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Comparison between Platelet Rich Fibrin (PRF) and Hyaluronic Acid cream- Platelet Rich Fibrin (PRF) in topical treatment of diabetic foot base on Image J processing

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ABSTRACT

Background Diabetic foot ulcer (DFU) is a major complication of diabetes mellitus. It has a high potential risk of secondary infection and amputation. Over the recent years, great progress has made in the techniques of wound healing, among which autologous platelet-rich fibrin (PRF) has attracted the most substantial attention. PRF is a platelet and leukocyte concentrate containing several cytokines and growth factors, is known to promote wound healing. Platelets are known to start the wound healing process through the release of locally active growth factor. The evidence from studies of autologous PRF to support its use in wound healing is not robust, and further rigorously designed blinded trials are needed. Hyaluronic acid as an anti-inflammation agent, had used for wound care product. It has promote growth factor release that released by PRF in diabetic foot ulcer care. The aim of the study was to evaluate the efficacy and safety of the combine hyaluronic acid and autologous PRF for diabetic foot ulcer compare with PRF alone therapy.

Patients and Methods The study included 30 patients with diabetic foot ulcers, who were divided into three groups: PRF (PRF group) and combine PRF Hyaluronic Acid cream (PRF-HA group). The PRF group was treated with autologous PRF in gel form as a dressing. The PRF HA group was treated with Combine PRF and Hyaluronic Acid cream as a dressing. Other group is Sodium Chloride 0.9% group that accept only its gausses as topical therapy. The frequency of dressing change for each group was twice weekly. Each wound was treated with routine dressings base his group, whereas the wound was treated for a period of day 3, day 7 and follow up until 14 days. Epithelialization of wound healing rate and granulation index will calculated use Image J.

Results The healing rate of the PRF HA group was found higher than that of the PRF group alone although not significantly. Whether in this study show in granulation index per week of the PRF HA group was significantly higher than that of the PRP group and Sodium Chloride 0.9% (control) .The combination of hyaluronic acid cream with PRF seemed to accelerate skin wound healing in diabetic foot ulcer, probably via stabilization cytokine and growth factor that release by PRF in topical diabetic foot ulcer therapy.

Conclusion Combine PRF Hyaluronic Acid cream is effective and safe for treatment of diabetic foot ulcer. Use of PRF with Hyaluronic Acid cream was associated with significantly improved skin wound healing in diabetic foot ulcer compare with use PRF alone and Sodium Chloride 0.9% (control).

Keywords: diabetic foot ulcer, Hyaluronic Acid Cream, Platelet-Rich Fibrin

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1.Introduction

The increasing number of diabetes mellitus causes an increase in the incidence of diabetes complications, one of which is a wound in the diabetic foot (diabetic foot ulcer). Diabetic foot ulcers (DFU) are chronic wounds where the prolonged wound healing process will disrupt the patient's quality of life, productivity, and life expectancy. This is related to high maintenance costs and is a significant cause of morbidity[1]. There are three factors that support the emergence of diabetic foot, namely neurological disorders, infection, and blood flow disorders. Standard care for chronic wound care by performing an inflammatory balance for chronic ulcers which includes debridement of necrotic tissue, infection control and management of blood glucose1. Complete wound closure with DFU care standards in the form of Sodium Chloride compresses, can take months or even years in some patients. The use of blood derivatives (fibrin, or platelet concentrates known as PRP, platelet-rich plasma) [2] is often recommended in the last 50 years for the treatment of skin wounds as a regenerative treatment in modern medicine [3,4]. Fibrin matrix and platelet components (especially growth factors) become one of the adjuvant therapies in the treatment of skin wounds. PRF therapy is still not widely used because of the complexity and cost of use per application. previous[5]. Platelet Rich Fibrin (PRF) is a second generation platelet concentrate for topical use in wound therapy using autologous blood, which can be obtained quickly and at a low cost and is classified as a family of platelet concentrates different from traditional PRP [6]. PRF is produced from samples small peripheral blood (10 mL per tube), which is immediately centrifuged without any anticoagulation. Coagulation begins during centrifugation, and three parts quickly appear in the tube: the base of red blood cells at the bottom, acellular plasma as a supernatant (platelet-poor plasma), and the PRF clot in between. PRF clot, rich in fibrin, platelets (± 95% of initial blood) and leukocytes (± 50% of initial blood) [7]. The PRF membrane releases growth factors and protein matrix in very large numbers and for a period of time long time (for at least 7 days). In addition, PRF membranes remain intact for more than 7 days in vitro (even more than 28 days in culture) [8], due to the specific polymerization and architecture of the fibrin matrix, and they have several antibacterial effects. In vitro, PRF showed very strong stimulation of the proliferation of all cell lines tested, especially fibroblasts and pre keratinocytes for more than 28 days as a very attractive healing biomaterial for use for coverage of skin wounds, and initial results showed positive effects on chronic ulcer wounds. [9]

