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Dental Arch Expansion after Alveolar Cleft Repair using Autogenous Bone Marrow Derived Mesenchymal Stem Cells Versus Autogenous Chin Bone Graft

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Abstract

The reconstruction of alveolar cleft defects is well established, with the most widely accepted approach being secondary alveolar cleft osteoplasty in mixed dentition phase. To avoid morbidity at the donor site or if large amounts of autogenous bone are necessary, bone substitution materials can be used. Mesenchymal derived stem cells were applied to different kinds of bone substitute and compared in different animal models. This study was aimed to evaluate the bone quality and quantity at the alveolar cleft sites that were repaired with autogenous mesynchyal stem cell and its effect on orthodontic dental arch expansion and compare these results with cases treated with autogenous chin bone graft.

Patients and methods: We studied 16 patients with alveolar cleft repaired surgically, whose mean age was 9.5 years (Range 7-12) the patients divided into 2 groups (8 patients in each one) according to surgical technique of repair(Group I) : surgical repair was done by using autogenous bone marrow derived mesenchymal stem cells. (Group II): surgical repair was done by using autogenous chin bone grafting. The patients were undergo to orthodontic dental arch expansion and followed up to 18 months clinically and radiographically to evaluate and compare the effect of grafting types on arch expansion.

Results: The results of this study revealed that the patients in group I who treated by stem cell technology have a clinical results superior than the patients in group II who treated with chin bone grafting. Radiographic results revealed that in group I the bone quality and quantity were superior than that in group II.

Conclusion: The autogenous bone marrow derived mesenchymal stem cells is a good technique in repair of alveolar cleft as it promote the healing of bone with high quantity and quality as well as enhance orthodontic arch expansion.

Keywords: *Alveolar Cleft; Mesenchymal Stem Cell; Chin Bone Graft; Orthodontic Arch Expansion*

Introduction

Repair of bony defects continues to remain a challenging part of many reconstructive procedures. Currently, the gold standard for grafting of bone defects is the use of autogenous bone [1]. In conventional methods, autogenous bone grafting has become an essential step in treating patients with alveolar cleft, and allows the placement of dental implants for missing teeth in the final stages of treatment [2]. A successful graft supplies bone for erupting teeth and periodontal support for teeth adjacent to the cleft. It also gives more support and elevation of the alarbase on the affected side, thereby improving nasal symmetry. Alveolar grafting also stabilizes the separated maxillary segments and provides proper alveolar contour and prevents maxillary arch collapse. The graft also connects the disconnected segments to the mobile premaxilla in cases of bilateral cleft [3,4].

Fresh autogenous bone is the ideal graft because it supplies living immunocompatible bone cells essential for osteogenesis. Therefore, its transplantation is still the gold standard when harvested from sites such as iliac crest, mandible, tibia, rib, or calvarium [5,6]. However, autogenous bone grafting is often related to disadvantages such as

limited availability and donor site morbidity [7]. Another material, such as allogeneic bone, can present an advantage in terms of reduced morbidity, and can be used during alveolar bone grafting, but it is not as beneficial as autogenous bone [8,9]. Favorable results using bone morphogenetic protein 2 (BMP-2) for reconstruction of the alveolar cleft have been reported in the literature, but more studies are necessary to assess the bone quality in the long term [10]. Loss of the bone graft, reopening of the oronasal fistula, or both can happen, although secondary bone graft failures are considered uncommon [11].

Tissue engineering technique involving mesenchymal stromal/stem cells (MSC) of various sources is an alternative to the traditional iliac crest bone graft. MSC with osteogenic potential placed within a biocompatible platform to enhance bone regeneration or recovery in patients with CLP [12]. Mesenchymal stem cells (MSCs), which can be isolated from the marrow cavity as well as from the trabecular compartment, have been shown to have the ability to form new bone when transplanted [2]. Bone substitution materials can be combined with vital cells such as MSCs to increase bone formation [13-16]. Both synthetic and allograft materials allow adhesion and growth of osteoblastic cells, orosteogenic differentiation of precursor cells *in vitro* [17-19].

