Original Article

Efficacy of Concentrated Growth Factor with Autograft and Xenograft in Mandible Fractures: A Randomized Clinical Trial

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Abstract

Objective: To evaluate the efficacy of adjuvant therapy with Concentrated Growth Factor (CGF) along with xenograft and autograft in mandible fractures, in terms of bone density gain and healing over the period of 6 months.

Methodology: This was a Randomized Clinical Trial conducted at a public sector tertiary care hospital in Karachi from May 2019 to July 2022. It included patients with mandible fractures requiring bone grafts due to non-union, delayed union, or malunion. The patients were divided into three groups, each consisting of 20 patients. Group A underwent mandibular surgery using autograft alone, Group B received autograft combined with CGF, and Group C received xenograft combined with CGF. The participants were monitored using serial cone-beam computed tomography at the 4th and 6th months post-operatively to evaluate bone healing and bone density. By the end of the study, all cone-beam CT scans were evaluated for bone density.

Results: The results showed a significant increase in bone bulk formation across all three groups between the 4th and 6th month, highlighting the effectiveness of all treatment modalities ($p < 0.001$). However, intergroup comparison revealed that bone density was comparatively higher in groups B and C, where CGF was used as an adjuvant, than in group A. However, the mean difference in bone density over the 6 months period was similar for Group A (-229.2) and Group B (-227.7), while Group C showed a slightly greater mean difference of -237.9

Conclusion: CGF is equally effective with both autograft and xenograft. However, using CGF with xenograft is preferable, as it helps avoid donor site morbidity and reduces patient inconvenience associated with autograft harvesting.

Keywords: Concentrated Growth Factor, xenograft, autograft, Cone Beam Computed Tomography, mandible

Introduction

Road traffic accidents remain the major cause of maxillofacial injuries worldwide, while trauma, assault, and sports causality are also amongst reasons behind fracture of mandible. Any change in mandible orientation due to fracture may cause occlusal discrepancies and difficulty or inability of jaw opening and closing.[1,2] Malunion or nonunion are factors that make healing and restoration of normal functions and esthetics difficult resulting in a defect in fracture line. To reconstruct bony defects, many strategies are taken under consideration. However, indication of reconstruction of a defect is possible if the defect is >5mm but <5cm. [3,4]

Fractured bone healing phenomenon is a complex biological course that involves regeneration and changes in gene expression.[5] It heals by two mechanisms, direct intramembranous and indirect that involves callous formation.[6] Several techniques have been presented to enhance bone healing and tissue regeneration, Platelets are known to stimulate tissue regeneration by releasing several growth factors.[7] The first generation of platelet concentrates consists of Platelet-rich plasma (PRP) and Platelet Rich Growth Factors (PRGF). They stimulate fibrin polymerization with the help of chemical additives such as anticoagulants and thrombin or calcium chloride.[8] The second generation of platelet concentrates, consisting of Platelet-rich fibrin (PRF) and concentrated growth factors (CGF) that are scientifically proven modality for angiogenesis, collagen synthesis and accelerated healing and regeneration.[9] However, platelets drive growth factors are safer to use since they utilize the patient's venous blood to extract platelet concentrates.[10] CGF is used to fill extraction sockets and fill the cavity after cystectomy. CGF has proved to exhibit superior potential in sinus lift procedures and ridge augmentation surgeries. In procedures involving implants, CGF provides membrane support to promote osteointegration.[11]

The defects of mandible fracture should be addressed primarily to provide the patient with dental rehabilitation. The bone healing process depends on the technique acquired to fill the bone defect for early regeneration of bone. CGF is a platelet-derived substance that is believed to have a positive impact on tissue regeneration, angiogenesis, and bone healing. The study evaluated its efficacy of healing by using it as an adjuvant with two other bone graft materials that are xenograft and autograft and to compare it with autograft which is known as a gold standard for to restore the mandible fracture bone defects. The main objective of this study was to compare bone apposition capacity of CGF while using it with bone graft substitutes, that is CGF with autograft, CGF with xenograft and autograft alone over the period of 6 months in mandibular fracture defects.

