CLINICAL EXPERIENCE

Study on the Efficacy and Safety of Xueyou Mixture (血友合剂) in Treating Hemophilia

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ABSTRACT  Objective: To observe the effect of Xueyou Mixture (血友合剂, XYM) on blood coagulation factors and its safety in treating hemophilia. Methods: To the randomly selected 65 inpatients of hemophilia, XYM was administered accompanied with intravenous dripping of liver cell growth factor 60-100 mg once a day to protect the liver, with no blood products like concentrated FVIII and FIX factors or blood plasma given. The treatment lasted for 3 weeks. The short-term efficacy and adverse reactions were observed. The long-term efficacy in patients was observed in a follow-up study of 6-12 months after they were discharged from the hospital but continuously took XYM orally. Results: The short-term markedly effective rate in the patients was 95.38% (62/65). After they were treated for 3 weeks, the level of FVIII factor activity increased in 56 patients of type A from (3.32±2.21) % to (4.18±2.23) %, and in 9 of type B from (4.92±1.81) % to (5.64±1.96) %. Compared with that before treatment, the difference was significant in both of them (P<0.01). No obvious adverse reaction was found in the treatment period. The follow-up study showed that in 22 patients of type A, the FVIII factor activity ratio increased from (3.25±2.11) % to (6.31±2.16) %, (8.36±1.05) %, and (16.38±2.71) % in the 2nd, 3rd and 6th month after discharge respectively, all showing significant difference to that before treatment (P<0.01); and in 4 patients of type B, it increased from (4.15±2.26) % to 7.8% and 11.6% (mean value) in the 2nd and 6th month respectively. Conclusion: XYM could raise the activity of factors FVIII and FIX in patients with hemophilia, and the degree of the rise is related with the duration of the therapy, with no obvious adverse reaction, which strikes out a new path and new train of thinking for the treatment of the disease by non-blood preparation.

KEY WORDS  Xueyou Mixture, hemophilia, therapeutic efficacy

Hemophilia is a disease of deficiency in a group of hereditary coagulation factors, with its radical treatment still lacking in the whole world\(^1\). Research in gene therapy is still at the bottom of the valley because of its low level of expression, shortness in effect-maintaining time, strong immune reaction to adenoviral vector and reproductive chain transferring, etc\(^2\)–\(^4\); replacement therapy with blood preparation could be applied during hemorrhage, but could cause more harm than benefit gained due to the high occurrence of complication with hepatitis B and C, AIDS, and production of blood coagulation antibody, the last of which will, in particular, destroy the coagulation factors of the patients’ own, lower their activity and thus affect the efficacy of hemostasis to form a vicious cycle.

In order to seek new drugs for treatment of hemophilia, 65 patients of hemophilia were treated by the authors using Xueyou Mixture (血友合剂, XYM), a Chinese herbal non-blood preparation, as the dominant remedy combined with others for strengthening liver protection, and favorable effects have been obtained.

METHODS

Diagnostic Standard

The diagnosis of hemophilia was made in reference to the "Standard for diagnosis and efficacy evaluation of hematopathy"\(^5\), with the activity of factor FVIII (FVIII), FIX and F XII taken as the primary indexes and patients' history of inheritance and clinical manifestations like spontaneous bleeding or traumatic bleeding that is hard to stop taken into consideration, but with acquired coagulation factor deficiency and von Willebrand disease (vWD) excluded. All the patients were classified into four grades according to the activity of FVIII and FIX in them: Severe grade: <1%; moderate grade: >2% and <5%;
mild grade > 5% and < 25%; and sub-clinical grade > 25 but < 50%.

