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Changes in serum enzymes and related mechanisms of respiratory dysfunction in patients after venomous snake bite and analysis of anti-venomous snake serum treatment

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ABSTRACT

To explore the changes in serum enzymes in patients with a snake bite, the treatment of respiratory dysfunction, and the clinical effect of anti-snake serum treatment. Fifty snake bite patients admitted to the emergency medicine department were selected and rolled into a light group (n=27), heavy group (n=15), and critical group (n=8). Anti-venomous snake serum was injected intravenously. Patients with severe respiratory dysfunction were treated with mechanical ventilation. The white blood cell (WBC), C-reactive protein (CRP), interleukin-6 (IL-6), alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN), and creatinine (Cr) counts of the heavy group and the critical group were higher versus light group (P<0.05). The WBC, CRP, IL-6, ALT, AST, BUN, and Cr of the critical group were higher versus the heavy group (P<0.05). The prothrombin time (PT), activated partial thrombin time (APTT), and thrombin time (TT) of the heavy group and critical group were longer versus the light group (P<0.05). The PT, APTT, and TT of the critical group were longer than the heavy group (P<0.05). The fibrinogen (FIB) of the light group was higher in contrast to that in the other two groups (P<0.05), while the critical group was the lowest (P<0.05). In summary, the severity of snakebites in patients can be evaluated according to the indexes of WBC, IL-6, coagulation function, and liver and kidney function.

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Introduction

Venomous snake bite is one of the most common emergency cases in the clinic and usually occurs in hot summer. Most of the bite sites are concentrated in the extremities. There are more than 100,000 venomous snake bite patients in China every year (1-3). In recent years, with the warming of the climate, the number of patients with snakebites has increased year by year, and the vast majority of patients are from mountainous areas or rural areas (4-6). The severity of snakebite patients is related to the type of snake, the injured site, the time of treatment, and the amount of venom.

Snake venom contains various enzymes, among which proteolytic enzymes can directly damage the capillary endothelial cells of the body. Hyaluronic acid can lyse cells and fibrous stroma and damage the integrity of connective tissue (7-9). According to the nature of snake venom, it is classified into blood circulation poison, a nerve poison, and mixed poison. Among them, neurotoxicity directly affects the release of neurotransmitters, blocks the binding of acetylcholine and receptors, causes muscle paralysis and muscle weakness, and even causes respiratory dysfunction. In addition, the entry of neurotoxins into the autonomic nervous system triggers respiratory failure, affects gland secretion, and leads to shock (10-12).

Inflammatory reactions are involved in the pathogenesis of snakebites, among which C-reactive protein (CRP) is correlated with inflammatory reactions and the degree of tissue damage, and its level can reflect the severity of snakebites to a certain extent. The thrombin in snake venom may lead to coagulopathy, induce subcutaneous hemorrhage, and even cerebral hemorrhage in severe cases (13-15). Therefore, accurate assessment and treatment of snakebite patients in clinical practice can improve the prognosis of patients effectively. With the widespread application of antivenoms, the number of deaths caused by snakebites has gradually decreased (16-19). Refined antivenin is prepared from horse plasma after the horses are immunized with snake venom and have antigenic specificity. Generally, intravenous injection is used to treat patients bitten by snake venom, which can effectively neutralize the components of snake venom and has a considerable therapeutic effect.

In this study, 50 patients with snakebites admitted to the emergency medicine department were selected and grouped into a light group (n = 27), heavy group (n = 15), and critical group (n = 8) based on the specific disease condition of the patients. This study evaluated the relationship between serum enzyme changes and the severity of the patient's condition and observed the mechanism of anti-venomous snake serum in the treatment of venomous snake bites to give treatment ideas for patients with a venomous snake bite.