On the base of complications of traditional bone graft, the aim of this study was to evaluate the bone quality and quantity at the alveolar cleft sites that were repaired with autogenous mesenchyal stem cell and its effect on orthodontic arch expansion and compare these results with cases treated with autogenous chin bone graft.

Patients and methods

Sixteen patients with unilateral alveolar clefts were included in this retrospective study. The age of patients were ranging between (7-12) years. They were all treated by secondary grafting procedures of their alveolar clefts. The patients were selected, examined both clinically and radiographically and surgically managed at the Oral and Maxillofacial surgery Department, Faculty of Dentistry, Tanta University. Maxillary expansion was done at the Orthodontic Department, Faculty of Dentistry, Tanta University.

Careful extra oral and intraoral clinical examinations were performed to determine the main chief complaint and also to evaluate the stability of maxillary segments, presence of old scar, asymmetry of the alar base, presence of oronasal fistula and the presence of erupting teeth in the cleft.

Panoramic radiographs were done for each patient and examined as regard: the morphology of the cleft area, the size of the cleft side, the presence or absence of permanent lateral incisor and canine, the development of root length, presence and position of supernumerary teeth and stage of eruption of permanent canine and lateral incisor. In addition, Quantitative axial computed tomography (CT) scans were done for each patient to assess and measure local bone mineral density.

Patients were divided into 2 groups according to surgical techniques used for alveolar cleft repair. Eight patients (group I) were treated by tissue engineering technology using autogenous mesenchymal stem cell and Nano bone according to our previous study which was published in January 2016 [20]. Another eight patients (group II) were treated with autogenous chin bone grafting. This study was performed after receiving the approval of the ethical committee of Faculty of Dentistry, Tanta University. Written consents were signed by the parents or corresponding relatives to participate in this study.

The Surgical Procedures in Group I

Stem Cell Preparation

In the cell culture lab, human MSCs were isolated and loaded into scaffold according to Soleymani Shayesteh., et al. who was used the stem cells in human sinus augmentation [20].

Isolation and Cultivation of Mesenchymal Stem Cells

Two weeks before surgery a bone marrow aspirate (10-15 ml) was obtained from the posterior iliac crest. The aspirate was diluted at 1:3 in Dulbecco's modified Eagle's medium (DMEM) (Gibco, Paisley, UK). On day 1, non-adherent cells were discarded and adherent cells were washed with phosphate-buffered saline(PBS) (Gibco) and then cultured in DMEM medium with anti-biotics and 20% autologous serum.

Preparation of Human Serum

FCS was replaced by human serum because of concerns of the ethical committee. From each patient 20 ml of whole blood was drained into blood bags (Baxter, Deerfield, IL), quickly transferred to10 ml vacationer tubes

without anticoagulants (BD, Plymouth, UK),and allowed to clot for 4 h at 4oC - 8o C. Subsequently, the blood was centrifuged at 1800 g at 4 oC for 15 min. Serum was collected and filtered through a 0.2 m membrane (Sarstedt, Nümbrecht,Germany). Aliquots of the sterile serum were stored at 20 oC. The lab process and cultivation of the cells for each patient was performed.

Implant Preparation

-NanoBone® granulate *(ARTOSS GmbH Friedrich-Barnewitz-Straße3 18119 Rostock,Germany)* was used in this study. It is the first NanoBone® technology product and was launched in 2005. When mixed with blood NanoBone® takes on a paste-like consistency and can be applied easily and effectively with an augmentation spoon or spatula. It is vary from fine (0.6 x 2mm) and rough (1 x 2mm). One day before transplantation, implants were loaded by the cells obtained from the third subculture of the patient bone marrow derived stem cells. The cylinders were first washed with PBS and then loaded with MSCs by placing 5* 10^5 cells in 0.2 mL DMEM medium on top of it.

