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Research Article

Effect of Prophylaxis for Deep Venous Thrombosis in Traumatic Spinal Cord Injury

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Abstract

Aim: Injuries to prevent DVT. Incidence of deep venous thrombosis in traumatic spinal injury patients and effect of prophylaxis for deep venous thrombosis in traumatic spinal cord injury patients in a tertiary care hospital in Indian setting.

Objectives: To identify the risk factors for DVT in traumatic spinal cord injury patients in a tertiary care hospital in Indian.

Conclusion: These results suggest that active measures for prevention are important beginning from the acute stage of injury and pharmacological thromboprophylaxis can be considered for all patients with acute spinal cord injury patients unless there is not ongoing bleeding or severe coagulopathy.

Keywords: Deep Venous Thrombosis; Spinal Cord Injury; Trauma; Coagulopathy

Introduction

Thrombosis is defined as " hemostasis in the wrong place," and it is a major cause of morbidity and mortality in a wide range of arterial and venous diseases. Vascular integrityand blood fluidity are maintained by complex interplay between procoagulant and anticoagulant properties provided by the blood, the vasculature, and sub vascular elements.

Virchow's triad of hypercoagulability, endothelial injury, and venous stasis [1]. The primary forms of venous thrombosis are deep-vein thrombosis (DVT) in theextremities and the subsequent embolization to the lungs (pulmonary embolism),referred to together as venous thromboembolic disease [2-4].

Virchow's triad leads to recruitment of activated platelets, which release microparticles. Thesemicroparticles contain proinflammatory mediators that bind neutrophils, stimulating them to release their nuclear material and form web like extracellular networks called neutrophil extracellular traps. These prothrombotic networks contain histones that stimulate platelet aggregation and promote platelet dependent thrombin generation. Venous thrombi form and flourish in an environment of stasis, low oxygen tension, and upregulation of pro-inflammatory genes.

The factors associated with increased risk of thrombosis includes traumatic fracture, like headinjury, more than 3 ventilator days, chest injury, pelvic fractures, lower extremity injury, pine injury and shock which are all independent variables associated with this complicationsand non-traumatic risk factors like use of estrogen based oral contraceptives, genetically determined protein abnormalities [5,6].

Deep venous thrombosis and subsequent PE remain significant causes of morbidityand mortality in spinal cord injured patients. In

Western populations, the incidenceof DVT is 1-2 people per 1000 annually. In comparison, the incidence of DVT in Asian population is believed to be lower, with an incidence of 1.3-6.1% [7-10]. It has been observed that there is a 10-fold increase in risk of DVT in a paretic leg in stroke as comparedto non-paretic leg [11,12].

History and clinical examination are not reliable ways of diagnosing DVT. Lower extremity DVT can be symptomatic or asymptomatic. Patients with lower extremity DVT often do not present with erythema, pain, warmth, swelling, pitting edema or tenderness. Symptomatic patients with DVT may present with lower extremity pain, calf tenderness, lower extremity swelling and Homans' sign, pain on passive dorsiflexion of foot, may be demonstrable in DVT. However, in SCI patients, Homan's sign may not be demonstrable due to sensory impairment. Most of these features lack specificity; hence clinical evaluation usually impliesthe need for further evaluation [13-15].

The incidence of DVT is reported to be anywhere from 47% to 100% in lower limbs following SCI. Classical clinical features are seen in only one-fifth of patients. A veryhigh index of suspicion is, therefore, necessary to avoid this preventable complication [16-18].

A review of the general surgical literature shows that the incidence of DVT can bediminished by as much as 20% to 40% with mini dose prophylactic heparin.

