

# A comparative evaluation of bone regeneration using mesenchymal stem cells versus blood coagulum in sinus augmentation procedures

## ABSTRACT

**Objective:** The present study evaluated the quality and quantity of new bone formation in the maxillary sinus lift procedures and stability of implants in posterior atrophic maxilla.

**Materials and Methods:** This prospective randomized controlled split-mouth study included 20 patients (16 males and 4 females having a mean age of 36.7 years) having atrophic maxilla. They were divided randomly into two groups: Group A using mesenchymal stem cells and Group B into blood coagulum. They were radiographically evaluated using cone-beam computed tomography (CBCT) for residual bone height preoperatively and availability of new bone formation around implants, density, and stability of implants 6 months postoperatively.

**Results:** The placement of dental implants in posterior maxilla is challenging due to rapid resorption of alveolar bone after extraction of teeth due to pneumatization of maxillary sinuses. In both the groups, more pain and swelling were observed in the 2<sup>nd</sup> postoperative day which gradually decreased over a period of 7 days. Membrane perforation occurs in only four cases (20%). A significant gain in alveolar bone height was observed in Group A (7.69 mm ± 2.5 mm) and Group B (9.32 mm ± 2 mm) after 6 months. On comparing both the groups, there is a similar significant increase in bone density in Hounsfield units postoperatively at various levels buccally and palatally. Total 40 sinuses were lifted and 42 implants were placed, respectively. All implants showed primary stability.

**Conclusions:** Such findings provide a significant contribution in future perspective studies that the use of stem cells had the same success rate as blood coagulum.

**Keywords:** Blood coagulum, mesenchymal stem cells, sinus augmentation

## INTRODUCTION

Dental implants are boon to modern dentistry and one of the advances in dentistry since the 19<sup>th</sup> century. An ideal prosthesis restores the normal contour, esthetics, function, comfort, and health and also helps in articulation of voice. Implant dentistry helps in excellent replacement of the lost tissues of the oral stomatognathic system. This has positively increased the acceptance of osseointegrated implant-supported prosthesis by the patients.

However, implant dentistry has its own limitations such as less or no availability of bone height, width, poor quality of residual bone, and probability of damage to underlying vital structures. The placement of dental implants in the posterior


maxilla is a challenging procedure due to the resorption of the alveolar bone and the pneumatization of the maxillary sinuses after the loss of teeth in the region.<sup>[1]</sup>

**AKASH SANJAY GUPTA, JITENDER KUMAR AURORA, K. N. DUBEY, HIMANSHU CHAUHAN, MOHIT SAXENA, SAGAR RAMESH GANVIR**

Department of Oral and Maxillofacial Surgery, Saraswati Dental College, Lucknow, Uttar Pradesh, India

**Address for correspondence:** Dr. Jitender Kumar Aurora, Department of Oral and Maxillofacial Surgery, Saraswati Dental College, Lucknow, Uttar Pradesh, India.  
E-mail: jkauroramaxfac@gmail.com

**Received:** 18 April 2021, **Revised:** 09 June 2021, **Accepted:** 21 June 2021, **Published:** 13 December 2021

Access this article online	
<b>Website:</b> www.njms.in	<b>Quick Response Code</b> 
<b>DOI:</b> 10.4103/njms.njms_358_21	

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**How to cite this article:** Gupta AS, Aurora JK, Dubey KN, Chauhan H, Saxena M, Ganvir SR. A comparative evaluation of bone regeneration using mesenchymal stem cells versus blood coagulum in sinus augmentation procedures. *Natl J Maxillofac Surg* 2021;12:349-56.

The deficient bone both quantitatively and qualitatively in the atrophic maxilla can be overcome by maxillary sinus floor augmentation.<sup>[2,3]</sup> Autografts, allografts, xenografts, alloplasts, or combination of different graft materials are mainly used to fill the new space created between the floor of the maxillary sinus and the elevated sinus membrane to maintain space for new bone formation.<sup>[4-8]</sup>

Various other bone augmentation materials like Blood coagulum, Plasma rich fibrin (PRF) and Plasma rich platelet (PRP) have been used for sinus augmentation procedure alone or along with autogenous bone graft in recent past, studies have proven that autogenous bone graft along with PRF or PRP have more osteogenic potential than bone graft alone.<sup>[9-13]</sup> Recent development in bone regeneration using stem cells provides a reliable approach and therapeutic strategy.<sup>[14]</sup>

