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Original Article

Effects of low molecular weight heparin combined with hyperbaric oxygen on neurologic function and coagulation factors in patients with intracranial venous thrombosis

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Abstract: Objective: To investigate the effects of low molecular weight heparin (LMWH) combined with hyperbaric oxygen (HBO) on the neurologic function and coagulation factors of patients with intracranial venous thrombosis (ICVT). Methods: The clinical data of 80 patients with ICVT admitted to the No. 2 Hospital of Baoding from February 2020 to January 2021 were retrospectively analyzed. Patients were assigned to a control group (n=32) and a research group (n=48) according to different treatment methods. The neurological function score, and the levels of D-dimer (D-D), fibrinogen (FIB), tumor necrosis factor-α (TNF-α), and C-reactive protein (CRP) were compared between the two groups. The two groups were also compared regarding the curative effect, toxic and side effects, as well as quality of life (QoL). Results: After treatment, the National Institutes of Health Stroke Scale (NIHSS) score was significantly lower in the research group compared to the control group. At 1, 2 and 3 weeks after treatment, the levels of D-D and FIB, as well as inflammatory factors TNF-α and CRP were lower in the research group compared to the control group. The overall response rate was significantly higher in the research group compared to the control group, while there was no significant difference in the total incidence of toxic and adverse effects between the two groups. After treatment, the QoL of patients assessed by the Generic Quality of Life Inventory-74 (GQOLI-74) from the domains of physical, social, and psychological function as well as material life status was significantly better in the research group. Conclusions: LMWH combined with HBO can effectively improve the clinical efficacy and neurologic function of patients with ICVT and reduce the levels of coagulation factors and inflammatory factors.

Keywords: Low molecular weight heparin, hyperbaric oxygen, intracranial venous thrombosis, neurological function, coagulation factor

Introduction

Intracranial venous thrombosis (ICVT) is a rare and fatal type of stroke, accounting for only 0.5-1% of all strokes. Age >37 years old, being male, deep cerebral venous system thrombosis, and central nervous system infection are all risk factors for poor prognosis [1]. In addition, the disease is characterized by blood clotting in cerebral veins, dural sinuses, or rare veins [2], and presents a variety of clinical manifestations such as headache, optic disc edema, focal neurological deficits and disturbance of consciousness. ICVT has diverse clinical and imaging manifestations, with complex etiology and difficult early diagnosis [3]. Evidence has shown that the formation of thrombosis is mainly due to the interaction of vascular endothelial injury, blood hypercoagulability and venous block, as well as the involvement of vascular endothelial fibrin [4]. As markers of thrombosis, blood hypercoagulability, and fibrinolytic system lesions, fibrinogen (FIB) and D-dimer (D-D) are also important coagulation factors [5]. It was shown that increased FIB levels may lead to activation of the fibrinolytic system, along with the increase of D-D levels [6]. In the study of Shujun, the elevation of D-D was shown to be an independent risk factor for patients with venous thromboembolism (VTE), and that D-D was of predictive value in ICVT [7]. Therefore, exploring a therapeutic strategy that can effectively improve the neurologic function and coagulation factors of patients with ICVT is

of great significance for improving clinical symptoms and curbing disease progression.

