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Injectable Platelet-Rich Fibrin versus Advanced Platelet-Rich Fibrin with Xenograft in Alveolar Cleft Repair

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Abstract: In the present study, we present a technique to improve the results of using xenograft bone grafts in alveolar cleft repair instead of autogenous bone grafts, which cause donor site morbidity. This is achieved by mixing the xenograft with either injectable platelet-rich fibrin (I-PRF) or advanced platelet-rich fibrin (A-PRF), which can release higher concentrations of various growth factors for longer duration, speed up bone formation, and reduce bone resorption. The objective of this investigation is to evaluate the efficacy of I-PRF and A-PRF when compared to xenograft bone graft in alveolar cleft grafting. The clinical study was conducted on 10 patients with unilateral alveolar cleft. Patients were divided into two groups: Group I: five patients with unilateral alveolar cleft grafted with xenograft bone mixed with I-PRF; Group II: five patients with unilateral alveolar cleft grafted with xenograft bone mixed with A-PRF. Radiographic assessment included volumetric and density changes in alveolar cleft defect on cross-sectional cuts of CBCT. The data were collected and statistically analyzed using commercially available software (SPSS, Chicago, IL, USA). Both groups showed a statistically significant decrease in defect volume after 3 and 6 months with no significant difference. Moreover, both groups showed an increase in bone density after 3 and 6 months with no significant difference. Mixing xenograft bone grafts with either A-PRF or I-PRF improves bone augmentation outcomes in alveolar cleft repair.

Keywords: alveolar cleft repair, xenograft bone graft, injectable platelet-rich fibrin, advanced platelet-rich fibrin.

可注射富血小板纤维蛋白与异种移植高级富血小板纤维蛋白在牙槽裂修复中的应用

摘要：在本研究中，我们提出了一种技术来改善使用异种骨移植修复牙槽裂的效果，而不是使用自体骨移植，因为自体骨移植会导致供体部位发病率。这是通过将异种移植与可注射的富血小板纤维蛋白(I-PRF)或高级富血小板纤维蛋白(A-PRF)混合来实现的，它们可以在更长的时间内释放更高浓度的各种生长因子，加速骨形成，并减少骨吸收。本研究的目的是评估I-PRF和A-PRF与异种骨移植在牙槽裂移植中的疗效。这项临床研究针对10名单侧牙槽裂患者进行。患者

分为两组：第I组：5名单侧牙槽裂患者，移植了与I-PRF混合的异种骨；第II组：5名单侧牙槽裂患者，移植了异种骨和A-PRF。放射学评估包括CBCT横切面上牙槽裂缺损的体积和密度变化。使用市售软件（SPSS，美国伊利诺伊州芝加哥）收集数据并进行统计分析。两组在3个月和6个月后缺损体积均显着减少，差异不显著。此外，两组在3个月和6个月后骨密度均增加，差异不显著。将异种骨移植物与A-PRF或I-PRF混合可改善牙槽裂修复中的骨增量结果。

关键词：牙槽裂修复、异种骨移植、可注射富血小板纤维蛋白、高级富血小板纤维蛋白。

1. Introduction

Alveolar cleft is an anomaly resulting from lack of fusion between the medial nasal and maxillary processes. Concerning reconstruction of alveolar cleft, there is a great controversy regarding the timing, graft materials, surgical techniques, and methods of evaluation [1].

It is generally agreed that the most favorable time for grafting is the preceding eruption of the permanent canine. Concerning bone grafting, many sources have been used for the reconstruction of the alveolar cleft, including autogenous, alloplastic, and allogenic bone grafts. Autogenous bone graft remains the most preferred graft despite donor site morbidity [2].

Various studies have shown the advantages of I-PRF and A-PRF over traditional platelet-rich fibrin; I-PRF and A-PRF have the ability to release higher concentrations of various growth factors for longer durations than traditional platelet-rich fibrin [3]. I-PRf and A-PRF speed up bone formation, reduce bone resorption in alveolar cleft bone grafting, and inhibit bacterial growth due to the presence of leucocytes and macrophages in great amounts. The resorption rate of grafted bone can also be controlled to a large extent with the use of I-PRF and A-PRF [4, 5].

