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Original Article

Significance of detecting oxidative stress and inflammatory response in the treatment of vascular crisis after finger replantation

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Abstract: Objective: To explore the significance of detecting oxidative stress and inflammatory response in the treatment of vascular crisis after finger replantation. Methods: The data of 86 patients with replantation of severed finger were collected. According to whether vascular crisis occurred after the surgery, the patients were divided into crisis group and non-crisis group to analyze the risk factors of vascular crisis. Moreover, all patients with vascular crisis were divided into conservative treatment group (patients cured by conservative treatment) and secondary surgery group (patients treated by surgery again after the failure of conservative treatment). Blood samples of patients from two groups were collected and the changes of serum inflammatory cytokines and markers of oxidative stress response were compared between the two groups when they were admitted to hospital and when vascular crisis occurred. Results: Gender, age, smoking history, ischemic time, cause of injury, plane of division, complete or incomplete severance were related risk factors for vascular crisis after finger replantation. The nitric oxide (NO), malondialdehyde (MDA) and superoxide dismutase (SOD) levels as well as serum inflammatory cytokines interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) contents of patients in the secondary surgery group were higher than that of patients in the conservative treatment group (all $P<0.05$). Conclusion: The occurrence of vascular crisis is a key factor in the failure of finger replantation. The levels of NO, MDA, SOD, IL-6 and TNF-α can be used as important indicators to evaluate the vascular crisis after replantation of severed finger, and can also be used as potential targets for the treatment of vascular crisis after finger replantation, which has great clinical application value.

Keywords: Finger replantation, vascular crisis, oxidative stress response, inflammatory response

Introduction

With the rapid development of global industrialization, various mechanized operations have brought more mechanical injury accidents to the operators while improving production efficiency. Among them, severed finger of hand trauma is the main type of accidents, and the incidence is increasing year by year [1-3]. Although the accelerated advancement of medical technology has improved the success rate of finger replantation, postoperative vascular crisis is still the main influencing factor for the success rate of finger replantation [4, 5]. Therefore, it is of major clinical significance to study the mechanism and treatment of postoperative vascular crisis to improve the success rate of replantation of severed fingers.

Previous studies suggested that gender, age, smoking history, ischemic time, cause of injury, plane of division, complete or incomplete severance were risk factors for vascular crisis after replantation of severed fingers. However, the above conclusions were only based on the patient's own data [6, 7], while few researches have studied the occurrence of vascular crisis after finger replantation from the microscopic conditions of the body. Recent studies have shown that trauma combined with surgery can stimulate and aggravate the local oxidative stress and inflammatory response of the severed finger, thus affecting the vascular function after replantation of severed finger, and finally leading to the occurrence of vascular crisis [8]. There are two treatment methods for vascular crisis, one is conservative treatment and the

other is reoperation after failure of conservative treatment. Whether the degree of oxidative stress and inflammatory response is related to the effect of conservative treatment has never been studied before. In view of this, this study, based on the oxidative stress and inflammatory response of the body, explored the changes and significance of the two in the treatment of vascular crisis after replantation of severed fingers, with a hope to provide new theoretical basis and possible intervention targets for improving the success rate of finger replantation in clinical practice.

Materials and methods

The general information

Clinical data of 86 patients with severed finger and treated with finger replantation during August 2016 to August 2018 were collected in this case-control study. According to whether vascular crisis occurred after surgery, they were divided into crisis group and non-crisis group, including 28 cases in crisis group and 58 cases in non-crisis group. The risk factors of crisis were explored by comparing the preoperative baseline data of the two groups. Besides, all patients with postoperative vascular crisis were divided into conservative treatment group (patients cured by conservative treatment) and secondary surgery group (patients treated by surgery again after the failure of conservative treatment) according to the therapeutic effect of conservative treatment, including 10 cases in the conservative treatment group and 18 cases in the secondary surgery group.

Inclusion criteria: Patients with simple severed fingers, and all severed fingers were kept dry and eligible for replantation; patients who were admitted to hospital within six hours of being injured; patients who were 20 to 75 years old. Exclusion criteria: Patients who were pregnant; patients with past history of mental illness; patients with poor compliance; patients with past history of peripheral vascular disease; patients with other major organ dysfunction; patients with coagulation dysfunction; patients with malignant tumor; patients who lacked complete clinical data. This study was approved by the Ethics Committee of Zhongshan Hospital of Traditional Chinese Medicine.