At present, anticoagulant therapy, such as heparin (HP), is used to treat ICVT. However, research has shown that most patients develop hemorrhage at the thalamic infarction site when receiving treatment [8]. HP is widely used in clinical treatment of ICVT. Unfractionated heparin (UFH) is commonly used in microvascular surgery to prevent the formation of microvascular thrombosis. Fixed-dose HP infusion, which was previously considered adequate for the prevention of VTE, has now beenfound to be inappropriate for most patients [9]. Low molecular weight heparin (LMWH) is a depolymerizer of HP, which has similar pharmacological effects as HP and more prominent antithrombotic effects than HP [10]. Studies have shown that LMWH has significant efficacy and safety in the treatment of lower limb deep vein thrombosis in patients with hypertensive intracerebral hemorrhage and can significantly improve the quality of life (QoL) of patients [11]. However, LMWH has also been reported to induce bleeding [12]. Hyperbaric oxygen (HBO) is a treatment method that increases atmospheric pressure by 100% oxygen to achieve therapeutic purposes, which can be used to treat diseases such as poor wound healing and carbon monoxide poisoning [13]. Also, HBO can be used to treat cerebral venous air embolism and prevent VET [14]. However, it may also induce barometric injury, oxygen poisoning, decompression sickness and other toxic and side reactions [15]. Considering that both treatments have therapeutic effects on VET, we combined these two treatments to evaluate their clinical effects in ICVT.

The innovation of this study is that we compared and analyzed the clinical effects of LMWH combined with HBO therapy and HBO monotherapy, and evaluated the therapeutic efficacy, neurologic function and coagulation factors of patients with ICVT, to provide a reference for treatment of ICVT.

Materials and methods

Clinical data collection

In this retrospective study, 80 patients with ICVT admitted to the No. 2 Hospital of Baoding from February 2020 to January 2021 were selected and assigned to a control group (n= 32) and a research group (n=48) based on different treatment methods. Patient inclusion criteria: patients who met the diagnostic criteria of ICVT and were confirmed by computed tomography (CT) or magnetic resonance imaging (MRI) [16]; Patients with an age ≥18 years old, with stable vital signs, independent thinking ability, complete clinical general information, and confirmed diagnosis of ICVT by supersonic inspection or color Doppler ultrasonography. This study was approved by the Ethics Committee of the No. 2 Hospital of Baoding. Exclusion criteria: patients who were lost to follow-up; patients with sensory, motor, cognitive, speech and intellectual dysfunction; patients who were unable to receive preventive measures at admission due to existing contraindications; patients with mental illness, abnormal liver and kidney function, or abnormal immune system; dropouts; and patients who discharged themselves from the hospital against medical advice.

Treatment regimens

Patients in the control group were treated with HBO therapy once daily for 100 minutes each time, with a treatment pressure of 0.2 MPa, and intermittent oxygen inhalation for 60 minutes during treatment. The intermittent oxygen inhalation process was implemented by 3 times (20 minutes/time), with a 5-minute rest in between. The patients were treated for two courses and 15 times for each course, with a one-week break in between.

Patients in the research group were additionally given LMWH (Qilu Pharmaceutical, Jinan, CHN, H20030429) 10 mg per os, once a day, for 3 days. Patients received HBO therapy first and then oral LMWH therapy.

Outcome measures

Neurological function score: The National Institutes of Health Stroke Scale (NIHSS) score [17] was used to evaluate the neurological function of patients. The score ranges from 0-42, with 0-1 for normal, 2-4 for mild, 5-15 for moderate, 16-20 for moderate-severe, and 21-42 for severe. Lower scores indicated better neurological recovery.

Detection of coagulation factors: The levels of D-D and FIB were measured before and 1, 2 and 3 weeks after treatment. 5 ml of venous blood were collected from each patient and centrifuged at 1500 × g (4°C) for 10 min, and the resultant serum was refrigerated at -70°C for use. A hemagglutination analyzer (Bohui

Biotech, Beijing, China, b026) was used to detect serum D-D and FIB levels.

Detection of inflammatory factors: The levels of tumor necrosis factor-α (TNF-α) and C-reactive protein (CRP) were detected before and 1, 2 and 3 weeks after treatment. After samplings of 5 mL venous blood from each patient were collected and centrifuged at 1500 × g (4°C) for 10 min the resulting serum was frozen at -70°C for testing. Serum levels of TNF-α and CRP were determined using enzyme-linked immunosorbent assay (ELISA) [18] according to the instructions of TNF-α and CRP ELISA kits (EK-Bioscience Biotech, Shanghai, CHN, EK-H12145, EK-H10077).