This study aims to follow the benefits of the application of a combination of PRF and Hyaluronic Acid Cream compared to the application of topical PRF alone in DFU foot ulcers by measuring changes in wound area and granulation index through J image by noting patient's exclusion of changes in pain levels over time.

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2. Methods

We performed study included 30 patients with diabetic foot ulcers. This is a prospective cohort study were conducted at Koja District Hospital and Gatot Soebroto Central Army Hospital between August 2019 and February 2020. This was an experimental study on humans that compared two treatment groups that is PRF (PRF group), combine PRF Hyaluronic Acid cream (PRF HA group) and control Sodium Chloride 0.9%. The PRF group was treated with autologous PRF in gel form as a gel. The PRF HA group was treated with Combine PRF and Hyaluronic Acid cream as a dressing. Other group is Sodium Chloride 0.9% group as a control that Diabetic Foot Ulcer accept only Sodium Chloride 0.9%. gausses as topical therapy. The frequency of dressing change for each group was twice weekly.

The study protocol was approved by the Health Research Ethics Committee, Faculty of Medicine, Universitas Indonesia-Cipto Mangunkusumo Hospital.

The study also evaluate epithelialization (wound area), granulation index and inflammation reactions (pain, fever, edema, and hyperemia) in diabetic foot wound healing. An clinical symptom evaluation was conducted at days 3, 7, and 14. Photo-analysis also performed use the Image J software by observing macroscopic changes.

Data were analyzed with the Statistical Package for the Social Sciences software version (SPSS; IBM Corporation) 20.0. P values <0.05 were considered significant.

2.1. Selection Criteria

Patients who meet the inclusion criteria are age 18 years, large wounds less than 40 cm^2, There are no signs of infection, hyperemia and tenderness) pressure control when using this therapy. Exclusion criteria were: suboptimal standard wound care, peripheral arterial disease (distal pulse or foot-brachial competition index <0.8 and / or> 1.2), active cancer, pyoderma gangrenous, tissue connections, skin granulomatous disease, mycobacteria or fungal infections, sufferers of chronic kidney failure.

2.2.PRF Preparation

The blood was collected without anticoagulant or a gel separator in plastic-coated glass test tubes (BD Vacutainer tubes for serum 9.0 mL, Milan, Italy), for the production of L-PRF clots and membranes. The blood was collected quickly with a wing 23″ and immediately (within 1

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min) centrifuged at a temperature greater than 21 °C (between 21 and 30 °C) according to the protocol described earlier with acceleration 12 min at 1900 rpm9.10.11.

After the centrifugation, three layers were formed in the tube: the red blood cells at the bottom, a fibrin clot that represents the PRF in the middle, and the acellular plasma at the top. The fibrin clot was extracted from the tube with sterile forceps and the PRF was obtained by removing the red clot from its lower end. The success of this technique depends on the blood collection and the transfer speed in the centrifuge[11]

2.3.PRF Hyaluronic Acid Cream Preparation

The resulting PRF is mixed with Hyaluronic Acid Cream with a ratio of the amount of PRF: Hyaluronic Acid crem is 3: 2. A mixture of PRF and Hyaluronic Acid cream is placed in a 50 cc plastic tube, and mixed using a vortex machine for 30 seconds to produce a homogeneous substance

