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THE EFFICACY OF NANO-CRYSTALLINE HYDROXYAPATITE COMBINED WITH PARATHYROID HORMONE VERSUS NANO-CRYSTALLINE HYDROXYAPATITE ALONE ON HEALING OF BONE DEFECT AFTER CYST ENUCLEATION: A RANDOMIZED CLINICAL TRIAL (RCT)

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ABSTRACT

Objective: This study aimed at evaluation clinical and radiographic efficacy of using Nano-crystalline hydroxyapatite combined with parathyroid hormone versus Nano-crystalline hydroxyapatite only on healing of bone defects after cyst enucleation.

Methods: 20 patients with bone defects were included, they were equally allocated in two groups; intervention group (group I) where the defect was filled with Nano-crystalline hydroxyapatite (Nano-bone®) combined with parathyroid hormone (PTH 1-34) and control group (group II) where the defect was filled with Nano-crystalline hydroxyapatite alone (Nano-bone®). Surgical procedure was made under local or general anesthesia. Radiographic assessment using cone beam computed tomography (CBCT) was performed to measure defect size (preoperative and six months post-operatively).

Results: There weren't post-operative complications. Radiographically, in intervention group, average defect dimensions 2.8 ± 0.41 cm^3 preoperatively, 3.88 ± 0.55 cm^3 immediately postoperatively, and 1.20 ± 0.15 cm^3 six months postoperatively. Meanwhile, in group II, they were 2.2 ± 0.33 cm^3 preoperatively, 2.5 ± 0.3 cm^3 immediately postoperatively and 1.5 ± 0.4 cm^3 six months postoperatively with a significant difference between both groups (< 0.001). Moreover, the average dimensions of the graft surface area, in group I were 144.52 ± 14.78 mm^2 preoperatively, and 86.56 ± 15.57 mm^2 six months postoperatively. While in group II the measurements were 152.62 ± 12.78 mm^2 preoperatively, and 100.54 ± 13.57 mm^2 six months postoperatively with a significant difference between both groups (< 0.001).

Conclusion: Using the combination of Nano-crystalline hydroxyapatite combined with parathyroid hormone has a positive impact on healing of bone defect after cyst enucleation.

KEYWORD: Nano-Crystalline Hydroxyapatite, Parathyroid Hormone, bone defect, CBCT

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INTRODUCTION

An odontogenic cyst is defined as an intra-bony pathological cavity lined by odontogenic epithelium; this cavity contains a fluid or semifluid content. According to the World Health Organization (WHO), odontogenic cysts represent up to 90% of jaw cysts. They are classified into two main categories: inflammatory or developmental. [1]

There are various approaches for the treatment of oral and maxillofacial cysts; the choice of the treatment modality depends on the cyst etiology, size and localization. While treating any cyst, the ultimate goals are to eliminate the lesions, reduce their recurrence rate and restore the function & esthetics with minimal trauma to the surrounding vital structures. Among the available treatment options, cyst decompression +/- cyst enucleation, enucleation with primary closure without grafting and enucleation combined with various adjuvant therapies. Literature advocated the restoration of large cystic lesions (1-2 cm) in order to avoid the risk of pathological fracture and to restore long term functional/esthetic outcomes. [2–4]

For the treatment of large cysts, methods of filling the bone cavities with graft material are widely performed. Grafting options that can be used either autogenous -which still the gold standard-, allogenic, xenogenic and alloplastic materials. Among the synthetic grafting materials that are recently applied which was introduced with the evolution of Nanotechnology is Nano-crystalline hydroxyapatite (Nano-bone®). This material has a chemical composition resembling that of the bone mineral and a particle size approximately 18 mm and allows for quicker vital bone substitution. Moreover, it is biocompatible, osteo-conductive and has a role in bone regeneration. Recently, it has many clinical applications including maxillary sinus floor augmentation and periodontal tissue regeneration [5–9]

