Efficacy analysis of methylprednisolone plus adrenaline to treat wasp sting injury

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ABSTRACT

الأهداف: عرض أثر ميثالبريدييناسولين (MP) و الادرنالين لعلاج المرضى المصابين بلسعة الزنبور.

الطريقة: أجريت هذه الدراسة كلية الطب للعلوم الصحية – الصين – جامعة جورج الثالث – مدينة يتشنغ – محافظة هيوبي – الصين خلال الفترة من يونيو 2008 حتى نوفمبر 2008. تم تقسيم 45 حالة إلى مجموعتين،تم استخدام عقار MP بمفرده في مجموعة التحكم و MP مع الادرنالين في مجموعة الملاحظة. قمنا بمقارنة الأثر الطبي بين المجموعتين.

النتائج: كان معدل مستويات أنزيم أمين الألانين 64.05±59.31 مقابل 124.14±80.01 U/L و أنزيم كيناز الكرياتين 90.32±85.19 مقابل 216.68± 277.58µmol/L لمجموعة الملاحظة أعلى من مجموعة التحكم. كانت مدة الإقامة في المستشفى لمجموعة الملاحظة أقل من مجموعة التحكم 7.23±2.93 مقابل 11.23±8.02. بينما مضاعفات لسعة الزنبور أقل من مجموعة التحكم. إضافة إلى ذلك، مستوى كريات الدم المحيطة مرتبط بشكل إيجابي مع عدد اللسعات (p=0.001، r=0.733)، و مستويات أنزيم أمين الألانين و كيناز الكرياتين،p=0.001، r=0.627 وr=0.705 ومدة البقاء بالمستشفى p=0.001, r=0.677.

خاتمة: تلعب استجابات الحساسية و الالتهاب دور مهم إضافة إلى التأثيرالمباشر لسم الزنبور في جسم الإنسان. مقارنة مع عقار MP بمفرده، يساعد اتحاد الادرنالين منع مقاومة نقل الحساسية والالتهاب للخلية ومن ثم خفض درجة الإصابة.

Objectives: To observe the effect of methylprednisolone (MP) plus adrenaline to treat patients injured by wasp stings.

Methods: This study was carried out at The First College of Clinical Medical Science, China Three Gorges University, Yichang, Hubei Province, China, from June to November 2008. A total of 45 cases were divided into 2 groups. The MP was used alone in the control group, and MP plus adrenaline was used in the observation group. We compared the clinical effect between the 2 groups.

Results: The alanine aminotransferase (ALT) (64.05 ± 59.31 versus 124.14 ± 80.01 U/L), and creatine kinase isoenzyme (CKMB) (90.32 ± 85.19 versus 216.68 ± 277.58 µmol/L) levels of the observation group were significantly lower than those of the control group. The length of hospital stay of the observation group was significantly shorter than that of the control group (7.23 ± 2.93 versus 11.23 ± 8.02), while complications from the wasp sting were fewer than those of the control group. In addition, the level of peripheral blood leukocytes was positively correlated with the number of stings (r=0.733, p=0.001), levels of ALT and CKMB (r=0.627, p=0.001, and r=0.705, p=0.001), and length of hospital stay (r=0.667, p=0.001).

Conclusion: Allergic and inflammatory responses play an important role in addition to the direct effect of wasp venom on the human body. Compared with MP alone, early combination of adrenaline helps to further inhibit the diffusion of allergy and inflammatory cytokines, and therefore reduce the severity of injury.

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Wasp sting injuries are common in the mountain area, and frequently happen in autumn. Different kinds of wasp venom cause various degrees of damage to the human body. In recent years, research progress has been made in wasp sting injuries.[1-3] It is known now that allergy and inflammatory cytokines are involved in its pathogenesis.[1,2] Our previous report had shown that a combination of high-dose methylprednisolone

(MP) and blood purification therapy had some effects on hemolysis, and multiple organ dysfunction caused by wasp sting injury.[3] However, due to the lack of specific treatment so far, wasp sting injury is still a serious threat to a patient's life. Therefore, it is necessary to further explore the treatment options for wasp sting injuries. Currently, adrenaline is known to ameliorate anaphylactic shock, laryngeal edema, and pulmonary edema caused by wasp sting injury. However, the use of adrenaline for the treatment of wasp stings injury is rare, especially for patients without the above serious symptoms, mainly due to the complex pathogenesis of wasp sting injuries, and unavailability of standardized treatment plan to clinicians. The aim of this present study is to observe the effect of methylprednisolone (MP) plus adrenaline to treat patients injured by wasp stings. So, we recently tested the clinical effect of MP and adrenaline combination in treating wasp sting injury, and summarized the clinical data of 44 patients in this study.

