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**Efficiency of advanced-PRF usage in the treatment of alveolar cleft with iliac bone graft: a retrospective study.**

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**Efficiency of advanced-PRF usage in the treatment of alveolar cleft with iliac bone graft:  
a retrospective study.**

**ABSTRACT:**

The aim of this study was to evaluate the efficiency of a new alveolar bone grafting protocol using advanced-PRF (a-PRF) by comparing the volume of newly formed bone after a bone graft combining autogenous iliac crest bone with either PRF or a-PRF.

Patients presenting an uni- or a bilateral alveolar cleft were included retrospectively in 2 groups: one group was grafted using cancellous iliac crest bone with PRF (group PRF), whereas a-PRF was used for the other group (group a-PRF). Pre-operative (3 months) and post-operative (6-months) CBCT were performed. The volume of newly formed bone was measured by subtracting the post-operative to the pre-operative cleft volume. The mean volume of newly formed bone was compared between the 2 groups using a student's *t*-test.

Twenty-four patients were included, twelve allocated to each group. Forty-eight CBCT were analysed. The mean volume of newly formed bone was 0,29 ( $\pm$  0,09) cm<sup>3</sup> in the a-PRF group, versus 0,20 ( $\pm$  0,08) cm<sup>3</sup> in the PRF group (student's *t*-test,  $p=$  0,024). The percentage of newly formed bone was 60,4 ( $\pm$  10,4) % in the a-PRF group versus 51,4 ( $\pm$ 18,4) % in the PRF group (student's *t*-test,  $p =$  0,165).

The present study is in favour of improved bone regeneration in group a-PRF. Within the limitations of the present study, this procedure should be adopted in cleft bone grafting whenever possible.

**Keywords:**

**PRF – Advanced-PRF – Alveolar secondary bone graft – Cleft lip and palate – CBCT**

**This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.**

## **INTRODUCTION:**

Alveolar bone grafting is currently considered the gold standard for the reconstruction of maxillary alveolar defect (Kang, 2017) in cleft patients. Although the literature is inconclusive regarding the perfect timing for alveolar bone grafting, secondary bone grafting seems to be preferred in order to limit maxillofacial growth disturbances (Brudnicki et al., 2017). It is usually performed before permanent canine eruption, between 5 and 11 years-old (Seifeldin, 2016; Brudnicki et al., 2019), with a current tendency to early bone grafting around 5-6 years-old (Dissaux et al., 2016; Garcia et al., 2018; Fahradyan et al., 2019), and involves for most teams the grafting of autogenous bone (Farronato et al., 2014; Dao and Goudy, 2016; Shirani et al., 2017). Cancellous iliac crest bone is usually the preferred donor material, due to its easy surgical access and great osteogenic potential (Rawashdeh and Telfah, 2008). There is, however, no clear international consensus about any of these points, and each team continues to follow its own specific protocol (Shaw et al., 2001; Urbanova et al., 2016).

Platelet-rich fibrin (PRF) was first introduced in 2001 by Choukroun and his team, and comes as a gel like material that can be used in conjunction with bone substitutes (Dohan et al., 2006). PRF is a second generation of platelet concentrate produced by simple blood centrifugation without biochemical manipulation, unlike platelet-rich plasma (PRP) which is obtained with use of anticoagulants. PRF is made of an autologous bio scaffold of a dense fibrin matrix with integrated growth factors, which are released from the scaffold over a sustained period of time to promote healing of hard and soft tissues (Clark et al., 2018; Canellas et al., 2019). A modification of the centrifugation protocol was proposed in 2017 (Ghanaati et al., 2014), the new formulation of advanced-PRF (a-PRF) obtained releasing in vitro significantly higher quantities of growth factors when compared to traditional PRF (Kobayashi et al., 2016).

At our institution, the use of PRF combined to autogeneous iliac crest bone grafting was integrated in 2013 for gingivoperiosteoplasty procedures, with very satisfying results in terms of bone integration and mucosal healing. Due to the promising results of a-PRF on bone osteogenesis (Caruana et al., 2019), the alveolar bone grafting protocol was modified in cleft patients in 2018, and switched from using PRF to a-PRF.

The aim of this study was to evaluate the efficiency of this new protocol by comparing the volume of newly formed bone after alveolar bone grafting combined with either PRF or a-PRF.

## **MATERIALS AND METHODS:**

### **1/ Patients population:**

In this monocentric study, patients who underwent alveolar bone grafting for an uni- or bilateral alveolar cleft, and for whom a pre- and post-operative cone beam computed tomography were available, were included retrospectively in the study. This study was conducted in accordance with the Helsinki Declaration of 1975, as revised in 2013, and registered at our institution under PI2021 843 0074.

All patients had been managed and operated since their birth by the same experienced surgeon. The surgical timetable was as follow:

- 2-3 weeks: use of a passive alveolar plate to enable the realignment of the maxillary arch.
- 6 months: cheiloplasty according to Malek's modified Tennison technique, rhinoplasty according to Mac Comb and Talmant, and intravelar veloplasty according to Sommerlad.