2.4.Preparation of wounds and application of materials according to the group

Before cleansing the wound, peripheral blood samples are obtained from the forearm veins, with the volume depending on the area of the wound. (20-40 cc). Partial blood was examined for Complete Blood, GDS, HbA1C, Albumin, Ureum Creatinne, SGOT, SGPT as preliminary data. Venous blood obtained was processed into PRF and PRF-HA according to the group. In group 1, the PRF fibrin wadding was applied directly to the wound (Figure 1A). The same was done in group 2 using PRF Hyaluronic Acid Cream. After application, the wound was closed with thin gauze and transparent plastic. The control group used moist gauze moistened with NaCl and covered with transparent plastic to avoid evaporation

At the time of wound control (at 3 daily intervals), the same protocol was repeated. During the visit the patient's wound is gently cleaned through irrigation with Sodium Chloride 0.9% solution to remove all exudates

At the beginning, and at every second and third follow-up visit, digital photographs (camera, CPH type 1933) were made perpendicular to the fixed focus distance of about 10 cm. All ulcer photographs are framed with a calibration sticker scale of 0-10 cm, mounted just outside the wound limit. The resolution of digital photos is at least 300 × 300 dpi (> 900 kb). The ulcer area was calculated using Image J software (Advanced Plan metric Services, NJ, USA).

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In this article, we look at the effect of topical application of PRF combination with Hyaluronic Acid cream compared to topical therapy of PRF alone or standard Sodium Chloride 0.9% therapy. The observed parameters are wound reduction (wound area) and granulation index. Granulation index is obtained from (granulation area: area of wound area) x 100%. The results of the parameters are statistically processed by ANOVA test and Kruskall Wallis as a statistical unit.

