October University for Modern Sciences and Arts University
MSA Dental Journal

https://msadj.journals.ekb.eg/ PRINT ISSN: 2812 - 4944 VOL. 3, Issue 2, 21 - 31 April, 2024

Volumetric Bone Regeneration Of Maxillary Cystic Defect Grafted With Mineralized Plasmatic Matrix Versus Nano Crystalline Hydroxyapatite Bone Graft Mixed With Platelet Rich Fibrin. A Randomized Clinical Trial

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ARTICLE INFO.

Keywords:
Maxillary cysts, bone regeneration, PRP, mineralized Plasmatic matrix (MPM), nanocrystalline hydroxyapatite bone graft (nHA)

Abstract

Background: One of the most prevalent conditions in the oral and maxillofacial region is jaw cysts. Enucleation of cysts is a commonly embraced treatment method which may result in bony irregularities that need to be filled with grafting material. The purpose of this study was to evaluate bone regeneration of maxillary cystic defects grafted with mineralized Plasmatic matrix (MPM) in comparison to nanocrystalline hydroxyapatite (nHA) bone graft mixed with platelet rich fibrin.

Methods: A randomized controlled clinical trial conducted on 16 subjects (six females and ten males) collected from the outpatient clinic of the Department of Oral and Maxillofacial Surgery, Faculty of Dentistry, October University of Modern Sciences and Arts. Cairo, Egypt. Allocated to one of two equal groups: Group (I): received a mineralized Plasmatic matrix (MPM). Group (II): received a nanocrystalline hydroxyapatite (nHA) bone graft mixed with platelet-rich fibrin. Defects sizes, volumetric bone fill & bone density will be evaluated by CBCT at six months post-operative to determine the amount of bone fill & healing.

Results: Indicate improvements in the healing of bone defects and increase in bone density observed in both MPM group & nHA group. nHA group showed statistically significant decrease of cyst sizes & volume than MPM group. In terms of bone density nHA group had statistically significant higher density levels than MPM.

Conclusion: It was concluded that cavities filled with a combination of nHA mixed with PRF achieved better bone fill compared to those treated with MPM.

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1 Introduction

One of the most prevalent conditions in the oral and maxillofacial region is jaw cysts [1], which frequently result in severe bone lesions and particular clinical symptoms such as localized discomfort, swelling, and loosening of teeth.[2] The cystic cavity is a well-defined radiolucent lesion lined with epithelium.[3]

The enucleation of cysts is a commonly embraced treatment method, which entails the removal of the cystic

wall to prevent its recurrence. Other commonly utilized techniques such as marsupialization and decompression serve the purpose of reducing pressure on the lesion and promoting bone formation. Enucleation has traditionally been the preferred approach for managing jaw cysts due to its conservative nature, ensuring thorough removal of the lesion.[4- 6]

Enucleation of cysts may result in bony irregularities in the oral and maxillofacial region. The resulting cavity may heal spontaneously through bone mending, or it may need to be filled with grafting material [7- 10].To fill up the defects, a range of bone grafts were utilized, including synthetic bone replacements, autografts, allografts, and xenografts [11-13]. Despite extensive literature documentation indicating the necessity of grafting crucial size defects to attain complete regeneration [14].

Since platelet regenerative capabilities were introduced in the 1970s,[15] a variety of platelet concentrates have been employed to improve the healing process of both hard and soft tissues. Among these, platelet-rich fibrin (PRF) and mineralized plasmatic matrix (MPM) stand out as well-established adjunct options for filling bony defects and promoting optimized healing.

PRF is acknowledged as the second generation of platelet concentrate, encompassing a fibrin mesh, platelets, cytokines, and growth factors. Its introduction in oral surgery was first presented by Dohan et al. [16, 17] Hard and soft tissue repair are thought to be improved by PRF's stimulation of angiogenesis and release of many growth factors.[18] The subject of guided bone regeneration has extensively investigated the use of PRF.[19]

Perisse [20] developed the modified platelet concentrate known as Mineralized Plasmatic Matrix (MPM). It comprises a platelet concentrate with a fibrin network combined with a bone substitute.[21] The distinctive aspect of MPM lies in its incorporation of platelets and growth factors, known to provide osteoinductive properties, alongside a graft material that offers osteoconductivity, stability, and volume preservation.[22] The recent utilization of MPM as a regenerative material has demonstrated improved healing of both hard and soft tissues. [22 - 24]

