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Effects of folic acid combined with vitamin B12 on DVT in patients with homocysteine cerebral infarction

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Abstract. – OBJECTIVE: To investigate the effects of folic acid combined with vitamin B12 on deep vein thrombosis (DVT) in patients with homocysteine cerebral infarction.

PATIENTS AND METHODS: 90 patients with homocysteine cerebral infarction with DVT that were admitted to our hospital from January to July 2015 were selected as study subjects. They were divided into 2 groups randomly, the treatment group (n=45) and the non-treatment group (n=45). The treatment group was administered folic acid and vitamin B12, while the non-treatment group wasn't administered folic acid and vitamin B12. We compared and analyzed the levels of Hcy, folic acid and vitamin B12 of both groups. We investigated the correlation between the groups of patients with Hcy and folic acid and vitamin B12 treatment. We performed a comparative analysis of both groups of patients with an anticoagulant international normalized ratio (INR). The INR was recorded in detail for the first time as standard time, stable value time, obtain stable INR value time, activated partial thromboplastin time (APTT) and Prothrombin Time (PT) by color Doppler ultrasound observation of both groups with recurrent thrombosis.

RESULTS: We compared results of the intervention and treatment groups, and the prognosis of Hcy decreased significantly ($p<0.05$). While in the treatment group, folic acid and vitamin B12 levels increased significantly ($p<0.05$), the non-treatment difference of Hcy, folic acid, and vitamin B12 levels, before and after the patients in the intervention group, were not statistically significant ($p>0.05$). In the treatment group, Hcy was negatively correlated with folic acid (r=-0.376, $p<0.05$) while the Hcy of the treatment group was negatively correlated with vitamin B12 (r=-0.583, $p<0.05$). The intervention treatment group INR first standard time, stable value time and stable INR values were higher than those of non-treatment group ($p<0.05$). The treatment group APTT average was lower than in the non-treatment group ($p<0.05$). The average Pt in the treatment group was lower than non-treatment group ($p<0.05$). In the treatment group, lower limb deep static vein thrombosis recurrence rate was 4.4%, which was lower than the non-treatment group where the lower limb deep vein thrombosis recurrence rate was 28.9% ($p<0.05$).

CONCLUSIONS: Hcy is negatively correlated to folic acid and vitamin B12. Folic acid and vitamin B12 can reduce the recurrence rate of thrombosis in patients with lower extremity deep venous thrombosis in patients with Hcy disease. The mechanism of action may be to prevent the recurrence of thrombosis by reducing the levels of Hcy.

Key Words:
Folic acid, Vitamin B12, Homocysteine, Lower limb, Deep vein thrombosis.

Introduction

In recent years, the number of patients with DVT keeps increasing. DVT tends to cause vein thrombosis sequel, which can bring about serious results. It has been reported[1,2] in the literature that increased Hcy concentration is an independent risk factor for deep vein thrombosis. High plasma Hcy can promote the proliferation of vascular smooth muscles and restrain the growth of endothelial cells. Then, it can further induce damage to endothelial cells and break the dynamic balance between coagulation and anti-coagulation, which may finally lead to occlusive vascular diseases[3]. The relationship between homocysteine and deep venous thrombosis has been a research hotspot in recent years. Various studies[4,5] have shown that the metabolic process of high plasma Hcy is closely related to folic acid and vitamin B12. Therefore, the research focus is whether folic acid combined with vitamin B12 will have certain effects on deep venous thrombosis in patients with Hcy diseases. This study mainly investigates the effects of folic

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acid combined with vitamin B12 on the prevention and recurrence of deep venous thrombosis in patients with Hcy diseases.

