

Clinical effects of joint application of β -sodium aescinate and mannitol in treating early swelling after upper limb trauma surgery

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Abstract. The aim of the present study was to examine the clinical merits of joint application of β -sodium aescinate and mannitol for the treatment of early swelling of upper limb trauma after surgery. We verified whether the expression of serum aquaporin 1 (AQP-1) was involved in swelling mechanism. A total of 102 patients with swelling after upper limb trauma surgery were enrolled into the study and divided randomly into 3 groups (n=34 cases per group). Group A was treated with β -sodium aescinate; group B was treated with mannitol and group C was treated with both β -sodium aescinate and mannitol. The expression level of AQP-1, and clinical effects and complications before and after treatment were compared. The time of swelling subsidence in group C was significantly shorter than that of the other two groups and differences were statistically significant ($P<0.05$). The recovery ratio and total efficiency in group C were significantly higher than those in other two groups and differences were statistically significant ($P<0.05$). Three and seven days after treatment, the AQP-1 levels in group A and group C were decreased and AQP-1 level decreased further with time. Differences of comparison within groups were statistically significant ($P<0.05$), although the differences of comparison between the groups showed no statistical significance ($P>0.05$). We also compared the AQP-1 level in group B before and after treatment, and the differences were not statistically significant ($P>0.05$). When the complication incidence in the 3 groups was compared, no statistical significance was detected ($P>0.05$). We concluded that the joint use of β -sodium aescinate and mannitol in treating early swelling after upper limb trauma surgery produced satisfactory outcomes. This might be related to reduction of the AQP-1 level.

Introduction

Early swelling after upper limb trauma surgery needs timely and effective treatment. Any delay may lead to compression of the adjacent nerves and vascular system and may even cause serious complications of bone compartment syndrome. Clinical incidence is rather high at approximately 12.5% (1). Currently, the treatment of choice for swelling is primarily mannitol, lactulose and diuretics. However, mannitol may cause acute kidney injury (2), lactulose can cause the metabolism of blood sugar and electrolyte (3) and the effects of diuretics for local inflammatory edema are poor (4).

β -sodium aescinate is a sodium containing compound extracted from the Saul son fruit (traditional Chinese medicine), with anti-inflammatory properties (5). It is known (6) that β -sodium aescinate has relatively good efficacy in treating ischemia-reperfusion injury after acute cerebral hemorrhage and brain edema. Previously, the application of β -sodium aescinate and mannitol, respectively, was compared on edema after upper limb trauma and whether the effects of swelling subsidence of β -sodium aescinate are better than mannitol was examined (7). There are limited number of studies explaining the mechanism of action for β -sodium aescinate, however, it is probable that serum aquaporin 1 (AQP-1) is somehow involved in this mechanism.

The aim of the present study was to examine the clinical merits of joint application of β -sodium aescinate and mannitol for the treatment of early swelling of upper limb trauma after surgery.

Patients and methods

General data. From July, 2011 to July, 2014, we enrolled 102 patients with swelling after upper limb trauma surgery for this study. The inclusion criteria were as follows: i) Patients were >18 and <75 years old; ii) patients had history of clear upper limb trauma surgery, and all had blunt trauma; iii) patients did not have any swelling associated with severe neurological and vascular damage; and iv) time of trauma was <8 h. The exclusion criteria were as follows: i) Swelling caused by other reasons, such as burns, upper limb venous or lymphatic compression, tumor swelling; ii) other serious

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Table I. Comparison of time of swelling subsidence and efficacy in patients in the 3 groups.

Group	Cases	Time of swelling subsidence	Recovery	Effective	Ineffective	Total efficiency
A	34	6.38 \pm 1.37	9 (26.5)	18 (52.9)	7 (20.6)	79.4
B	34	6.61 \pm 1.63	7 (20.6)	17 (50.0)	10 (29.4)	70.6
C	34	4.16 \pm 1.72	21 (61.8)	11 (32.3)	2 (5.9)	94.1
F (χ^2)		5.625				6.339
P-value		0.027				0.042

Group A, simple application of β -sodium aescinate; Group B, simple application of mannitol; Group C, joint application of β -sodium aescinate and mannitol.

organ disease, such as heart, kidney and brain disease; and iii) patients who refused to participate in this study.

