Evaluation of Soluble Fibrin Monomer Complex and D-Dimer as Early Markers for Diagnosis of Deep Venous Thrombosis

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**Abstract**

**Background:** Venous thromboembolism (VTE) is the third most frequent vascular disease worldwide; it is a significant preventable cause of in-hospital death. Early screening of DVT in high-risk groups is crucial to prevent the disease & its sequelae. D-dimer has the advantage of excluding venous thromboembolism (VTE) due to its high sensitivity. However, its low specificity is disadvantageous for diagnosing VTE. A method to increase the usefulness of D-dimer in the diagnosis of VTE is warranted.

**Aim of Study:** Is to examine the possible role of the plasma level of SFMC & D-dimer in the prediction of hypercoagulable state and the subsequent VTE and to assess whether it can be used to indicate anticoagulant therapy.

**Patients and Methods:** This cross sectional case control study on 85 subjects was performed at a vascular department between July 1, 2021 and December 31, 2021. Subjects were divided as: 60 patients with confirmed DVT positive by Compression ultrasonography (CUS) considered as patients group, and 25 apparently healthy individuals considered as control group with age and sex matched. For both groups levels of D-dimer and SFMC were measured simultaneously. Using ELISA kit supplied by SUNRED BIOTECHNOLOGY COMPANY China.

**Results:** Compared with the control group, there was a statistically significant difference in levels of both SFMC & D-Dimer in the patient group (higher) than they were in control group.

**Conclusion:** Monitoring serum DD and SFMC levels enables early detection and treatment intervention of VTE.

**Key Words:** DVT – D-dimer – SFMC.

**Introduction**

VENOUS thromboembolism (VTE), which is the third most common vascular illness, is a condition that is influenced by various genetic and non-genetic risk factors. The pathogenesis of VT includes Virchow's triad, which is a combination of hypercoagulability, reduced blood flow or stasis, and damage to blood vessels [1].

Venous thromboembolism (VTE) is an important preventable cause of death in the hospital. VTE, which includes deep vein thrombosis (DVT) and pulmonary embolism (PE), affects approximately 1,000,000 new cases each year in Europe and the United States combined. Among survivors, VTE is associated with recurrent events, post-thrombotic syndrome, pulmonary hypertension, and bleeding events (due to anticoagulation), all of which contribute to increased mortality, disease burden [2].

It is still difficult to accurately diagnose deep vein thrombosis (DVT) or pulmonary embolism (PE), and confirmation requires a multimodal approach that includes computing a clinical pre-test probability (PTP) score, measuring DD concentrations and other fibrinogen markers, performing serial compression ultrasonographies (CUS), and using computed tomography pulmonary angiograms [3].

D-dimer testing is frequently used for VTE screening. When utilized in high-sensitivity assays for the diagnosis of VTE, D-dimer has the benefit of a high negative predictive value of 97-100 percent and a high sensitivity of 93-100 percent. Circulating D-dimer is also elevated in patients with liver disease, coronary artery disease and other cardiovascular diseases, cancer, trauma, pregnancy, infections, inflammatory diseases, severe renal disease, recent surgical procedures, and advanced age. However, D-dimer has a low positive predictive value and low specificity. D-dimer has mostly been used to rule out VTE; if the screening
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is positive, VTE must then be definitively confirmed using imaging, which is not always accessible [4].

A quantitative approach for measuring the amount of soluble fibrin monomer complex (SFMC) in plasma has been developed. SFMC is a serological marker for activation of the coagulation system. The clinical significance of D-dimer and SFMC differs; SFMC represents the very early stage of a thrombotic event, whereas D-dimer represents secondary fibrinolysis following clot formation. SFM concentration represents thrombin activity, and because its levels can be detected earlier than DD, SFM can be used as an alternative to DD to assess thrombosis [5].

SFMC has also been proposed as a marker for VTE, similar to D-dimer. However, the findings of earlier investigations into the efficacy of SFMC for VTE diagnosis are inconsistent. In one study, a sensitivity of 98.5 percent and a specificity of 80.1 percent were obtained by adjusting the cutoff value of SF to 5.9g/mL. According to the authors, SFMC is helpful for VTE diagnosis and exclusion. However, in a different study, reducing the cutoff value of SF to 7.0g/mL resulted in a sensitivity of just 38.9 percent and a specificity of only 64.3 percent, demonstrating that SFMC is not helpful for VTE diagnosis or exclusion [6]. An optimal cutoff level for orthopaedic surgery was 13.9 g/mL, which produced a sensitivity and specificity of 67.9 and 78.2 percent, respectively [7]. Despite the fact that SFMC and D-dimer have not been extensively compared in prior research on VTE, SFMC appears to have a higher specificity than D-dimer [4].

