

ORIGINAL RESEARCH

Padua prediction score-guided use of low-molecular-weight heparin calcium treatment for the prevention of venous thromboembolism in elderly patients with intracerebral hemorrhage: a clinical observation

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Abstract

This study used the Padua Prediction Score (PPS) to guide low-molecular-weight heparin calcium (LMWHC) treatment for the prevention of venous thromboembolism (VTE) in elderly patients with intracerebral hemorrhage (ICH). This study retrospectively analyzed 225 elderly patients who were admitted to the intensive care unit (ICU) between June 2016 and June 2022. Patients were divided into control (n = 124) and study (n = 101) groups. Control patients received routine prevention and treatment of VTE, while patients in the study group received PPS-guided LMWHC treatment for the prevention of VTE. Multiple analytical parameters were assessed including thromboelastography indices, coagulation function parameters, venous blood flow velocity, and the incidence of VTE and recurrent ICH. Thromboelastography indices, coagulation function parameters, and the venous blood flow velocity did not differ significantly between the control and study groups ($p > 0.05$) before intervention and treatment. However, following PPS-guided LMWHC treatment, a significant improvement in these parameters was observed in the study group compared to the control group ($p < 0.05$). Furthermore, the incidence of VTE was significantly lower in the study group (5.6%) than the control group (14.5%; $p = 0.038$). No significance differences in the incidence of recurrent ICH were observed ($p > 0.05$). Our PPS data indicate that LMWHC treatment could significantly improve the coagulation function of elderly patients with ICH, as well as increase the venous blood flow velocity and prevent the occurrence of VTE.

Keywords

Padua prediction score; Low-molecular-weight heparin calcium; Intracerebral hemorrhage; Venous thromboembolism; Elderly patients

1. Introduction

Intracerebral hemorrhage (ICH) is the most fatal type of stroke, and survivors suffer high rates of functional disability. The incidence of ICH in the elderly population is high [1]. Due to severely impaired consciousness and long-term bed rest, elderly patients with cerebral hemorrhage are prone to venous thromboembolism (VTE) in the early stage, which significantly increases the mortality rate [2].

VTE is a serious, but preventable medical condition that occurs when a blood clot forms in the deep veins resulting in a partial or complete blockage of the blood vessel. VTE encompasses both deep vein thrombosis (DVT) and pulmonary embolism (PE) and is the most common cause of preventable in-hospital death [3]. In addition, VTE is the third most frequent acute cardiovascular syndrome, and its incidence con-

tinues to increase as the life expectancy of the world population increases [4]. Although the overall incidence of VTE is approximately 1–2 per 1000 each year, the incidence increases to 1% in the elderly, and the risk doubles every decade beyond the age of 40 [5–7]. Moreover, the risk for postoperative VTE is higher in patients over 70 years of age, and in elderly patients presenting with co-morbidities, for example, cardiovascular disorders, malignancy or renal insufficiency [8]. Early assessment of VTE risk factors in elderly patients with ICH is, therefore, crucial for the prevention and treatment of VTE. Indeed, the prevention and management of VTE has become an important indicator of the quality of hospital medical care, while the development of effective prevention strategies is a critical clinical need.

Although low-molecular-weight heparin calcium

(LMWHC) is considered to be the cornerstone of VTE prevention, clinicians still have concerns about increasing the risk of recurrent ICH. As a result, in a recent study, only 20% of patients received anticoagulant therapy with LMWHC, while a higher proportion of patients were given intermittent pneumatic compression devices to prevent VTE [9].

The Padua Prediction Score (PPS) has been used for a decade, and can help discriminate between medical patients at high and low risk of VTE [10, 11]. The American College of Chest Physicians (ACCP) recommends the use of PPS for screening non-surgical patients with thrombus [12]. However, the benefits of PPS in the diagnosis and treatment of elderly patients are not well documented. This retrospective study aimed to explore and analyze the effects of PPS-guided LMWHC for the prevention of VTE in elderly patients with ICH.