Calcium phosphate ceramics are active in promoting bone growth, also serving as conducive materials for osteogenesis. Extensive experimental data supports their ability to not only encourage the formation of new bone but also to stimulate the differentiation of stem cells into bone-forming cells. Additionally, they aid in the growth of new blood vessels, a crucial aspect of tissue regeneration. Among ceramics, Beta-tricalcium phosphate (β-TCP) is frequently used in the fields of orthopaedics & dentistry. It is often applied in the form of cements or particle grafts. [25- 28]

The inception of hydroxyapatite (HA) in regenerative science dates back to the 1950s, when bioceramics were first utilized as inert scaffolds for filling bone defects. Because the composition of hydroxyapatite is comparable to that of apatite found in naturally occurring bone, it is well known for having great biocompatibility. [29] Hydroxyapatite is a popular material to use as a scaffold for bone regeneration with many advantages including osteoinductivity, osteoconductivity, bioactivity, and biocompatibility.[30] However, concerns have been raised regarding the brittleness and limited degradation properties of hydroxyapatite, including its slow degradation rate.[31]

The inorganic phase of bone consists of carbonated apatite, typically in a nanoscale and amorphous state when initially formed. On the other hand, macroscopic HA is a brittle substance that resorbs slowly, if at all, despite certain resemblance to bone mineral.[32] Advancements in nanotechnology have enabled the development of nanoscale hydroxyapatites (nHA), characterized by a crystal structure more akin to that of native bone.[33] Due to their high surface area and the methods used for their creation, such as wet precipitation techniques, nanostructured HA particles exhibit bioresorbability more similar to that of natural HA found in bone.[34] Nanoscale hydroxyapatites (nHA) offer enhanced bioactivity compared to macroscale HA, presenting another advantage. Furthermore, the larger surface area and rougher texture of nHA promote improved cell adhesion and interaction with the extracellular matrix. Additionally, both clinical and in vivo studies indicate that nanoscale hydroxyapatite (nHA) promotes enhanced bone tissue regeneration, suggesting that bio-inspired nHAs outperform block or particulate HA when used as bone graft substitutes.[35]

Cone-beam computed tomography (CBCT) is being used more frequently in the maxillofacial field due to its accessibility, reduced radiation dose and superior performance at a lower cost. Compared to the multi-detector computed tomography (MDCT) standard dental protocol scan the CBCT effective dose is 1.5 to 12.3 times less. Preoperative radiography evaluation decreases surgical stress and complications following surgery. A highly accurate method for evaluating maxillofacial lesions prior to surgery is CBCT.[36]

The use of CBCT in the assessment of orofacial structures has become more indicated due to newer systems that offer lower radiation exposure and high-contrast pictures that are nearly as good as bone window computed tomography (CT). Bone density measurement, complex diagnosis, treatment planning, surgical pathology assessment and numerous other tasks have been demonstrated to benefit from CBCT scans. Numerous studies have demonstrated a linear relationship that can be utilised to estimate bone density between the Hounsfield unit (HU) in a CT scan and the grey scale in a CBCT.[37]

The purpose of this study was to evaluate bone regeneration of maxillary cystic defects grafted with mineralized Plasmatic matrix in comparison to nanocrystalline hydroxyapatite bone graft mixed with platelet rich fibrin.

2 Methods

2.1 Sample size:

The sample size for this study was calculated according to ***Charan & Biswas***[38] equation & P value of ($P \leq 0.05$) using the study by ***AbdUllah I. Abd Rabbouh, et al.***[39] as a reference. The sample size calculations revealed that a sample size should be at least 16 samples for the two groups.

2.2 Patient selection and study design:

The study was a randomized controlled clinical trial conducted on 16 subjects (6 females and 10 males). Patients were collected from the outpatient clinic of the Department of Oral and Maxillofacial Surgery, Faculty of Dentistry, October University of Modern Sciences and Arts.

The current study was performed in agreement with principles of the Declaration of Helsinki on medical research and was approved by the ethical committee of October University of Modern Sciences and Arts. NO (834)

All patients were asked to sign a written consent including the details of the surgical procedure along with the possible complications. Following proper diagnosis patients selected were suffering from maxillary cystic lesions requiring to be grafted after surgical enucleation.

Inclusion Criteria:

- Patients with cystic lesion of size equal to or exceeding 3 cm^2.
- Patients who agreed to follow all study procedures and signed the written consent form.
- Patient age ranging from 20-55 years.
- Free medical history.
- Availability of two CBCT examinations before and after surgical intervention.

Exclusion criteria:

- Medically compromised patients, with any systemic condition that could contraindicate the surgical procedure or interfere with normal bone healing.
- Scans which did not have optimum diagnostic value,
- Failure of patient follow-up
- Patients who refused the written informed consent.