The study was approved by the Ethics Committee of the The Third People's Hospital of Qingdao (Shandong, China). Informed consent of patients or their families was obtained. Patients were randomly divided into 3 groups (34 cases per group) according to the order of their hospitalization. We used the 'Gu Yudong's Operative Hand Surgery' (edition 1999) to grade the swelling degree. Group A was treated with β -sodium aescinate; group B was treated with mannitol; and group C was treated with both β -sodium aescinate and mannitol.

Group A comprised 24 men and 10 women, aged 24-73 years (average 45.3 \pm 7.6 years). Time of trauma ranged from 0.7 to 8 h (average 5.6 \pm 1.1 h). In group A, we identified 18 grade II and 16 grade III cases. In group B, we had 18 men and 16 women, aged 29-70 years (average 46.8 \pm 7.3 years). Time of trauma ranged from 0.6 to 7.6 h (average 5.4 \pm 1.5 h). There were 15 cases of grade II swelling and 19 cases of grade III swelling in group B. In group C, there were 19 men and 15 women, aged 26-69 years (average 45.8 \pm 6.3 years). Time of trauma ranged from 0.8 to 7.5 h (average 5.8 \pm 1.3 h). A total of 17 cases of grade II and 17 cases of grade III swelling were identified in group C. We compared the gender, age, time of trauma and grading of swelling of the patients in the three groups, and the differences were of no statistical significance ($P>0.05$).

Experimental methods. Group A received 20 mg/time of β -sodium aescinate (trademark: Beishutai, H22025070; approved by the state and Jilin Jinsheng Pharmaceutical Co., Ltd., Jilin, China) and qd ivgtt. Group B received 20% mannitol, 125 ml/time and q12 h ivgtt. Group C received β -sodium aescinate for 10 mg/time, qd ivgtt plus mannitol (125 ml/time and qd ivgtt). Patients were monitored and the time of swelling subsidence was recorded, and were also closely monitored for complications.

Observation index and evaluation criteria. Differences in AQP-1 level, clinical effects and complication occurrence before and after treatment were compared. For AQP-1 measurement 5 ml of early morning fasting venous blood was collected and the samples were sent to laboratory immediately. Double antibody sandwich enzyme-linked immunosorbent assay (ELISA) was employed using kits purchased from the Shenzhen Pinmei Biological Engineering Co., Ltd., Shenzhen, China.

To examine the clinical effects, we determined that if the time of swelling subsidence was <3 days the treatment was

Table II. Comparison of AQP-1 level in patients in 2 groups before and after treatment ($\mu\text{g/l}$).

Group	Before treatment	3 days after treatment	7 days after treatment
A	16.54 \pm 3.06	11.34 \pm 2.52	7.28 \pm 1.23
B	16.87 \pm 3.21	16.23 \pm 3.52	16.42 \pm 3.48
C	17.24 \pm 3.26	11.36 \pm 2.85	7.31 \pm 1.52
F	0.638	4.268	4.568
P-value	0.417	<0.001	<0.001

AQP-1, aquaporin 1.

considered as being fully recovered and if that time ranged from 3 to 7 days it was considered as remitted. If the time of swelling subsidence was longer than 7 days then we considered the treatment as ineffective. We used the following formula for our calculations: Total efficiency = (recovery + remission)/total cases \times 100%. Complications included fever, allergy, renal impairment, phlebitis, tension blisters and bone compartment syndrome.

Statistical analysis. SPSS 19.0 software (SPSS, Inc., Chicago, IL, USA) was used for data analysis. Measurement data were presented as mean \pm standard deviation and analysis of variance was employed for comparisons among groups. Countable data were presented by the number of cases (%) and χ^2 test was used for comparisons among groups. $P<0.05$ was considered to indicate a statistically significant difference.

