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Research Article

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Literature Review on Prophylaxis of Deep Venous Thrombosis and Pulmonary Embolism

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ABSTRACT

Background: *Deep Venous Thrombosis (DVT) and subsequent Pulmonary Embolism (PE) are one of the most eminent causes of preventable deaths in nosocomial settings. The prevalence is increasing and they have variable clinical presentations encountered in community settings as well as hospitalized patients requiring timely and obligatory prophylaxis.* ***Objective:*** *This study aims to review prophylactic measures for deep venous thrombosis/pulmonary embolism highlighting implemented pharmacologic and mechanical interventions, newer and yet investigational techniques such as neuromuscular electrical stimulation towards reducing prevalence of venous thromboembolism.* ***Materials and Method****s: A review of relevant articles published between the years of 2000 to 2019 in English language was done using the databases of PubMed Pico, Google Scholar and Google, using the predetermined keywords.* ***Conclusion:*** *Venous thromboembolism prevalence is increasing and among the various available methods for thromboprophylaxis, pharmacologic approach is the most superior which involves making use of either unfractioned or low molecular weight heparin although the most efficacious is low molecular weight heparin as evidenced by several meta-analyses. Anticoagulants have numerous side effects leading to limitations of their use and in such situations, mechanical methods such as intermittent pneumatic compression (most effective), graduated compression stockings, and venous foot pump scan can be used. In circumstances where both medicines and mechanical approach become impractical, neuromuscular electrical stimulation can be implemented even though additional research is required to further elucidate its efficacy and implications.*

Key words: *Deep Venous Thrombosis, Pulmonary Embolism, Anticoagulants, Compression Stockings, Venous Foot Pumps, Neuromuscular Electrical Stimulation.*

INTRODUCTION

Deep venous thrombosis (DVT) and pulmonary embolism (PE) are two diseases collectively called venous thromboembolism (VTE), a broad term that comprises both conditions. The formation of a blood clot in the deep

veins is defined as deep venous thrombosis, and mostly occurs in the lower extremities and to a lesser extent in the upper extremities. On the other hand, the formation of a blood clot in the pulmonary artery or its branches called pulmonary embolisms, mostly originate from embolization of a thrombus from the deep veins of the legs. Pulmonary embolism is estimated to occur in about one-third to one-half of the patients diagnosed with DVT [1]. Therefore, deep venous thrombosis prevention is established to decrease the incidence of pulmonary embolism, which is recognized as a life-threatening condition [2]. Prophylaxis plays an important role in culminating the occurrence of these serious blood clot related conditions in both medical and surgical patients [3]. A variety of prophylaxis methods are available, each with its own advantages and limitations, which we intend to explore in this literature review.

MATERIALS AND METHODS

Sample:

A comprehensive literature review was done using the available biomedical databases; including Google scholar, Google, and PubMed Pico. Only the studies published between the years 2000-2019 in English language were included. The keywords used to search through the databases were deep venous thrombosis, pulmonary embolism, anticoagulants, heparin, low molecular weight heparin, unfractioned heparin, intermittent pneumatic compression, graduated compression stockings, venous foot pumps and neuromuscular electrical stimulation. Additional relevant articles were recruited from reference lists of each of the included studies.

Analysis:

No software was employed for the analysis of the extracted data; however, multiple revisions were done by each of the authors to ensure the validity of the extracted information and, to minimize the errors made by individual perception.

DISCUSSION

The development of blood clot in the legs and/or lungs is considered to be one of the most common causes of preventable hospitals mortality [4]. The incidence of venous thromboembolism (VTE) in the absence of prophylaxis is estimated to range between 10 to 80 percent [5, 6]. Before exploring the available prophylactic measures for these grave conditions, it is relevant to understand their underlying pathophysiology. The pathogenesis of DVT and PE can be attributed to the presence of an amalgam of conditions that collectively increase the likelihood of blood clotting. The triad of blood clot risks includes blood stasis, hypercoagulable state, and injury to the endothelial layer of the blood vessel, which collectively comprise the Virchow's Triad [7, 8]. Despite being a naturally occurring commonality, Virchow's Triad must be met with aggressive prophylactic measures to encumber serious blood clot associated complications. Risk factors that predispose to Virchow's Triad include but are not limited to obesity, immobilization, malignancy, congenital factors like factor V Layden, thrombophilia, etc., trauma, surgery, tobacco smoking, diabetes, and dyslipidemia [9]. According to Stones et al. (2017) [10], among the preventable causes of morbidity and mortality is venous thromboembolism. An estimated 1 per 1000 people is affected and contributes in total to about 60, 0000 – 100,000 deaths annually. Any changes in Virchow's Triad will cause the lack of balance between pro- and anti-coagulant factors which will conceptively lead into thrombus formation following venous stasis, vascular injury, and hypercoagulability. Several diagnostic tools are used to increase the sensitivity and specificity for diagnosing of DVT and these includes D-dimer assay, Diagnostic imaging such as Ultrasound scan with real-time imaging such as duplex and color-flow Doppler to characterize the clot, Conventional Contrast Venography, Computed Tomography (CT) Venography, and Magnetic Resonance (MR) Venography [10].