Clinical efficacy: The clinical efficacy of both groups was observed after treatment. Markedly effective: the NIHSS score of the patient decreased by 46%-90% after treatment, with relieved or basically disappeared clinical symptoms. Effective: the NIHSS score decreased by 18%-45% after treatment, with improved clinical symptoms. Ineffective: the NIHSS score decreased by <18%, with no improvement in clinical symptoms. The overall response rate (ORR) was calculated as (markedly effective + effective) cases/total cases × 100%.

Toxic and side effects: The toxic and side effects, including anemia, bleeding, contusion and nausea, were observed and recorded in both groups.

QoL assessment: The Generic Quality of Life Inventory-74 (GQOLI-74) [19] was used to assess the QoL of patients from the domains of physical, social and psychological functioning as well as material life state before and after treatment. Higher scores indicate better QoL.

Among the above outcome measures, the primary ones of this study were NIHSS score, levels of D-D, FIB, TNF-α, and CRP, toxic and side reactions, and GQOLI-74 score; the secondary outcome measure was clinical efficacy.

Statistical analysis

The data were statistically analyzed by SPSS21.0 (SPSS, Inc., Chicago, IL, USA) and visualized using GraphPad Prism 6.0 (GraphPad Software Inc., San Diego, CA, USA). Categorical data were described as cases/percentages [n (%)], and the difference between groups was identified by Chi-square test or Chi-square continuity correction (applied when theoretical frequency <5 in the Chi-square test). Quantitative data were expressed as mean ± standard deviation (mean ± SD); the difference between groups was identified by independent samples t-test, and that within the group before and after treatment was identified by paired t-test; repeated-measures analysis of variance (ANOVA) was used for intra- and inter-group comparisons at different time points, and the Bonferroni method was used for post-hoc pairwise comparisons. Differences were considered to be significant at $P<0.05$.

Results

Patient baseline data

The comparison of baseline data showed no statistical difference in average age, gender, body mass index (BMI), mean course of disease, bleeding site, history of coronary heart disease, diabetes, hypertension, smoking and alcoholism, as well as residence and exercise habits between the two groups ($P>0.05$), indicating comparability (**Table 1**).

Comparison of neurologic function between the two groups before and after treatment

The NIHSS score showed no significant difference between the two groups before treatment ($P>0.05$); After treatment, the NIHSS score reduced significantly in both groups ($P<0.05$), with a lower score in the research group compared with the control group ($P<0.05$, **Table 2**).

Comparison of the levels of coagulation factors between the two groups before and after treatment

The levels of D-D and FIB showed no significant difference between the two groups before treatment ($P>0.05$). At 1, 2 and 3 weeks after treatment, D-D and FIB levels were reduced in both groups ($P<0.05$), with lower levels in the research group compared with the control group ($P<0.05$, **Figure 1**).

Comparison of inflammatory factors between the two groups before and after treatment

The levels of TNF-α and CRP were not statistically different between the two groups before treatment ($P>0.05$). At 1, 2 and 3 weeks after treatment, TNF-α and CRP levels decreased significantly ($P<0.05$), especially in the research group ($P<0.05$, **Figure 2**).

Table 1. Baseline data of patients in both groups [n (%) (Mean ± SD)]

