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Comparative Study between Bone Marrow Derived Stem Cells and Platelet-Rich Plasma on Treatment of Chronic Wounds

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ABSTRACT

Background: Chronic wounds constitute a real challenge for the clinicians as they do not respond to traditional treatment and they are not rare. Stem cell therapies have emerged as potential treatment of such wounds. Platelet-rich plasma is known to be a rich source of cytokines and growth factors that are important for healing and re-epithelialization of chronic wounds.

Aim of the work: To compare bone marrow derived stem cells and platelet-rich plasma for treating chronic wounds.

Patients and Methods: A prospective randomized comparative study included 30 patients complaining of chronic wounds with average surface area less than 10 cm^2 divided into 2 groups; group (A) were managed by injection with BMSCs and group (B) were managed by injection with PRP. The study was done at Al-Azhar University Hospitals, Center for Genetic Engineering at faculty of science, Al-Azhar University and Elsalam specialized hospital.

Result: Regarding the demographic characteristics of the studied cases including gender, age, causes of the wound and the sites of wound, our results indicated no statistically significant difference between both groups. Regarding the relationship between the percentage of improvement among BMSCs injection patients and the cause of the wound, our results indicated that the longer the period after treatment with BMSCs or PRP, the lesser the size of the wound became.

Conclusion: It could be concluded that each of bone marrow derived stem cells and platelet-rich plasma are effective for the treatment of chronic wounds.

Keywords: *Stem cells; Platelet-rich plasma; Wounds.*

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INTRODUCTION

Chronic wounds constitute a real challenge for the clinicians as they do not respond to traditional treatment and they are not rare.[1] During wound healing, mesenchymal stem cells (MSCs) participate in all stages of healing and are settled to persist at the wound site even after the completion of this process.[2]

Management of chronic wound varies from traditional wound dressings to skin substitutes, hyperbaric oxygen, negative pressure wound therapy, novel platelet-rich plasma (PRP), nanofat injection and Stem cell therapy.[3]

Stem cell therapies have emerged as a progressive field of research because of their potential for the treatment of such wounds. Bone marrow-derived stem cells (BMSCs) represent a heterogeneous population from the non-blood-forming fraction of bone marrow it represents a novel approach in management of chronic skin injuries.[4]

Platelet-rich plasma (PRP) is known to be a rich source of cytokines and growth factors that are important for healing and re-epithelialization of chronic wounds.[5]

The work aimed to compare the results of clinical application of bone marrow derived stem cells and Platelet-rich plasma for treatment of chronic wounds.

PATIENTS AND METHODS

Study Design:

A prospective randomized comparative study included 30 patients complaining of chronic wounds with average surface area less than 10 cm^2 divided into 2 groups; group (A) were managed by injection with BMSCs and group (B) were managed by injection with PRP. The study was done at Al-Azhar University Hospitals, Center for Genetic Engineering at faculty of science, Al-Azhar University and

Elsalam specialized hospital with approval of the ethical committee.

Inclusion criteria: Patients with chronic wound "duration of the wound > 3 months", average surface area of the wound is less than 10 cm^2 and age between 15 and 60 years.

Exclusion criteria: Patient in critical condition (e.g., shock, debilitating disease, and serious infections), significant co-morbidities, history of any hematological disease, post radiation wounds, psychiatric disorders or pregnant female.

Preoperative:

Clinical assessment: Careful history taking, general condition, local examination of the chronic wound and measurement of the wound surface area.

Investigation: CBC, PT, PTT, INR and HBA1C "for diabetic patients"

Stem Cell Preparation:
The posterior iliac spine was sterilized, and local anesthesia was injected to the skin and periosteum of that area. Bone marrow was aspirated under complete aseptic conditions on preservative-free heparin.

Stem cells were then isolated from bone marrow aspirates. Mononuclear cells were resuspended in complete culture medium. After 24 hours, non-adherent cells were discarded, and of the adherent cells, the spindle-shaped cells were morphologically evaluated. The cell population was characterized by typical immunophenotyping, fibroblast-like morphology and ability to differentiate.