2. Methods

2.1 Patients

The present study is a retrospective study comprised of 225 elderly patients with ICH, who were admitted to the Affiliated Hangzhou First People's Hospital of Zhejiang University School of Medicine between June 2016 and June 2022. Patients were divided into control ($n = 124$) and study ($n = 101$) groups based on the use of LMWHC. The inclusion criteria were as follows: (1) all patients were ≥ 70 years of age, (2) patients had been diagnosed with acute cerebral parenchymal hemorrhage by computerized tomography and computerized tomography angiography, and (3) bed rest lasted for more than one week after surgery. The exclusion criteria included: (1) patients who were diagnosed with VTE upon hospital admission, and (2) patients with active bleeding or coagulation disorders.

2.2 Intervention and treatment

The PPS was used to assess the risk of VTE in the patients. Therapies and interventions were implemented following assessment of the PPS, which was carried out within 24 hours of hospital admission. Risk factors for PPS included: active cancer (3 points), decreased activity (3 points), history of VTE (3 points), thrombosis-prone condition (3 points), recent trauma/surgery (≤ 1 month) (2 points), acute myocardial infarction/stroke (1 point), cardiopulmonary failure (1 point), advanced age (≥ 70 years) (1 point), acute infection/rheumatic disease (1 point), hormone therapy (1 point), and obesity (body Mass Index ≥ 30 kg/m²) (1 point). The risk level of VTE was determined by the PPS score. Patients with a PPS score of 1–3 were classified as low risk, while a PPS score of ≥ 4 was considered to be high risk.

The control group received routine treatment, including appropriate limb function exercise and catheter maintenance. The study group received a daily subcutaneous injection of LMWHC (5000 units) for 14 days.

2.3 Observation indicators

The analytical parameters examined in this study included thromboelastography, coagulation function, venous blood

flow velocity and incidence of VTE. Thromboelastography parameters included coagulation reaction time (R), maximum clot strength (MA), coagulation angle (Angle) and comprehensive coagulation index (CI). In addition, coagulation indicators including fibrinogen and D-dimer levels were assessed. A portable color ultrasound diagnostic system (Philip Medical Equipment Co. Ltd.; Probe: L12-3 high-frequency linear array probe, Amsterdam, Netherlands) was used to detect the venous blood flow velocity in patients. The incidence of VTE was determined using the diagnostic criteria outlined by the ACCP [12]. Blood tests and ultrasound examination were carried out between 9–11 AM. Differences between the control and study groups were compared after treatment of the study group with one course of LMWHC.

2.4 Incidence of VTE

The incidence of VTE during hospitalization included PE and DVT in the upper and lower extremities. Diagnosis was based on the CHEST Guideline and Expert Panel Report and ACCP [12, 13].

2.5 Statistical analysis

SPSS 24.0 software (IBM Corp., Armonk, NY, USA) was used for statistical analysis. The Chi-square test was used for counting data, and the *t*-test was used for measurement data. Descriptive statistics were presented as the mean \pm standard deviation (SD) for continuous variables or percentage for categorical variables. A *p*-value of less than 0.05 was considered to be statistically significant.

3. Results

3.1 Patient characteristics

As shown in Fig. 1, we initially assessed 278 elderly patients with ICH. Thereafter, we excluded fifty-three patients according to exclusion criteria and ultimately, 225 elderly patients with ICH were recruited. Patient characteristics are shown in Table 1. There were no significant differences in the age ($p = 0.327$) and gender between the two groups ($p = 0.815$). In addition, no significant differences in the number and proportion of major primary diseases such as tumor ($p = 0.564$), heart failure ($p = 0.293$) and hypertension ($p = 0.714$) were observed between the two groups. The incidence of VTE was significantly lower in the study group (5.9%) than the control group (14.5%) ($p = 0.038$). However, the incidence of recurrent ICH did not differ significantly between the two groups ($p = 0.222$). No significant differences between the D-dimer ($p = 0.362$), oxygenation index ($p = 0.133$), serum creatinine ($p = 0.238$) and blood urea nitrogen ($p = 0.182$) were observed between the control and study groups.