Stem cells are characterized by property of pluripotent (giving rise to all three germ layers). Adult stem cells derived from mesodermal derivatives are known as mesenchymal stem cells (MSCs).<sup>[15,16]</sup> The application of MSC increases angiogenesis and osteogenesis, thereby promoting repair and regeneration of bone. However, very few clinical trials reporting the use of MSCs have been reported in the recent literature till to date.<sup>[17]</sup>

The aim of the present study was to evaluate the new bone formation in the maxillary sinus after sinus membrane elevation using stem cells and blood coagulum and to evaluate and compare the density of the new bone. In this study, we hypothesized that superior quality and quantity of bone regeneration might take place when using stem cells as compared to blood coagulum.

## MATERIALS AND METHODS

This prospective randomized control study was conducted in the Department of Oral and Maxillofacial Surgery of our institute from December 2017 to September 2019.

A total of 20 patients requiring sinus augmentation (40 sinuses) for implant placement belonging to the age group of 18 years to 65 years, as per inclusion and exclusion criteria, were included. Patients were divided into Group A and Group B in this split-mouth study. Group A patients underwent sinus lift + sinus augmentation with MSCs in gel form along with implant placement and Group B patients underwent sinus lift + sinus augmentation with blood coagulum along with implant placement.

The following patients were included in this study (inclusion criteria):

1. Patients between age of 18–65 years, good general health, and optimal oral hygiene
2. Patients with atrophic maxilla having residual alveolar ridge height of 4–6 mm
3. Healthy maxillary sinuses (no signs of sinusitis)
4. American Society of Anesthesiologists I and II patients who are compliant.

The following patients were excluded in this study (exclusion criteria):

1. History of maxillary sinus pathologic features and/or maxillary sinus surgery
2. Medically compromised patients (lactating mother and pregnancy)
3. Noncompliant patients
4. Chronic smokers
5. Poor oral hygiene.

Detailed case histories were recorded. All selected patients underwent routine blood examination along with viral markers. All patients were explained in detail about the surgical procedure in local language, and informed written consent was obtained.

## Radiographic analyses

Preoperative radiographic examination was done using Intra oral periapical/Radiovisography, Orthopantomogram (if and when required), and cone-beam computed tomography (CBCT) (Machine Imaging Science International [USA] I-CAT CB-500, software I-CAT vision, voxel size 0.200 in X-Y-Z planes) to evaluate maxillary sinus lining and height of bone present between the floor of sinus membrane and the maxillary alveolar ridge and density of bone.

## Surgical protocol

All patients were operated under strict aseptic conditions. The surgical procedure was performed under local anesthesia 2% lignocaine (1:200,000) with guiding splint fabrication. The buccal maxillary wall was accessed via mid-crestal incision, and anterior and posterior releasing vestibular incisions were made to raise full-thickness trapezoidal mucoperiosteal flap. The position of antrostomy was determined by the size and location of the maxillary sinus. With the help of sterilized graphite pencil or marker, rectangular-shaped bony window was marked with 0.5–1 cm superior to the sinus floor. A bony window of 15–30-mm diameter was osteotomized with the help of a round bur and tapered fissure bur (701) under constant copious saline irrigation, using a medium-speed (12,000 rpm) straight surgical handpiece and a tungsten carbide bur with a 2.3-mm diameter.

