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The Impact of Platelet Rich Plasma in Repairing Unilateral Cleft Lip. A Randomized Controlled Clinical Study

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ORIGINAL ARTICLE

The Effect of Platelet-rich Plasma in Repairing Unilateral Cleft Lip: A Randomized Controlled Clinical Study

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Abstract

Background: **The most prevalent congenital disorders affecting children are cleft lip and palate. By restoring skin tissue and texture, platelet-rich plasma (PRP) has been demonstrated in the study to be a good treatment for muscle damage, and chronic wounds, including atrophic and contractile scars.**

Aim and objectives: **The objectives were to examine the effects of PRP on esthetic results and scar formation after unilateral cleft lip restoration.**

Patients and methods: **A total of 30 patients (12 females and 18 males) with a complete unilateral cleft lip were chosen from the outpatient clinic of the Department of Cosmetic Procedures, Faculty of Medicine, Al-Azhar University facilities to participate in this research, which was a randomized control clinical trial.**

Result: **The mean scar width measured by ultrasonography at 6 months in the control group was 4.96 ± 0.929 mm and in the study group was 3.8 ± 0.886 mm. As a result, there was a statistically significant difference between the two groups regarding the mean scar width as determined by ultrasonography. The scar was considerably less in the study group than in the control group at both the first point (0.831 ± 0.231 mm compared with 1.49 ± 0.442 mm; $P = 0.00$) and the second point (1.015 ± 0.103 vs. 2.275 ± 0.984; $P = 0.00$). The mean Vancouver Scar Scale of the research group at 1 month was 3.792 ± 1.054, whereas for the control group was 5.708 ± 0.656.**

Conclusion: **In addition to reducing the formation of scar tissue, autologous PRP treatment promoted the healing of cutaneous and muscle wounds.**

Keywords: Cleft lip, Platelet-rich plasma, Scar

1. Introduction

The most frequent congenital disorders affecting children are cleft lip and palate.[1] They affect the child's look, resulting in psychological and social problems.[2] It affects approximately one in every 1000 newborn newborns, though its prevalence has decreased significantly in affluent countries where prenatal screenings allow for early identification and the mother can terminate her pregnancy if a fetal anomaly is discovered.[3] To restore cleft lip, many procedures and modifications were employed. The Millard method and its variations were the most prevalent. The scar, on the contrary, is the outcome of a complicated wound healing process following damage, and it is an inescapable component of wound healing. Many efforts were made to minimize the scar following initial cleft lip surgery by employing botulinum toxin (Botox), scar-reducing gel, and fat grafting.[4] However, Botox and scar reduction gel are artificial materials that are quite costly. Furthermore, fat grafting surgery is not appropriate for all individuals.

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When compared with the usual human platelet count in the blood, which varies from 150 000/1 L to 350 000/1 L, platelet-rich plasma (PRP) is a volume of autologous plasma that contains 1 000 000/1 L of platelet in a 5-ml volume of plasma. It has assisted in the acceleration as well as stimulation of bone and cartilage healing as it is a rich source of Growth factor (GFs).[5] By producing signaling proteins that draw macrophages to the location of the wound, platelets in PRP help the host defense response.[6] A small number of leukocytes that generate interleukins are part of an immune response that is nonspecific and may also be present.[7] *Escherichia coli*, *Staphylococcus aureus*, methicillin-resistant *S. aureus*, *Candida albicans*, and *Cryptococcus neoformans* have all been demonstrated to be susceptible to antibacterial effects of PRP.[8] As a result, PRP is helpful in soft tissue and skin wound healing.[9]

Different PRP preparation methods might provide varying platelet concentrations, which could result in a range of biological consequences. Instead of using the single-spin method, the inquiry used the double centrifugation method. Double centrifugation results in the highest therapeutic concentration of platelets, as the first spin is at 250 g for 10 min to ensure that the platelets are retained in the plasma, and during the second spin, the platelets are compressed at the bottom of the tube into a pellet by spinning at a high speed of 1000 g for 10 min10. On the contrary, a true PRP would not be produced by a single spin. Instead, a PRP/PPP mix would be produced, leading to disappointingly low platelet levels.[11] The yield of PRP was affected by a number of parameters, including blood draw speed, duration, and temperature.[12]

