The Clinical Efficacy of Maizhiling Combined with Low Molecular Weight Heparin in the Treatment of Deep Vein Thrombosis after Spinal Cord Injury

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This research aims to discuss the clinical efficacy of Maizhiling combined with low molecular weight heparin calcium in the treatment of deep vein thrombosis after spinal cord injury, in the meantime to discuss the effects of the drug combination on coagulation function, hemodynamics and clinical safety. We chose 40 patients with deep vein thrombosis after spinal cord injury in our hospital as the study cohort divided them into control group (n=20) and observation group (n=20) randomly. The control group received low molecular weight heparin calcium subcutaneous injections while the observation group received low molecular weight heparin calcium intravenous infusion of low molecular weight heparin calcium and oral Maizhiling. Then make a contrast of the affected limbs detumescence time, lower limb circumference, coagulation parameters, overall response rate, incidence of complications and adverse drug reactions after treatment between both groups. After treatment, the observation group’s swelling time and the average difference of lower limb circumference were significantly reduced (p<0.01), prothrombin time, activated partial thromboplastin time and D-dimer both were significantly lower (p<0.01) and the clinical effective rate was higher (p<0.05). Both groups incidence of complications and adverse drug reactions have no significant difference (p>0.05). Low molecular weight heparin calcium combined with Maizhiling is effective on spinal cord injury deep vein thrombosis patients. The lower extremity swelling time is significantly shortened, the blood coagulation function and blood viscosity are improved, and the adverse drug incidence and complications are not increased. The combined use is used to treat patients with deep vein thrombosis. It is worth widely using in clinical practice.

Key words: Maizhiling, low molecular weight heparin calcium, spinal cord injury, deep vein thrombosis

Spinal cord injury is on the rise in China, with an estimated annual incidence of 14 000 cases[1]. Spinal cord injury is the most common in middle-aged men and traffic accidents are the most common cause[2]. The most common complications of spinal cord injury are Deep Vein Thrombosis (DVT) and pulmonary embolism[2,3]. DVT can easily cause tissue edema, varicose veins, lower limb dyskinesia and even serious complications such as pulmonary embolism caused by thrombosis, venous blood stasis and hypercoagulability, which are life-threatening[4]. The incidence of spinal cord injury complicated by DVT reported in the literature is relatively high, as high as 65 % in some studies[5]. In one previous study of 94 spinal cord injury patients, it was found that most venous thromboembolism occurred within 3 mo after spinal cord injury. Although the risk of DVT decreases with the time of injury, it will never return to the baseline level[6].

Studies have reported that if DVT is not treated in time, it can lead to patients with large-scale pulmonary embolism and the incidence rate is 20 %-30 %[7]. DVT treatment includes a lot of joint contents such as thrombolytic therapy, anticoagulation, Inferior Vena Cava (IVC) filter indwelling, mechanical thrombectomy, Traditional Chinese Medicine (TCM), acupoint compression and psychological intervention[8,9]. We should create individualized treatment plans in line with the patient’s age, etiology, course of disease, thrombus classification etc., in clinic. For DVT, anticoagulation therapy has a better effect. Low Molecular Weight Heparin Calcium (LMWH-Ca) not only decrease activity of coagulation factor or blood viscosity but
also can remarkably relieve the hypercoagulable state. Maizhiling has effects on extending clotting time, inhibiting thrombosis and improving the patient’s lower limbs microcirculation. Most spinal cord injury patients are in bed with hypercoagulability state or vascular injury caused by surgery and they belong to the high-risk group of DVT. There are some studies on LMWH-Ca or Maizhiling alone in the treatment of DVT, but there is still a lack of studies on combination therapy for patients with spinal cord injury and DVT inside and outside of China[10,11]. Therefore, we mainly discussed the clinical efficacy analysis of LMWH-Ca combined with Maizhiling in treatment of spinal cord injury patients with DVT, as well as the effects on lower limb circumference, coagulation function, clinical efficiency, complications and adverse reactions, then to guide our clinical therapy.

MATERIALS AND METHODS

General information:

We chose 40 inpatients with spinal cord injury complicated by DVT in our hospital from February 2016 to March 2021 as the study cohort. Divided them into treatment group and control group, each groups contained 20 patients. The general information of both groups is shown in Table 1. This study is approved from Medical Ethics Committee of our hospital.

Inclusion criteria-Patients who met the DVT diagnostic criteria proposed in "Guidelines for the diagnosis and treatment of DVT"[12,13] and patients in the acute phase of DVT were diagnosed by lower limb venography, color Doppler ultrasound and D-dimer; patients who were not allergic to the used drugs in this research; all of them obtained informed consent for treatment.

Exclusion criteria-Patients with bleeding; severe liver disease or renal dysfunction in children; patients received relevant antithrombotic therapy within 1 w; critically ill patients with mental illness before admission; patients with cognitive impairment.