- 18 months: two planes uranoplasty in residual cleft palate < 15 mm, or calvarial periosteal graft after closure of the nasal plane in residual cleft palate > 15 mm.
- 4-5 years or 9-10 years (if early management was not possible): pre-surgical expansion with a quadhelix or rapid maxillary expander, followed by alveolar bone grafting with an autogenous anterior iliac crest bone graft.

Patients were allocated into 2 groups according to the adjunction of PRF (Group PRF) or a-PRF (Group a-PRF) to the grafting material.

A CBCT was performed 3 months pre-operatively, and 6 months post-operatively for each patient. The DICOM files were treated with the Planmeca Romexis Viewer 5.2.1.R software. The volume of the alveolar cleft was segmented cut by cut from the piriform aperture to the alveolar crest of the teeth adjacent to the cleft in a cephalocaudal direction, and from the anterior border of the alveolar bone to the mesial surface of the teeth adjacent to the cleft in an anteroposterior direction (Figure 1). The volume of newly formed bone in each group was measured by subtracting the post-operative cleft volume to the pre-operative cleft volume. To assess osseous integration, the absolute value of newly formed bone volume was expressed as a percentage of the initial cleft volume.

To ensure the reliability and reproducibility of the results, all measures were taken twice by the same operator, and their mean value calculated.

## **2/ Surgical procedure:**

The patient was installed on a supine position, with hyperextension of the head and neck. Venous blood was withdrawn under general anaesthesia, via venipuncture with a butterfly needle. Four sterile plastic tubes of 10 mL without external anticoagulants were used to collect 40 mL of blood, immediately placed in the centrifuge (Adip'spin®, Adip'sculpt).

- PRF group: centrifugation at 2700 rpm during 12 minutes. Careful removal of the clot, and separation from the red blood cell fraction with scissors (Figure 2).
- a-PRF group: centrifugation at 1300 rpm during 5 minutes, collection of 1 cc of the supernatant, and centrifugation at 1300 rpm during 3 minutes. Careful removal of the clot, and separation from the red blood cell fraction with scissors.

Meanwhile, cancellous iliac crest bone was harvested following the usual surgical procedure.

For patients of group a-PRF, it was mixed with 1 cc of the supernatant previously collected, in order to obtain a cohesive bone graft, easier to manipulate.

The oral mucosal lining was closed, and a membrane of PRF (PRF group) or a-PRF (a-PRF group) was put over the suture line. The alveolar cleft was then filled with cancellous iliac crest bone along its entire height. A new membrane of PRF (PRF group) or a-PRF (a-PRF group) was placed over the bone graft, in order to enclose and protect it (Figure 3). Finally, muco-periosteal flaps were advanced and sutured without tension over the alveolar crest.

### **3/ Statistical analysis:**

Descriptive statistics were produced using the MS Excel 2016 software (MICROSOFT, Redmond, USA) and the R 3.5.2 software (Foundation for Statistical Computing, Vienna, Austria). A  $\chi^2$  test was performed to assess the comparability between groups. A student's *t*-test was performed to compare the pre- and post-operative volume of the alveolar cleft, and the volume of newly formed bone between groups. A p-value less than 0,05 was considered statistically significant. The Pearson correlation coefficient (*r*) was measured to evaluate intra-observer reliability.

## RESULTS:

Twenty-four patients presenting uni- or bilateral alveolar cleft were included. Twelve were allocated to group PRF, and 12 to group a-PRF. Both groups were comparable regarding the sex, the age (mean age  $7,7 \pm 1,96$  years), and the type of alveolar cleft (unilateral or bilateral). Patients characteristics are described in Table 1.

A total of 48 CBCT (24 pre-operative, and 24 post-operative) were analysed. The results are presented in Table 2, and an example of pre and post-operative CBCT is shown in Figure 4. The mean pre-operative volume of the alveolar cleft was comparable in both groups ( $0,41 \text{ cm}^3 (\pm 0,11)$  for the PRF group,  $0,47 \text{ cm}^3 (\pm 0,16)$  for the a-PRF group,  $p = 0,248$ ).

The mean volume of newly formed bone was  $0,29 \text{ cm}^3 (\pm 0,09)$  in the a-PRF group, and  $0,20 \text{ cm}^3 (\pm 0,08)$  in the PRF group, this difference being statistically significant ( $t$ -test,  $p = 0,024$ ) (Figure 5). The percentage of newly formed bone was also greater in the a-PRF group ( $60,4\% \pm 10,4$ ) than in the PRF group ( $51,4\% \pm 18,4$ ), with an increase of almost 10% of newly formed bone, although this result was not statistically significant ( $t$ -test,  $p = 0,165$ ). The distribution of results in both groups is presented in figure 4. Intra-observer reliability was good, with a Pearson correlation coefficient of 0,96 (Figure 6).

