. The approximate risk for DVT following general surgery procedures is 15% to 40%.

Pathogenesis

The pathogenesis of deep vein thrombosis depends on three basic mechanisms. It includes formation of thrombosis: venous stasis, vascular injury, and hypercoagulability. Venous stasis is the most consequential of the three factors and cause formation of thrombus in the blood vessels. However, the concurrent occurrence of venous stasis and vascular injury or hypercoagulability greatly increases the risk of blood clot in the vascular stream.[11-12] The clinical conditions most closely associated with DVT are fundamentally related to the elements of Virchow's Triad; these include surgery or trauma, malignancy, prolonged immobility, pregnancy, congestive heart failure, varicose veins, obesity, advancing age, and a history of DVT. Venous thrombosis tends to occur in areas with decreased or mechanically altered blood flow to valves in the deep veins of the leg. The valves help to promote blood flow through the venous circulation; they are also potential locations for venous stasis and hypoxia. The flow of blood flow is slow which ultimately increase hematocrit count. The hypercoagulable micro-environment that ensues may downregulate the antithrombotic proteins that are preferentially expressed on venous valves including thrombomodulin and endothelial protein C receptor. Thrombus formation appears to require both tissue factor and P-selectin. Fibrin and extracellular DNA complexed with histone proteins forms the outer scaffold, which may be important in determining thrombus susceptibility to tissue plasminogen activator (TPA) and thrombolysis.[13-16] As the ratio of procoagulants to anticoagulants increases, so does the risk of thrombus formation. The proportion of proteins is in part determined by the ratio of endothelial cell surface to blood volume. A decreased cell surface to blood volume ratio (i.e., large vessels) favors procoagulants. Factor VIII, von Willebrand factor, factor VII and prothrombin seem to be particularly influential in tipping the scale towards coagulation. In addition to promoting thrombin generation, prothrombin inhibits the anticoagulant properties of activated protein C, thereby dampening a natural anticoagulant pathway. There are three such pathways: the protein C anticoagulant pathway (protein C, protein S, thrombomodulin, and perhaps EPCR), heparin-antithrombin pathway, and tissue factor inhibitor pathway. Defects in these pathways are associated with an increased risk for thrombus formation. In humans, less is known regarding the role of tissue factor inhibitor pathway.[17-19] There are also a number of familial variants that predispose to thrombus formation by increasing the levels of factor VII, VIII, IX, von Willebrand factor, and prothrombin. The aging is associated with an increased risk for thrombosis. The greater prevalence of obesity, increased frequency of illness and periods of prolonged immobility,

comorbid medical conditions, and increase pro-coagulants without a commensurate increase in anticoagulants such as protein C.

Complications of DVT

Pulmonary embolism

It is the most common complication of DVT and can be life threatening. It happens when a piece of a blood clot becomes dislodged and makes its way through the bloodstream into the lungs.[20-22] The clot becomes stuck and disrupts the flow of blood in one of the blood vessels in the lung.

Post-thrombotic syndrome

- Persistent swelling in the calf
- Feeling of heaviness in the leg
- Pulling sensation in the leg
- Excessively tired leg
- Fluid buildup in the affected leg
- Redness of the skin
- Varicose veins
- Thickening skin around the area of the DVT
- Leg ulcers for people with severe post-thrombotic syndrome

Causes

Veins are the blood vessels which carry the blood from the tissues of the body back to the heart. Veins that lie just beneath the skin surface are referred to as "superficial veins" while veins found deep inside the muscles are referred to as deep veins.[23-27] When a blood clot occurs in a vein it is referred to as a venous thrombosis. DVTs can occur in any of the deep veins but most commonly occur in the leg veins. The clot will completely block the flow of blood through the affected vein.

