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Original Article

The combination of a local injection of insulin and vacuum sealing drainage in patients with diabetic foot disease

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Abstract: Objective: To investigate the effect of a local injection of insulin in combination with vacuum sealing drainage (VSD) in patients with diabetic foot disease. Methods: A total of 98 patients with diabetic foot disease were randomly assigned to an observation group or a control group, with 49 patients in each group. The patients in the control group were assigned to VSD, and those in the observation group were given a local injection of insulin in addition to the treatment received by those in the control group. The clinical therapeutic effects of the regimens were compared between the two groups. The degree of granulation tissue regeneration was observed in both groups. The levels of insulin-like growth factor 1 (IGF1), serum inflammatory cytokines, oxidative stress, and the activities of lactate dehydrogenase (LDH) and succinate dehydrogenase (SDH) in the granulation tissues were measured and compared between the two groups. Results: After treatment, the effective rates and the degree of granulation tissue regeneration were significantly higher in the observation group than they were in the control group (both $P<0.05$); the levels of IGF1, vascular endothelial growth factor (VEGF), total antioxidant capacity (TAC) of serum, catalase (CAT), and SDH were significantly elevated in both groups (all $P<0.001$), with significantly higher levels of the markers in the observation group (all $P<0.001$); in contrast, the levels of interleukin 6 (IL-6), malondialdehyde (MDA), and LDH in both groups were reduced considerably (all $P<0.001$), with substantially lower levels in the observation group (all $P<0.001$). Conclusion: Conventional VSD and a concomitant local injection of insulin improved the clinical manifestations, reduced the inflammatory reaction, and promoted the regeneration of granulation tissues in patients with diabetic foot disease. Thus, it is worthy of generalization in clinical practice.

Keywords: Insulin, vacuum sealing drainage, diabetic foot disease, granulation tissue, therapeutic effect

Introduction

Diabetic foot disease, a major contributor of which is the disorder of glucose metabolism in the body, is jointly caused by factors such as neuropathy in the lower extremities, vascular disease, and infections. The clinical symptoms of the disease primarily include muscular atrophy and limited motor function. If no appropriate treatment measures are taken in time at the onset of diabetic foot disease, the disease is most likely to deteriorate into ulcers or gangrene, or even to the point of requiring an amputation. This may seriously affect the patients' physical and mental health as well as their families' quality of life [1, 2]. However, there are no specific regimens for the treatment of diabetic foot disease in clinical practice. Vacuum sealing drainage (VSD), a widely-used drainage technique, has played a role in the treatment of many refractory wounds in recent years [3]. A previous study found that a local injection of insulin improves the clinical symptoms of diabetic foot disease, reduces the inflammatory response, and promotes healing of the wounds [4]. Nevertheless, there are no clinical studies on the effect of the addition of local insulin therapy to VSD on insulin-like growth factor-1 (IGF1) and oxidative stress in patients with diabetic foot disease. Hence, the current study was designed to explore the therapeutic efficacy of insulin in combination with

VSD in patients with diabetic foot disease and the combination's effects on granulation tissue regeneration, IGF1, and oxidative stress in such patients. The results of the study are presented in the following sections.

Materials and methods

General information

A total of 98 patients with diabetic foot disease admitted to our hospital from January 2018 to July 2019 were recruited for this study. They were randomly assigned to the observation group or the control group, and 49 patients were in each group.

Inclusion criteria: Patients who met all the following conditions were eligible to participate in the study: patients who met the diagnostic criteria for diabetic foot disease developed by the American Diabetes Association in 2010, and they were initially given the combined treatment of a local insulin injection and VSD, had no contraindications, had Grade 2-3 diabetic foot ulcers according to Wagner's classification, were 50-58 years of age, and achieved good glycemic control without fluctuation [5].

Exclusion criteria: Patients who met any of the following conditions were excluded from the study: premature withdrawal from the study, failure to follow the doctor's instructions, poor compliance, severe complications related to diabetes mellitus, malignant tumors, other endocrine disorders, necrosis in the affected foot (or feet), cognitive impairment, or the inability to communicate. This study was approved by the Medical Ethics Committee of our hospital, and the patients signed written informed consents.