Scar evaluation methods include qualitative, quantitative, and semiquantitative approaches. Qualitative scar evaluation may be done by a patient or a clinician, but quantitative scar assessment needs tools to measure the physical characteristics of the scars.[13] The most well-known and widely used scar assessment tool is the Vancouver Scar Scale (VSS). Although it was first designed to assess burn scars, it is now used in clinical research to assess linear surgical scars.[14]

Ultrasound is a less intrusive, less costly method of evaluating distinct tissues on both the healthy and rebuilt sides of a cleft lip repair. It may also assess bone and its shape, degree of mineralization, cleft width and length, scar breadth and extension, alveolar process surface, hard palate, and muscle thickness.[15] As a result, Zhang et al.[16] employed ultrasonography to better understand the nature of the upper lip orbicularis oris muscle and to offer clinical data for assessing the outcome of cleft lip repair surgery. Additionally, Chang et al.[4] and Nuridinovich[17] used ultrasonography to determine scar breadth following cleft lip surgery.

Finally, several studies have shown that PRP may improve scarring caused by atrophic and contractile scars, chronic wounds, and muscle injury by rebuilding skin tissue and texture.[18] Nevertheless, other studies have not shown a statistical difference between the PRP and control groups in terms of wound healing.[19] As a result, the goal of this study was to see how PRP affects scars from cleft lip repair.

2. Patients and methods

This research study was a clinical randomized control trial. For this research, 30 patients with complete unilateral cleft lips (12 female and 18 male) were chosen from the outpatient clinic of the Department of Plastic Surgery, Faculty of Medicine, Al-Azhar University hospitals. This research used PRP during the surgical intervention to measure scar width in children less than 6 months old with unilateral complete or partial cleft lips. According to a prior work by Chang et al.,[4] the scar's breadth was 0.33−0.25 mm smaller on the side of the intervention. A total of 30 patients, 15 in each group, were required at an 80% power and a 5% significance level to be the sample size.

Patients with primary unilateral cleft lip, nonsyndromic cleft lip, and ages between 3 and 6 months were all included in the inclusion criteria, as did patients of both sexes. Exclusion criteria included bilateral cleft lips, secondary lip surgery (previously operated cases), kids older than 6 months, and concomitant cardiac defects. All patients had evaluation of their overall health, their family history, their use of drugs in the past, any related congenital conditions, the kind of cleft, and the breadth of the cleft gap at its narrowest point.[20] Preoperative tests were performed on all patients, including full blood counts, bleeding profiles (Prothrombin Time (PT), Partial Thromboplastin Time (PTT), and International Normalized Ratio (INR), cardiac ultrasounds, and examinations of the chest by pediatricians and anesthesiologists. Guardians of every patient were given information regarding the surgery, and potential postoperative consequences and were asked to sign an Arabic-translated informed permission form.

The patients were randomly allocated to the following groups: study group (group A), where PRP injections and the modified Millard method were used to treat patients with unilateral cleft lips. Patients with a unilateral cleft lip in the control group (group

B) received just the modified Millard procedure. According to the description by Garcez et al.,[21] PRP was made from the patient's own blood in an aseptic setting concurrent with the surgical process.

The incision locations were then noted. To enable inferior rotation of the rotation flap and extension of the lip segment, a curvilinear line was formed on the side without the cleft. A line was drawn from point 3 to the base of the columella, bending up toward 1 mm caudal (point 5). As seen in Figs. 1 and 2, a slight back cut was made at point X to enable more rotation. Following thorough labeling, roughly 3 ml of 2% lidocaine and 1 : 200 000 epinephrine were injected into the lip and alar base to help with hemostasis. Using a Bard-Parker number 15 blade scalpel, the lateral lip flap was initially lifted at the gingival sulcus on the oral side, and the lateral lip segments were released by dissecting across the lateral maxilla in the subperiosteal plane. On either side, care was given to protect the infraorbital nerves. A full-thickness incision was made running from point 3 to point 5 plus X, 1 mm caudal.