Risk factors

It includes

- Obesity
- Smoking
- Being older than 40 years
- Having previously had a DVT

- Family history of DVT
- Paralysis, eg: following a stroke or injury
- Having a leg in a plaster cast or splint
- Sitting for long periods of time while travelling
- Injury to a vein, eg: as a result of a broken bone or severe muscle injury
- Surgery[28-29]
- Heart disease
- Varicose veins
- Phlebitis
- Hormone medications – some research studies have indicated that there may be a small increased risk of DVT associated with some types of oestrogen-containing oral contraceptive pills, as well as some menopausal hormone therapies.
- Inherited disorders – such as the deficiency of some blood clotting factors
- Inflammatory bowel diseases, eg: Crohn's disease or ulcerative colitis

Diagnosis

D-dimer assay

D-dimer is a degradation product of cross-linked fibrin that is formed after thrombin-generated fibrin clots are degraded by plasmin. It activates the blood coagulation and fibrinolysis. These assays will differ in sensitivity, specificity, likelihood ratio, and variability among patients with suspected VTE. Hence a negative value of D-dimer may safely rule out both DVT and PE. False positive D-dimer results have been noted in inflammation, pregnancy, malignancy, and the elderly.[30] Clinical usefulness of the measurement of D-dimer has been shown to decrease with age. The use of age-dependent cut-off values of D-dimer assays is still a matter of controversy.

Levels of D-dimer can be popularly measured using three types of assay:

- Enzyme linked immunosorbent assay
- Latex agglutination assay.

Venous ultrasonography

Venous ultrasonography is the investigation of choice in patients stratified as DVT likely.[50] It is noninvasive, safe, available, and relatively inexpensive. There are three types of venous ultrasonography: compression ultrasound (B-mode imaging only), duplex ultrasound (B-mode imaging and Doppler waveform analysis), and color Doppler imaging alone. In duplex

ultrasonography, blood flow in normal vein is spontaneous, phasic with respiration, and can be augmented by manual pressure. In color flow sonography, pulsed Doppler signal is used to produce images.[31] Compression ultrasound is typically performed on the proximal deep veins, specifically the common femoral, femoral, and popliteal veins, whereas a combination of duplex ultrasound and color duplex is more often used to investigate the calf and iliac veins.

Contrast venography

Venography is the definitive diagnostic test for DVT, but it is rarely done because the noninvasive tests (D-dimer and venous ultrasound) are more appropriate and accurate to perform in acute DVT episodes. It involves cannulation of a pedal vein with injection of a contrast medium, usually noniodinated, eg, Omnipaque. A large volume of Omnipaque diluted with normal saline results in better deep venous filling and improved image quality.[32-33] The most reliable cardinal sign for the diagnosis of phlebothrombosis using venogram is a constant intraluminal filling defect evident in two or more views.

Impedance plethysmography

The technique is based on measurement of the rate of change in impedance between two electrodes on the calf when a venous occlusion cuff is deflated. Free outflow of venous blood produces a rapid change in impedance while delay in outflow, in the presence of a DVT, leads to a more gradual change.

Magnetic resonance imaging

This investigative modality has high sensitivity in detecting calf and pelvic DVTs,[62] and upper extremity venous thrombosis.[34-35] It is also relevant in ruling out differential diagnoses in patients suspected of DVT.

Clinical symptoms

- Pain in the affected limb that begins in the calf
- swelling in the affected limb
- a warm feeling in the swollen, painful region of the leg
- red or discolored skin
- slow breathing or sudden breathlessness
- chest pain, usually more severe while breathing deeply
- Faster heart rate

Prevention of deep vein thrombosis

- Lose weight, if you are overweight
- Stay active
- Exercise regularly; walking is fine
- Avoid long periods of staying still
- Regular exercise for at least every hour whenever you travel on a plane, train, or bus, particularly if the trip is longer than 4 hours.
- Drink a lot of water
- Wear loose fitted clothing while travelling

Treatment

Medications are a mainstay in the treatment of deep vein thrombosis. Anticoagulants are the most common type of DVT medications.

Initial Management

Prompt diagnosis and treatment of VTE with appropriate medications may prevent thrombus extension and embolization, relieve acute symptoms, prevent cardiopulmonary collapse, and reduce the risk of long-term complications. Empiric treatment during the evaluation period is controversial and not evidence-based.[36] In a hemodynamically unstable patient with a high probability of VTE, intravenous thrombolytic therapy can be considered. After diagnosis, most patients with DVT can be treated as an outpatient, except in cases of limb ischemia, significant comorbidities (e.g., end-stage renal disease), functional limitations, high bleeding risk, or nonadherence concerns.

Anticoagulation Choices

Once VTE is diagnosed and the patient is stabilized if needed, anticoagulation should be initiated unless contraindicated. Guideline recommendations for anticoagulation are divided into phases: initial phase (first week after diagnosis), long-term phase (second week to three months), and extended phase (beyond three months). In the initial phase of anticoagulation, a decision must be made between using the vitamin K antagonist warfarin or a direct-acting oral anticoagulant. If warfarin is selected, concomitant parenteral anticoagulation is required for at least five days; if dabigatran (Pradaxa) or edoxaban (Savaysa) is selected they should be initiated after five to 10 days of initial therapy with a parenteral anticoagulant.

