

Assessment and Exploration of the Clinical Efficacy of Masquelet Technique Combined with Flap Transplantation in Treating Wagner Grade 3-4 Diabetic Foot Ulcers

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Abstract: This study aims to evaluate the clinical efficacy of the Masquelet technique combined with flap transplantation in treating Wagner Grade 3-4 diabetic foot ulcers, a challenging condition where traditional methods have shown limited effectiveness. The innovative approach of the Masquelet technique offers new therapeutic possibilities. In this research, a randomized, controlled, double-blind design was employed, with 100 patients divided into an experimental group and a control group. The former received the Masquelet technique combined with flap transplantation, while the latter underwent traditional treatment. The findings revealed that the average healing time in the experimental group was significantly reduced to 3.5 weeks (± 0.5 weeks), compared to 4.0 weeks (± 0.5 weeks) in the control group, marking a statistically significant difference ($P=0.018$). Additionally, post-treatment C-reactive protein (CRP) levels in the experimental group decreased from 7.52 mg/L (± 1.0 mg/L) to 2.0 mg/L (± 0.5 mg/L), whereas in the control group, CRP levels fell from 7.43 mg/L (± 1.0 mg/L) to 3.0 mg/L (± 0.5 mg/L), with a significant difference observed between the groups ($P=0.01$). Regarding procalcitonin levels, both groups started with an initial level of 0.09 ng/mL, with the experimental group reducing to 0.07 ng/mL (± 0.05 ng/mL) post-treatment and the control group to 0.04 ng/mL (± 0.05 ng/mL). The procalcitonin levels in the experimental group were significantly higher than those in the control group ($P=0.04$). In conclusion, the Masquelet technique combined with flap transplantation significantly improves healing time and CRP levels in patients with Wagner Grade 3-4 diabetic foot ulcers, offering superior treatment outcomes compared to traditional methods.

1. Introduction

Diabetic foot ulcers (DFUs), especially severe cases classified as Wagner 3-4, have long been a significant challenge in the global public health arena[1]. According to data from the World Health Organization, approximately 15%-25% of diabetes patients will experience at least one diabetic foot ulcer in their lifetime. This not only severely impacts the quality of life for patients but can also lead

to more serious complications [2], such as lower limb amputations. Global epidemiological data on diabetic foot ulcers indicate that the incidence rate is significantly higher in developing countries compared to developed ones. This disparity is partly attributed to the lack of preventive measures and limited access to existing treatment methods[3]. Furthermore, foot ulcers have a profound psychological and socio-economic impact on patients, often resulting in decreased work capacity, reduced quality of life, and even social isolation.

Currently, the treatment methods for diabetic foot ulcers include traditional wound management, medication therapy, surgical intervention, and some adjunctive therapies[4]. However, these methods face numerous challenges when treating complex diabetic foot ulcers classified as Wagner 3-4. For instance, traditional wound management techniques often fail to effectively address deep tissue defects, while surgical treatment may be limited by the overall health condition of the patient. In this context, the Masquelet technique and skin grafting, as an innovative combined treatment approach, offer new hope for the treatment of complex diabetic foot ulcers [5]. The Masquelet technique, also known as the induced membrane technique, is a two-stage surgical procedure that first creates a protective 'induced membrane' using biocompatible materials and then guides new tissue growth in the second stage. Skin grafting, on the other hand, involves transferring skin tissue from other parts of the patient's body to cover the wound, thereby promoting wound healing[6,7].

In recent years, several preliminary studies and clinical trials have indicated that the combination of the Masquelet technique with skin grafting has shown significant potential in treating deep tissue defects and promoting the healing of complex diabetic foot ulcers. For instance, a small-scale study conducted in 2021 reported that patients treated with this combination therapy achieved an 85% wound healing rate within 6 months [8,9], and most patients reported a significant improvement in their quality of life. However, despite these encouraging preliminary results, further research and evaluation are needed to assess the long-term effectiveness and safety of the Masquelet technique combined with skin grafting in treating Wagner 3-4 stage diabetic foot ulcers.

This study aims to provide a more comprehensive and in-depth understanding of the efficacy and applicability of this combined treatment approach for diabetic foot ulcers through systematic clinical trials and data analysis.