Methods

The measures including glycemic control and dietary adjustment (not eating foods with high sugar and glucose) were initially taken by the patients in both groups. For the patients in the control group, VSD alone was performed. The specific procedures were as follows: the insulin dosage was calculated according to the actual conditions of the patients, and a subcutaneous injection of Novolin 30R was administered in the abdomen twice a day. In addition, a thorough cleaning was given to the wounds and the surroundings (including devitalized tissues and pus), and then the dressings were cut to match the area of the wounds. The negative pressure source was connected, the dressings were placed onto the wound surface, and then VSD was performed. The parameters for the equipment were adjusted to 125-450 mmHg. VSD was effective if the dressings were observed to be sunken and hardened. At 48 hours, the wounds were washed with 0.9% NaCl solution under negative pressure. The flow rate was set to 40 mL/h. The treatment lasted for 48 consecutive hours. The exudation and granulation tissues under the dressings were observed 7 days after the drainage. In addition to the above-mentioned treatment assigned to the patients in the control group, those in the observation group also received a local injection of Novolin 30R [6]: the dosage of insulin was calculated based on the actual conditions of each patient. Of all the doses for each patient, 50% of insulin was injected subcutaneously in the abdomen, and the remaining 50% was diluted with 0.9% NaCl solution and then injected twice a day into the peripheral skin of the wounds, enabling the injected mixture to penetrate as close to the wounds as much as possible. All the patients in both groups received three, 4-day cycles of treatment.

The outcome measures and the assessment of the clinical efficacy

At the completion of the three cycles, the patients' clinical therapeutic effects were tested and compared between the two groups by the specialists. A diabetic foot was considered cured if the ulcer healed completely compared to what it was like before the treatment, and if dressing changes were not required; treatment for a diabetic foot was considered extremely effective if the ulcer area after the treatment was reduced by 50% compared with what it was like before the treatment, the healthy growth of the peripheral skin and the regeneration of granulation tissues were observed, and regular dressing changes were also required; treatment for a diabetic foot was considered effective if the ulcer area after the treatment was reduced by no more than 50% compared with what it was like before the treatment, and new granulation tissues grew healthily, but reg-

Table 1. Comparison of the clinical data of the two groups

Group	Observation group (n=49)	Control group (n=49)	t/χ^2	P
Gender (n/%)			0.164	0.686
Male	25/51.02	27/55.10		
Female	24/48.98	22/44.90		
Age (year)	53.4±2.3	52.7±2.5	1.442	0.152
Mean course of diabetic foot disease (month)	7.2±0.2	7.3±0.1	1.963	0.053
Wagner grade (n/%)			0.391	0.531
Grade 2	17/34.69	20/40.82		
Grade 3	32/65.31	29/59.18		
Glycated hemoglobin (%)	8.38±0.71	8.27±0.73	0.756	0.451
Serum albumin (g/L)	32.19±7.85	33.02±7.67	0.529	0.598

ular dressing changes were still required; treatment for a diabetic foot was considered ineffective if the ulcer was not improved, and no new granulation tissues were observed. The formula for calculating the effective rate was: Effective rate = (Cure + Extremely effective + effective) cases/Total cases × 100%. The degree of granulation tissue regeneration was assessed by drawing the wounds on transparent graph paper and then the degree was calculated as follows: Degree of granulation tissue regeneration = Area covered by new granulation tissues/Total wound area * 100%.

From each patient in the two groups 5 mL of fasting venous blood was collected before the treatment and at Cycle 3, respectively. After serum isolation, the supernatant was collected and stored at -20°C for measurement. The changes in the IGF1 levels were tested and compared between the two groups. The tests were performed strictly in accordance with the kits' instruction manuals (Wuhan Bosk Bioengineering Co., Ltd., China). The levels of interleukin 6 (IL-6) and vascular endothelial growth factor (VEGF) were measured with the use of an enzyme-linked immunosorbent assay (ELISA). The assays were conducted strictly according to the kits' instruction manuals (Jiangsu Baolai Biotechnology, China). The markers for oxidative stress response, including the total antioxidant capacity (TAC) of the serum, catalase (CAT), and malondialdehyde (MDA) in both groups were determined using ELISA. The procedures were performed strictly in accordance with the kits' instruction manuals (Wuhan Bosk Bioengineering Co., Ltd., China). The granulation tissues which had been collected from the center of the patients' wound surfaces in both groups were stored in liquid nitrogen and were measured and compared before the treatment and at Cycle 3, respectively. The granulation tissues were ground, to which some phosphate buffered saline (PBS) was added and mixed fully. The mixture was put into a centrifuge and centrifuged at 2,500 r/min for 20 min. After centrifugation, the supernatant was collected. The changes in the lactate dehydrogenase (LDH) and succinate dehydrogenase (SDH) levels were determined with the use of ELISA. The assays were performed strictly following the kits' instruction manuals (Shanghai Xinyu Biotechnology Co., Ltd., China).