This study was designed to mix xenograft bone grafts with either I-PRF or A-PRF, which may enhance bone regeneration and decrease postoperative resorption to variable degrees.

2. Patients and Methods

2.1. Study Setting and Population

This clinical study was conducted on 10 patients (six males and four females) with unilateral alveolar cleft with non-collapsed maxilla. Patients were selected from an outpatient clinic of the Oral and Maxillofacial Surgery Department, Faculty of Dental Medicine, Al-Azhar University, Assiut Branch. The age ranged from 9 to 12 years. Informed consent was obtained from all participants included in the study. Ethical approval was obtained from the ethical committee at the Faculty of Dental Medicine, Al-Azhar University, Assiut Branch. This study followed the Declaration of Helsinki on Medical Protocol and Ethics.

2.2. Inclusion Criteria

Medically fit patients to avoid any systemic disease affect results, patients with age range 9-11 years old, as lateral erupted and two thirds of the canine root has been formed, patients suffering from unilateral cleft alveolus, alveolar cleft should not be pre-operated before to avoid the presence of fibrosis, which affect proper dissection of tissues and coverage of bone graft with soft tissue.

2.3. Exclusion Criteria

Patients with systemic bone diseases, medically compromised patients, collapsed maxilla, non-motivated patients.

2.4. Grouping and Intervention

The patients selected in this study were classified into two equal groups:

Group 1: Five patients with unilateral alveolar cleft included 3 males and 2 females grafted with xenograft bone mixed with I-PRF.

Group 2: Five patients with unilateral alveolar cleft included 3 males and 2 females grafted with xenograft bone mixed with A-PRF.

2.5. Preoperative Evaluation

A detailed history was obtained, including personal data, chief complaint, history of the chief complaint, past and present medical history, family history, psychosocial history, and dental history. These collected data were recorded in patient's chart.

2.6. Ethical Considerations and Patient Consent

• The research protocol was approved by the ethical committee of the Faculty of Dental Medicine, Al-Azhar

University, Assuit Branch (N:AUAREC202300010-6).

• All details about the surgical procedure, postoperative follow-up, research procedures, and associated risks of the study procedures were explained to all patients.

• All patients agreed to participate in the study and signed an appropriate informed consent form from Al-Azhar University.

2.7. Surgical Procedure

2.7.1. Patient Preparation

All patients underwent the following investigations and assessments before definitive treatment: complete blood picture, coagulation tests, chest x-ray, and medical consultation to assess fitness for general anesthesia. All patients were instructed to fast for 8 h prior to surgery and were administered a prophylactic antibiotic, Unasyn 750 mg (Ampicillin/Sulbactam, Pfizer Egypt S.A.E, Cairo, A.R.E.) intravenously. Additionally, they received Decadron 40 mg (Dexamethasone sodium phosphate 2 ml vial, manufactured by E.I.P.I.CO., Egyptian Pharmaceutical Industries Co., A.R.E., Merck & Co. Inc., Rahway, NJ, U.S.A.) intravenously every 12 hours starting the day before surgery and continuing up to the 5th day postoperatively.

2.7.2. Exposure of Alveolar Clefts

All patients in the non-cleft side of the nose underwent nasoendotracheal intubation, executed under complete aseptic conditions, including all procedures.

The surgical site was scrubbed using the antiseptic agent Betadine (The Nile Co. for pharmaceuticals, Cairo, Egypt). Eyes were protected with eye ointment and covered by adhesive tape, and local anesthesia (Articain 4% with adrenaline 1/200000) was injected into the soft tissue around the cleft defect for hemostasis.

