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ORIGINAL ARTICLE

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Evaluation of the efficacy, safety and satisfaction rates of platelet-rich plasma, non-cross-linked hyaluronic acid and the combination of platelet-rich plasma and non-cross-linked hyaluronic acid in patients with burn scars treated with fractional CO_2 laser: A randomized controlled clinical trial

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Abstract

Skin scarring can result from burns, injuries, stretch marks and acne, leading to cosmetic and functional difficulties. Treatments for burn scars encompass a range of options, such as lasers, corticosteroid injections, surgery and regenerative techniques such as platelet-rich plasma (PRP). Hyaluronic acid-based products offer skin hydration and shield against aging effects. A study is being conducted to evaluate how effective PRP injection, hyaluronic acid and their combination improve burn scars and their effects on quality of life and potential disabilities. In our study, PRP and non-cross-linked hyaluronic acid treatments were compared in 10 individuals with burn scars between 2022 and 2023. Patients received CO_2 fractional laser treatment followed by injections in scar areas. Evaluations included the Vancouver scar scale (VSS), biometric assessments, ultrasounds and satisfaction ratings. Two therapy sessions were

Abbreviations: PDL, pulsed dye laser; PPP, platelet-poor plasma; PRP, platelet-rich plasma.

Masoumeh Roohaninasab and Alireza Jafarzadeh contributed equally to this study and shared co-first authors.

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conducted at 1-month interval, and assessments were done before treatment, 1 month after the first session, and 3 months after the first session. Biometric assessments showed significant improvements in various parameters (tewametry, corneometry, erythema index, melanin index, cutometry, thickness and density) in the intervention groups compared to the placebo group (p <0.05). PRP-non-cross-linked hyaluronic acid, PRP and non-cross-linked hyaluronic acid treatments exhibited the best clinical responses with significant differences between groups (p <0.05). Dermal thickness did not show significant improvement during treatment sessions, and changes among subjects were not significantly different. The colorimetry parameter improved in all groups except the placebo group, with no significant difference between intervention groups. The VSS significantly decreased in all treatment groups except the placebo group. PRP, non-cross-linked hyaluronic acid and especially the combination of these two treatment options are very effective in treating burn scars.

KEYWORDS

atrophic scar, burn scar, clinical trial, non-cross-linked hyaluronic acid, platelet-rich plasma, PRP, RCT, scar

Key Messages

- The study highlights the significant efficacy of platelet-rich plasma (PRP), non-cross-linked hyaluronic acid and their combination in treating burn scars, leading to notable improvements in various skin parameters, satisfaction rates and Vancouver scar scale (VSS) scores.
- Treatment with combined PRP and hyaluronic acid showed particularly promising clinical responses compared to individual treatments or a placebo.

1 | INTRODUCTION

The primary reasons for skin scarring are burns, injuries, stretch marks and acne. Burns, resulting from heat exposure, radiation or contact with chemicals or electricity, can lead to skin and tissue damage. Scars from burns not only alter the skin's appearance but also result in shrinkage, hypertrophic changes and the growth of keloid tissue, impacting a person's quality of life. These scars frequently manifest symptoms such as itching, prolonged redness, ongoing follicle inflammation and restricted movement.[1–3]

Multiple treatments have been suggested for burn scars, including hypertrophic and atrophic scars, each with varying levels of healing potential. These treatments encompass fractional CO_2 lasers, pulsed dye lasers, corticosteroid injections, surgical procedures and the utilization of regenerative medicine.[1,4]

PRP is a component of blood plasma containing a higher concentration of platelets than usual. When the platelets are activated, they release growth factors that play a role in healing wounds. The use of various growth factors appears to enhance the healing process.[5,6] PRP is obtained through either manual techniques or automated devices or kits. In the manual procedure, blood is extracted from the patient, mixed with an anticoagulant and then centrifuged. With the double spin technique, the blood is divided into three layers within the tube: platelet-poor plasma (PPP) on top, PRP in the middle and red blood cells (RBCs) at the bottom.[7–9]

The use of hyaluronic acid-based products is a modern approach to harnessing the natural properties of this biomolecule. These formulations help enhance skin hydration and offer anti-inflammatory, antibacterial, antifungal and antioxidant benefits. These characteristics create a favourable environment for biological processes and energy metabolism while shielding the skin from external factors that contribute to aging.[10,11]

As the significant impact burn scars have on patients' quality of life and their potential to create disabilities, this study compares the effectiveness of PRP injection, non-

cross-linked hyaluronic acid and their combination in healing burn scars.