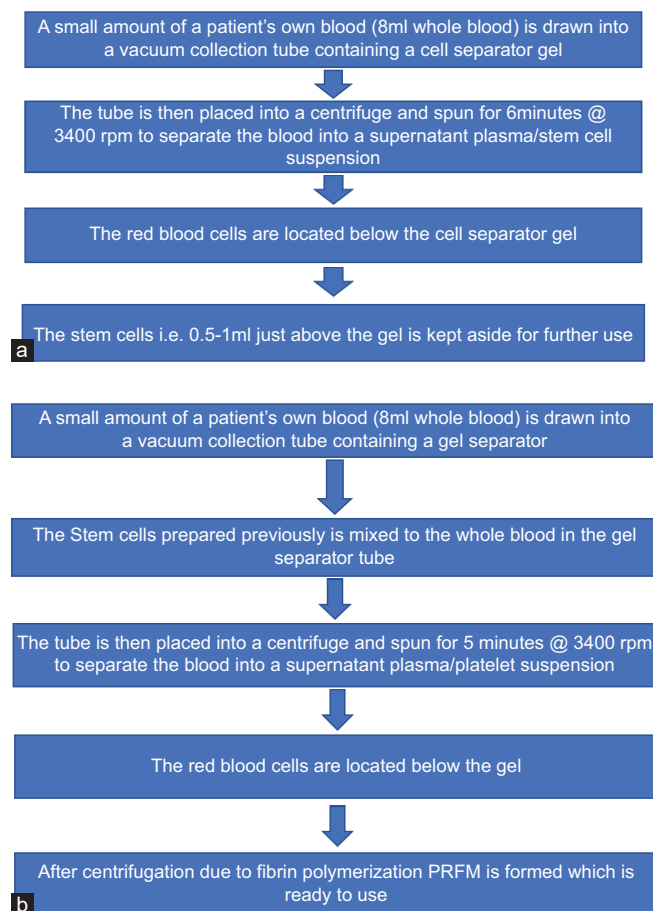
An elevated antrostomy with the cortical wall intact and adherent to the Schneiderian membrane was completed. It was lifted inside

the maxillary sinus in trapdoor fashion and acted as the future sinus floor. Careful elevation of Schneiderian membrane was done with caution not to perforate the sinus using antral curette, and the sinus membrane was elevated in all directions (medially, anteriorly, and posteriorly) before intruding the trapdoor inwardly. A space was created between the lifted sinus lining and the sinus floor.

In our study, implants (Alpha-Bio Tec) of 13-mm length were placed in every patient and installed in the residual alveolar ridge. Implant sites were prepared using sequential drill as per the diameter of implant with careful undersized drilling from the residual alveolar crest. Primary stabilization was achieved by the residual alveolar bone at the torque of 25–30 Ncm.

In Group A patients, MSCs in gel form [Flowchart 1] were placed between the sinus floor and membrane [Figure 1], and in Group B patients, the space shall be allowed to be filled with blood from the surrounding wall and clot [Figure 2].

Kit containing two sterile tubes: (1) Supercell tube containing thixotropic gel and Ficoll and (2) glue tube containing



Flowchart 1: (a) Preparation of stem cells, (b) Preparation of glue

thixotropic gel, Ficoll, and activator (0.5 ml calcium gluconate).

In both the groups, the bony window was closed using a resorbable collagen membrane 5 cm × 5 cm (Kollagen-M®) followed by suturing of the mucoperiosteal flap using 3-0 round body vicryl. All patients were advised to maintain good oral hygiene along with postoperative instructions and regular postoperative follow-up. Postoperative medications were antibiotics (amoxicillin 500 mg and clavulanic acid 125 mg and tablet Flagyl 400 mg), analgesic (diclofenac and paracetamol), antihistaminic (levocetirizine 5 mg) for 5–7 days, and nasal decongestants (xylometazoline nasal drops) for 10 days.

Sinus care instructions and postoperative extraction instructions were advised:

1. To avoid spitting or swishing for 24 h
2. To apply ice packs intermittently to the outside of face for a minimum of 20 min after your surgery to decrease swelling
3. To remain only on soft and cold liquid diet for the next 24 h
4. To irritate the wound with the tongue or any kind of external pressure
5. To sneeze with his/her mouth wide open
6. Strict instructions were given to keep the area clean and take the prescribed medications for 5 days.

Six to seven months after the first surgical procedure, another surgery was performed to take out the screw and prosthesis was installed using conventional implant installation protocols.

All patients were evaluated as per the following criteria:

1. Radiographic assessment: Postoperative radiographs were obtained to assess the bone levels (height of bone formed between floor of sinus and alveolar ridge) formed after