Methods. Between June and November 2008, after approval from the medical ethics committee of China Three Gorges University and the informed consent of the human subjects, we carried out this study in The First College of Clinical Medical Science, China Three Gorges University, Yichang, Hubei Province, China. This study was conducted on 45 persons attending a gathering in the mountain forest who were attacked by wasps. Forty-five patients (32 males, 13 females) were hospitalized, 30 minutes after the attack due to severe injury. The age of the patients ranged from 23-66 years. Stings were mainly localized at the head and neck, and 5-30 sting injuries were detected. The main symptoms at the time of admission included pain at sting sites, severe headache, and groaning in 5 cases, 5 cases passed soy sauce colored urine after 2-3 hours of injury, and some patients had oliguria, or anuria. Swelling was seen at the sting sites of all patients, and pus spots could be observed the next day, but no wasp needles were found after careful physical examination. In one case that was allergic to penicillin, headache was particularly severe at the time of admission. Symptoms of this patient included anxiety, gross hematuria at first, and soy sauce colored urine later, whole body myalgia, abdominal pain, tenderness of the whole abdomen, and no obvious rebound tenderness. Twenty days later, numbness and weakness appeared at both lower extremities, and the patient was diagnosed as Guillain-Barré syndrome, based on lumbar puncture result. One patient had complication of Henoch-Schönlein purpura, and one patient died from respiratory and circulatory failure within 24 hours of admission. Serial number was assigned to each patient based on the order of admission, and patients were divided into 2 groups using random number table. There were 23 cases in the control group and 22 cases in the observation group.

Treatment. Patients were given 5% glucose solution 250 ml intravenous injection plus 80 mg MP immediately after admission, and patients with soy sauce colored urine received additional intravenous injection of 0.5 g MP for 3-5 days. In addition to the above treatment, patients in the observation group were immediately given subcutaneous injection of 0.5 mL 0.1% adrenaline, while those with severe headache and soy sauce colored urine received a repeated dose after 4-6 hours. In addition, 5% sodium bicarbonate was intravenously injected to those with soy sauce colored urine. Intravenous somatostatin was administrated to patients who suffered from gastrointestinal bleeding. All patients received hemoperfusion to clear the venom in the blood circulation. The patients with acute renal failure received hemodialysis. The aged and physically weak patients, or patients who had unstable hemodynamics were treated with continuous renal replacement therapy. Blood samples were collected at the first, third, fifth, and seventh day in the hospital. Since individual reaction to wasp sting varies among patients, damage to organs occurs at different time points in different patients. Therefore, data were collected at the time when the most severe damage occurred. In addition, one patient died within 24 hours after admission, and this case was excluded from the statistical analysis.

Monitored parameters. Severity of clinical symptoms before and after treatment in the 2 groups, degree of organ involvement, length of hospital stay, and correlation between increased level of white blood cell (WBC), and degree of organ damage were monitored.

Statistical analysis. Experimental data were shown as mean ± SD, and comparison between the 2 groups was performed using t test. Correlation comparison among all factors was carried out using Pearson correlation analysis, and comparison of numeration data was made by chi-square test. The software program Statistical Package for Social Sciences for Windows version 13.0 (SPSS Inc., Chicago, IL., USA) was used for the statistical analysis. The level of significance was set at $p<0.05$.

Results. ***Comparison of clinical indicators between the 2 groups.*** There were no statistical differences between the 2 groups for age, gender, and the number of wasp sting. The values of ALT and CKMB in the observation group were significantly lower than those in the control group ($p=0.034$). However, no statistical differences in the number of WBC and serum creatinine (SCr) values were detected between the 2 groups (**Table 1**).

Comparison of complications between the 2 groups. The complications such as proteinuria, soy sauce colored urine, hemolysis, and alimentary tract hemorrhage in the observation group were fewer than that of the control group, but there was no statistical significant difference (**Table 2**).

Correlation analysis of clinical indicators. Peripheral blood leukocytes level was positively correlated with the number of wasp stings (r=0.733, p=0.001), as well as with the levels of ALT and CKMB (r=0.627, p=0.001, and r=0.705, p=0.001), and length of hospital stay (r=0.667, p=0.001). However, it was not significantly correlated with the SCr level (r=0.205, p>0.05).

Observation of side-effects. After subcutaneous injection of adrenaline in the observation group, increased heart beats at a bearable level appeared in some patients, but no headache and vomiting were noticed. Short-term use of MP had no serious side-effects, and it did not aggravate the symptoms of patients with gross hematuria and abdominal pain.

Table 1 - Comparison of clinical indicators between control, and observation group (mean ± standard deviation).