2 | MATERIALS AND METHODS

2.1 | Patients

Between 2022 and 2023, a double-blind, randomized clinical trial was conducted on patients referred to a dermatology clinic. The study involved 10 individuals aged between 25 and 55 years with skin types ranging from 1 to 4. These individuals had burn scars in four different regions that had been present for at least 6 months. Exclusion criteria included pregnancy, breastfeeding, coagulation disorders, anticoagulant medication usage, connective tissue diseases, viral infections, history of cancer and chemotherapy intake. Before the study began, patients were informed about the procedure and completed consent forms detailing their age, gender, scar location, formation time and prior treatments. Each participant had multiple burn scars in different body parts, categorized as atrophic with varying severity. Following the initial evaluation, the burn scars were randomly divided into four sections, with three designated as intervention areas and one as the control. The portion designated for injections measured 5 cm in both length and width.

2.2 | Randomization and blinding

The treatment allocation was done using a simple randomization method. Each patient had four scar areas labelled A, B, C and D. Four sealed envelopes marked P, H, C and L were provided to the patients. Initially, a patient chose an envelope, determining the treatment for area A based on the letters P, H, C and L drawn. This selection process continued for areas B, C and D using the remaining envelopes. This clinical trial operates on a double-blind basis, where both patients and physicians assess the outcomes while statisticians are unaware of each lesion's treatment assignments. Normal saline acted as a placebo to ensure patient blinding.

2.3 | Preparation of PRP

30 cc of blood was drawn from all patients under sterile conditions. The blood sample was transferred to a tube containing 1.5 cc of anticoagulant (sodium citrate 4%). Subsequently, the blood samples were centrifuged at 1500 rpm for 8 min. After centrifugation, the RBCs settled at the bottom of the tube, and the patient's plasma was carefully transferred to another tube. This plasma was then subjected to a second round of centrifugation at 3500 rpm for 8 min. After this centrifugation step, the top two-thirds of the tube was collected as PPP, while the lower one-third was carefully preserved as PRP (PRP) for injection.

2.4 | Preparation of non-cross-linked hyaluronic acid

This study used 5 cc vials containing 32 mg of non-cross-linked hyaluronic acid (CYTOCARE®, REVITACARE, France) to obtain non-cross-linked hyaluronic acid.

2.5 | Intervention methods

Before initiating the study, all patients underwent CO_2 fractional laser treatment for their burn scars. At the beginning of the study, the patients' scars were categorized into four areas, with each area undergoing one of the following interventions: PRP injection, non-cross-linked hyaluronic acid injection, a combination of PRP and hyaluronic acid, and regular saline injection.

In the PRP group, the injection volume was 3 cc with a 30 G needle, administered at 0.1 cc per point. In the non-cross-linked hyaluronic acid group, a 3 cc injection was administered with a 30 G needle at 0.1 cc per point. The group receiving the combined treatment of PRP and non-cross-linked hyaluronic acid was injected with a volume of 1.5 cc of each mentioned item or a 0.1 cc volume using a 30 G needle at each point. The group receiving normal saline received a 3 cc injection of normal saline, with 0.1 cc at each end, using a 30 G needle. Two therapy sessions were conducted, with 1-month interval between sessions. Evaluations were conducted before the initiation of treatment, 1 month after the first session, and 3 months after the first session.

2.6 | Assessment method

All patients were evaluated before the study began and again 2 months after its completion, following these procedures:

1. A Vancouver scar scale (VSS) assessment examined four aspects of the lesion: vascularity, pigmentation, height, and flexibility. Each characteristic was assigned a score based on the guidelines in Figure 1.
2. Biometric evaluations were performed before and 2 months after the treatment completion in both

Scar characteristic	Score
Vascularity	
Normal	0
Pink	1
Red	2
Purple	3
Pigmentation	
Normal	0
Hypopigmentation	1
Hyperpigmentation	2
Pliability	
Normal	0
Supple	1
Yielding	2
Firm	3
Ropes	4
Contracture	5
Height (mm)	
Flat	0
<2	1
2~5	2
>5	3
Total score	13

FIGURE 1 Vancouver scar scale.

groups. Using quantitative measures and a 75 Hz probe, the following assessments were conducted:

- Corneometer: measures hydration in the stratum corneum layer.
- Mexameter: evaluates melanin and erythema levels in the lesion.
- Tewameter: quantifies transepidermal water loss.
- Colorimeter: analyses skin colour changes.
- Cutometer: assesses tissue elasticity with parameters such as R2 for viscoelasticity, R5 for pure elasticity and R7 for immediate recovery percentage post-suction.