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3.Conseptual Framework

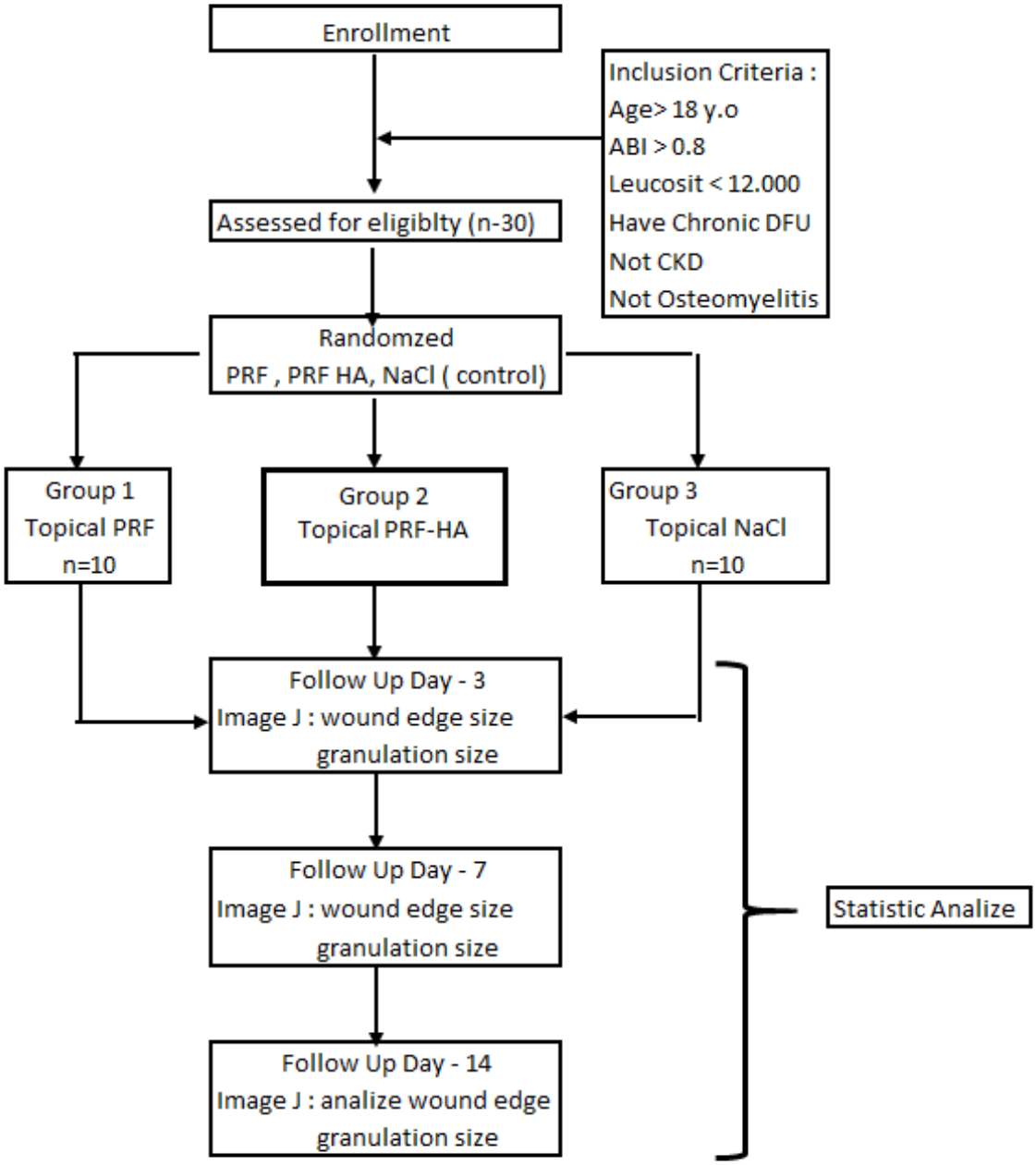

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Table 1. Patient Characteristic

	Group I Topical PRF N= 10	Group II Topical PRF HA N= 10	Group III NaCl (kontrol) N= 10
Sex			
Male	5 (50%)	5 (50%)	3 (30%)
Female	5 (50%)	5 (50%)	7 (70%)
Age			
Mean+ SD	63.6 ± 13.99	62.3 ± 14.79	62.1 ± 13.52
Min	79	80	72
Max	28	28	28
Duration of Diabetes (years)			
Mean+ SD	10.7 ± 3.433	10.9 ± 3.871	10.8 ± 3.359
Min	13	15	13
Max	2	2	2
Comply to take medicine			
Yes	8 (80%)	7 (70%)	9 (90%)
No	2 (20%)	3 (30%)	1 (10%)
Blood Picture			
Hemoglobin			
Mean+ SD	12.36 ± 1.91	12.01 ± 1.39	11.35 ± 1.304
Min	15.8	13.6	12.9
Max	10.1	10.1	9.2
Platelet			
Mean+ SD	230800±145686	250600±149966	513200 ± 82021.41
Min	609000	609000	711000
Max	145000	150000	466000
Blood Sugar			
Mean+ SD	325.4 ± 138.5	252.6 ± 117.07	187.9 ± 57.59716
Min	533	566	300
Max	180	180	115
HbA1C			
Mean+ SD	12.338 ± 1.436275	11.175 ± 1.803584	11.48 ± 1.593598
Min	14.1	13.75	13.1
Max	9.8	8.7	8.9
Albumin			
Mean+ SD	2.92 ± 0.16193	2.91 ± 0.417532	3.02 ± 0.319026
Min	3.2	3.4	3.4
Max	2.7	2.4	2.4

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Tabel 2. Wound Characteritic

	Group I Topical PRF N= 10	Group II Topical PRF - HA N= 10	Group I Topical NaCl N= 10
Wound Location			
Dorsum Pedis	4 (40%)	4(40%)	5 (50%)
Plantar Pedis	2 (20%)	2 (20%)	2 (20%)
Tibial	4 (40%)	4 (40%)	3 (30%)
Initial Wound Area			
Mean+ SD	7.4362 ± 6.252638	10.42 ± 9.155828	6.9482 ± 6.242093
Min	19.757	31.916	20.563
Max	2.282	3.094	1.962

Tabel 3. Index Granulation

	Group I Topical PRF N= 10	Group II Topical PRF - HA N= 10	Group I Topical NaCl N= 10	p
Index Granulation Day 0				
Mean+ SD	37.1744 ± 16.22380	36.1335 ± 14.08349	37.2800 ± 12.28917	1.000
Min	14.09	18.38	19.62	
Max	58.94	57.57	52.60	
Index Granulation Day 3				
Mean+ SD	60.8356 ± 18.64079	90.3967 + 14.82970	54.3800 ± 11.75752	0.001
Min	28.02	64.02	37.15	
Max	83.98	115.31	7570	
Index Granulation Day 7				
Mean+ SD	79.0700 ± 17.93592	96.5670 + 10.35789	65.5273 ₊ 12.21262	0.029
Min	48.40	84.63	47.65	
Max	96.76	121.88	86.38	
Index Granulation Day 14				
Mean+ SD	84.5444 + 28.25892	101.3564 + 6.05922	78.8991+ 14.47863	0.006
Min	10	91.69	43.08	
Max	102.71	111.09	96.71	