Patients and Methods

Patients

90 Patients with homocysteine cerebral infarction with DVT that were admitted to our hospital from January to July 2015 were selected as the study subjects. The Ethics Committee of the 1st Hospital of Lanzhou University approved this investigation. Among all patients, 50 patients were male and 40 were female, with an age range between 43 to 78, and averaged at (64.7±2.5) years old. Patients with heart failure, coagulation disorders and diseases of other vital organs, as well as patients that had taken folic acid and vitamin B12, were excluded. Patients were divided into the treatment group (n=45) and the non-treatment group (n=45) randomly. Comparison of data between the two groups revealed no statistical significance.

Methods

The treatment group (n=45) was administered 5 mg of folic acid (Fujian Minghua Pharmacy Co., Ltd., State Medical Permit No. H19993229, Fujian Province, China,) and 0.25 mg of vitamin B12 orally (Datong Changxing Pharmacy Co., Ltd., State Medical Permit No. H14022782, Shanxi Province, China) once per day for 3 straight months. The non-treatment group (n=45) didn't take folic acid and vitamin B12.

Observation Index

(1) The levels of Hcy before and after intervention were determined using the automatic biochemical analyzer (Shanghai Hengsheng Medical Apparatus and Instruments Co., Ltd., Shanghai, China,) by enzymatic cycling assay. The folic acid and vitamin B12 levels were determined with the automatic micro-particles chemiluminescence immune assay system (Jinan Biobase Co., Ltd., Jinan, China) and matched kits. Blood samples of the treatment group were collected to determine the levels of Hyc, folic acid and vitamin B12 before administration, and three months after administration. The non-treatment group, which was not administered medication, was re-examined three months after the determination of Hcy, folic acid and vitamin B12 levels to serve as a comparison. The correlation between Hcy and levels of folic acid and vitamin B12 of the treatment group were studied.

(2) The anticoagulant international normalized ratio (INR) was detected weekly, and when INR achieved the first standard level and INR got stable, the duration of staying was recorded in detail.

(3) Activated partial thromboplastin time (APTT) was detected using the coagulation method before and after treatment, and the Prothrombin time (PT) was determined with the method of one-stage[6].

(4) Color Doppler ultrasound (Jiangsu Jiahua Electric Equipment Co., Ltd., Jiangsu, China) was applied to observe the recurrence of thrombosis. Patients' complaints and clinical features were integrated with color ultrasonography examination to judge the preventive effects on patients, including excellent, effective, and invalid. Being invalid means thrombosis recurrence[7].

Statistical Analysis

Data was processed using the statistical analysis software SPSS 20.0 (IBM, New York, NY, USA). Enumeration data was expressed by % and detected by X^2-test. The measurement data was expressed by $\bar{X}\pm S$ and statistically analyzed using the *t*-test. Pearson was adopted to analyze the pertinence of the indexes. All detections took a=0.05 as the test standard.

Results

Comparison of Hcy, Folic Acid and Vitamin B12 Levels of Patients in Both Groups before and After Intervention

Compared to the condition before the intervention, the Hcy level of the treatment group decreased significantly ($p<0.05$). While the levels of folic acid and vitamin B12 increased significantly ($p<0.05$) after intervention, the comparison of levels of Hcy, folic acid and vitamin B12 levels of the non-treatment group before and after intervention revealed no statistical significance ($p>0.05$) (Table I).

The Correlation between Hcy and Levels of Folic Acid and Vitamin B12 of the Treatment Group

In the treatment group, Hcy was negatively correlated to the folic acid levels (r=-0.376, $p<0.05$) and was negatively correlated with Vitamin B12 levels (r=-0.583, $p<0.05$) (Figures 1 and 2).

Changes of Indexes Related to INR of Both Groups after Intervention

After intervention, the treatment groups behaved better than the non-treatment groups in the

Table I. Comparison of Hcy, Folic Acid and Vitamin B12 levels of patients in both groups before and after intervention.

