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Effects of intermittent pneumatic compression on serum HMGB1 levels of deep venous thrombosis of lower extremity in severe traumatic brain injury patients

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Abstract

Objective: To investigate the efficacy of intermittent pneumatic compression (IPC) in prevention of deep venous thrombosis (DVT) in severe traumatic brain injury (TBI) patients and to observe the effects of IPC on hemorheological and coagulation indices, as well as high-mobility group box 1 (HMGB1) in severe TBI patients. *Methods:* The present prospective open randomized controlled research recruited 332 severe TBI cases seen during May 2017~November 2019. All patients were randomly divided into two groups, with 166 cases in the control group and 166 cases in the IPC group. The serum levels of HMGB1 were determined using an enzyme linked immunosorbent assay (ELISA). The flow velocity of common femoral vein was also evaluated using Doppler ultrasound before treatment, as well as at 1 d, 3 d, 7 d and 14 d after admission. Levels of prothrombin time (PT), activated partial thromboplastin time (APTT), fibrinogen (FIB) and D-Dimer (D-D) were also evaluated before treatment, as well as at 7 d and 14 d after admission. *Results:* DVT occurred in a total of 35 (10.54%) cases of all patients, with 6 (3.61%) cases in IPC group, which was significantly lower than 29 (17.47%) cases in the control group. Serum FIB levels were significantly lower in the IPC group at 7 d and 14 d after treatment compared with the control. At 3 d, 7 d and 14 d after treatment, the levels of flow velocity of common femoral vein were markedly higher in IPC group compared with the control and after 3 d treatment, the levels of HMGB1 at 1 d, 3 d, 7 d and 14 d were all markedly lower in IPC group than the control. After admission, the serum levels of HMGB1 were markedly higher in DVT patients compared with the non-DVT patients at 1 d, 3 d, 7 d and 14 d and were negatively correlated with the flow velocity of common femoral vein at 3 d, 7 d and 14 d. *Conclusion:* IPC treatment could prevent DVT in severe TBI patients, which was associated with increased velocity of common femoral vein and decreased FIB and HMGB1 levels. HMGB1 may be useful as a potential biomarker for DVT in severe TBI patients.

Keywords: Intermittent pneumatic compression, deep venous thrombosis, traumatic brain injury, HMGB1

INTRODUCTION

Deep venous thrombosis (DVT) is one of the common complications following traumatic brain injury (TBI), especially for severe TBI, in which coagulation factors can be released due to bleeding, leading to venous thromboembolism (VTE).[1-3] In a clinical analysis containing 603 severe TBI patients, VTE was found in 119 (19.7%) patients, with 102 (16.9%) patients of DVT.[4] In another study including 424,929 TBI patients, 16,690 (3.9%) developed VTE, in which severe TBI patients had higher risk for VTE.[2] The delay in prevention and treatment of DVT may lead to higher risk for mortality and morbidity for severe TBI patients.[5] Though low molecular weight heparin can be used in prevention of VTE,

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its risk for hemorrhage limits its use under some conditions.[6,7]

The intermittent pneumatic compression (IPC) is a physical method for prevention of DVT by intermittent pressure to lower limbs to promote venous reflux.[8] IPC is already applied to many surgeries to prevent DVT, including in neurosurgery.[9] In TBI, some studies also used IPC in TBI patients.[7,10] However, very few studies focused on the effects of IPC in severe TBI patients, especially for how IPC treatment influences the hemorheological and coagulation indices, as well as thrombosis-related factors in TBI. High-mobility group box 1 (HMGB1) protein is an inflammation-related factor[11], which is correlated with thrombosis.[12] However, the relationship between HMGB1 and DVT in TBI patients is unclear.

In the present study, we designed a randomized-controlled research to investigate the efficacy of IPC in prevention of DVT in severe TBI patients and to observe the effects of IPC on hemorheological and coagulation indices, as well as HMGB1 in severe TBI patients.