Surgical treatment methods

All patients underwent replantation of severed fingers under brachial plexus anesthesia. The surgical procedures included thorough debridement of the injured fingers, exploration and separation of blood vessels, nerves and other tissues, marking of potentially attachable blood vessels and nerves, proper fixation of the severed fingers, and completion of tendon, nerve and arteriovenous anastomosis. After surgery, antibiotics were used for infection prevention, low molecular dextran and aspirin for anticoagulation, and papaverine for anti-vasospasm, which were routinely used for one week.

Evaluation of vascular crisis

The evaluation of vascular crisis of the replanted severed finger started in 2 hours after the surgery. The average time for the diagnosis of vascular crisis of the study subjects in this group was 28.1±13.6 h after surgery. The diagnostic criteria for arterial crisis included pale replanted limbs, disappearance of capillary filling sign, and low tension of finger pulp. The diagnosis of venous crisis included purple color of the replanted limbs and significantly increased tension of finger pulp; after cutting the side of the fingertip, there was dark purple blood flowing out, and later there was bright red blood flowing out; meanwhile, the blood filling of capillary and the finger temperature recovered, but the tension of the finger pulp did not change.

Treatment of vascular crisis

The treatment of arterial crisis was mainly to relieve arterial spasm. Conservative treatment methods included intramuscular injection of 30 mg of papaverine on both sides of the root of the severed finger, combined with moderate analgesic methods. Emergency surgical exploration was conducted after 1 hour of conservative treatment if the symptoms of arterial spasm and ischemia were not alleviated or even aggravated. The treatment of venous crisis mainly included the immediate replacement of dressings and removal of partial sutures to relieve the compression. If there was no relief, it was necessary to bleed on the side of the fingertip and inject heparin intramuscularly. If there was still no improvement, a secondary surgery was timely performed [9].

Detection method for each related factor

When all patients were admitted to the hospital, and when patients were diagnosed with postoperative vascular crisis, their peripheral venous blood was extracted into anticoagulant

Table 1. Comparison of baseline data

Group	Crisis group (n=28)	Non-crisis group (n=58)	t/χ^2	P
Gender (n)			4.846	0.028
Male	23	32		
Female	5	26		
Age (year)	56.5±3.2	47.8±2.9	12.603	<0.001
Smoking history	20	19	9.887	0.002
Ischemic time (h)	5.06±1.03	4.25±0.89	3.775	<0.001
Finger			2.886	0.577
Thumb	7	14		
Index finger	9	11		
Middle finger	4	16		
Ring finger	3	10		
Little finger	5	7		
Cause of injury			12.796	0.002
Sharp injury	16	11		
Blunt injury	10	40		
Crush injury	2	7		
Plane of division			4.991	0.025
Distal phalanx	20	25		
Other	8	33		
Complete severance			4.285	0.038
Yes	17	20		
No	11	38		

Table 2. Comparison of postoperative data

Category	Crisis group (n=28)	Non-crisis group (n=58)	t/χ^2	P
Time of crisis (h)	28.1±13.6			
Arterial crisis (n, %)	16 (57.14)			
Venous crisis (n, %)	12 (42.86)			
VAS scores	5.67±1.32	5.01±1.15	2.376	0.020
Survival cases (n, %)	19 (67.86)	58 (100)	33.075	<0.001

tube with a volume of about 5-7 mL, then centrifuged at a speed of 3,000 r/min for 10 min. Supernatant was taken and stored at -80°C for later use. The serum levels of IL-6 and TNF-α were detected using an enzyme-linked immunosorbent assay kit (Infinite F50, Tecan, Switzerland; kit, Santa Inc., USA), and the specific operation method was in accordance with the kit method. The content of superoxide dismutase (SOD) was determined by chemical colorimetry, nitric oxide (NO), was determined by nitrate reductase method, and malondialdehyde (MDA) was determined by thiobarbituric acid method.

Scoring of pain degree

Visual analogue scale (VAS) was used to evaluate the degree of postoperative pain in the two groups at 24 hours [10].

Statistical analysis

All data were analyzed by SPSS20.0 statistical analysis software. The measurement data were expressed as mean ± standard deviation ($\bar{x}$ ± sd). The independent t test was used for comparison between the groups, and paired t test was used for intra-group before-after comparison. The count data were tested by the χ^2 test. P<0.05 was considered as statistically significant.

Results

Comparison of baseline data

There were statistically significant differences between the crisis group and the non-crisis group in terms of gender, age, smoking history, ischemic time, plane of division, cause of injury and complete or incomplete severance (all P<0.05), which confirmed that the above factors were the risk factors of vascular crisis after replantation of severed finger. See **Table 1**.