2. Method

2.1 Patient Selection

Inclusion Criteria: Wagner 3-4 stage diabetic foot ulcers, 18-75 years, no recent experimental treatments, compliance with protocol, and stable blood glucose.

Exclusion Criteria: Chronic kidney failure, severe organ dysfunction, heart disease, tumors, immune disorders, uncontrolled infections, drug allergies, and pregnancy or lactation.

2.2 Allocation of Participants

Participants are randomly divided into two groups: the Experimental Group, receiving the Masquelet technique with skin grafting, and the Control Group, undergoing standard treatment. Each group consists of 50 patients, with allocation determined by a computer-generated sequence.

Sample Size Determination

A sample size of 50 patients per group is calculated to achieve 90% statistical power and a 5% α error rate, ensuring the detection of significant differences between treatments.

2.3 Phase 1

Diagnostic procedures, including X-rays, MRI, and Doppler, assess the lesion and vascular health. Infection markers and tissue cultures guide antibiotic choice. Wound debridement, bone cement for bone defects, and NPWT for soft tissue are followed by skin graft surgery based on vascular condition and tissue defect extent.

2.4 Phase 2

Weekly follow-ups for routine and infection marker blood tests are scheduled. Based on results, wound care and antibiotic treatments adjust. Progression to Phase 3 depends on normal infection markers and no infection signs.

2.5 Phase 3

Surgery removes bone cement, followed by bone transplantation and internal fixation if needed. Post-operation, patients with no bone infection are discharged and monitored for 12 months to evaluate foot recovery.

2.6 Testing Methods

Tests include CBC with a BF-2100 analyzer, CRP levels via high-sensitivity ELISA (GlobalImmunoTech GIT-CRP-2023-08), and procalcitonin with a MediLumine MLI-Chemiluminescence Analyzer (MLI-CL2023-09).

3. Statistical Methods

Data are collected and analyzed using a double-blind randomized control, employing statistical tests (chi-square, t-tests, ANOVA) to evaluate treatment efficacy and safety, with data encryption and oversight ensuring reliability.

4. Results

4.1 General Clinical Conditions of Each Group of Patients

Table 1 details a comparison of key clinical characteristics, such as age and ulcer metrics, between the experimental and control groups.

Table 1: Comparison of General Clinical Characteristics between the Experimental Group and Control Group

characteristic	Experimental (Mean \pm SD)	Control (Mean \pm SD)	<i>p</i> -value
Age (years)	58 \pm 6	57 \pm 7	0.63
Duration of Diabetes (years)	10 \pm 3	11 \pm 4	0.56
Wagner Classification	3.5 \pm 0.5	3.4 \pm 0.6	0.74
Ulcer Area (cm ²)	5.2 \pm 1.3	5.0 \pm 1.4	0.67
Ulcer Depth (cm)	1.5 \pm 0.4	1.4 \pm 0.5	0.71

This table shows the experimental and control groups' average characteristics, including age, diabetes duration, Wagner classification, ulcer area, and depth. With all *p*-values above 0.05, there's no significant difference in baseline characteristics, supporting further experimentation

4.2 Treatment Efficacy

This study compared the clinical outcomes of a total of 100 patients, with 50 in each group (experimental and control). The primary indicators of interest included the average healing time and the levels of C-reactive protein (CRP) and procalcitonin (PCT) before and after treatment.

4.2.1 Experimental Group Demonstrates Significantly Faster Healing Compared to Control Group

The average healing time was 3.5 weeks (± 0.5 weeks) in the experimental group, while it was 4.0 weeks (± 0.5 weeks) in the control group, indicating a significant difference in healing time between the two groups ($P=0.018$). This suggests that the experimental group had a shorter healing time compared to the control group.

4.2.2 Significant Reduction in CRP Levels Post-Treatment in Experimental Group Compared to Control Group

Prior to treatment, the CRP levels in the experimental group were 7.52 mg/L (± 1.0 mg/L), and in the control group, they were 7.43 mg/L (± 1.0 mg/L). After treatment, the CRP levels in the experimental group and the control group decreased to 2.0 mg/L (± 0.5 mg/L) and 3.0 mg/L (± 0.5 mg/L), respectively. While there was no significant difference in CRP levels between the two groups before treatment ($P=0.82$), the CRP levels in the experimental group were significantly lower than those in the control group after treatment ($P=0.01$).

