The Effect of Bone Marrow Stem Cells Harvested From the Iliac Crest Versus Mandibular Ramus in Alveolar Cleft Regeneration

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Abstract

Purpose: This study aimed to assess clinically and radiographically the degree of alveolar cleft regeneration using Bone Marrow Mesenchymal Stem Cells (BMMSCs) harvested from the mandibular ramus versus BMMSCs harvested from Iliac bone. Patients and methods: This comparative and prospective study was conducted on 10 patients with alveolar cleft defects. Patients with alveolar cleft defects were randomly selected and randomly divided into two equal groups: group A: received Autologous (BMMSCs) harvested from the mandibular ramus and seeded on a collagen sponge in combination with nanohydroxyapatite. Group B: received Autologous (BMMSCs) harvested from the lilac crest and seeded on a collagen sponge in combination with nanohydroxyapatite. Results: Based on the data given, the percentage of volume reduction was significantly different between both groups being better in group A compared with group B ($P = 0.047$). Whereas there was an insignificant difference between both groups regarding the preoperative and post-operative volume area. Conclusion: The utilization of Mandibular Ramus-derived BMSCs presents a groundbreaking advancement in maxillofacial reconstruction. This approach offers numerous advantages, including reduced surgical complications, improved precision and localization, higher osteogenic potential, and lower risks of graft rejection. Moreover, the combination of BMMSCs, nanohydroxyapatite, and PRF extracted from the mandible proves to be a viable alternative to traditional Iliac crest grafting, promoting effective bone regeneration in alveolar cleft defects. By adopting this novel technique and harvesting site, it can optimize surgical interventions, paving the way for enhanced standards of care and improving the quality of life for patients with maxillofacial challenges.

Keywords: Alveolar cleft regeneration, Bone marrow stem cells, Iliac crest, Mandibular ramus

1. Introduction

Cleft lip and palate condition is one of the most challenging congenital craniofacial abnormalities that affects children. This anomaly is the result of a lack of fusion of the frontonasal and maxillary processes during development. Cleft lip and palate can affect appearance, speech, hearing, growth, psychosocial well-being, and social integration [1].

Alveolar cleft repair is a surgical procedure done by utilizes a graft, where the bone defect is filled with bone or bone substitute, and any gaps between the mouth and the nose are closed. The goals of surgery are to stabilize the maxilla, facilitate the healthy eruption of teeth that are adjacent to the cleft, improve the esthetics of the base of the nose, create a bone base for dental implants, and close any oronasal fistulas [2].

Autologous or autogenous bone grafting involves utilizing bone obtained from same individual receiving the graft. Bone can be harvested from many sites, such as from Iliac crest, mandibular symphysis (chin area), and mandibular ramus (coronoid process). Autogenous bone is the most preferred because there is less risk of graft rejection

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as the graft originates from the patient's body. It would be osteoinductive and osteogenic, as well as osteoconductive. The disadvantage of autologous grafts is that an additional surgical site is required, another potential location for postoperative pain and complications [3].

An autogenous bone graft harvested from the anterior or the posterior Iliac crest is considered the optimal source of autogenous bone for alveolar cleft reconstruction, and hence it is termed the ‘gold standard bone graft’ because of easy access and availability of a sufficient amount. However, a harvest of the autogenous Iliac crest bone graft has some potentially serious complications. The most common include short- and long-term pain and sensory disturbances [4].

With the advent of tissue engineering techniques, alternatives to the traditional Iliac crest bone grafting techniques were introduced. Many techniques and materials can be used for regeneration of alveolar cleft defects. More attention is given to the use of bone marrow-derived stem cells seeded on a resorbable collagen matrix sponge [5].

Bone marrow mesenchymal stem cells (BMMSCs) are clinically relevant stem cells found in bone marrow's stromal component. Many studies have shown that BMMSCs can regenerate dental and maxillofacial tissue defects, such as an alveolar bony defects, and significantly increase the rate of tooth movement. The results of these studies suggest that BMMSCs play a key role in regenerative oral and maxillofacial therapies [6e8].

Grafts from the ramus of the mandible are a convenient source of autogenous bone for alveolar reconstruction. Bone harvested from the mandible appears to have biological benefits because of its embryologic origin. The mandible develops embryologically as intramembranous bone, while the condyles develop by endochondral bone formation [9].