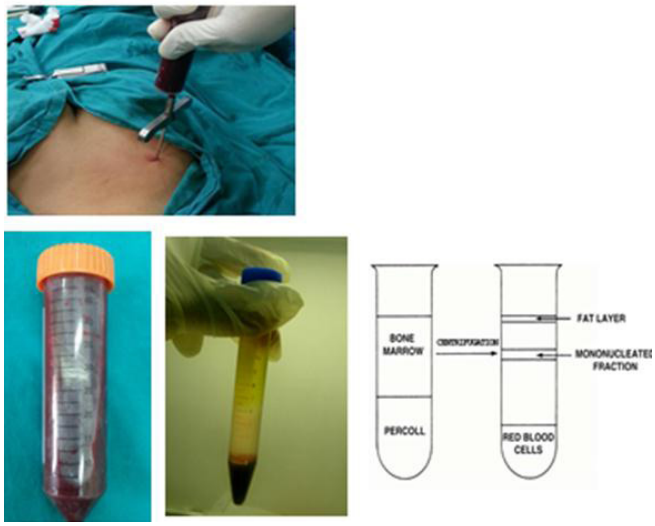

Figure 1: Isolation and cultivation of Mesenchymal stem cells

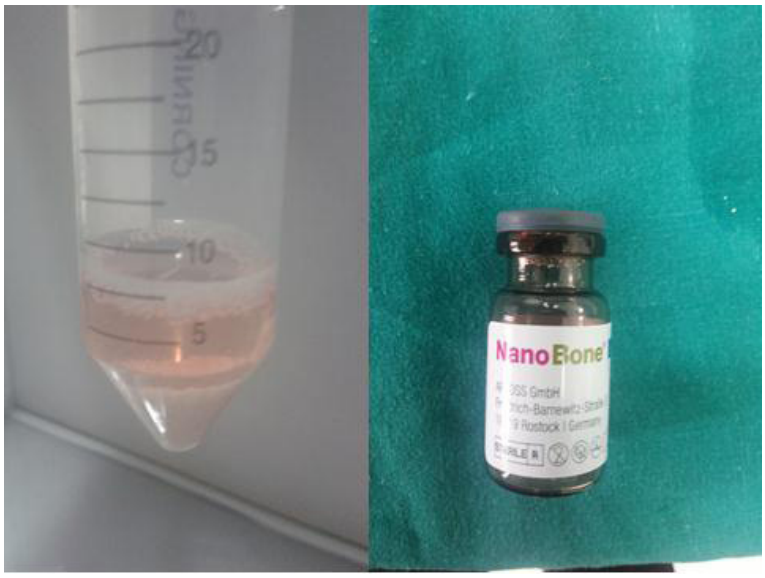

Figure 2: Implant preparation

Surgical Technique

Surgery was carried out under general anesthesia. Following a crestal incision at the level of the gingival sulcus, dissections were made to reach the bony surface of the cleft walls. The mucoperiosteal flaps were then elevated to the levels of the anterior nasal spine anteriorly, the lateral piriform rim superiorly, and to the alveolar ridges inferiorly. Palatal flaps were developed by starting reflection of the palatal flaps from a sulcular incision that is placed on the palatal side of the dentition toward the palatal defect. The palatal flaps then separated from the nasal tissue along the cleft margin by sharp dissection. Once the buccal and palatal flaps have been developed, access is readily obtained to

the nasal mucosa, which is then reflected and sutured, burying the knots to obtain a watertight nasal closure. Once the nasal mucosa is closed, the palatal defect is closed by first closing the palatal flaps, converting the cleft palate into a single flap. The scaffold NanoBone® loaded with cells was transferred to the defect by micro forceps then the wound was closed in a watertight manner.