The quantitative plasma D dimer enzyme linked immunosorbent assay (ELISA) rises in the presence of DVT or PE because of the breakdown of fibrin by plasmin. Elevation of D dimer indicates endogenous although often clinically ineffective thrombolysis. The sensitivity of theD dimer is > 80% for DVT (including isolated calf DVT) and > 95% for PE. The D dimer is less sensitive for DVT compared to PE as thrombus in DVT is smaller. A normal D dimer is a useful 'rule out' test. However, the D dimer assay is not specific. Levels are also increased in myocardial infarction, pneumonia, sepsis, cancer, and the postoperative state and those in second and third trimester of pregnancy.

Ultrasound of deep venous system relies on venous compression loss as the primary criteria for DVT. When normal vein is images in cross section, it readily collapses with gentle manual pressure from the ultrasound transducer. This creates illusion of a "wink". With acuteDVT, veins losses its compressibility because of passive distension by acute thrombus. The diagnosis of acute DVT is even more secure when thrombus is directly visualized. It appears homogeneous and has low echogenicity. The vein itself often appears mildly dilated, and collateral channels may be present.

Other modalities which help in diagnosis of DVT are chest roentgenography, chest CT, lungscanning. Contrast enhanced magnetic resonance imaging, echocardiography and invasive modalities like pulmonary angiography and contrast phlebography.

The incidence of venous thromboembolism in SCI patients among Asians has been topic of controversy. While some question its existence, others believe that the incidence is at par with that reported from the west. Low incidence among Asians has been attributed to severalfactors like high fibrinolytic activity, complete lack of Activated Protein C resistance, a higher incidence of blood group 'O', low intake of fat, lower incidence of obesity, climatic differences etc. However, the most important factor appears to be lack of comprehensive studies about its incidence in SCI patients in the Asian countries. The Assessment of the Incidence of Deep vein thrombosis in Asia (AIDA) multicenter multinational prospective study reported that the rate of venographic thrombosis in the absence of thromboprophylaxis after major joint surgery in Asian patients was similar to that previously reported in Westernpatients. Therefore, the incidence of venous thromboembolism after major orthopaedic surgery in Asian patients may not be low. It may be consistent with the rates observed in Western countries.

Though the reports on its incidence after hip and knee surgeries have started appearing fromIndia, its incidence in SCI patients is still unreported, resulting in uncertainty about thromboprophylaxis for our patients.

Prevention of thromboembolism in spinal cord injury (SCI) is important clinically as DVT and PE are not only common complication in acute spinal injury (SCI) but also major cause ofmorbidity and mortality. The aim of this study is to account for the efficacy of the prophylactic measures used in cases of traumatic spine injuries to prevent DVT.

Aim

Incidence of deep venous thrombosis in traumatic spinal injury patients and effect of prophylaxis for deep venous thrombosis in

traumatic spinal cord injury patients in a tertiary care hospital in Indian setting.

Objectives

To identify the risk factors for DVT in traumatic spinal cord injury patients in atertiary care hospital in Indian setting

Materials And Methods

A prospective hospital based randomized clinical trial done in department of orthopaedics , cio, safdarzang hospital , New Delhi for a period of 2 year (2016-2018). A total of 100 patients enrolled and divided equally into study and control group.

Inclusion criteria

Patient age >18 years with Cervical spinal cord injury with quadriplegia or Thoracolumbarspinal cord injury with paraplegia

Exclusion criteria

Incomplete spinal cord injury patient or without neurological deficit, Pathological fractures ofspine, Congenital deformity of spine, Localized infection in extremities, Deranged PT/INR values.

Methodology

After achieving an informed consent, patients meeting the inclusion criteria were recruited into the study. Date of injury along with mode of injury were noted and demographics of patient were noted including sex and age. Additionally, severity of injury and associated musculoskeletal injury were noted. presence of co-morbidities like hypertension, diabetes, thyroid disorder noted. They were then assessed for evidence of DVT using clinical assessment, D-dimer test and Doppler sonography. Clinical evidence of DVT in the lower limbs was assessed as follows

Measurement of calf circumferences, Presence of pitting edema, Positive Homan's sign,Presence of collateral superficial veins (non-varicose), Skin changes such as redness,warmth, and blisters.