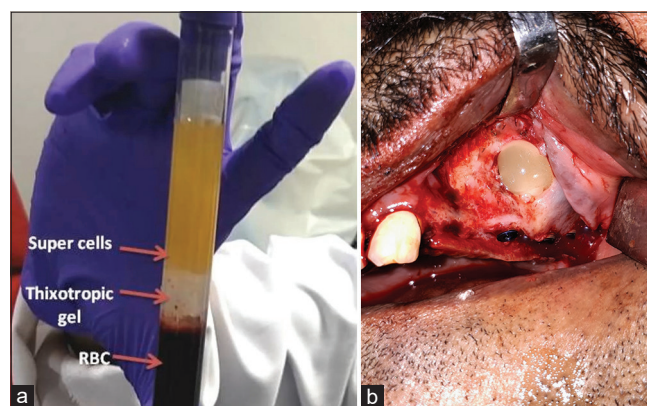


Figure 1: (a) Supercell glue (b) placed along with placement of crestal implants



**Figure 2: Formation of blood coagulum within the sinus followed by crestal placement of implants**

sinus lift procedure. The values determined the average height of the floor of the maxillary sinus from the maxillary alveolar ridge in each group. This value was obtained and recorded preoperatively and 6 months postoperatively. Evaluation of bone formation using CBCT at the following three different levels: 2 mm, 8 mm, and 14 mm both buccally and palatally from the residual alveolar crest at the following intervals preoperatively and 6<sup>th</sup> month postoperatively.

2. Pain was recorded using a 10-cm Visual Analog Scale (VAS) with 1-cm graduations (VAS) preoperatively and immediate postoperative 2<sup>nd</sup> and 7<sup>th</sup> days.
3. The baseline facial measurement was done by a 3-0 silk suture using a modification of the method by Neupert *et al.* and Schultze-mosgau *et al.*

### Statistical analysis

The statistical analysis was performed. The Mann–Whitney U-test and Wilcoxon test were used to compare the pain at various time intervals in both the groups. Levene's and Independent T test were used to assess swelling in each group. Also these tests were used to compare gain in bone height and bone density in Hounsfield unit pre and 6 months post-operatively buccally and palatally at 2 mm, 8 mm, and 14 mm in both groups (stem cells and blood coagulum). The results were considered significant at the 5% level ( $P < 0.05$ ). The accuracy was >90% in both the groups.

### RESULTS

The age of patients ranged from 18 to 65 years, with a mean age of 36.7 years. Out of 20 patients enrolled in the study, 16 were males (80%) and (20%) 4 were females with total 40 sinuses in all patients were augmented. Membrane

perforation did occur in four cases out of forty sinuses (20%). All implants achieved primary stability and showed good osseointegration during the 6-month follow-up period.

In both the groups, more pain was reported on immediate postoperative and 2<sup>nd</sup> postoperative days which gradually decreased over a period of week time. It was observed that there is no statistically significant difference between the two groups.

The measurements of swelling were obtained on 2<sup>nd</sup> day and 7<sup>th</sup> day post-operatively. The preoperative values in Groups A and B of facial measurements were 11.9350 and 11.9300, respectively. It was seen that swelling was maximum on the 2<sup>nd</sup> day postoperative in Groups A and B which gradually regressed by the 7<sup>th</sup> day. After evaluating the mean values for the swelling seen in the two groups at various time intervals, statistically, there is no significant difference in the swelling seen in the two groups.

Preoperatively residual alveolar height in Groups A and B was 4.90 mm and 4.67 mm, respectively, which increased postoperatively to 12.60 mm and 14 mm after 6 months [Table 1 and Graph 1].

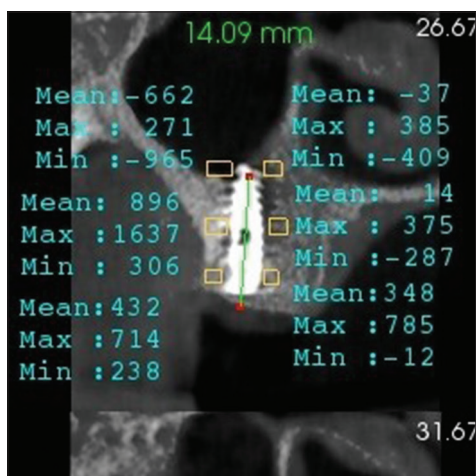
The Hounsfield unit (HU) value measurement was obtained preoperatively for primary assessment, followed by 6 months postoperatively to determine long-term healing. In Group A, the mean buccal 2-mm readings were 148.10 HU and 260.30 HU, respectively, and the mean palatal 2-mm readings at various intervals were 132.70 HU and 308.80 HU, respectively. In Group B, the mean buccal readings at various intervals, i.e. preoperatively and at 6 months postoperatively, were 153.30 HU and 365.80 HU, respectively, and the mean palatal 2-mm readings were 151.10 HU and 324.50 HU, respectively. In Group A, the mean buccal 8-mm readings were –86.90 HU and 280.30 HU, respectively, and the mean palatal 8-mm readings were –113.80 HU and 177.60 HU, respectively. In Group B, the mean buccal 8-mm readings at various intervals were –114 HU and 331.30 HU, respectively, and the mean palatal 8-mm readings were –119.70 HU and 311.90 HU, respectively. In Group A, the mean buccal 14-mm readings were –548.80 HU and –281.80 HU, respectively, and the mean palatal 14-mm readings were –607.70 HU and –322.80 HU, respectively. In Group B, the mean buccal 14-mm readings at various intervals were –541.10 HU and –155.5 HU, respectively, and the mean palatal 14-mm readings were –484.00 HU and –237.80 HU, respectively [Figure 3 and Table 1].