3. Ultrasound assessments included various types, such as complete thickness sonography, epidermal thickness sonography, dermal thickness sonography, complete density sonography, epidermal density sonography and dermal density sonography, examining parameters such as dermis and epidermis thickness and density.
4. Patient and physician satisfaction with treatment in both groups was evaluated through overall ratings, ranging from little response to excellent response, based on feedback from patients and physicians (Tables 1 and 2).

2.7 | Data analysis

The data were analysed using the Statistical Package for the Social Sciences (SPSS) software. Quantitative variables were presented as mean ± standard deviation (SD), while qualitative variables were expressed as percentages. The normality of variable distributions was assessed using the K–S test in SPSS. Depending on the type of variable (quantitative or qualitative), statistical tests such as the Mann–Whitney *U* test, Student's *t*-test, or chi-square test were applied to compare the two groups. Statistical significance was determined by a *p*-value below 0.05. All analyses were conducted using SPSS version 22. Regression models were utilized to investigate associations while controlling for confounding factors.

TABLE 1 Evaluating the satisfaction levels of physicians and patients across underrepresented groups.

Intervention group	Satisfaction level based on patient global assessment score	Satisfaction level based on physician global assessment score
PRP-non-cross-linked hyaluronic acid	An 'excellent' response was found in 100% of patients	An 'excellent' response was observed in 90% of patients, with 'good' in 10%
PRP	'Excellent' responses were seen in 20% of patients, 'good' responses in 60% and 'somewhat' responses in 20%.	'Excellent' responses were observed in 20% of patients, 'good' responses in 70% and 'somewhat' responses in 10%.
Non-cross-linked hyaluronic acid	'Good' responses were observed in 10% of patients, 'somewhat' responses in 80% and 'little' responses in 10%.	'Good' responses were observed in 10% of patients and 'somewhat' responses in 90%.
Placebo	'Little' responses were noted in 10% of patients.	'Little' responses were reported in 10% of patients.

Abbreviation: PRP, platelet-rich plasm.

3 | RESULTS

A total of 10 cases, age range 25–52 years, were included; among them, 8 (80%) cases were females. The average age of the studied patients was 42.20 ± 8.10 years.

3.1 | Biometric assessment

According to the trend of chronometry scores in each group over time, the scores decreased significantly in all groups except the control group ($p = 0.001$). The scores

TABLE 2 Comparing the physician's and patient's satisfaction between understudied groups.

Factor	Satisfaction level		PRP-non-cross-linked hyaluronic acid	PRP	Non-cross-linked hyaluronic acid	Placebo	*p*
Patient global assessment score	Little	*N*	0.00	0.00	1.00	10.00	0.001
		%	0.00	0.00	10.00	100.00	
	Somewhat	*N*	0.00	2.00	8.00	0.00	
		%	0.00	0.20	80.00	0.00	
	Good	*N*	0.00	6.00	1.00	0.00	
		%	0.00	60.00	10.00	0.00	
	Excellent	*N*	10.00	2.00	0.00	0.00	
		%	100.00	20.00	0.00	0.00	
Physician global assessment score	Little	*N*	0.00	0.00	0.00	10.00	0.002
		%	0.00	0.00	0.00	100.00	
	Somewhat	*N*	0.00	1.00	9.00	0.00	
		%	0.00	0.10	90.00	0.00	
	Good	*N*	1.00	7.00	1.00	0.00	
		%	0.10	0.70	10.00	0.00	
	Excellent	*N*	9.00	2.00	0.00	0.00	
		%	0.90	0.20	0.00	0.00	

Abbreviation: PRP, platelet-rich plasm.

decreased from 16.32 to 6.63, 12.45 to 7.73 and 12.23 to 10.33 in the PRP-non-cross-linked hyaluronic acid, PRP, and non-cross-linked hyaluronic acid groups, respectively. The difference between the groups was significant ($p = 0.03$) (Table 3).