Preparation of PRP:
30 mL of the whole blood was taken from the patient under existence of ACD-A solution. The mixing rate was 9:1 in volume. Eight 5-mL syringes were prepared via cutting their finger- holders using scissors.

4 ml of the blood was put into each syringe and then centrifuged. The rotation speed was 3000 rpm for 3 minutes to separate red blood cells (RBCs) from plasma. The syringes were taken out from the centrifuge then arranged on a holder.

After centrifugation a 3-way cock and an extension tube were connected together, and the syringe was attached to the other end of the extension tube. Four syringes were prepared for the second centrifugation by the same previous method. 1 microgram of PGE1 diluted in 0.05 mL of saline was added to each syringe. After that the syringe was connected to the 3-way cock then the plasma was aspirated. The second centrifugation was done for 15 minutes at 4000 rpm. The supernatant was discarded leaving 0.65 mL which was mixed with the sediment using a vortex mixer. At the end, we got 0.65 mL of PRP solution from 16 mL of the blood.

Injection: At outpatient clinic: Sterilization, injection of local anesthesia, debridement of the wound and injection was done from wound edges to the center at circumferential manner. Debridement and Injection was done once for all the patients of both groups.

Follow up:
We followed up the patients for two months.
Digital photographs of the wounds were taken pre-operatively, 3 days postoperatively then weekly for two months. Wound healing rate was calculated as follows:
(The original wound surface area – residual wound surface area)/the original wound surface area × 100%.

RESULTS

		Group A (BMSCs)		Group B (PRP)		Chi square test	
		No	%	No	%	x^2	p value
Sex	Female	4	26.7%	7	46.7%	1.292	0.256
	Male	11	73.3%	8	53.3%		
Age	Mean ± SD	39.20	10.28	40.20	13.31	0.230	0.820

Table 1: Shows demographic data in both groups.

	Group A		Group B		Independent t test	
	Mean	SD	Mean	SD	t	p value
Duration of the wound in months	11.33	16.91	5.47	5.30	-1.282	0.210
Surface area of the wound in cm^2	4.93	1.00	5.60	1.92	1.169	0.253

Table 2: Shows wound duration in months and surface area in cm^2.

		Group A		Group B		Chi square test	
		No	**%**	**No**	**%**	**x^2**	**p value**
Cause of the wound	Diabetic foot	4	26.7%	4	26.7%	1.234	0.745
	Post burn ulcer	3	20.0%	4	26.7%		
	Traumatic wound	5	33.3%	6	40.0%		
	Venous ulcer	3	20.0%	1	6.7%		
Site of wound	Rt arm	0	0.0%	2	13.4%	20.800	0.235
	Dorsum of lt foot	2	13.4%	2	13.4%		
	Sole of lt foot	0	0.0%	1	6.7%		
	Sole of rt foot	0	0.0%	1	6.7%		
	Dorsum of rt foot	2	13.4%	5	33.4%		
	Dorsum of lt hand	0	0.0%	1	6.7%		
	Dorsum of rt hand	1	6.7%	0	0.0%		
	Dorsum of rt big toe	0	0.0%	1	6.7%		
	Planter surface of lt big toe	1	6.7%	0	0.0%		
	Lt knee	1	6.7%	0	0.0%		
	Lt leg	5	33.3%	0	0.0%		
	Lt thigh	1	6.7%	0	0.0%		
	Rt heel	1	6.7%	0	0.0%		
	Rt knee	1	6.7%	0	0.0%		
	Rt leg	0	0.0%	2	13.3%		

Table 3: Shows the cause and site of the wound in both groups.

