

CHINESE MEDICAL SCIENCES JOURNAL

ORIGINAL ARTICLE

Fresh Frozen Plasma for the Treatment of Hereditary Angioedema Acute Attacks

Rui Tang¹, Shi Chen², and Hong-yu Zhang^{1*}

¹Department of Allergy, ²Department of Endocrinology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing 100730, China

Key words: hereditary angioedema; acute attacks; fresh frozen plasma; treatment

Objective To determine the safety and efficacy of fresh frozen plasma (FFP) infusion for the treatment of hereditary angioedema (HAE).

Methods The medical records of patients with HAE admitted to Peking Union Medical College Hospital who had received FFP infusion during 2004 and 2010 were reviewed and PubMed database from 1966 to the present were searched using the following key words: hereditary angioedema and fresh frozen plasma. The patient's age, sex, body location of HAE attacks, the dose of FFP infusion, time of beginning to improvement, time to complete remission, complication, C1 inhibitor activity, and outcome were analyzed.

Results A total of 13 enrolled patients (7 male and 6 female) received 16 times of FFP infusion, including 2 patients undergoing FFP infusion in Peking Union Medical College Hospital and 11 patients reported in the literature. The mean dosage of FFP infusion was 586 ± 337 mL. Two cases suffered from worsening abdominal pain and one case experienced skin rash. Only 1 patient had no improvement in symptom owing to transfusion related reaction. There was a definite improvement in symptom 49 ± 19 minutes after beginning FFP infusion. The remission time decreased from 61.7 ± 27.0 hours to 3.3 (2.0, 12.0) hours after FFP infusion. FFP infusion was effective for both type I and type II HAE.

Conclusion FFP seems to be safe and effective for acute attacks of HAE.

Chin Med Sci J 2012; 27(2):92-95

HEREDITARY angioedema (HAE) is a rare autosomal dominant disease with an estimated prevalence of 1:50 000, characterized by episodic edema of the skin, subcutaneous tissues or mucous membranes. Life may be threatened when laryngeal edema appeared. The disease is due to deficiency

of the quantity and/or function of C1 inhibitor (C1INH). HAE can be usually divided into two types. HAE type I is up to 85% of all patients, and there is a deficiency in the amount of C1INH protein. In HAE type II, the circulating C1INH concentration is normal or high, but C1INH not fully functional.¹

Treatment for HAE includes prophylaxis and acute attacks. C1INH concentrates,² nanofiltered C1INH,³ recombinant C1INH,⁴ kallikrein inhibitor ecanllantide⁵, and bradykinin B2 receptor antagonist icatibant⁶ are the options

for acute attacks of HAE. But at present the above-mentioned therapies are unavailable in China and there is also no experience on treatment for acute attacks of HAE. Fresh frozen plasma (FFP) is often used as a source of C1INH to treat acute attacks in the United States.⁷ We first reported a Chinese HAE patient successfully treated with FFP for acute attack in 2009.⁸ In this study, we retrospectively analyzed 2 patients undergoing treatment for HAE at Peking Union Medical College Hospital and 11 patients reported in the medical literatures who received FFP infusion, to determine if there was evidence that FFP infusion was safe and effective for acute attacks of HAE patients.

PATIENTS AND METHODS

Data collection

We retrospectively searched the medical records in Peking Union Medical College Hospital during 2004 and 2010 to identify the patients diagnosed with HAE receiving FFP infusion. All patients were diagnosed according to 2010 international HAE consensus.⁹ Patient having angioedema caused by allergen or medicine was excluded. Meanwhile, we searched PubMed database from 1966 to the present using the following key words: hereditary angioedema and fresh frozen plasma. We identified relevant articles written in English.

Data analysis

The following information was recorded: patient's age, sex, body location of HAE attacks, the dose of FFP infusion, time of beginning to improvement, time to complete remission, complication, C1INH activity, and outcome, to determine the safety and efficacy of FFP infusion for acute attacks of HAE patients.