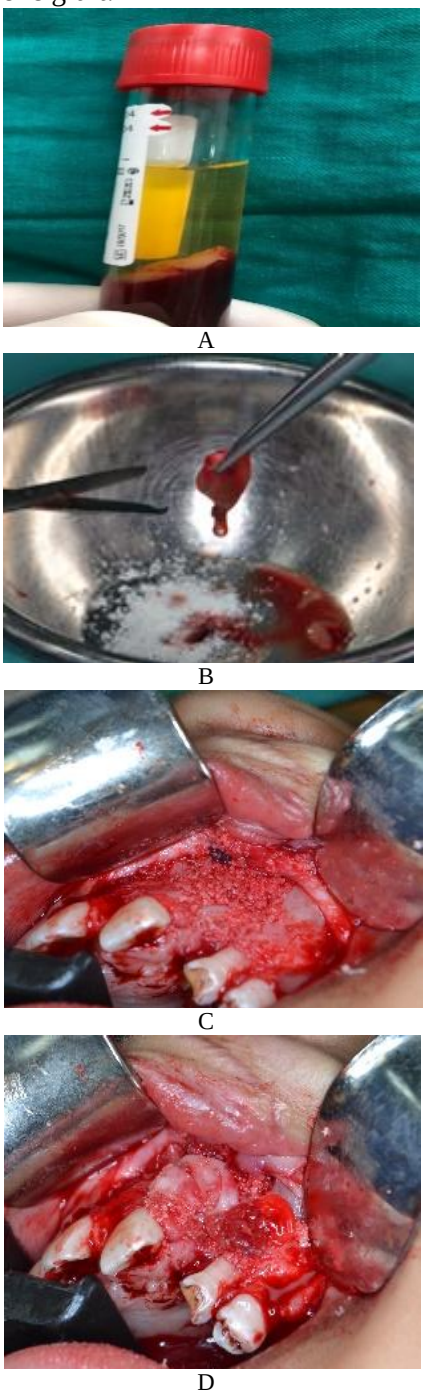
An incision was made through the mucoperiosteum overlying the cleft down to the bony margins, next incision was a gingival sulcular incision made on both sides of the alveolar cleft labially extending at least 2 teeth on each side. Two releasing incisions were made at the lateral ends of the sulcular incision.

2.7.3. Suturing of the Nasal Mucosa

The meticulous dissection of mucoperiosteal flaps is crucial to prevent soft tissue laceration. In this procedure, the nasal mucosa was carefully separated from the oral mucosa. Then, the edges of the nasal mucosa were sutured with 4/0 vicryl without tension.

2.7.4. Preparation of I-PRF in Group 1

Patients in this group were administered a combination of xenograft bone graft Tutobone (manufactured by Tutogen Medical GmbH, Germany) and I-PRF. The platelet-rich fibrin was prepared by centrifuging venous blood at 700 rpm for three minutes, resulting in an orange-colored superficial layer (Fig. 1A) that was collected using a syringe and mixed with the xenograft bone graft.



A

B

C

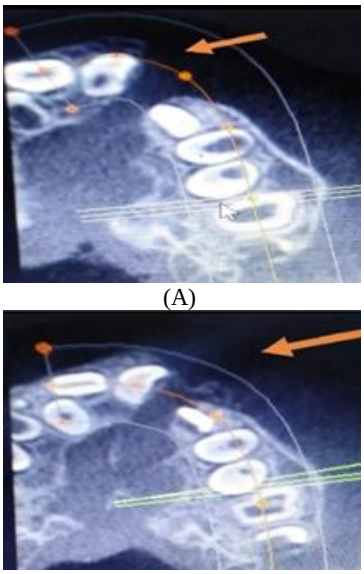
D

Fig. 1 A - I-PRF, B - A-PRF, C - mix of A-PRF and xenograft filling defect, D - platelet-rich fibrin membrane covering the bone graft before suturing (The authors)

2.7.5. Preparation of A-PRF in Group 2

Patients in this cohort were administered a combination of xenograft bone graft and A-PRF in their alveolar cleft. The process for preparing the fibrin

involved centrifuging venous blood at 1800 rpm for eight minutes to separate the clot from the blood. The clot was then removed with forceps, and the fibrin was separated from the red portion of the clot by cutting it approximately 2 mm below the dividing line using scissors. This was done because the part of the blood clot attached to the fibrin contains stem cells (Fig. 2B). Finally, the fibrin was mixed with the xenograft bone graft.



