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Venous Thromboembolism: A Persian Perspective to Prevention, Diagnosis, and Treatment

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Introduction and Epidemiology:

Historically, Avicenna, the great Persian physician, philosopher and scientist described several issues concerning deep vein thrombosis (DVT) almost 1000 years ago in his book “*Ghanoon*” (*the Canon of Medicine*), which was a major reference book for biomedical sciences in Europe until the 17th century. [1] Hundreds of years of research and experience have brought us a much clearer understanding of venous thromboembolism (VTE), nevertheless, he had correctly described varicose veins and parts of the clinical picture of DVT, and had indicated the association of both conditions with old age. The major recommended treatment for lower extremity venous thrombosis at that time was open surgical thrombectomy. Although we could not find clear description of pulmonary embolism in his *Canon of Medicine*, he had cautioned that “...*care should be taken while cleaning the veins from the obstructing material or the particles might migrate to the upper organs...*”. Remarkably, he had also recommended leg elevation and compression bandage for varicose veins. [2]

In the current era, nationwide epidemiologic studies on VTE are missing in Iran, even though the figures are expected not to be far from that of the Western society. So far, the NRITLD (write out abbreviation first time used) DVT registry is the largest prospective registry of objectively-confirmed DVT patients [3], however, since the NRITLD is a referral tertiary care center, extrapolation of the findings of that registry to all Iranian VTE patients is limited. The NRITLD DVT registry has so far provided promising data. In terms of risk factors and presenting signs and symptoms, no marked differences were present between the data from the European and North American registries and that of our registry. Our registry also has focused on some newer issues, namely suggesting that significant differences do exist about clinical outcomes and coexisting conditions, based on thrombus sidedness. Patients with right-sided DVT were shown to have a higher rate of pulmonary embolism, embolic burden score, and massive pulmonary embolism. Moreover, right-sided DVT was significantly more common in cancer patients. [3] Further details are beyond the scope of this manuscript but such findings are now under investigation in collaboration with other international investigators. The few existing studies in Iran suggest that predisposing factors to VTE are similar in Iran and the Western society.

Interestingly, injection drug use has been commonly found in patients with lower extremity DVT. [3,4] Moreover, tuberculosis (TB), which is not so common as before, is still a major health problem in some parts of Iran. Since TB can affect all three parts of the Virchow's triad, at NRITLD, a referral center for tuberculosis in the Middle East, we evaluated the coexistence of TB and VTE. Our reported number of 46 cases, is up to now the largest ever reported in the literature. [5] More detailed assessment of this coexistence is now under investigation at our center.

Even though large case-control studies evaluating the three common genetic predisposing factors to VTE (i.e. factor V mutations, prothrombin G20210A mutant variants, and methylenetetrahydrofolate reductase gene mutations) are missing and the results of the available studies are limited by small number of enrolled patients or methodological problems, there is a general agreement that such mutations, particularly Leiden V mutation, occur more commonly in Iranian VTE patients, compared to healthy controls. [6-8]

Prophylaxis:

Until recently, thromboprophylaxis was infrequently considered at Iranian hospitals, mainly because of the disbelief that the Iranian people were not susceptible to VTE. A report from a university hospital in Tehran during the 1990s confirmed that none of the 210 patients with diagnosed symptomatic VTE had received thromboprophylaxis. [9] Other studies suggested that thromboprophylaxis appropriateness was likewise very low at several departments. [10]

In the past few years, however, several attempts have been made to enhance the physicians' knowledge and awareness of the significance of VTE, particularly for hospitalized patients in Iran. Much progress has been made in the last ten years to introduce computerized systems in Iranian healthcare facilities. However, even today now, there are no hospitals or medical centers with fully electronic medical records in Iran. Therefore, using electronic alerts systems for VTE prevention [11] are not feasible at Iranian hospitals. Accordingly, to improve VTE prophylaxis state and thromboprophylaxis appropriateness, we devised a study using sticker reminders that were pasted on the patients' files. Compared to the time period before intervention, our intervention effectively lead to improved thromboprophylaxis appropriateness (from 70.4% to 78.1%, $P=0.03$), reduced prophylaxis underutilization, and reduced thromboprophylaxis initiation delay in at-risk patients ($P=0.03$, and $P=0.01$ correspondingly) while it did not lead to increased risk of major bleeding or other major adverse events. [12] In a separate study, we also evaluated the different types of pharmacological and non-pharmacological prophylaxis options and thromboprophylaxis appropriateness, as well as local and systemic complications due to thromboprophylaxis at hospitalized patients at Masih-Daneshvari Hospital, NRITLD, prospectively (AssessMent of ProphylAxis for VenouS Thromboembollism in Hospitalized patients: The MASIH Study). The findings of this study will be published soon.

Mechanical prophylaxis is infrequently used at Iranian hospitals. While it is partly due to lack of the required equipment (e.g. paucity of intermittent pneumatic compression devices) and lack of knowledge of responsible physicians plays a major role. For several physicians in Iran

“*thromboprophylaxis*” is almost synonymous to “*pharmacological prophylaxis*”^[13] . Cardiac surgeons are exceptions, they commonly recommend compression stockings postoperatively.

A separate analysis of data from the MASIH (type out abbreviation first time used) study showed that the effects of our intervention of pasting sticker reminders did not extend far beyond the intervention period and prophylaxis appropriateness showed a declining trend in the MASIH study, compared to the post-intervention period after pasting sticker reminders for VTE prophylaxis. This issue needs further investigation but suggests that sticker reminders should be used continuously to keep the thromboprophylaxis appropriateness close to the desired standards.

Currently, in order to raise the staff awareness for VTE prophylaxis assessment in hospitalized patients, we utilize a group of VTE nurses who check the clinical files of all the hospitalized patients right after admission, and every ten days if the duration of stay of the patients will be beyond 10 days, or every time the patient’s condition changes dramatically (e.g. need for unforeseen surgical procedure).