Materials and Methods

Research objects

Fifty patients with snakebites admitted to the Emergency Medicine Department of The First Affiliated Hospital,

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Guangxi Medical University from July 2020 to July 2021 were selected, including 26 males and 24 females, with 42.84±5.35 as the average age. According to the severity of the disease, patients were grouped into three: a light group (n=27), a heavy group (n=15), and a critical group (n=8). There was no considerable difference in sex, age, bite site, or other general information among the three groups (P> 0.05), suggesting comparability. This study was approved by the medical ethics committee of The First Affiliated Hospital, Guangxi Medical University. Patients and their family members were aware of this study and signed informed consent forms.

Patients included had to satisfy all of the below conditions: (i) patients aged over 18 years old; (ii) the onset time was less than 48 hours; (iii) patients confirmed by laboratory indicators, it was a venomous snake bite, with redness and swelling in the bite site, severe pain in the wound, and systemic poisoning symptoms.

Patients with any of the below conditions had to be excluded: (i) patients with malignant tumors and severe cardiovascular diseases; (ii) patients with major organ complications (heart, liver, and kidney); and (iii) patients with coagulation dysfunction.

Therapeutic methods

Antiviper serum was administered by intravenous infusion. Cobra bites were treated with 2,000 IU anti-cobra venom (Shanghai Sailun Biotechnology Co., Ltd., China). Patients bitten by Bungarus multicinctus were injected with anti-Bungarus multicinctus venom 10,000 IU serum. Patients bitten by Agkistrodon halys were injected with 6,000 IU antivenom. Patients bitten by Ancistrodon acutus were injected with 8,000 IU anti-Agkistrodon venom serum. Before infusion, anti-allergy drugs were injected intramuscularly, usually diphenhydramine hydrochloride injection (Changchun Changqing Pharmaceutical Group Co., LTD., SFDA approval number H11020603) or 10 mg of chlortrimeton. The intramuscular injection was performed with 20 mg furosemide (Tianjin Jinyao Pharmaceutical Co., LTD., SFDA approval number H31021074). One dose of 10 mg of refined antivenomous snake serum and dexamethasone needle was added to 250 mL or 500 mL of 10% glucose by intravenous infusion.

Treatment with mechanical ventilation was as follows. Patients with severe respiratory dysfunction were intubated and mechanically ventilated with a Servo300A ventilator (Siemens, Germany). The machine mode was auxiliary/control (A/C). The oxygen concentration (FiO_2) was 0.35-1.0. The respiratory rate was 12-16 breaths/min. The tidal volume (Vt) was 8-10 mL/kg. The respiration ratio (I/E) was 1:2.

Observation indexes

Changes in pain were observed. The visual analog scale (VAS) (20) was employed to evaluate the pain index at 0 h, 12 h, 24 h, 36 h, and 48h. A scale with 10 scales was used, with 0-10 on the corresponding scale, “0” for painless and “10” for intense pain.

The liver function indexes included alanine aminotransferase (ALT) and aspartate aminotransferase (AST). The indexes of renal function included blood urea nitrogen (BUN) and creatinine (Cr).

The determination of inflammatory factors was as follows. Immediately after the admission of the patient bitten by a poisonous snake, 3 mL of peripheral venous blood was centrifuged, and the upper serum was separated for routine blood testing and determination of white blood cell counts (WBCs). Serum CRP was determined by immunonephelometry. Enzyme-linked immunosorbent assay (ELISA) was used to determine interleukin-6 (IL-6).

The determination of the coagulation function was as follows. Immediately after the admission of the patient bitten by a poisonous snake, 3 mL of venous blood was centrifuged, and the plasma was separated. The prothrombin time (PT), thrombin time (TT), activated partial thrombin time (APTT), and fibrinogen (FIB) were detected by a Sysmex Sisenmeikang CA1500 blood coagulation apparatus (Sysmex, Japan).

The incidence of hospitalization, infection, respiratory failure, etc., was monitored.

Statistical methods

All the data in this study were set up in the Excel database and analyzed by SPSS 21.0. The measurement data are exhibited in the form of the mean ± standard deviation ($\bar{x}\pm s$), and a t-test was used. The counting data were given as percentages (%) and were tested by the χ^2 test. The difference was considered statistically significant at P< 0.05.

