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Original Article

Low-molecular-weight heparin reduces the formation of lower limb deep venous thrombosis in patients with hypertensive intracerebral hemorrhage

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Abstract: Objective: To demonstrate that low-molecular-weight heparin (LMWH) can reduce the formation of lower limb deep venous thrombosis (DVT) and improve the quality of life (QOL) of patients with hypertensive intracerebral hemorrhage (HICH). Methods: Totally, 98 patients with HICH were selected according to different treatment and intervention schemes. Patients receiving routine intracranial pressure reduction and blood pressure regulation intervention were included in group A (n=46) and those receiving LMWH calcium on the basis of treatment in group A were included in group B (n=52). The total effective rate of patients was compared between the two groups, and the prothrombin time (PT), activated partial thromboplastin time (APTT), fibrinogen degradation product (FDP), D-dimer, and inflammatory factor levels as well as complications and QOL scores before and after treatment were recorded and compared. Results: The FDP and D-dimer showed an increasing trend in both groups after treatment, with the increase being significantly lower in group B than in group A ($P<0.001$). Serum tumor necrosis factor-α and interleukin-1β levels increased significantly in the two groups after treatment, with the increase being significantly lower in group B than in group A ($P<0.05$). Complications of pulmonary embolism, DVT, intracranial hemorrhage, and gastrointestinal hemorrhage were better in group B than in group A ($P<0.05$). In terms of QOL, physical and mental health, material life, and social functioning were significantly higher in patients of group B than for those in group A ($P<0.001$). Conclusions: The application of LMWH in patients with HICH can reduce the formation of lower limb DVT.

Keywords: Low-molecular-weight heparin, hypertensive intracerebral hemorrhage, lower limb deep venous thrombosis, quality of life

Introduction

Hypertension-related complications can easily lead to disability in patients. Specifically, hypertensive intracerebral hemorrhage (HICH) is a common disease in neurosurgery and is a late complication that frequently occurs in hypertensive patients [1-3]. Studies have shown that the incidence of HICH continues to increase with the acceleration of the aging population, with the mortality and mortality ranking the first, thereby seriously threatening the lives of patients [4, 5]. Currently, the mainstay treatments of HICH are craniotomy and conservative treatment, but the prognosis of patients remains poor [6, 7].

In recent years, with the wide application of minimally invasive and microscopic techniques, the mortality and disability rates of patients with HICH have greatly reduced [8, 9]. However, HICH is prone to be complicated by deep venous thrombosis (DVT) in the treatment process, and lower limb DVT seriously affects the quality of life (QOL) and prognostic rehabilitation of patients [10, 11]. If lower limb DVT is not treated in time after the onset of HICH, it will lead to progressive disease and cause sudden death of patients due to pulmonary embolism (PE) [12, 13]; thus, it is suggested that preventive anticoagulant therapy is paramount for patients with cerebral hemorrhage. In this study, through comprehensive comparison, we confirmed that low-molecular-weight heparin (LMWH) can reduce the formation of lower limb DVT and improve the QOL of patients with HICH, so as to provide reference for reducing the formation of lower limb DVT in treating patients with HICH.

Methods and materials

Patient information

Totally, 98 patients with HICH admitted to our hospital from April 2018 to April 2019 were selected. According to different treatment interventions, patients who received routine intracranial pressure reduction and blood pressure regulation intervention were included in group A, aged 45-75 years (average age, 47.40±1.20 years). On the basis of treatment in group A, patients treated with LMWH were included in group B, aged 48-78 years (average age, 47.60±1.80 years). With the written informed consent obtained, all participants volunteered to be included in the experiment and cooperated with the medical staff to complete the relevant diagnosis and treatment and had no allergies to the drugs used during the surgical treatment. This study was approved by the Medical Ethics Committee of Shijiazhuang People's Hospital (NCT0218626).

Inclusion and exclusion criteria

Patients who had not received relevant diagnosis or treatment in other hospitals, with complete cases, were included in the study, whereas those with severe hepatorenal dysfunction, those with coagulopathy, those who did not cooperate with the examination, and those with cognitive impairment and communication disorders were excluded.

Methods and outcome measures

Treatment methods: Patients in group A received routine treatment. Base on the patient's condition, the intracranial pressure was reduced and blood pressure was adjusted. Then, drugs were administered to nourish the brain cells and physical intermittent air pump and stretch socks were used when necessary. On the basis of treatment in group A, patients in group B were administered 4,000 IU/d of LMWH (State Drug Approval Document Number: H20060190; Shenzhen Sciprogen Bio-pharmaceutical Co., Ltd., Shenzhen, China) by subcutaneous injection. Patients in both groups received treatment for 5 days to observe the effect.