Variable	Control group (n=32)	Research group (n=48)	t/χ^2	P
Average age (years)	62.15±6.22	60.08±6.09	1.477	0.144
Gender			0.076	0.783
Male	15 (46.88)	21 (43.75)		
Female	17 (53.13)	27 (56.25)		
BMI (kg/m^2)	21.86±1.95	21.58±1.93	0.633	0.529
Average course of disease (h)	2.06±0.22	2.09±0.31	0.473	0.637
Bleeding site			0.417	0.937
Cerebral lobe	4 (12.50)	6 (12.50)		
Thalamencephalon	13 (40.63)	17 (35.42)		
Basal ganglia	10 (31.25)	15 (31.25)		
Cerebellum	5 (15.63)	10 (20.83)		
History of coronary heart disease			0.413	0.521
Yes	19 (59.38)	25 (52.08)		
No	13 (40.63)	23 (47.92)		
History of diabetes			0.309	0.578
Yes	20 (62.50)	27 (56.25)		
No	12 (37.50)	21 (43.75)		
History of hypertension			0.833	0.361
Yes	18 (56.25)	22 (45.83)		
No	14 (43.75)	26 (54.17)		
History of smoking			1.524	0.217
Yes	23 (71.88)	28 (58.33)		
No	9 (28.13)	20 (41.67)		
History of alcoholism			1.368	0.242
Yes	24 (75.00)	30 (62.50)		
No	8 (25.00)	18 (37.50)		
Residence			1.212	0.271
Urban	20 (62.50)	24 (50.00)		
Rural	12 (37.50)	24 (50.00)		
Exercise habits			2.537	0.111
Yes	23 (71.88)	26 (54.17)		
No	9 (28.13)	22 (45.83)		

Note: BMI: body mass index.

Table 2. Comparison of neurologi function between both groups before and after treatment (Mean ± SD)

Groups	n	NIHSS scores	
		Before treatment	After treatment
Control group	32	15.22±1.02	9.57±0.94#
Research group	48	15.24±1.09	7.35±0.29#
t	-	0.082	15.350
P	-	0.935	<0.001

Note: NIHSS, National Institutes of Health Stroke Scale. #indicates P<0.01 *vs* before treatment.

Comparison of curative effects between the two groups after treatment

The ORR, evaluated based on the Response Evaluation Criteria In Solid Tumors (RECIST), was 89.58% in the research group and 71.88% in the control group, with a significant difference between the two groups (P<0.05, **Table 3**).

Incidence of toxic and side effects during treatment

The statistical analysis showed that the incidence of toxic and side reactions during treatment was 27.08% in the research group and 21.88% in the control group, with no significant difference between the two groups (P>0.05, **Table 4**).

Comparison of GQOLI-74 scores between the two groups before and after treatment

There was no significant difference in the GQOLI-74 score between the two groups before treatment (P>0.05), but the GQOLI-74 score assessed from physical, social and psychological functioning as well as material life status increased significantly in both groups after treatment, and was higher in the research group compared to the control group (P<0.05, **Table 5**).

Discussion

Venous thromboembolism (VTE) and the resulting complications adversely affect human health, with more than 5 million new cases every year, among which 30% of patients die within 30 days after diagnosis [20], posing a

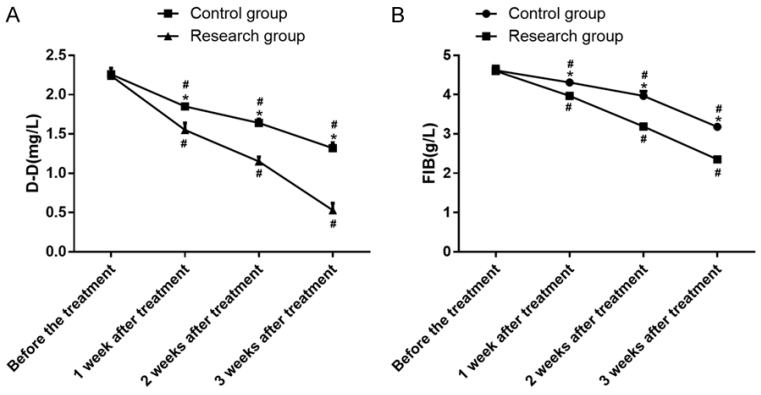

Figure 1. Comparison of the levels of coagulation factors between the two groups before and after treatment. A. Comparison of the expression of D-D between the two groups before and after treatment. B. Comparison of the expression of FIB between the two groups before and after treatment. Note: D-D: D-dimer; FIB: fibrinogen; *indicates P<0.05 compared between the two groups; #indicates P<0.01 *vs* before treatment.