A Note:

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IG 0 = (GA 0: WA 0) x 100%

IG 3 = (GA 3: WA 3) x 100%

IG 7 = (GA 7: WA 7) x 100%

IG 14 = (GA 14: WA 14) x 100%

Index Granuasi (IG) ; Wound Area (WA) ; Granulation Area (GA)

4.Results

Thirty consecutive patients (18 females, 12 male), mean age at first application 62.5 ± 11.9 years) were enrolled in this cohort study. The patient demographics are summarized in Table I. They suffer from chronic ulcers that are at least three months refractory to optimal standard wound care. Most patients suffer from systemic diseases, especially diabetes or hypertension. Diabetic foot ulcer characteristics are found in the lower extremity and foot (table 2) with an average area of initial wound area of 8.268 cm2, S.D. 1,879 cm2). Wound parameters after wound care after application of material are wasting based on the wound area and granulation index (expressed in percentage). The highest granulation index was expressed in therapy with PRF HA followed by PRF and control on days 3, 7 and 14. However, new topical PRF therapy made a significant difference compared to control therapy on day 14.

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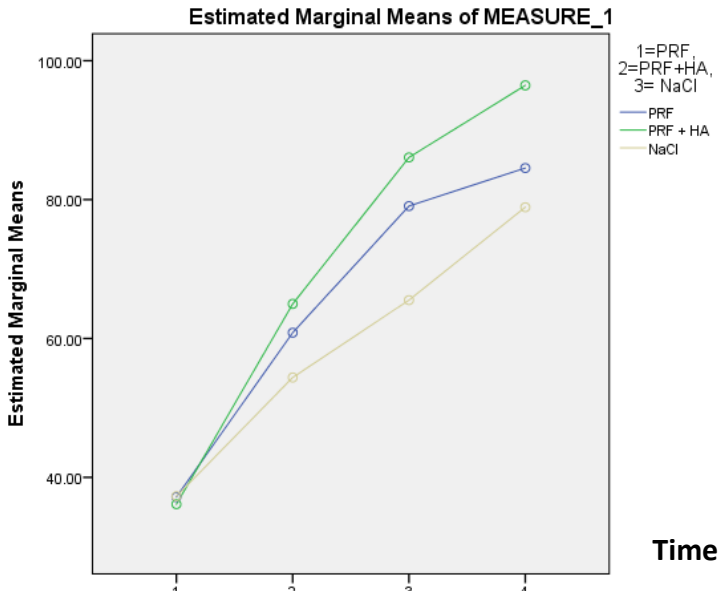

Figure 1.Granulation Index (PRF vs PRF HA vs NaCl 0.9% (control)

Figure 2 .Treatment of Diabetic Foot Ulcer with Platelet Rich Fibrin (PRF)

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Figure 3 .Treatment of Diabetic Foot Ulcer with Combine Platelet Rich Fibrin (PRF) And Hyaluronic Acid Cream (PRF – HA)

Figure 4 .Treatment of Diabetic Foot Ulcer with Natrium Chlorida 0.9% (control)