This work aimed to assess clinically and radiographically the degree of alveolar cleft regeneration using Bone Marrow Stem cells harvested from mandibular Ramus versus Bone Marrow Stem cells harvested from Iliac Bone.

2. Patients and methods

The study was conducted on 10 patients who were seeking reconstruction of the alveolar cleft defects. The Patients were selected from the outpatient clinic of the Oral and Maxillofacial Surgery Department, Faculty of Dental Medicine for Girls, Al-Azhar University, Egypt. This research was approved by the Research Ethics Committee (REC) of Al-Azhar University's Faculty of Dental Medicine for Girls code: REC-SU-24-01.

The participants were stratified into two groups, each comprising five individuals, to evaluate the efficacy of different treatment approaches. They were randomly recruited from the outpatient clinic of the Oral and Maxillofacial Surgery Department, Faculty of Dental Medicine for Girls, Al-Azhar University. Before any procedure, all the patients’ guardians were informed about the steps of the procedure, and written informed consent (in the Arabic language) was obtained and signed.

Inclusion criteria were patient aged 8e15 years, not received any surgery for alveolar cleft defect, nonsyndromic unilateral alveolar cleft with or without cleft palate, good oral hygiene, and good compliance with the plaque-control instructions, and medically fit for a major surgical oral procedure. Exclusion criteria were pre-existing infection at the cleft site, and patients with systemic diseases that may affect bone healing.

2.1. Sample size and grouping

A total of 10 patients were included in the study, with five patients assigned to each group. The sample size was determined based on the following formula to ensure robust comparisons between groups:

$$n = \frac{\left(Z_{\alpha/2} + Z_{\beta}\right)^2 \cdot \left(\sigma_1^2 + \sigma_2^2\right)}{\left(\mu_1 - \mu_2\right)^2}$$

Where:

n is the sample size per group,

$Z_{\alpha/2}$ is the Z-score corresponding to the chosen confidence level,

Z_{β} is the Z-score reflecting the desired statistical power,

σ_1^2 and σ_2^2 are the variances of the groups, and

$\mu_1 - \mu_2$ are represents the expected difference in means.

This approach ensured that the study was adequately powered to detect meaningful differences between the groups. Patients with alveolar cleft defects were randomly divided into two equal groups: group A: received Autologous BMMSCs harvested from the mandibular ramus and seeded on a collagen sponge in combination with nanohydroxyapatite. Group B: received Autologous BMMSCs harvested from the lilac crest and seeded on a collagen sponge in combination with nanohydroxyapatite.

3. Methods

All patients were subjected to taking personal history, present and past medical and dental history, clinical examination, radiographic evaluation (Orthopantogram radiography, computer tomogram (CT)). The Orthopantogram radiography was used for each patient as a primary assessment preoperatively, as well as at 3 and 6 months.

Patients and their guardians were motivated to follow the proper oral hygiene measures by regular brushing. Before surgery, it is advisable to remove any appliances, like retainers, to enable the patient to thoroughly clean the area and allow for gingival healing.

The surgical procedure for harvesting and collecting BMMSCs from the Iliac bone crest (group B) was conducted following the methodology outlined by Al-Ahmady *et al.* [10]. Using a gauge 13 bone marrow trocar, a puncture was made at the anterior superior Iliac spine with a watch-wind motion. Both groups underwent the procedure under general anesthesia, with thorough aseptic preparation of the external and internal oral areas before aspiration. In group A, where BMMSCs were harvested from the mandible ramus, a trocar was used to penetrate the oral mucosa along the external oblique ridge for access to the bone marrow (Fig. 1). The trocar was repositioned after every 10 ml to target different areas within the cancellous bone. The depth of insertion was guided by a preaspiration three dimensional CT scan to avoid any damage to the inferior alveolar nerve. BMMSCs were isolated from the bone marrow aspirate utilizing Ficoll density gradient centrifugation. After centrifugation, the mononuclear cell layer was obtained, washed, and resuspended in platelet plasma containing gentamicin and dexamethasone.