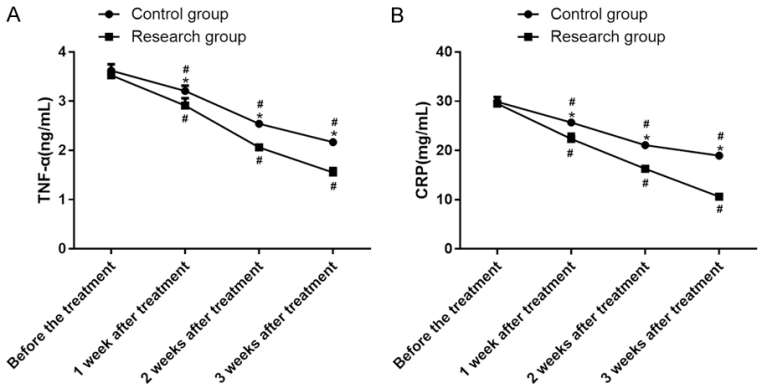

Figure 2. Comparison of the level of inflammatory factors between the two groups before and after treatment. A. Comparison of the expression of TNF-α between the two groups before and after treatment. B. Comparison of the expression of CRP between the two groups before and after treatment. Note: TNF-α: tumor necrosis factor-α; CRP: C-reactive protein; *indicates P<0.05 compared between the two groups; #indicates P<0.01 *vs* before treatment.

Table 3. Comparison of curative effects between both groups after treatment (Mean ± SD)

Group	n	Markedly effective	Effective	Ineffective	Overall response rate
Control group	32	8 (25.00)	15 (46.88)	9 (28.13)	23 (71.88)
Research group	48	25 (52.08)	18 (37.50)	5 (10.42)	43 (89.58)
χ^2	-	-	-	-	4.170
p	-	-	-	-	0.041

grave threat to people's health and life safety [21]. Therefore, it is particularly important to study the disease deeply and propose scientific and standardized treatment schemes to help patients relieve clinical symptoms, hinder disease progression and improve the curative effect.

In this study, LMWH combined with HBO was used to treat patients with ICVT, and it was found that the neurological function of patients was significantly improved after treatment. ICVT can cause ischemia, hypoxia, necrosis of brain tissue cells in patients, resulting in corresponding neurological deficits and other symptoms [22]. Liu et al. [23] showed that LMWH can inhibit neuronal apoptosis and improve the growth performance of neurites, thus playing a neuroprotective role in cerebral ischemia-reperfusion injury. In addition, Chang et al. [24] reported that HBO therapy can protect rats from cerebral artery occlusion by enhancing the viability of neurons and the antioxidant defense system. All the above studies have confirmed that combined therapy has a beneficial effect on improving the neurological function of patients with ICVT. Evidence has shown that the occurrence of ICVT is closely associated with the abnormalities of coagulation and fibrinolysis system; the larger the area of ICVT is, the higher the D-D content will be, and the more serious the nerve function will be damaged [25]. This dose-effect relationship between D-D level and the degree of neurological impairment suggests that the hypercoagulation process is consistently stronger than the fibrinolytic process in patients, which leads to the hindered dissolving of thrombosis, and even the formation of new thrombosis [26]. LMWH has been confirmed to have a beneficial effect on

Table 4. Incidence of toxic and side effects in both groups during treatment [n (%)]

Group	n	Anaemia	Hemorrhage	Contusion	Nausea	Total incidence (%)
Control group	32	2 (6.25)	1 (3.13)	1 (3.13)	3 (9.38)	7 (21.88)
Research group	48	4 (8.33)	3 (6.25)	2 (4.17)	4 (8.33)	13 (27.08)
χ^2	-	-	-	-	-	0.278
p	-	-	-	-	-	0.598