3.2 Thromboelastography data

As shown in Table 2, no significant differences in thromboelastography indices including Angle, R, CI and MA were observed between the two groups before treatment and intervention ($p = 0.074$, $p = 0.432$, $p = 0.721$, $p = 0.063$). However, following treatment and intervention, the thromboelastography

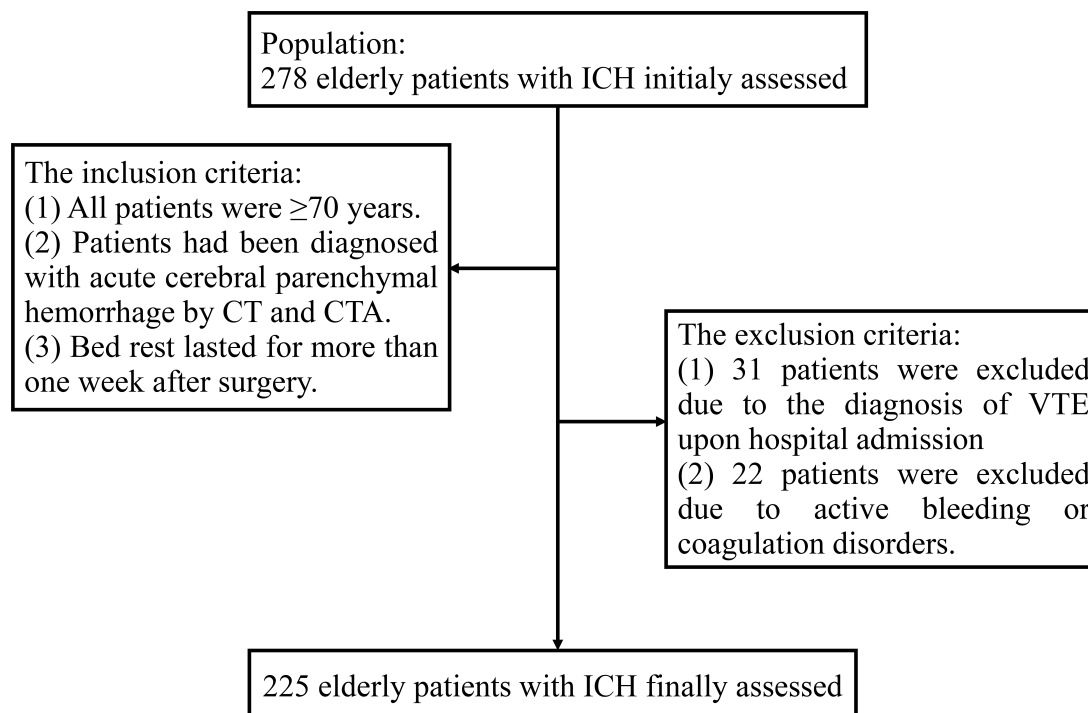


FIGURE 1. Flow chart of selecting eligible patients. Initially, 278 elderly patients with ICH assessed, thereafter, we excluded 53 patients; and ultimately, 225 patients were recruited. ICH: intracerebral hemorrhage; CT: computerized tomography; CTA: computerized tomography angiography; VTE: venous thromboembolism.

indices were significantly improved in the study group than the control group ($p = 0.019$, $p = 0.034$, $p = 0.046$, $p = 0.027$) (Table 2).

3.3 Coagulation function and venous blood velocity

The coagulation function and venous blood velocity data are shown in Table 3. No significant differences in coagulation parameters such as fibrinogen and D-dimer levels were found between the control and study groups before treatment and intervention ($p = 0.362$). However, following treatment and intervention, significantly improved blood coagulation was observed in the study group compared to the control group. In the study group, the levels of coagulation markers decreased ($p = 0.027$), while the blood flow velocity increased ($p = 0.011$).

4. Discussion

PPS is applicable to a wide range of patients, has strong clinical operability, and its reliability has been validated in patients from multiple countries. PPS has high specificity for screening hospitalized patients at high risk of VTE, especially non-surgical hospitalized patients [14]. Our study showed that PPS can assess the risk of VTE in elderly patients with ICH, as well as quantify the different risk levels of VTE.