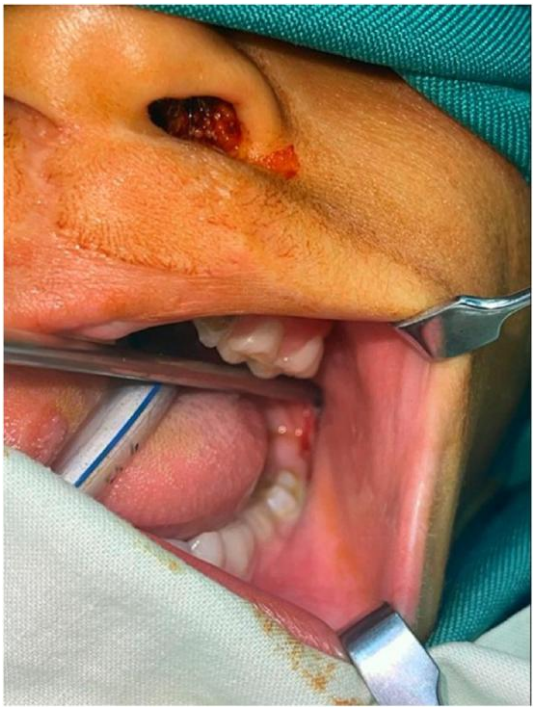

Fig. 1. Intraoperative photograph showing the penetration of the oral mucosa along the external oblique ridge of mandibular ramus during aspiration.

For both patient groups, a 20 ml sample of fresh venous blood was collected and divided into two 10 ml Vacutainer tubes. The blood was centrifuged at 3300 rpm for 2e3 min, resulting in the formation of platelet-rich fibrin (PRF). This process yielded three distinct layers: platelet-poor plasma (PPP), the PRF clot, and the red blood cell layer, with the PRF gel subsequently removed for use.

To expose the defect area in both groups, a No. 15 blade scalpel was employed to incise the papillae adjacent to the teeth surrounding the defect through a gingival incision. Additionally, vertical and horizontal incisions were made to permit adequate mobilization of mucosa for closure both palatally and buccally. Subperiosteal dissection was performed using a mucoperiosteal elevator, revealing the alveolar defect, the piriform aperture, and part of the anterior maxilla. The periosteum was incised to facilitate tissue mobilization toward the cleft, enabling tension-free closure.

Careful dissection of both the nasal and oral mucosa was performed to separate the layers for optimal anatomic reconstruction. The lateral nasal mucosa was closed using interrupted inverted resorbable sutures, followed by closure of the oral mucosa with everting interrupted resorbable sutures. A composite of BMMSCs-seeded collagen sponge, Nano Hydroxyapatite, and PRF was packed into the alveolar cleft defect, which was then closed with advanced gingival mucoperiosteal flaps. For all cases, PRF pieces were strategically placed, one towards the nasal side and another towards the oral side. The buccal layer was closed by advancing the buccal mucosa toward the cleft.

Postoperative care instructions for patients included abstaining from eating or drinking for 6 h following the procedure. Patients were advised to consume soft, cold foods for three days postsurgery and to use cold packs on the first day. To minimize the risk of infection, saline rinses with a syringe were recommended three times a day starting 24 h postsurgery. Antibiotics, analgesics, and anti-inflammatory medications were also prescribed.

3.1. Statistical analysis

Statistical analysis was conducted using SPSS v28. The normality of the data was evaluated through the ShapiroeWilks test and histograms (IBM Limt. USA). Parametric quantitative data were presented as mean ± standard deviation (SD) and analyzed using the unpaired Student's *t*-test, while qualitative variables were reported as frequency (%) and analyzed using Fisher's exact test. A two-tailed *P* value of less than 0.05 was considered statistically significant. Pearson correlation analysis was used to examine the relationship between quantitative variables.

4. Results

There was an insignificant difference between both groups regarding the demographic data (age and sex) (Table 1).

There was an insignificant difference between both groups regarding the cleft site, as shown in Table 2.

Based on the data given, the percentage of volume reduction was significantly different between both groups, being better in group A compared with group B ($P = 0.047$). Whereas there was an insignificant difference between both groups regarding the preoperative and postoperative volume area, as shown in Table 3.

There was an insignificant difference between both groups regarding the factors affecting alveolar bone graft, as shown in Table 4.

5. Discussion

Alveoloplasty (alveolar cleft regeneration), is a crucial procedure in the surgical treatment of cleft palate and cleft lip. Its main objective is to restore the continuity of the alveolar bone to facilitate proper dental eruption. In cases where there were malformations or missing teeth, alveoloplasty also allows for future prosthetic treatment [11].