According to the trend of erythema index of mexameter scores in each group over time, this score decreased significantly in all groups except the control group. The scores decreased from 351 to 157.43, 319.43 to 217.96 and 300.59 to 266.02 in the PRP-non-cross-linked hyaluronic acid, PRP and non-cross-linked hyaluronic acid groups, respectively ($p = 0.001$). The difference in the amount of changes between the groups is significant ($p = 0.004$) (Table 3).

According to the trend of melanin index of mexameter scores in each group over time, this score decreased significantly in all groups except the control group. The scores decreased from 247.63 to 117.88, 250.52 to 177.46 and 235.41 to 203.12 in the PRP-non-cross-linked hyaluronic acid, PRP and non-cross-linked Hyaluronic acid groups, respectively ($p = 0.001$). The difference in the amount of changes between the groups is significant ($p = 0.008$) (Table 3).

According to the trend of tewametry index of mexameter scores in each group over time, this score decreased significantly in all groups except the control group. The scores decreased from 11.94 to 3.28, 10.34 to 6.00 and 8.92 to 6.75 in the PRP-non-cross-linked hyaluronic acid, PRP and non-cross-linked hyaluronic acid groups, respectively ($p = 0.001$). The difference in the amount of changes between the groups is significant ($p = 0.001$) (Table 3).

According to the trend of cutometry R2 scores in each group over time, this score decreased significantly in all groups except the control group. The scores decreased from 1.68 to 0.34, 1.32 to 0.69 and 1.17 to 0.87 in the PRP-non-cross-linked hyaluronic acid, PRP and non-cross-linked hyaluronic acid groups, respectively ($p = 0.001$). The difference in the amount of changes between the groups is significant ($p = 0.001$). Cutometry R5 and R7 also showed a significant decrease over time in all groups except the control group ($p = 0.001$). The most significant decrease was observed in the PRP-non-cross-linked hyaluronic acid, PRP and non-cross-linked hyaluronic acid groups, respectively. The difference between these groups was statistically significant ($p < 0.05$) (Table 3).

According to the trend of complete thickness of the dermis and epidermis in each group over time, this score decreased significantly in all groups except the control group. The scores decreased from 1781.2 to 964.4, 2302.2 to 1826.1 and 1397.0 to 1217.7 in the PRP-non-cross-linked hyaluronic acid, PRP and non-cross-linked hyaluronic acid groups, respectively ($p = 0.001$). The difference in the amount of changes between the groups is significant ($p = 0.001$). The results regarding epidermal thickness were also consistent with the complete thickness trend (Table 3).

TABLE 3 The comparison changes of understudied indices between different groups over time.