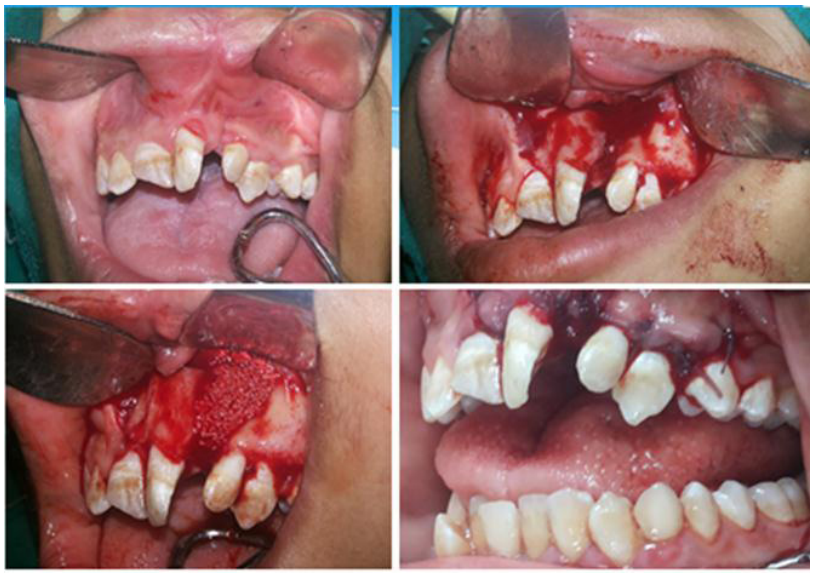

Figure 3: surgical technique

The surgical technique in group II

It was performed in programmed steps for all patients as follow:

All patients were operated under general anesthesia using nasal intubations of the normal side. Local anesthetic solution with vasoconstrictor agent (Mepivacaine HCL 2 % with Levonordefrin 1\20000)*** was infiltrated in the surgical field to aid in homeostasis and facilitate soft tissue dissection.

The recipient site was approached first to prepare the graft bed before bone harvest to shorten the time needed for transportation of the graft and to preserve the vitality of the bone graft.

The surgical technique for closure of the cleft site (Recipient site):

The surgical approach was performed according to as following : Creation of labial mucogingival flap on either side of the alveolar cleft, the incision continued for elevation of greater segment labial flap through the gingival sulci of both central incisors, the submucosal dissection superiorly to the oronasal fistula separating the muscle and connective tissue from the nasal mucosa, the nasal mucosa was reflected palatally from the walls of the cleft, and superiorly from the nasal septum on one side and the lateral nasal wall on the other side.

A palatal incision was then made around the teeth beginning posteriorly at each first molar until the fistula site was approached at the alveolar cleft; the nasal mucosa was separated at its point of attachment to the palatal mucosa. The separated nasal mucosa was swept back into the floor of the nose, the nasal mucosa wound edges were freshened and sutured to achieve closure with 4-0 Vicryl suture material. The elevated palatal flap was freshened along the previous fistula tract with removal of any granulation tissue and sutured using 3-0 Vicryl suture to achieve a watertight palatal closure [21].

The Surgical Technique for Bone Graft Harvest:

A local anesthetic containing vasoconstrictor was infiltrated into the soft tissues overlying the anterior mandible prior to making the incision. A vestibular incision was made on the alveolar mucosa just below the attached gingiva between the second premolar regions. The mandibular symphysis was widely exposed until the lower border of the mandible. A 5 mm safety margin below the apices and 3-5 mm thickness of the lower border was respected. After harvesting a mono block cortico cancellous bone graft, cancellous bone was harvested from the bony cavity with large curettes, the lingual cortex was left intact.

The cleft site was filled with mono block the bone graft then the remaining spaces was filled by cancellous bone. The soft tissue coverage of the graft (oral layer) was done using local mucoperiosteal flaps.

Post-operative follows up

The patients in both groups were followed up for 18 months postoperatively both clinically and radio graphically: Clinically to evaluate the wound healing, infection and postoperative edema and pain outcome, eruption of cleft related teeth through the graft and radio graphically to determine graft incorporation and measure local bone mineral density at the follow up periods (1st, 3rd 6th and 18 month)

Maxillary expansion which was in need to correct posterior cross bite was performed by using Bonded Hyrax maxillary expander. This type of appliance used a special type of screw called HYRAX (Hygienic Rapid Expander). The screws have heavy gauge wire extension to be adapted to follow the contour of the palate. The jack screw was attached to a splint covering variable numbers of teeth. The activation was performed as two turns each day for 4-5 days and then one turn per day till the desired expansion was achieved [24]. The expansion appliance must be used as a retainer at least for 3 months after expansion to prevent the relapse. Maxillary expansion was examined by measuring (C-C) from a point that is 8 mm below the crest of interdental papilla distal to the canine on one side to the other (if canine fossa was notobviously distinguishable), intermolar width (M-M) (measured from central fossa of maxillary first molar to the central fossa of the other maxillary first molar) and inter tuberosity distance (T-T) (measured from the heist point of convexity of the tuberosity) pre and postoperatively for both groups.