Group	Time	Hcy (μmol/L) (μg/L)	Folic Acid	Vitamin B12 (μg/L)
Treatment Group (n=45)	Before	30.13±1.84	7.25±2.35	323.52±93.76
	After	10.45±2.62*	15.13±5.23*	645.92±102.48*
Non-treatment Group (n=45)	Before	30.17±1.88	7.23±2.41	324.63±96.85
	After	29.06±2.32	7.05±2.65	326.31±98.16

Note: compared with the condition before intervention, *p<0.05.

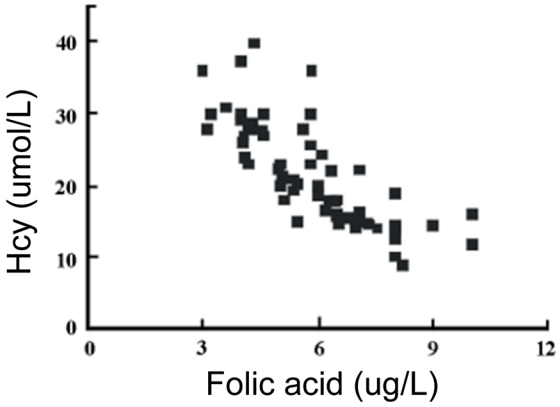

Figure 1. Correlation analysis of Hcy and folic acid of the treatment group.

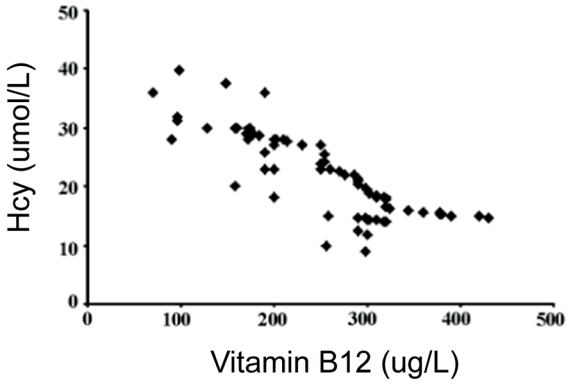

Figure 2. Correlation analysis of Hcy and Vitamin B12 level of the treatment group.

initial recovery time, stable value duration, and the time to get stable INR value (p<0.05) (Figures 3, 4 and 5).

Comparison of Changes of APTT and PT after Intervention

After the intervention, the average APTT value of the treatment group was lower than that of the non-treatment group (p<0.05), (Figure 6). The average PT value of the treatment group was lower than that of the non-treatment group (p<0.05) (Figure 7).

Comparison of Thrombosis Recurrence of the Two Groups

After the intervention, the recurrence rate of lower limb deep venous thrombosis of the treatment group was 4.4%, which was significantly lower than that of the non-treatment group at 28.9% (p<0.05) (Table II). Two patients suffered acute thrombosis in the treatment group and 8 patients suffered acute thrombosis in the non-treatment group. The ultrasound elastography image of acute thrombosis was mainly red (Figure 8). Three patients suffered sub-acute thrombosis

Table II. Comparison of Thrombosis recurrence of the two groups.

Groups	No.	Excellent	Effective	Invalid	Deep Vein Thrombosis Occurrence Rate
Treatment Group	45	10	33	2	4.4*
Non-treatment Group	45	2	30	13	28.9

Note: compared with non-treatment, *p<0.05.

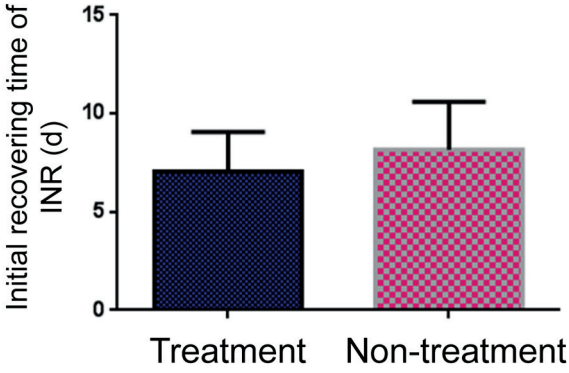

Figure 3. Comparison of initial recovering time of INR.

