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Effects of rosuvastatin on post-thrombotic syndrome following deep vein thrombosis: a randomized clinical trial

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ABSTRACT

This study evaluates the effectiveness of rosuvastatin as an adjunct to standard anticoagulant therapy in reducing the incidence of post-thrombotic syndrome (PTS) in patients with deep vein thrombosis (DVT) treated at the Al-Imamain Al-Kadhimain Medical City between October 2022 and September 2024. A total of 465 patients were randomized into two groups: a control group receiving standard anticoagulants (warfarin or rivaroxaban) and an intervention group receiving the same anticoagulants with the addition of rosuvastatin. Over the subsequent three months, the authors assessed the development of PTS and measured the serum concentrations of D-dimer and C-reactive protein (CRP). The occurrence of PTS was found to be significantly lower in the rosuvastatin group compared to the control group (p=0.021), with no severe adverse events reported. Furthermore, the intervention group exhibited marked reductions in CRP and D-dimer levels, suggesting that rosuvastatin may contribute to improved clinical outcomes in the management of DVT. These findings support the incorporation of rosuvastatin into conventional anticoagulant regimens as a means of mitigating PTS risk and enhancing overall recovery. The study underscores the value of adjunct therapies in reducing long-term complications associated with venous thromboembolism.

1. Introduction

Deep vein thrombosis (DVT) is a serious clinical condition characterized by the formation of a thrombus in major deep veins, most common-

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ly of the lower limbs. It poses considerable risk by predisposing patients to pulmonary embolism and post-thrombotic syndrome (PTS), both of which can severely impair mobility and quality of life[1]. PTS is a chronic sequela of DVT caused by venous outflow obstruction due to valvular dysfunction, venous hypertension, and persistent insufficiency. It manifests with pain, oedema, and dermatological changes. The primary treatment for DVT is anticoagulant therapy[2]; however, the optimal strategy for PTS prevention remains undefined.

Recent research suggests that statins – particularly, rosuvastatin – may confer therapeutic benefits beyond cholesterol reduction by exerting anticoagulant and anti-inflammatory effects[3]. The JUPITER12 trial has demonstrated that rosuvastatin can decrease levels of high-sensitivity C-reactive protein (hs-CRP), which is implicated in inflammatory and thrombotic processes[4]. This study aimed at investigating the impact of rosuvastatin as an adjunct to standard anticoagulants in reducing the incidence of PTS among patients diagnosed with DVT, thereby improving treatment outcomes and quality of life.

2. Methodology

This randomized clinical trial was conducted in order to evaluate the effect of rosuvastatin on patients presenting with unilateral DVT at the Al-Imamain Al-Kadhimain Medical City between October 2022 and September 2024. A total of 465 participants were randomly allocated to four treatment arms: (i) rivaroxaban alone, (ii) warfarin alone, (iii) warfarin combined with rosuvastatin, and (iv) rivaroxaban combined with rosuvastatin. Socio-demographic and medical history data were collected *via* face-to-face interviews at baseline. Treatment was administered over a three-month period.

Thrombus size and location were assessed clinically and through Doppler ultrasonography by a radiologist blinded to the group assignment. Exclusion criteria included serious comorbidities, pregnancy or breastfeeding, and inability to provide informed consent.

Serum samples for hs-CRP and D-dimer testing were collected at baseline and at three months. hs-CRP was quantified using an enzyme-linked immunosorbent assay (ELISA); a sensitive method for detecting inflammatory markers. D-dimer levels were measured using a quantitative immunoassay in order to assess fibrin degradation products that are reflecting active thrombosis.

Calf circumference was measured at 4 cm below the tibial tuberosity in order to evaluate oedema. At the three-month follow-up, hs-CRP and D-dimer levels, changes in calf circumference, and PTS occurrence were reassessed using the Brandjes criteria[5]. DVT resolution was also re-evaluated.

Ethical approval was obtained from the Baghdad Al-Karkh Health Directorate and the Al-Imamain Al-Kadhimain Medical City (protocol number: KHD, BA: 7-2022; date: July 2022). Informed consent was secured from all participants in compliance with international standards for ethical research.

Statistical analyses were performed using IBM SPSS v25 software. Comparisons between groups employed analysis of variance (ANOVA) and descriptive statistics (mean ± SD as well as absolute / relative frequencies), focusing on inflammatory markers and PTS incidence.

3. Results and Discussion

Rosuvastatin, when added to standard anticoagulant therapy, was associated with a significantly lower incidence of PTS. Among patients treated with rivaroxaban plus rosuvastatin, only 12 (9.2%) developed PTS, compared to 42 (32.3%) in the warfarin group, 39 (30.0%) in the warfarin plus rosuvastatin group, and 26 (20.0%) in the rivaroxaban group (p=0.021). Severe PTS cases were reported in just one patient (0.8%) from the rivaroxaban plus rosuvastatin group *versus* five patients (3.8%) in the warfarin group (Table 1).