2.3 Patients grouping:

16 eligible candidates included in the study were randomly allocated to one of two equal groups as follows:

Group (I): received a mineralized Plasmatic matrix **(MPM)** bone graft.

Group (II): received a nanocrystalline hydroxyapatite **(nHA)** bone graft mixed with platelet-rich fibrin.

2.4 Pre-Operative Phase:

Comprehensive preoperative clinical and radiographic evaluations were conducted for all patients. Teeth associated with the cystic lesion were meticulously assessed for vitality and restorability. Those requiring endodontic treatment were addressed prior to surgery, while those lacking sufficient bony support were planned for extraction during the surgical procedure. Preoperatively, the cystic fluid was aspirated, and subsequently, the aspirated fluid was forwarded for histopathological examination. For all patients, cone beam computed tomography (CBCT) scans were conducted to assess bone density and determine the dimensions of the cystic lesion.

Root canal treatment:

All teeth related to the lesion were cleaned, shaped, and obturated in a single visit. Local anesthesia was established using local infiltration with 4% articaine with 1:100,000 epinephrine (Laboratories Inibsa, Barcelona, Spain). Endodontic access cavity was achieved by using 014 round carbide and Endo Z burs (Dentsplysirona). The crowndown technique was employed for the canals after establishing A glide path

with stainless steel hand instruments size #10. Patency was established and verified. The ideal working length was determined using an electronic apex locator (Dentaport ZX, Morita, Tokyo, Japan) and confirmed with periapical radiographs. The canals were cleaned and shaped using Pepsi Gold rotary system (Mpro , China).The final instrumentation size was determined as three sizes larger than the first file binding at the working length. Master apical files ranged from #25 to #50, depending on both root anatomy and initial diameter of the root canal. Irrigation was always performed with 5.25% NaOCl solution. Obturation using gutta-percha (Aceone-Endo, Aceonedent. Co. Geonggi-Do, Korea). AH Plus was mixed according to the manufacturer's instructions and the master gutta-percha cone was coated with AH Plus **(Fig. 1).**

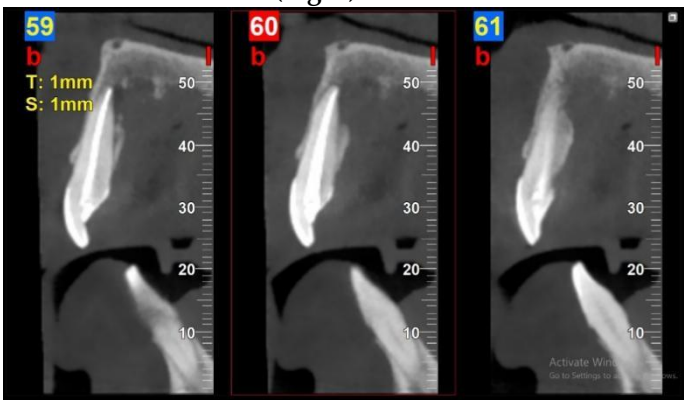

Figure 1. Showing endodentically treated related teeth

2.5 Operative Phase:

Surgical Procedure:

Before the surgical procedure, all patients were scrubbed & draped in a standard fashion. All patients were operated under local anaesthesia (Articane 4 % with 1: 100 000 epinephrine, UbistesinTM forte, 3M ESPE, Germany).

A full-thickness pyramidal muco-periosteal flap was carefully raised to access the cystic lesion completely. The bone covering the lesion was meticulously removed with aid of fissure bur and bone rongeur. The cyst lining was then meticulously identified and delicately dissected from the muco-periosteal layer, as well as from the surrounding bone. Complete cyst enucleation was then carried out & sent for histopathology. Non restorable teeth were extracted while those that were endo treated received retro grade filling material of Mineral trioxide aggregate (MTA) after root apicectomy. The undermined bony edges were removed & cystic cavity was irrigated.

Preparation of platelet-rich fibrin (PRF):

For PRF preparation the protocol presented by ***Dohan et al***.[17] was followed. Venous blood was collected from the antecubital vein into 9ml sterile non-coted tubes without any additives. Then blood was immediately centrifuged at 3,000 rpm, for ten minutes **(Fig. 2)** .

Figure 2. Showing PRF preparation

Group (I)

The upper yellowish liquid portion from each tube was withdrawn using syringes(PRF). Then, it was mixed with Particulate bone graft (Beta tri calcium phosphate β-TCP) to obtain **MPM.** The mixture was then used to fill the maxillary bony defect **(Fig. 3,4).**

Figure 3. Showing MPM preparation

Figure 4. Showing grafting of maxillary defects with MPM.