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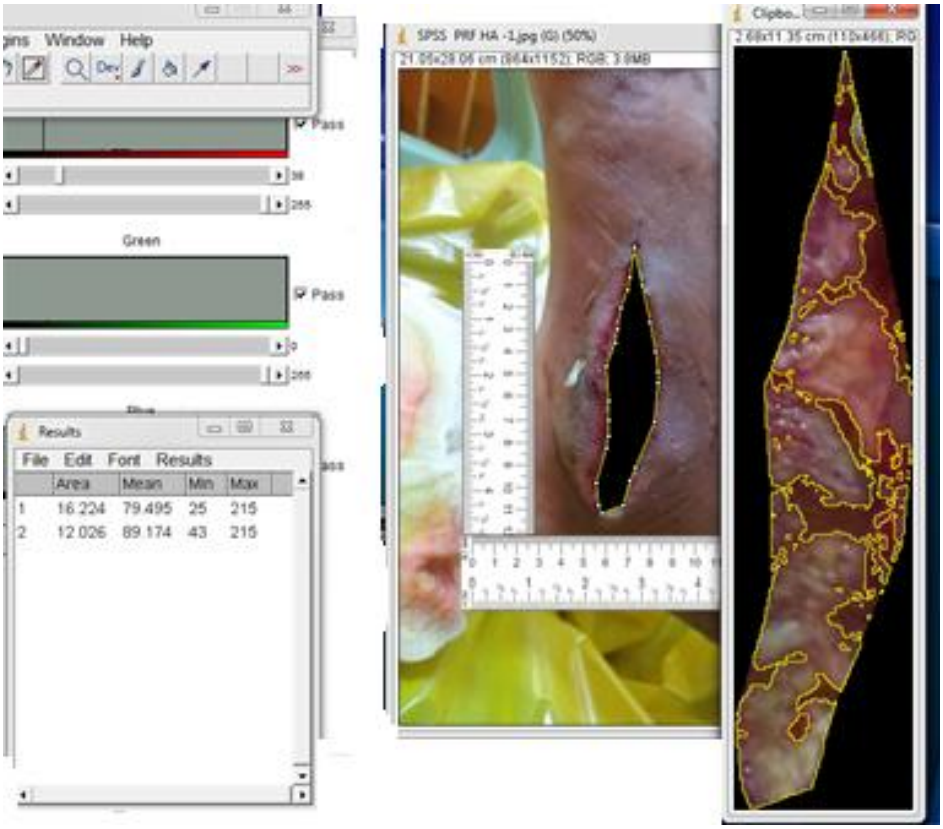

Figure 5 .Measure Wound Area and Index Granulation use Image J Program

5.Discussion

When diabetic foot ulcers do not heal after standard treatment within 4 weeks, which is marked by a significant reduction in wounds (30-50%), further therapy is recommended. A recent meta-analysis of continued therapy of diabetic foot ulcers only shows little benefit from this advanced treatment strategy. Most of these advanced therapies produce no more than 50% of wound closure. Considering the results mentioned above for continued therapy, the application of PRF seems to provide promising results[12]. The application of PRF in our study was used for luas 40 cm^2 of wound area. Diabetic foot ulcer patients with topical PRF appear to be very efficient because the patient's pain complaints are reduced. The beneficial effect of PRF membranes in the healing of chronic leg ulcers can be explained by high platelet and leukocyte concentrations, along with the release of long-term growth factors specifically for the PRF13 fibrin matrix. PRF clots do contain almost all platelets and more than 50% of leukocytes (the majority of lymphocytes) from the initial

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blood. As evidenced in vitro, membranes, with special fibrin tissue, progressively release a number of growth factors (eg β1 growth factor (TGFß-1), growth factor AB platelet derivative growth (PDGF-AB), vascular endothelial growth factor (VEGF) 14. This study will report the results of using the PRF membrane to treat chronic wound healing where these wounds are a complication of diabetes mellitus. Platelets are currently widely used throughout the world in the field of tissue regeneration. The first generation uses Platelet Rich Plasma (PRP). In other platelet concentrates, with higher costs in preparation and with the use of additives (PRP, platelet-rich fibrin patches, or matrices), less favorable clinical observations are reported.Platelet Rich Fibrin is explained by differences in physical, antimicrobial, biochemical, and cellular properties between various concentrates PRF platelets are used with consideration of efficiency, low costs and the safety of using an autologous "optimized blood clot" to cover these wounds, therapeutic options are considered for the treatment of skin ulcers that are difficult to cure[13,14].

Hyaluronic acid (HA) has been proven effective to help cure diabetic foot ulcers. HA is widely involved in all phases of wound healing. HA is a hygroscopic, highly osmotic macromolecule, making it possible to control hydration during periods of wound repair and inflammation

HA also has special relevance to cellular proliferation and migration[15].

During the inflammatory phase of the wound healing process, HA binds to fibrinogen to start the clotting pathway and inhibits neutrophil migration to dampen the inflammatory response. The inflammatory phase is continued with a proliferation phase of wound healing characterized by fibroblast migration. HA stimulates MMP for angiogenesis and promotes migration and proliferation of keratinocytes. HA also contributes to normal and pathological scarring during the regeneration phase[15].