Elderly patients with ICH are often admitted to the ICU for treatment. Due to the use of mechanical ventilation, as well as sedative and analgesic drugs, these patients are prone to limb dysfunction, which leads to slow venous blood flow and blockage of the venous lumen. Advanced age is an important factor in high-risk VTE patients. Thus, the present study was

comprised of elderly surgical patients. In addition, increased risk of VTE may be associated with a variety of other factors. For example, the incidence of VTE has been reported to be over 90% in patients who had 5 or more risk factors. Furthermore, the risk of VTE in patients with malignant tumors was found to be 6 times higher than that observed in non-malignant patient [15–18]. Some of the patients in this study had been diagnosed with diseases such as cancer and were, therefore, at increased risk of VTE. Despite these previous reports, awareness of the prevention of VTE in elderly patients following ICH surgery is generally low, and not enough attention is paid to these patients, even though VTE prophylaxis reduces the risk of developing VTE [19]. In the present study, the PPS was used to evaluate the risk factors of elderly patients with ICH. The PPS was calculated by assessing 11 potential risk factors, and corresponding preventive measures were implemented for patients depending on their score. Based on PPS-guided LMWHC treatment, the incidence of VTE was significantly reduced in the study group (5.6%) compared to the control group (14.5%) [15]. Thus, our findings suggest that PPS may be beneficial in the prevention of VTE.

Preventive treatment was also implemented for low-risk patients including dietary guidance, life habit changes and management of glucose and lipids. In addition, preventative intravenous infusion or puncture to the lower extremities was carried out. Specific attention was also paid to the physical training of patients to ensure that they got out of bed each day. Air pressure pumps and thrombotic stockings were also used to prevent thrombosis. For patients with higher PPSs, such as those at intermediate or high risk, these parameters were used in combination with daily LMWHC treatment to prevent thrombosis. In addition, the coagulation function, especially

TABLE 1. Characteristics of patients.

	Study group (n = 101)	Control group (n = 124)	p-value
Age (yr)	75.62 ± 2.78	76.67 ± 2.15	0.327
Gender (male/female)	62/39	78/46	0.815
Oxygenation index (mmHg)	381.16 ± 20.12	341.74 ± 17.95	0.133
Padua Prediction Score	4.7 ± 2.1	5.1 ± 1.8	0.737
D-dimer (mg/L)	2.61 ± 0.46	2.53 ± 0.35	0.362
Serum creatinine (μmol/L)	80.19 ± 23.62	84.21 ± 28.19	0.238
Blood urea nitrogen (mmol/L)	7.21 ± 3.46	7.43 ± 4.05	0.182
Tumor (%)	27 (26.7)	29 (23.4)	0.564
Heart failure (%)	64 (63.4)	70 (56.5)	0.293
Hypertension (%)	821 (81.2)	103 (83.1)	0.714
Venous thromboembolism (%)	6 (5.9)	18 (14.5)	0.038
Recurrent intracranial hemorrhage (%)	3 (3.0)	1 (0.8)	0.222

TABLE 2. Thrombelastography indicators.

	Before intervention		p-value	After intervention		p-value
	Study group (n = 101)	Control group (n = 124)		Study group (n = 101)	Control group (n = 124)	
R (min)	6.29 ± 0.98	6.21 ± 0.96	0.432	5.21 ± 0.18	4.24 ± 0.92	0.034
Angle (deg)	64.55 ± 13.31	63.55 ± 13.32	0.074	67.55 ± 14.38	76.55 ± 11.33	0.019
CI	0.20 ± 0.24	0.20 ± 0.21	0.721	1.23 ± 0.21	2.01 ± 0.22	0.046
MA (mm)	59.37 ± 9.15	60.35 ± 9.14	0.063	61.37 ± 9.77	70.37 ± 9.88	0.027

CI: comprehensive coagulation index; MA: maximum clot strength.

TABLE 3. Coagulation function and venous blood velocity.