On comparing various densities measured at different heights within each group, it was observed that within the stem cell

**Table 1: Gain in alveolar bone height and increase in bone density in both the groups postoperatively**

Parameters	MSCs				Blood coagulum			
	Preoperative (mm)		Postoperative (mm)		Preoperative (mm)		Postoperative (mm)	
Residual alveolar height	4.90		12.6		4.67		14	
Parameters	Buccal	Palatal	Buccal	Palatal	Buccal	Palatal	Buccal	Palatal
<b>Bone density (HU value) at various levels (mm)</b>								
2	148.10	132.70	260.30	308.80	153.30	151.10	365.80	324.50
8	-86.90	-113.80	280.30	177.60	-114	331.30	-119.70	311.90
14	-548.80	-607.70	-281.80	-322.80	-541.10	-484	-155.5	-237.80

MSCs: Mesenchymal stem cells, HU: Hounsfield unit



**Figure 3: Assessment of bone density at various levels, i.e. 2 mm, 8 mm, and 14 mm using cone-beam computed tomography preoperatively and 6 months postoperatively**

group, there is a statistically significant difference in the bone density in HFU pre- and postoperatively buccally as well as palatally at various levels. Similarly that within the blood coagulum group, there is a statistically significant difference in the bone density in HFU pre- and postoperatively buccally and palatally at various levels.

On comparing the densities on both Groups A and B at various levels, it was seen that the density of the new bone increased significantly over time. The density increased is due to new bone formation in the maxillary sinus. When both the groups were evaluated over time, a similar increase in bone density during a 6-month period was found [Graph 2].

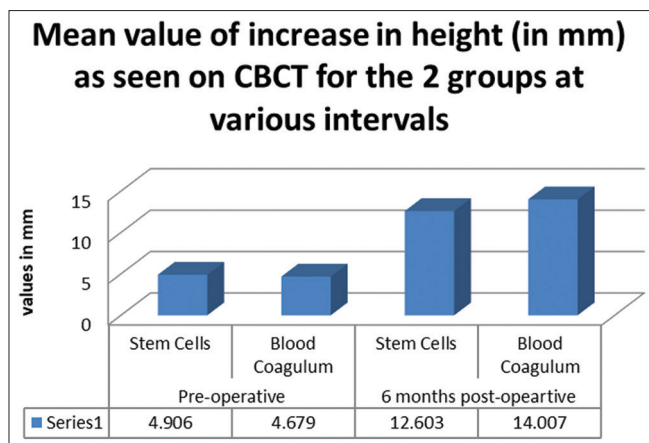
In the present study, all implants were tested by reverse torque technique using 30-Ncm torque with wrench ratchet at the time of abutment placement (6-month follow-up). No surgical complications such as infection, hematoma, dehiscence, and implant failure were observed. Sinus membrane perforation was observed in four cases out of forty sinuses which was repaired using collagen membrane or allowed to resolve on its own if perforation is <5 mm.