C1INH activity in FFP was 60 000. Normal range of C1INH activity was 60 000-100 000.¹⁰

Statistical analysis

Statistical analysis was performed with SPSS software version 11.0 for Windows. The normally distributed data were presented as mean $\pm$ SD. Significant differences between the groups were evaluated using Student's *t*-test. The abnormally distributed data were accessed by median (P25, P75). Significant differences between the groups were compared using Fisher's exact test. A value of $P<0.05$ was considered statistically significant.

RESULTS

General information

A total of 13 patients (7 male and 6 female) experiencing 16 acute attacks were enrolled. The mean age was 30 $\pm$ 17 years old. The mean age of male and female patients was 27 $\pm$ 15 and 28 $\pm$ 18 years, respectively. There was no significant difference between male and female in the mean age ($t=-0.061$, $P=0.952$). One type-I and one type-II HAE patients were diagnosed in Peking Union Medical College Hospital. Other 11 HAE patients reported in the literature included 4 type-I and 7 unknown type.¹⁰⁻¹⁷ The 13 HAE patients received 16 times of FFP infusion (Table 1).

Clinical manifestation

Acute attacks manifested as laryngeal edema for 5 cases, abdominal pain for 5 cases, and facial edema for 3 cases (Table 1).

The mean age of 5 cases experiencing laryngeal edema was 20 $\pm$ 5 years old, and that of other 8 cases without laryngeal edema was 35 $\pm$ 20 years old (Table 1). So there was a trend the patients suffering from laryngeal edema were younger, although difference was not statistically significant ($t=-2.086$, $P=0.056$).

Infusion dose of FFP

The mean dose of FFP infusion was 586 $\pm$ 337 mL (Table 1). There was no significant difference between male and female in the dose of FFP infusion (581 $\pm$ 259 vs. 519 $\pm$ 451 mL, $t=1.322$, $P=0.209$). The FFP dosage was lower in the laryngeal edema group (375 $\pm$ 128 vs. 657 $\pm$ 256 mL, $t=-2.760$, $P=0.016$).

Adverse events

Symptoms of all cases were improved except 1 because of transfusion reaction. The only adverse event recorded was rash, fever and chilling occurred in 1 case, which were considered to be allergic reaction to FFP infusion. Abdominal pain of 2 cases was exacerbated in the first few minutes of FFP infusion, but the symptom completely disappeared within 1.5 to 2.5 hours of FFP treatment (Table 1).^{10, 13}

C1INH activity

There were two records of change of C1INH activity in the literature.¹⁰ After 400 mL of FFP infusion, C1INH activities in both patients after plasma infusion increased from 10 000 to 26 500 and from 16 000 to 25 000, respectively.

Outcome

The mean time of beginning to improvement was 49 $\pm$ 19 minutes for 8 acute HAE attacks (Table 1).

Table 1. Clinical characteristics of patients with HAE undergoing FFP infusion for acute attacks

Case no. (reference)	Sex	Age (yr)	Body location of HAE attacks	Type	Dose of FFP infusion (mL)	Time of beginning to improvement (min)	Time to complete remission (h)	Time to remission without FFP infusion (h)	Outcome	Adverse event
1 ¹⁰	M	29	Laryngeal edema	I	400	45	12	Unkown	Remission	None
2 ¹⁰	F	22	Abdominal pain	Unknown	400	45	1.5	72	Remission	Abdominal pain
3 ¹¹	M	29	Facial edema	I	400	Unkown	Unkown	Unkown	Improvement	None
4 ¹²	F	19	Laryngeal edema	Unknown	1500	40	0.67	Unkown	Remission	None
4 ¹²	F	19	Laryngeal edema	Unknown	500	30	2	Unkown	Remission	None
5 ¹³	M	41	Abdominal pain	Unknown	1000	90	12	48	Remission	None
6 ¹³	F	71	Abdominal pain	Unknown	750	Unkown	2.5	Unkown	Remission	Abdominal pain
7 ¹³	M	17	Abdominal pain	Unknown	750	40	2	Unkown	Remission	None
8 ¹⁴	M	19	Facial edema	I	900	Unkown	Unkown	24	Remission	None
9 ¹⁵	M	56	Facial edema	Unknown	400	Unkown	Unkown	Unkown	Improvement	None
10 ¹⁶	F	24	Abdominal pain	I	Unkown	Unkown	Unkown	Unkown	Improvement	None
11 ¹⁷	F	26	Laryngeal edema	Unknown	200	Unkown	Unkown	Unkown	Improvement	None
12	M	13	Laryngeal edema	II	400	30	4	48	Remission	None
12	M	13	Laryngeal edema	II	400	720	72	48	No Remission	Uncontinued rash, fever, and chilling
13	F	20	Laryngeal edema	I	400	60	12	96	Remission	None
13	F	20	Laryngeal edema	I	400	60	24	96	Remission	None