## DISCUSSION:

PRF and a-PRF membranes present a vast regenerative potential by releasing a broad spectrum of cytokines, chemokines, growth factors and other mediators (Dohan et al., 2006; Ghanaati et al., 2014). Unlike PRP membranes, PRF and a-PRF membranes do not require the use of anticoagulants that might interfere with the natural healing process (Kobayashi et al.,

2016). Changing the centrifugation protocol in terms of centrifugation time and speed also leads to a different distribution pattern for neutrophilic granulocytes and growth factor release, in favour of a-PRF membranes compared to PRF and PRP-membranes (Ghanaati et al., 2014; El Bagdadi et al., 2019). The increased cell distribution of neutrophilic granulocytes of the a-PRF membrane might indeed be the basis for a better functionality of the transplanted monocytes/macrophages and lymphocytes, and their deployment to support tissue regeneration (Ghanaati et al., 2014). Furthermore, the increased growth factor release of the a-PRF membrane might influence positively wound healing and biomaterial-based tissue regeneration (Kobayashi et al., 2016; El Bagdadi et al., 2019).

However, if the literature regarding PRF is rich and tends to support its beneficial effects on bone regeneration (Zumarán et al., 2018; Canellas et al., 2019; Karayürek et al., 2019), a standardization of PRF protocols is required in order to perform reproducible studies with a higher scientific level of evidence (Ghanaati et al., 2018). PRF efficiency on bone formation in maxillary alveolar cleft reconstruction is also debated, with conflicting results in the literature (Marukawa et al., 2011; Shawky and Seifeldin, 2016; Saruhan and Ertas, 2018; Omidkhoda et al., 2018). As for a-PRF, due to its recent description, its efficiency on bone regeneration has yet to be proven for that indication.

Although this is a retrospective study, this modification of the gingivoperiosteoplasty procedure shows promising results, and the adjunction of a-PRF to the grafting material seems to increase the volume of newly formed bone compared to PRF ( $t$ -test,  $p = 0,024$ ). The gain of almost 10% of newly formed bone in the a-PRF group, although not statistically significant ( $t$ -test,  $p = 0,165$ ), is also in favour of the superiority of the new a-PRF protocol. The use of PRF and a-PRF membranes might also improve soft tissue healing, as there was no wound dehiscence to declare in this small cohort of patients.

It was unfortunately not possible to dispose of a control group in this study owing to its retrospective character. Indeed, PRF membranes started to be used at our institution in 2013, and a-PRF membranes in 2018, and no CBCT evaluation was available for patients grafted without PRF before 2013. Yet, if a new prospective study with a control group was to be considered, it might represent a potential loss of opportunity for the patients that would not benefit from the use of PRF or a-PRF membranes. To date, only one other study is available comparing the use of a-PRF versus no PRF with iliac crest bone graft (Dayashankara Rao et al., 2020), and is in favour of less bone resorption in the a-PRF group. However, this study only used two-dimension radiography to assess bone loss, thus not taking into account the whole volume of grafted bone.

CBCT is an efficient tool to evaluate bone remodelling (Spin-Neto et al., 2011). It allows the delivery of lower radiation doses with short scanning times (10-70 seconds) compared to medical CT scanning (Feragalli et al., 2017), these two points being essentials when it comes to the paediatric population. CBCT is also capable of providing a 3-dimensional representation of the maxillofacial skeleton, with minimal distortion and sub-millimetre resolution (Kamperos et al., 2020). It provides satisfactory information about linear distances and volumes, and was used in this study to measure the pre- and post-operative alveolar cleft volume, and the volume of newly formed bone (Stasiak et al., 2019). Intra-observer reliability was good (Pearson correlation coefficient = 0,96) and supports the validity of the measures taken pre- and post-operatively.

Autogenous cancellous iliac crest bone was used in the current study, as it is considered the gold standard to stimulate bone healing and fill bone defects, and is associated with a higher success rate (Seifeldin, 2016). Particulate cancellous iliac grafts were used as they are more readily incorporated and remodel to the adjacent alveolus. For all patients in a-PRF group, particulate bone grafts were also mixed with liquid PRF supernatant in order to

secure the bony particles, this modification of protocol having been proposed by Choukroun in his first description of a-PRF. As this study is a retrospective one, it was not possible to standardize this technique in both groups. However, this should not represent any bias in term of volume added as only a minimal amount of liquid was used to this extent.

## **CONCLUSION:**

A-PRF membranes combined with cancellous iliac grafts seem to improve bone regeneration compared to PRF. Within the limitations of the present study, a-PRF should be adopted in cleft bone grafting whenever possible..

**Declaration of interest: none.**

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## **FIGURE LEGENDS:**

**Table 1: Patients characteristics of group PRF and a-PRF. SD: standard deviation.**

**Table 2: Volume of newly formed bone in group PRF and a-PRF. SD: standard deviation.**

**Figure 1: Segmentation of the cleft volume (in blue) with the Planmeca Romexis Viewer 5.2.1.R software.**

**Figure 2: Removal of the PRF clot after centrifugation.**

**Figure 3: Alveolar cleft bone grafting technique. A PRF or a-PRF membrane is placed over the oral mucosal suture line. The alveolar cleft is filled with cancellous iliac crest bone and a new membrane of PRF or a-PRF is placed over the bone graft.**

Figure 4:

**Figure 5: Box-plot showing the distribution of results in group PRF and a-PRF.**

**Figure 6: Measure of Pearson correlation coefficient to evaluate intra-observer reliability.**

Figure 1

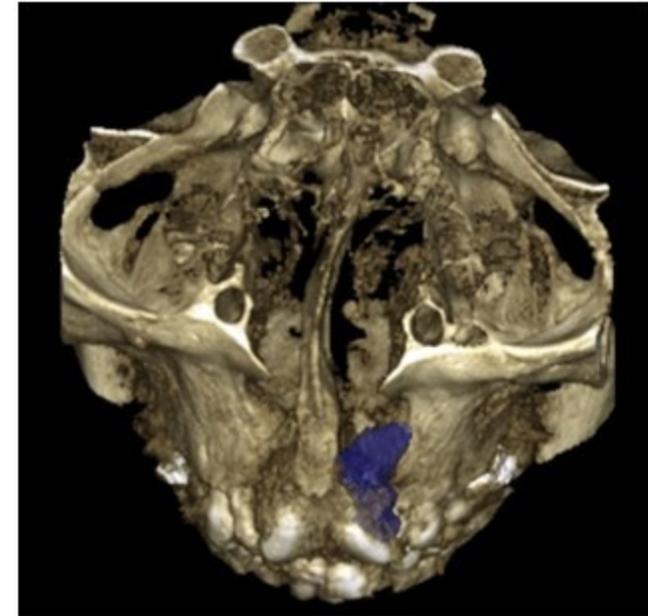
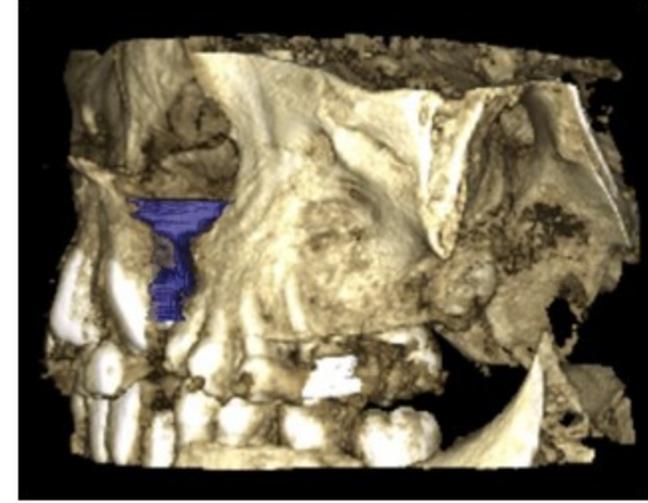
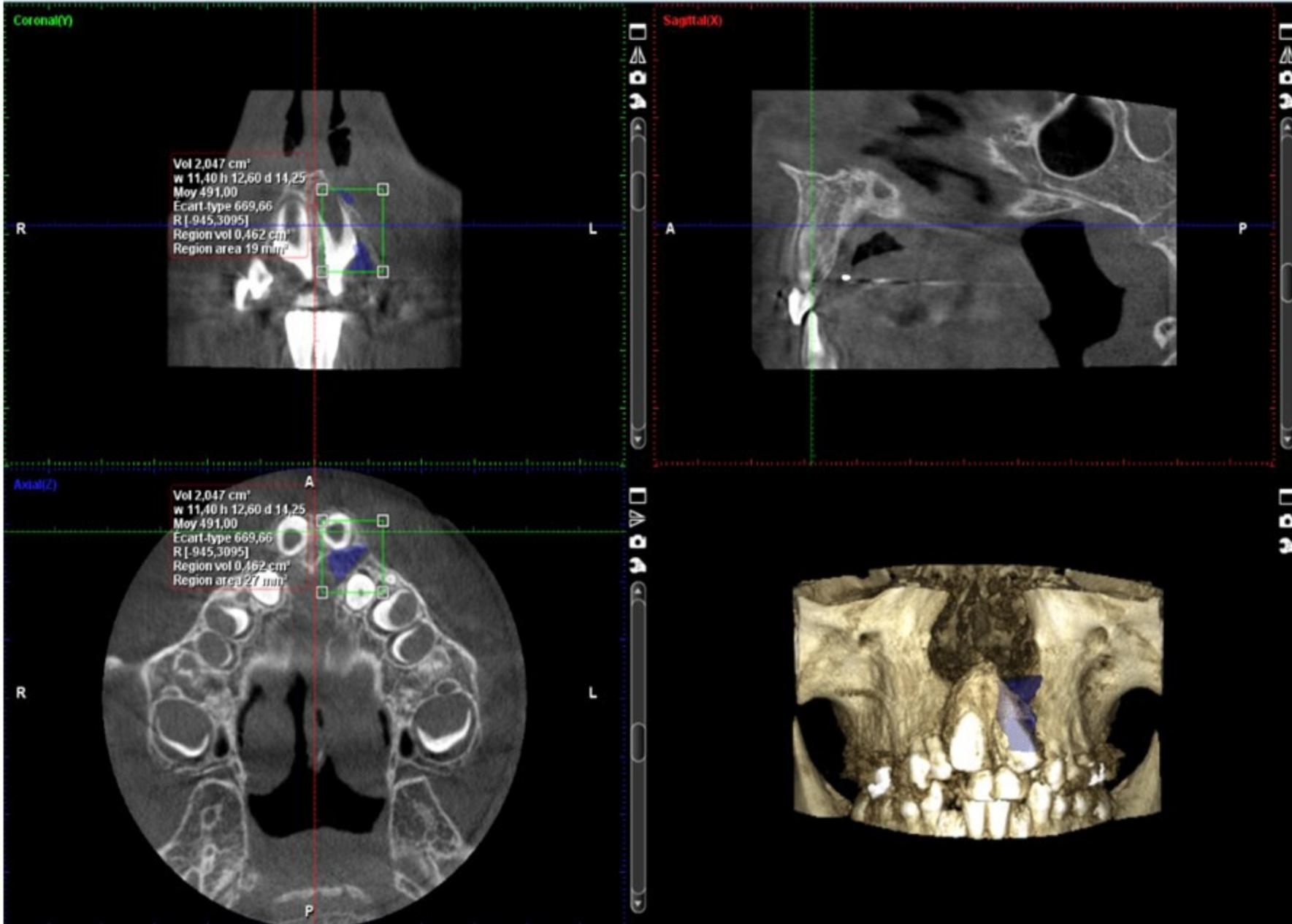