Screening for DVT was done with the help of D-dimer assay. D-Dimer assay was done with the help of Elite Pro machine which works on the principle of latex agglutination assay.

Those who had positive D-Dimer assay were examined by Doppler ultrasonography. The anterior and posterior tibial veins, peroneal veins popliteal veins, deep femoral veins and saphenofemoral junction were examined. Inferior vena cava was examined only in the patientsdiagnosed with DVT. Examination was done using a 15 Hz linear transducer. Presence of an intramural thrombus, increase in vein diameter, incompressibility, no flow on color Doppler,loss of augmentation and loss of plasticity were considered as signs of DVT.

A positive Doppler confirmed DVT. Those who had a negative Doppler test and a negative D-dimer test were continued with prophylactic therapy and followed up for 2 months. Patients with negative Doppler and positive D-dimer test were examined with repeat Doppler in one week. Blood samples were taken for D-dimer assays on the day of admission and were repeated every fortnight with D dimer values and clinical evaluation both in study and in control group. Enoxaheparin was stopped on the day of surgery and resumed next morning. The following algorithm was followed for diagnosis and management.

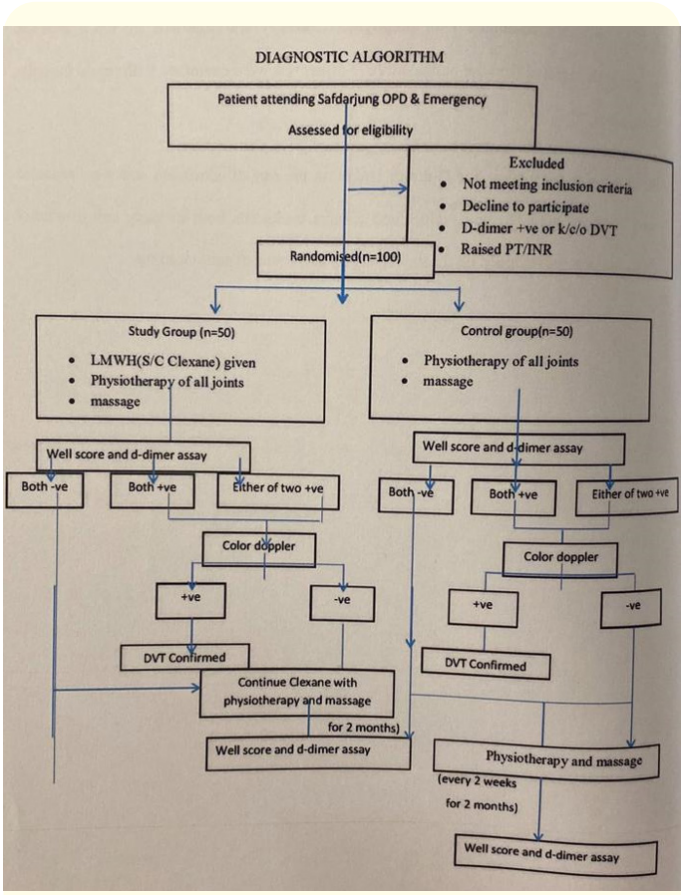

Figure 1

Observations and Results

In this study a total of 100 patients with spinal cord injury, who met the inclusion criteria, were enrolled in the study. Patient were then randomly divided into study group and control group with 50 patients each. Demographics of all the patients who were included in the studygroup as well as control group were noted and the patient underwent clinical assessment for DVT and D-Dimer assay and color Doppler were done as specified in material and methods. All the patients included in the study as well as control group underwent surgical decompression and fixation.

In this study there were 100 patients with 64 males (64%) and 36 females (36%)There were a total of 30 males (60%) and 20 females (40%) in the study group. There were a total of 34 males (68%) and 16 females (32%) in the control group.