HAE: hereditary angioedema; FFP: fresh frozen plasma; M: male; F: female.

A total of 7 acute attacks (5 cases) had definite records of remission time without FFP treatment, which was 61.7 ± 27.0 hours. The median of remission time of 10 acute attacks shortened to 3.3 (2.0, 12.0) hours after FFP infusion ($P < 0.01$, Table 1).

DISCUSSION

HAE is a rare autosomal dominant disease, characterized by edema of the skin, subcutaneous tissues or the mucous membranes of the gastrointestinal and upper respiratory tracts. Laryngeal edema occurred in 48%-78% of HAE patients, and the risk for asphyxial death was 30%-50%.¹⁸ The manifestation is similar to the angioedema caused by allergen or medicine, so in the emergency room antihistamines, glucocorticoid or epinephrine is usually administrated to control angioedema, but the upper-mentioned medicines have no effect for angioedema attacks of HAE.

HAE is caused by deficiency in C1INH. C1INH is not only the main regulator of the early steps of the classic complement pathway, but also important inhibitor of kallikrein. C1INH deficiency will activate the classic complement pathway and bradykinin, leading to edema. At present, replacement therapy with C1INH is recommended to treat an acute attack of HAE, but which is unavailable in China.

FFP is separated from the whole blood within 6-8 hours after collection, which can be conserved for 1 year under

-18°C. FFP contains all coagulation factors except for platelet, so FFP can be used for treatment of acute attacks of HAE.¹⁹ We reported FFP infusion as the treatment for acute attacks of HAE in China in 2009.⁸ But it is hypothesized FFP might worsen an acute attack of HAE for it contains potentially harmful substrates.²⁰

Angioedema attacks various organs. In this report, the manifestation of FFP treated cases ranged from abdominal pain to facial angioedema to life-threatening laryngeal edema. The patients with laryngeal edema were younger than those with abdominal pain or facial edema, so the clinical doctor should pay attention to the laryngeal edema among the younger patients. In this cohort, 375 ± 128 mL of FFP seemed to be able to achieve an improvement in symptoms of patients with laryngeal edema, meanwhile 657 ± 256 mL of FFP seemed effective for the other cases. So 400-600 mL of FFP seemed enough for acute attacks of HAE.

Improvement in symptom appeared in all cases except one because of transfusion reaction. FFP was an efficacious remedy for every type of exacerbation. And 2 cases reported in the literature suffered from worsening abdominal pain within the first few minutes of FFP infusion for an acute attack, but achieved complete resolutions within 1.5 to 2.5 hours of treatment.^{10, 13} We can not identify if the abdominal symptom are due to FFP infusion.

After 49 ± 19 minutes of beginning the infusion, there was a definite improvement. At 3.3 hours of infusion, HAE patients were completely free of laryngeal edema,

abdominal pain or facial edema. The remission time was obviously shorter than that of patients without FFP transfusion (61.7 ± 27.0 hours). There was an increase in C1INH activity after the infusion, which indicated that the plasma infusion provided the patients with C1INH, leading to the release of acute attacks.

FFP can induce allergic reaction or virus infection as blood products. The only adverse event recorded was rash, fever and chilling, which were considered to be allergic reaction to FFP, and were easily alleviated with antihistamines. So plasma derived C1INH and recombinant C1INH is required in China to treat acute HAE attacks.