Group (II):

The PRF layer was withdrawn from tube & then mixed with nanocrystalline hydroxyapatite **(nHA)** bone graft. The resultant mixture was used to fill the maxillary bony defect **(Fig. 5,6,7).**

Figure 5. Showing the PRF layer

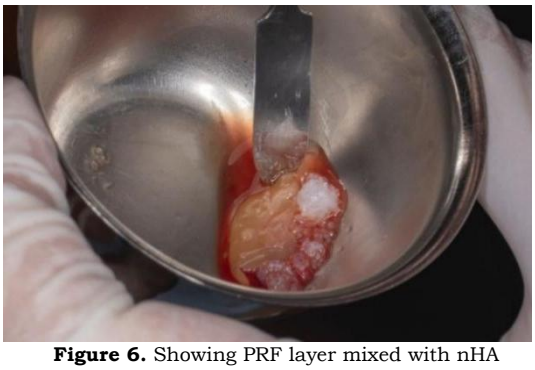

Figure 6. Showing PRF layer mixed with nHA

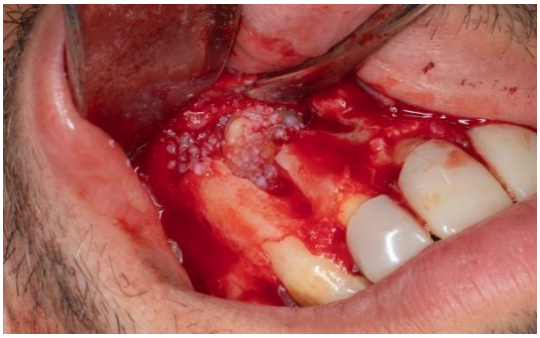

Figure 7. Showing maxillary bone defects filled with nHA mixed with PRF

The mucoperiosteal flap was then repositioned and secured in place using 3/0 black silk suture in both groups.

2.6 Post-operative phase:

Post-operative care

Post-operative instructions were provided to all patients as follows:

- Extra-oral ice packs were applied for the first six hours postoperatively.
- Rinsing is not recommended for the initial 24 hours following surgery.
- Soft diet and liquids were recommended. Regular oral hygiene practices could be resumed after 24 hours.

Post-operative medications

- All patients were prescribed antibiotics in the form of 1 gm of Augmentin (amoxycillin + clavulanatepotassium,GSK) twice per day for five days.
- Non-steroidal anti-inflammatory analgesic in the form of Catafast 50 mg (Diclofenac potassium 50mg, Novartis Pharma AG, Cairo, Egypt.)

Follow up:

Patients were scheduled for a follow-up appointment after seven days to remove sutures and ensure they were free of any post-operative complications such as fenestration.

Radiographic assessment

Radiographic images were measured by using the working tools of NewTom Giano HR and the OnDemand 3D software for the CBCT scans of maxilla before and 6 months after treatment, in buccopalatal, mesiodistal, and superoinferior dimensions. Also bone density evaluation and fusion for both dimension and volume comparison were made.

The scan before and after the surgical procedure was used to conduct volume reduction calculations. The second CBCT was conducted with careful attention to obtain adequate information on the state of the healing process. In all instances, CBCT was done using CBCT NewTom Giano HR (QR s.r.l., Verona, Italy) (FOV 8X6 cm at 90 kV and 0.3 mm isotropic voxel size). For each patient, data from pre-operative CBCT scans and those after 6 month of surgical procedure were transferred for visualization and analysis using OnDemand 3D (Cybermed.Co., Seoul, Korea.) software application. Using the editing tool, sectioning was performed manually to pick the cystic area in each slide in all three spatial projections (i.e., coronal, axial, and sagittal) concurrently with the three-dimensional (3D) visual examination.

The procedure for a cystic lesion using the NewTom Giano HR CBCT Machine and OnDemand 3D software application for digital 3D model reconstruction and volumetric measurements in both pre-operative and post-operative periapical cyst is shown in **(Fig. 8,9).**

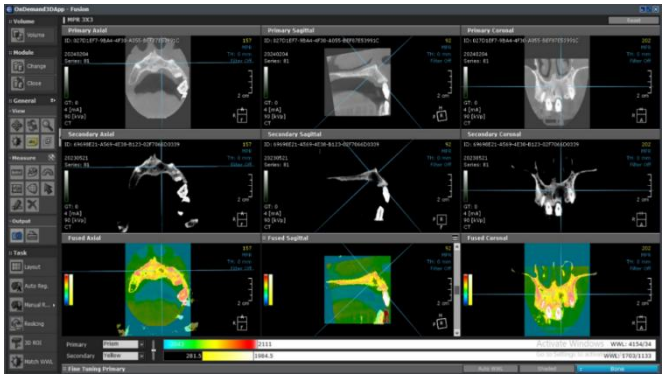

Figure 8. Showing dimensional fusion measurement and comparison.