In this study, the main inquiry was to assess the efficacy of harvesting BMMSCs from the mandibular ramus combined with nanohydroxyapatite for enhancing the process of bone formation in alveolar cleft repair. The ability of BMMSCs from different anatomical locations to differentiate into mesenchymal lineages was evaluated by Lee *et al.* [9] who concluded that BMMSCs obtained from the mandibular ramus exhibited superior proliferative activity compared with those from the Iliac marrow. Another finding was concluded by Prahasanti *et al.* [8] in their study when mixing BMMSCs with a hydroxyapatite scaffold before grafting it into the bone defect. They reported that this combination resulted in improved bone regeneration and increased success rate compared with using BMMSCs alone [8,9].

The efficacy of BMMSCs was affected by the type of separating media, the concentration, and the

Table 1. Comparison between group A and group B regarding demographic data.

	Group A mandibular ramus $N = 5$	Group B Iliac $N = 5$	*P* value
Age	9.80 ± 0.84	8.20 ± 1.64	0.088
Sex			
Female	3 (60.0)	3 (60.0)	0.092
Male	2 (40.0)	2 (40.0)	

Data is expressed as the mean ± SD or frequency (%) *P* value set at less than 0.05.

Table 2. Comparison between group A and Group B regarding the cleft area.

Cleft area	Group A mandibular ramus No. = 5	Group B Iliac No. = 5	*P*-value
Uni-lateral	2 (40.0)	3 (60.0)	1.000
Bilateral	3 (60.0)	2 (40.0)	

P value set at less than 0.05.

Table 3. Comparison between group A and group B regarding volume pre, post and % of volume reduction.

Volume area	Group A mandibular ramus $N = 5$	Group B Iliac $N = 5$	*P* value
Pre	501.81 ± 117.72	401.67 ± 106.29	0.196
Post	332.38 ± 124.46	313.12 ± 102.33	0.796
P value	0.008*	<0.001*	
% reduction	−169.43 ± 76.46	−88.56 ± 10.05	0.047*

*Significant *P* value less than 0.05.
P < 0.05.

Table 4. Comparison between group A and group B regarding factors affecting alveolar bone graft.

	Group A mandibular ramus $N = 5$	Group B Iliac $N = 5$	*P* value
Postoperative pain at site of harvesting			
No	5 (100.0)	5 (100.0)	NA
Wound dehiscence			
No	5 (100.0)	4 (80.0)	0.292
Yes	0	1 (20.0)	
Soft tissue healing			
No	0	1 (20.0)	0.114
Yes	5 (100.0)	4 (80.0)	
Preoronasal fistula			
No	3 (60.0)	1 (20.0)	0.197
Yes	2 (40.0)	4 (80.0)	
Postoronas Fistula			
No	5 (100.0)	5 (100.0)	NA
Eruption			
No	3 (60.0)	3 (60.0)	1.000
Yes	2 (40.0)	2 (40.0)	

P value set at less than 0.05.

methods of transportation. In this study, we used density gradient separation medium namely Ficoll-paque for isolating BMMSCs from whole bone marrow. This technique helped the separation of the different cell populations based on their density, allowing for the enrichment of the desired cell types, such as BMMSCs. Using Ficoll-paque helped the removal of unwanted components like red blood cells and platelets, which could interfere with the isolation and characterization of BMSCs. Ficoll-paque was compared with Lymphoprep in a study by Yeo *et al.* [12] who stated that by utilizing Ficoll-paque as a separating medium, the purity and viability of the harvested stem cells was enhanced. This was supposed to improve the outcomes in cell-based regenerative therapies and allow for the acquisition of a high yield of potent stem cells. This, in turn, was believed to maximize the regenerative potential of the grafts with improved outcomes [12].

In this study, combining these benefits with careful handling, and immediate transfer of the concentrated BMMSCs helped to ensure that the cells remained viable and retained their regenerative potential. This was considered important as minimizing manipulation might help preserve the integrity and functionality of the cells. In the context of the comparisons between concentrated fresh and cultured BMMSCs in the setting of segmental bone defect repair, the studies had shown that concentrated fresh BMMSCs might have advantages over invitro-expanded stem cells allowing minimally manipulation cells, avoiding complications associated with in vitro culture, and reducing the risk of contamination [13e15].