Figure 2



Figure 3

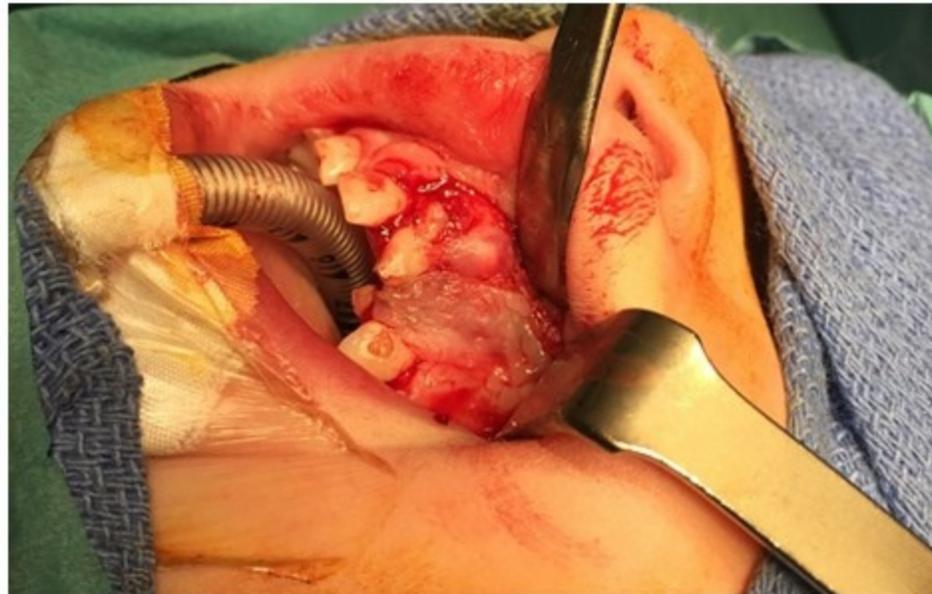
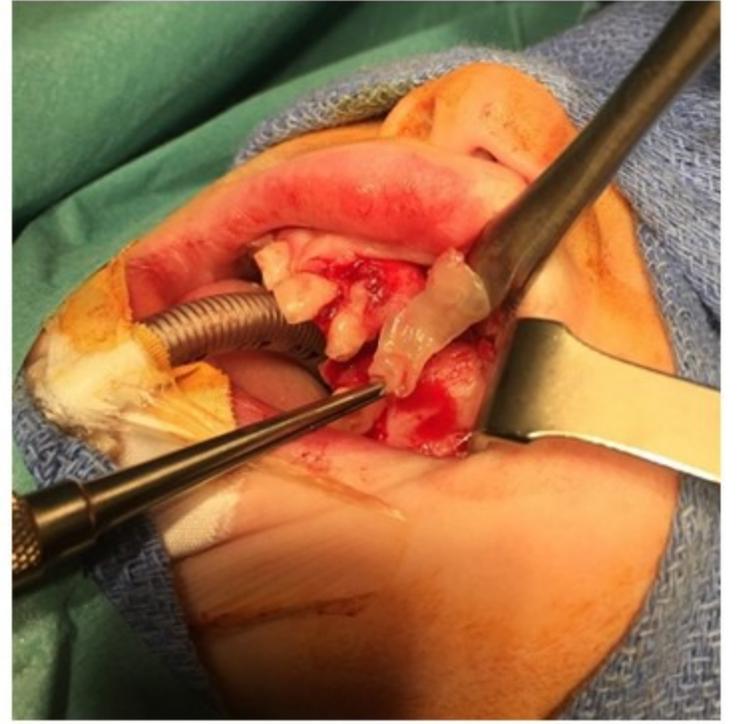
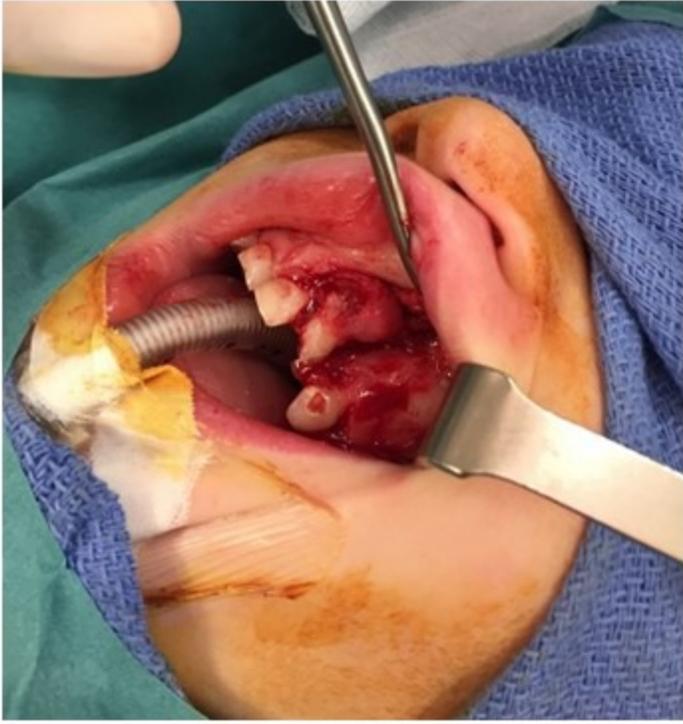