The use of HA in combination with PRP is developing rapidly in clinical practice. However, the effect of HA on angiogenesis and granulation from PRF is unknown. Therefore, the aim of this study was to investigate the angiogenesis properties of PRF after it was combined with HA[16,17].

HA has been proven as an anti-inflammatory molecule that can increase the viscosity of PRF, therefore the addition of HA can require additional components to increase bioactivity. PRF has become very important in the treatment of diabetes ulcers because of its simple production, low cost and minimally invasive nature. PRF has also been proven to play an important role in network

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repair. The growth factor in PRF is an active cellular signal, which can modify the expression of chondrocyte genes. However, PRP does not contain macromolecules such as HA, which is the main ingredient for triggering connective tissue regeneration [18,19]. Developing new formulations of PRP and HA can benefit from their different biological mechanisms, combining the rheological properties of HA with the regenerative potential of PRP, thus, leading to new and more effective treatments for diabetic foot ulcers20. The nature of HA as an anti-inflammatory also reduces the effects of pain and edema on diabetic foot ulcers that get a combination of topical PRF HA[20].

The combination of PRF with Hyaluronic Acid represents additional therapy that is safe, comfortable, easy to use with significant potential to close chronic wounds without side effects.

The combination treatment of PRF with Hyaluronic Acid seems to be a promising alternative to the advanced treatment strategies mentioned above, if standard therapy fails. In addition, recurrence of ulcers, a problem that often occurs in these patients, was not observed in the first year of follow-up. This might imply that the combination of PRF with Hyaluronic Acid not only supports good wound closure, but also helps achieve better quality of regenerated tissue. Considering the efficiency, low cost, and safety of using an autologous "blood clot" to cover these wounds, this therapeutic option must be recognized and considered for treatment of diabetic foot injuries that are difficult to cure.

Platelet-rich growth factor (PRF) is a natural source of growth factor (GF), while hyaluronic acid (HA) is a biopolymer found in the extracellular matrix of the skin, cartilage, bone and brain, among other tissues. Both are involved in the pathophysiological mechanisms underlying wound healing. The aim of this study was to evaluate the clinical efficacy (as measured by ulcer area) and safety (as measured by pain levels) of PRF and PRF added HA in the treatment of diabetic foot ulcers (DFU). Patients (N = 30) with randomized Stage I-II DFU. For the control group (n = 10 DFU) for standard care or case group for treatment with group one (n = 10 DFU) getting PRF therapy. For group two (n = 10 DFU) topical PRF plus HA with a ratio of 3: 2 All the wound is followed up every 3 days for a 7 day period. On the 14th day a final evaluation was conducted. Significant reduction in the ulcer area ($p \leq 0.001$) was observed in the treatment group, with an average reduction of more than 48.0% compared to baseline. The largest mean reduction (80.4% vs baseline) was obtained with the PRF plus HA regimen. Total wound healing was observed in 32.0% DFU treated with two PRF doses ($p \leq 0.002$) and in 37.5% treated with two doses of PRGF

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plus HA ($p \leq 0.004$). There were no signs of infection in any DFU for 14 days of follow-up. The extent of wound healing is inversely correlated with baseline GDS and HbA1 C blood in patients.But the rate of wound healing correlates with the level of albumin from the patient's peripheral blood at the start of therapy.

Image J is a Java-based computer program where image checking with the program can analyze the granulation index of diabetic foot wounds receiving therapeutic treatment according to their group (PRF, PRF-HA combination, and Sodium Chloride 0.9% control). From diabetes wound data processed with Image J, the best granulation index was obtained in patients receiving PRF-HA combination treatment, followed by PRF. This was in accordance with the function of Hyaluronic Acid as an anti-inflammatory and worked together with PRF in accelerating the formation of granulation tissue significantly.

Conclusion

The use of PRF HA combination in the treatment of diabetic foot wounds can be promising by providing the best granulation index compared to topical PRF alone and Sodium Choliride 0.9%. Still more research is needed to determine the pathway of Hyaluronic Acid in accelerating the formation of granulation tissue with PRF.

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