Statistical analysis

The study data were statistically analyzed using the SPSS software, version 20.0. The measurement data were expressed as the means ± standard deviations ($\bar{X} \pm s$). Comparisons of the measurement data before and after treatment were made using paired t tests, and the between-group comparisons were performed with the use of independent t tests, represented by t. The count data were represented by number of cases/percentage (n/%), measured by a chi square test, and represented by chi square. The differences were statistically significant at a level of P<0.05.

Results

Comparison of the clinical data between the two groups

No significant differences were observed between the two groups in terms of the major clinical data (gender, age, mean course of diabetic foot disease, Wagner grade, glycated hemoglobin and serum albumin) at baseline (all P>0.05; **Table 1**).

Table 2. Comparison of the clinical efficacy in the two groups

Group	Cure (n)	Extremely effective (n)	Effective (n)	Ineffective (n)	Effective rate (n, %)
Observation group (n=49)	10	22	12	5	44 (89.80)
Control group (n=49)	5	18	13	13	36 (73.47)
χ^2					4.356
P					0.037

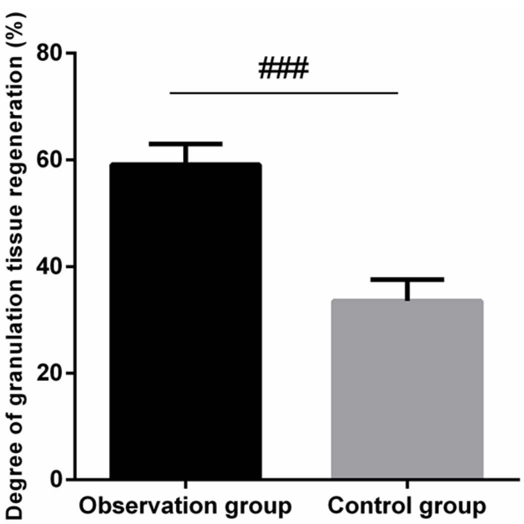

Figure 1. Comparison of the degree of granulation tissue regeneration between the two groups after treatment.

Comparison of the clinical efficacy between the two groups

The effective rate in the observation group was significantly higher than it was in the control group, and the difference was significant between the two groups (P<0.05; **Table 2**).

Comparison of the degree of granulation tissue regeneration between the two groups after the treatment

The degree of granulation tissue regeneration was (59.11±3.87)% in the observation group and (33.54±4.02)% in the control group. The degree of granulation tissue regeneration was significantly higher in the observation group, and the difference was significant (P<0.001; **Figure 1**).

Changes in the IGF1 levels in the two groups before and after treatment

There were no significant differences in the IGF1 levels between the two groups before treatment (P>0.05). The IGF1 levels of both groups rose more significantly after the treatment than they did before the treatment (P<0.001), with a significantly higher IGF1 level in the observation group (P<0.001; **Table 3**).

Comparison of the inflammatory cytokine levels between the two groups before and after treatment

The statistical comparisons between the two groups before treatment showed no significant differences in the levels of inflammatory cytokines (All P>0.05). After treatment, the IL-6 levels in both groups were significantly lower (P<0.001), but the VEGF levels were significantly higher (P<0.001), and the differences between the two groups were significant (P<0.001; **Table 4**).

Comparison of the oxidative stress between the two groups before and after treatment

The statistical comparisons between the two groups before treatment demonstrated no significant differences in the levels of markers for oxidative stress (All P>0.05). After the treatment, the MDA levels in both groups were significantly lower (P<0.001), but the TAC and CAT levels were significantly higher (P<0.001), and the two groups differed significantly (P<0.001; **Table 5**).