Patient who had shown elevated D- dimer value (i.e., > 500ng/ml) at the time of study where notincluded in the study. The mean D-Dimer levels at the time of admission in the study group were 274.74 ng/ml with a standard deviation of 35.74ng/ml. The median levels of D-Dimer atthe time of admission in the study group were 273.5 ng/ml with a range of 210-347 ng/ml withinter quartile range of 251 to 293. The mean D-Dimer levels at the time of admission in the control group were 286.88 ng/ml with a standard deviation of 45.58 ng/ml. The median levelsof D-Dimer at the time of admission in the control group were 277.5 ng/ml with a range of 211-369 ng/ml with inter quartile range of 258-325ng/ml.

The mean D-Dimer levels after 2 weeks in the study group were 327.3 ng/ml with a standard deviation of 88.42 ng/ml. The median levels of D-Dimer at the time of admission in the studygroup were 305 ng/ml with a range of 210-643 ng/ml with inter quartile range of 275.5-354. The mean D-Dimer levels after 2 weeks in the control group were 347.46ng/ml with a standarddeviation of 118.48 ng/ml. The median levels of D-Dimer after 2 weeks in the control group were 307.5 ng/ml with a range of 234-753 ng/ml with inter quartile range of 283-358ng/ml.

The mean D dimer value after 2 weeks developing DVT in the study group were 521.4ng/ml with a standard deviation of 135.85, with median 444ng/ml whereas the mean D dimer value after 2 weeks developing DVT in the control group were 572ng/ml with a standard deviation of 141.27, with median of 588. On stastical analysis, the relationship between D-Dimer levelsat 2 weeks and occurrence of DVT was found to be statistically significant (p value 0.001).

The mean D-Dimer levels after 4 weeks in the study group were 340.31 ng/ml with a standarddeviation of 98.13 ng/ml. The median levels of D-Dimer at the time of admission in the studygroup were 314.5 ng/ml with a range of 254-710 ng/ml with inter quartile range of 298- 342ng/ml. The mean D-Dimer levels after 4 weeks in the control group were 345.15ng/ml witha standard deviation of 119.86 ng/ml. The median levels of D-Dimer after 4 weeks in the control group were 317 ng/ml with a range of 245-788 ng/ml with inter quartile range of 291-346ng/ml. On stastical analysis, the relationship between D-Dimer levels at 4 weeks and occurrence of DVT was found to be statistically significant (p value <0.0001).

The mean D dimer value after 4 weeks developing DVT (3 patients) in the study group were 699ng/ml with a standard deviation of 11, with median 699ng/ml whereas the mean D dimer value after 4 weeks developing DVT (4 patients) in the control group were 705ng/ml with a standard deviation of 77.58, with median of 715.5ng/ml. On stastical analysis, the relationship between D-Dimer levels at the time of admission and occurrence of DVT was found to be statistically significant.

The mean D-Dimer levels after 6 weeks in the study group were 315.66 ng/ml with a standarddeviation of 23.06 ng/ml. The median levels of D-Dimer after 6 weeks in the study group were313 ng/ml with a range of 267-378 ng/ml with inter quartile range of 301-331. The mean D- Dimer levels after 6 weeks in the control group were 318.14ng/ml with a standard deviation of 26.91 ng/ml. The median levels of D-Dimer after 6 weeks in the control group were 318ng/mlwith a range of 249-387 ng/ml with inter quartile range of 299-330ng/ml.

The mean D-Dimer levels after 8 weeks in the study group were 313.84ng/ml with a standard deviation of 44.28 ng/ml. The median levels of D-Dimer after 8 weeks in the study group were308 ng/ml with a range of 238-445 ng/ml with inter quartile range of 280-341ng/ml. The meanD-Dimer levels after 8 weeks in the control group were 316.33ng/ml with a standard deviationof 34.97 ng/ml. The median levels of D-Dimer after 4 weeks in the control group were 316 ng/ml with a range of 233-401 ng/ml with inter quartile range of 288-338ng/ml.