To enhance bone regeneration, the use of nano-HA powder in combination with BMMSCs has several benefits for bone regeneration. Its biocompatibility, osteoinductive potential, and angioconductive properties make it a suitable scaffold material that can promote the growth, proliferation, and differentiation of BMMSCs. This is in accordance with Pepla *et al.* [16] who concluded that BMMSCs prepared with nano-HA composites had greater cell viability and proliferation ability compared with those prepared with traditional HA and ultimately led to enhanced bone regeneration and improved functional outcomes [16].

In this study, the soft tissue healing in all cases was complete with successful closure of the oronasal fistula, while wound dehiscence was observed in only one case in group A. These results were consistent with those of Elhadidi *et al.* [17], who demonstrated that alveolar cleft grafting with PRF and bone marrow stem cell concentrate resulted in improved soft tissue healing, decreased rates of dehiscence, and reduced pain and edema ratings at the recipient site. These findings support the notion that this combination therapy promotes better tissue healing and contributes to the overall success of the procedure [17].

Yu *et al.* [18], using CT imaging and three-dimensional reconstruction techniques were able to accurately measure and assess the bone fill rate after alveolar cleft grafting procedures. A higher bone fill rate indicated a greater amount of bone regeneration and healing, while a lower bone fill rate suggested less successful bone formation and healing. The formula for calculating the bone fill rate was bone fill rate=(VOLpost - VOLpre)/VOLpre * 100 % where VOLpost is the postoperative cleft volume at the 6-month follow-up and VOLpre is the preoperative cleft volume. By using this formula, we were able to express the amount of bone formation in each case [18].

The current study findings indicated that although there were significant differences in bone fill rate and volume reduction between group A and group B, group B demonstrated superior volume area reduction compared with group A ($P = 0.047$). There was no significant difference in preoperative and postoperative volume areas. This suggests that the treatment or interventions used in both groups were effective in reducing the overall volume of the cleft area. Furthermore, previous studies investigating the relationship between initial cleft defect and outcomes of secondary alveolar bone grafting (SABG) have reported varied results with no significant correlation between cleft size and bone fill rate. Similarly, the correlations between SABG outcomes and other parameters such as cleft width, cleft type, and the characteristics of cleft-side, lateral incisors, and canines also showed discrepancies. These findings suggest that other factors beyond the initial cleft defect may play a more significant role in determining the success of SABG outcomes [18,19].

Conversely, in the current study, bone marrow chips were not used as the source of bone graft material. Instead, bone marrow aspirate containing MSCs was used, and the focus was on observing the differentiation of MCs to osteoblasts and the formation of new bone. Our findings suggested that although MSCs differentiation showed some osteogenic potential, it was not sufficient to fill the bony defect area during the 6-month follow-up [20].

The findings from the studies suggest that the addition of bone marrow concentrate to Iliac bone grafts may potentially improve the outcomes of bone graft procedures. Tai *et al.* [21] found that without the addition of bone marrow concentrate, there was a significant volume loss in the graft

material over time, likely due to resorption. However, Naujokat *et al.*'s [22] study suggested that the incorporation of stem cells from the bone marrow can enhance bone quality and decrease the rate of resorption [21,22].

The current study's limitations, such as the small sample size and short-term follow-up, highlight the need for additional research to confirm the validity of these findings. It is crucial to assess the long-term outcomes and potential clinical applications of these regenerative therapies to fully understand their effectiveness and safety.

5.1. Conclusion

In conclusion, the regeneration of alveolar clefts through the innovative application of Mandibular Ramus-derived BMMSCs stands as a transformative advancement in maxillofacial reconstruction. The compelling evidence highlights the superior potential of these stem cells, offering not just enhanced bone regeneration but also a myriad of advantages that significantly reduce surgical complications and elevate precision in surgical outcomes.

With their remarkable osteogenic capabilities and minimized risk of graft rejection, Mandibular Ramus-derived BMMSCs emerge as a groundbreaking solution, paving the way for optimized surgical interventions. Moving forward, embracing this powerful approach promises to redefine the standards of care in maxillofacial reconstruction, ultimately enhancing the quality of life for countless patients.

Ethics information

The study was approved by the Research Ethics Committee in the Faculty of Dental Medicine for Girls, Al-Azhar University (approval no: REC-SU-24-01).

Biographical information

Patients were recruited at the outpatient clinic of the Oral and Maxillofacial Surgery Department, Faculty of Dental Medicine for Girls, Al-Azhar University, Cairo, Egypt.

Conflicts of interest

There are no conflicts of interest.

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