Based on our experience, we have found three major categories of problems concerning inappropriate VTE prophylaxis:

- 1) Lack of proper knowledge of VTE prophylaxis among healthcare providers (risk assessment, evaluation of contraindications, and deciding the proper prophylaxis strategies)
- 2) Neglect of the healthcare providers because of excessive workload or lack of desired experience
- 3) Lack of determination and/or overly-conservative decisions to abstain scientifically-unproven risks or to exaggerate the scientifically-proven risks (mainly bleeding)

The first problem could be tackled using several educational strategies including (but not limited to) more comprehensive discussion of VTE at medical schools’ core curricula, and CME programs for healthcare providers. The second obstacle could be dealt with in two different ways, one is to reduce the physicians’ workload so that each physician provides a higher standard of care for a lesser number of patients. Since this is less practical in many settings because of economical limitations, the alternative could be providing various reminder systems to inform the responsible physicians from the risk level of their patients. The last issue is very difficult to resolve, but perhaps could be improved by case presentation sessions in which clear evidence about the risks and benefits of thromboprophylaxis would be thoroughly reviewed. An audit system can monitor how the above steps will be undertaken. Recently, a series of adapted recommendations were developed for VTE prophylaxis, but their widespread use was limited. ^[14]

Diagnosis:

Several pretest clinical prediction models, especially the Wells models for diagnosis of DVT and PE ^[15,16] are used or over-used at several medical centers in Iran, particularly at academic hospitals. However, some studies, with retrospective design and certain methodological limitations, suggested

that diagnostic accuracy of the Wells and Geneva clinical prediction rules are moderately lower in Iranian patients. [16,17] In those studies, Wells criteria could correctly predict the likelihood of pulmonary embolism in almost two thirds of PE patients, while one-third of cases with symptomatic objectively-confirmed PE were designated as “unlikely” to have PE, by the aforementioned criteria. The modified Geneva score showed lower false-negative rates, although not as good as that of the derivation set. [17-19] Those studies, however, mostly enrolled hospitalized patients (rather than those with initial evaluation at the emergency room), in whom the d-dimer levels were already expected to be higher than normal. Accordingly, solo reliance on the clinical prediction rules, to supplant rather than as a supplement to clinical decision making, was not feasible.

In the prospective NRITLD DVT registry, PE Wells score could not predict the occurrence of PE ($P=0.50$), or massive PE ($P=0.81$). In addition, there was no association between the embolic burden score and PE Wells score, either. Interestingly, the DVT Wells scores were inversely associated with subsequent diagnosis of PE ($P=0.001$). [3]

Even though multidetector computed tomography machines are currently available at some medical centers in Iran, the standard para-clinical diagnostic procedures for assessment of VTE include lower limb ultrasonography, single-detector computed tomography pulmonary angiography, and less frequently ventilation/perfusion scanning. Although lack of widespread availability of multidetector CT scans may lead into missing patients with subsegmental PE, evidence exists that adverse outcomes of this problem are negligible and serial ultrasonography could be useful for at-risk patients with negative results for PE with single-detector scans. [20,21] Transthoracic echocardiography is routinely performed for those with suspected massive-PE, or patients with suspected PE who have major underlying cardiorespiratory problems. Recently, digital photoplethysmography (DPPG) has been used as a simple diagnostic tool for DVT at our center with appreciable sensitivity, although the ideal clinical setting for its use needs further investigation. [22,23]

Treatment:

In February 2008, guidelines for VTE management for primary care physicians in Iran were developed in collaboration with the World Health Organization (WHO). [24]

No national practice guidelines or protocols for VTE treatment for specialists exists in Iran, and the majority of current practice is based on the American College of Chest Physicians (ACCP) recommendations [25], with adjustments based on the availability/ functionality of recommended statements at the local settings.

Unfractionated heparin is the mainstay of VTE treatment in Iran, and the most commonly used treatment plan is 80U/kg as bolus, followed by heparin infusion with adjustments according to the Raschke’s nomogram. [26] Enoxaparin sodium (Clexane®) was first launched in Iran in 2001 and is also used widely although home treatment for acute VTE is rarely performed in Iran. Whereas drugs such as rivaroxaban, apixaban, bivalirudin, hirudin, fondaparinux, and idraparinux are not available in Iran, dabigatran is available at a few major cities, although without insurance coverage. For patients with proven or suspected heparin-induced thrombocytopenia (HIT), danaparoid is the only choice, which is just available at a few institutions at major medical centers.

Open surgical thrombectomy has been performed with excellent results at experienced centers for patients with massive PE or severe chronic thromboembolic pulmonary hypertension (CTEPH) [27-29], however, percutaneous mechanical thrombectomy (PMT) is not an available option in Iran. Interventional cardiologists perform several procedures in Iran, however, PMT is not included in their list, or the educational curriculum of interventional cardiology fellows in Iran. Similarly, catheter-directed thrombolysis for lower extremity DVT is extremely rare.

Public Awareness

In general, public awareness about venous thromboembolism is low in Iran. Several websites with the native (Farsi) language provide a wide array of information about manifestations, complications, diagnosis, treatment, and prevention of VTE, however, web access is almost limited to educated people in Iran. Whereas there is substantial contribution to awareness programs about coronary artery disease and stroke using various media, this is not the case with VTE. Nevertheless, attempts have been made to inform passengers of overseas flights to observe the safety precautions for VTE prevention.

Summary

In summary, much progress has been made in prevention, diagnosis, and treatment of venous thromboembolic disease in Iran. However, it is still a long way away from the North American standards. In this evolutionary process, academic centers such as NRITLD have provided substantial contribution.

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