The sensitivity of D-Dimer assay at the time of admission for detecting DVT was 42.86% and the specificity for the same was found to be 100%. The positive predictive value for D-Dimer assay at the time of admission was 100% (95% confidence interval 29.24%-100%) whereas thenegative predictive value for the same was 91.49% (95% confidence interval 79.62%-97.63%).The 95% confidence interval for sensitivity of D-Dimer assay at the time of admission was 9.90%-81.59% and for specificity it was found to be 91.78%-100%

Discussion

It has been known for a long time that DVT is quite likely to develop in a patient with SCI considering the fact that all the three factors i.e., venous stasis, hypercoagulability and loss ofendothelial integrity can occur in a patient with SCI. Keeping this in mind, this study was carried out over a period of 14 months in a tertiary care center in New Delhi. In this study 50patients meeting the inclusion criteria were enrolled in the study.

In this study we found that the incidence of DVT in the patients enrolled in the study was 10% (5 patients developed DVT). This is comparable to the incidence of DVT observed in thestudy carried out by Waring., *et al*. in the where the incidence was found to be 14.5%. the results are also comparable to the incidence of DVT seen in a study carried out by Saraf K., *et al*. in a tertiary care hospital in which the incidence of DVT was found to be 10%. This challenges the conventional view that the occurrence of DVT in Asian population is a relatively uncommon event. The incidence of DVT observed in our study was somewhat comparable to other studies carried out in India. However, in 2015 a study carried out by Matsumoto., *et al*. the incidence reported was as high as 41.4% in Japanese population. Similartrend was also observed in a study carried out by Chung., *et al*. in Korean study group where the incidence of DVT was found to be 43%. These finding of previous and current studies suggest that the incidence of DVT in Asian population without thromboprophylaxis may not be appreciably lower than those in Western population, but instead may be similar. Also in some studies like the one carried out by Aggarwal., *et al*. incidence was found to be lower than what was observed in our study. Similar trend was also seen in study carried out by... There are some possible explanations for such trends. In some previous Asian based studies, Doppler USG was carried out only upon clinical suspicion. Thus, asymptomatic DVT mighthave been missed in those studies. There's a possibility that the actual incidence would behigher if all the patients had been screened with Doppler USG. This speculation is supported by a recent prospective study carried out by chung., *et al.* where all patients were routinely screened for DVT by color doppler. The incidence of DVT after SCI was higherthan previous study for Asian population. Another possible explanation may be changes in environmental factors. With the advent of industrialization and rapidly lifestyle, risk factors for occurrence of DVT such as obesity and heart disease are alsoincreasing in Asian countries.

However in earlier studies carried like those carried out by Aggarwal., *et al*. the incidence of DVT was observed as low as 3% of the patients without any thromboprophylaxis. Also in thestudy carried out by Arsh., *et al.* in Pakistani population, the incidence reported was as low as 2.7%. These findings are in conjunction with the literature that reveals wide variations in incidence of DVT from population to population and from country to country. Watson, at twodifferent times, using the same diagnostic modality in the same population, revealed different incidences (17%,14%). Silver and Watson, at the same time using the same diagnostic method but at two different places in the UK, revealed a different incidence of DVT (25% and 17% respectively. This indicates that there is wide variation in the incidence of DVT. Whether this difference is because of the difference in patient sample or patient care is not clear.

Similar trends were seen in other studies were also it was observed that age, sex and the modeof injury of the patient had no corelation with the occurrence of DVT.