Outcome measures: Before and after treatment, 10 mL of venous blood was drawn from patients. The specific outcome measures were as follows.

The total effective rate of patients in groups A and B was compared. Biochemical analysis of the prothrombin time (PT), activated partial thromboplastin time (APTT), fibrinogen degradation product (FDP), and D-dimer and detection of serum levels of inflammatory factors represented by tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β) were performed before and after treatment. Complications (PE, DVT, intracranial hemorrhage [ICH], and gastrointestinal hemorrhage) of patients in groups A and B were determined. The QOL scores of physical and mental health, material life, and social functioning, as assessed using the Quality of Life Questionnaire Core 30 (QOL-C30) [14], were compared between the two groups.

Statistical methods

SPSS 19.1 software system (Beijing StrongVinda Information Technology Co., Ltd., Beijing, China) was used for statistical analysis. Figures were drawn using GraphPad Prism 8.0 (GraphPad Inc, US). Counting data were represented by percentage (n [%]), and the difference between the two groups was compared using the chi-square test. Measurement data were expressed as mean ± SD, the difference between the two groups was compared using t-test, and the comparison of multiple time points within the group was performed using repeated measures ANOVA. $P<0.05$ indicated a statistically significant difference.

Results

Comparison of patient clinical data

To make the experimental results accurate and credible, we compared general data of patients in both groups and found no significant difference ($P>0.05$), indicating comparability (**Table 1**).

Total effective rate in groups A and B

The total effective rate was significantly higher in group B than in group A ($P<0.05$) (**Table 2**).

Biochemical analysis before and after treatment

Analysis of the PT and APTT before and after treatment: There were no significant differences in the PT and APTT between the two groups before treatment ($P>0.05$); however, the two increased gradually in both groups after treat-

Table 1. Basic information of patients in the two groups [n (%)]

Groups	Group A (n=46)	Group B (n=52)	X^2	P
Gender			0.036	0.849
Male	23 (50.00)	25 (48.08)		
Female	23 (50.00)	27 (51.92)		
Age (years old)			2.308	0.129
≤47	16 (34.78)	26 (50.00)		
>47	30 (53.57)	26 (50.00)		
Weight (kg)			0.737	0.391
≤55	3 (6.52)	6 (11.54)		
>55	43 (93.48)	46 (88.46)		
Diabetes			1.773	0.183
Yes	16 (34.78)	25 (48.08)		
No	30 (53.57)	27 (51.92)		
Smoking			0.044	0.834
Yes	31 (67.39)	34 (65.38)		
No	15 (32.61)	18 (34.62)		
Alcoholism			0.009	0.926
Yes	12 (26.09)	14 (26.92)		
No	34 (73.91)	38 (73.08)		
GCS scores (point)			0.743	0.389
≤10	19 (41.30)	26 (50.00)		
>10	27 (58.70)	26 (50.00)		
Hematoma type			0.727	0.867
Basal ganglia	28 (60.87)	34 (65.38)		
Ventricle	8 (17.39)	7 (13.46)		
Lobe	5 (10.87)	7 (13.46)		
Cerebellum	5 (10.87)	4 (7.69)		

Table 2. Total effective rate of patients in group A and group B

Groups	Group A (n=46)	Group B (n=52)	X^2	P
Markedly effective	12 (26.09)	26 (50.00)	-	-
Effective	17 (36.95)	22 (42.31)	-	-
Ineffective	17 (36.96)	4 (7.69)	-	-
Total effective rate	29 (63.04)	48 (92.31)	12.420	<0.001

ment, without significant difference (P>0.05) (**Figure 1**).

Analysis of FDP and D-dimer before and after treatment: There were no statistically significant differences in FDP and D-dimer between the two groups before treatment (P>0.05); however, FDP and D-dimer increased gradually in both groups after treatment, with the increase being significantly lower in group B than in group A (P<0.001) (**Figure 2**).

Changes in serum inflammatory factor levels

Serum TNF-α and IL-1β levels did not show any significant differences between the two groups before treatment; however, the two increased notably in both groups after treatment, with the increase being significantly lower in group B than in group A (P<0.05) (**Figures 3**, **4**).

Complications and QOL of patients in groups A and B

Complications of patients in groups A and B: The complications of PE, DVT, ICH, and GIH were better in group B than in group A (P<0.05) (**Table 3**).