Despite the previously mentioned advantages of the Nano-crystalline hydroxyapatite, it is associated with many limitations that encourage further research to improve its outcome and this had led to the introduction of using parathyroid hormone (PTH) which is normally secreted by parathyroid gland. This hormone is present in the market as recombinant PTH to treat bone disorders as it has the ability to stimulate bone formation. [10]

PTH has an essential role in the regulation of calcium and phosphate metabolism. Presently PTH is FDA approved for use as an anabolic treatment for osteoporosis. Studies proved that Parathyroid hormone (PTH 1-34) promotes bone formation via stimulating both cortical & cancellous bone regeneration, increase bone volume along with improving mechanical bone strength. [10,11]

Nevertheless, there was limited evidence concerned with the effect of adding PTH to Nano-crystalline hydroxyapatite on the healing of intra-bony defects of the oral cavity. Accordingly, this clinical trial aimed to compare the efficacy of using Nano-crystalline hydroxyapatite combined with parathyroid hormone versus Nano-crystalline hydroxyapatite alone on the healing of bone defect after cyst enucleation.

MATERIALS AND METHODS

Study Design

Twenty patients with bone defects after cyst enucleation were enrolled in the current study. They were recruited from the out-patient clinic of Oral and Maxillofacial Surgery Department, Faculty of Dentistry, Cairo University (from June 2023 to August 2024). This study was approved by the research ethics committee of Faculty of Dentistry, Cairo University with the reference number: 52723.

The patients were randomly allocated equally in two groups; the intervention group (group I) where the bone defect was filled with Nano-crystalline hydroxyapatite (Nano-bone®, Artoss GmbH, Rostock, Germany) combined with parathyroid

hormone (PTH 1-34, human Kaneka Eurogentec SA, Seraing, Belgium) and control group (group II) where the bone defect was filled with Nano-crystalline hydroxyapatite material alone (Nano-bone®). Nano-bone® is a combination of Nano-crystalline hydroxyapatite and silica gel to provide optimal bone regeneration with easy handling.

The patients included in this study had the following inclusion criteria; (1) bone defect size not less than 1.5mm×20mm×20mm after cyst enucleation, (2) All ages and both sexes were included, (3) patients who were free from any systemic disease that may affect normal healing of bone and (4) patients with physical and psychological tolerance. However, the exclusion criteria were as follows: (1) recurrent cases, (2) cases required marsupialization, (3) uncooperative patients & (4) medically compromised patients.

Parathyroid hormone laboratory investigation was ordered for patients in the group I

Intervention

Surgical Procedure:

All the patients underwent treatment in aseptic conditions under either local or general anesthesia with the following sequence; (1) vestibular/rectangular incision, was placed with two releasing incisions, (2) flap elevation was carried out using muco-periosteal flap and bone was removed cautiously to gain access to the cystic lesion, then (3) a plane of cleavage was performed between the cystic epithelial lining and the surrounding bone, (4) the entire lesion was enucleated and bone curettage was performed, (5) After the capsule was transferred to the pathology lab for histological investigation in 10% formalin, periodontal cyst was conclusively reported later on. (6) All sharp edges were smoothed, (7) defect irrigation and inspection for any cystic remnants were done, (8) bone defect was filled with Nano-crystalline hydroxyapatite (Nano-bone®) combined with PTH 1-34 in the group of intervention (the amount of solution mixed with the graft was 1 ml). While in the other group the defect was filled with only Nano-crystalline hydroxyapatite (Nano-bone®) **figure (1)**. Moreover, collagen membrane (Tutopatch, TUTOGEN Medical GmbH, Neunkirchen am Brand, Germany) was applied and fixed with either titanium mini pins into the surrounding bone or sutures. (9) Primary closure was made using 4-0 chromic cat gut suturing material. (10) Afterwards surgery along with taking medication Augmentin tablets1 gm (GlaxoSmithKline, Cairo, Egypt) every 12 hours for three days, Ibuprofen 600 mg (Brufen, Abbott Int., Cairo, Egypt) every eight hours for three days, and post-operative strict instructions.