Fifty two percent (26) of the patients belonged to AIS grade A, 12% (6) of the patients belongedto AIS grade B, 22% (11) of the patients belonged to AIS grade C and 14% (7) of the patients belonged to AIS grade D. It was seen that two out of the twenty-six patients with AIS grade Ainjury developed DVT, two out of the 6 patients with AIS grade B injury developed DVT, twoout of the 11 patients with AIS grade C injury developed DVT and one out of the 7 patients with AIS grade D injury developed DVT. On statistical analysis it was observed that the relationship between ASIA grading and occurrence OD DVT was not statistically significant. Similar trend was also observed in a number of other studies. However this is in contrast to other studies which shows complete motor paralysis to be a proven risk factor for development of DVT. Such a difference may be attributed to the intensive physiotherapy and passive

rangeof motion exercises that are strictly followed in our department which in turn reduces the venous stasis and thus decreases the risk of DVT.

In our study it was seen that although presence of pitting edema has low sensitivity (developed in 9 patients) but it is associated with high specificity for development of DVT (all 9 patients with pitting edema developed DVT). It was observed that presence of pitting edema and occurrence of DVT was statistically co-related (p value less than 0.05). Similarly presence of Homan's sign and skin changes were found to be statistically corelated with the development of DVT. In patients diagnosed with DVT it was observed that the average difference in the leg (increase in leg circumference as compared to the affected side) circumference was 3.7cm.On stastical analysis it was found that the relationship between difference in thigh and leg circumference and occurrence of DVT is statistically significant. (P value 0.045). this is in affirmation with the findings seen in a study done by Agarwal., *et al*.

However it was observed that not all the patients who developed DVT had developed clinicalfeatures of the same. Pitting edema was seen in 9 out of the 13 patients who developed DVT, and skin changes were seen in 9 out of the 13 patients who developed DVT (including both study and control group). This indicates clinical assessment is not a reliable parameter for diagnosis of DVT. These findings from our study are in affirmation with the study done by Oudega., *et al*. which demonstrated the limited role of history and physical examination in diagnosis of DVT. Also another study done by Oudega R to assess the reliability of Well's score, to assess the probability of developing DVT, it was observed that even in the low risk patients, the incidence of DVT was as high as 12% thus further strengthening our view that clinical assessment is not a reliable way of diagnosing DVT.

The mean D-Dimer levels at the time of admission were 303.26 ng/ml, the mean D-Dimer levels on post operative day 7 were 364.34 ng/ml and the mean D-Dimer levels on post operative day 15 were 377.34 ng/ml. In the seven patients where DVT was diagnosed, it was observed that the mean D-Dimer levels at the time of admission was 500.71 ng/ml, levels on the post-operative day 7 were 644.57 ng/ml and levels on post-operative day 15 was 674.43 ng/ml. The elevated levels at the time of admission may be attributed to the late presentation of the patients in our hospital. Ours being a tertiary referral center, a large number of patients presents to our hospital after getting primary management from other hospitals, usually days to weeks after the injury. On statistical analysis it was observed that the relationship between D-Dimer levels at time of admission, on post operative day 7 and 15with occurrence of DVT was statistically significant. However the elevated levels of D-Dimerduring the post-operative day 7 and post-operative day 15 assays may be attributable to surgery.In a study done by Lippi., *et al*. it was observed that Patients undergoing laparoscopic cholecystectomy showed D-dimer concentrations persistently increased from the baseline to the 15th postoperative day, whereas patients undergoing hip surgery were characterized by a double peak, on the 1st and 7th postoperative days. The markedly heterogeneous fluctuation of plasma D-dimer suggests that the postoperative activation of the hemostatic system depends on the type and time since surgery, thus limiting the clinical usefulness of D-dimer testing in the diagnostic approach to venous thromboembolism in the post operative period.