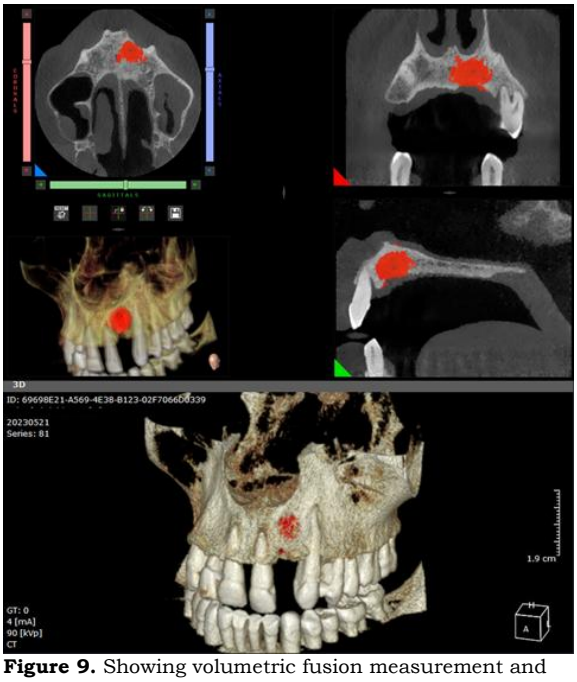

Figure 9. Showing volumetric fusion measurement and comparison.

Statistical analysis:

The collected data were statistically analysed. The significance of the difference between the preoperative and six month postoperative data regarding bone height,width, depth and volume at the same group was assessed using the Student T test (paired and unpaired). The two groups were compared to each other using also the Student T test (paired and unpaired) in difference in bone height, width, depth and volume also the density of the two groups were compared together using the same test. The statistical analysis was carried out using SPSS ver. 22 software (statistical package for social science on windows 2013). A probability value(P≤ 0.05).

3 Results

The current study involved 16 eligible patients (ten males & six females) with maxillary cystic defects, patients mean age was 37.5 years.

Patients were divided into two groups. Group I (four females and four males) received MPM as bone grafts following cysts enucleation and Group II (two females and six males) received Nano hydroxyapatite (nHA) plus PRF as grafting material following cysts enucleation.

Cysts sizes and volumes within the same Group

A statistical significant decreases (P≤0.05) at cysts sizes (height-depth-width) also at cysts volume were obvious at the CBCT for both groups at the follow up interval (Six month post-operative) **(Table 1,2) (Fig. 10, 11)**.

Table 1. Comparison of mean, standard deviation values of cysts sizes and volume in Group I

MPM (Group I)					
		Height	Width	Depth	Volume
	Mean	17.13	20.88	22	2,702.88
Pre-operative	SD	0.99	1.46	1.69	444.98
	Min	16	19	20	2189
	Max	19	23	24	3602
Six Month Post-operative	Mean	7.18	8.93	9.38	337.5
	SD	0.57	0.86	0.81	66.65
	Min	6.4	7.7	8.6	264
	Max	8	10	11.2	478
	P value	0.000	0.000	0.000	0.000

Table 2. Comparison of mean, standard deviation values of cysts sizes and volume in Group II

Nano HA with PRF (Group II)					
		Height	**Width**	**Depth**	**Volume**
Pre-operative	**Mean**	**16.88**	**20.63**	**22.75**	**2,582.38**
	SD	**1.36**	**1.3**	**2.19**	**635.85**
	Min	**15**	**18**	**20**	**1802**
	Max	**19**	**22**	**27**	**3615**
Six Month Post-operative	**Mean**	**5.3**	**6.14**	**6.81**	**142.75**
	SD	**0.99**	**1.03**	**1.09**	**73.32**
	Min	**4.1**	**4.7**	**5.4**	**72**
	Max	**6.9**	**7.8**	**8.3**	**263**
P value	**0.000**	**0.000**	**0.000**	**0.000**	**0.000**