Table 5. Comparison of GQOLI-74 scores between both groups before and after treatment (mean ± SD)

Group	n	Physical functioning		Social functioning		Psychological function		Material life state	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Control group	32	49.06±4.15	55.31±5.11#	49.23±4.25	55.72±5.35#	51.37±5.02	58.16±5.27#	49.25±4.14	55.39±5.05#
Research group	48	48.87±4.23	66.32±6.27#	48.67±4.19	63.27±6.14#	51.29±5.19	67.59±6.04#	49.79±4.29	61.43±6.16#
t	-	0.198	8.266	0.582	5.666	0.068	7.191	0.559	4.607
P	-	0.843	<0.001	0.562	<0.001	0.946	<0.001	0.578	<0.001

Note: GQOLI-74: Generic Quality of Life Inventory-74; #indicates P<0.01 *vs* before treatment.

the prevention of thrombosis, which can not only improve coagulation dysfunction, but also reduce the risk of death caused by thrombosis events [27]. The results of this study showed lower D-D and FIB levels in the research group at 1, 2 and 3 weeks after treatment, suggesting that LMWH combined with HBO therapy can not only reduce FIB and D-D in blood, alleviate ICVT, but also effectively lower the neurological function score, indicating that the combined therapy has obvious anticoagulant and defibrination effects.

When the brain tissue is injured, the level of CRP increases greatly to aggravate brain injury, while TNF-α is directly proportional to the degree of injury [28]. Around the hematoma of early ICVT, nerve cells and local vascular tissues are destroyed, which can induce a variety of serious reactions and produce a large amount of TNF-α. Therefore, TNF-α and CRP can be used as vital cytokines to reflect the degree of disease activity in patients with ICVT [29, 30]. Zheng et al. [31] showed that LMWH can significantly inhibit the secretion of TNF-α and CRP to alleviate the inflammatory response of patients. The study of Mulawarmanti et al. [32] also confirmed that HBO can inhibit the serum CRP level of diabetic rats, thus reducing the inflammatory state associated with periodontitis. Similarly, this study found that the levels of TNF-α and CRP in the research group were lower than those in the control group at 1, 2 and 3 weeks after treatment. This shows that the combined therapy can effectively reduce the inflammatory reaction in patients with ICVT, thus playing an effective role in anti-embolism treatment. Studies have shown that compared with UFH, LMWH can not only prevent thromboembolism after traumatic brain injury, but also significantly improve the survival rate of patients [33]. Similarly, this study determined a significantly higher ORR in the research group, while there was no significant difference in the total incidence of toxic and side effects between the two groups, indicating that the combined therapy can greatly improve the curative effect of patients without causing obvious toxicity. Cerebral artery disease is one of the main causes of global disability and death. For decades, brain injury caused by cerebral artery disease has always been the focus of scientific research. ICVT also causes a serious impact on patients' QoL [34]. In this study, the QoL of patients with ICVT was more significantly improved after intervention with LMWH combined with HBO compared to the control group, as the QoL assessed by the GQOLI-74 from the domains of physical, social, and psychological functioning as well as the material life status elevated more significantly. This shows that LMWH combined with HBO intervention has a favorable curative effect and can improve the QoL of patients.

There are some deficiencies in this study. First, animal experiments haven't been done to explore the protective effect of combination therapy on ICVT, by which the underlying mechanism could be further understood. Second, the

long-term efficacy has not yet been explored. Third, the relevant factors that affect the curative efficacy can be investigated from the molecular level. Finally, the sample size can be expanded to further improve the accuracy of the test results. We will address these limitations in future studies to improve our research.

In conclusion, LMWH combined with HBO can significantly improve the clinical efficacy and neurologic function of ICVT patients, and reduce the levels of D-D, FIB, and inflammatory factors.

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Disclosure of conflict of interest

None.

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