Patients were recalled after two days for clinical and radiographic assessments. The wounds were inspected and irrigated with saline. Clinical assessment of post-operative pain, wound dehiscence and infection were obtained at intervals of 1 week and 1 month.

After two weeks, the sutures were taken out, then the wound was cleaned well with saline and the patient was checked for any postoperative complications such as infection or irritation.

Radiographic Assessment:

CBCT scanning was performed for all the patients 3 times; before the surgery, immediate post-operative (2 days) and 6 months postoperative. The scans were taken in Oral and Maxillofacial Radiology department of the faculty of Dentistry, Cairo University, Egypt. The scans were acquired by Promax 3D Planmeca® system (Helsinki, Finland). The scanning parameters were 90 kV, 6 mA, and a voxel size of 0.2 mm. The DICOM data sets were then imported into a 3D image reformatting software, OnDemand3D software (by Cybermed Inc., South Korea), for data analysis and primary reconstruction.

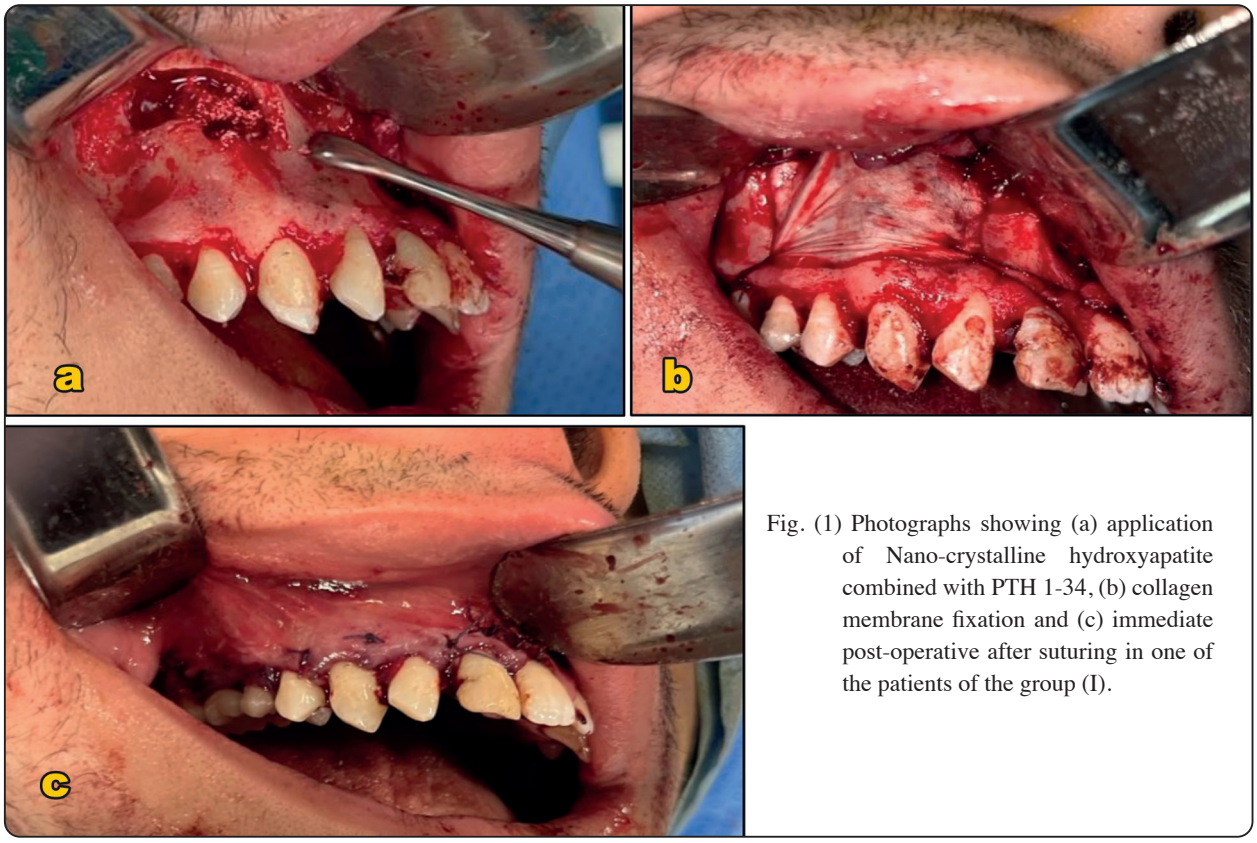

Fig. (1) Photographs showing (a) application of Nano-crystalline hydroxyapatite combined with PTH 1-34, (b) collagen membrane fixation and (c) immediate post-operative after suturing in one of the patients of the group (I).

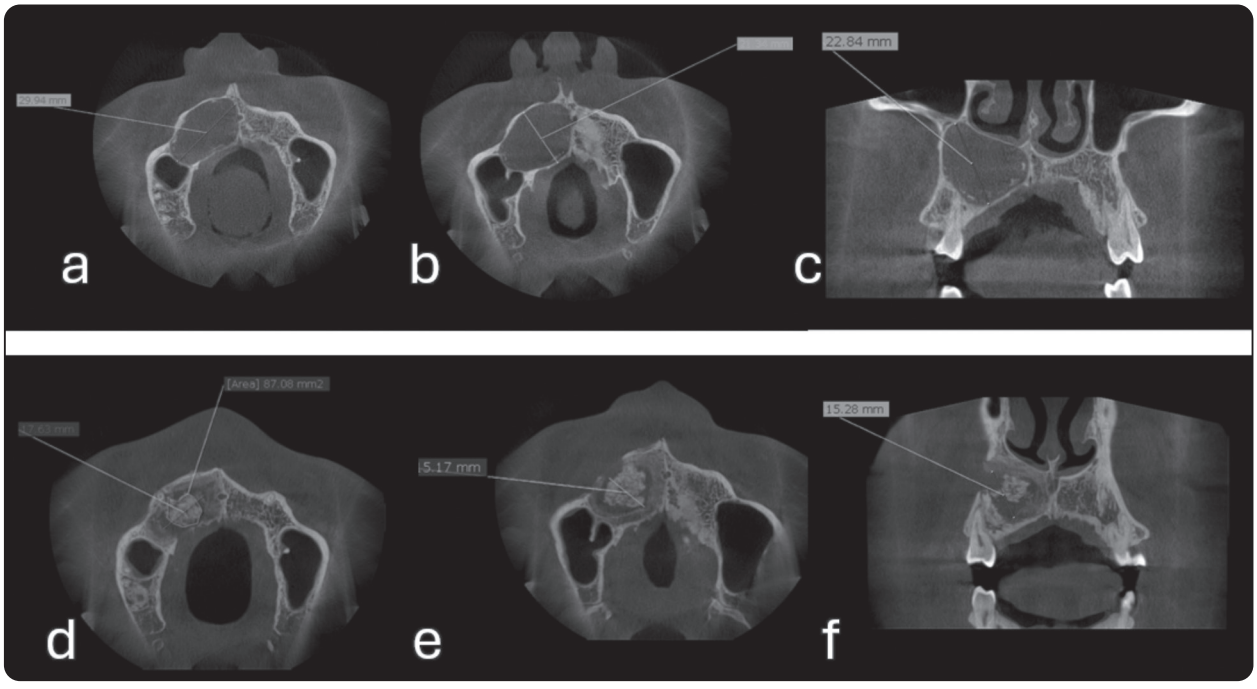

Fig. (2) Defect size measurements: Preoperative a & b axial plane for mesio-distal and buccolingual dimensions and c coronal plane for occluso-gingival dimension. Postoperative (6 month) d & e axial plane for mesio-distal and buccolingual dimensions and f coronal plane for occluso-gingival dimension in one of the patients of the group (I).