Results

Comparison of time of swelling subsidence and efficacy of patients in the 3 groups. The time of swelling subsidence in group C was significantly shorter than that in the remaining groups and the difference was statistically significant ($P<0.05$). The recovery ratio and total efficiency in group C were significantly higher than those in other two groups and the difference was statistically significant ($P<0.05$; Table I).

Comparisons of AQP-1 level of the patients in the 3 groups before and after treatment. We compared AQP-1 level in all the patients in the three groups before treatment, and the

differences showed no statistical significance ($P>0.05$). Three and seven days after treatment, the AQP-1 level in group A and group C was decreased and the decrease intensified with time. Differences of comparison within groups were statistically significant ($P<0.05$). When we compared between groups, the differences were not statistically significant ($P>0.05$). Comparing the AQP-1 levels in group B, before and after treatment, revealed no statistical significant difference ($P>0.05$; Table II).

Comparisons of complication incidence of the patients in the 3 groups. In group A, there were 3 cases with tension blisters, 1 case of allergy and 2 cases of phlebitis, and the total incidence was 17.65%. In group B, there were 4 cases of renal impairment, 2 cases of tension blisters, 1 case of allergies and 2 cases of electrolyte imbalance, and the total incidence was 23.53%. In group C, there was 1 case of tension blisters and 1 case of phlebitis, and the total incidence was 5.88%. We compared the complication incidence in all three groups, and the differences were not statistically significant ($\chi^2=4.151$, $P=0.125$).

Discussion

One week after trauma is the peak stage of forming edema, mainly because of bleeding after injury, cascade expanded inflammation and uneven distribution of local body fluid caused by stress. Thus, body fluid constantly gathers interstitially to form edema (8). If the early swelling is not subsided with time, it can deteriorate the situation and negatively influence the healing process.

Mannitol is a kind of osmotic diuretic that is widely used in clinic to promote tissue dehydration and has a rather good efficacy for all edemas due to various reasons. Mannitol can promote the secretion of prostaglandin, expand renal blood vessels and increase blood flow. However, renal tubular has a limited absorptive capacity of mannitol; renal tubular can keep a rather high concentration of mannitol, decrease the back absorption of moisture and promote the discharge of urine (9). The above mechanisms promote and cooperate with each other to facilitate the dehydration and diuretic function of mannitol.

β -sodium aescinate is a sodium containing compound extracted from the Saul son fruit (traditional Chinese medicine), with anti-inflammatory properties (5).

Prior findings have shown that β -sodium aescinate promoted the release of prostaglandin F_{2a} and cortisol and the increase of vascular permeability as well (10). Additionally, β -sodium aescinate can eliminate oxygen-free radicals and has a strong diuretic effect. β -sodium aescinate mainly enters the liver through the intestinal tract and is suitable for patients with poor renal functions (11). β -sodium aescinate for cerebral edema after acute intracerebral hemorrhage, showed that the mechanism of swelling subsidence of β -sodium aescinate may be related to the expression of serum AQP. Serum AQP-1 (AQPs) is a family of specific channel proteins, which widely exists on cell membranes of prokaryotes and eukaryotes and can transport water molecules selectively and efficiently (12). AQPs function is not influenced by temperature or the component of lipid membrane and as long as there is osmotic pressure

gradient, water molecules can get through along osmotic pressure gradient (13). AQP-1 exists widely throughout the body and participates in the regulation of a variety of physiological functions in human body (14).

We showed that joint application of β -sodium aescinate and mannitol could reduce the time of swelling subsidence. Reduced dose of the two drugs was related to the decrease of complication incidence. The swelling subsidence mechanism of β -sodium aescinate and mannitol are different. AQP-1 expression is related to the mechanisms of swelling subsidence of β -sodium aescinate, however, it did not show any connection to mannitol.

We conclude that joint application of β -sodium aescinate and mannitol is a very efficient method of treatment for early swelling after upper limb trauma surgery, which may be related to reduction of the AQP-1 level. We believe this method of treatment deserves to become more widely used in clinical application.

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