Methods:

Both groups of patients received conventional treatment and nursing, and they were instructed to routinely press limbs to prevent thrombosis. We recommended a low-fat, high-vitamin and high-protein diet to make sure to defeate smoothly and prevent thrombosis or embolism from falling off.

Drug treatment: The control group was given subcutaneous injection of LMWH-Ca2500 International unit (IU) each time twice a day for 2 w; the observation group received the same LMWH-Ca dose and also Maizhiling (0.3 g; orally (po); twice a day (BID)) made by Cesra Arzneimittel GmbH & Co. KG.

Observation indicators: Main outcome indicators-Observe and record the swelling time of the two groups of patients; compare the calf and thigh diameters of both groups; 14 d after treatment, compare the treatment effects of both groups: Ineffective-vascular ultrasonography showed that the recanalization rate of popliteal and femoral veins was less than 40 %, there was no collateral circulation and there was no relief of swelling and pain on affected limbs. Improved-vascular ultrasound examination showed that the recanalization rate of popliteal and femoral veins was 40 %-75 %, insufficient collateral circulation and relief of local swelling and pain of the limbs; Cure, complete relief-vascular ultrasound examination showed that the recanalization rate of popliteal vein and femoral vein was 76 %-90 %, adequate collateral circulation and the swelling and pain symptoms were significantly relieved.

Detection and comparison of the secondary results:

Compared the coagulation function of the two groups: Fibrinogen (FIB), Prothrombin Time (PT), Activated Partial Thromboplastin Time (APTT) levels; compared D-dimer and deep vein color Doppler ultrasound of both groups lower limbs; comparison of complications during treatment, such as thrombocytopenia, hematuria, dyspnea, melena, bleeding gums, hemoptysis, epistaxis, etc. During the treatment, compare both group’s adverse drug reactions such as nausea, rash, dizziness, vomiting, diarrhea and abdominal pain.

Statistical methods:

We adopt Statistical Package for the Social Sciences (SPSS) 20.0 to analyze the data, use n % to express technical data and use $\chi^2$ to test. Use mean±standard deviation to indicate measurement data that is accord with normal distribution and homogeneity of variance, compare both groups by independent sample t test before and after treatment and within the same group comparison was expressed by paired t test. Use median and interquartile range to show data that did not accord with normal distribution. The Wilcoxon test was used for group’s comparison and the Wilcoxon signed rank test was used for comparison before and after treatment within the same group, p<0.05 was supported to possess statistical significance.

RESULTS AND DISCUSSION

General information of both groups was compared.
There was no any significant differences between two groups in terms of age, gender, location of thrombus, type of thrombus formation, etc., and there was no statistical significance (p>0.05). These two groups possessed comparability (Table 1).

Coagulation indexes and D-dimer between both groups after treatment were compared. There was no any significant differences in FIB, PT, APTT or D-dimer between both groups before cure (p>0.05) and there was no statistical significance. There was no statistical difference between both groups before and after horizontal treatment; PT, FIB, APTT and D-dimer levels after cure in the control group were remarkably higher the other (p<0.05), with statistical significance (Table 2).

Various clinical symptom scores of both groups before and after treatment were compared. There was zero difference in various clinical symptoms scores (swelling of the affected limb, skin temperature) and circumference of the upper and lower legs before treatment for both groups (p>0.05), it has no statistical significance. Both group’s clinical symptom scores decreased remarkably and the upper and lower legs circumference was significantly reduced. Make comparison of the same group before treatment, the differences had statistical significance (p<0.05). Various clinical symptoms scores and the upper and lower legs circumference were different between both groups after treatment and both of them had statistical significance (p<0.05) (Table 3).

Overall response rate between both groups were compared. The observation group total remission rate remarkably exceeds the other (p<0.05) (Table 4).

Complication rates of both groups were compared. The difference in the incidence of complications (hematuria, allergic reactions, thrombocytopenia, dyspnea) between both groups is of no statistically significance (p>0.05) (Table 5).

Incidence of adverse drug reactions of both groups was compared. Within observation group, 6 cases (30 %) had adverse reactions, including 1 case of skin rash, 1 case of nausea and vomiting, 2 cases of abdominal pain and diarrhea and 2 cases of loss of appetite. Within control group, 4 cases (20 %) had adverse reactions, including 2 cases of skin rash, 1 case of nausea and vomiting, and 1 case of abdominal pain and diarrhea. Adverse drug reactions between both groups has no statistical difference (p>0.05) (Table 6).