METHODS

Patients

This prospective open randomized controlled research included 332 severe TBI cases seen from May 2017 to November 2019. The inclusion criteria were: 1) the diagnosis of TBI confirmed by MRI and CT scan; 2) patients had Glasgow Coma Scale (GCS) scores within 3~8; 3) the predicted survival duration was >2 d. The exclusion criteria were: 1) patients who had DVT on admission; 2) patients who had received anticoagulation treatment before the study; 3) patients who could not receive IPC treatment due to lower extremity disease; 4) patients with severe co-morbidities including malignant tumor, or severe kidney, liver or cardiovascular pathologies; 5) patients who had surgery within 3 months before the study. All patients received general care for TBI, including ICU monitoring, the maintenance of airway patency, prevention and treatment of cerebral edema, reduction of intracranial pressure, supplement of neurotrophic, prevention and treatment of various complications, as well as surgery like intracranial hematoma clearance, decompressive craniectomy, epidural and subdural hematoma clearance, fracture fragment clearance and cranioplasty when indicated. Patients' basic clinical characteristics were collected and recorded. All patients or the family members signed the written informed consent. The present study was approved by the ethical committee of the Shuguang hospital.

Treatment and nursing

For sample size calculation, the formula of $\frac{[(t\alpha+t\beta)s]2}{\delta}$ was used, with the flow velocity of common femoral vein as the primary clinical outcome. The mean flow velocity of common femoral vein was determined as 11.0±2.0 cm/sec based on our experience. The mean velocity of common femoral vein increased by at least 1 m/sec was considered as effective treatment. Thus, δ=1, s=2, α=0.05, β=0.10. The minimal sample size was 42. All patients were then randomly divided into two groups using a computer-generated list by Rv. Uniform formula using SPSS software (SPSS Inc., Chicago, USA), with 166 cases in the control group and 166 cases in the IPC group.

For both groups, general nursing care and treatment were carried out for prevention of DVT. This include: 1) education to introduce DVT and the necessity for DVT prevention; 2) after admission in ICU, appropriate fluid infusion was conducted and patients were given adequate amount of and digestible diet, as well as to do moderate ankle movement every day (when patients were not able to do ankle movement, the nurse would help). This routine treatment lasted for 14 d during the whole study period. The control group only received the general treatment and nursing care.

For IPC group, the patients also received IPC treatment using a Flowtron Excel AC550 system (Huntleigh Healthcare, UK) after admission in ICU. Briefly, the inflation and pressurization were performed from the ankle to the thigh for 10~15 s with 25~45 mmHg, following with venting for 50~60 s. The procedure was repeated for 30 min every time. Patients received treatment for 3 times/d at morning, afternoon and night. The treatment lasted for 14 d.

For diagnosis of DVT, the examination of Homan symptom was performed every day and Doppler ultrasound was conducted when Homan symptom appeared for confirmation. Besides, Doppler ultrasound was performed every week during the study period. The whole study lasted for 14 d after admission.

Measurement of serum HMGB1

The blood samples of all patients were collected before any treatment, as well as at 1 d, 3 d, 7 d

and 14 d after admission. Serum samples were obtained after centrifugation. The serum levels of HMGB1 were determined using an enzyme linked immunosorbent assay (ELISA) kit (MyBioSource, cat no. MBS701378).

Evaluation of hemorheological and coagulation indices

The flow velocity of common femoral vein was also evaluated using Doppler ultrasound before treatment, as well as at 1 d, 3 d, 7 d and 14 d after admission. Besides, coagulation related biomarkers of prothrombin time (PT), activated partial thromboplastin time (APTT), fibrinogen (FIB) and D-Dimer (D-D) were also evaluated before treatment, as well as at 7 d and 14 d after admission using an automatic biochemical analyzer (Hitachi 7600, Hitachi Corporation, Japan).

Statistical analysis

The measurement data was expressed as mean ± SD. Comparison for continuous data were analyzed by Student t test. Rates were compared by Chi square test. Pearson's correlation was used for analysis of the correlation. The ROC curve was used for evaluating the diagnostic value of HMGB1 in DVT. P <0.05 was considered as statistically significant. All calculations were made using SPSS 22.0.