Direct-Acting Oral Anticoagulants

In 2012, rivaroxaban became the first direct-acting oral anticoagulant approved by the U.S. Food and Drug Administration for treatment of DVT and PE. Several others followed. These agents belong to two classes: direct thrombin inhibitors (dabigatran) and direct factor Xa inhibitors (apixaban, edoxaban, and rivaroxaban). There are logistic benefits of direct-acting anticoagulants compared with warfarin primarily that no regular monitoring is required because of their predictable pharmacokinetics. Other benefits compared with warfarin include fewer dietary restrictions, fewer drug interactions, and relatively fixed dosing. Rivaroxaban should be taken with food, and it interacts with cytochrome P450 3A4 and P-glycoprotein inhibitors. Dabigatran may be affected by P-glycoprotein inducers or inhibitors. Dose adjustment may be required for these medications.[37]

Inferior Vena Cava Filters

An inferior vena cava filter is rarely indicated, and evidence for safety and effectiveness is lacking. Routine use of inferior vena cava filters in patients on anticoagulation does not reduce mortality, even in high-risk patients, and current guidelines recommend against their use in these patients. Possible complications from inferior vena cava filter placement include thrombosis and arteriovenous fistula.

Anticoagulants

Injectable anticoagulants

Injectable anticoagulants can go into an IV (intravenous) line or you can inject them under the skin subcutaneously. Your doctor may discuss these medicines:

- **Heparin** is the traditional choice for injectable anticoagulants. It used to be the only one available.
- **Low molecular weight heparin (LMWH):** It is a newer alternative to standard heparin. These drugs are smaller molecules or fractions that come from standard heparin. The dose depends on your weight, so they don't need the same monitoring as heparin.
- **Fondaparinux (Arixtra)** is another injectable anticoagulant. It belongs to a class called Xa inhibitors. It is a synthetic drug similar to the other two injectable anticoagulants, but works slightly differently.

Oral anticoagulants

Oral anticoagulants are medicines you take by mouth. These medicines include:

- **Warfarin (Coumadin)**, like heparin, is the traditional oral anticoagulant because it was the only one available in the past.
- **Dabigatran (Pradaxa)** works differently than warfarin. As a result, it does not require the same close monitoring and dose adjustment.
- **Xa inhibitors** are also newer alternatives to warfarin. They do not require an injectable medicine to get started. Drugs in this class include apixaban (Eliquis), betrixaban (Bevyxxa), edoxaban (Savaysa), and rivaroxaban.

Thrombolytics

Thrombolytics are intravenous medicines for use in the hospital. There are two ways to administer thrombolytics. The first is systemic. This thrombolysis procedure involves injecting the drug through an IV so it can circulate through the body and dissolve clots. Doctors may use this to treat an emergency PE.

It includes

- Alteplase
- Reteplase
- Streptokinase
- Uroknase

Novel drugs for the treatment of deep vein thrombosis

The novel oral anticoagulants have advantages over warfarin in many of these respects, including more predictable pharmacokinetics which eliminates the need for routine monitoring, a rapid onset of action and shorter half- life, and fewer drug and food interactions.[38] The novel oral anticoagulants include the direct factor Xa inhibitors, rivaroxaban, apixaban, and edoxaban, as well as the direct thrombin inhibitor dabigatran. Of these, rivaroxaban is currently the only NOAC currently FDA-approved for the treatment of DVT, having been approved for this indication in November 2012. Rivaroxaban is also approved for VTE prevention following total knee and total hip arthroplasty and in stroke prevention in atrial fibrillation. Dabigatran and apixaban are both approved in the United States for the single indication of stroke prevention in atrial fibrillation, though approval for DVT treatment is being sought for dabigatran in the United States.