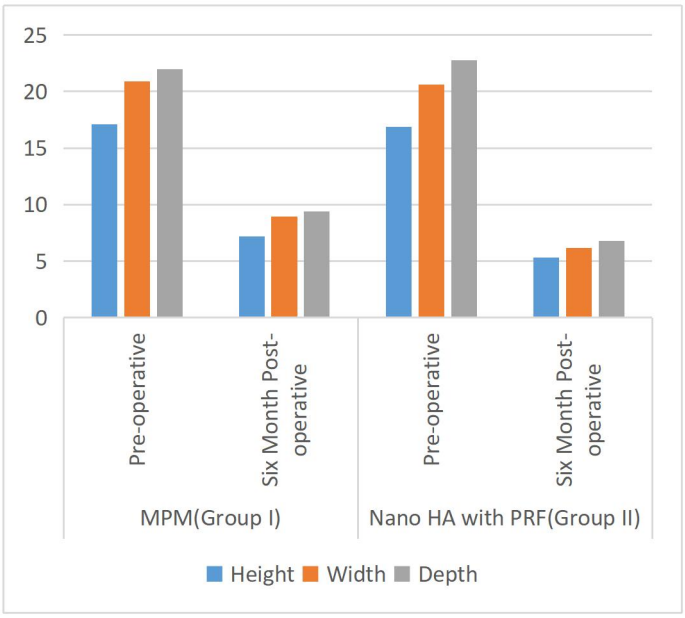

Figure 10. Showing the mean decrease at the cysts sizes of the two groups Pre-operatively and at 6 month follow up period

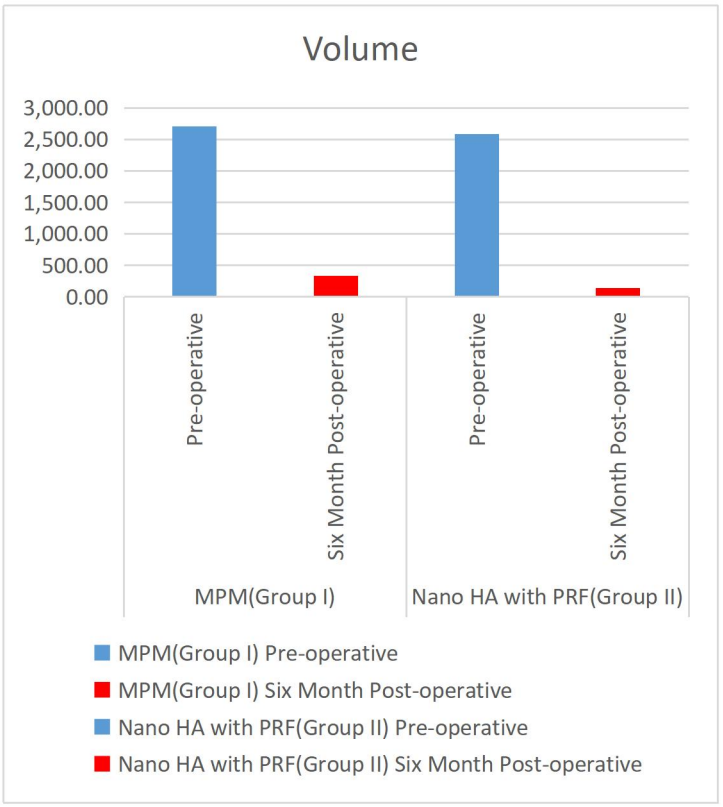

Figure 11. Showing the mean decrease at the cysts volume of the two groups Pre-operatively and at 6 month follow up interval

Cysts sizes, volumes and Densities between Groups

Comparing the two groups together, pre-operative and at six month post-operative, there was no statistical significant difference (P>0.05) between the two groups preoperatively regarding cysts sizes (height-width-depth) and volume **(Table 3) (Fig. 10,11)** , while at the follow up interval of six month post-operative, Group II had statistically significant (P≤0.05) higher decrease at the cysts sizes (height-width- depth) and volume than Group I **(Table 4) (Fig. 10,11).**

Regarding comparison of the two groups densities at the follow up interval (six month post-operative), Group II showed statistical significant (P≤0.05) higher density levels than Group I **(Table 4) (Fig. 12).**

Table 3. Comparison of pre-operative mean, standard deviation values of cysts sizes and volume between the two groups.

Pre-operative					
		Height	Width	Depth	Volume
MPM (Group I)	Mean	17.13	20.88	22.00	2,702.88
	SD	0.99	1.46	1.69	444.98
	Min	16	19	20	2189
	Max	19	23	24	3602
Nano HA with PRF (Group II)	Mean	16.88	20.63	22.75	2,582.38
	SD	1.36	1.30	2.19	635.85
	Min	15	18	20	1802
	Max	19	22	27	3615
	P Value	*0.06*	*0.09*	*0.73*	*0.49*

Table 4. Comparison of six month post-operative mean, standard deviation values of cysts sizes, volume and density between the two groups.