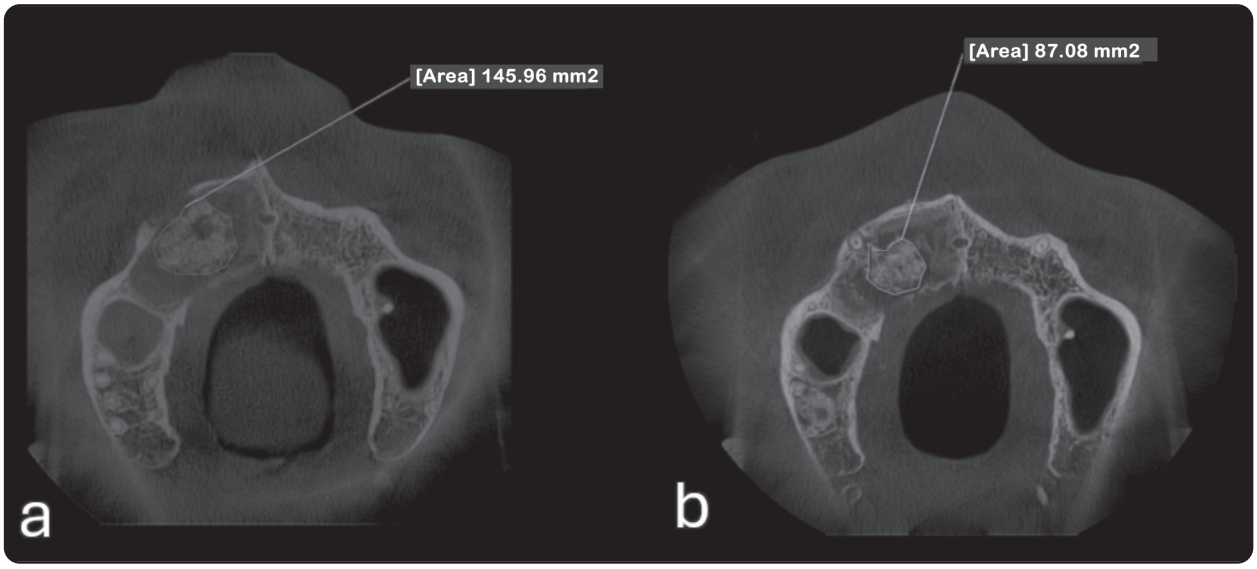

Fig. (3) measurements of the graft material's surface area: a preoperative, b postoperative (6 months) in one of the patients of the group (I).

1. For each patient, the defect size was measured three times in the preoperative CBCT scan, immediate postoperative and 6 months postoperative on the same image planes for standardization **figure (2)**. The widest defects dimensions were measured in the 3 dimensions (mesio-distal, bucco-lingual, Occluso-gingival) as follows: the mesio-distal and buccolabial dimensions were measured on the axial plane, while the occluso-gingival were measured on the coronal plane.
2. Also, the surface area of the graft material was measured at its widest dimensions on the same axial plane of both immediate post-operative and 6 months post-operative **figure (3)**. All the data were recorded and prepared for statistical analysis.

Statistically analysis:

The data were entered into a computer and analyzed using IBM SPSS software, version 24.0 (Armonk, NY: IBM Corporation). The student's t-test was employed to compare the two groups for quantitative variables that were normally distributed.

RESULTS

Clinical results

At baseline, the gender and age of the two groups were equivalent. Every patient had a successful initial recovery with only minor side effects, for instance, mild soreness and/or swelling. There was no graft rejection, infection, wound dehiscence or any graft reactions.

Radiographic results

Measuring the defect dimensions

In the test group, the average defect dimensions measured on CBCT scans were 2.8±0.41cm^3 preoperatively, 3.88±0.55cm^3 immediately postoperatively and 1.20±0.15cm^3 six months postoperatively. In the control group, the average defect dimensions were 2.2±0.33 cm^3 preoperatively, 2.5±0.3 cm^3 immediately postoperatively and 1.5±0.4 cm^3 six months postoperatively **figure (4)**.