Results

General data statistics

Fifty patients with snakebites, including 26 males and 24 females, were included and their age was 42.84 ± 5.35 years old on average. According to the severity of the disease, patients were arranged into a light group (n = 27), a heavy group (n = 15), and a critical group (n = 8). The bite site of the light group was on the hand in 18 cases (66.66%) and the foot in 9 cases (33.33%). The bite site of the heavy group was on the hand in 9 cases (60.00%) and

Table 1. General data of patients.

Item	Light group (n = 27)	Heavy group (n = 15)	Critical group (n = 8)	P
Sex				0.172
Male	14 (51.85)	8 (53.33)	4 (50.00)	
Female	13 (48.14)	7 (46.66)	4 (50.00)	
Average age (years old)	43.39±5.37	42.93±5.46	41.92±5.36	0.351
Height (cm)	161.53±11.46	162.42±11.32	162.35±11.37	0.235
Weight (kg)	57.43±11.35	56.47±10.43	56.46±11.65	0.152
Bite site				
Hand	18 (66.66)	9 (60.00)	5 (62.50)	0.216
Foot	9 (33.33)	6 (40.00)	3 (37.50)	

the foot in 6 cases (40.00%). The bite site of the critical group was on the hand in 18 cases (62.50%) and the foot in 9 cases (37.50%). No considerable difference was observed in sex, age, height, weight, or bite site of patients in different groups ($P > 0.05$). The specific statistical results were listed in Table 1.

Comparison of visual analog pain scores

The light group, heavy group, and critical group were treated with antivenoms. The visual analog pain scores at 0 h were compared with those at 12h, 24 h, 36 h, and 48h, and the differences were substantial ($P< 0.05$). The visual analog pain scores of the three groups showed statistically obvious differences with the score from high to low is the critical group, heavy group, and light group in order ($P< 0.05$), as exhibited in Figure 1 below.

Comparison of leukocyte count, CRP, and IL-6 among the three groups of patients

Comparison between the heavy and light groups told us that the WBC, CRP, and IL-6 levels in the heavy group were higher ($P< 0.05$), while the comparison between the critical and heavy groups suggested that those in the critical group were much higher, showing substantial difference ($P< 0.05$). In addition, the critical group showed higher WBC, CRP, and IL-6 levels compared with the light group ($P< 0.05$). The specific comparison results were illustrated in Figure 2.

Coagulation indexes among the three groups

Comparison between groups showed that the PT, APTT, and TT of the heavy group were longer than those of the light group ($P < 0.05$), while those in the critical group were the longest among all groups, and the comparative differences here all showed $P < 0.05$.

The comparison between groups showed that the FIB of the critical group was the lowest, followed by that in the heavy group and light group in order, so the FIB in the light group was the highest. The difference between any two of the three groups was statistically observable with $P < 0.05$. Such results were clearly demonstrated in Figure 3 below.

Liver and kidney function among the three groups of patients

Comparison between groups showed that ALT, AST, BUN, and Cr of the critical group were the highest, followed by those in the heavy and the light groups, so those in the light group were the lowest, and all the differences were substantial statistically ($P < 0.05$). Figure 4 illustrated the specific data and comparative results.

Antitoxic serum treatment results

The success rate of rescue for patients with coma, respiratory arrest, and phlegm blockage reached 100%, and all patients were cured and discharged. Patients in the light group were hospitalized for 1-3 days, with an average length of stay of 2.18±0.28 days; patients in the heavy group were hospitalized for 3-6 days, with an average length of stay of 6.49±1.45 days; and patients in the critical group were hospitalized for 6-12 days, with an average length of stay of 9.74±2.89 days. The differences among the three groups were substantial ($P< 0.05$). The above results were obtained from Figure 5.