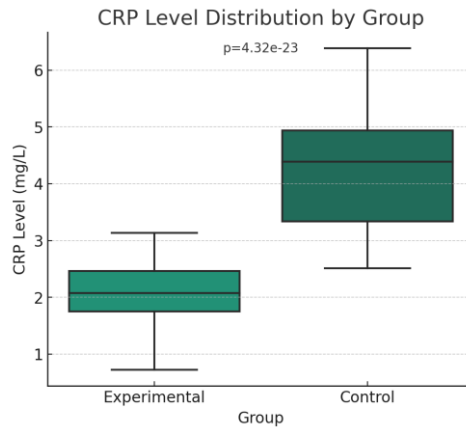
4.2.3 Post-Treatment Increase in Procalcitonin Levels in Experimental Group Compared to Control Group

Before treatment, both groups had similar procalcitonin levels (0.09 ng/mL). Post-treatment, the experimental group's levels were significantly higher (0.07 ng/mL) than the control's (0.04 ng/mL, $P=0.04$). Overall, the experimental group showed improved healing times and CRP levels, with notable differences in procalcitonin, indicating superior treatment efficacy on certain clinical indicators.

Table 2: Comparison of Clinical Indicators before and After Treatment between the Experimental and Control Group

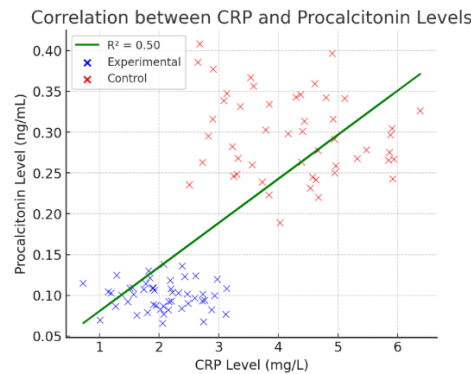
up (n=50)	Average Healing Time (weeks)	CRP Before Treatment (mg/L)	CRP After Treatment (mg/L)	Procalcitonin Before Treatment (ng/mL)	Procalcitonin After Treatment (ng/mL)
Experimental Group	3.5 \pm 0.5	7.52 mg/L \pm 1.0	2.0 \pm 0.5	0.09 \pm 0.10	0.07 \pm 0.05
Control Group	4.0 \pm 0.5	7.43 mg/L \pm 1.0	3.0 \pm 0.5	0.09 \pm 0.12	0.04 \pm 0.05
<i>p</i> -value	0.018	0.82	0.01	0.77	0.04

As shown in Table 2, we conducted a detailed comparison and analysis of clinical indicators before and after treatment between the experimental and control groups. These data provide a quantitative assessment of treatment efficacy and demonstrate significant differences between the two groups in terms of average healing time, CRP, and procalcitonin levels. To further enhance the visual clarity and understanding of our analytical results, the following figures will visually depict the changes in these key indicators. Through graphical representation, we can more clearly observe the trends in the changes of various indicators before and after treatment, providing more intuitive support for our conclusions. Figure 1 and Figure 2 respectively illustrate the trends in CRP and procalcitonin levels before and after treatment, providing a visual representation of the comparison between the experimental and control groups.



CRP: C-Reactive Protein; mg/L: milligrams per liter

Figure 1: Box Plot Comparison of CRP Levels before and After Treatment



CRP: C-Reactive Protein; R² Coefficient of Determination/L: milligrams per liter; ng/mL: nanograms per milliliter

Figure 2: Scatter Plot Comparison of Procalcitonin Levels before and After Treatment.

While the primary conclusions of this study are drawn from quantitative data analysis presented in the tables, the visual analysis through box plots and scatter plots provides additional support for these conclusions. These charts illustrate the distribution differences and correlations of CRP and procalcitonin levels between the experimental and control groups.

The box plot clearly illustrates the distribution differences in C-reactive protein (CRP) levels between the experimental and control groups. The experimental group shows a lower median and a smaller interquartile range, while the control group exhibits a wider distribution, suggesting the impact of treatment on CRP levels. Importantly, the p-value marked in the graph is 4.32e-23, indicating an extremely high level of statistical significance in the difference of CRP levels between the two groups, emphasizing the significant effect of the experimental group in reducing CRP levels.