To retain more orbicular oris muscle for closure, this incision was gently beveled. At the vermilion cutaneous boundary, parallel incisions were done along the advancement flaps from points 4–9. Following this, the skin was separated from the orbicularis oris muscle by 1–2 mm using a scalpel. This allowed the mucosa, orbicularis oris muscle, as well as dermis to close into three layers. The nasal base's soft tissue attachments were then freed from the piriform opening. The lip abnormality was ready for closure after the dissection of the nasal cavity was finished.

To ensure that there was sufficient release with the least amount of strain across the cleft incision, skin hooks were used to oppose the lip segments

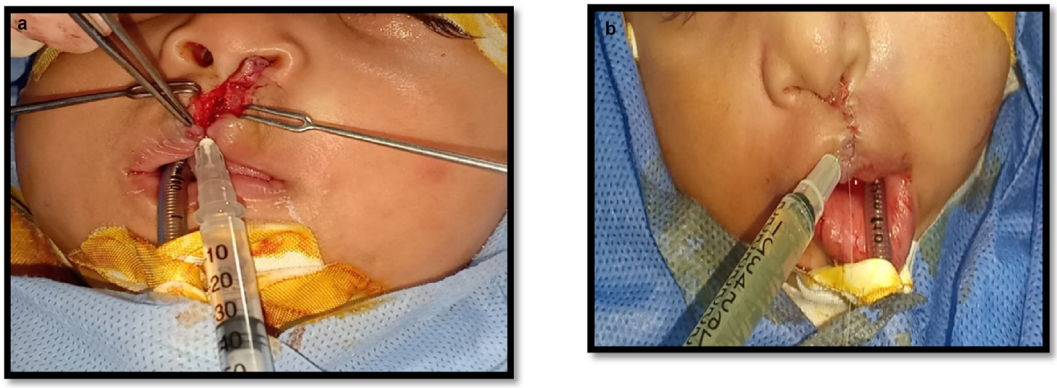

Fig. 1. (a) A photograph showing PRP injection along the suture line of the muscle and (b) along the suture line of the dermis layer. PRP, platelet-rich plasma.

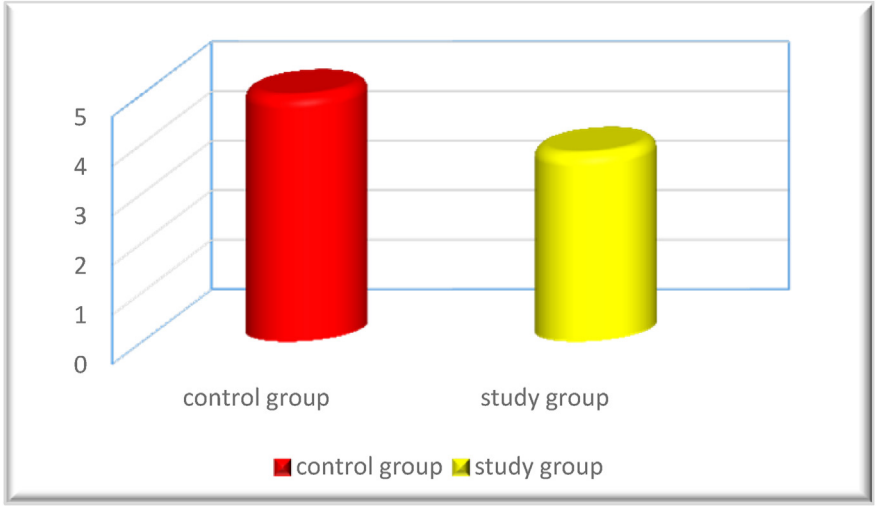

Fig. 2. Bar chart showing the mean scar width by ultrasonography.

together before suturing. If there was too much strain, more dissection was done medially or laterally across the maxilla and superiorly over the bony piriform. Whenever required, a crescent of extra skin was removed from each lip segment's superior side (above points 3 and 4). Beginning with the buried knots, 4-0 Vicryl resorbable sutures were used to close the wound, re-establishing the orbicularis oris muscle sphincter. After the muscle was closed, 0.25 ml of PRP was injected into each side along the muscle layer's suture line. After that, 6-0 Vicryl absorbable sutures were used to seal the dermis. Utilizing 5-0 Vicryl absorbable sutures, the vermilion cutaneous boundaries were precisely approximated. Finally, 0.25 ml more PRP was injected at the dermis layer's suture line.