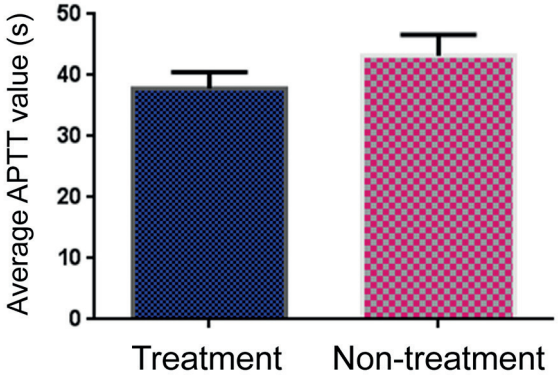

Figure 6. Comparison of average APTT value.

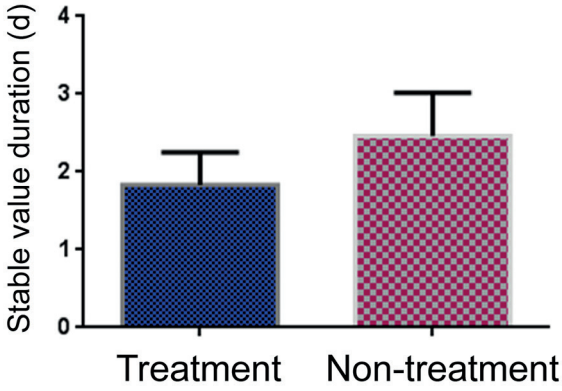

Figure 4. Comparison of stable value duration of two groups.

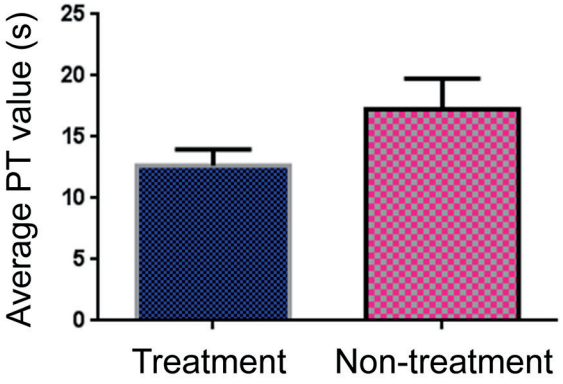

Figure 7. Comparison of average PT value.

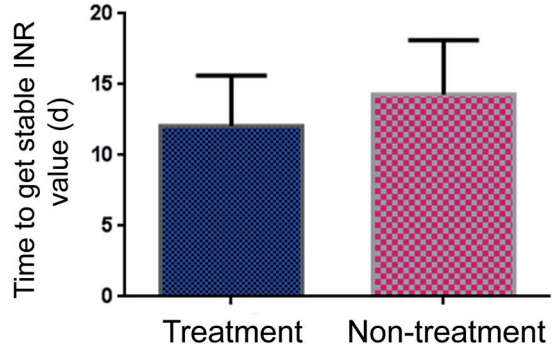

Figure 5. Comparison of time to get stable INR value of two groups.

in the non-treatment group. The ultrasound elastography image was mainly green (Figure 9). There were two cases of chronic thrombosis in the non-treatment group and its ultrasound elastography image was mainly blue (Figure 10).