	Session	PRP-non-cross-linked hyaluronic acid	PRP	Non-cross-linked hyaluronic acid	Placebo	Time	Time*group	Between group
Colorimetry	1	53.9 ± 16.27	45 ± 11.06	46.8 ± 12.89	42.1 ± 11.02	0.001	0.01	0.55
	2	36.2 ± 10.16	37 ± 7.94	42.7 ± 10.67	43.1 ± 11.86			
	3	27.7 ± 21.85	31.7 ± 13.44	39.2 ± 10.79	45.2 ± 11.4			
Tewametry	1	11.94 ± 2.49	10.34 ± 0.81	8.92 ± 1.33	9.77 ± 1.34	0.001	0.001	0.001
	2	6.22 ± 1.43	7.85 ± 1.35	7.79 ± 1.46	10.07 ± 1.4			
	3	3.28 ± 1.4	6.00 ± 1.58	6.75 ± 1.91	10.21 ± 1.44			
Corneometry	1	16.32 ± 5.47	12.45 ± 2.03	12.33 ± 2.34	12.8 ± 2.22	0.001	0.001	0.03
	2	9.8 ± 2.18	9.31 ± 2.14	10.96 ± 1.53	12.77 ± 1.49			
	3	6.63 ± 2.25	7.73 ± 1.51	10.23 ± 1.6	12.49 ± 1.63			
Erythema index of mexameter	1	351 ± 70.88	319.43 ± 42.42	300.59 ± 53.66	303.98 ± 42.13	0.001	0.001	0.004
	2	220.12 ± 12.62	254.92 ± 25.03	266.02 ± 54.05	310.16 ± 39.71			
	3	157.43 ± 28.65	217.96 ± 28.05	248.18 ± 55.31	311.33 ± 39.47			
Melanin index of mexameter	1	247.63 ± 44.18	250.52 ± 23.18	235.41 ± 34.96	219.06 ± 40.31	0.001	0.001	0.008
	2	162.64 ± 23.95	206.01 ± 31.46	215.23 ± 31.93	223.77 ± 40.75			
	3	117.88 ± 32.23	177.46 ± 33.34	203.12 ± 33.19	225.14 ± 43.37			
Cutometry R2	1	1.68 ± 0.44	1.32 ± 0.17	1.17 ± 0.33	1.2 ± 0.35	0.001	0.001	0.001
	2	0.79 ± 0.11	0.95 ± 0.06	1.0 ± 0.26	1.22 ± 0.36			
	3	0.34 ± 0.06	0.69 ± 0.11	0.87 ± 0.21	1.23 ± 0.37			
Cutometry R5	1	1.29 ± 0.16	0.96 ± 0.42	0.97 ± 0.41	1.49 ± 0.43	0.001	0.001	0.001
	2	0.68 ± 0.15	0.69 ± 0.37	0.84 ± 0.41	1.45 ± 0.35			
	3	0.37 ± 0.12	0.56 ± 0.33	0.75 ± 0.41	1.49 ± 0.34			
Cutometry R7	1	1.28 ± 0.51	1.34 ± 0.3	1.45 ± 0.41	1.39 ± 0.14	0.001	0.001	0.004
	2	0.67 ± 0.32	1.06 ± 0.21	1.31 ± 0.38	1.37 ± 0.35			
	3	0.38 ± 0.2	0.87 ± 0.12	1.2 ± 0.35	1.52 ± 0.21			
Complete thickness	1	1781.2 ± 408.84	2302.2 ± 327.12	1397.0 ± 340.13	1234.1 ± 172.68	0.001	0.001	0.001
	2	1307.5 ± 384.69	2002.5 ± 344.8	1289.4 ± 303.55	1254.4 ± 206.78			
	3	964.4 ± 285.91	1826.1 ± 371.69	1217.7 ± 297.3	1301.5 ± 189.89			
Epidermal thickness	1	124.8 ± 22.2	125 ± 22.32	104.5 ± 17.6	111.6 ± 15.25	0.001	0.001	0.001
	2	71.2 ± 5.96	103.7 ± 18.32	94.5 ± 15.67	117.3 ± 18.69			
	3	40.2 ± 11.15	83.0 ± 14.53	83.3 ± 14.35	118.7 ± 17.23			

TABLE 3 (Continued)

	Session	PRP-non-cross-linked hyaluronic acid	PRP	Non-cross-linked hyaluronic acid	Placebo	Time	Time*group	Between group
Dermal thickness	1	1888.6 ± 613.25	2154.0 ± 392.47	1397.6 ± 386.36	1391.9 ± 606.87	0.40	0.07	0.12
	2	1291.2 ± 372.94	1852.0 ± 317.36	1263 ± 326.81	1467.8 ± 601.55			
	3	900.3 ± 388.73	1640.5 ± 315.56	1175.3 ± 265.97	2461 ± 3143.83			
Complete density	1	61.23 ± 11.97	69.45 ± 12.65	57.73 ± 14.42	68.87 ± 9.55	0.001	0.001	0.004
	2	94.5 ± 10.49	84.24 ± 14.57	64.73 ± 15.51	64.64 ± 12.78			
	3	127.63 ± 9.26	100.01 ± 16.56	73.28 ± 16.68	64.2 ± 13.9			
Epidermal density	1	133.85 ± 15.3	143.84 ± 23.63	121.12 ± 9.61	139.0 ± 12.06	0.001	0.001	0.001
	2	199.56 ± 14.42	174.85 ± 17.81	133.39 ± 8.03	132.17 ± 13.24			
	3	247.18 ± 28.78	193.96 ± 19.36	142.82 ± 10.52	126.37 ± 13.65			
Dermal density	1	74.42 ± 23.8	72.82 ± 21.75	66.66 ± 29.24	72.36 ± 21.81	0.001	0.001	0.001
	2	127.51 ± 32.19	99.15 ± 24.47	78.33 ± 29.86	67.4 ± 24.32			
	3	168.47 ± 33.17	118.64 ± 27.87	88.13 ± 32.52	65.86 ± 25.03			
Vancouver scar scale (VSS)	1	9.8 ± 0.92	9.3 ± 0.95	9.8 ± 1.14	9.0 ± 0.82	0.001	0.001	0.001
	2	4.7 ± 0.95	6.1 ± 0.57	7.9 ± 0.99	9.0 ± 0.82			
	3	2.1 ± 0.99	3.2 ± 0.42	5.7 ± 1.06	9.0 ± 0.67			