% of improvement	Diabetic foot		Post burn ulcer		Traumatic wound		Venous ulcer		One way ANOVA	
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**f**	**P value**
after 3 days	11.75	3.40	12.67	2.08	11.00	1.22	7.00	2.00	3.673	0.047
after 1 wk	27.00	6.98	35.67	4.51	28.40	3.05	15.00	4.36	9.333	0.002
after 2 wk	50.25	12.61	64.33	5.03	52.80	5.81	28.67	6.35	9.964	0.002
after 3 wk	67.50	20.82	84.00	7.21	70.60	8.32	37.67	8.96	6.954	0.007
after 4 wk	82.25	24.01	96.33	6.35	85.60	10.31	45.33	11.02	6.751	0.008
after 5 wk	89.25	21.50	100.00	0.00	94.00	7.78	51.00	11.36	8.976	0.003
after 6 wk	91.25	17.50	100.00	0.00	98.00	4.47	56.67	11.72	11.281	0.001
after 7 wk	93.25	13.50	100.00	0.00	99.20	1.79	60.00	11.36	15.542	0.001
after 8 wk	95.00	10.00	100.00	0.00	100.00	0.00	61.85	11.90	20.506	0.001

Table 4: Shows the % of improvement and the wound cause in group A.

% of improvement	Diabetic foot		Post burn ulcer		Traumatic wound		Venous ulcer		One way ANOVA	
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**F**	**P value**
after 3 days	8.75	1.50	9.25	1.50	10.00	3.90	4.00	0.00	1.288	0.327
after 1 wk	19.50	3.00	28.25	6.85	26.00	12.77	12.00	0.00	1.197	0.356
after 2 wk	37.75	7.54	51.00	11.22	46.50	18.83	24.00	0.00	1.247	0.34
after 3 wk	52.50	10.38	66.25	12.39	61.83	23.10	32.00	0.00	1.225	0.347
after 4 wk	63.00	11.75	78.25	12.92	72.83	23.84	38.00	0.00	1.497	0.27
after 5 wk	71.75	13.23	87.00	13.04	80.67	23.71	44.00	0.00	1.597	0.246
after 6 wk	80.00	15.43	93.00	10.92	82.60	24.41	49.00	0.00	1.532	0.266
after 7 wk	86.75	16.19	95.75	8.50	87.00	20.93	53.00	0.00	1.679	0.229
after 8 wk	90.21	12.88	97.67	4.67	88.33	19.15	55.00	0.00	2.241	0.141

Table 5: Shows the % of improvement and the wound cause in group B.

surface area of the wound in cm^2	Mean	SD	Paired t test	
			T	**p value**
Before injection	4.93	1.00	--	--
after 3 days	4.47	1.06	3.122	0.008
after 1 wk	3.60	0.99	7.870	<0.001
after 2 wks	2.53	0.99	11.839	<0.001
after 3 wks	1.73	1.33	12.388	<0.001
after 4 wks	1.20	1.47	12.599	<0.001
after 5 wks	0.80	1.26	13.350	<0.001
after 6 wks	0.67	1.11	16.173	<0.001
after 7 wks	0.60	1.12	15.000	<0.001
after 8 wks	0.53	1.06	15.070	<0.001

Table 6: Shows wound size after injection with BMSCs.

surface area of the wound in cm^2	Mean	SD	Paired t test	
			T	**p value**
Before injection	5.60	1.92	--	--
after 3 days	5.07	1.71	4.000	0.001
after 1 wk	4.36	1.95	10.670	<0.001
after 2 wks	3.40	1.88	15.199	<0.001
after 3 wks	2.67	1.76	16.144	<0.001
after 4 wks	1.87	1.77	16.362	<0.001
after 5 wks	1.53	1.68	14.321	<0.001
after 6 wks	1.21	1.67	15.070	<0.001
after 7 wks	0.87	1.41	15.764	<0.001
after 8 wks	0.80	1.21	15.401	<0.001

Table 7: Shows wound size after injection with PRP.

