Tropical Journal of Pharmaceutical Research July 2023; 22 (7): 1475-1481
ISSN: 1596-5996 (print); 1596-9827 (electronic)

Available online at http://www.tjpr.org
http://dx.doi.org/10.4314/tjpr.v22i7.17

Original Research Article

Effect of co-administered dalteparin sodium and alteplase on clinical and biochemical parameters in postpartum patients with lower extremity deep venous thrombosis

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Sent for review: 29 March 2023 *Revised accepted: 30 June 2023*

Abstract

Purpose: *To investigate the clinical efficacy of co-administration of dalteparin sodium and alteplase in the treatment of postpartum lower extremity deep venous thrombosis.*
Methods: *A total of 88 patients with postpartum lower extremity deep venous thrombosis admitted to Jiangxi Provincial People's Hospital of The First Affiliated Hospital of Nanchang Medical College, Nanchang, China from January 2020 to December 2022 were enrolled in this study and divided into study group (treated with dalteparin sodium and alteplase) and control group (treated with alteplase only), with 44 patients in each group. Clinical parameters (limb circumference, pigmentation and ulcer area), hemorheological parameters [D-Dimer (D_D), fibrinogen (FIB), centipoise (CP), red cell assembling index (RCAI)], inflammatory factors (hs-CRP, IL-6, THF-a, NMP-9) and cell adhesion factors {platelet endothelial cell adhesion molecule-1 (PECAM-1) and vascular cell adhesion molecule 1 (VCAM-1)} were determined and recorded.*
Results: *Post-treatment, all the clinical and biochemical parameters in the study group were significantly improved compared with pre-treatment levels and the respective levels in the control group ($p < 0.05$). The overall response rate (ORR) in the study group was 95.45 %, which was higher than the 79.55 % for the control group ($p < 0.05$).*
Conclusion: *Concomitant administration of dalteparin sodium and alteplase is more efficacious than treatment of with alteplase alone in the management of postpartum lower extremity deep venous thrombosis. However, further clinical trials on this combination therapy is required for the validation of findings obtained in this work.*

Keywords: *Dalteparin sodium, Alteplase, Postpartum lower extremity deep venous thrombosis, Hemorheology, Cell adhesion factor*

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INTRODUCTION

The physiological status of women undergoes considerable changes during pregnancy, and their blood is in a hypercoagulable state. While in the postpartum period, they need to stay in bed for a long time and rest. Due to lack of activity during pregnancy, blood flow in the deep veins of the lower extremities in the body is slow, and the blood may even coagulate and obstruct blood

vessels, and does not return normally, causing deep venous thrombosis of the lower extremities[1]. Studies have shown that the incidence of lower extremity deep venous thrombosis after cesarean section increases by 2 - 4 times, and if not treated in time, may give rise to skin pigmentation, ulcer and swelling of the affected limb [2]. In severe cases, it causes pulmonary embolism and endangers the patient's life. The aim of clinical treatment of lower extremity deep venous thrombosis is to prevent the spread of thrombosis, recurrence of thrombosis and pulmonary embolism, as well as reduce the incidence of post-thrombotic syndrome [3,4].

In recent years, dalteparin sodium and alteplase have been used in the prevention of postpartum lower extremity deep venous thrombosis [5]. Being that it is activated after entering the body, alteplase directly induces the conversion of plasminogen to plasmin, and promotes fibrin degradation and clot lysis [6]. Dalteparin sodium injection acts through the vascular or fibrinolytic system [7]. Therefore, the aim of this study was to determine the effect of the two drugs on postpartum lower extremity deep venous thrombosis in patients.

METHODS

Clinical profile of subjects

A total of 88 patients with postpartum lower extremity deep venous thrombosis admitted to Jiangxi provincial People's Hospital of The First Affiliated Hospital of Nanchang Medical College, Nanchang, China from January 2020 to December 2022 were enrolled in the study and divided into study group and control group, with 44 patients in each group. There were no significant differences in the clinical profile of both groups. All procedures performed in studies involving human participants were in accordance with the standards stipulated by the Ethics Committee of Jiangxi Provincial People's Hospital, the First Affiliated Hospital of Nanchang Medical College (approval no. 202001), and complied with the guidelines of 1964 Helsinki Declaration for ethical research involving human subjects and its later amendments [8]. Written informed consent was obtained from legally authorized representative(s) for anonymized patient information to be published in this article.