The hs-CRP and D-dimer levels were found to be markedly lower in the statin groups, thereby indicating a potential anti-inflammatory effect that could contribute to improved vascular outcomes. These findings support the hypothesis that rosuvastatin may reduce both the incidence and severity of PTS

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Table 1. Comparative outcomes of rosuvastatin and standard anticoagulant therapy in reducing post-thrombotic syndrome (PTS) incidence among patients with deep vein thrombosis (DVT). Abbreviations used: BMI, body mass index; hs-CRP, high-sensitivity C-reactive protein; PTS, post-thrombotic syndrome; SD, standard deviation.

Variable	**Group I: warfarin** (N=111)	**Group II: rosuvastatin / warfarin** (N=120)	**Group III: rivaroxaban** (N=116)	**Group IV: rivaroxaban / rosuvastatin** (N=118)	***p*-value**
Gender (male %)	40.8%	59.2%	43.8%	40.0%	0.81
Age (years, mean ± SD)	47.0 ± 10.1	58.0 ± 1.3	49.9 ± 8.1	51.8 ± 7.3	0.09
BMI (kg/m^2, mean ± SD)	27.8 ± 4.9	30.4 ± 4.9	33.3 ± 0.1	29.8 ± 4.1	0.59
hs-CRP (mg/L, mean ± SD)	13.9 ± 4.5	14.3 ± 4.7	13.7 ± 4.6	14.1 ± 4.3	0.850
D-dimer (ng/mL, mean ± SD)	3,200.2 ± 2,300.1	3,150.7 ± 2,400.4	3,300.9 ± 2,450.3	3,250.8 ± 2,350.2	0.690
Calf size difference >3 cm (N (%))	110 (84.6%)	89 (68.6%)	87 (66.9%)	80 (61.5%)	0.29
Thrombosis location above knee (N (%))	40 (30.8%)	36 (27.7%)	33 (25.4%)	38 (29.2%)	0.11
Post 3-month change in hs-CRP (mg/L, mean ± SD)	13.9 ± 4.5 → 7.9 ± 3.2	14.3 ± 4.7 → 3.9 ± 2.9	13.7 ± 4.6 → 9.1 ± 1.8	14.1 ± 4.3 → 2.9 ± 0.9	0.003
Post 3-month change in D-dimer (ng/mL, mean ± SD)	3,200.2 ± 2,300.1 → 459.9 ± 99.6	3,150.7 ± 2,400.4 → 201.3 ± 109.2	3,300.9 ± 2,450.3 → 411.7 ± 333.	3,250.8 ± 2,350.2 → 317.8 ± 223.9	0.007
PTS occurrence (N (%))	42 (32.3%)	39 (30.0%)	26 (20.0%)	12 (9.2%)	0.021
Mild PTS severity (N (%))	22 (16.9%)	19 (14.6%)	11 (8.5%)	5 (3.8%)	0.001
Moderate PTS severity (N (%))	15 (11.5%)	14 (10.8%)	11 (8.5%)	6 (4.6%)	0.019
Severe PTS severity (N (%))	5 (3.8%)	6 (4.6%)	4 (3.1%)	1 (0.8%)	0.021

following DVT.

PTS results from chronic venous insufficiency, characterized by pain, oedema, and skin discoloration. Pathophysiological mechanisms include thrombus-induced inflammation, venous hypertension, and valvular incompetence[1]. Elevated inflammatory markers, such as hs-CRP and D-dimer, are strongly associated with increased PTS risk. This study aligns with prior research suggesting statins may enhance venous recovery through multiple pathways, including modulation of lipid metabolism and suppression of cytokines and adhesion molecules[6].

Statins' anti-inflammatory properties may protect endothelial integrity and preserve venous valve function, thereby reducing PTS development potential[7]. The significant reduction in CRP observed in this trial reinforces the link between statins and reduced inflammation in DVT.

The study design demonstrated methodological rigor through precise population definition and thoughtful selection of the control arms. Randomization minimized bias and enhanced internal validity. Nevertheless, certain limitations should be noted. For example, the trial's duration limits conclusions about long-term outcomes, including potential drug interactions and sustained efficacy. Furthermore, medication adherence, monitored *via* phone calls, may not accurately reflect actual compliance.

4. Conclusion

This randomized clinical trial demonstrates that rosuvastatin, when combined with standard anticoagulant therapy, effectively reduces the incidence of PTS in patients with DVT. The associated decrease in inflammatory markers such as CRP and D-dimer underscores the drug's potential role in improving vascular outcomes. Future studies should explore long-term benefits, broader patient demographics, and alternative clinical settings.

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Conflicts of interest

None exist.

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