Comparison of QOL of patients in groups A and B: QOL-C30 scale was performed to compare the QOL scores, and result revealed that the physical and mental health, material life, and social functioning were significantly higher for patients in group B than for those in group A (P<0.001) (**Table 4**; **Figure 5**).

Discussion

The mechanism of lower limb DVT is related to the postoperative use of a large amount of hormones and intracranial release of substantial hypercoagulable substances in patients with HICH [15, 16]. In current clinical practice, thrombolytic drugs should be used with great caution to avoid the recurrence of cerebral hemorrhage, but instead, anticoagulant therapy shows higher clinical safety [17, 18]. Therefore, this study aimed to compare the effects of conventional intermittent pneumatic compression (IPC) combined with LMWH calcium injection and sodium phosphocreatine intervention alone on oxidative stress and inflammation in patients with HICH.

As the instability of blood pressure control and formation of DVT after operation are high risk factors for recurrent hemorrhage in patients

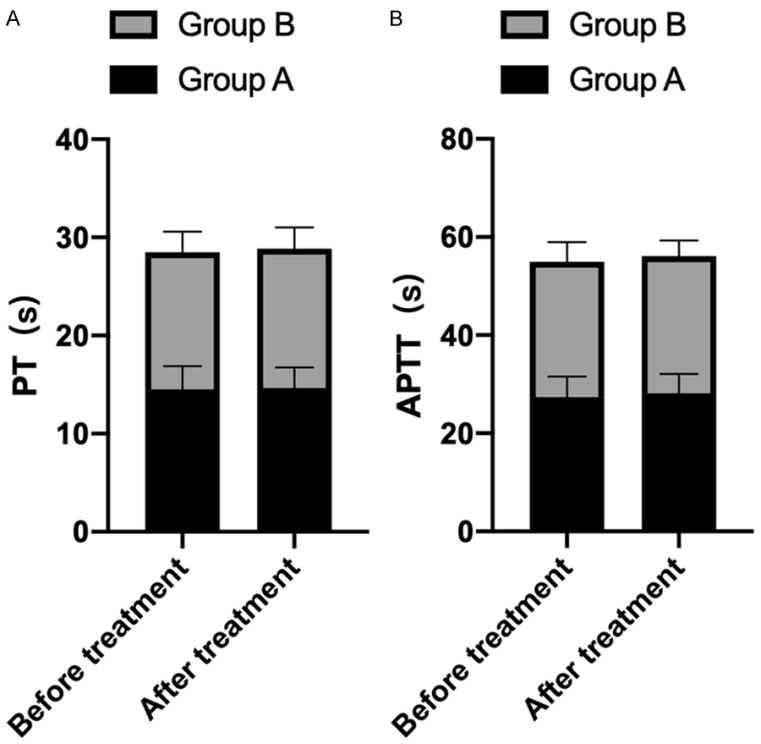

Figure 1. Analysis of myocardial injury markers before and after hand treatment. Compared with before treatment, the PT (A) and APTT (B) showed an increasing trend after treatment in both groups, and the increase differed insignificantly between the two groups (P>0.05).

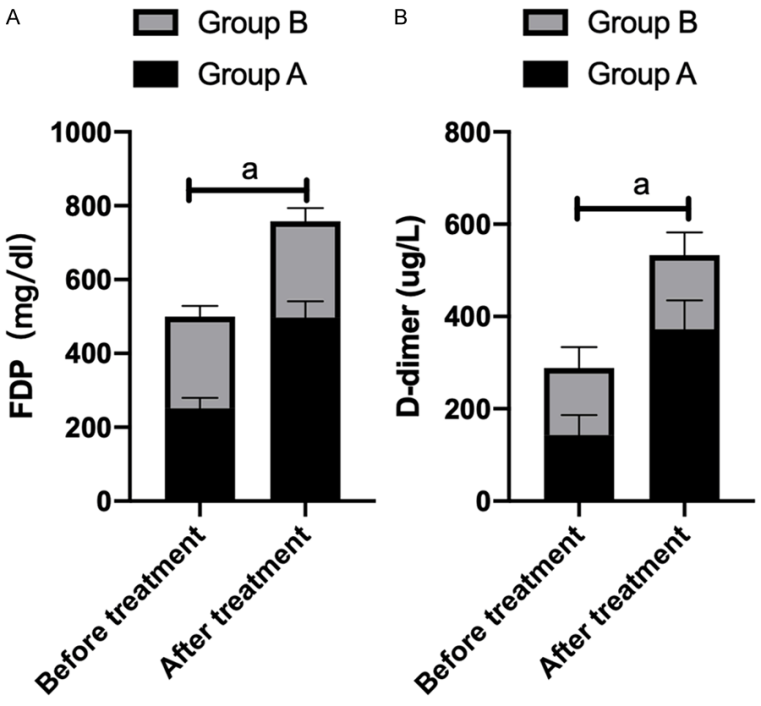

Figure 2. Analysis of FDP and D-dimer before and after treatment. Compared with before treatment, the FDP and D-dimer increased gradually in both groups after treatment, and the increase was significantly lower in group B than in group A (P<0.001). Note: a indicates P<0.001.