Abbreviation: PRP, platelet-rich plasm.

According to the trend of complete density of dermis and epidermis in each group over time, this score increased significantly in all groups except the control group. The scores increased from 61.23 to 127.63, 69.45 to 100.01 and 57.73 to 73.28 in the PRP-non-cross-linked hyaluronic acid, PRP and non-cross-linked hyaluronic acid groups, respectively ($p = 0.001$). The difference in the amount of changes between the groups is significant ($p = 0.004$). The results regarding epidermal and dermal density were also consistent with the complete density trend (Table 3).

On summarizing the results of biometric parameters, tewametry, corneometry, erythema index of mexameter, melanin index of mexameter, ctometry R2, cutometry R5, cutometry R7, complete thickness, epidermal thickness, complete density, epidermal density and dermal density, all showed significant improvement during the treatment sessions in the intervention groups (except the placebo group) ($p < 0.05$).

Furthermore, in comparing the treatment methods, the PRP-non-cross-linked hyaluronic acid group, PRP and non-cross-linked hyaluronic acid showed the best clinical response, with statistically significant differences between the groups ($p < 0.05$).

On the contrary, the dermal thickness parameter did not show significant improvement in any of the groups during the treatment sessions ($p = 0.07$), and the characteristics of the changes among the subjects were not significantly different from each other ($p = 0.12$).

While the colorimetry parameter improved in all groups except the placebo group during the treatment sessions ($p = 0.001$), no significant difference was observed between the intervention groups ($p = 0.55$).

3.2 | Vancouver scar scale (VSS)

The VSS criterion decreased significantly during the treatment sessions in all groups except the placebo group ($p = 0.001$). The criterion decreased from 9.8 to 2.1, 9.3 to 3.2 and 9.8 to 5.7 in the PRP-non-cross-linked hyaluronic acid, PRP and non-cross-linked hyaluronic acid groups. The difference in the amount of changes among the different groups was significant ($p = 0.001$) (Table 3, Figures 2A,B, 3A,B, 4A,B).

3.3 | Physicians and patient's satisfaction

According to patient self-evaluation, 100% of patients in the PRP-non-cross-linked hyaluronic acid group and 20% in the PRP group considered the response of their lesions as excellent ($p = 0.001$). In physician assessment, an excellent response was observed in 90% of patients in the PRP-non-cross-linked hyaluronic acid group and 20% in the PRP group ($p = 0.002$) (Tables 1 and 2, Figures 2A,B, 3A,B, 4A,B).

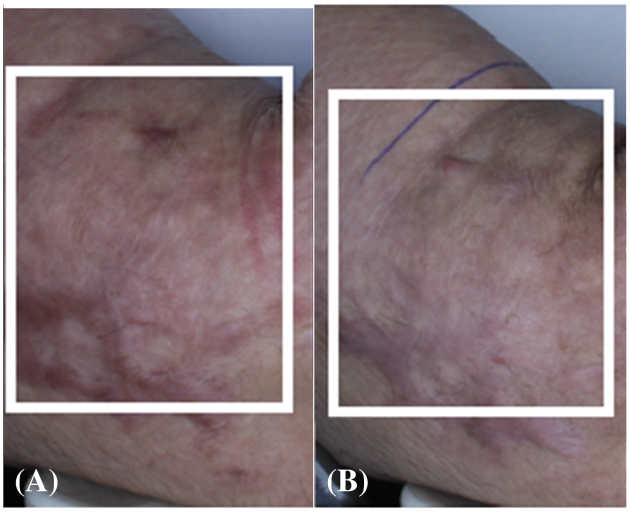

FIGURE 2 Clinical appearance of the lesion before (A) and 2 months after the second session of platelet-rich plasma injection (B).