Inclusion criteria

(1) All the patients met the clinical diagnostic criteria for lower extremity deep venous thrombosis; (2) no relevant treatment and intervention before enrollment; (3) prenatal examination was carried out on time in the hospital.

Exclusion criteria

(1) Abnormal liver and kidney function; (2) arterial occlusion; (3) vascular damage; (4) presence of blood diseases.

Treatments

Control group

Patients in this group were treated parenterally. Twenty (20) mg alteplase (Boehringer Ingelheim Pharma GmbH & Co KG; approval no. of imported drug registration certificate no. S20160054; strength: 20 mg/vial). It was added to 500 mL of normal saline and administered to the patients by intravenous pump at a controlled rate of 14 - 20 mL/h.

Study group

Dalteparin sodium (Hebei Changshan Biochemical Pharmaceutical Co. Ltd, State medical permit no. H20143110; strength: 5000 IU/0.2 ml) was subcutaneously injected once a day (200 U/kg). Both groups were observed and compared after 7 days of treatment.

Evaluation of outcomes/parameters

The clinical parameters assessed were limb circumference, pigmentation, and ulcer area, while the hemorheological parameters included D_D, FIB, CP and RCAI. Inflammatory factors, *viz*, hs-CRP, IL-6, THF-a, and NMP-9 were also determined whereas cell adhesion factors - PECAM-1 and VCAM-1- were evaluated also assessed.

Statistical analysis

Data were statistically processed by SPSS 23.0 software. Enumeration data are presented as percentage while χ^2 test and t-test were applied for comparison between the two groups. Measurement data are expressed as mean ± SD, and $p < 0.05$ indicated significant difference.

RESULTS

Patients' clinical data

There were no significant differences between the two groups with regard to their clinical profile/data, as shown in Table 1.

Clinical symptoms

Before treatment, there was no significant difference between the various clinical parameters/indicators for both groups. After treatment, symptoms in the two groups significantly reduced, and the study group showed lower symptoms than the control group ($p < 0.05$). The results are shown in Table 2.

Hemorheological parameters

Before treatment, there was no significant difference in hemorheological parameters between the two groups ($p < 0.05$). After treatment, the hemorheological parameters of the two groups were significantly reduced, with lower values for the study group than the control group ($p < 0.05$), as displayed in Table 3.

Inflammatory factors

Before treatment, no significant difference in various inflammatory factors was observed between the two groups. After treatment, the inflammatory factors in both groups decreased significantly, and but decreased was more pronounced in the study group than in the control group ($p < 0.05$). The results are shown in Table 4.

Cell adhesion factors

Prior to treatment, no significant difference in cell adhesion factors was seen between the two groups. After treatment, cell adhesion factors decreased in both groups, but the decrease was greater in the study group than in the control group ($p < 0.05$). The results were shown in Table 5.

Clinical efficacy

The overall response rate in the study group was 95.45 %, which is significantly higher than the 79.55 % in the control group ($p < 0.05$). The results were listed in Table 6.

DISCUSSION

The coagulation of certain components in the blood, that is, the production of clots which turn into clumps in the blood of the deep veins, is the formation of deep venous thrombosis in the lower extremities, which frequently occurs after surgery The incidence of the disease has risen with the increasing rate of cesarean sections. Patients are likely to have post-thrombotic sequelae if clinical treatment is not timely and countermeasures are not appropriate [10]. In severe cases, pulmonary embolism can be life-threatening due to thrombus shedding.

Table 1: Comparison of patients' clinical profile/data between both groups (mean ± SD, n = 44)