with HICH, we attempted LMWH calcium injection to prevent postoperative lower limb DVT after HICH [19, 20]. First, we conducted a biochemical analysis before and after treatment. The PT and APTT increased in both groups after treatment compared with those before treatment, but the increase was not significantly different between the two groups. In addition, the post-treatment FDP and D-dimer were found to be increased gradually in both groups, and the increase in group B was significantly less than that in group A. Both FDP and D-dimer are important indicators for predicting the presence of th rombi [21, 22]. The content of FDP elevates in the secondary increased fibrinolytic activity caused by hypercoagulability, PE, and venous thrombosis [23], whereas D-dimer is a specific product of fibrin degradation and can show high values in diseases such as DVT and PE [24]. Blood concentration caused by surgical blood loss and postoperative tissue trauma can enhance platelet aggregation and adhesion and promote the formation of thrombus, which are high risk factors for lower limb venous thrombosis. During the period within 5 days after surgery when intracranial coagulation factors are active in patients with HICH, LMWH calcium injection is the recommended therapeutic regimen according to the guidelines of antithrombotic and thrombolytic therapy. The LMWH calcium injection is made of LMWH by depolymerization of unfractionated heparin, which can rapidly and continuously resist thrombosis [25]. Therefore, we speculate that conventional IPC therapy combined with

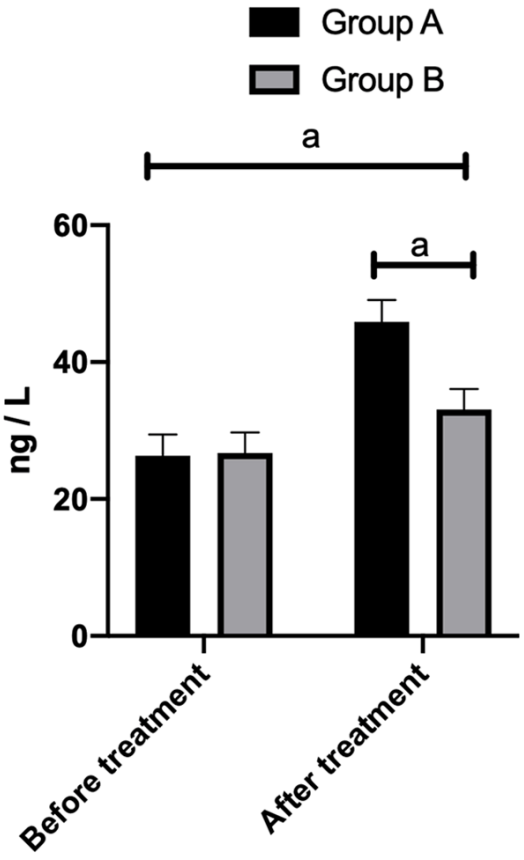

Figure 3. Changes in serum TNF-α levels. Serum TNF-α levels did not show any significant difference between the two groups before treatment (P>0.05); however, it increased notably in both groups after treatment, and the increase was significantly lower in group B than in group A (P<0.05). Note: a indicates P<0.001.