(A)

(B)

Fig. 2 A - Preoperative axial cut, B - postoperative axial cut 6 months after augmentation of the defect with bovine bone graft with I-PRF showing formation of bone bridging at the defect (The authors)

2.7.6. Preparation of the PRF Membrane

Venous blood was centrifuged at 2500 rpm for 15 minutes. At the end of centrifugation, the yellow part extracted from the tube and found in jelly consistency presenting platelet-rich fibrin membrane was placed on the grid of the box and covered with the tray for a few minutes to form a PRF membrane.

After preparation of the mix between the xenograft bone graft and I-PRF in Group 1 or between the xenograft bone graft and A-PRF in Group 2, the previous prepared defect was filled with this mix (Fig. 1C); then, the mix was covered with PRF membrane (Fig. 1D), and the labial and palatal flaps were sutured with 4/0 vicryl sutures.

2.7.7. Suturing of the Labial Mucosa

After complete packing of the defect and covering with PRF membrane, labial and palatal flaps were raised and mobilized to achieve a watertight tension-free closure of the mucosa using 4/0 vicryl sutures. The sutures are placed in an interrupted manner to provide primary closure over the bone graft.

2.8. Postoperative Care and Instructions

Immediately following the procedure, cold fomentation should be applied for the first 24 hours. A clear liquid diet should be followed for 3-4 days, after which a soft diet can be resumed for an additional 2 weeks. Avoidance of milk products for the first 48 hours is essential to reduce the risk of wound infection. Starting 24 hours post-operatively, hot normal saline mouthwashes should be used 6 times a day, in addition to a local antiseptic mouthwash. It is advisable to begin hot fomentations as soon as possible after the first 24-hour period.

Patients were additionally instructed to refrain from applying any trauma to the area, including the use of tongue pressure, for a period of 8 weeks. They were prescribed Unasyn 750 mg, an injection containing Ampicilin/Sulbactum, administered IM/12 hours for 5 days following the surgical procedure. Patients were also prescribed Voltarine 75 mg, a medication in injection form used for pain and inflammation, administered IM twice daily for two days. To prevent nasal congestion, patients were advised to use Otrivin nasal drops, containing Xylometazoline 0.1%, administered three times daily. The medication was provided by NOVARTS PHARM, S.A.E. Cairo, Egypt.

2.9. Postoperative Evaluation

2.9.1. Clinical Assessment

The examination included an assessment of suture breakdown, dehiscence, swelling, infection, edema, hematoma, graft rejection, the presence of oronasal fistula, and the patient's reported pain and nasal regurgitation.

2.9.2. Radiographic Evaluation

CBCT radiographs (Fig. 2A and B) were performed for each patient at the end of third and sixth months to assess:

1) Bone density: Utilizing the Blue Sky Plan 4.ink software, we calculated changes in bone density within the alveolar defect using a gray scale. Areas of interest were constant throughout the examinations. The mean bone density was recorded before surgery and after 3 and 6 months, and the average density was determined.

2) Cleft volume: Volumetric analysis of the defect was performed preoperatively, after 3 months, and after 6 months to detect changes in the size of the defect.