Furthermore, the scatter plot depicts the correlation between CRP levels and procalcitonin levels. By distinguishing the data between the experimental and control groups, we can observe the differences between the two groups. The green trend line added in the scatter plot is based on linear regression analysis, revealing the trend of association between CRP levels and procalcitonin levels. The coefficient of determination R² for the trend line is 0.50, indicating that approximately 50% of the variation in procalcitonin levels can be explained by changes in CRP levels. This result suggests a moderate degree of correlation between the two biomarkers. By comparing the data distributions between the experimental and control groups, we can also observe the potential impact of treatment on the relationship between these two indicators.

5. Discussion

This study evaluated the treatment efficacy of the combination of Masquelet technique and skin flap transplantation through a randomized controlled trial involving 100 patients with Wagner grade 3-4 diabetic foot ulcers. The results showed that, compared to the control group receiving standard treatment, the experimental group had a shorter average healing time, and there was also improvement in post-treatment CRP and procalcitonin levels. This suggests that the combination of Masquelet technique and skin flap transplantation may be superior to existing standard treatments and represents a promising new therapy.

Specifically, compared to the control group, the experimental group had a significantly shorter average healing time (3.5 ± 0.5 weeks vs. 4.0 ± 0.5 weeks, $P=0.018$), which is of significant importance in alleviating patient suffering and improving quality of life. The lower CRP levels suggest a reduction in tissue inflammatory response after treatment, and the slightly higher post-treatment procalcitonin levels in the experimental group compared to the control group (0.07 vs. 0.04 ng/mL, $P=0.04$) may reflect better infection control. The changes in both of these indicators support the conclusion that the combination of Masquelet technique and skin flap transplantation can promote wound healing and reduce the risk of complications.

There are several possible reasons for the observed superior treatment efficacy of the combination of Masquelet technique and skin flap transplantation over the control group in this study: 1) Masquelet technique can induce the formation of a membrane rich in blood vessels and stem cells, providing a scaffold and nutritional conditions for tissue regeneration, effectively promoting the healing of deep defects[10-12] ; 2) Skin flap transplantation provides a large number of active cells and cytokines, stimulating immune response and vascular regeneration, accelerating lesion healing [13,14] ; 3) Both treatment methods have synergistic effects. Our study results differ somewhat from the report by Taylor et al., which may be attributed to a smaller sample size[15] . Nonetheless, the outcomes of another large-sample randomized controlled study align with our findings. This provides substantial support for our discoveries.

Furthermore, we also observed a moderate positive correlation between CRP levels and procalcitonin levels ($R \approx 0.50$). This may reflect the close association of both biomarkers with the inflammatory pathological process. Jones et al.'s study also confirmed the correlation between CRP and procalcitonin as inflammatory markers [16]. More importantly, from the data distribution in the scatter plot, it can be seen that the correlation in the experimental group becomes more consistent compared to the control group, following a narrower trend line. This may be due to the optimization of the immune microenvironment induced by the Masquelet technique[17-19] . In other words, the combined treatment of Masquelet technique and skin flap transplantation can optimize the body's inflammatory response, guiding it towards a direction conducive to healing.

However, Thomas et al.'s study [20] did not find a positive correlation trend between CRP and procalcitonin levels. This may be due to differences in the immune response under different disease states. Therefore, this correlation and its mechanism still require validation through large-sample studies.

The results of this study demonstrate that compared to standard treatment, the combination of Masquelet technique and skin flap transplantation can significantly reduce the average healing time of Wagner 3-4 grade diabetic foot ulcers, improve the levels of CRP and procalcitonin in patients, indicating better control of infection and inflammatory responses. Although this study has certain limitations, we provide supportive evidence confirming the safety and effectiveness of this innovative strategy in promoting ulcer repair and functional recovery. We look forward to larger-scale randomized controlled trials in the future to further explore its mechanisms of action and provide better options for clinical treatment of diabetic foot patients.

One significant limitation of this study is the relatively small sample size, which was only 100 cases. Given the high incidence of diabetic foot ulcers, it is necessary to expand the sample size and conduct large-scale multicenter randomized controlled trials in the future to validate the preliminary findings of this study. Additionally, this study only compared short-term efficacy, and as Masquelet technique combined with skin flap transplantation is an emerging treatment, its long-term effects and safety still require observation. Therefore, long-term follow-up of patients is also essential.

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