- Preoperative comparison: Significant difference ($p < 0.001$)
- Immediately postoperative comparison: Significant difference ($p < 0.001$)

- Six months postoperative comparison: Significant difference ($p < 0.001$)

Measuring the surface area of the graft material:

In the test group, the average graft size measured on CBCT scans were 144.52 ± 14.78 mm^2 preoperatively, and 86.56 ± 15.57 mm^2 six months postoperatively. In the control group, the average graft size measured on CBCT scans were 152.62 ± 12.78 mm^2 preoperatively, and 100.54 ± 13.57 mm^2 six months postoperatively **figure (5)**.

- **Preoperative Comparison**: p-value ≈ 0.03 (significant at the 0.05 level)
- **Postoperative Comparison**: p-value < 0.001 (highly significant)

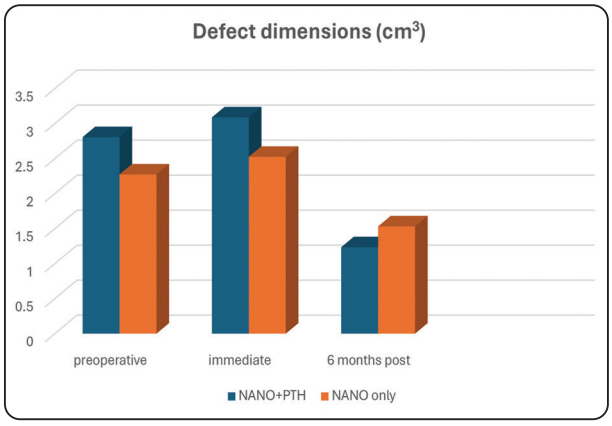

Fig. (4) Bar chart showing the reduction in bone defect size in both the test and control groups, as observed through various CBCT scans.

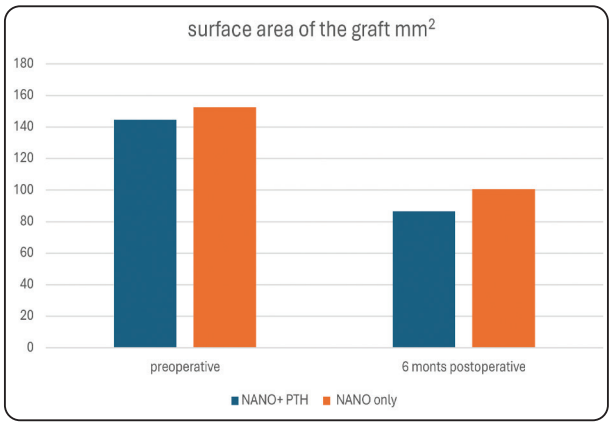

Fig. (5) Bar chart showing the reduction in surface area of the graft material in both the test and control groups, as observed through various CBCT scans.

DISCUSSION

Odontogenic cysts are commonly seen pathological lesions in the oral and maxillofacial region with plenty of treatment approaches that are currently applied. With regards to bone grafting materials, there are many available options including autogenous bone grafts which are still the gold standard. Although, autogenous bone grafts have the following drawbacks: (1) donor site morbidity and mortality, (2) availability of large quantities and (3) increase surgical time. Accordingly, other grafting options are introduced such as allogenic, xenogenic and alloplastic materials which solve many of the limitations encountered with autogenous bone grafts. A promising synthetic material was recently used with the Nano-technology rise, the Nano-crystalline hydroxyapatite with many advantages including; bio-compatibility, nano particle size that allows rapid vital bone substitution and bone regeneration potential[1,8,12].