Postoperative care including immediate instructions and medications were carried out. Patients were scheduled for the following follow-up visits: first visit at 1 week postoperative to assess any lip dehiscence or wound infection, second visit at 1 month postoperatively to assess the patient with VSS clinically, third visit at 3 months postoperatively to assess the patient with VSS clinically, fourth visit at 6 months postoperatively to assess the patient with VSS clinically, as well as assess scar width by ultrasound and photography. Scar width was assessed by ultrasound as described by Nuridinovich,[17] photograph, and VSS according to Chang et al.[4]

2.1. Statistical analysis

Two sets of participants' data were gathered, collated, statistically evaluated, and shown in tables and figures. SD and mean were used to represent the data. The SPSS software (IBM, Version 25, Chicago, IL, USA) was used to do the statistical analysis. To compare the changes between each group's follow-up intervals and determine the significance between the two groups, an independent *t* test was conducted. The threshold of significance for all statistical analyses was set at 5% (0.005).

3. Results

A total of 30 patients were recruited for the study and they are equally allocated by random distribution into two groups ($n = 15$ patients per group). Overall, 18 (60%) patients were males and 12 (40%) were females. Their ages ranged from 99 to 175 days. There were nine (30%) patients with right-side cleft and 21 (70%) patients with left-side cleft. The mean ± SD cleft width before surgery was 3.9 ± 0.72. All patients completed the follow-up examination period with no attrition (Table 1).

Both groups underwent surgery successfully and without any issues, except for one case in group B that had wound dehiscence during the first week. Wound healing was uneventful in all cases with no indication of infection, hemorrhage, wound dehiscence, or hypertrophic scar except for one case in group B that showed wound dehiscence and Antibiotic ointment and wound irrigation were used to treat the case. After 3 months of healing, a hypertrophic scar developed.

In WB, the platelet count was 315.33 ± 26.12; in PRP, it was 1138.88 ± 179.10, with a considerable rise. However, the white blood cell (WBC) count was 9.31 ± 1.05 in the Whole Blood (WB), and it substantially dropped to 0.824 ± 0.06 in the PRP. The mean scar width measured by ultrasonography at 6 months for the control group was 4.96 ± 0.929 mm and for the study group was 3.8 ± 0.886 mm. As a result, there was a statistically significant difference between the two groups in the mean scar width as determined by ultrasonography ($P = 0.00$) (Table 2).

Fig. 3 shows that the scar was considerably less in the study group compared with the control group at both the first point (0.831 ± 0.231 vs. 1.49 ± 0.442 mm; $P = 0.00$) and the second point (1.015 ± 0.103 vs. 2.275 ± 0.984 mm; $P = 0.00$). After 1

Table 2. Descriptive statistics of scar width assessment by ultrasound.

Scar width by ultrasound	Control group		Study group		*P* value
	Mean	SD	Mean	SD	
	4.967	0.929	3.8	0.886	0.00

Table 1. Description of demographic information for sex, age, and cleft side.

	Group A ($N = 15$) [*n* (%)]	Group B ($N = 15$) [*n* (%)]	Total ($N = 30$) [*n* (%)]
Sex			
Male	8 (53.3)	10 (66.7)	18 (60)
Female	7 (46.7)	5 (33.3)	12 (40)
Age (days)	138.416 ± 29.57	118.91 ± 0.492	128.66 ± 25.6
Side			
Right	5 (33.3)	4 (26.7)	9 (30)
Left	10 (66.7)	11 (73.3)	21 (70)