Figure 4

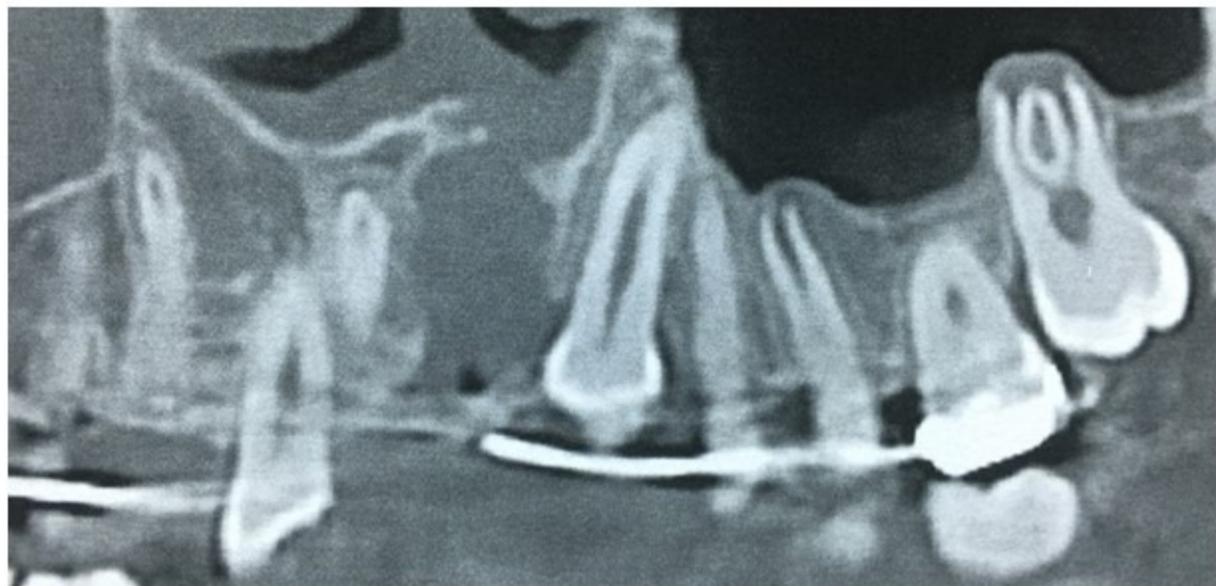


Figure 5

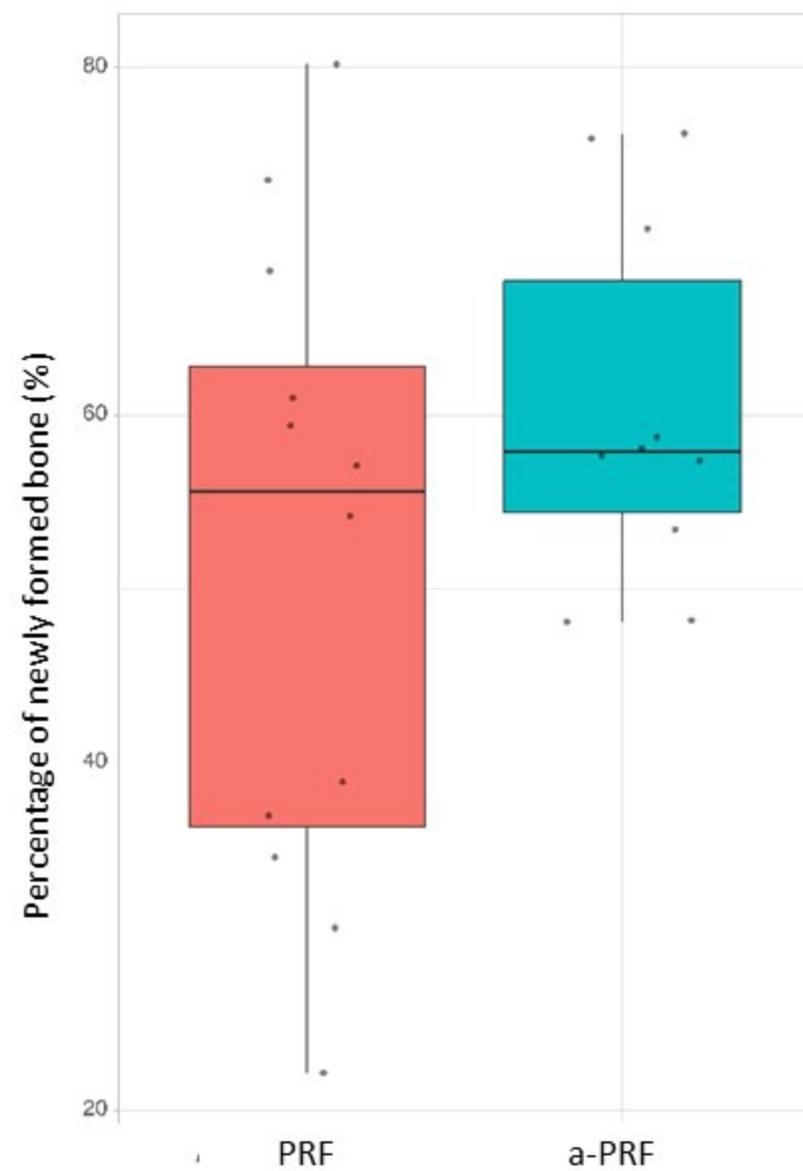