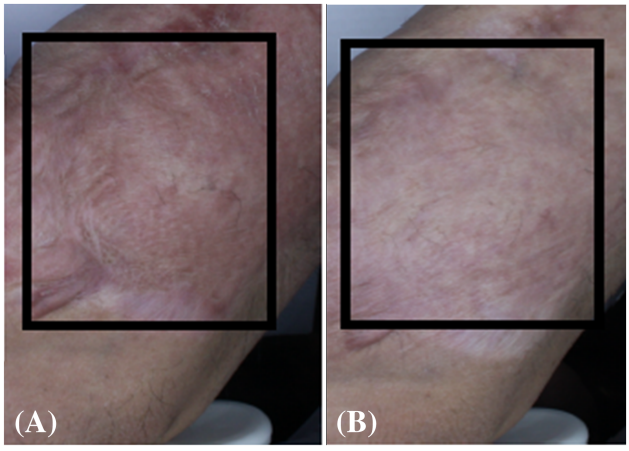

FIGURE 3 Clinical appearance of the lesion before (A) and 2 months after the second session of the combination of platelet-rich plasma and non-cross-linked hyaluronic acid injection (B).

4 | DISCUSSION

Scars, as secondary skin lesions, constitute a high percentage of visits to the skin clinic, with burn scars□including atrophic and hypertrophic scars□forming a significant part of the complaints from these patients. These scars are associated with a significant social burden for patients, making it essential to choose an effective treatment method.[12,13]

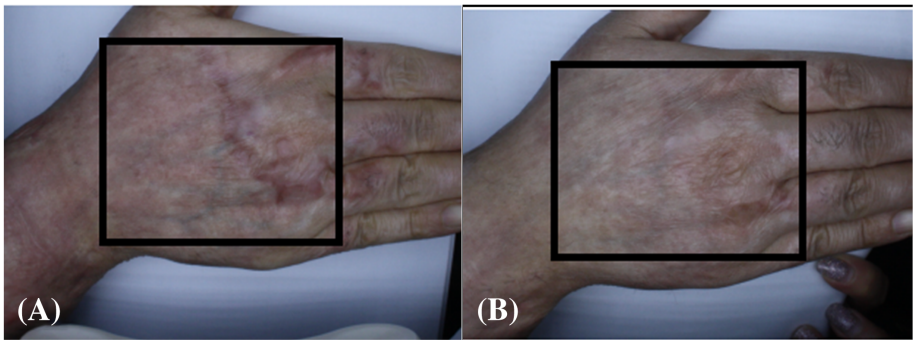

FIGURE 4 Clinical appearance of the lesion before (A) and 2 months after the second session of the non-cross-linked hyaluronic acid injection (B).

The results of our study have shown that PRP and non-cross-linked hyaluronic acid are effective in healing burn scars. Additionally, the combination of these two treatment methods has resulted in significant improvement compared to each method alone.

In this regard, in a study conducted by Elsayed et al.[14] on 38 patients with burn scars, the results showed a significant improvement in the group receiving PRP injections compared to the control group. Moreover, the effective role of PRP in increasing the speed of wound healing and reducing the duration of wound healing has been confirmed in a systematic review by Zheng et al.[15]

The potential reason for the enhancement of scars following PRP injection is linked to the elevated concentration of platelets present in the plasma. Platelet α granules release a range of growth factors, such as platelet-derived growth factor (PDGF) and transforming growth factor beta (TGF-β). The heightened TGF-β levels may trigger a feedback loop in its signalling pathway, resulting in a reduction in the expression of connective tissue growth factor (CTGF). This mechanism ultimately aids in the healing of scars.[3,16,17]

In the systematic review study by Jafarzadeh et al.,[3] which focused on regenerative medicine in the treatment of hypertrophic and keloid scars; the most commonly effective method in the reviewed studies was related to PRP, followed by SVF and stem cell-conditioned medium.