Wound size	Group A		Group B		Independent t test	
	Mean	**SD**	**Mean**	**SD**	**t**	**p value**
After 3 days	4.47	1.06	5.07	1.71	1.155	0.258
After 1 wk	3.60	0.99	4.36	1.95	1.336	0.193
After 2 wks	2.53	0.99	3.40	1.88	1.578	0.126
After 3 wks	1.73	1.33	2.67	1.76	1.637	0.113
After 4 wks	1.20	1.47	1.87	1.77	1.122	0.271
After 5 wks	0.80	1.26	1.53	1.68	1.348	0.188
After 6 wks	0.67	1.11	1.21	1.67	1.045	0.305
After 7 wks	0.60	1.12	0.87	1.41	0.574	0.571
After 8 wks	0.53	1.06	0.80	1.21	0.643	0.526

Table 8: Shows wound size after injection in both groups.

% of improvement of Wound size	Group A		Group B		Independent t test	
	Mean	**SD**	**Mean**	**SD**	**t**	**p value**
After 3 days	9.07	2.94	10.73	2.87	1.573	0.127
After 1 wk	23.93	9.65	26.80	8.14	0.879	0.387
After 2 wks	43.87	14.91	49.60	14.04	1.084	0.288
After 3 wks	58.53	18.14	65.87	19.53	1.066	0.296
After 4 wks	69.33	19.44	78.80	22.42	1.235	0.227
After 5 wks	77.53	19.86	85.33	21.56	1.031	0.312
After 6 wks	82.43	19.70	88.33	19.26	0.816	0.422
After 7 wks	87.00	18.24	89.93	17.49	0.450	0.656
After 8 wks	89.10	16.61	91.04	16.57	0.320	0.752

Table9: Shows the % of improvement of wound size after injection in both groups.

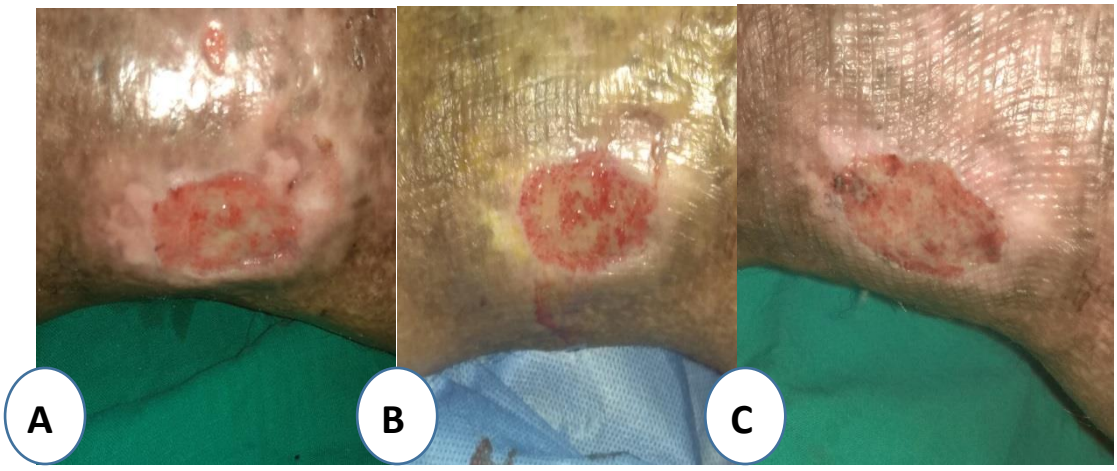

Fig. 1: (Group A) A: preoperative, B: first week, C: second week.

Fig. 1: (Group A) D: 4th week, E: 6th week, F: 8th week.