Methodology

It was a Randomized Clinical Trial conducted at Dow University of Health Sciences and associated hospitals. Simple random sampling technique was used for recruited participants as the criteria for inclusion in any one of the allocated groups. Study population was mostly males since RTA and fractures are more commonly reported in males whilst few females were also reported, however, almost all of the females refused to participate in the study, hence only one female who voluntarily agreed to participate was included. Consent, both written and verbal, was taken from the participants.

The participants were then well informed about the entire procedure and its outcome, both unfavorable and favorable. Once the patient agreed to the terms, the consent was documented with the participant's initials. The next steps after preliminary inclusion were taking detailed systemic history and documenting it over Proforma. The pre-operative radiographs and simultaneous clinical features were then used to assess the type of fracture. The envelop method was utilized for randomization, where 60 envelopes were devised, out of which three groups were made with 20 subjects in each group. However, every subject was asked to pick the envelope and was allocated to their respective group.

Trial registration and ethical approval DUHS (Dow University of Health Sciences) provided the ethical approval for the study and the reference number for ethical approval is IRB-1835/Approval/2020. The study took around 3 years to complete from May 2019 to July 2022. The research protocol was registered with the Protocol Registration and Results System at ClinicalTrials.gov Identifier: NCT05480631 https://clinicaltrials.gov/ct2/show/NCT05 480631. Dates of recruitment and follow-up can be found there as well.

It included patients with mandible fractures requiring bone grafts due to non-union, delayed union, or mal-union. The patients were divided into three groups, each consisting of 20 patients. Group A underwent mandibular surgery using autograft alone, Group B received autograft combined with CGF, and Group C received xenograft combined with CGF. The subjects considered for inclusion were participants aged 18-40 irrespective of gender, while mandible fractures, either symphysis, body or para symphysis having fracture gap size ranging from >5mm to <5cm were included. Subjects with bone disorders, and medically compromised conditions were excluded along with anyone undergoing radio/chemo therapy.

Data Collection Procedure

The participants were allocated to their respective group via envelope method. The fracture assessment was done by detailed history examination and evaluation of radiograph to be categorized into either mal-union, delayed union and/or non-union fracture. The preparation of CGF was done following standardized guidelines, [12] an automated centrifuge machine was used to dispense the CGF.

The surgical procedures started off with taking all the necessary aseptic measures and under general anesthesia, the adequate exposure for better access was done and the exposed part was scrubbed gently. The oral cavity was then scrubbed with pyodine, and the intra-oral assessment was done to plan the incision. Local anesthesia was then injected that contained adrenaline 1:200,000 & xylocaine 2% and incision was made in buccal and/or labial vestibule and full-thickness flap was reflected to get sufficient visibility and access to the fracture site. Necessary measures were taken to avoid insulting mental nerve, and simultaneously bleeding was managed and controlled via cautery, suction and gauze packs to get visibility of fractured bone segments.

Fracture segments were then made devoid of granulation tissue and the defect was assessed for reconstruction. Fracture parts were held close to anatomic position to achieve pre-existing occlusion as accurately as possible. The fracture was secured with mini-plates and desired modality was introduced either autograft which was derived from intra-oral site utilizing grid type cortical bone harvesting from ascending ramus to avoid bone marrow invasion used alone to fill the gap, CGF with xenograft (bovine) or CGF with autograft. The soft tissue was then placed over the bone and secured in placed with the help of resorbable suture that was vicryl 3.0.

Post-Operative Bone Density Assessment Using Cone-Beam CT Scans

All patients underwent post-operative cone-beam CT (CBCT) scans at the 4th and 6th months. A radiology specialist analyzed the grey levels on CBCT to evaluate and record Bone Mineral Density (BMD) from the region of interest, located occlusal to the fracture site. Bone Mineral Density was quantified using Planmeca Romexis 6 software. By the end of the study, all cone-beam CT scans were evaluated for bone density.

Results

Demographic Data

Out of the 64 selected subjects, 20 were assigned to each of the three groups, with 4 patients missing their follow-up visits. The male-to-female ratio was skewed, with only one female participant, indicating that the majority of fracture cases reported between 2020 and 2022 were in adult males. Regarding socioeconomic status and occupation, most participants were either employed or self-employed, while 13 were unemployed.