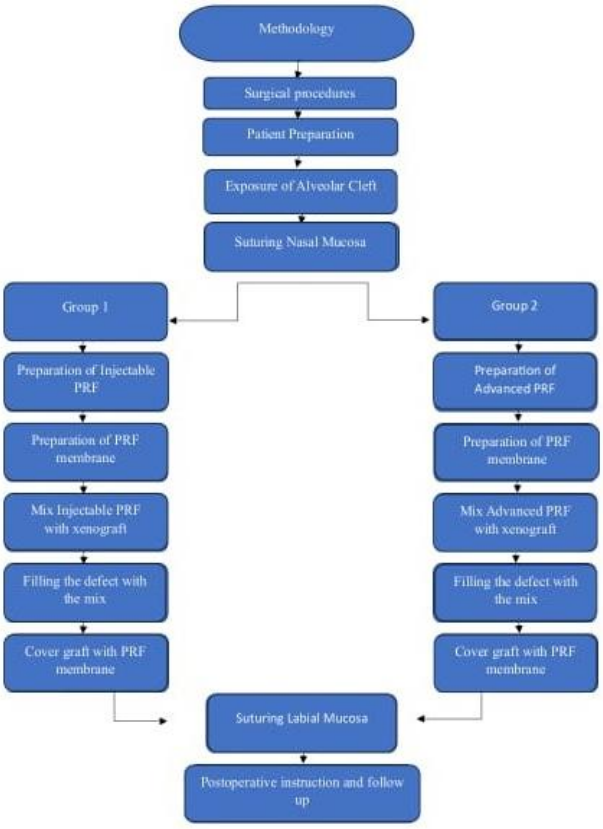


Fig. 3 Flowchart of the methodology (The authors)

2.10. Statistical Analysis

Statistical analysis was performed using commercially available software (SPSS, Chicago, IL, USA). Numerical data are described as mean and standard deviation or as median and range as appropriate according to the normality of the data. Data were compared using the Mann-Whitney U or independent t-test, depending on normality. The level of significance was set at $P \leq 0.05$.

3. Results

3.1. Postoperative Clinical Evaluation

Comparing between two groups, including edema, dehiscence, suture breakdown, infection, and graft rejection on Day 10, indicated no significant difference between them.

3.2. Volumetric Changes in the Two Groups

A notable reduction in the size of the defect was observed in both groups after 3 and 6 months. When comparing the volume change between the two groups after 3 and 6 months, no statistically significant difference was found.

Table 1 Volumetric changes in the two groups (The authors)

	Bovine bone/I-PRF		Bovine bone/A-PRF		t	p
	Mean	±SD	Mean	±SD		
Volume						
0	1.48	0.39	1.26	0.45	.832	0.430
3	0.70	0.17	0.76	0.18	-.524	0.614
6	0.43	0.12	0.57	0.19	-1.381	0.205
Volume change						
0-3	0.78	0.37	0.50	0.26	1.372	0.207
0-6	1.04	0.40	0.68	0.26	1.661	0.135

Notes: t - Student t-test; p - p value for comparison between the two groups

3.3. Comparison between the Two Groups in Terms of Density Changes

Comparing the two studied groups according to density and density changes indicated a significant increase in density in both groups with no significant difference in density between the two groups after 3 ($p = 0.588$) and 6 ($p = 0.394$) months.

4. Discussion

Numerous sources of grafts were used in alveolar cleft reconstruction (autogenous, allogenic, alloplastic, and tissue-engineered materials), and the most accepted type is autogenous bone grafting in mixed dentition. However, donor site morbidity, potential infection, and operative trauma are among the limitations of autogenous bone graft harvesting [6].

In this research endeavor, we employed Tutobone, a solvent-preserved cancellous bovine bone substitute material (Tutogen Medical GmbH, Germany), which displays temporary structural support, integration with the surrounding bone, bioresorption, and subsequent replacement with vital bone. This, as per the findings of Meyer and Floerkemeier, appears to offer a promising alternative to autogenous bone grafting [7].

The PRF used in the present study has certain advantages such as single-stage centrifugation and the absence of bovine thrombin, with no risk of human-to-human disease transmission. PRF has a very dense meshwork of fibrin that protects growth factors from proteolysis and keeps them active for longer periods [8].

Platelet-rich fibrin membranes serve to shield the surgical site and expedite the healing process of soft tissue. Moreover, when its particles combine with graft material, it functions as a "biological connector" linking the diverse components of the graft [9].

In this investigation, the age range of nine to eleven years was chosen to achieve optimal function while minimizing the impact on growth. Additionally, bone grafting was employed to facilitate the eruption of canines, in accordance with the findings of Fahradyan and Tsuha [10].

Regarding our clinical findings, no cases of dehiscence or suture breakdown were observed in the

group that utilized bovine bone with A-PRF after 10 days, as reported by Aishwarya and Priyanka [11]. This suggests that A-PRF plays a significant role in promoting periodontal healing due to its high concentration of autologous growth factors, which ensures proper soft tissue coverage for the newly formed bone. In contrast, one patient in the group that used bovine bone with I-PRF experienced suture breakdown and dehiscence after 10 days.