Variables	Observation group (n=22)	Control group (n=22)	t-value	*P*-value
Age	46.73 ± 9.51	41.36 ± 12.89	0.98	>0.05
Number of sting wounds	12.68 ± 8.24	12.55 ± 6.08	0.06	>0.05
Length of hospital stay	7.23 ± 2.93	11.23 ± 8.02	2.19	0.034
WBC ($\times 10^9$/L)	16.34 ± 6.98	14.60 ± 6.76	0.84	>0.05
ALT (U/L)	64.05 ± 59.31	124.14 ± 80.01	2.83	0.007
SCr (umol/L)	82.32 ± 19.83	158.81 ± 284.59	1.25	>0.05
CKMB (IU/L)	90.32 ± 85.19	216.68 ± 277.58	2.04	0.048

WBC - leukocyte (or white blood cell), ALT - alanine amino transferase, SCr - serum creatinine, CKMB - creatine kinase isoenzyme

Table 2 - Comparison of complications between the control group and observation group (chi-square test).

Complications	Control group n=22	Observation group n=22	χ^2
Proteinuria	6	4	0.51
Soy sauce colored urine	4	1	0.90
Hemolysis	2	0	0.52
Alimentary tract hemorrhage	2	0	0.52
χ^2=3.84, p>0.05			

Discussion. The components of wasp venom are complex, mainly including biogenic amines, peptides, polisteskinin, and enzymes. Biological amines include: histamine, acetylcholine, catecholamines, and so forth. Peptides include neurotoxin, hemolysin, mast cell degranulating peptide, and others. Enzymes include phospholipase A, and hyaluronase, and so forth.[4,] Wasp venom not only can directly damage human tissue and organs, but also can further damage the body through allergic and inflammatory responses produced by the human body. After entering the body, wasp venom can activate the cytokine network to produce a cascade effect, and further magnify its biological effect,[5,6] resulting in a series of stress response and systemic inflammatory responses, and causing more extensive damages to organs and tissues. Among all damages such as hemolysis, and nerve, heart, liver, and kidney dysfunctions; hemolysis, liver, and kidney dysfunction are the most common.[7,8] The prognosis of patients depends on the timely treatment, types of wasp, sting site, age, health status, degree of inflammatory response, and method of first aid.

After being stung by wasps, the human body first reacts with pain at the sting sites, often a headache, followed by upset body, soy sauce colored urine in severe cases, and some patients have anaphylactic shock, laryngeal edema, pulmonary edema, and breathing difficulty, which leads to death if not timely treatment. Allergic response is a threat to patients' life, and a main cause of early death.[9] In our study, one patient with a history of penicillin allergy appeared to have symptoms of gross hematuria, severe headache, abdominal pain, and lower extremity sensory and movement disorders after wasp sting, indicating that wasp venom is more dangerous to allergy-prone individuals. During allergic response, inflammatory cytokines increase *in vivo.*[10] The inflammatory response is a complicated physiological response of the body against wasp sting injury, which involves a variety of factors in the regulation process.[11] We observed systemic inflammatory response in the progress of wasp sting injury such as; WBC increased after wasp sting attack 1-2 hours later, which was closely correlated with the severity of the disease. The peripheral blood leukocytes reached 12,000-35,000x10^9/L for patients with impaired organ function. It has been reported that relevant inflammatory cytokines significantly increase in patients after a wasp sting injury, and the increase of multiple inflammatory cytokines synergically participates in the onset and development of wasp sting injury, and affects the prognosis. The more severe the wasp sting poisoning, the higher the inflammatory cytokines in the blood,[5] which indicates that the progress of wasp sting injury, not only involves the direct effect of wasp venom on the human body, but also allergy, and

inflammatory responses generated by the body against wasp venom. Therefore, it is essential to effectively inhibit the diffusion of allergic and inflammatory responses in the body at an early stage. The MP has antitoxic, anti-inflammatory, and anti-immune effects, which can effectively inhibit the diffusion of allergic and inflammatory cytokines *in vivo*, while MP takes effect quickly, has strong efficacy, and helps to improve the prognosis of patients.[3] Subcutaneous injection of adrenaline can prevent and treat the anaphylactic shock, laryngeal edema, and pulmonary edema caused by wasp sting injury, as well as, helps to alleviate systemic allergy and inflammatory responses.[12]

Our results suggest that a combination of adrenaline and MP can reduce clinical symptoms of the patients, decrease the degree of functional damages to organ, and shorten the length of hospital stay. This indicated that the combination of these 2 drugs can more effectively inhibit allergy, reduce chemotaxis of inflammatory cells, and eventually reduce damage to the body caused by wasp venom.

In conclusion, during the progress of wasp sting injury, in additional to the direct effect of wasp venom on the human body, allergic, and inflammatory responses play an important role. Therefore, medical treatment should be promptly applied after wasp sting. Furthermore, in additional to hemodialysis, combination of MP, and adrenaline at an early stage is more effective than MP alone in inhibiting allergy and diffusion of inflammatory cytokines, in order to reduce disease severity, and improve the prognosis of patients. However, for the aged patients with hypertension and coronary heart disease, we should be cautious in using adrenaline. Because of a few cases and deficient indexes of inflammatory cells, the clinical significance of MP and adrenaline combination in treating wasp sting injury deserves further observation.

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