Clinical Characteristics

Clinical characteristics that were examined as an integral part of the study were fracture site, causes of trauma and the size of the defect. Symphysis fractures were the most frequently encountered ones among all accounting for 60% cases in group A, 50% in group B and 50% in group C. Para symphysis fracture were second most occurring fractures making up 25% of group A cases, 30% of group B and 30% of group C. Body fracture was least found fracture making up to 15% in group A, 20% in group B, and 20% in group C. From the concerning causes of fracture, the most frequent cause was RTA followed by assault and abuse which were the least observed causes of fracture, making up only 1% of all the participants (Table 1)

Table 1: Clinical characteristics of fracture

Clinical Characteristics	A N = 20 (%)	B N = 20 (%)	C N = 20 (%)
Site of fracture			
Body of the mandible	3 (15.0)	4 (20.0)	4 (20.0)
Parasymphysis of the mandible	5 (25.0)	6 (30.0)	6 (30.0)
Symphysis of the mandible	12 (60.0)	10 (50.0)	10 (50.0)
Cause of fracture			
Accident	14 (70.0)	15 (75.0)	13 (65.0)
Fall	3 (15.0)	2 (10.0)	4 (20.0)
Sports injury	2 (10.0)	3 (15.0)	2 (10.0)
Abuse/assault	1 (5.0)	0 (0.0)	1 (5.0)
Defect Size (mm) , Mean ± SD	6.2 ± 1.10	6.3 ± 1.21	5.9 ± 0.74

Comparing bone density within group (Intra-Group Comparison)

Bone density was compared across all three groups between the 4th and 6th months to evaluate whether it increased over time with each individual modality. Groups A, B, and C all demonstrated a significant increase in bone density during this period, with a corresponding p-value of <0.001. However, the mean difference in bone density was similar for Group A (-229.2) and Group B (-227.7), while Group C showed a slightly greater mean difference of -237.9 Hounsfield Units (HU) (Table 2).

Table 2: Comparison of Mean Bone Density at 4th and 6th Months and the Mean Difference Across Groups A, B, and C

Clinical Characteristics	A N = 20	B N = 20	C N = 20
Mean ± SD			
4th	807.8 ± 69.75	1024.7 ± 172.3	1032.8 ± 187.8
6th	1037 ± 150.2	1252.4 ± 194.8	1270.7 ± 193.1
Mean difference (p-value¥)			
6th to 4th Month	-229.2 (<0.001)	-227.7 (<0.001)	-237.9 (<0.001)

Inter-Group Comparison of Acquired Bone Density in Hounsfield Units (HU)

When the inter-group comparison of group A, B and C was done it was revealed that the mean difference between group A and B and group A and C was significant corresponding to p-value <0.001 whilst on comparing group B and C the mean difference was not significant showing close differences that cannot be categorized as significant (Table 3).

Table 3: Inter-group comparison of group A, B and C of acquired bone density.

Months	B vs. A	C vs. A	C vs. B
Mean difference (p-value¥)			
4th	-216 (<0.001)	225 (<0.001)	-8.05 (0.868)
6th	-215.4 (<0.001)	233.7 (<0.001)	18.3 (0.750)