The high prevalence and gravity of outcomes of PE and DVT make the implementation of prophylactic measures indispensable. Additionally, pulmonary embolism not only results in considerable pulmonary distress but may even lead to death [11]. The available prophylactic measures for DVT and PE prophylaxis range from pharmacologic to mechanical methods. The pharmacologic prophylaxis is considered the most effective approach which is evidenced by several randomized clinical trials [12, 13]. These studies reveal that prophylaxis with unfractionated heparin (UFH), low molecular weight (LMW) heparin, and fondaparinux are superior to both mechanical approaches as well as placebo [14]. The most preferred medication, among the variety of medications

available, is low molecular weight heparin. This is supported by a multi-center meta-analysis that points out that LMW heparin is superior to other forms of heparin, especially in the high-risk patient population [15]. Stones et al. (2017) noted that anticoagulation is an essential component in treatment of DVT even though in some exceptional cases, oral anticoagulants alone can be used as a therapy for DVT while in cases of proximal deep vein thrombosis which is of an extensive burden, mechanical- and catheter-directed thrombolysis (CDT) therapy can be instituted in rapid lysis of clot in the acute phase of DVT especially to reduce the risk of post-thrombotic syndrome. Their study further noted that DVT is diagnosed with increasing precision using the Wells criteria [10]. In the meta-analysis, data was collected from 36 different randomized trials including patients at both low and high risk of developing venous thromboembolism. The study compared heparin to placebo for prevention of both DVT and PE. The results reveal that both forms of heparin, namely unfractioned heparin and LMW heparin decreased the risk of both deep venous thrombosis (risk ratio [RR] = 0.33; 95%; RR = 0.56; 95%, respectively) and pulmonary embolism (RR = 0.64; 95%; RR = 0.37; 95%, respectively). Compared to unfractioned heparin, LMW heparin was found to be superior as it was associated with a lower risk of DVT (RR 0.68; 95% CI 0.52-0.88), without any significant difference in the side effects of thrombocytopenia and bleeding [15]. Therefore, the most superior approach for prevention of both DVT and PE is low molecular weight heparin.

According to Stones et al. (2017), Anticoagulation is considered the mainstay of therapy for DVT and also considered as the first option in preventing progression of DVT to PE and to help prevent the recurrence of thrombosis. It is documented that patients with DVT without anticoagulation treatment have a 3% increase in 30-day mortality rate, and this risk increases 10 fold in DVT patients who develop PE [16, 17]. The rise of direct oral anticoagulants (DOACs) as treatment option for DVT has encouraged the need to compare these newer agents with the more traditional vitamin K-antagonists (VKAs).

DOACs are an excellent alternative to VKAs among which warfarin can be called which is for many reasons like they do not require bridging, can be taken orally, have less drug-drug interactions, and they do not need frequent laboratory monitoring, and finally they have shown to treat DVT as effective as VKA therapy. On the other hand, the main disadvantages of DOACs is their long half-life which makes them less appropriate for inpatient treatment and also contraindicated in case of poor hepatic and/or renal function. Also, DOACs is considered as a novel therapy; therefore, it has not been investigated completely in various populations; accordingly, it is not recommended in cases of thrombocytopenia, active malignancy, or high bleeding risk [16, 18].

