



## Effectiveness of Sucralphate and Platelet-Rich Plasma Combinations for Vascular Endothelial Growth Factor (VEGF) Expression in Diabetic Ulcer Healing

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### Abstract

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**Background :** Diabetic ulcer is one of the most feared chronic infections due to Diabetes Mellitus because it can lead to amputation and death. The aims of this study was to prove the effectiveness of sucralfate and platelet-rich plasma (PRP) combination for Vascular Endothelial Growth Factor (VEGF) expression in diabetic ulcer healing.

**Methods :** This research is an experimental study of Phase I Clinical Trial with post-test only group design. There were 20 patients with diabetic ulcers divided into two groups, namely the treated group that was given sucralfate and PRP therapy and the control group was given standard therapy of normal saline drainage and gauze covered. Parameters were VEGF expression levels, wound area after being given therapy, and side effect from the treatment. Data on VEGF expression levels were obtained by means of examination with the Quantikine Human VEGF-ELISA Quantikine, R&D System, Inc, Minneapolis. The measurement of the wound area was assessed based on several criteria, namely grade 0 (no change), grade 1 (wound size reduced to less than of the previous wound), grade 2 (wound size was reduced to less than of the previous wound, but granulation was visible), and grade 3 (wound has closed completely).

**Results :** In unpaired t-test, the mean VEGF expression was 98.18+10.96 in the treatment group and 66.69+23.79 in the control group which showed significant difference in VEGF expression levels ( $p = 0.003$ ). In Mann-Whitney test, the mean wound area was 0.68+0.40 in the treatment group and 0.77+0.67 in the control group which showed that there was not any significant difference in wound area ( $p = 0.152$ ). There were no side effects in both study group.

**Conclusion :** The combination of sucralfate and PRP can increase VEGF levels significantly in diabetic ulcer patients but does not show a different effect in reducing wound area compared to standard treatment. The combination did not cause any side effects in the study subjects, as well as those using standard treatment.

**Keywords:** sucralfate, platelete-rich plasma topical, VEGF expression, wound area, side effect, diabetic ulcer

## INTRODUCTION

Diabetic ulcer is an injury to all layers of the skin, can be in the form of necrosis or gangrene that can occur in any part of the body, due to peripheral neuropathy or peripheral arterial disease in patients with diabetes mellitus (DM). Diabetic ulcer can be followed by bacterial invasion resulting in infection and decay, especially in the distal lower limbs. Diabetic ulcer can cause disability (amputation) and death.<sup>1,2</sup> The incidence of diabetic ulcer continues to increase worldwide. The study by Leone *et al* estimated that 15% of DM patients will experience complications of diabetic ulcer.<sup>3</sup> The prevalence rate of diabetic foot ulcer differs in each country, but is estimated to be between 4–27% worldwide.<sup>4</sup> The prevalence of diabetic ulcer sufferers in the United States is 15–20%.<sup>5</sup> The data from Dr. Cipto Mangunkusumo showed the mortality rate of DM patients was 16% and the amputation rate due to foot ulcers was 25%.<sup>6</sup> The main goal of diabetic ulcer management is wound closure. Several treatments for diabetic ulcers are debridement, reduction of the burden on the wound area, management of infection and wound care with topical dressings or dressings on the ulcer area.<sup>7</sup> There are various innovative topical dressings to heal diabetic foot ulcers, one of which is sucralfate.<sup>8,9</sup> Study by Nagalakshmi *et al*, showed that topical sucralfate is a more effective modality than conventional dressings and debridement.<sup>10</sup> Sucralfate induces proliferation of dermal fibroblasts and keratinocytes. Sucralfate increases fibroblasts by increasing prostaglandin E2 synthesis in basal keratinocytes, increasing stimulation of interleukin-1 and interleukin-6 release from fibroblasts.<sup>11</sup> Besides sucralfate, platelet-rich plasma (PRP) is another non-invasive technique that can be used to treat diabetic ulcers. Demands for PRP is increasing because of its potential to induce and accelerate tissue healing.<sup>12</sup> PRP is derived from a person's blood, where after centrifugation, a plasma fraction is obtained with a higher concentration of platelets than in circulating blood. Platelets play an important role in the wound healing process because they have hemostatic functions and their cytokines and growth factors. There are several growth factors that are known to be involved in the wound healing process, one of which is vascular endothelial growth factor (VEGF).<sup>13</sup> VEGF plays a role in the process of angiogenesis or neovascularization in the wound healing process.<sup>17</sup> Based on the research by Carter *et al*, the use of PRP in the form of a gel applied to wounds can accelerate wound healing and reduce the incidence of infection in patients.<sup>14</sup> As well as the study by Vilela *et al*, which stated that PRP was clinically proven to give good results in wounds.<sup>15</sup> PRP has also been shown to be safe and efficient in the treatment of diabetic foot ulcers, and provides a faster healing time.<sup>16</sup> In a study conducted by Renni *et al*, regarding the administration of topical

sucralfate and topical Platelet-rich plasma in rats with diabetic ulcers, it was shown that the combination of sucralfate and PRP supported each other to improve wound healing. Sucralfate contributes to the inflammatory phase by inducing prostaglandin E2 thereby increasing wound protection and increasing the production of growth factors in the proliferative phase. Meanwhile, PRP contributes to every phase of wound healing by releasing various growth factors.<sup>18</sup>

Previous studies have shown that the use of sucralfate or platelet-rich plasma can accelerate healing in diabetic ulcers. This study aims to prove the effectiveness of the use of a topical combination of sucralfate and platelet-rich plasma in healing diabetic ulcers using VEGF expression parameter so that it is expected to be used as a new, safer and more efficient alternative modality in the management of diabetic ulcers.