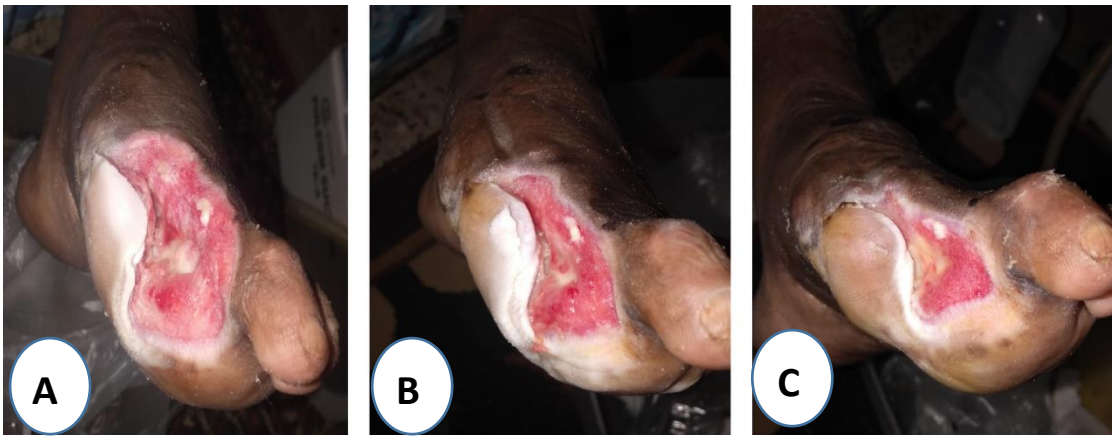

Fig. 2: (Group A) A: preoperative, B: first week, C: second week

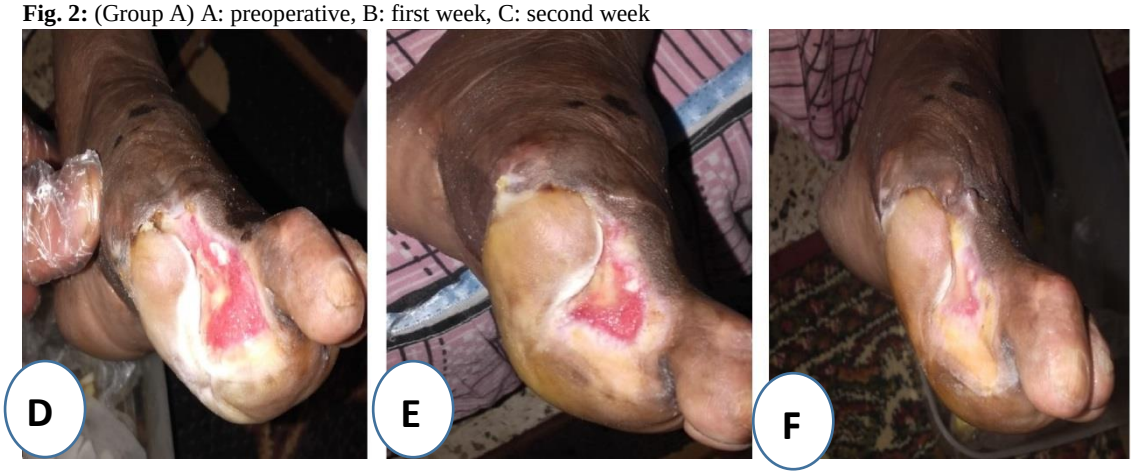

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Fig. 2: (Group A) D: 4th week, E: 6th week, F: 8th week.

Fig. 3: (Group B) A: preoperative, B: first week, C: second week.

Fig. 3: (Group B) D: 4th week, E: 6th week, F: 8th week.