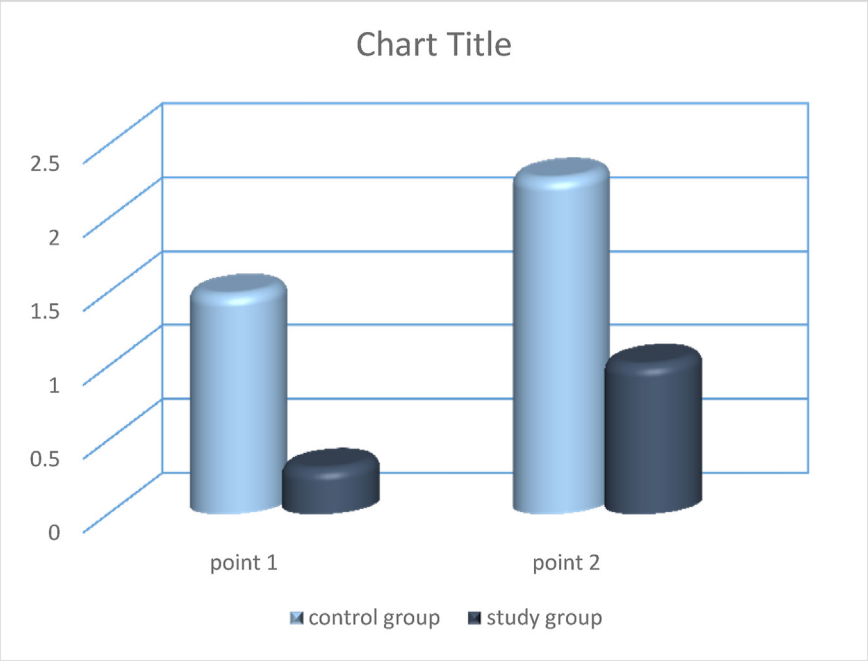

Fig. 3. Bar chart showing the mean scar width by a photograph.

month, the study group's mean VSS was 3.792 ± 1.054, whereas of the control group was 5.708 ± 0.656. As a result, the independent *t* test showed a difference between the two groups, which was significant ($P = 0.00$). After 3 months, the mean VSS values in the study and control groups were 3.792 ± 1.076 and 6.208 ± 1.157, respectively. As a result, the independent *t* test showed a difference between the two groups, which was significant ($P = 0.00$). After 6 months, the mean VSS value of the study group (3.208 ± 1.076) was substantially lower than that of the control group (5.417 ± 1.276) (Table 3).

The variation in VSS over time was investigated using an independent *t* test. Fig. 4 illustrates that neither group had statistically significant variations throughout the various follow-up intervals. In terms of the philtral ridge symmetry value percent, the mean value in the control group was 89.69 ± 5.98, whereas in the research group was 80.06 ± 15.46. Therefore, the independent *t* test demonstrated that the difference between the two groups was not statistically significant.

Table 3. Descriptive statistics of scar width assessment by a photograph.

Scar width by a photograph	Control group		Study group		*P* value
	Mean	SD	Mean	SD	
Point 1	1.49	0.442	0.31	0.231	0.00*
Point 2	2.275	0.984	1.015	0.103	0.00*

* significant at *P* Value <0.05.

4. Discussion

Apart from the surgeon's skills, treatment of cleft lip defects depends on numerous factors such as the choice of the operative method, timing, sequence of surgical repair, and cleft gap. In this study, the cleft lip was repaired around 3–6 months of age, because the lip musculature is better developed by that time, thus allowing proper reconstruction, besides the risk of anesthesia-related complications is reduced, and this time is suitable for the parents to accept the malformation. Our selection followed Shkoukani et al.[22] Regarding the technique chosen in our study, it followed Salyer et al.[23] where the philtral dimple was preserved while the rotation advancement procedure was modified to extend the lip via rotation incision. By releasing the medial lip element, this adjustment improves the positioning of the scars on the lip and vermillion while also enabling the Cupid bow to move downward into its usual position.

Nasoalveolar molding is used in the protocol of management of Cleft Lip and Palat (CLP) as it approximates the lip segments and thus reduces cleft gap up to 5 mm or less and decreases tension on the wound after lip repair.[24] In this study, it was used for these benefits and to make the cleft gap width a controlling factor for both groups. In this study, PRP was injected during unilateral complete cleft lip repair to aid in improving the resultant scar. This intervention was advantageous to use over other