In relation to edema, on Day 10 in the bovine bone/I-PRF group, two individuals exhibited edema, which resolved completely within 10 days. In contrast, one patient in the bovine bone/A-PRF group experienced edema, with no significant difference observed between the two groups with regard to edema. Postsurgical edema is an inherent aspect of the body's healing process, and some degree of swelling should be anticipated.

Regarding the incidence of infection on Day 10 for bovine bone/I-PRF and bovine bone/A-PRF, one patient in each group exhibited infection. The patient in the bovine bone/A-PRF group did not adhere to the instructions for oral hygiene, and the difference between the two groups was not statistically significant in terms of infection.

With regard to graft rejection, one patient exhibited rejection of the bovine bone/I-PRF graft on Day 10 due to dehiscence and suture breakdown as a result of the patient failing to adhere to proper oral hygiene measures. On the other hand, one patient in the bovine bone/A-PRF group experienced graft rejection, with no statistically significant difference observed between the two groups in terms of graft rejection.

The volume of alveolar defects demonstrated a substantial decrease after 3 and 6 months in both groups, with no significant discrepancy between them, which aligns with the findings of Dayashankara and Bhatnagar [5] and Richard [3], who reported that the utilization of A-PRF and I-PRF led to reduced resorption of formed bone. Both A-PRF and I-PRF contain a considerable quantity of growth factors, such as PDGF, TGF-β, IGF, EGF, fibroblast growth factor, and bone morphogenic protein. These growth factors hold a pivotal role in hemostasis, angiogenesis, osteoblastic proliferation, and differentiation, making A-PRF and I-PRF advantageous.

Our findings align with those of Nesligul and Niyaz [12], who demonstrated an improvement in the quantity of grafted material using both I-PRF and A-PRF. This is likely due to the mechanical role played by PRF during bone grafting, which helps to maintain and support the grafted material. PRF keeps graft particles together and provides suitable areas for new bone formation, especially during the early bone healing period.

In terms of the density and quality of newly formed bone, there was a substantial rise in the density of bone formed in the alveolar defect after 3 and 6 months in both groups, with no significant variation between the two groups. This finding is inconsistent with the results of Shawky and Seifeldin [13], which demonstrated that the use of PRF in combination with autogenous bone was helpful in enhancing the volume of newly formed bone. However, it does not enhance bone density, while our findings align with those of Osorio and Escobar [14] and van Hout and Molen [15] as PRF contains BMP2, which is recognized as an osteoinductive factor, in conjunction with a synthetic matrix of bovine bone. This combination enhances the density of formed bone, promotes proper bone healing, and eliminates the need for autologous bone grafts.

5. Conclusions

1. The main finding of the present study indicates a decrease in the volume of defects and an increase in bone density after 3 and 6 months in both groups, with no significant difference between them.

2. The results of the present study agree with those of Dayashankara and Bhatnagar [(5)] and Richard [(3)], who concluded that the use of A-PRF and I-PRF shows less chances of resorption of formed bone as both A-PRF and I-PRF carry a large quantity of growth factors, which play a central role in hemostasis, angiogenesis, osteoblastic proliferation, and differentiation, making A-PRF and I-PRF advantageous.

3. Upon comparing the clinical outcomes on Day 10 between the two examined groups, it was determined that there was no discernible disparity between them regarding edema, dehiscence, suture breakdown, infection, and graft rejection. This aligns with the findings of Aishwarya and Priyanka [11], who highlight the substantial function of A-PRF in promoting periodontal healing due to its elevated concentration of autologous growth factors, thereby ensuring adequate soft tissue coverage for the newly formed bone.

4. Mixing a bovine bone graft with either A-PRF or I-PRF improves bone augmentation.

6. Recommendations and Future Research Directions

More future studies with more samples are required in the future to evaluate the differences between I-PRF and A-PRF and their effects on bone grafting.

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