RESULTS

Basic characteristics of all patients

This study enrolled 332 severe TBI cases. A total of 69 cases who did not meet the inclusion criteria or quit the study were excluded. Among all patients, the mean GCS score was 5.37±1.61. A total of 165 (49.7%) cases received surgery and 316 (86.3%) cases received mechanical ventilation. No significant difference was found for all characteristics between the two groups (Table 1).

IPC treatment reduced DVT incidence and influenced hemorheological and coagulation indices

The impact of IPC treatment on DVT incidence, hemorheological and coagulation indices was investigated. As shown in Table 2, DVT occurred in 35 (10.54%) cases, with 6 (3.61%) cases in IPC group, which was significantly lower than 29 (17.47%) cases in the control group (P<0.05). The levels of flow velocity of common femoral vein, PT, APTT, D-D and FIB all showed no significant difference between the two groups on admission. Only serum FIB levels were significantly lower in the IPC group at 7 d and 14 d after treatment compared with the control (P<0.05). No other significant difference was found for coagulation

Table 1: Basic characteristics of all patients

Variables	IPC group, n=166	Control group, n=166	P
Age, y	46.71±9.73	46.33±10.52	0.733
Sex, female (%)	71 (42.77)	67 (40.36)	0.730
BMI, kg/m^2	24.74±3.09	24.16±3.17	0.093
Pathological type, n (%)			0.849
Subarachnoid hemorrhage	69 (41.57)	65 (39.16)	
Severe contusion	43 (25.90)	51 (30.72)	
Intracranial hemorrhage	21 (12.65)	18 (10.84)	
Epidural or subdural hematoma	13 (7.83)	17 (10.24)	
Diffuse axonal injury	20 (12.05)	15 (9.04)	
Complications, n (%)			0.616
Diabetes	23 (13.86)	19 (11.45)	
Hypertension	25 (15.06)	27 (16.27)	
GCS score	5.27±1.59	5.46±1.63	0.293
SOFA score	8.20±4.76	8.51±4.65	0.553
APACHE II score	18.02±4.43	17.45±4.69	0.254
Open surgery, n (%)	81 (48.80)	84 (50.60)	0.799
Mechanical ventilation, n (%)	157 (94.58)	159 (95.78)	0.692

Table 2: DVT incidence during study, as well as velocity of common femoral vein and coagulation indices

Variables		IPC, n=166	Control, n=166	P
DVT, n (%)		6 (3.61)	29 (17.47)	0.001
Flow velocity of common femoral vein on admission, cm/s		12.32±1.48	12.42±1.40	0.521
PT, s	Before	15.19±1.77	15.24±1.75	0.822
	7 d	14.27±2.16	14.26±1.98	0.975
	14 d	13.39±1.49	13.43±1.47	0.767
APTT, s	Before	38.31±2.17	38.43±1.97	0.603
	7 d	37.32±2.77	36.98±2.71	0.260
	14 d	34.79±2.93	35.21±2.99	0.197
D-D, μg/ml	Before	1.38±0.37	1.37±0.39	0.806
	7 d	1.27±0.30	1.29±0.32	0.560
	14 d	1.25±0.33	1.26±0.31	0.894
FIB, g/L	Before	4.45±0.96	4.41±0.95	0.668
	7 d	3.52±0.81	4.04±0.95	<0.001
	14 d	3.59±0.82	3.97±0.88	<0.001

indices. However, at 3 d, 7 d and 14 d after treatment, the levels of velocity of common femoral vein were markedly higher in IPC group compared with the control (P<0.05, Figure 1).