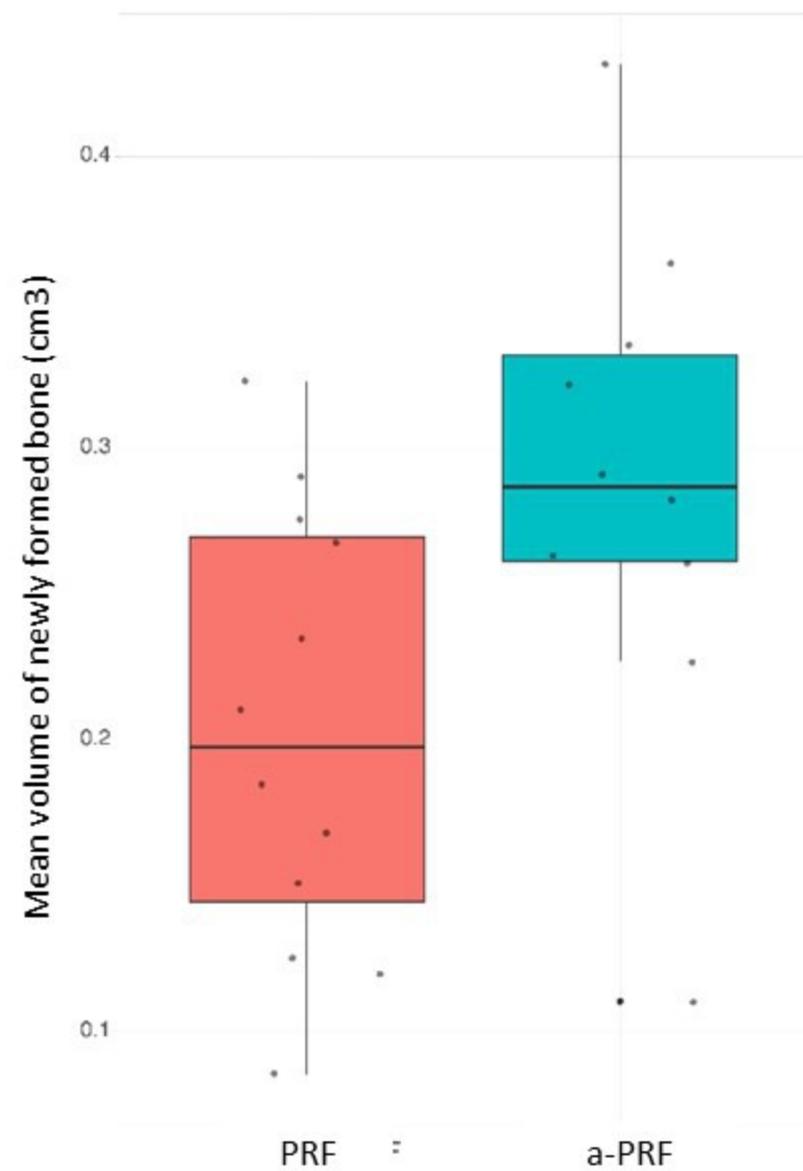
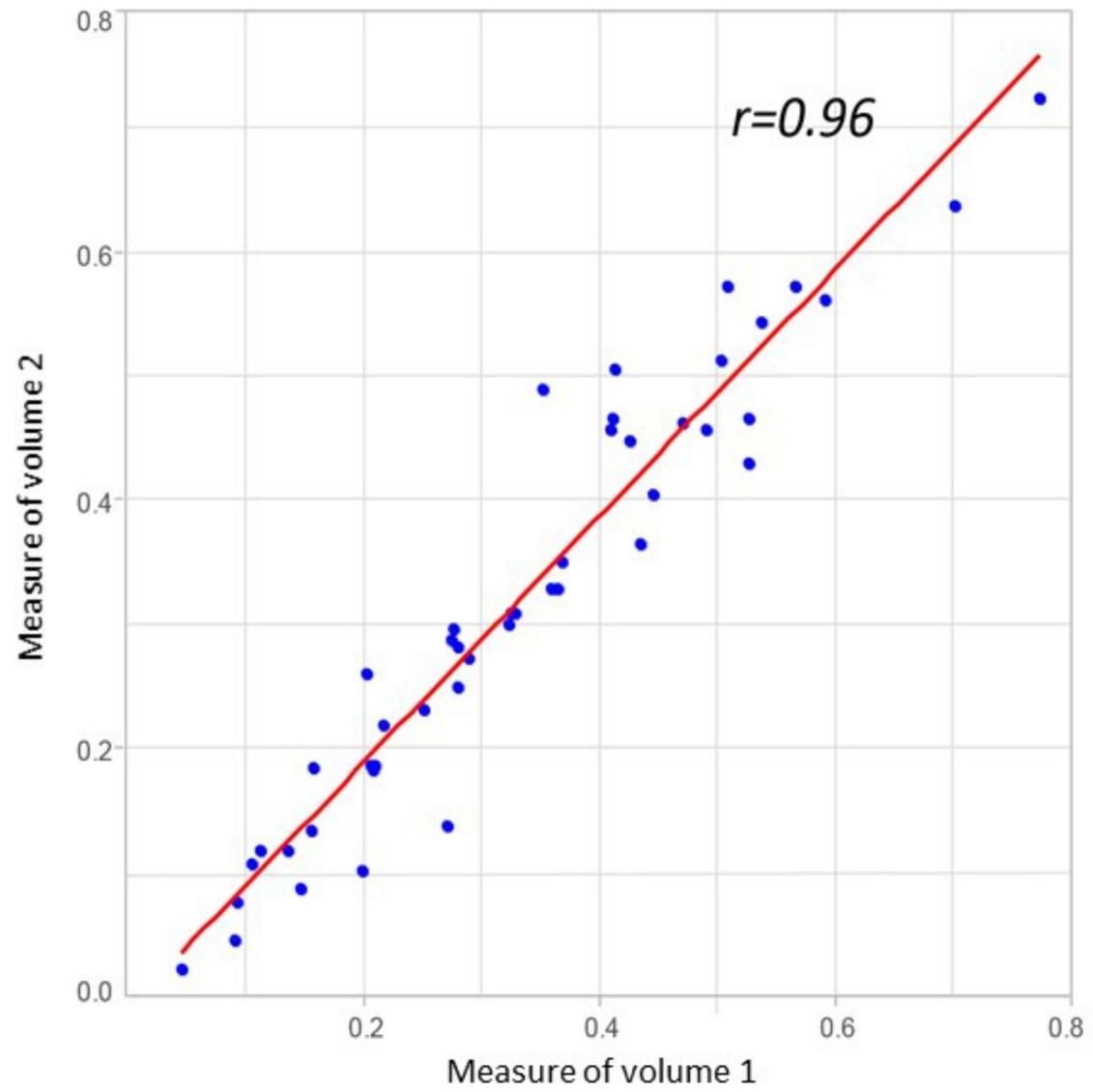