Discussion

Hcy and its derivatives can increase the thromboxane generated by the blood platelets so as to make an effect on platelet aggregation and on the activity of coagulation factor V, which would achieve similar effects on both coagulation and anti-coagulation. Therefore, some studies[8-10] found that Hcy may be regarded as a type of thrombotic forming agent[11,12]. Previous researches[13-15] have found that the mechanism through which high levels of Hcy in the blood can result in venous thrombosis may be related to the toxin function of high Hcy levels, which can exert toxicity on vein vascular endothelium in order to cause vascular wall damage and blood platelet aggregation, finally leading to thrombosis. This work has shown that, compared to the condition before intervention, the Hcy levels of the treatment group decreased signi-

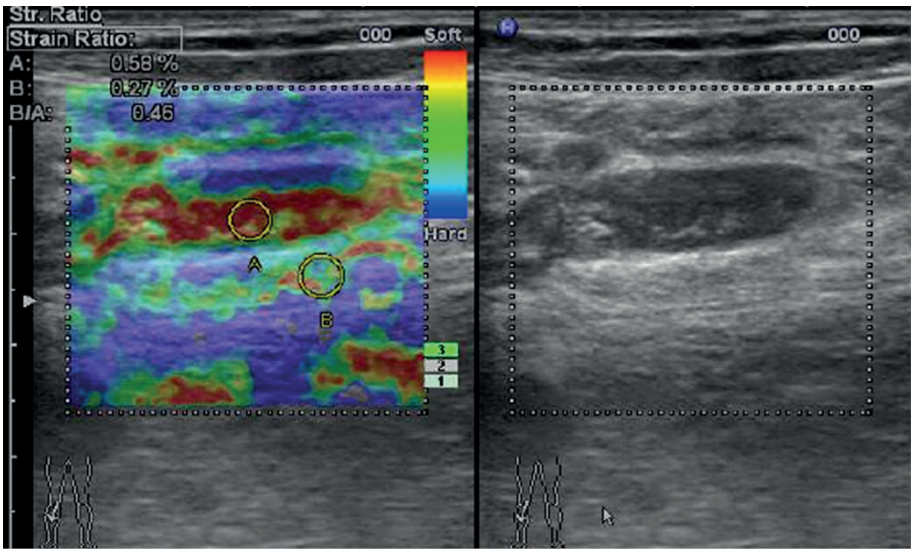

Figure 8. Ultrasound elastography image of acute thrombosis.

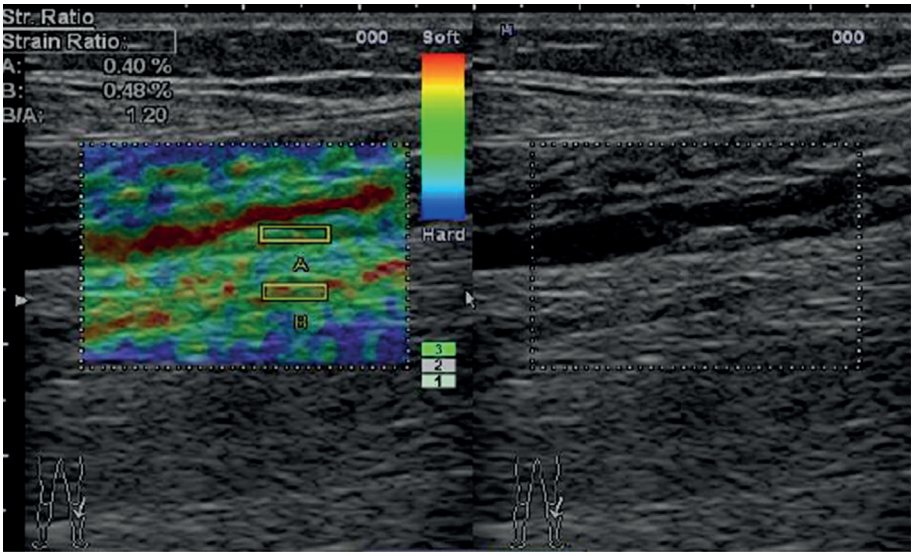

Figure 9. Ultrasound elastography image of sub-acute thrombosis.