	Before intervention		p-value	After intervention		p-value
	Study group (n = 101)	Control group (n = 124)		Study group (n = 101)	Control group (n = 124)	
Fibrinogen (g/L)	3.31 ± 1.05	3.29 ± 1.01	0.134	2.27 ± 0.66	2.74 ± 0.77	0.024
D-dimer (mg/L)	2.61 ± 0.46	2.53 ± 0.35	0.362	1.39 ± 0.27	1.88 ± 0.32	0.027
Venous blood velocity (cm/s)	20.57 ± 3.04	24.92 ± 3.16	0.061	27.07 ± 3.59	19.98 ± 2.95	0.011

changes in D-dimer levels, were monitored. These factors were beneficial in determining whether a patient would be at high risk of VTE, and whether intervention would help prevent the development of VTE [20–22].

LMWHC is a fragment of unfractionated heparin produced by enzymatic or chemical depolymerization, which can enhance the inhibitory effects on activated coagulation factors II, IX, X, XI and XII. In addition, LMWHC can promote fibrinolysis by stimulating vascular endothelial cells to release a large number of anticoagulant substances, enhance the activity of protein C, and stimulate the release of plasminogen activator by vascular endothelial cells. LMWHC has previously been reported to help prevent VTE without affecting the procalcitonin and coagulation functions of patients, and is therefore clinically safe [23]. Studies have also shown that the use of low-dose LMWHC to prevent DVT in high-risk patients has great clinical significance for improving the clinical prognosis

of ICU patients [24].

Our study showed that thromboelastography indices such as Angle, R, CI and MA, were not significantly different between the control and study groups before intervention. However, PPS-guided LMWHC treatment and intervention significantly improved these parameters in the study group compared to the control group. The levels of coagulation function indices including fibrinogen and D-dimer levels did not differ significantly between the control and study groups before the intervention, but were significantly reduced following LMWHC treatment. In addition, following intervention, a venous blood flow velocity of 27.07 ± 3.59 cm/s was observed in the study group, which was significantly faster than that found in the control group. Therefore, we speculated that PPS-based VTE risk assessment of elderly patients in the ICU and targeted LMWHC treatment could reduce the occurrence of VTE in patients. Spyropoulos *et al.* [25] previously reported that

preventive interventions in patients without formal VTE risk stratification did not reduce the incidence of VTE, highlighting the importance of VTE risk assessment before treatment. The present study demonstrated that the use of PPS to identify the risk of VTE followed by implementation of effective measures to prevent VTE minimized the occurrence of VTE in patients and improved the quality of medical care. Therefore, the use of PPS-guided LMWHC has clinical significance in preventing the occurrence of VTE in elderly patients with ICH.

There were some limitations to the present study. First, the study population was relatively small. Second, this was a single-center, retrospective cohort study. Thus, further multi-center, large-scale, prospective studies are needed to verify the findings of the present study. Finally, although our results may have been limited by the sample size and study design, the present study still provides novel information for the management of VTE in elderly patients with ICH.

5. Conclusions

In conclusion, the use of PPS-guided LMWHC in elderly patients with ICH could significantly improve the coagulation function of the patients. In addition, PPS-guided LMWHC may be beneficial for increasing the venous blood flow velocity and controlling the incidence of VTE. Our findings highlight the clinical relevance of PPS-guided LMWHC in the prevention and treatment of VTE in elderly ICH patients.

ABBREVIATIONS

VTE, venous thromboembolism; DVT, deep vein thrombosis; PE, pulmonary embolism; ICU, intensive care unit; PPS, Padua Prediction Score; ACCP, American College of Chest Physicians; LMWHC, low-molecular-weight heparin calcium; ICH, intracerebral hemorrhage; CT, computerized tomography; CTA, computerized tomography angiography.

AVAILABILITY OF DATA AND MATERIALS

The authors declare that all data supporting the findings of this study are available within the paper and any raw data can be obtained from the corresponding author upon request.

AUTHOR CONTRIBUTIONS

JFZ and FLZ—designed the study and carried them out, prepare the manuscript for publication and reviewed the draft of the manuscript; LHZ, LS and FLZ—supervised the data collection, analyzed the data, interpreted the data. All authors have read and approved the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The present study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Hangzhou First People's Hospital (Approval no. IIT-20220606-0088-01). Written informed consent was obtained

from all participants.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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