Figure 6



**Table 1 :**

	<b>PRF</b> (n = 12)	<b>a-PRF</b> (n = 12)	<b>p-value</b>
<b>Mean age</b>	7,76 [SD : 1,99]	7,77 [SD : 2,02]	0,984
<b>Sex</b>			1
F	5 (41,7%)	5 (41,7%)	
M	7 (58,3%)	7 (58,3%)	
<b>Type of flap</b>			0,761
Bilateral	7 (58,3%)	5 (41,7%)	
Right	2 (16,7%)	3 (25%)	
Left	3 (25%)	4 (33,3%)	
<b>Side</b>			0,413
Right	4 (33,3%)	7 (58,3%)	
Left	8 (66,7%)	5 (41,7%)	

**Table 2 :**

	<b>PRF</b> (n = 12)	<b>a-PRF</b> (n = 12)	<b>p-value</b>
<b>Mean pre-operative cleft volume (cm<sup>3</sup>)</b>	0,41 [SD : 0,11]	0,47 [SD : 0,16]	0,248
<b>Mean post-operative cleft volume (cm<sup>3</sup>)</b>	0,20 [SD : 0,11]	0,20 [SD : 0,10]	0,984
<b>Mean volume of newly formed bone (cm<sup>3</sup>)</b>	0,20 [SD : 0,08]	0,29 [SD : 0,09]	0,024
<b>Percentage of newly formed bone (%)</b>	51,4 [SD : 18,4]	60,4 [SD : 10,4]	0,165