Rivaroxaban

It reaches maximum plasma concentration and anticoagulation effect 2–4 hours after administration with a half-life of 7–13 hours. Of a given dose of rivaroxaban, approximately one third is cleared unchanged by the kidneys, one-third is excreted by the kidneys as inactive metabolites, and the remaining one-third is metabolized by the liver. The influence of renal dysfunction, even when severe, on rivaroxaban clearance is only minimal to moderate, with area under the concentration curve (AUC) increases of 1.44, 1.52, and 1.64 in patients with mild (CrCl 50 – 80 mL/min), moderate (CrCl 30 – 49 mL/min), and severe (CrCl < 15 mL/min) renal impairment, respectively. While rivaroxaban has far fewer drug-drug interactions than warfarin, there are several that clinicians should be aware of. These interactions are related primarily to concomitant use of CYP3A4 and P-glycoprotein (P-gp) inducers and/or inhibitors. The co-administration of rivaroxaban with strong CYP3A4 and P-gp inducers (e.g. rifampin, phenytoin) may decrease rivaroxaban exposure up to 50%, potentially also reducing systemic anticoagulation and thus, rivaroxaban's efficacy. As such, rivaroxaban use in patients who are also taking strong CYP3A4 and P-gp inducers, including rifampin, phenytoin, carbamazepine, and St. John's wort, should be avoided. Drugs that are weak or moderate inhibitors of CYP3A4 and P-gp, such as the azole antifungals, the HIV protease inhibitors, and rifampin, increase rivaroxaban exposure. Rivaroxaban should be avoided in patients who are concomitantly taking these agents, particularly if these patients also have renal dysfunction, which may synergistically increase rivaroxaban exposure and the associated risk of bleeding.

Dabigatran

Dabigatran is administered as a pro-drug and reaches peak anticoagulant effect approximately 1–3 hours after ingestion. The half-life of dabigatran is 12–14 hours in patients with normal renal function. Dabigatran undergoes approximately 80% renal clearance, and the average half-life of dabigatran increases progressively to 15.3 hours, 18.4 hours, and 27.2 hours in patients with mild (CrCl 50 – 80 mL/min), moderate (CrCl 30 – 49 mL/min), and severe (CrCl < 15 mL/min) renal insufficiency, respectively. For patients in the United States, the current FDA-approved dose of dabigatran for AF (e.g. 150mg BID) should be reduced to 75mg BID if the creatinine clearance is 15–30 mL/min. Dabigatran should be avoided in patients with a creatinine clearance < 15 mL/min. Dabigatran's major drug interactions are solely related to concomitant use of P-gp inducers and inhibitors. The pro-drug of dabigatran, but not its active metabolite, is a substrate for P-gp. Thus, the absorption of the pro-drug can

be significantly altered by the co-administration of medications that are P-gp inducers or inhibitors. For example, rifampin, a strong P-gp inducer, decreases the AUC of dabigatran by approximately 66%. Separation of the rifampin and dabigatran dosing is unlikely to significantly reduce this interaction.

Apixaban

Apixaban is an oral direct, reversible factor Xa inhibitor. Apixaban is rapidly absorbed, reaching maximum plasma concentrations about 3–4 hours after ingestion, and has a half-life of approximately 8–15 hours in healthy subjects. Approximately 25% of apixaban is excreted by the kidneys and 75% through the hepatobiliary system.

CONCLUSION

Normal blood physiology allows the blood for coagulation in the appropriate setting, but a variety of disease states can alter the balance of pro- and anti-coagulant factors lead to thrombus formation in the blood vessels. DVT is diagnosed with increasing precision using D-dimer assay, and an expanding array of imaging modalities including US, CT, and MR venography. The antithrombotic therapy prevents the coagulation without promoting bleeding. The molecules that contribute to thrombosis continue to be identified, and these could be new targets for the next generation of antithrombotic therapy. The identification of deep vein thrombosis risk patients and measuring the concentrations of circulating factors, such as tissue factor could helpful for prevention of disease complications. Venous thromboembolism is a potentially life-threatening event. To date different agents are available for the effective treatment of acute VTE and the prevention of recurrence. Based on individual clinical characteristics and laboratory parameters, patient-specific treatment modalities should be tailored and clinical decision-making should be followed by necessary guidelines, risk assessment scores would beneficial for prevention of venous thrombo embolism. DVT is a potentially life threatening condition that can lead to cause morbidity and mortality. A proper disease diagnostic pathway involving pretest probability, use of novel oral anticoagulant therapy, D-dimer assay, and venous ultrasound serves as a more reliable way of detecting DVT. Prevention consists of both mechanical and pharmacological modalities and is encouraged in high risk category.

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