The aim of this study was examine the possible role of the plasma level of SFMC & D-dimer in the prediction of hypercoagulable state and the subsequent VTE and to assess whether it can be used to indicate anticoagulant therapy.

Patients and Methods

This study was a cross sectional case control study and was approved by the Research Ethical Committee. Oral and written consents were obtained from all patients and controls after a full explanation of the study.

This study included eightyfive subjects with their ages & sex matched Subjects were classified into:

1- Control group: Included 25 apparently healthy individuals (not affected by any comorbidity and not treated with any medications at the time of study recruitment) confirmed negative to DVT by Compression ultrasonography (CUS) with matched age and sex.

2- Patient group: Included 60 patients with confirmed positive DVT by Compression ultrasonography (CUS) presented to Al-Azhar Hospitals (Al-Husain and Bab Al-Sharia Hospitals). During the period from July, 2021 to December, 2021.

Inclusion criteria:
- Patients with acute DVT first discovered.
- Age and sex matched.

Exclusion criteria:
- Patients diagnosed with Disseminated Intravascular Coagulation.
- Patients diagnosed with malignancy.
- Patients diagnosed with atrial fibrillation.
- Patients diagnosed with acute myocardial Infarction.

All individuals included in this study were thoroughly clinically assessed, full history, as well as, family history of any symptom or any drug intake that may affect the result were taken & the following data were collected (age, sex, body mass index (BMI), smoking habits, history of contraceptive pills drugs intake, & chronic disease as Diabetes mellitus, hypertension or being bedridden for long time) then both the patient and control group were subjected to the following investigations: Complete blood picture (CBC), Prothrombin Time activated partial thromboplastin time D-dimer & SFMC levels was measured In both control and patient groups, Nine volumes of blood were collected in 1 volume 3.2% trisodium citrate were withdrawn then centrifuged for 10 minutes at 2500g, and the plasma was separated and stored at (−20°c) until assessed for D-dimer & SFMC levels ELISA kit supplied by SUNRED BIOTECHNOLOGY COMPANY China.

Statistical analysis:

Data were analyzed using Statistical Package for the Social Sciences (SPSS) version 24. Probability (p-value): p-value <0.05 was considered significant.

Results

Compared with the control group, there was a statistically significant differences in both SFMC, D-Dimer in the patient group, SFMC in cases group [mean 12.4 SD (±8.6)] while in control group
[mean 2.64 SD (±1.68)] thus at cut off (5.5ug/ml) $p$-value <0.001, Area under curve (AUC) 0.97, Sensitivity 89.7%, Specificity 90%, Positive predictive value (PPV) 90% & (NPV) Negative predictive value 89.7%, and D-dimer in cases group [mean 3.8 SD (±5.1)] while in control group [mean 0.459 SD (±0.23)] thus at cut off (8.5ng/ml) $p$-value <0.001 Are under curve (AUC) 0.89 Sensitivity 84.7% Specificity 95% Positive predictive value (PPV) 94% & (NPV) Negative predictive value 86%.

There was a strong statistically positive correlation of both D-dimer & SFMC results in cases Confirmed of DVT ($p$-value=0.001) positive correlation ($r=0.734$).

Table (1): Diagnostic performance of SFMC & D-dimer in prediction of DVT.

<table>
<thead>
<tr>
<th>Cut off</th>
<th>AUC</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>$p$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SFMC</td>
<td>&gt;5.5</td>
<td>0.97</td>
<td>89.7%</td>
<td>90%</td>
<td>90%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>D-Dimer</td>
<td>&gt;0.85</td>
<td>0.89</td>
<td>84.6%</td>
<td>95%</td>
<td>94.4%</td>
<td>86.1%</td>
</tr>
</tbody>
</table>

Discussion

Our study results are concordant with Hayashi et al., study 2022 [8] that Concluded that Early detection and treatment intervention of VTE following HBP surgery are made possible by monitoring serum DD and SFMC levels.

Our study is in agreement with Imuro, T., & Saito, M. study (2022) [3] that concluded that For patients with increased d-dimer levels, lower extremities with a grade 3 MMT (manual muscle test), or DVT positivity, preoperative US DVT screening is advised. Patients who have increased SFMC levels on post-operative day 1 may consider receiving postoperative ultrasound.

Also in keeping with Takeshima, et al., study 2021 [9] who found that The diagnosis of VTE in mental patients with positive D-dimer findings was enhanced by SFMC.

Furthermore, The results of current study show agreement with Kochi, et al., study of 123 patients in 2017 That found that Compared to clinical risk factors and other fibrin related indicators, the SFMC on Post-operative Day 1 strongly predicted the hypercoagulable condition after gastroenterological surgery.