Anticoagulants, however despite being superior to other forms are not without adverse effects. Some of the established side effects of anticoagulants include active bleeding, including gastrointestinal bleeding and intracranial hemorrhage. Anticoagulants are contraindicated in patients undergoing surgery in the immediate 6 to 12 hours, in patients with a severe coagulopathy, and in patients with a severe bleeding diathesis or thrombocytopenia [19]. In such circumstances where the use of pharmacology becomes unfeasible, mechanical methods such as graduated compression stockings, intermittent pneumatic compression, and venous foot pumps are advised for the prevention of VTE [20]. Intermittent pneumatic compression (IPC) is a mechanical approach for VTE prophylaxis that prevents venous stasis by enhancing blood flow in the deep veins of the legs [21]. Additionally, IPC increases the endogenous fibrinolytic activity by decreasing plasminogen activator inhibitor-1 (PAI-1) [22]. The efficacy of IPCs is demonstrated by a large randomized trial involving 2876 patients with acute stroke. The results revealed that the use of IPC when compared to using no device at all, decreased the incidence of VTE within 30 days (12 versus 8.5 percent) without affecting mortality (13 versus 11 percent) [23]. The well-recognized side effect of IPC is skin breakdown particularly observed in elderly patients. Moreover, IPC is contraindicated when there is evidence of leg ischemia owing to peripheral vascular disease.

Graduated compression stockings and venous foot pumps are also used for prevention of VTE; however, there is a comparative lack of data available on efficacy and safety of these methods. A meta-analysis, on graduated compression stockings, revealed this method to be of limited benefit [24]. Another randomized trial revealed graduated compression stockings to be associated with a four-fold increase in the risk of skin necrosis and ulcers [25]. Similarly, studies performed on venous foot pumps are deficient; however, the available literature supports their use in surgical patients [26]. Theoretically, venous foot pumps prevent VTE by stimulating lower limb venous flow at the level of the foot [27]. While mechanical methods are increasingly implemented in clinical practice, the transition to a pharmacologic agent is recommended as soon as the bleeding risk of the patient is reversed or decreased to an acceptable level [28]. Several clinicians prefer using a combined approach for thromboprophylaxis that is a combination of mechanical and pharmacologic methods. One large scale randomized trial assessing the efficacy of a combined approach concluded no added benefit on the risk of VTE or mortality of using graduated compression stockings with low dose LMW heparin in medical patients [29]. Another

randomized trial involving as many as 2003 patients revealed encouraging results with reduced incidence of VTE with a combination of intermittent pneumatic compression (IPC) and LMW heparin. However, the mortality remained the same in both groups (26 percent each) [30]. Further research is therefore required to establish recommendations for combined implementation of pharmacological and mechanical methods.

Due to the complexity of medical histories of patients, both pharmacologic and mechanical interventions may sometimes become unfeasible. In such circumstances, neuromuscular electrical stimulation (NMES) systems are often used which work by sending electrical pulses through tissues to activate specific leg muscle groups causing muscle contractions that have been shown to augment the speed at which blood travels through those vessels; therefore, increasing blood flow mitigates the risk factor of stasis [31]. Neuromuscular electrical stimulation systems can be added as an additional layer of prevention for DVT and/or PE in patients at risk of thrombosis based upon the evidence of an overall decreased incidence of these blood clot associated conditions compared to the use of no prophylaxis at all [32, 33] The wide availability and low-cost of neuromuscular electrical stimulation systems make it approachable to most patients for aiding recovery as an attractive protective measure [34].

CONCLUSION

Deep venous thrombosis and pulmonary embolism are fairly prevalent conditions that health care professionals are expected to encounter in day to day settings. Several methods are available for prophylaxis but need to be tailored to best suit the individual needs of patients. Any changes in Virchow's Triad will cause the lack of balance between pro- and anti-coagulant factors which will conceptively lead into thrombus formation following venous stasis, vascular injury, and hypercoagulability. Several diagnostic tools are used to increase the sensitivity and specificity for diagnosing of DVT and these includes D-dimer assay; Diagnostic imaging such as Ultrasound scan with real-time imaging such as duplex and color-flow Doppler to characterize the clot; Conventional Contrast Venography; Computed Tomography (CT) Venography, and Magnetic Resonance (MR) Venography. The treatment of DVT has usually included VKAs such as warfarin with heparin or fractionated heparin bridging. With the arrival of direct oral anticoagulants (DOACs), therapeutic options for DVT were encouraged, but the important factor was the safety and efficacy of recently introduced agents compared to conventional therapy. The most preferred method of DVT treatment of all is pharmacologic in particular low molecular weight heparin. In circumstances where, heparin cannot be used due to bleeding or thrombocytopenia risk or other contraindications, mechanical methods such as intermittent pneumatic compression can be employed. Due to the complex nature of medical histories, when both medicines and compression techniques can no longer be considered for the prevention of DVT, NMES can serve as a savior. Owing to the ease of availability and low cost, it should remain as a considerable addition if not alternative to the essential prophylaxis of blood clot associated diseases.

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