ficantly ($p<0.05$), while the levels of folic acid and vitamin B12 increased significantly ($p<0.05$) after intervention. When comparing levels of Hcy, folic acid and vitamin B12 levels of the non-treatment group before and after the intervention, there was no statistical significance ($p>0.05$). In the treatment group, Hcy was negatively correlated with the folic acid levels (r=-0.376, $p<0.05$), and was negatively correlated with the Vitamin B12 level (r=-0.583, $p<0.05$), suggesting that Hcy is closely related to the levels of folic acid and Vitamin B12. Intervention with folic acid and Vitamin B12 can significantly decrease the levels of Hcy in blood. Therefore, our results suggest that a combined treatment with folic acid and Vitamin B12 can decrease the Hcy levels of patients suffering from high Hcy in blood complicated with lower limbs deep venous thrombosis[16-19]. High levels of Hcy tend to trigger thrombosis[20-22] and lead us to the question: will folic acid and vitamin B12 have a preventive effect on patients with high Hcy level and lower limb deep static vein thrombosis? We carried out research and observation on this. Our results have indicated that, after the intervention, the treatment group behaved better than the non-treatment group in the initial recovery time, stable value duration,

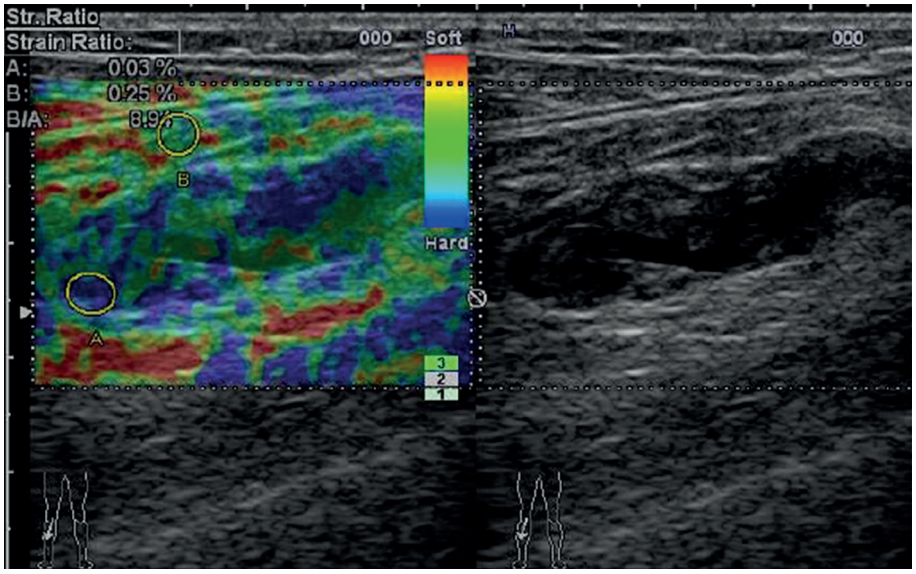

Figure 10. Ultrasound elastography image of chronic thrombosis.

and the time to get stable INR value ($p<0.05$). The average APTT value of the treatment group was lower than that of the non-treatment group ($p<0.05$). The average PT value of the treatment group was lower than that of the non-treatment group ($p<0.05$). The recurrence rate of lower limb deep venous thrombosis of the treatment group was 4.4%, which was significantly lower than that of the non-treatment group at 28.9% ($p<0.05$). These above results suggest that folic acid and vitamin B12 can effectively decrease thrombosis and further prevent the recurrence of thrombosis in patients suffering high Hcy levels complicated by lower limbs deep venous thrombosis.

Conclusions

Above all, Hcy was found to be negatively correlated with folic acid and vitamin B12. Folic acid and vitamin B12 can reduce the recurrence rate of thrombosis in patients with lower extremity limp deep venous thrombosis and in patients with Hcy disease suffering from high Hcy levels complicated by lower limbs deep venous thrombosis, maybe by reducing the levels of Hcy to prevent the recurrence of thrombosis.

Acknowledgements

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Conflict of interest

The authors declare no conflicts of interest.

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