Six month Post-operative						
		Height	Width	Depth	Volume	Density
MPM (Group I)	Mean	7.18	8.93	9.38	337.50	706.50
	SD	0.57	0.86	0.81	66.65	32.57
	Min	6.4	7.7	8.6	264	660
	Max	8	10	11.2	478	764
Nano HA with PRF (Group II)	Mean	5.30	6.14	6.81	142.75	812.63
	SD	0.99	1.03	1.09	73.32	43.99
	Min	4.1	4.7	5.4	72	765
	Max	6.9	7.8	8.3	263	873
	P Value	0.0001	0.0000	0.0000	0.0000	0.0001

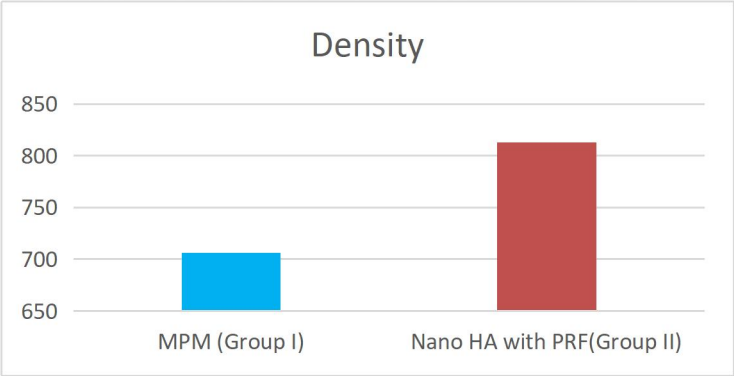

Figure 12. Showing the mean cysts density of the two groups at 6 month follow up interval

Difference in Cysts sizes and volumes between Groups

Comparing the difference in cysts sizes (height, width, depth) and volume which occurred in the two groups before cysts enucleation and grafting (pre-operative) and after cysts enucleation and grafting (six month post-operative), there was a statistical significant difference (P≤0.05) between the two groups regarding difference in cysts sizes (height-width-depth), better results were in favor for Group II more than Group I. Meanwhile, the difference in cysts volumes which occurred in the two groups, there was a non-significant statistical difference (P>0.05) between the two groups, but Group II showed better results in decreasing of cysts volume than Group I **(Table 5)** (**Fig. 13, 14).**

Table 5. Comparison of difference in mean, standard deviation values of cysts sizes and volume between the two groups.

Difference Between Six Month post-operative and Pre-operative intervals					
		Height	Width	Depth	Volume
MPM (Group I)	Mean	9.95	11.95	12.63	2,365.38
	SD	0.55	0.74	1.25	407.75
	Min	9.2	10.9	11	1817
	Max	11	13.3	14.7	3124
Nano HA with PRF (Group II)	Mean	11.58	14.49	15.94	2,439.63
	SD	0.55	1.26	1.67	573.43
	Min	10.9	12.9	14.1	1705
	Max	12.3	16.9	19.7	3392
	P Value	0.0000	0.0004	0.0006	0.7702

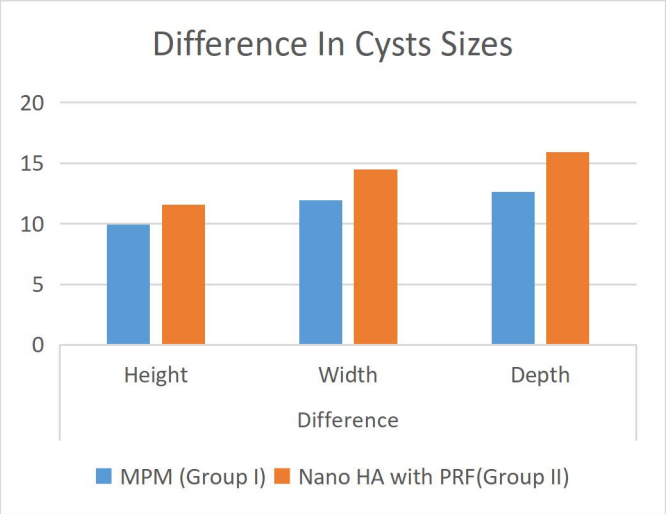

Figure 13. Showing the mean difference in decrease at the cysts sizes of the two groups from Pre-operative to 6 month follow up interval