Statistics

The quantity and quality of bone formation after surgery during the follow up periods were compared between the two groups using a Mann-Whitney test. Data were expressed as mean ± SD. A value of $p<0.05$ was considered statistically significant.

Results

Clinical Results

In Group I:

Early post-operative follow up showed that successful healing left no fistula or oronasal communication. No problems of wound healing, no swelling or discharge were seen during follow-up. The patients gained closure of the alveolar arch and stabilization of the teeth adjacent to the cleft. The clinical follow up after 18 months post-surgery as palatal expansion was performed revealed that the rate of expansion as correction of cross bite took about 4-6 weeks with a significant increase in C-C, M-M widths and T-T distance. The clinical examination of the grafted sites was appeared with normal ridge width that was good to accommodate the erupting permanent lateral incisor and canine (Figure 4 Tables 1, 2).

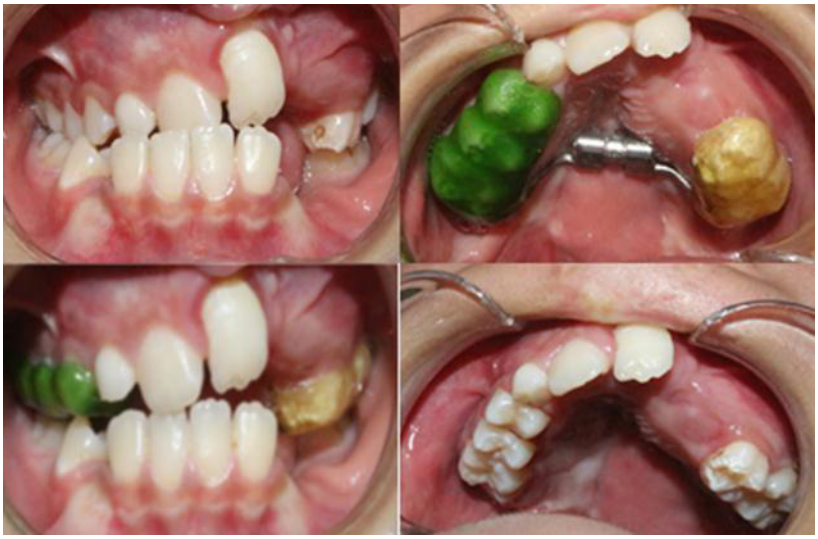

Figure 4: Postoperative photos for patient in group I during periods of palatal expansion

In group II:

Early post-operative follow up showed that two patients at 3rd week postoperative complain from graft dehiscence with loss of some graft particles. These cases were treated by daily irrigation with sterile normal saline and application of periodontal back and maintenance of good oral hygiene by using cholorihexidene mouth wash 3times daily until

the wound was completely healed.

The clinical follow up after 18 months post-surgery as palatal expansion was preformed revealed that palatal expansion was performed with a significant increase in C-C, M-M widths and T-Tdistance. Cross bite was corrected taking 4-6 weeks.

	Before	After	t. test	p. value
G I (C – C)	24.50 ± 2.14	30.00 ± 2.45	22.892	0.001*
G II (C – C)	24.50 ± 2.33	28.63 ± 2.50	11.638	0.004*
G I (M - M)	34 ± 1.6	38.2 ± 1.5	6.524	0.032*
G II (M - M)	34.5 ± 1.9	37.5 ± 1.8	5.984	0.043*
G I (T – T)	35.50 ± 1.60	43.00 ± 1.69	82.895	0.001*
G II (T – T)	36.50 ± 2.27	42.75 ± 2.60	26.189	0.001*

Table 1: Intercanine width (C-C), intermolar width (M-M) and intertuberosity distance in group I (G I) and group II (G II) before and after maxillary expansion

	G I	G II	t. test	p. value
(C – C) After	30.00 ± 2.45	28.63 ± 2.50	1.113	0.287
(M – M) After	38.2 ± 1.5	37.5 ± 1.8	0.743	0.421
(T – T) After	43.00 ± 1.69	42.75 ± 2.60	0.234	0.823

Table 2: Comparison of C-C, M-M widths and T-T distance between both groups after maxillary expansion

Radiographic results

In group I

The radio-opacity of serial CTs slicing the middle level of the alveolar cleft in the grafted region increased gradually over the time as the mean of bone mineral density of bone bridge was 552 +15.3 immediately postoperative. This value was increased by time to 563+ 19.3 and 583+ 28.04 at 3months and 6 months postoperatively respectively.