Effects of IPC treatment on serum HMGB1 level

To further investigate the effects of IPC on DVT incidence, serum HMGB1 levels were evaluated on admission, as well as at 1 d, 3 d, 7 d and 14 d after admission. As shown in Figure 2, no significant difference was found for HMGB1 on admission between the two groups of patients. However, after 1 d treatment, the levels of HMGB1 at 1 d, 3 d, 7 d and 14 d were all markedly lower in IPC group than the control (P<0.05), indicating that IPC treatment might reduce the serum HMGB1 level in SEVERE TBI patients.

HMGB1 level was correlated with velocity of common femoral vein and DVT incidence

Then, patients were divided into DVT and non-DVT patients and the expression of HMGB1

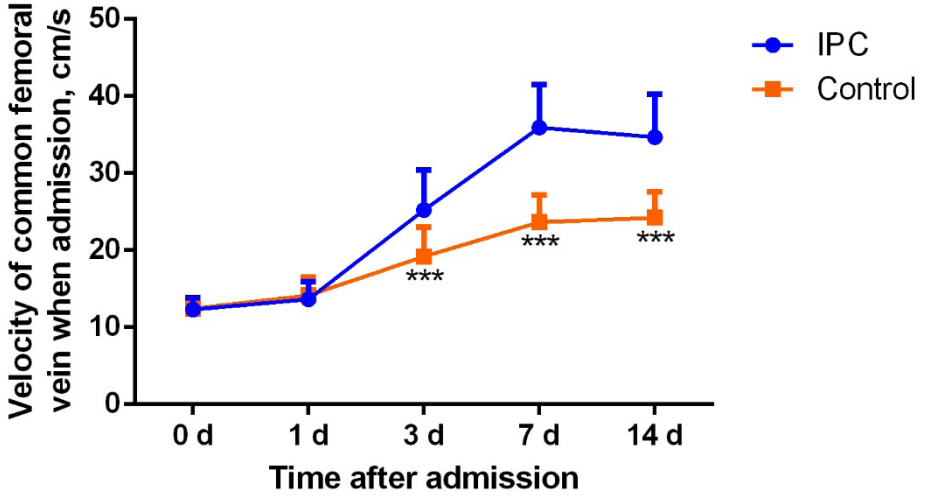

Figure 1. Dynamic changes of flow velocity of common femoral vein in two groups of patients. ***P<0.001 vs IPC group.

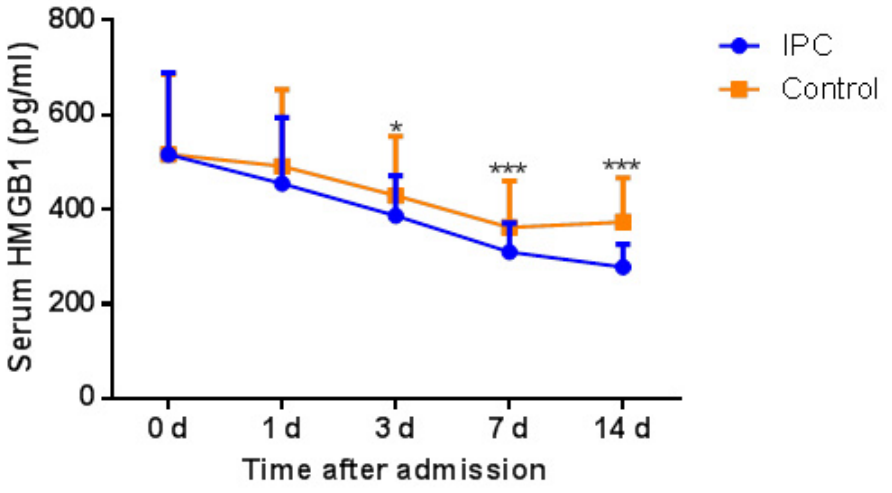

Figure 2. Dynamic changes of serum HMGB1 in two groups of patients. *P<0.05, ***P<0.001 vs IPC group.