**General Materials**

The sixty-five enrolled patients of hemophilia selected randomly from the inpatients came from various areas of China, hospitalized in the authors’ hospital within the period from Jan. 2006 to Sep. 2006, 64 males and 1 female, aged 0.8-56 years, with the median age of 12.6 years. Eighteen (27.7%) of them had hereditary history, and whether the other 47 (72.3%) had it or not was unknown. Among them, 56 (86.2%) were of type A and the other 9 (14.9%) of type B; their condition of disease was classified as of severe grade in 18 (27.7%), moderate grade in 30 (46.2%), mild grade in 17 (26.2%), with no case of sub-clinical grade. As to the three coagulation factors (FⅧ, FⅨ and FⅪ), 45 patients (69.2%) suffered from deficiency in one, 15 (23.1%) from deficiency in two and 5 (7.7%) from deficiency in all the three.

Twenty-eight patients had their activity of coagulation factor determined 1-4 times before, among whom the activity had been lowering continuously along with the growth in age in 18 patients (64.3%), unchanged in 9 (32.1%) and increased in 1 (3.6%).

Forty-eight patients (73.9%) had complications of hypocalcemia, 39 (60.0%) with anemia, 44 (67.7%) with hemophilic arthropathy, 6 (9.2%) with hepatitis B, 3 (4.6%) with hepatitis C and 3 (4.6%) with each of the following diseases of hematocyte, infected hematoma, renal stone, peripheral nerve injury, contracture of muscular tendon and hydronephrosis, and none with AIDS or syphilopathy. Anti-factor Ⅷ antibody detection showed positive in 2 out of the 4 tested patients.

**Treatment**

XYM, which consists of 13 kinds of Chinese herbs, including *Radix Rehmanniae praeparata*, *Radix Moromdae officinalis*, *Radix Ginseng*, *Radix Angelicae*, *Radix Notoginseng*, *Radix Rubiae* and *Radix Astragalus membranaceus*, etc., was given one dose every day, decocted in water twice, with the two decoctions mixed (about 200 mL) for intake in two times in the morning and at evening. At the same time, liver cell growth factor (product of Beisheng Pharmaceutical Co., Ltd.) was given 60-100 mg per day by intravenous dripping to strengthen liver protection. Instead of XYM, to children patients aged below 1 year, Xueyou Capsule (血友胶囊, of the constituents same to that of XYM, but made into powder, each gram containing ingredients equivalent to 5 g of crude drugs, and packaged in capsule, 0.25 g/capsule) was given orally after meal, three times a day, 4 capsules each time.

The treatment lasted for 3 weeks and the short-term effect of treatment was evaluated then. Blood preparation like concentrated factor Ⅷ and Ⅸ, or blood plasma was not allowed in the whole therapeutic course.

After the patients were discharged from the hospital, they would be asked to take XYM or its capsule form continuously for 6-12 months, and then recheck of blood coagulation factor was performed in the locality every 3 months for long-term efficacy observation.

**Detection of Coagulation Factors Activity**

With the one-stage method adopted, the activity of three kinds of coagulation factors were detected with the coagulation factor deficient plasma purchased from Fisher Scientific International Inc., USA.

**Detection of Adverse Reaction and Complications**

The changes in clinical symptoms, ECG, liver and renal function, blood sugar, electrolytes and routine tests on blood and urine were observed and detected before and after treatment to assess the adverse reaction to the testing treatment. The complications such as arthropathy, hematoma and hematocyte were supervised with MRI and color ultrasonography.

**Evaluation of Short-term Efficacy**

For the sake of excluding deviation from laboratory detection, and also for the observation of long-term effect, the therapeutic effect was evaluated after the 3-week treatment by a re-check of FⅧ or FⅨ activity. Increase of the activity by 0.3% over the baseline value was regarded as effective, otherwise as ineffective.

**Statistical Analysis**

Paired t-test and $\chi^2$ test were adopted for inter-group comparison with SPSS 11.0 Software.

**RESULTS**

**Short-term Efficacy**

The treatment showed to be effective in 62 of the 65 patients, which accounted for 95.38%, and ineffective in 3 (4.62%). Of the failed treated cases, one had anti-factor Ⅷ antibody (0.75 UI/mL plasma), and the other two were treated for only 2 weeks.