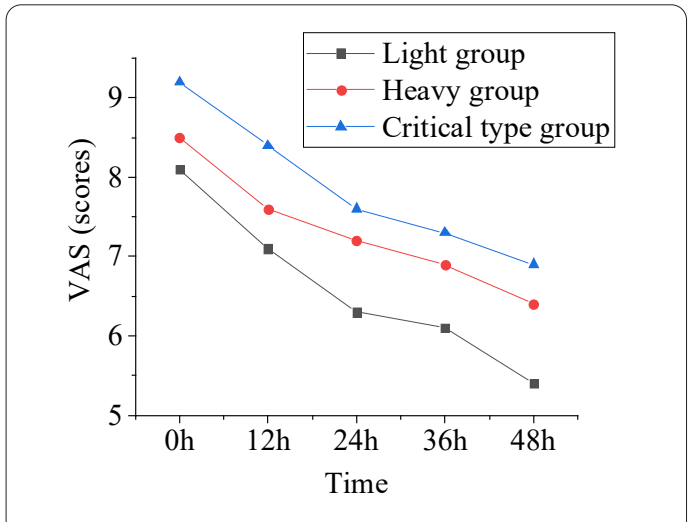

Figure 1. Visual analog pain (VAS) scores among the three groups.

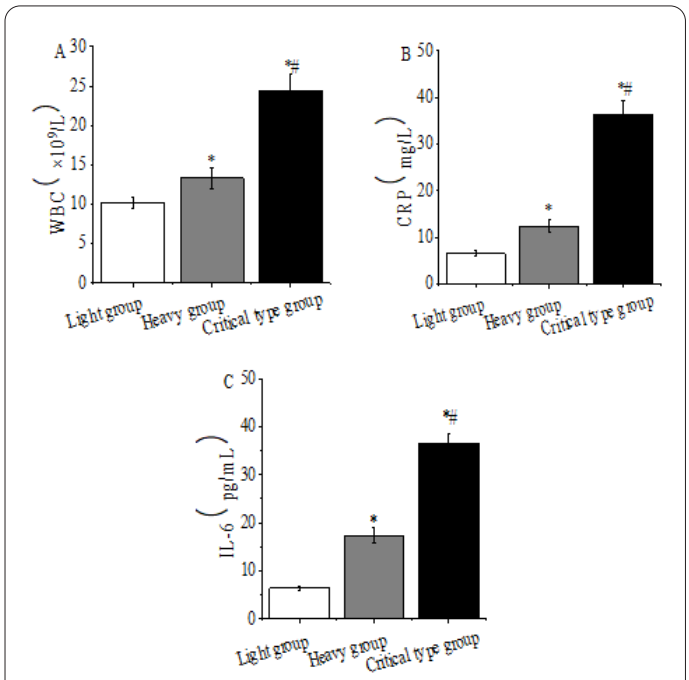

Figure 2. WBC, CRP, and IL-6 in the three groups of patients. A, B, and C: comparisons of WBC, CRP, and IL-6, respectively. Note: * and # meant $P < 0.05$ compared with the light group and the heavy group, respectively.

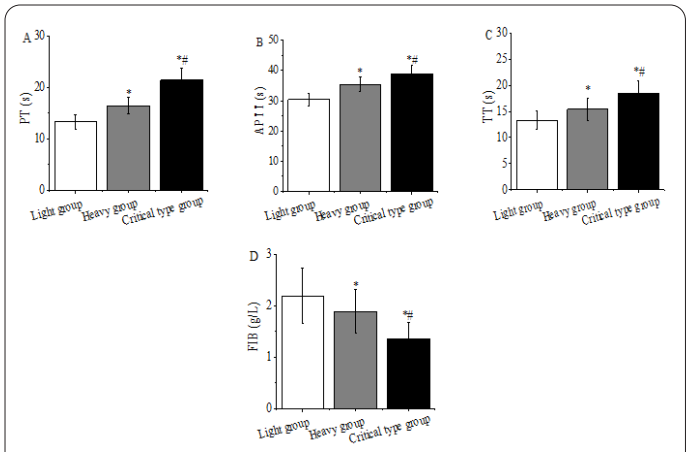

Figure 3. Changes in coagulation indexes in each group. A: PT; B: APTT; C: TT; D: FIB. Note: compared with the light group, *$P< 0.05$; compared with the heavy group, the difference was considerable #$P<0.05$.