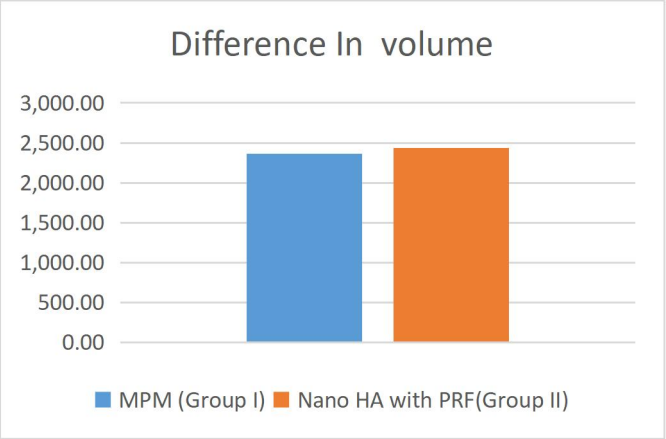

Figure 14. Showing the mean difference in decrease at the cysts volume of the two groups from Pre-operative to 6 month follow up interval

This suggested that there was a reduction in cystic volume after surgical treatment evaluated with CBCT radiographic images. Differences in dimension, volume and bone density were compared and noted.

4 Discussion

When treating odontogenic cysts that have a diameter of three centimetres or more, the normal procedure involves meticulous enucleation and the use of various bone substitutes to totally obliterate the defect. Studies have shown that defects of such dimensions, if not obliterated, do not heal entirely and spontaneously, regardless the duration of observation. [40, 41] Thus, A significant risk of infection, weakening of the bones, and pathological fracture is typically linked to the un-healing process

There is insufficient evidence in the literature to favour one type of filling material over another.[42] The use of platelets concentrates including **MPM** & **PRF** in bone regeneration has greatly revolutionized owing to it is unique criteria. [20 21 43 44 45] In the current study two grafting materials were evaluated, mineralized Plasmatic matrix **(MPM)** utilizing **β-TCP** in comparison to nanocrystalline hydroxyapatite **(nHA)** bone graft mixed with platelet-rich fibrin **(PRF).** This study aimed to evaluate bone regeneration of maxillary cystic defect grafted with mineralized Plasmatic matrix in comparison to nanocrystalline hydroxyapatite bone graft mixed with platelet-rich fibrin.

CBCT is a diagnostic tool that, when combined with volumetric measures for various cancers and cysts in the jaw, can assist a specialist address a variety of situations. When it comes to visualizing a cystic lesion, its proximity to important structures, and the loss of cortical bone, a 3D study is superior to a 2D examination. It is also helpful in analyzing the creation of new bones. [46] Hence its use in evaluation in this study.

The findings of the present study indicate advancements in the healing of bone defects and a rise in bone density observed in both experimental groups. Both **MPM** group & **nHA** group showed a significant decrease in cyst size & volume when compared pre-operative and at six month follow-up period. However, when the two groups where compared to each other, **nHA** group showed statistically significant decrease of cyst size & volume than **MPM** group. In terms of bone density **nHA** group had statistically significant higher density levels than **MPM**.

When dimensional differences occurred in cyst sizes & volume pre-operative to post-operative between the two groups were compared, there was a statistically significant difference between the two groups in terms of size with better results in **nHA** group. However, differences in cyst volume was statisticaly non-significant between the two groups, though **nHA** group still had better results.

The findings from the present study indicate that the **MPM** group exhibited sufficient bone regeneration, as evidenced by a notable reduction in cyst cavity size and an increase in bone density during the 6-month follow-up period.This is in agreement with results reported by ***Nader Nabil Elbokle, et al.***[45] they reported significant decrease in cyst size & increased bone density in cystic cavities filled with **MPM** when compared to cavities filled with PRF alone.

The current study demonstrates that the combination of **nHA** with PRF facilitated bone regeneration, this in accordance with ***AbdUllah I. Abd Rabbouh, et al.***[39] they stated that utilizing a combination of nHA and PRF as grafting material around the implant following narrow alveolar ridge splitting had superior results to immediate implants alone in terms of implant stability & bone density.

Our results showed that the use **nHA** mixed with PRF had better effect on regeneration of bony defects following cyst enucleation, when compared to **MPM**. This could be attributed to the nanostructure of the nHA bone graft, increasing its surface area with rougher texture promoting cell adhesion & interaction with the extracellular matrix therefore enhancing bone regeneration. These facts are in agreement with ***Hruschka et al.***[35] study comparing different particle size & content.

5 Conclusion

It was concluded that cavities filled with a combination of **nHA** mixed with PRF achieved better bone fill compared to those treated with **MPM**.

Authors' Contributions

All authors have read and approved the manuscript.

Conflict of interest

The authors declare that they hold no competing interests.

Funding

The research study was self- funded by the authors.

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