Parameter		Study group (n=44)	Control Group (n=44)	χ^2	*P*-value
Mean age (years)		27.57±1.30	27.61±1.45	0.1362	0.8919
Mean disease duration (day)		4.14±0.46	4.18±0.50	0.3905	0.6971
Mode of delivery [n, %]	*Spontaneous delivery*	32(72.73)	3, (75.00)	0.0589	0.8083
	Cesarean section	12(27.27)	1(25.00)		
Thrombus distribution (n, %)	*Unilateral*	28(63.64)	29(65.91)	0.0498	0.8234
	Bilateral	16(36.36)	15(34.09		
Parity ≥ 2 (n, %)	*Yes*	5，11.36	6，13.64	0.1039	0.7472
	No	39，88.64	38，86.36		
History of abortion (n, %)	*Yes*	6，13.64	7，15.91	0.0903	0.7639
	No	38，86.36	37，84.09		
Singleton pregnancy (n, %)	*Yes*	44，100.00	43，97.73	1.0115	0.3145
	No	0，0.00	1，2.27		
Combined diabetes (n, %)	*Yes*	6，13.64	7，15.91	0.0903	0.7639
	No	38，86.36	37，84.09		
Combined hypertension (n, %)	*Yes*	8，18.18	9，20.45	0.0729	0.7871
	No	36，81.82	35，79.55		
Anemia (n, %)	*Yes*	3，6.82	2，4.55	0.2120	0.6452
	No	41，93.18	42，95.45		
Household registration (n, %)	*Non-local*	1，2.27	2，4.55	0.3451	0.5569
	Local	43，97.73	42，95.45		

Table 2: Comparison of clinical symptoms between the two groups (mean ± SD, n = 44)

Group	Limb circumference (mm)		t value	*P*-value	Pigmentation (point)		t value	*P*-value	Ulcer area (mm^2)		t-value	*P*-value
	Pre-treatment	*Post-treatment*			*Pre-treatment*	*Post-treatment*			*Pre-treatment*	*Post-treatment*		
Study	36.25±3.12	30.21±2.06	10.7162	0.0000	14.64±1.24	6.34±0.48	41.406	0.0000	5.97±0.46	1.52±0.50	43.4464	0.0000
Control	36.32±3.05	33.45±2.14	5.1095	0.0000	14.52±1.30	9.64±0.72	21.7825	0.0000	5.98±0.51	3.39±0.49	24.2915	0.0000
t value	0.1064	7.2353	—	—	0.4431	25.2963	—	—	0.0966	17.7184	—	—
P-value	0.9155	0.0000	—	—	0.6588	0.0000	—	—	0.9233	0.0000	—	—

Table 3: Comparison of hemorheological parameters between both groups (mean ± SD, n = 44)

Group	D-D (ng/Ml)		t-value	*P*-value	FIB (g/L)		t-value	*P*-value	CP (mPa/s)		t-value	*P* - value
	Pre-treatment	*Post-treatment*			*Pre-treatment*	*Post-treatment*			*Pre-treatment*	*Post-treatment*		
Study	325.34±22.36	114.35±16.34	50.5359	0.0000	396.36±29.35	131.35±12.35	48.9559	0.0000	1.98±0.21	1.23±0.24	15.6001	0.0000
Control	328.15±21.98	224.65±19.35	23.4444	0.0000	397.37±27.94	224.36±16.31	35.4727	0.0000	1.99±0.17	1.64±0.18	9.377	0.0000
t value	0.5945	28.8889	—	—	0.1653	30.157	—	—	0.2455	9.0654	—	—
P-value	0.5538	0.0000	—	—	0.8691	0.0000	—	—	0.8066	0.0000	—	—

Table 4: Comparison of inflammatory factors between both groups (mean ± SD, n = 44)

Group	Hs-CRP (mg/L)		t value	*P*-value	IL-6 (pg/mL)		t value	*P*-value	TNF-α (ng/mL)		t value	*P*-value
	Pre-treatment	*Post-treatment*			*Pre-treatment*	*Post-treatment*			*Pre-treatment*	*Post-treatment*		
Study	25.34±2.16	14.26±1.34	28.9141	0.0000	26.35±2.34	9.42±0.51	46.8911	0.0000	2.79±0.24	1.16±0.12	40.2947	0.0000
Control	25.42±2.09	19.06±1.64	15.88	0.0000	26.41±2.21	14.35±1.34	30.9525	0.0000	2.78±0.26	1.68±0.16	23.9007	0.0000
t value	0.1766	15.0341	—	—	0.1237	22.8083	—	—	0.1875	17.2464	—	—
P-value	0.8603	0.0000	—	—	0.9019	0.0000	—	—	0.8517	0.0000	—	—

Table 5: Comparison of cell adhesion factors between both groups (mean ± SD, n = 44)