The studies mentioned above highlighted the role of PRP in treating burn scars. In the first study, we examined the combination of PRP and non-cross-linked hyaluronic acid in burn scar treatment. It is worth noting that the effectiveness of this combination in treating female androgenetic alopecia was investigated in Wang et al.'s 2023 study.[18] The results of this study demonstrated a significant improvement in hair loss control and an increase in hair density in patients. This study differed from ours in terms of the method, as 4 injections were administered at 4-week intervals. However, the evaluation was similar to our study, conducted at 1 and 3 months after the initial treatment.

In Omar et al.'s study,[19] which involved 45 patients with a history of cancer and complaints of vulvovaginal atrophy; the patients were divided into three groups: one treated with PRP, another with a combination of PRP and non-cross-linked hyaluronic acid, and the third group receiving vaginal hyaluronic acid gel. The results indicated a significant improvement in the group receiving combined treatment and the group receiving PRP compared to the group receiving local vaginal treatment. Evaluation intervals in this study were conducted at the beginning of the study, 1 month later, 2 months later, and finally, 3 months after the last treatment session.

The potential hypothesis regarding the synergistic effect of PRP and non-cross-linked hyaluronic acid is that fibrinogen present in autologous plasma enhances the absorption of hyaluronic acid once converted into fibrin. This interaction establishes a structured framework that enhances the stability, biocompatibility, and elasticity of PRP. It prolongs the efficacy of PRP, enhances its stiffness and regulates the release of growth factors.[18,20]

In the study by Amer et al.,[21] which compared PRP and non-cross-linked hyaluronic acid in the treatment of acne scars, the results showed a significant improvement with both modalities in treating acne scars, while no significant difference was observed between these two methods. The results of this study are consistent with our study in terms of the significant effectiveness of these two methods in scar healing. However, the results of our study regarding the greater effectiveness of PRP compared to non-cross-linked hyaluronic acid in the treatment of burn scars were not consistent with the results of this study.

In the study by Cheng et al.,[22] which investigated 5 injections of hyaluronic acid in 28 patients with the aim of rejuvenation; the results were evaluated with biophysical criteria. The results confirmed improvement in transepidermal water loss 1 and 3 months after the last therapy session. However, the study did not show any significant difference in the erythema index, melanin index, as well as the R2 parameter after the injection. These findings were not consistent with the findings of

our study, where all these parameters improved after the injection of non-cross-linked hyaluronic acid. The differences in injection techniques and patient selection criteria may justify this disparity.

Finally, it should be noted that our study delved into the efficacy of PRP, non-cross-linked hyaluronic acid, and their combination in healing burn scars. Previous studies have demonstrated the effectiveness of PRP in treating burn scars,[3,5,14] whereas the utilization of non-cross-linked hyaluronic acid in this context is a novel exploration. The combination of PRP and non-cross-linked hyaluronic acid has been studied in a few instances, such as in addressing androgenetic alopecia, vulvovaginal atrophy, and joint osteoarthritis.[18,19,23] In our study, we proposed a novel application for this combined treatment.

5 | CONCLUSION

Non-cross-linked hyaluronic acid, PRP and the combination of these two have shown to be successful treatments for patients with burn scars. The results of our study have indicated that the combined treatment of non-cross-linked hyaluronic acid and PRP had the highest healing rate in burn scars. We have conducted the first study examining the combination of non-cross-linked hyaluronic acid and PRP in burn scars, and it is suggested to conduct more comprehensive studies with a larger sample size in the near future.

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CONFLICT OF INTEREST STATEMENT

All the authors declare that there is no conflict of interest for this project.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

All information obtained from patients was kept confidential and evaluated anonymously. All patients studied adhered to the Helsinki ethical principles, and the study protocol was registered at the Iranian Registry of Clinical Trials with code, IRCT20220808055641N1; Registration date, 2022-09-11; URL, https://www.irct.behdasht.gov.ir/trial/65445. This project was approved by the Ethics Committee of Tehran University of Medical Sciences with the title: 'Evaluation of the efficacy, safety, and satisfaction rates of platelet-rich plasma, non-cross-linked hyaluronic acid, and the combination of platelet-rich plasma and non-cross-linked hyaluronic acid in patients with burn scars treated with fractional CO_2 laser: a randomized controlled clinical trial', with the ethical code IR.TUMS.MEDICINE.REC.1401.377, date of approval: 2022-08-13. The patients signed informed consent for participating in the study.

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