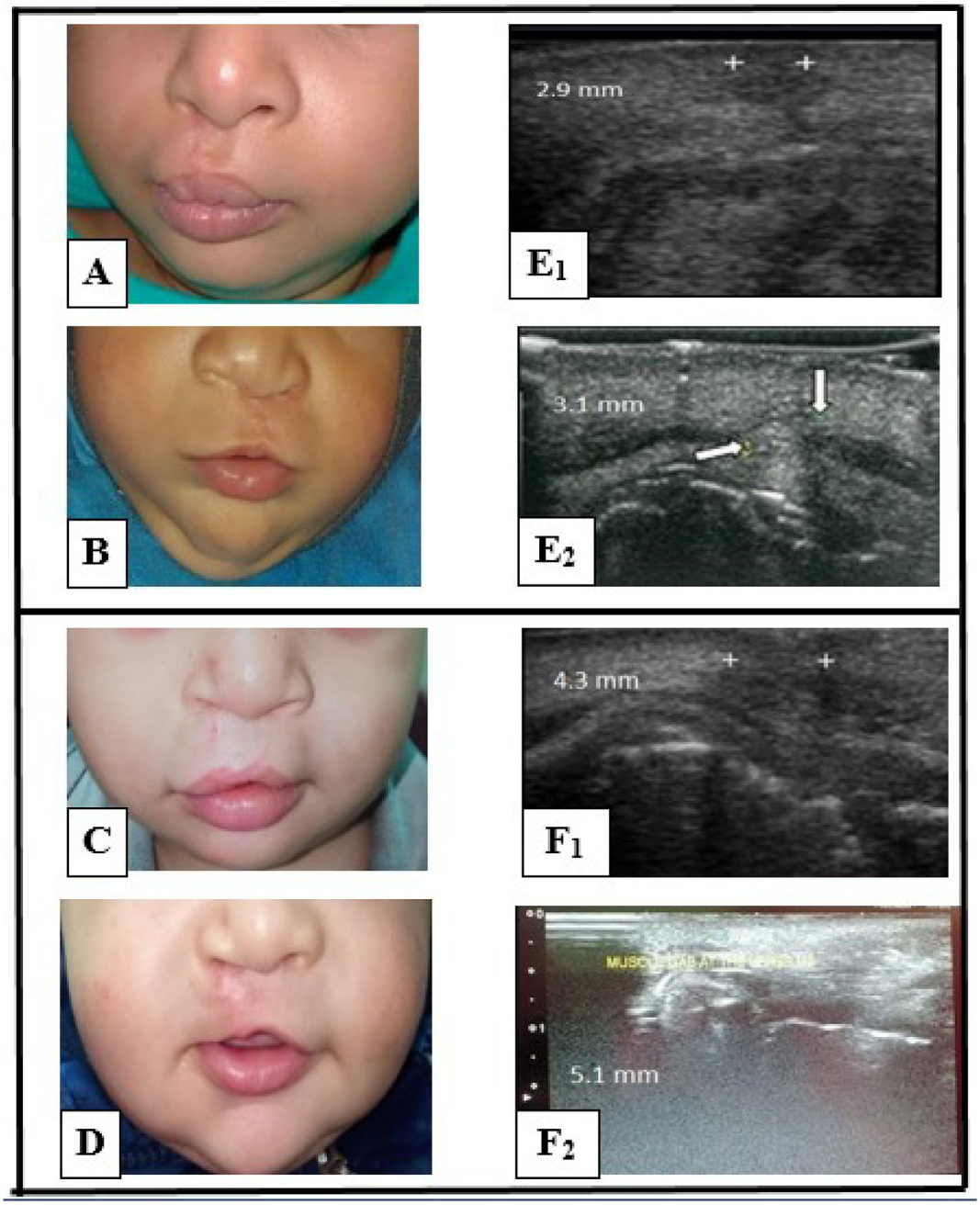

Fig. 4. Six months postoperative photograph of case 1 in group A (a) and its ultrasound view (E_1), case 2 in group A (b) and its ultrasound view (E_2), in comparison with those of case 1 in the control group (C and F_1), and case 2 in the control group (D and F_2).

treatments because it is beneficial as it is an autologous body product.[25] It was also a good source of GFs, which aid in tissue regeneration after injury and the natural healing of wounds[26] and lead to a reduction in the incidence of wound infection. A PRP injection was done for a number of reasons. The amount of PRP needed was decreased owing to the selective distribution that injection offered in the target areas of the wound that need greater assistance in the healing process. The injection methods were also straightforward and practical.[27] Owing to its benefits over the conventional gel form, the injectable form was chosen.