Group	PECAM-1 (ng/L)		t value	*P*-value	VCAM-1 (μg/L)		t value	*P*-value
	Pre-treatment	*Post-treatment*			*Pre-treatment*	*Post-treatment*		
Study	453.45±43.25	276.35±20.15	24.6208	0.0000	297.35±22.35	119.35±10.52	47.7983	0.0000
Control	454.35±42.15	320.15±33.26	16.5794	0.0000	299.35±20.94	188.35±17.65	26.8854	0.0000
t value	0.0989	7.4712	—	—	0.4332	22.2751	—	—
P-value	0.9215	0.0000	—	—	0.6660	0.0000	—	—

Table 6: Comparison of clinical efficacy {n (%)}

Group	N	Marked response	Moderate response	No response	Overall response
Study	44	23（52.27）	19（43.18）	2（4.55）	42（95.45）
Control	44	19（43.18）	16（36.36）	9（20.45）	35（79.55）
χ^2 value	—		——		5.0909
P-value	—		——		0.0241

Among intravenous thrombolytic drugs, alteplase is often used in clinical practice nowadays because of its good thrombolytic effect. Glycoproteins are the key components that are administered intravenously to patients by combining fibrin with lysine residues, thereby activating plasminogen and converting it into plasmin, which dissolves fibrin and thrombus [11]. Compared with general heparin, dalteparin sodium injection is more effective in antithrombotic activity and in inhibiting coagulation factor Xa [12]. Its benefits are mainly due to its antithrombotic effect which results from the application of the fibrinolytic system or the function of vessel wall [13]. Hence, this study was aimed to further evaluate the efficacy of combining the above two drugs for the management of lower extremity deep venous thrombosis. The results indicate that in the study group, which was given the combination of dalteparin sodium and alteplase, limb circumference, pigmentation and ulcer area of the patients were significantly improved compared with the control group. Thus, increased dose dalteparin sodium may further improve the clinical symptoms of patients.

As an acute phase reactive protein, hs-CRP enables monocytes to secrete tissue factor, which allows the body to accelerate the coagulation waterfall reactions, resulting in thrombosis [14]. MMP-9 acts to degrade the extracellular matrix and accelerate the release of inflammatory factors at the site of vascular injury, while exacerbating local inflammatory response [15]. Inflammatory factor IL-6 causes inflammatory damage to blood vessels and mediates PLT concentration, making TNF-α an inflammatory mediator and accelerating the rate of automatic adhesion of leukocytes to the vascular wall. Hence, its expression level was reduced and thromboinflammation decreased [16]. Based on the serum parameters of the patients after treatment, the symptoms of the patients in the study group improved significantly; hence, the alleviation of LDVT inflammatory response by the combination treatment.

VCAM-1 and PECAM-1 serve as common indicators of cell adhesion, and the results obtained indicate accelerated platelet adhesion [17]. The results showed that these serum-related inflammatory factors were ameliolerated in the study group after treatment compared with the control group. The results further showed that the combination treatment inhibits the inflammatory response process in patients with postpartum lower extremity deep venous thrombosis and exerted a significant protective effect on the patient's body.

Hemorheological parameters are a group of important indicators that may provide predictive judgment for some clinical diseases. As previously reported [18], changes in hemorheological parameters often appear earlier than the clinical symptoms in patients. A certain degree of change in the early stage of the symptom-free period in patients, may provide a critical reference for the diagnosis and treatment of clinically relevant diseases, especially those related to blood vessels and blood. D-D, FIB and CP are essential hemorheological parameters, and their trend may reflect the alteration of overall hemorheological parameters. In this study, these indicators significantly decreased in both groups after treatment, but the changes were more evident in the study group. Thus, the combination treatment improved the hemorheological status of patients.

CONCLUSION

The use of dalteparin sodium/alteplase combination in the treatment of postpartum lower extremity deep venous thrombosis improves clinical efficacy and the hemorheological status of patients. It also inhibits the inflammatory response process of patients, and reduces adhesion of thrombus body cells. However, this study has some limitations in that it was a single-center study and the study sample size was not large. Besides, subsequent follow-up time of patients was relatively short. Therefore, long-term, multicenter clinical trials of the combination therapy is required for validation of the present findings.

DECLARATIONS

Acknowledgements

None provided.

Funding

None provided.

Ethical approval

This work was approved by the Ethics Committee of Jiangxi Provincial People's Hospital, the First Affiliated Hospital of Nanchang Medical College, China (approval no. 202001).

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them.

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