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**TABLE 1: COMPARISON OF GENERAL INFORMATION OF BOTH GROUPS**

|                      | Observation group (n=20) | Control group (n=20) | t/χ² | p   |
|----------------------|--------------------------|----------------------|------|-----|
| Age                  | 63.4±8.72                | 62.9±8.75            | 0.21 | 0.82|
| Gender (female)      | 12 (60 %)                | 11 (55 %)            | 0.10 | 0.74|
| Location of thrombus |                          |                      | 0.44 | 0.50|
| Left lower limb      | 6 (30 %)                 | 8 (40 %)             |      |     |
| Right lower limb     | 14 (70 %)                | 12 (60 %)            |      |     |
| Type of thrombus     |                          |                      |      |     |
| Intermediate type    | 8 (40 %)                 | 11 (55 %)            | 0.9  | 0.34|
| Peripheral type      | 7 (35 %)                 | 5 (25 %)             | 0.48 | 0.49|
| Mixed type           | 5 (25 %)                 | 4 (20 %)             | 0.14 | 0.71|

**TABLE 2: COMPARISON OF COAGULATION INDEXES AND D-DIMER BETWEEN BOTH GROUPS AFTER TREATMENT**

| Group          | The number of cases | FIB (g/l) Before cure | PT (s) Before cure | APTT (s) Before cure | D-dimer Before cure | After cure | t   | p   |
|----------------|---------------------|-----------------------|--------------------|---------------------|---------------------|------------|-----|-----|
| Control group  | 20                  | 3.68±0.48             | 11.6±2.94          | 32.35±4.79          | 143.9±12.65        | 3.06±0.55  | -0.20| 0.83|
| Observation group | 20                 | 3.71±0.45             | 11.7±2.92          | 32.5±4.82           | 144.65±11.61       | 3.45±0.50  | -2.46| 0.02|
| t              | -0.20               | -2.46                 | -0.10              | 2.39                | -0.29              | 2.07       | -0.19| 0.85|
| p              | 0.83                | 0.02                  | 0.97               | 0.02                | 0.76               | 0.04       | 0.00 | 0.00|
TABLE 3: COMPARISON OF VARIOUS CLINICAL SYMPTOM SCORES OF BOTH GROUPS BEFORE AND AFTER TREATMENT

|                      | Observation group (n=20) | Control group (n=20) | t   | p   |
|----------------------|--------------------------|----------------------|-----|-----|
| **Swelling**         |                          |                      |     |     |
| Before cure          | 2.71±0.47                | 2.72±0.52            | -0.06 | 0.94 |
| After cure           | 0.95±0.46                | 1.57±0.46            | -4.26 | 0.001 |
| **Skin temperature** |                          |                      |     |     |
| Before cure          | 2.65±0.48                | 2.61±0.57            | 0.24 | 0.8  |
| After cure           | 1.06±0.24                | 1.76±0.92            | -6.31 | 0.000 |
| **Swelling time**    |                          |                      |     |     |
| Before cure          | 2.94±0.52                | 3.04±0.50            | -0.43 | 0.66 |
| After cure           | 0.98±0.24                | 1.42±0.54            | -3.23 | 0.003 |
| **Thigh circumference** |                        |                      |     |     |
| Before cure          | 55.6±10.9                | 54.75±9.58           | 0.26 | 0.79 |
| After cure           | 45.1±6.88                | 50.1±7.11            | -2.26 | 0.00 |
| **Calf circumference** |                        |                      |     |     |
| Before cure          | 42.16±4.65               | 43.26±3.98           | -0.80 | 0.43 |
| After cure           | 32.20±7.20               | 38.55±8.13           | -2.59 | 0.01 |

TABLE 4: COMPARISON OF THE OVERALL RESPONSE RATE BETWEEN THE TWO GROUPS

|                      | Apparent effect | Effective rate | Inefficiency rate | Total effective rate |
|----------------------|-----------------|----------------|-------------------|----------------------|
| Observation group    | 11 (55 %)       | 7 (35 %)       | 2 (10 %)          | 18 (90 %)            |
| Control group        | 8 (40 %)        | 4 (20 %)       | 8 (40 %)          | 12 (60 %)            |
| \( \chi^2 \)        |                 | 4.80           |                   | 0.03                 |
| p                    |                 |                |                   | 0.03                 |

TABLE 5: COMPARISON OF THE INCIDENCE OF COMPLICATIONS BETWEEN BOTH GROUPS

|                      | Hematuria | Allergic reactions | Thrombocytopenia | Dyspnea | Total |
|----------------------|-----------|--------------------|-----------------|---------|-------|
| Observation group    | 1 (5 %)   | 1 (5 %)            | 2 (10 %)        | 0 (0 %) | 4 (20 %) |
| Control group        | 1 (5 %)   | 2 (10 %)           | 1 (5 %)         | 1 (5 %) | 5 (25 %) |
| \( \chi^2 \)        | 4         |                   |                 |         | 0.14  |
| p                    |           |                   |                 |         | 0.75  |