In conclusion, FFP seems to be safe and effective when used for treatment of acute HAE attacks.

REFERENCES

1. Cicardi M, Bork K, Caballero T, et al. Evidence-based recommendations for the therapeutic management of angioedema owing to hereditary C1 inhibitor deficiency: consensus report of an International Working Group. *Allergy* 2012; 67:147-57.
2. Craig TJ, Bewtra AK, Bahna SL, et al. C1 esterase inhibitor concentrate in 1085 hereditary angioedema attacks—final results of the I.M.P.A.C.T.2 study. *Allergy* 2011; 66: 1604-11.
3. Zuraw BL, Busse PJ, White M, et al. Nanofiltered C1 inhibitor concentrate for treatment of hereditary angioedema. *N Engl J Med* 2010; 363:513-22.
4. Zuraw B, Cicardi M, Levy RJ, et al. Recombinant human C1-inhibitor for the treatment of acute angioedema attacks in patients with hereditary angioedema. *J Allergy Clin Immunol* 2010; 126:821-7.
5. Cicardi M, Levy RJ, McNeil DL, et al. Ecallantide for the treatment of acute attacks in hereditary angioedema. *N Engl J Med* 2010; 363:523-31.
6. Cicardi M, Banerji A, Bracho F, et al. Icatibant, a new bradykinin-receptor antagonist, in hereditary angioedema. *N Engl J Med* 2010; 363:532-41.
7. Prematta M, Gibbs JG, Pratt EL, et al. Fresh frozen plasma for the treatment of hereditary angioedema. *Ann Allergy Asthma Immunol* 2007; 98:383-8.
8. Tang R, Zhang HY, Gan J. Fresh frozen plasma for the treatment of a Chinese patient with hereditary angioedema. *Chin Med Sci J* 2009; 24:246-7.
9. Bowen T, Cicardi M, Farkas H, et al. 2010 International consensus algorithm for the diagnosis, therapy and management of hereditary angioedema. *Allergy Asthma Clin Immunol* 2010; 6:24.
10. Pickering RJ, Good RA, Kelly JR, et al. Replacement therapy in hereditary angioedema: successful treatment of two patients with fresh frozen plasma. *Lancet* 1969; 1:326-30.
11. Hamilton AG, Bosley ARJ, Bowen DJ. Laryngeal oedema due to hereditary angioedema. *Anaesthesia* 1977; 32: 265-7.
12. Cohen G, Peterson A. Treatment of hereditary angioedema with fresh frozen plasma. *Ann Allergy* 1972; 30: 690-2.
13. Beck P, Wills D, Lachmann PJ, et al. A family study of hereditary angioneurotic oedema. *QJM* 1973; 42: 317-39.
14. Ohela K, Rasanen JA, Wager O. Hereditary angio-neurotic oedema: genealogical and immunological studies. *Ann Clin Res* 1973; 5:174-80.
15. Wall RT, Frank M, Hahn M. A review of 25 patients with hereditary angioedema requiring surgery. *Anesthesiology* 1989; 71:309-11.
16. Cohen N, Sharon A, Golik A, et al. Hereditary angio-neurotic edema with severe hypovolemic shock. *J Clin Gastroenterol* 1993; 16:237-9.
17. McGlinchey PG, Golchin K, McCluskey DR. Life-threatening laryngeal oedema in a pregnant woman with hereditary angioedema. *Ulster Med J* 2000; 69:54-7.
18. Farkas H. Management of upper airway edema caused by hereditary angioedema. *Allergy Asthma Clin Immunol* 2010; 6:19.
19. Bowen T, Cicardi M, Bork K. Hereditary angioedema: a current state-of-the-art review, VII: Canadian Hungarian 2007 International Consensus Algorithm for the Diagnosis, Therapy, and Management of Hereditary Angioedema. *Ann Allergy Asthma Immunol* 2008; 100:S30-40.
20. Donaldson VH. Therapy of the neurotic edema. *N Engl J Med* 1972; 286:835.