Comparison of LDH and SDH in granulation tissues in the center of the wound surface between the two groups before and after treatment

The statistical comparisons between the two groups before treatment revealed no significant differences in the levels of LDH and SDH in the granulation tissues in the centers of the wound surfaces (All P>0.05). After the treatment, the LDH levels in both groups were reduced significantly (P<0.001), but the SDH levels were elevated markedly (P<0.001), and

Table 3. Changes in the IGF1 levels in the two groups before and after the treatment ($\bar{X} \pm s$, ng/mL)

	Observation group (n=49)	Control group (n=49)	t	P
Before treatment	210.44±7.19	211.37±8.02	0.604	0.547
After treatment	337.02±5.44###	297.35±5.13###	37.138	<0.001

Note: ###indicates compared to before treatment group, P<0.001.

Table 4. Comparison of the inflammatory cytokines levels in the two groups before and after treatment ($\bar{X} \pm s$)

	Observation group (n=49)	Control group (n=49)	t	P
IL-6 (pg/mL)				
Before treatment	8.83±1.79	8.81±1.80	0.055	0.956
After treatment	3.28±0.16###	5.01±0.12###	60.550	<0.001
VEGF (pg/mL)				
Before treatment	87.09±5.96	87.10±5.89	0.008	0.993
After treatment	162.44±8.58###	132.44±7.83###	18.079	<0.001

Note: ###indicates compared to the before treatment group, P<0.001.

Table 5. Comparison of the oxidative stress levels in the two groups before and after treatment ($\bar{X} \pm s$)

	Observation group (n=49)	Control group (n=49)	t	P
TAC (U/mL)				
Before treatment	3.68±1.17	3.67±1.20	0.042	0.967
After treatment	8.79±0.93###	5.22±0.38###	24.875	<0.001
CAT (U/mL)				
Before treatment	13.02±2.14	13.01±2.09	0.023	0.981
After treatment	23.44±3.84###	17.35±1.86###	9.991	<0.001
MDA (μmol/L)				
Before treatment	6.74±1.05	6.73±1.02	0.048	0.962
After treatment	4.26±0.88###	5.02±0.65###	4.863	<0.001

Note: ###indicates compared to the before treatment group, P<0.001.

Table 6. Comparison of LDH and SDH in the granulation tissues in the centers of the wound surfaces in the two groups before and after treatment ($\bar{X} \pm s$, U/L)

	Observation group (n=49)	Control group (n=49)	t	P
LDH				
Before treatment	202.11±15.79	202.14±16.04	0.009	0.993
After treatment	125.02±15.20###	154.31±16.55###	9.124	<0.001
SDH				
Before treatment	1.87±0.20	1.86±0.19	0.254	0.800
After treatment	2.88±0.34###	2.50±0.28###	6.039	<0.001

Note: ###indicates compared to the before treatment group, P<0.001.

the two groups differed significantly (P<0.001; **Table 6**).

Discussion

According to the findings of international clinical trials, the amputation rate resulting from diabetic foot disease ranks first among patients with non-traumatic amputation, and the mortality rate of the amputated patients is high-up to 1.0-13.0% [7]. In addition, multiple studies have found that diabetic foot disease, a lesion in the lower extremities caused by multiple factors, may induce progressive foot ulcers, and the wounds are generally refractory [8, 9]. Other clinical studies found that the costs for the treatment of diabetic foot disease account for 20% of the total medical resources in developed countries, including those in Europe and America, while the corresponding costs reach as high as 40% of the total medical resources in developing countries such as India and China, costs which impose a heavy financial burden on the patients and their families [10, 11]. Measures such as the injection of antibiotics and local dressing changes were traditionally done in clinics, but the methods were not effective for some patients. A wide range of studies have shown that VSD significantly improves the microcirculation around the refractory wounds and promotes the regeneration of the granulation tissues [12, 13]. If this method is used alone, however, the hypoxia environment formed by the sealed space decreases the activity of the growth factors, resulting in a reduction in the wounds' healing rates.