was evaluated. It was found that on admission, no significant difference was found between the DVT and non-DVT patients. However, at 1 d, 3 d, 7 d and 14 d after admission, the serum levels of HMGB1 were markedly higher in DVT patients compared with the non-DVT patients (P<0.05, Figure 3). Further Pearson's analysis showed that HMGB1 at 3 d, 7 d and 14 d was negatively correlated with the velocity of common femoral vein at the same time points in all patients (P<0.05, Table 3). Then we used ROC curve to investigate the diagnostic role of HMGB1 at 1 d, 3 d and 7 d for diagnosis of DVT. It was found HMGB1 at 1 d had AUC 0.658 (95% CI 0.563~0.752), with cutoff value 481.61 pg/ml, sensitivity 60.0% and specificity 53.2% for diagnosis of DVT; HMGB1 at 3 d had AUC 0.633 (95% CI 0.525~0.740), with cutoff value 407.87 pg/ml, sensitivity 60.0% and specificity 53.9% for diagnosis of DVT; HMGB1 at 7 d had AUC 0.635 (95% CI 0.513~0.758), with cutoff value 361.09 pg/ml, sensitivity 60.0% and specificity 65.7% for diagnosis of DVT (Figure 4).

DISCUSSION

DVT is a common complication after severe diseases and surgery. Many treatment methods have been developed for treatment of DVT.[13,14] In the present research, we demonstrated in a randomized control research to reveal that IPC

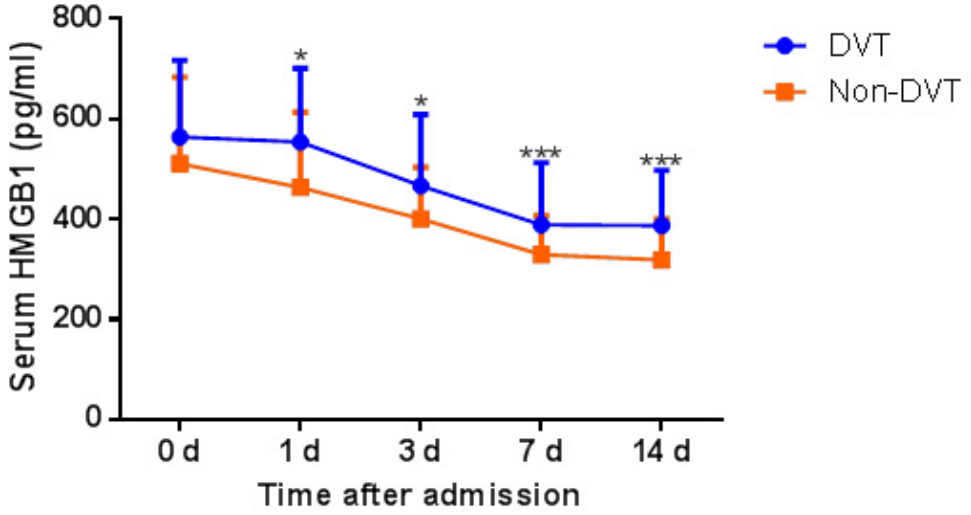

Figure 3. Dynamic changes of serum HMGB1 in DVT and non-DVT patients. ***P<0.001 vs non-DVT group.

Table 3: Correlation between HMGB1 at different time points and corresponding flow velocity of common femoral vein

	HMGB1				
	0 d	**1 d**	**3 d**	**7 d**	**14 d**
Pearson	-0.065	0.009	-0.175	-0.285	-0.486
P	0.239	0.874	0.001	<0.001	<0.001

treatment could reduce the incidence of DVT for severe TBI patients, and the efficacy might be through enhancing velocity of common femoral vein and reducing FIB levels. Moreover, IPC could reduce the serum HMGB1 levels, which might be correlated with DVT incidence and might be a potential biomarker for DVT.