The radio-opacity of serial CTs slicing the middle level of the alveolar cleft in the grafted region after 18 months and complete the expansion of the palate was increased and as the mean of bone mineral density of Bone Bridge was 620+ 19.5 which was nearly as the normal adjacent bone (Figure5, Table 3).

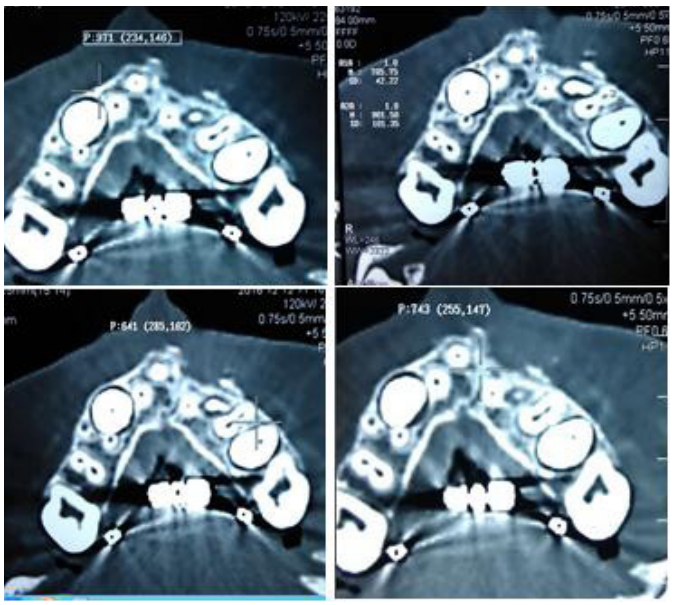

Figure 5: Postoperative photo radiographs for group I

In Group II

The radio-opacity of serial CTs slicing the middle level of the alveolar cleft in the grafted region was decreased gradually over the time as the mean of bone mineral density of Bone Bridge was 548 +27.3 immediatelly postoperative. This value was decreased by time to 254.25 + 41.27at 3months then increased to370 + 23.3 at 6 months postoperatively respectively.

The radio-opacity of serial CTs slicing the middle level of the alveolar cleft in the grafted region after 18 months and complete the expansion of the palate was increased and the as the mean of bone mineral density of bone bridge was 563 +16.19 which lower than the normal adjacent bone (Figure 6, Table 3).

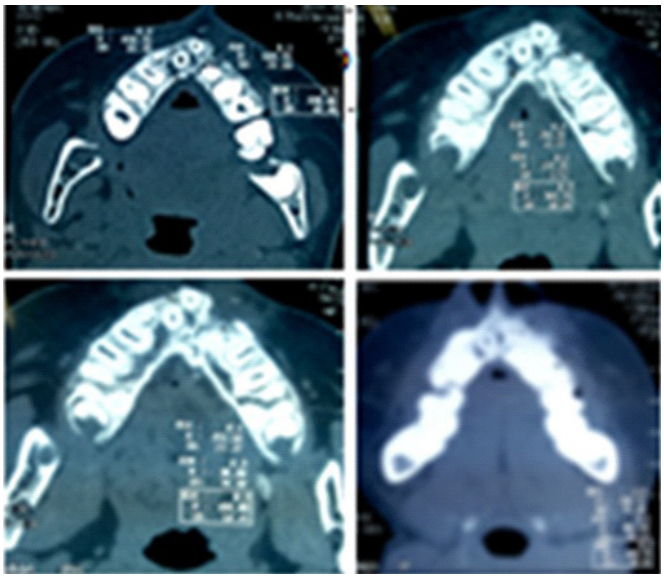

Figure 6: Postoperative photo radiographs for group II.