It is generally recognized in the medical community that insulin has anti-inflammatory, hypoglycemic, and other effects. Moreover, insulin also plays a certain role in the protection of vascular endothelial cells and the inhibition of platelet aggregation. The findings of some scholars indicate that insulin is active in promoting the healing of the wounds [14]. Local insulin therapy is currently the method used to treat diabetic foot disease, but there is still a need for further consensus on its use and dosage. In the present study, based on the basic injected dose, the insulin doses of each patient in the observation group were divided into halves and used for local injections in the abdomen and the basal wounds, respectively. The results showed that the effective rate in the observation group was significantly higher than it was in the control group, and the degree of granulation tissue regeneration was also considerably greater. This suggests that the addition of local injections of insulin to VSD could significantly improve the patients' therapeutic effect and promote the regeneration of granulation tissues. For patients with diabetic foot ulcers, the body is in a high glucose environment, and an unstable blood glucose level is prone to fluctuate, so the body is in a state of oxidative stress. On the one hand, oxidative stress is closely associated with the pathogenesis of the disease; on the other hand, the resultant oxidative stress injuries also affect the body's other organs, which further delays the repair and healing of tissues and cells [15]. In a study involving the establishment of a diabetic rat model, some scholars found that the oxidative stress response created in the body significantly inhibited the healing of the wounds by releasing oxygen free radicals, promoted the severity of infection in the wounds to some extent, and further prolonged the time it took for the wounds to heal [16]. Moreover, the results of some earlier clinical trials indicate that infection and oxidative stress supplement each other [17, 18]. Inflammation functions as a pathological self-defense reaction in the body, it is in a stress state after the abnormal stimulation, inducing the body to secrete a variety of substances that inactivate the tissues. With the persistence of the above-mentioned process, it significantly reduces the cells' antioxidant capacity, thereby damaging the structure and functions of the proteins. The results of the current study demonstrate that, compared to those before the treatment, after treatment, the MDA levels were reduced significantly in both groups, but the TAC and CAT levels were elevated significantly, and the differences between the two groups were significant; the Il-6 levels decreased remarkably, the VEGF levels were elevated significantly, and the two groups differed significantly. This suggests that the addition of insulin local injection to VSD markedly improves oxidative stress in the body, alleviates inflammation, elevates VEGF levels, and promotes local angiogenesis. It might be attributed to the fact that with an increase in the drug content in the wound area by VSD, the patient's medical absorption improves after washing and drainage, even though the permeability of insulin is limited.

According to previous studies, IGF1, a multifunctional cytokine, effectively inhibits the degradation of muscular protein and reduces blood glucose levels [19, 20]. Also, IGF-1 also promotes angiogenesis and tissue proliferation, and accelerates wound healing. In one study, in the treatment of diabetic patients, the appropriate supplementation of IGF1 helped to maintain the regular circulation of the circulatory system, repair and regenerate damaged cells, and play a positive role in recovery of the patients [21]. In the present study, in order to get a better understanding of the effect of the combined regimen of conventional VSD and the local injection of insulin in patients with diabetic foot disease, the LDH and SDH levels in the granulation tissues were measured. The LDH effectively reflected the anaerobic metabolism ability of the body, and a higher LDH level indicated more severe damage to the body. A lower SDH level suggested the body was in a state of hypoxia. Also, a finding from the present study reveals that, compared with those before treatment, the levels of IGF1 and SDH in both groups were elevated significantly after the treatment, but the LDH levels dropped considerably, and there were significant differences between the two groups. This implies that the combination of a local injection of insulin and VSD significantly improves the levels of IGF1 and promotes granulation tissue regeneration. The reasons might be as follows: on the one hand, the use of VSD results in good control of inflammation, a reduction in the levels of inflammatory cytokines, and a restoration of the IGF1 levels; on the other hand, the local injection of insulin via different approaches significantly improves drug absorption, thereby controlling the progress of the disease. However, the number of samples in the current study was limited. Therefore, more large-scale, multi-centered studies are required to further explore the exact mechanisms of the effect of the combination therapy of the local injection of insulin and VSD on IGF1.

In conclusion, the combined regimen of conventional VSD and the local injection of insulin resulted in a significant improvement in clinical performance, less severe inflammation, and a better regeneration of the granulation tissues in patients with diabetic foot disease. Therefore, it is worthy of clinical generalization.

Disclosure of conflict of interest

None.

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