## METHODS

This study is an experimental study of Phase I Clinical Trial with post-test only control group design which was conducted from January to March 2022 at Kariadi Hospital and the Central Laboratory of the Faculty of Medicine, Diponegoro University, Semarang. The research subjects were patients with type 2 diabetes mellitus who were more than 18 years old, diagnosed with Wegner's diabetic ulcers 1 to 2 who visited the Outpatient Room for Skin and Venereal Diseases and Internal Medicine, RSUP Dr. Kariadi Semarang, and willing to participate in the research and fill out the informed consent form.

The research subjects were selected by consecutive sampling, based on the patient's arrival at Kariadi Hospital Semarang who met the criteria until the minimum sample size was met (20 research subjects) they divided into two groups, the treatment group (administered sucralfate and PRP) and the control group who received standard therapy (normal saline drainage, covered with gauze, and antibiotics). Subjects have received written informed consent and ethical clearance form has passed the ethical review of the Health Research Ethics Committee of Kariadi Hospital Semarang with the number: 590/EC/KEPK-RSDK/2020.

Data on VEGF expression levels were obtained by means of examination with the Quantikine Human VEGF-ELISA Quantikine, R&D System, Inc, Minneapolis. The measurement of the wound area was assessed based on several criteria, namely grade 0 (no change), grade 1 (wound size reduced to less than of the previous wound), grade 2 (wound size was reduced to less than of the previous wound, but granulation was visible), and grade 3 (wound has closed completely). Data were analyzed using the Statistical Package for the Social Sciences (SPSS) for Windows version 16 program.

## RESULTS

Table 1 shows the characteristic data and laboratory results for all research subjects.

Table 2 shows the normality test for VEGF data and wound area was carried out using the Saphiro-Wilk test. From the test results, the data on VEGF expression were normally distributed ( $p > 0.05$ ). Meanwhile, in the normality test of wound area, the data was not normally distributed ( $p < 0.05$ ).

Based on the t test, the results showed that the VEGF expression in the treatment group was significantly lower than the control group ( $p = 0.003$ ) (Table 3).

Based on the Mann-Whitney test, the results showed that there was no significant difference in wound

area between the treatment and control groups, and there was no significant reduction in wound area in either the treatment or control groups (Table 4).

## DISCUSSION

The results of this study showed that the combination of sucralphate and PRP succeeded in increasing VEGF levels significantly compared to controls. This study is in line with the research conducted by Yuniati *et al.* regarding the use of sucralphate and topical PRP in the healing process of diabetic ulcers in rats, where the number of macrophages, VEGF, and PDGF levels all increased significantly.<sup>18</sup>

In this study, it was found that there was no significant difference in the area of the wound in the two

TABLE 1  
Characteristics of research subjects

Characteristics	Groups		p value
	Treatment (n=10)	Control (n=10)	
Mean age (years)	52 ± 6.89*	57.20 ± 10.27*	0.200
Sex	Male	4 (40)	0.66
	Female	6 (60)	
Lab Value	Hemoglobin	13.30 ± 1.59*	0.731
	Blood Sugar Level	194.40 ± 42.23*	0.621
	Ureum	34.10 ± 22.32*	0.900
	Creatinin	1.07 ± 0.22*	0.609
	HbA1c	7.29 ± 0.94*	0.210

TABLE 2  
Normality test for VEGF data and wound area

	Statistics	df	Sig.
VEGF	.158	20	.200
Wound Area	.334	20	.000

TABLE 3  
Comparison of mean VEGF levels of the 2 study groups

Categories	Mean VEGF ± SD*		p
	Treatment Group	Control Group	
VEGF After treatment	98.18 ± 10.96	66.69 ± 23.79	0.003*

**TABLE 4**  
**Comparison of the average area of diabetic wounds from the 2 study groups**

Categories	Mean of Wound Area ± SD*		p value
	Treatment Group	Control Group	
Before treatment	2.77 ± 2.03	2.14 ± 2.12	0.325
After treatment	2.09 ± 1.63	1.37 ± 1.45	0.173
p	0,353	0.190	
Difference between before and after treatment	0.68 ± 0.40	0.77 ± 0.67	0.152

study groups. There is slightly different from other studies related to the administration of PRP monotherapy to decrease wound area. In a study conducted by Tripathi *et al*, there was a significant difference in wound area in the PRP-treated group compared to the control group. In the study by Harry *et al*, it was also found that there was a significant difference in the reduction in wound area in the PRP-administered group and the control group. In patients with Wagner grade 1, there was an average reduction in wound area of 33.8% in the PRP-treated group and an average reduction of 18.6% in the control group. Meanwhile, in patients with Wagner grade 2, there was an average reduction in wound area of 31.9% in the PRP group and 19.27% in the control group.<sup>45</sup>

The difference between the results of this study and these studies could be due to the difference in the duration of the research conducted on the research subject, which in this study was carried out for 20 days while the studies varied between 3-4 weeks. This study also used research subjects with variations in Wagner grades I and II wounds and did not differentiate the outcomes based on these grades, which is also a limitation of this study.

### CONCLUSION

The combination of sucralfate and PRP can increase VEGF expression significantly in diabetic ulcer patients but does not show a different effect in reducing wound area compared to standard treatment. The combination did not cause any side effects in the study subjects, as well as those using standard treatment.

### Conflict of interest

The author declares there is no conflict of interest regarding publication of the current study.

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