Postoperative VAS pain scores of patients in both groups and the outcome of patients in the crisis group

The postoperative pain scores of patients in the crisis group were higher than those in the non-crisis group (P<0.05). In addition, the survival rate of the non-crisis group was higher than that of the crisis group (P<0.05), indicating that postoperative vascular crisis was an important factor affecting the survival after replantation of severed finger. See **Table 2** for details. After treatment, 19 patients survived in the crisis group, while all patients survived in the non-crisis group.

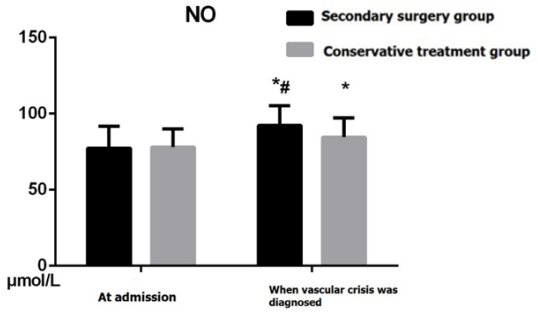

Figure 1. The comparison of NO serum levels. Compared with the level at admission, *P<0.05. Secondary surgery group compared with conservative treatment group, #P<0.05. NO, nitric oxide.

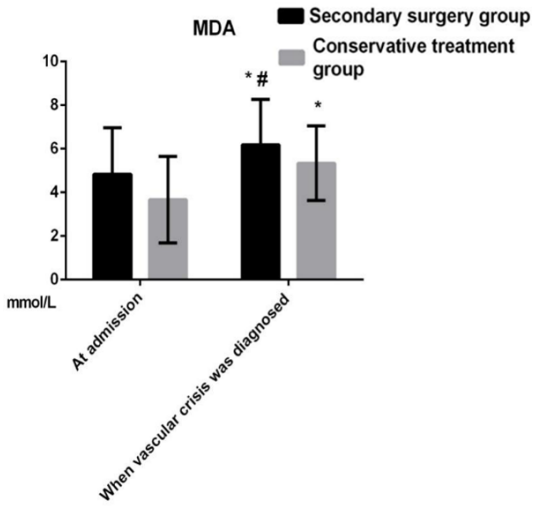

Figure 2. The comparison of MDA serum levels. Compared with the level at admission, *P<0.05. Secondary surgery group compared with conservative treatment group, #P<0.05. MDA, malondialdehyde.

Comparison of serum NO and MDA levels in patients with vascular crisis

Among the 28 patients in the crisis group, 10 patients were cured by conservative treatment and survived, while 18 patients underwent secondary surgery after failing to respond to conservative treatment and finally 9 patients survived, so 19 patients survived together in the crisis group.

The oxidative stress response indicators of patients in the conservative treatment group were compared with those in the secondary surgery group. The results showed that there were no significant differences in serum NO and MDA levels between the two groups at admission (P>0.05). However, when vascular crisis occurred after the first operation, serum NO and MDA levels in the two groups increased compared with those before the operation, and the levels of serum NO and MDA were higher in the secondary surgery group (P<0.05), indicating that the oxidative stress response of patients failing to respond to conservative treatment was stronger than that of patients who effectively responded to conservative treatment, as shown in **Figures 1** and **2**.

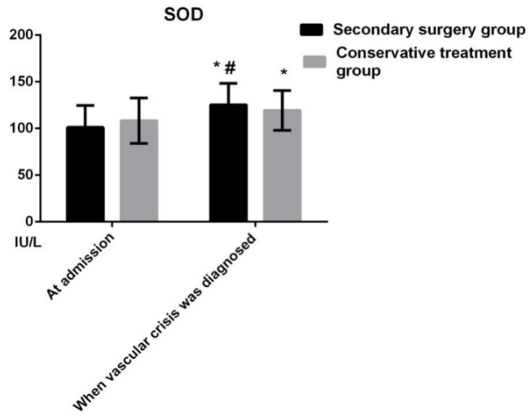

Figure 3. The comparison of SOD serum levels. Compared with the level at admission, *P<0.05. Secondary surgery group compared with conservative treatment group, #P<0.05. SOD, superoxide dismutase.