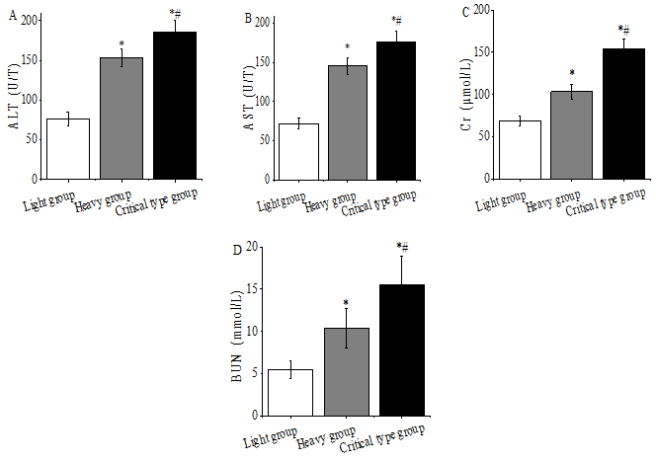

Figure 4. Comparison of liver and kidney function among the three groups of patients. A: ALT (alt); B: AST; C: BUN; D: Cr. Note: *: $P < 0.05$ compared with the light group; #: $P < 0.05$ to the heavy group.

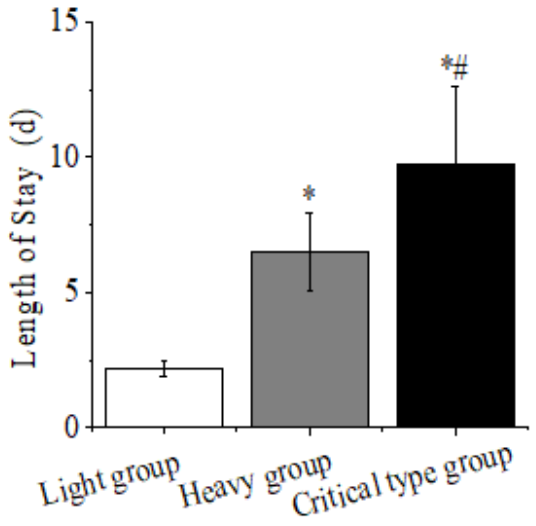

Figure 5. Comparison of hospitalization time between the two groups. Note: *: $P < 0.05$ compared with the light group; #: $P < 0.05$ to the heavy group.

Discussion

There are more than 50 kinds of venomous snakes in China. In subtropical climate areas, plant growth is dense, which is very suitable for the growth and reproduction of venomous snakes, and the number of patients bitten by venomous snakes is up to 100,000 per year (21-23). Venoms from venomous snake bites rapidly enter the blood circulation and spread mainly through lymphatic absorption, resulting in rapid onset and severe respiratory failure, circulatory failure, liver and kidney failure and even death in a short period of time. Absorption is characterized by rapid absorption in the early stage and slow absorption in the later stage (24). The refined antivenomous snake serum has antigenic specificity and is injected into the human body by intravenous drip. Allergic reactions occur between antigens and antibodies. During this period, attention should be given to the prevention of anaphylactic shock.