Time	Group I	Group II	P value
Immediate postoperative	552+ 15.3	548 +27.3	0.213
3 months post	563+19.3	254.25 +41.2	0.001
6 months post	583+ 28.04	370+ 23.3	0.002
18 months post	620+ 19.5	563 +16.19	0.06

Table 3: The radio-opacity of serial CTs slicing the middle level of the alveolar cleft in the grafted region over the follow up periods in both groups

In comparing the radiographic results of both groups, it was revealed that the radio opacity of the bone bridge in group I is higher than that of group II with significant difference at 3 and 6 months postoperative as P values were 0.001 and 0.002 at 3 and 6 months postoperative respectively (Table 3).

Discussion

CLP management by reconstruction of the alveolar process through an alveolar bone graft has many benefits. These benefits include restoring of continuity of the dental arch, correction of upper lip and nose deformations, and speech disturbance, eruption of permanent teeth, posterior dental prosthetic rehabilitation. Alveolar grafting also supports and gives stability to the wing of the nose, improving nasal emission and phonetics by closure of oronasal communication, orthodontic movement, and the insertion of dental implants. Also, better oral hygiene establishment, and limitation of growth disturbances can be achieved [25-27].

Alveolar bone defects can be reconstructed by autogenous bone. Multiple donor sites have been suggested including the anterior and posterior iliac crest, proximal tibia, rib, and calvarial bone [28,29]. Regeneration of alveolar bone defect described in 1965 was done by Gingiva Periosteo Plasty (GPP). It was considered as an alternative technique without the potential complications of having a donor site at early age [30]. Although it had a variable rates of success of bone regeneration on the alveolar defects, it showed long term complications on facial growth [31]. Although reconstruction of alveolar bone defects by autogenous bone graft has many objectives, it remains controversy. These controversies include optimal time to complete bone graft, origin of bone graft material, limited amount of bone needed, resorption of grafted bone, soft tissue necrosis especially of the palate and morbidity of donor site [32].

Tissue engineering studies have identified alternative methods that may allow early rehabilitation and decreased average number of operations until adult age. MSC differentiation capacities into damaged tissues are still not well understood [33]. Accordingly, the aim of this study was to evaluate the bone quality and quantity at the alveolar cleft sites that were repaired with autogenous Mesenchymal stem cell and its effect on orthodontic dental arch expansion and compare these results with cases treated with autogenous chin bone graft.

Many authors prefer maxillary expansion after grafting of bone as the graft is set under a dynamic load during healing, soft tissue defect will be small to be closed and the bony defect will be narrow so it will be regenerated more rapidly [26,34]. While, presurgical orthodontic expansion is preferred by others to give easier expansion due to less resistance, closing the nasal floor can be done by enhancing access to the cleft, better postoperative cleaniness and hygiene, and less possibility of reopening the oronasal fistula [7,26].

As the main difference in the treatment convention in the management of cleft lip and palate is the time at which the graft is performed, alveolar bone graft can be classified as primary, secondary and tertiary. Bone graft is considered primary when it occurs early in life. This early intervention can cause impairment of the maxillary growth as it believed by some authors [35]. Bone graft is considered secondary, when it is placed in the mixed dentition before or after eruption of the permanent canines in order to provide adequate periodontal support for their eruption and preservation of the teeth adjacent to the cleft. By the age of eight 95% of the anteroposterior and transverse growth is completed. When bone graft is placed in the permanent dentition, it is considered as Tertiary. Tertiary bone graft cannot repair bone loss in teeth adjacent to the cleft but it assists in the closure of persistent oronasal fistulae and it helps prosthodontics and periodontal rehabilitation [32].

Accordingly, secondary bone graft was performed in this work between the age 7-12 years as most of anteroposterior and transverse growth is completed by 8yrs and only vertical growth remains. So, grafting does not have much effect on growth of midface and will give adequate bony support for the eruption of the canine [36]. Were in line with this work as they stated that when bone graft is performed in older patients with cleft lip and/or cleft palate, they may experience slow wound healing, bone graft absorption or recurrent fistulae, leading to failure of tooth eruption, while, early treatment may stay away from these unsuitable results [12].