Conclusion

In our study conducted in a tertiary care hospital in New Delhi, the incidence of DVT withoutpharmacologic thromboprophylaxis after SCI was found to be 16% suggesting that the incidenceof DVT is not as low in Asian populations as it was suspected, further incidence of DVT withprophylaxis i.e., in enoxaheparin 0.4ml once daily subcutaneously for 2 months reduces the incidence to 10%. the p value came out to be 0.55 which is not significant but to reach a conclusion a larger study would be required to conclude definitely on the role of pharmacological prophylaxis in the Indian population. The incidence of DVT in Indian population is comparable with those in western population. DVT and its subsequent complications are a source of additional burden both for the patient in terms of additional co- morbidities as well as for the hospital in terms of prolonged hospital stay and economic burden. These results suggest that active measures for prevention are important beginning from the acute stage of injury and pharmacological thromboprophylaxis can be considered forall patients with acute spinal cord injury patients unless there is not ongoing bleeding or severe coagulopathy.

Bibliography

1. Kearon C. "Natural history of venous thromboembolism". *Circulation* 107.23.1 (2003): 122-130.

2. Fujii Y., *et al*. "Thrombosis inspinal cord injury". *Thrombosis Research* 68 (1992): 357-368.

3. Brandstater ME., *et al*. "Venous thromboembolism in stroke: Literature review and implications for clinical practice". *Archives of Physical Medicine and Rehabilitation* 73.5 (1992): S379-S391.

4. Bravo G., *et al*. "Cardiovascular alterations after spinal cord injury: an overview". *Current Medicinal Chemistry Cardiovascular and Hematological Agents* 2 (2004): 133-148.

5. Miranda AR and Hassouna HI. "Mechanisms of thrombosis in spinal cord injury". *Hematology/Oncology Clinics of North America* 14 (2000): 401-416.

6. Kahn SR., *et al*. "Long-term outcomes after deep veinthrombosis: postphlebitic syndrome and quality of life". *Journal of General Internal Medicine* 15.6 (2000): 425-429.

7. Oudega R., *et al*. "Limited value of patient history and physical examination in diagnosing deep vein thrombosis in primary care". *Family Practice* 22.1 (2005): 86-91.

8. Tapson VF., *et al*. "The Diagnostic Approach to Acute Venous Thromboembolism. Clinical Practice Guideline. American Thoracic Society". *American Journal of Respiratory and Critical Care Medicine* 160.3 (1999): 1043-1066.

9. Kahn SR. "The clinical diagnosis of deep vein thrombosis: integrating incidence, risk factors and symptoms and signs". *Archives of Internal Medicine* 158.21 (1998): 2315-2323.

10. Wells PS., *et al*. "Evaluation of D-dimer in the diagnosis of suspected deep-vein thrombosis". *The New England Journal of Medicine* 349 (2003): 1227-1235.

11. Brotman DJ., *et al*. "Limitations of D-dimer testing in unselected inpatients with suspected venous thromboembolism". *The American Journal of Medicine* 114.4 (2003): 276-282.

12. Eichinger S. "D-dimer testing in pregnancy". *Pathophysiology of Haemostasis and Thrombosis* 33 (2003): 327-329.

13. Curry N and Keeling D. "Venous thromboembolism: the role of the clinician". *Journal of the Royal College of Physicians of Edinburgh* 39 (2009): 243-246.

14. Antonelli F., *et al*. "Ruling out the diagnosis of venous thromboembolism in the elderly: is it time to revise the role of D-dimer?" *American Journal of Emergency Medicine* 25.6 (2007): 727-728.

15. Hirsh J and Lee AY. "How we diagnose and treat deep vein thrombosis". *Blood* 99 (2002): 3102-3110.

16. Kearon C., *et al*. "The role of venous ultrasonography in the diagnosis ofsuspected deep venous thrombosis and pulmonary embolism". *Annals of Internal Medicine* 129.12 (1998): 1044-1049.

17. Rose SC., *et al*. "Symptomatic lower extremity deep venous thrombosis: accuracy, limitations, and role of color duplex flow imaging in diagnosis". *Radiology* 175.3 (1990): 639-644.

18. Kearon C., *et al*. "Noninvasive diagnosis of deep vein thrombosis. McMaster Diagnostic Imaging Practice Guidelines Initiative". *Annals of Internal Medicine* 128.8 (1998): 663-677.