Studies have shown that inflammation increases the disability rate of snakebite patients. White blood cell count, as a sensitive index in the inflammatory response, is easy to measure and can reflect the development and progress of the disease. The content of CRP in the serum of healthy people is low. As an acute time-phase reaction protein produced by hepatocytes, the content of CRP increases immediately when tissue injury or infection occurs (25). IL-6 exerts a key role in the inflammatory response and immune regulation. It can directly affect the function of T and B lymphocytes and promote the production of CRP (26). The results showed that the WBC, CRP, and IL-6 levels in the light group were the lowest ($P< 0.05$); while those in the critical group were the highest, and the differences were statistically great ($P< 0.05$). This result was in line with the research results of Nina-Cueva et al. (2020) (27). This finding indicates that the higher the WBC, CRP, and IL-6 levels are, the more severe the inflammatory response of patients with increasing severity. After the snake bite, the tissue cells of the patient were severely damaged, which stimulated the activation of monocytes and macrophages, released a large amount of IL-6, and induced the synthesis of CRP. With the aggravation of severity, the level of CRP increased. Therefore, the WBC, CRP, and IL-6 levels should be closely monitored when patients are admitted to the hospital to evaluate the severity of the disease as early as possible and provide a reference for clinical treatment.

Snakebite patients have physiological disorders, especially abnormal blood coagulation systems, and even diffuse intravascular coagulation syndrome. In clinical practice, PT, TT, APTT, and FIB are commonly used to detect coagulation functions to check for coagulation disorders in the human body. The results in this work showed that the PT, APTT, and TT of the heavy group and the critical group were longer ($P< 0.05$), and those in the heavy group were the longest among the three groups ($P < 0.05$). The FIB levels of the critical group and heavy group were lower ($P< 0.05$), and that in the critical group was the lowest after comparison ($P< 0.05$). This result was consistent with the research results of Sarkar et al. (2021) (28). The more severe the disease, the more severe the coagulopathy. Toxic substances such as thrombin and plasmin in snake venom enter the blood of patients, which increases the content of coagulation factors, reduces the content of FIB, and increases PT, APTT, and TT. With the gradual aggravation of poisoning, the balance of the coagulation system of patients was destroyed, and the degree of wound bleeding was aggravated and even caused diffuse intravascular coagulation. Therefore, attention should be given to correcting the abnormal balance of the coagulation system in the treatment of snakebites to improve the prognosis of patients.

The liver is an important detoxifying organ of the human body. Poisonous snake bites may cause substantial damage to stem cells and increase the burden on the liver. Important indicators of liver function include ALT and AST. At the same time, snake venom can cause abnormalities in renal tubular cells in the kidneys, leading to kidney failure. The results showed that the critical ALT, AST, BUN, and Cr levels in the heavy group were higher and lower than those in the light and critical groups, respectively, and the differences among them were significant ($P < 0.05$). This result was consistent with the research results of Garcia Bonilla et al. (2020) (29). This indicates that with the aggravation of the patient's condition, the degree of liver and kidney function injury is more serious. The hemagglutinin contained in snake venom can coagulate blood, cause the liver and kidney to be in a state of ischemia, aggravate the depth of poisoning of patients, release massive inflammatory mediators, and cause liver and kid-

ney function failure. Therefore, targeted treatment of patients with abnormal liver and kidney function can avoid the aggravation of the disease. It is reported that camellia oil has also been used for snake bites (30, 31).

In summary, patients with snakebites have inflammatory reactions, coagulation dysfunction, and abnormal liver and kidney function. The efficacy of antivenom in the treatment of venomous snake bites was remarkable.

This work focused to evaluate the relationship between serum enzyme changes and the severity of the patient's condition, as well as the mechanism of using antivenomous snake serum in the treatment of venomous snake bites, and to observe its clinical treatment effect, hoping to provide treatment ideas for patients with venomous snake bites. The results showed that patients with snakebites had inflammatory reactions, coagulation dysfunction, and abnormal liver and kidney function. The severity of the patient's condition could be evaluated according to the WBC, inflammatory factors, coagulation function indexes, and liver and kidney function indexes. However, the limitation was that it is a single-center study with insufficient sample size. Moreover, funds and time were limited, and no further monitoring of tumor necrosis factor, speech, oxygen-free radicals, or other indicators was performed. In conclusion, this work pointed out some ideas for the pathogenesis and treatment of snakebites.

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