TABLE 6: COMPARISON OF THE INCIDENCE OF ADVERSE DRUG REACTIONS BETWEEN BOTH GROUPS

|                      | Nausea and vomiting | Abdominal pain and diarrhea | Skin rash | Loss of appetite | Total adverse reaction rate |
|----------------------|---------------------|-----------------------------|-----------|------------------|-----------------------------|
| Observation group    | 1 (%)               | 2 (%)                       | 1 (%)     | 2 (%)            | 6 (30 %)                    |
| Control group        | 1 (%)               | 1 (%)                       | 2 (%)     | 0 (0 %)          | 4 (20 %)                    |
| \( \chi^2 \)        | 0.53                |                             |           |                  |                             |
| p                    | 0.46                |                             |           |                  |                             |

DVT is a common but preventable complication of hospitalized patients with spinal cord injury. If effective preventive measures are not taken, nearly 60 % of patients with spinal cord injury will be complicated by DVT. However, the timing and drugs of anticoagulant thrombolytic therapy determine the prognosis of DVT\(^{[14]}\). A total of 96 patients with malignant tumor complicated with DVT were included in the study by Chen et al.\(^{[15]}\). Treat the control group with LMWH-Ca and treat the observation group in the same way, then with another Ligustrazine hydrochloride. The results proved that both groups lower limbs swelling went down varying degrees after treatment, but combined drugs application has a better influence on improving DVT, thus it has more superiority. This study attempts to estimate the clinical efficacy, safety and clinical application value of LMWH-Ca combined with Maizhiling in DVT treatment after spinal cord injury.

The main ingredient of Aescuven Forte tablets is aescin\(^{[16]}\). Previous studies have shown that aescin
in patients treatment with DVT is mainly to improve
the blood circulation of the lower extremities and
reduce edema and pain\(^{17}\). Wang \textit{et al.}\(^{18}\) studied 40
patients with Chronic Venous Insufficiency (CVI) of
lower extremities in Peking Union Medical College
Hospital and divided them into two groups which are
observation group (\(n=23\)) and control group (\(n=17\)) by
random. Treat control group with elastic stockings and
observation group with Maizhiling. The experiment
results showed that the improvement of Transcutaneous
Oxygen (\(\text{TcPO}_2\)), skin temperature and temperature-
controlled blood flow in the lower extremity circulation
in observation group was greater than the other. It
shows that Maizhiling can significantly improve the
blood circulation and coagulation function of the lower
branch of the patient. In our study, patients in the
observation group received LMWH-Ca combined with
Maizhiling, the observation group clinical effective
rate was significantly higher than the other compared
with patients who used LMWH-Ca alone. Both groups
incidence of complications have no difference which
indicates that LMWH-Ca combined with Maizhiling
is more effective in clinic and safer in DVT treatment
with spinal cord injury.

APTT and PT, as indicators to reflect endogenous
and exogenous coagulation pathways level and
activity, have been widely used to determine the
coagulation function\(^{19}\). PT mainly reflects its own
ability of organizing coagulation factors, for example,
coaugulation factors I, II, V, VII and X. However, APTT
mainly reflects coagulation factors levels such as VIII,
IX, XI, XII in the blood. Platelets (PLT) can accumulate
in the bleeding site and promote hemostasis. The
activated PLT has a good effect on coagulation, so
does its cleavage products. FIB can adjust plasma
viscosity from endogenous and exogenous coagulation
mechanisms\(^{20}\). In our study, compared with LMWH-
Ca alone, the treatment effect of patients receiving
LMWH-Ca with Maizhiling was significantly better
and the improvement of blood coagulation indexes (PT,
APTT) was remarkably better than the other, and the
results have no divergence with the results of similar
studies\(^{21}\). In addition, contrast control group, the
circumference of the thigh and calf in the observation
group was significantly smaller, and the swelling time
of the calf was also shorter. It shows LMWH-Ca joint
Maizhiling has better effect on DVT patients improving
coagulation function and inhibiting thrombosis contrast
LMWH-Ca alone. In addition, both groups are of no
differences in total incidence of adverse drug reactions,
indicating that Maizhiling enriching is safe and it will
not enhance the side effects of the drug.

This study also has certain limitations. Because 40
samples of our study are small and there are individual
differences among patients, the test results are not very
convincing. In the future, it is necessary to design
scientific and rigorous large-sample randomized
controlled experiments. Moreover, we did not follow
up patients with recurrent DVT after discharge from the
hospital. Future studies also need to compare the clinical
efficacy of the combination of these two drugs for long-
term recurrence of DVT patients. In short, LMWH-
Ca combined with Maizhiling has effect on treating
spinal cord injury DVT patients, significantly shorten
the lower limbs swelling time, improve coagulation
function and blood viscosity, and the combined use of
treatment of DVT is worthy of clinical promotion.

\textbf{Conflict of interests:}

The authors declared no conflict of interest.

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