Our results also are in keeping with Nakagawa, et al., study 2016 [10] that found that DD and SFMC measurements can be used to assess the pathophysiology of PE and DVT.

Consistent with our findings,Mitani, et al., study in 2015 [11] a retrospective study of 50 patients concluded that An efficient hemostatic marker for DVT early identification is SFMC concentration. The relevance of D-dimer concentration alone as a hemostatic marker for DVT early diagnosis is limited. A more accurate diagnostic tool than SFMC.
concentration alone may include the measurement of D-dimer and SFMC concentrations.

On the other hand, other studies found that SFMC or D-dimer was not always useful to detect VTE development.

In contrast with our results Yoshimura, et al. study in 2018 [12] discovered that sometimes it was difficult to detect the onset of VTE using SFMC or D-dimer.

Also, in study conducted by Yano S, et al., 2019 [6] they found that Measurement of DD but not SF was suggested to be helpful for incident VTE screening, particularly in non-operative inpatients.

The differences in experimental design, sample size, patient selection criteria, geographic differences, racial differences, and ethnic differences may have contributed to the discrepant results between our study and earlier research.

Due to the study's design, it's possible that the current study has certain limitations. First, a case-control study conducted at a hospital made it difficult to rule out potential selection bias. Second, the statistical power may have been limited by the sample size, which could have resulted in the chance occurrence of statistical deviations and the missed detection of weak associations.

References
تقييم الغيبرين الذائب والدي دايمير في الكشف المبكر
عن التخثر الوريدي العميق

خلفية البحث: بالرغم من كون تخثر الأردة العميق ممكن الوقاية منه إلا يعتبر سبب رئيسي للوفيات والمضارعات المرضية في جميع أنحاء العالم حيث يتسبب التحور الأردة العميق ومضاعفتها من الإنسداد الرئوي في وفاة 10000 سنةً في الولايات المتحدة.
يمكن الوقاية من التخثر الوريدي العميق عن طريق معالجة الإسباب المؤدية إليه والتشخيص المبكر للحماية من المضارعات التي قد تنتج عنه.

بالرغم من كون الدي دايمير يعتبر حجر الزاوية في تشخيص تكون الجلطات ومتابعتها إلا أن مستويات الدي دايمر تكون عالية في كثير من الأمراض الأخرى بدون تكون جلطات مما يقلل من فائدته كمؤشر أساسي لتكوين الجلطة.
يعتبر وحدات الغيبرين الذائب من أهم نواتج تشخيص الفيبرين أثناء مراحل تكوين الجلطة ويعتبر بعض العلماء أنه قد يكون مؤشراً جيداً لتشخيص الجلطات مع الدي دايمير بينما يرى آخرون أنه أقل منه كفاءة.

هدف البحث: هو فحص النور المرتبط لمستوى البراهم لـ SFMC & D-dimer في التنبؤ بحالة فرط التخثر وبالتالي إمكانية حدوث التخثر الوريدي العميق وتعيين ما إذا كان يمكن استخدامه لإشارة لبدء العلاج المضاد للتخثر.

المرضى وطرق البحث: تم دراسة عدد من الحالات التي كانت ترتكب على عبادة الأردة الدمية بمختلف سفن السفريات التابعة لجامعة الزهراء في سنة 2018.
من عدد 50 حالة تم دراستهم حيث تم استخدام أشعة السينو للضفيرة أن حالة يعانون بالفعل من تخثر وريدي عميق في الجزء السفلي من الجسم (تم اعتبارهم الحالات المصابة) بينما تأكد باستخدام السوبر الشعاعي لعدد 40 حالة عدم وجود أي تخثر وريدي عميق (تم اعتبارهم المجموعة الحاكمة).

ككل من المجموعتين تم أخذ التاريخ المرضي وتم سؤالهم عن عاداتهم من تدخين ونحوه والأدوية التي يتناولوها وبين إنجرافات لأي عمليات جراحية تستخدم إما بالسري أو بغيرها كما تم قياس الوزن لحساباً للBody Mass Index وتم قياس مستويات الدي دايمير ووحدات الفيبرين الذائب لكل من المجموعتين.

النتائج: تم معالجة النتائج إحصائياً وتبين النتائج النتيجة أن:

هناك فارق إحصائي بين المجموعتين في نسبة كلا من مستويات الدي دايمير ووحدات الفيبرين الذائب والمن والغيرها لنتائج INR.
كما يوجد تفاوت إحصائي بين زيادة وحدات الفيبرين الذائب وكل من زيادة مستويات الدي دايمير وقياس الهيموجلوبين وزيادة معدلات الالاستنتاج: يعتبر كل من وحدات الفيبرين الذائب والدي دايمير من المؤشرات القوية للتجلط وينصح باستخدامهما لتشخيص المبكر لحالات التخثر الوريدي العميق.