## DISCUSSION

Rehabilitating posterior maxilla has been a challenge since ages and requires detailed evaluation, meticulous planning, and skill. As per Carl Misch, the bone quality and quantity in posterior maxilla is of D3 or D4 types and thereby requires grafting prior to or immediate implant placement.<sup>[18]</sup> Sinus lift using lateral approach was performed and described by Tatum in 1986.<sup>[2]</sup> Lateral window technique is mostly preferred as it allows better visualization of floor and positioning of implant.<sup>[19]</sup> In our study, total 20 patients were enrolled, 16 males (80%) and 4 females (20%), and the age ranged from 18 to 65 years (36.7 years). The study of Atlintas *et al.* included 14 patients (7 men and 7 women), ranging in age from 23 to 80 years (mean, 49.5 years).<sup>[20]</sup>

In this study, Group A patients had gained an average bone height of 7.7 mm and Group B gained 9.33 mm which statistically signifies new bone formation at apical region of implant. The significant bone formation is due to anterolateral cortical wall which was turned inward post osteotomy to serve as a new sinus floor. The results showed that the space created underneath the Schneiderian membrane by elevation using blood coagulum and MSCs led to new bone formation in the maxillary sinus similar to results reported in studies<sup>[21-23]</sup> by Balleri Piero *et al.*,<sup>[24]</sup> Ta-Wei Chen *et al.*,<sup>[13]</sup> Seung-Mi Jeong *et al.*,<sup>[25]</sup> Naoki Hatano *et al.*,<sup>[26]</sup> with average bone height of 3-10mm was reported.

In a review by T. C. Nino-Sandoval *et al.*,<sup>[27]</sup> increase in bone height was evaluated on radiographs around 4-5 months in studies by Kaigler *et al.*, Sauerbier *et al.* and Prins *et al.* using stem cells. The average bone height achieved was 12.2 mm. Studies conducted by Ohya *et al.*,<sup>[28]</sup> Pieri *et al.*,<sup>[29]</sup> and Sauerbier *et al.*<sup>[30]</sup> showed that the use MSCs as a scaffold can significantly promote bone growth in sinus augmentation techniques.<sup>[31,32]</sup> This difference in average gain in bone height between peripheral blood and iliac crest MSCs is due to less osteogenic and chondrogenic potential of peripheral MSCs as compared to iliac crest MSCs.

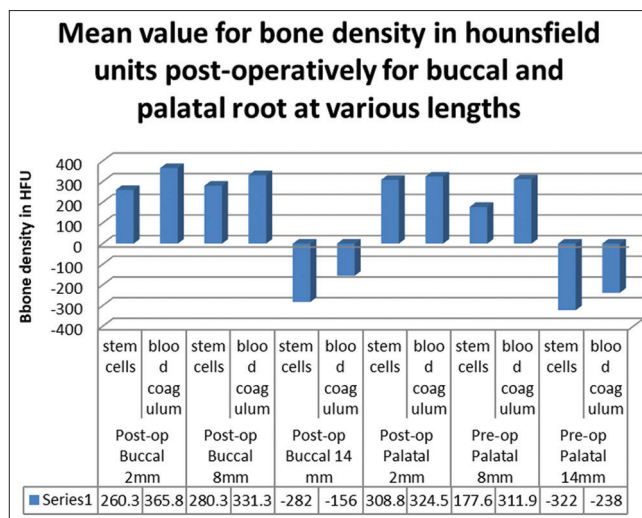


Graph 1: The gain in height (in mm) as seen on cone-beam computed tomography for the two groups at various time intervals

In the study of Hatano *et al.*, they stated that growth factors which are capable of stimulating bone formation are present in blood as well as placement of additional venous blood collected from the patient during surgery, further facilitating the bone formation.<sup>[26]</sup>

Using HU values for determining bone densities helps in determining the quality of new bone formation using CBCT with greater accuracy and specificity.<sup>[33]</sup> This method of using HU values to compare the bone healing pre-operatively and at 6th month post-operatively is observed in studies of Altintas *et al.*<sup>[20]</sup> and Tai-Wei Chen *et al.*<sup>[13]</sup> where bone density values were evaluated by cone beam computed tomography (CBCT); and the new bone formation at the apices of implants were observed.