IPC treatment has been reported in several studies. In total knee arthroplasty, it was found that IPC could reduce the DVT incidence compared with the rivaroxaban.[15] In a systematic review, Pavon *et al*. found IPC and anticoagulation showed similar efficacy for prevention of VTE, while IPC showed lower risk for major bleeding than anticoagulation.[16] In another research, the authors demonstrated that IPC treatment could increase the peak blood velocity of superficial femoral vein (PBVFV) and the popliteal vein (PBVPV) for both resting at supine and the sitting position in patients with plaster-cast immobilization of the lower limb.[17] However, up to now, clinical evidence for application of IPC in prevention of TBI-induced DVT is still lacking. In our study, we demonstrated that IPC could reduce the DVT incidence, which may be associated with the increased flow velocity of common femoral vein and inhibition of FIB.

HMGB1 is reported to be involved in many diseases, especially for inflammation. In recent years, HMGB1 is also found to contribute to thrombosis. Dyer *et al*. showed platelet HMGB1 could increase DVT and other microvascular complications through enhanced neutrophil recruitment and the formation of neutrophil extracellular traps.[18] In another study, it was found increased HMGB1 was associated with increasing dietary cholesterol, and higher HMGB1 level predicted shorter thrombus formation time.[19] Other early studies also found platelet-derived HMGB1 contributed and was a main mediator for

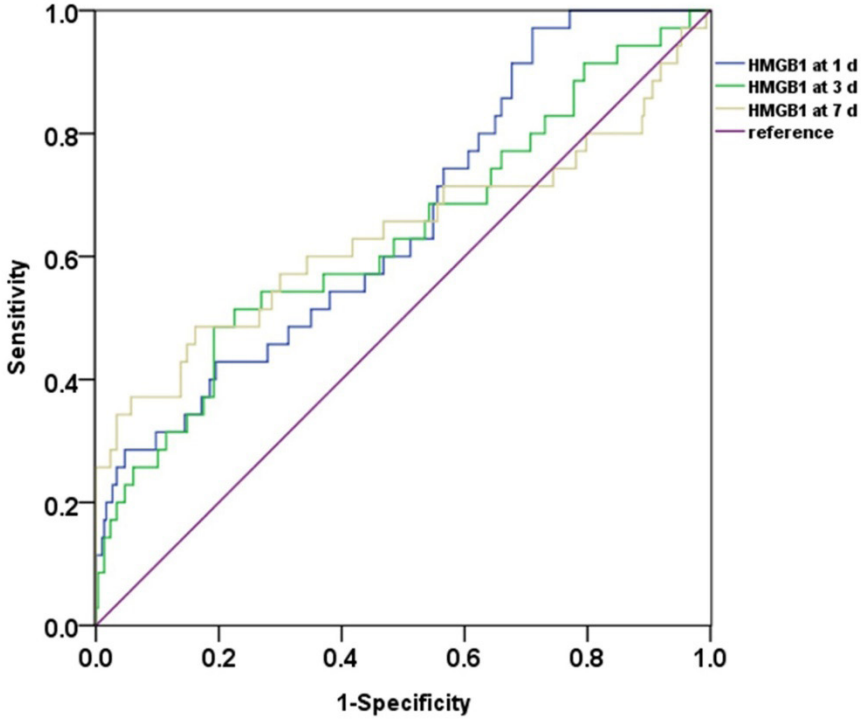

Figure 4. ROC curve for HMGB1 at 1 d, 3 d and 7 d in for diagnosis of DVT in severe TBI patients.

thrombosis.[20,21] However, there is still no clinical study reporting HMGB1 in DVT.

In our study, we observed that severe TBI patients with DVT showed significantly higher HMGB1 serum levels than the non-DVT patients. Besides, IPC treatment could reduce the incidence of DVT, and indirectly reduced the level of HMGB1. These results further indicated that HMGB1 is involved in thrombosis. However, more evidence is still needed to confirm our results.

In conclusion, this randomized control study found IPC treatment could prevent DVT in severe TBI patients, which was associated with increased velocity of common femoral vein and decreased FIB and HMGB1 levels. Meanwhile, HMGB1 might be used as a potential biomarker for DVT in severe TBI patients.

DISCLOSURE

Financial support: None

Conflict of interest: None

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