In the current study, the efficacy of using Nano-crystalline hydroxyapatite combined with parathyroid hormone versus Nano-crystalline hydroxyapatite only on the healing of bone defect after cyst enucleation were assessed clinically and radiographically. Human parathyroid hormone (PTH) is an 84-amino acid polypeptide which is normally secreted by parathyroid gland with an essential role in calcium and phosphate metabolism regulation and acting predominately on bone and kidneys. The use of PTH intermittently results in what is called "anabolic window" which means increasing bone formation stimulation without increasing bone resorption. Consequently, it has been approved by FDA as a treatment modality of osteoporosis in postmenopausal women. Presently, Teriparatide (PTH 1-34) is the N-terminal fragment of the intact hormone and had been introduced with approval for using in treating osteoporosis. [11,13]

Neer RM. et al. performed a study to assess the effect of PTH-34 on fractures and bone mineral

density in postmenopausal women with osteoporosis and they concluded that increasing bone density with decreasing the risk of bone fractures was evidenced as a result of using PTH-34. [14]

Additionally, Aspenberg P et al., Jepsen DP et al. and Che J. et al. demonstrated similar results where PTH-34 had a positive impact on the repair of bone fractures and the bone mineral density in osteoporosis. [15–17]

In our study, a preoperative, immediate postoperative and 6 months postoperative CBCT was performed on the selected patients for the assessment of the extension of the cystic lesion and the assessment of the graft size post-operatively. CBCT was done with the same machine and exposure parameters as in the three scans for standardization purpose.

Intra-operatively, the bone defect in the intervention group (group I) was filled with Nano-crystalline hydroxyapatite combined with PTH 1-34 while in the control group (group II) it was filled with Nano-crystalline hydroxyapatite material alone. Surgical procedure was made under local or general anesthesia under aseptic condition.

The postoperative recovery and healing phase was uneventful in all patients. There were only minor side effects, such as mild soreness and/or swelling which were treated by irrigation, wound care and anti-inflammatory medications. There was no graft rejection, infection, wound dehiscence or any graft reactions. In agreement with the clinical results of this study, Eldibany RM. el al reported that there no post-operative complications were encountered in patients included in their study. [18]

With regards to the radiographic results of the current study, radiographic assessment included measuring the defect dimensions and measuring the surface area of the graft material using CBCT scan in the following intervals: preoperative, immediate postoperative and six months postoperative. For the defect dimensions measurements, there was a reduction in the bone defect size in both the test and control groups with a more favorable outcome met in the test group that showed a significant statistical difference between both groups (< 0.001).

Measurements of the surface area of the graft material showed reduction in the surface area of the graft material in both groups 6 months postoperatively. A more favorable outcome met in the test group with a significant statistical difference between both groups (< 0.001).

In agreement with the radiographic results, Eldibany RM. el al. and Chatzipetros et al. reported that there was a decrease in the surface area by 51% and an increase in bone density by 50.8%. [18,19]

In consistent with the present study, Wodja et al. investigated the efficacy of local delivery of PTH using a scaffold on bone regeneration and they concluded that there was a marked increase bridging of the critical size bone defects evidenced when using the scaffold to deliver PTH 1-84 (3 or 10 μg). [20]

Additionally, studies performed by Orth P. et al. concluded that PTH 1-34 has a positive impact on bone repair with volume enhancement and increase bone mineral density. [21,22]

Nevertheless, a study conducted by Kempen DHR et al. concluded that a limited potential of bone formation encountered when utilizing PTH 1-34 alone, while significant bone regeneration was evidenced when it was mixed with bone morphogenetic protein (BMP-2). [23]

From the present study and results, it was evident that PTH 1-34 has a positive outcome on the repair of bone defects. However, in this study, there were some limitations in the availability and cost of PTH 1-34.

CONCLUSION

Using the combination of Nano-crystalline hydroxyapatite combined with parathyroid hormone has a positive impact on healing of bone defect after cyst enucleation. Studies including larger sample size & longer follow up are recommended for better assessment of the efficacy of PTH 1-34.

Funding

The study was self-funded.

Competing interests

No conflict of interest

Ethical approval

The Ethics and research committee, Faculty of Dentistry, Cairo University approved the study and patients' consent was obtained.

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