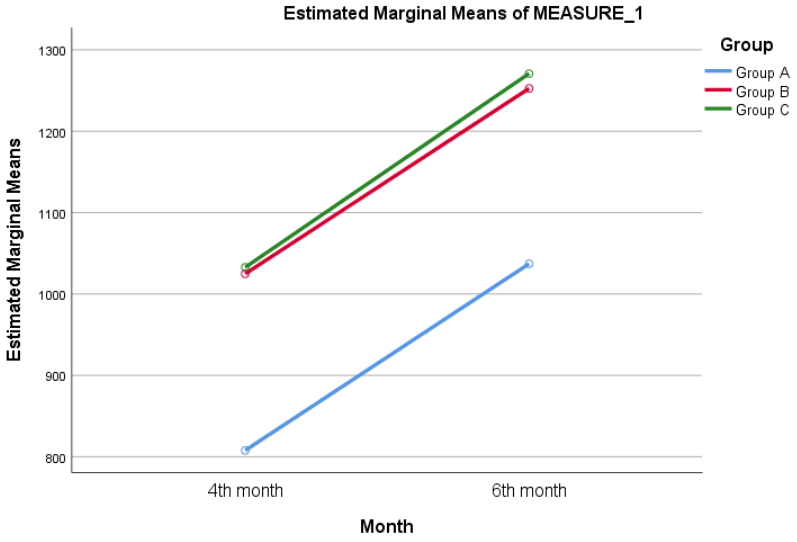

Figure 1. Inter-group comparison of group A, B and C

The results were consistent with another published study in regards of acquiring bone density; however, the pain at donor site was managed via acetaminophen with combination of diclofenac sodium. 3 patients reported with lingering donor site post-operative pain that took three weeks to subside. Thirteen patients reported with post-operative infection which expressed itself via redness, swelling but no draining sinus were formed. Post-operative infections were managed with 1g amoxicillin and 400mg of metronidazole. By the end of the study there were no long-term side effects found in all three modalities.

Discussion

This randomized clinical trial assessed the effectiveness of CGF combined with autograft and xenograft in treating mandibular fractures by measuring bone density improvements and comparing results across the three groups. Over the six-month period, all groups demonstrated significant increases in bone density, with noTable differences observed between the groups.

In terms of demographics, the majority of participants were employed or self-employed, with a smaller portion being unemployed, representing a diverse socioeconomic background. The analysis revealed a predominance of male participants, with only one female participant, aligning with global trends that show mandible fractures are more prevalent in adult males.

Clinically, the mandibular symphysis was the most frequent fracture site across all groups, consistent with the region's anatomical vulnerability. Road traffic accidents (RTAs) were identified as the leading cause of fractures, supporting previous research highlighting RTAs as a major contributor to maxillofacial trauma. Other causes, such as falls and sports injuries, were observed but less common (Table 1).

An intra-group comparison between the fourth and sixth months showed a significant increase in bone density across all three groups ($p < 0.001$), demonstrating the effectiveness of each treatment in promoting bone regeneration. While the differences were modest, Group C (CGF with xenograft) exhibited the largest mean increase in bone density (-237.9 HU), suggesting slightly superior outcomes compared to Groups A and B (Table 2). These findings align with earlier studies emphasizing the osteogenic potential of CGF when combined with grafting materials.

The therapies' effectiveness was further confirmed through inter-group comparisons. Significant differences were observed between Groups A and B, as well as Groups A and C ($p < 0.001$), indicating that combining CGF with either autograft or xenograft leads to greater bone density improvements compared to CGF alone. However, the comparison between Group B (CGF with autograft) and Group C (CGF with xenograft) revealed no statistically significant differences, suggesting similar outcomes for both combinations (Table 3, Figure 1.). These findings highlight the clinical feasibility of xenografts as a viable alternative to autografts, particularly in cases where donor site morbidity is a concern. Furthermore, the results support the use of CGF for critical-sized bone defects to promote effective healing and regeneration. Consensus also provides us with data that supports its use along with other bone graft such as auto-graft, allograft and xenografts.[12, 13] However, the outcomes of this study are aligned with most of the studies that employed similar modality. The use of CBCT also aids i n assessing the bone mineral density in 3 dimensions to generate more accurate and reproducible results. A study conducted by Emad et al, (2012) incorporates the use of PRP within the fracture line and compares the results with that of control group, and the post-operative 3rd and 6th month evaluation over CBCT shows significant difference in cases in terms of elevated BMD in HU.[14,15] CBCT; it is a recent advancement in observing the 3-dimensional aspect of the subject with fewer radiation doses[16.] .Its application to assess the bone density of the maxillofacial region is sufficiently advocated through many studies, especially implant dentistry, orthodontics, and oral surgery.[17]

Xenogeneic bone substitutes have shown better outcomes when used in complicated mandibular fractures, Ekaterina et al. 2022 conducted an experimental study where an angle fracture was complicated with follicular cyst, the pre-operative assessment shows the custic dimension around 2cm. The case was managed with collagenous xenogeneic graft that fills the cystic cavity. Post-operative evaluation was done via plain radiographs; this process enables effective rehabilitation and bone regeneration.[18] The study also advocates the utilization of xenogeneic substitutes in complicated mandibular fractures; however, the current study evaluates its effectiveness of xenogeneic substitutes along with autologous platelets extracts to be assessed on bone mineral deposition levels.