Comparison of serum SOD level in patients with vascular crisis

There were no significant differences in serum SOD levels between the two groups at admission (P>0.05). When vascular crisis occurred after the first operation, serum SOD levels in the two groups increased compared with those before the operation, and the level of serum SOD was higher in the secondary surgery group (P<0.05), indicating that the antioxidant capacity of patients in the secondary surgery group was stronger than that in the conservative treatment group, as shown in **Figure 3**.

Comparison of serum IL-6 and TNF-α level in patients with vascular crisis

There were no significant differences in serum inflammatory factors IL-6 and TNF-α between the two groups at admission (P>0.05). However, when vascular crisis occurred after the first operation, serum inflammatory factors IL-6 and TNF-α in the two groups were increased com-

Table 3. Comparison of inflammatory response

Group	Conservative treatment group	Secondary surgery group	t	P
IL-6 (ng/L)				
At admission	25.57±4.28	25.01±4.11	0.584	0.561
When Vascular crisis occurred	30.07±2.54*	36.88±2.69*	11.420	<0.001
TNF-α (ng/L)				
At admission	36.54±5.76	36.37±5.40	0.134	0.894
When Vascular crisis occurred	45.33±4.08*	51.08±4.71*	5.821	<0.001

Note: IL-6: interleukin-6; TNF-α: tumor necrosis factor-α. Compared with the level at admission, *P<0.05.

pared with those before the operation, and their levels were higher in the secondary surgery group (P<0.05), indicating that the inflammatory response of patients in the secondary surgery group was stronger than that of patients in the conservative treatment group, as shown in **Table 3**.

Discussion

Fingers are one of the tissues with high precision in human organs, as a result, replantation of severed finger is of great clinical significance for patients' long-term quality of life [11]. With the rapid advancement of vascular and nerve anastomosis technology, though replantation of severed fingers is a highly accurate and meticulous operation, most of the severed fingers can be basically replanted at present [12, 13]. Therefore, the survival of the limbs after replantation is an important guarantee to further improve the level of diagnosis and treatment of finger replantation.

Vascular crisis is a vital factor affecting the success of replantation, and its pathophysiological basis is the dysfunction of connected blood vessels, which leads to the failure of replantation. This study confirmed that age, male, smoking history, and injury status were risk factors for vascular crisis. In addition, this study also proved that local oxidative stress and inflammatory reaction of replanted vessels were risk factors for vascular crisis after replantation of severed finger and a crucial reason for failure of conservative treatment for vascular crisis.

After vascular replantation, due to vascular fracture and re-suture, as well as surgical stress and other factors, the local oxidative stress substances NO and MDA in the blood vessels were increased. The above two substances directly damaged the vascular endothelial cells, and then caused the formation of vasospasm or local thrombosis, ultimately leading to the failure of conservative treatment for vascular crisis, which was consistent with previous research results [14, 15].

The body fights against oxidative stress by eliminating oxidative stress products in time through SOD in the body, so the change of its content reflects the oxidative stress response level of the body from the side. That is, the increase of SOD level indicates the degree of oxidative stress response. The results of this study also showed that SOD content of patients in the secondary surgery group was higher than that in the conservative treatment group, indicating that the increase in SOD content would foreshadow the failure of conservative treatment for vascular crisis [16, 17].

The mechanical injury of blood vessels and the operation process can cause local inflammatory reactions of blood vessels, such as the adhesion and aggregation of white blood cells, excessive synthesis of extracellular matrix, platelet activation and so on. Local inflammatory factors were released due to traumatic stress, mainly including IL-6 and TNF-α, the former mediated the inflammatory response, while the latter induced the inflammatory response [18, 19]. And the local inflammatory response of the blood vessel of replanted severed finger eventually caused platelet aggregation to further trigger the formation of thrombosis or vasospasm. The results of this study also showed that the level of inflammatory response in the body of patients in the secondary surgery group was higher than that of patients in the conservative treatment group, further confirming that inflammatory response played an important role in the potential mechanism of failure of conservative treatment for vascular crisis, and similar conclusions had been reached in previous studies [20, 21].

In conclusion, this study confirmed that oxidative stress and inflammatory response are important risk factors for the failure of conservative treatment for vascular crisis after replantation of severed finger, and the above two tests have certain predictive effects on evaluating the postoperative risk of patients and the effectiveness of conservative treatment. In addition, the above two research objectives can also be used as potential targets for clinical treatment of vascular crisis, which is of great significance for improving the survival rate of finger replantation in clinical practice [22, 23]. However, this study was a single-center study and the sample size was small, of which the results should be further confirmed by multi-center prospective randomized controlled studies with large samples.

Disclosure of conflict of interest

None.

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