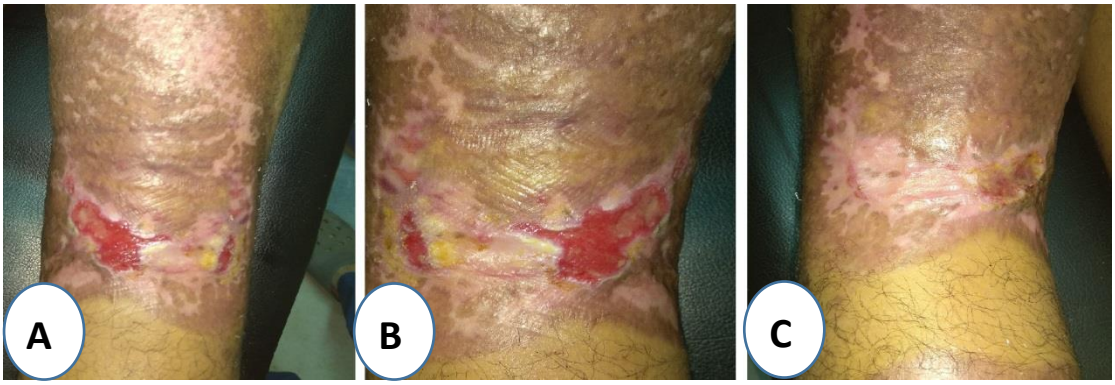

Fig. 4: (Group B) A: preoperative, B: first week, C: second week.

Fig. 4: (Group B) D: 4th week, E: 6th week, F: 8th week.

DISCUSSION

Chronic wounds have devastating consequences for patients. Bone marrow derived stem cells (BMSCs) play critical roles during all phases of cutaneous wound healing.[6] Platelet-rich plasma (PRP) contains abundant growth factors and has a healing effect on wounds and tissues as proved by previous animal trials.[7]

The aim of the present study was to compare bone marrow derived stem cells and platelet-rich plasma for treating chronic wounds.

Regarding the demographic characteristics of the studied cases, our results indicated no statistically significant difference between both groups. The mean age of cases in the present study was 40.20 years old in PRP group and 39.20 years old in BMSCs group. A previous study by Moneib et al. compared the clinical efficacy of PRP application in the treatment of chronic venous leg ulcers; the mean age was 32.5 ± 7.5 years old.[8]

Regarding the relationship between injections and the rate of wound size reduction, our results indicated no statistically significant difference between injections type and the wound size. Such findings were in agreement with Huber et al. that applied PRP in the management of chronic ulcers and showed a reduction in wound size and ulcer numbers with signs of wound healing when compared to saline solution.[9]

Similarly, Abdel-Gawad et al. indicated that BMSCs have a powerful healing property via regulating the wound healing mediators, restoring the normal skin structures and reducing the wound size in second degree burn model.[10] Abd El-Mabood and Ali indicated that the estimated time of wound healing was 12 weeks for 97.5% of the patients in treated with PRP.[11]

Our results showed there was no statistically significant difference between injection type in percentage of improvement and wound size after injection. Such findings were in agreement with a previous study by Rashed et al. on the effect of using BMSCs versus PRP on the healing of induced oral ulcer in albino rats and indicated that both PRP and BMSCs improve wound healing and increase the quality of the healing tissue with the notice that BMSCs were slightly more effective and faster.[12]

A previous study by Yan et al. indicated that mesenchymal stem cells in a rat model had a positive effect on the diabetic ischemic wound.[13]

Our results indicated that significant longer the period of treatment with PRP, the lesser the size of the wound became. Such findings were in agreement with Babaei et al. that treated a total of 150 diabetic foot ulcers with PRP and found that wound size reduction was detected in patients after four weeks of treatment, full closure after 8.8 weeks of treatment.[14]

Prabhu et al. study on 104 cases had chronic ulcers of different causes that were treated with PRP twice weekly for a maximum of 10 dressings, 81.73% of cases were healed at the time of the last dressing.[15]

Contrarily, a systematic review by Yotsu et al. stated that PRP treatment in chronic wounds is not fully determined and that PRP treatment might not as well be effective in diabetics, due to decreased amount of cytokines in platelets.[16]

The present results indicated that the longer the period of treatment with BMSCs, the lesser the size of the wound become. Such findings were in agreement with a previous study by Lu et al. which indicated that local injection of BMSCs is tolerated and effective at promoting foot ulcer healing and increasing lower limb perfusion in diabetic patient.[17]

A previous study by Moon et al. indicated that allogeneic adipose-derived stem cells allocated in a hydrogel sheet showed higher rate of complete wound closure.[18]

CONCLUSION

Each of bone marrow derived stem cells and platelet-rich plasma are effective for the treatment of chronic wounds of different etiologies.

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