Early post-operative follow up in group I (MSC group) showed that successful healing left no fistula or oronasal communication. No problems of wound healing, no swelling or discharge were seen during follow-up. The patients gained closure of the alveolar arch and stabilization of the teeth adjacent to the cleft. This can be explained by that the MSCs can promote the healing of both bone at the grafted site and also the healing of soft tissue coverage. This result is in agreement with study of Horswel and Henderson; 2003, as they stated that Mesenchymal stem cells (MSCs) are able to form new bone when transplanted(37).MSCs can secrete various bioactive molecules that regulate cell growth, proliferation, fibrosis, angiogenesis and immune suppression to facilitate their use for allogenic transplantation.

The clinical examination of the grafted sites after 12 months post-surgery revealed that they appeared with normal ridge width that was good to accommodate the erupting permanent lateral incisor and canine. While clinical early post-operative follow up in group II (chin bone graft) showed that there were postoperative complain from graft dehiscence with loss of some graft particles in some patients. The clinical examination of the grafted sites after 12 months post-surgery showed that they appeared with narrow width and short height.

Rawashdeh and Telfah; 2008 [38] were in line with the present work as they stated that chin bone graft derived from the mandible has superior integration into the cleft defect as both the donor bone and recipient bed have the same intramembranous origin. They added that volume of corticocancellous blocks used to graft facial bony defects can be maintained when a membranous bone source is used rather than an endochondral bone. However, symphysial bone graft is considered less suitable for large unilateral or bilateral cleft reconstruction because of its limited quantity available [38,39]. Radiographic CT scan showed that, the radio-opacity of serial CTs slicing the middle level of the alveolar cleft in the grafted region in group I was increased gradually over the time as the mean of bone mineral density of bone bridge was 552 + 15.3, 563+19.3, 583+28.04 immediately 3months and 6 months postoperatively respectively. This means that the new bone was continuously deposited at the graft site from the early stage of healing immediately postoperative and increased by time. After one year and complete the expansion of the density of palate bone was increased and as the mean of bone mineral density of bone bridge was 620+ 19.5 which was nearly as the normal adjacent bone. Results of the present study revealed no significant difference was found in rapid maxillary expansion (RME) between MSC group and group treated by autogenous chin bone graft. These results coincided with Huang et al; 2015 [40].

On regarding to the radiographic results in group II (chin bone graft group: The radio-opacity of serial CTs slicing the middle level of the alveolar cleft in the grafted region was decreased gradually over the time as radio-opacity were 548 +27.3, and254.25 +41.2, immediately and 3monthspostoperativerespectively. This value was increased to370+ 23.3 at 6 months postoperatively. The radio-opacity of serial CTs slicing in the same grafted region after one year and the expansion of the palate was increased to reach 563 +16.19 which is still lower than the adjacent normal bone.

In comparing the radiographic results of both groups, it was revealed that the radio opacity of the bone bridge in group I was higher than that of group II with significant difference at 3 and 6 months postoperative as P values were 0.001 and 0.002 at 3 and 6 months postoperative respectively. This supports the role of stem cell in early promotion of bone healing with good quantity as well as quality.

The results of this study were in agreement with studies of *Dimitriou et al* stated that combination of genetically engineered MSCs with synthetic bone substitutes, biomaterial scaffolds, decellularized allografts can stimulate the secretion of bone morphogenetic proteins (BMP) and regenerating the extracellular matrix by enhancing mechanical stability of the bone graft during formation and extending their long-term engraftment and differentiation in tissue. This combination can be used clinically for the treatment of non-healing wounds, scarring or functional replacement of tissue [41-44].

Thus, Nano Bone® was used in the current study. It was the first Nano Bone technology product and was launched in 2005. Meier and Wolf 2007go in line with this study as they found that no residual foreign substances can influence Nano Bone® natural biomechanics as the complete remodeling of Nano Bone® constitutes a decisive advantage. It can be totally substituted and remodeled by bone rather than xenogenic bone replacement material. Khalifa et al, 2008added that Nano Bone® has a huge surface so, it can achieve new dimensions because of the interconnection between the nanopores and the nanocrystalline HA [45,20].

Conclusion

1. No significant difference was found in RME between MSC group and autogenous chin bone graft group.

2. MSCs grafting technique for alveolar cleft repair has a good role in early promotion of bone healing with good quantity as well as quality so, it can be used as an alternative method for treatment of alveolar cleft.

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