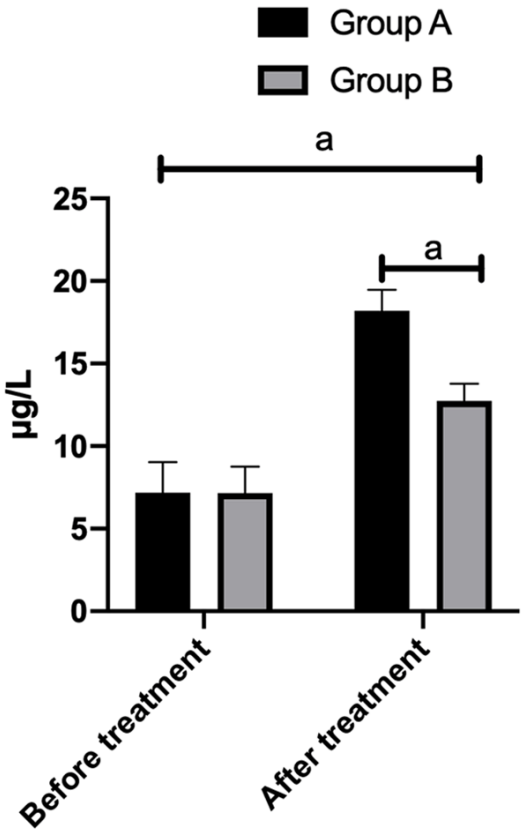

Figure 4. Changes in serum IL-1β levels. Serum IL-1β levels differed insignificantly between the two groups before treatment (P>0.05); however, it increased notably in both groups after treatment, and the increase was significantly lower in group B than in group A (P<0.05). Note: a indicates P<0.001.

LMWH calcium injection exert a better regulatory effect on the coagulation mechanism and has a rapid and continuous antithrombotic effect on the premise of reducing cerebral hemorrhage in patients with HICH.

We further analyzed changes in serum inflammatory factor levels during HICH and found that serum pro-inflammatory factor levels decreased remarkably in both groups during the perioperative period but the levels were significantly lower in patients who underwent conventional IPC therapy combined with LMWH calcium injection than in those who underwent routine intervention after the start of surgery. IL-1β is a typical pro-inflammatory factor with strong pro-inflammatory effects [26]. A large number of studies have confirmed the close relationship between post-traumatic inflammation and DVT, and monitoring IL-1β can predict the formation and prognosis of post-traumatic DVT [27]. Therefore, we believe that conventional IPC therapy combined with LMWH calcium injection play a significant role in inhibiting pro-inflammatory factors and has a significant effect on serum inflammatory reaction in patients with HICH.

Table 3. Comparison of complications between group A and group B [n (%)]

	Group A (n=46)	Group B (n=52)	X^2	P
PE	2	0	-	-
DVT	17	4	-	-
ICH	2	0	-	-
GIH	6	4	-	-
Total	27 (58.70)	8 (15.38)	19.940	<0.001

Finally, by assessing the complications and QOL scores of patients, we found that the com-

Table 4. Comparison of QOL between group A and group B

Groups	Group A (n=46)	Group B (n=52)	t	P
Physical health	43.19±5.18	54.39±5.76	10.070	<0.001
Mental health	61.13±5.09	75.35±5.83	12.900	<0.001
Material life	69.53±4.25	78.19±5.72	5.583	<0.001
Social functioning	65.18±5.63	72.23±5.24	6.419	<0.001

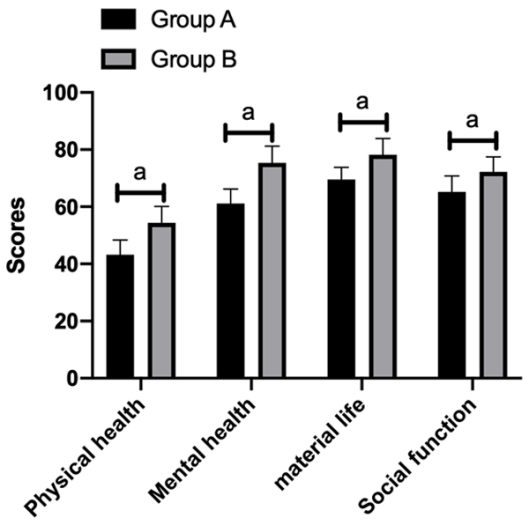

Figure 5. Comparison of QOL between groups A and B. The QOL-C30 scores of physical and mental health, material life, and social functioning were significantly higher in patients in group B than in those in group A. Note: a indicates P<0.001.

plications of PE, DVT, ICH, and GIH as well as each domain of the QOL-C30 scores were all better in patients treated with LMWH calcium injection than in those treated with routine treatment. Some studies have revealed that LMWH calcium can effectively control PE and play the largest role and is better and safer for lower limb DVT after HICH [28].

However, due to the limited medical resources in our hospital and small number of participants, there may be contingent of the results. In addition, it does not rule out that patients of different sexes or ages have different responses to anesthesia treatment. Therefore, we will conduct a longer follow-up investigation on the participants of this study and constantly improve and update our research in the future.

In conclusion, the application of LMWH in patients with HICH can reduce the formation of lower limb DVT to a certain extent and improve the QOL of these patients.

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Disclosure of conflict of interest

None.

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