This study evaluates bone density buccally and palatally at different levels (2 mm, 4 mm, and 6 mm) around implants to cover majority of areas around implants (360°). On comparing the densities of new bone formed in both the groups at various levels, at 6 months postoperatively, a statistically significant increase in density of bone was observed, that is, 1.5 times than preoperatively. This increase in density is a sign of new bone formation in the maxillary sinus. This showed that MSCs have similar bone formation quality and quantity as compared to blood coagulum. Similar results observed in the studies conducted by Nuray Yilmaz Altintas *et al.*<sup>[20]</sup> and Niño-Sandoval TC *et al.*<sup>[27]</sup> which reported better new bone formation with stem cells group in comparison to control group. which reported better new bone formation with the stem cell group in comparison to the control group. We compared bone densities at 2-mm, 8-mm, and 14-mm levels to provide a better picture of implant stability and better osseointegration. No studies till date have compared bone densities both buccally and palatally at various levels.



Graph 2: The mean value for bone density in Hounsfield units postoperatively for buccal and palatal root at various lengths

In the present study, all implants were tested by reverse torque technique using 30-Ncm torque with wrench ratchet at the time of abutment placement. In a study of Simeone *et al.*,<sup>[34]</sup> when reverse torque technique was used in 17 patients over 40 implants, there was complete absence of implant mobility after 6-month follow-up. This is a very effective noninvasive clinical method for early verification of initial bone integration around implants. Primary stability of implant is affected by the residual height of the alveolar crest which should be minimum of 4 mm and also by the diameter of the implants. Altintas *et al.*<sup>[20]</sup> and Jeong *et al.*<sup>[25]</sup> concluded that the residual bone height of 4–6 mm is enough for primary stability for dental implants.

In our study, both the groups reported mild-to-moderate pain on the 2<sup>nd</sup> postoperative day which gradually decreased over a week time using VAS. In study conducted by B Atalay *et al.*<sup>[35]</sup> and Balleri Piero *et al.*<sup>[24]</sup> pain was maximum for 3 days which gradually decreased after a week period.

The swelling was maximum on the 2<sup>nd</sup> postoperative day in Groups A and B which gradually resolved by the 7<sup>th</sup> day. A similar pattern of swelling was observed by Scarano *et al.*<sup>[36]</sup> and Delilbasi and Gurler<sup>[37]</sup> with maximum swelling on the 2<sup>nd</sup> postoperative day which gradually regressed by the 7<sup>th</sup>–14<sup>th</sup> day. Statistically, there is no significant difference ( $P \geq 0.05$ ) in the swelling seen in both the groups. This pain and swelling may be due to the surgical intervention performed bilaterally.

Postoperative infections in maxillary sinus are relatively infrequent, with infection rates reported between 2% and 5.6%, with no distinction being made between true sinus and sinus graft infections.<sup>[38]</sup> Properly performed sinus grafting

does alter neither sinus function nor the characteristics of voice.<sup>[39]</sup> In our study, none of the patients in either group suffered from infection or wound dehiscence. After surgery, healing was uneventful for all patients.

Sinus membrane perforation was observed in four cases out of twenty sinuses in our study which was repaired using collagen membrane or allowed to resolve on its own if perforation is <5 mm. Velázquez *et al.*<sup>[40]</sup> in their study has described about various classifications of sinus membrane perforation and various methods to repair it.

In both the groups, a significant increase in bone height was observed. Upon comparing both the groups, the amount of bone gain was significantly more in the blood coagulum group as compared to the stem cell group. Similarly, an increase in bone density is seen in both the groups suggestive of new bone formation.

## CONCLUSIONS

Augmentation of posterior maxilla is always difficult and requires detailed planning and precision. Very few literature is reported regarding the evaluation of quality of new bone formation in sinus lift procedures.

Our experience with peripheral MSCs and blood coagulum in sinus lift procedures showed promising results with respect to quantity and quality of bone formation and stability of implants after 6 months. The advantages of peripheral MSCs are easy procurement and minimally invasive as compared to iliac crest and it is less time-consuming. Growth factors which are capable of stimulating bone formation are present in blood as well as placement of additional peripheral MSCs collected from the patient during surgery, further facilitating the bone formation.

However, further studies with large sample size would be required to advocate the efficacy of peripheral MSCs in sinus lift procedures and to get more conclusive and affirmative results.

## Ethics statement

The study confirmed the ethical guidelines of the Helsinki Declaration, and it was evaluated and approved by Institutional Human Ethics Committee (IHEC).

## Acknowledgment(s)

This research was supported by Saraswati Dental College and Hospital. We thank our colleagues who provided insight and expertise that greatly assisted the research.

## Financial support and sponsorship

Nil.

## Conflicts of interest

There are no conflicts of interest.

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