The results of our study showed that the platelets in the PRP increased statistically significantly. According to findings by Choi et al.[28], there was a linear relationship between platelet concentration, GF production, fibroblast proliferation, and collagen

deposition. However, the WBCs in the PRP decreased statistically significantly, according to our data. Because neutrophils, catabolic cytokines, and matrix metalloproteinase break down tissue, WBCs have a harmful effect on the tissue. This outcome is in opposition to Cieslik-Bielecka et al.[29] but is in accordance with Anitua et al.,[5] who discovered a favorable association between the WBC count and antibacterial capabilities, who connected it to tissue damage, inflammation, and further scarring. In the conducted research, postsurgical scar evaluation was performed at 1, 3, and 6 months since scars typically form between 14 and 21 days following re-epithelialization.[30] They need at least 6–18 months to reach adulthood,[31] and the development of hypertrophic scarring often takes place 3–6 months after the original wound damage.[32] Numerous techniques for evaluating the success of cleft lip surgery are available and have been proven to be helpful, including the cleft lip repair scar evaluation developed by Truong et al.,[33] and VSS, which was used for linear surgical scar used to assess cleft lip repair scar by Chang et al.[4]

It evaluates four characteristics: vascularity, height/thickness, pliability, and pigmentation; however, the patient's assessment of his or her scars is not taken into account when calculating the final score.[34] Recent data from our research showed that the VSS in the study group decreased statistically significantly from 1 to 6 months, indicating that patients had improved wound healing and covert scar hypertrophy. This could be because PRP contains GFs, which control and stimulate cellular processes such as mitogenesis, chemotaxis, differentiation, metabolism. Cell division is triggered by attract undifferentiated cells to the freshly created matrix. PRP reduces inflammation and cytokine release, which lessen the production of scar tissue.[35]

Ultrasound was used to assess the width of the scar through the orbicularis oris muscle because it was safer, noninvasive, and less expensive and could be used several times for the same patient at any position (standing, sitting, or lying) and at any age. A statistically significant decrease was found regarding the scar width through the muscle by ultrasound in the study group, and this could be attributed to the presence of GFs in PRP, which control the inflammatory reaction and myogenesis and improve muscle recovery. This result goes with Dimauro et al.[36]

Recent data from the research showed there was a considerable reduction in surface width in the group, indicating that patients had unnoticed scar hypertrophy and wound healing. Again, the GFs of PRP deserve praise as they stimulate cellular functions such as mitogenesis, chemotaxis, differentiation, as well as metabolism. Cell division is triggered by attracting undifferentiated cells to the freshly created matrix. It decreases tissue development by suppressing cytokine release and inflammation.[37]

Moreover, there was a statistically insignificant decrease in philtrum symmetry value % in the group. This is probably owing to the presence of Tissue Growth Factor (TGF) β1 and TGF 32 which promote fibroblast and myofibroblast differentiation and wound contraction. These results are in concordance with the study by Farghali et al.[38], which concluded that the presence of TGFs and other cytokines in PRP, which start the conversion of fibroblasts into myofibroblasts, which are in charge of wound contraction and deposition of extra matrix proteins, was observed to boost both re-epithelization and wound contraction.

On the contrary, Garcez et al.[21] reported that after day 6, there was no statistically significant difference between the control and experimental groups in terms of contraction rate. They attributed this to GF overload, having a dose-dependent inhibitory effect and decreasing the efficiency of PRP tissue healing. The lack of wound dehiscence and hypertrophic scarring in the research group suggests that PRP is an abundant source of GFs, which are essential for wound healing and the regeneration of damaged tissues. GFs also lower the risk of wound infection and shield against wound sequelae. These findings are in agreement with Sevinç[25] and McAleer et al.[26]

5. Conclusion

In the present investigation, autologous PRP treatment promoted muscle and skin wound healing while reducing the formation of scar tissue.

Ethical approval and consent statement

Our protocol Approved by Ethical Committee of Faculty of Medicine, Al-Azhar university, Cairo. Written consent taken from the patient for research, photography, and surgical intervention and anesthesia. Also aim of the study and possible complications discussed with the patient. finally, investigations delivered to the patient.

Conflict of interest

There are no conflicts of interest.

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