Another clinical trial conducted by Dongdong et al. (2020) in mandible bone defects were assessed over the period of 12 weeks whilst using combination of bone particulates with healing adjuvants. Upon consecutive post-operative visits, it was observed that serum osteocalcin and serum alkaline phosphatase significantly indicated higher bone mineral deposition in subjects where platelet derived growth factor were combined with bone particulates [19].These findings are concordant with the above-mentioned research.[20]

An animal study was conducted by Yilmaz et al. (2018) on rabbits to evaluate the efficacy of CGF to induce proliferation, angiogenesis and healing of bone defects.[21] In this experiment, an intentional fracture at radius diaphysis creating a bone defect of 15mm was made following Masquelet technique, leaving 3mm of sound bone on the edges.[21] The defect was then treated in controls with Masquelet technique alone and in cases the Masquelet technique along with CGF was done. Histopathology and immunohistochemistry analyses revealed that groups treated with CGF exhibited a higher ratio of stem cells, more sTable angiogenesis and vascularization, and the formation of a thicker membrane.[21,22,23] In contrast, bone healing in our study was assessed using CBCT to measure the density of mineral deposition in three dimensions within the region of interest.

An update by Jaime et al. (2017) recommends the use of adjuvant modalities in combination with autogenous bone grafts for managing fractures in atrophic mandibles.[24] The current research also intends to propose the most effective method to reconstruct fracture defects with substitutes with lesser side effects and are accepTable for the recipient. Similarly, Nivedhitha et al, (2019) incorporates CGF after treating the peri-apical lesion with apicectomy and subsequent retrograde filling, the lesion was then filled with CGF squeezed to form membrane. The assessment of the lesion was done via Cone-beam CT pre-operatively and

post-operatively which dictates that the healing and bone deposition was sufficiently good in all 3 dimensions when treated alone with CGF. This research provides evidence for utilizing CBCT as a newer technology to assess bone healing both pre- and post-operatively.[25]

Limitations

Considering the limitations, the results cannot be applicable to larger bone defects that are more than 10mm in greatest dimension. If implant placement is indicted, different evaluations pertaining to bone deposition in Bucco-lingual dimension need to be evaluated. The results are limited to the assessment of bone mineral density in numeric form.

Conclusion

Bone mineral density in the region of interest increased in all three groups when assessed from the 4th to the 6th month post-operatively, demonstrating that all modalities used in the study promote bone density and accelerate healing over time. However, intergroup comparisons revealed higher bone density in groups B and C compared to group A, with similar results observed between groups B and C. This suggests that the combination of xenograft and CGF can effectively support bone healing. Therefore, xenograft with CGF may serve as a viable alternative to autograft, eliminating the need for harvesting autograft and reducing donor site morbidity.

Recommendations

Bone defects reconstruction can be done with either of the available graft and adding CGF can provide speedy healing and bone apposition. Critical size bone defects can easily be treated with CGF mixed with bone power that not only enhances the outcomes but also provide scaffolding effect to the graft. CGF can also be used alone as a membrane in various periodontal procedures. Combining CGF with powdered bone has the same efficacy as of autograft which was thought to be the gold standard for reconstruction. Thus this technique might help in reducing donor site morbidity and creating a second surgical site. Further studies can be conducted that also includes serum levels of osteocalcin and BAP (Bone Alkaline Phosphatases) where CBCT is not inducted or available to assess the healing process efficiency.The future studies can also be done in similar manner by using histomorphometric analysis procedures to avoid the undue exposure to cone beam tomographic rays as done in previous studies.

Authors' Contributions: AHS: Conceptualization, methodology, supervision; TA: Data curation, formal analysis; AR: Investigation, writing—original draft; HFK: Visualization, project administration; AH: Writing—review and editing.

Conflict of Interest: The authors declare that they have no conflict of interest.

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