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# EFFICIENCY OF CONCENTRATED GROWTH FACTORS ON IMMEDIATE IMPLANT STABILITY AND OSSEOINTEGRATION IN POSTERIOR MANDIBLE (RANDOMIZED CONTROLLED CLINICAL TRIAL)

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## ABSTRACT

**INTRODUCTION**: Plasma derivatives that include growth factors are shown to hasten osseointegration & boost implant stability. With growth factors it includes, concentrated growth factor (CGF), this can be accomplished.

**OBJECTIVES**: To evaluate both clinically and radiographically efficiency of concentrated growth factors on implant stability and osseointegration in immediately placed dental implants in lower posterior mandible.

**MATERIALS AND METHODS:** In lower posterior mandibular area 17 immediate implants were located in study group & a defect of 2 mm or more were filled with CGF, bone graft & covered with collagen membrane, while 17 immediate implants were placed in the control group and bone graft and collagen membrane were used to fill defect without CGF. Clinical evaluation was done to assess implant stability at first and fourth week, pain, edema and presence of infection at first week. Radiographic evaluation for peri implant bone density, peri implant crestal bone loss was also done.

**RESULTS:** Clinical evaluation included implant stability evaluation, pain and edema. Radiographic evaluation included peri-implant crestal bone loss and a peri-implant bone density evaluation. No statistically significant results had been shown between control and study group according to pain, edema and peri-implant bone loss values. There was highly significant results between study and control group according to peri-implant bone density with higher values according to study group.

**CONCLUSION:** Concentrated growth factor speeded implant osseointegration procedure & impacted stability values positively.

**KEYWORDS:** Dental implants, Concentrated growth factor, Growth factors, Osseointegration, Osteogenesis.

**RUNNING TITLE**: Efficiency of concentrated growth factors on implant stability.

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## INTRODUCTION

Dental implants' osseointegration is crucial for their long-term success & stability. Duration of osseointegration & timing of prosthesis loading are not standardised. This procedure can take zero to six months (1).

To reduce this time, number of solutions are being investigated. Improved primary stability & improved peri-implant tissue health resulted from modifications in implant surface characteristics & design. These modifications were made in effort to improve bone-implant surface connection & speed healing. Regulation of healing following implantation is another strategy for hastening osseointegration. Bioactive chemicals that boost osteoblastic differentiation & speed up bone repair around implant can then accomplish this modulation (2).

Growth factors are bioactive proteins that regulate how quickly wound heals. Bone morphogenetic protein, platelet-derived growth factor, insulin-like growth factor, vascular endothelial growth factor, transforming growth factor-β1, & transforming growth factor-β2 are just few of growth factors found in platelet-containing preparations made from human blood. These growth factors are important for bone healing (3-5). These growth factors draw undifferentiated mesenchymal cells to area of wound, promoting chemotaxis, angiogenesis, & cell growth (2).

Bone defects are repaired using variety of platelet concentrates, including concentrated growth factor, platelet-rich plasma, & platelet-rich fibrin (6). Numerous researches demonstrated that PRF produces excellent tissue engineering outcomes (7-9). Additionally, 2009 research by

Sohn et al. revealed that CGF has greater ability for regeneration & can be used for variety of purposes (10).

Due to presence of growth factor-containing fibrin network, fibroblast, platelet, leukocyte, & endothelial cells for angiogenesis & tissue remodelling, as well as matrix for cell migration, this preparation has potential (11). Particularly, platelets stimulate cell morphogenesis, development, & repair because they have large amounts of physiologically active proteins (12-14).
For implant to receive requisite bone formation after implantation & for best distribution of functional forces at implant-bone contact throughout healing, implant's post-implant stability is crucial (15-17).

Resonance frequency analysis is crucial tool for monitoring osseointegration procedure (18, 19). RFA is a method that enables monitoring stability variations not only throughout implant insertion but throughout healing & subsequent phases (20).

Products with growth factors are proven to hasten osseointegration & bone repair (2, 4). Purpose of this research is to assess how CGF affects implant stability. On basis of research's findings, it will be feasible to shorten time needed for osseointegration.

The null hypothesis of the present study is that no significant difference is expected between implants covered with CGF membrane and conventional implant placement protocol regarding stability and osseointegration.

## MATERIALS & TECHNIQUES

This study was approved by the ethics committee of Faculty of Dentistry, Alexandria University (0092-11/2019). It was conducted at the Faculty of Dentistry, Alexandria University, Egypt.

I. Study design

The present research was randomized controlled clinical trial.

II. Study sample and setting

Thirty-four implants were sum of control and study group. Studied cases were selected from outpatient Clinic of Oral & Maxillofacial Surgery Department, Faculty of Dentistry, Alexandria University In posterior mandible. 17 immediate implants were located in study group & a defect of 2 mm or more were filled with CGF membrane, bone graft & covered with collagen membrane, while 17 conventional immediate implants were placed in control group and bone graft & collagen membrane filled the defect without CGF.

Randomization and Allocation Concealment (Way of randomization)

The patients allocated via the block randomization method, using a (36) computer-generated random sequence into 2 groups of equal numbers (N=17 patient/group). Allocation was performed by a trial independent individually. The participant allocation was kept in opaque, sealed envelopes and arranged sequentially by a dental assistant, who was not involved in the study. Each envelope was opened after completing the oral examination and right before the application of the intervention.

Sample size calculation

Sample size was estimated based on the following assumptions: confidence level=95% and study power=80%. Pirpir et al., (21) reported that the mean difference in implant stability quotient (ISQ) between the immediate postoperative and the 4$^{th}$ week measurements in implant cavities covered with CGF membrane was 0.60±2.798 and -2.30±2.774 in the control group. Sample size was calculated to be 16 patients and this was increased to 17 to make up for cases lost to follow up. The total sample size = number of groups ×number of per group = 2 ×17 = 34 Patients.

Software

Sample size was based on Rosner's (22) method calculated by Gpower 3.0.10 (Universitat Dusseldorf. G*Power, 2019).

III. Criteria for patient selection

Inclusion criteria

Inclusion criteria included: Male or female patient ranging from 20-45 years old.

Site criteria: patients having lower hopeless posterior teeth (lower right or left first or second molars) ready for extraction, periimplant bone gap ≥ 2mm (class I alveolar socket), adequate bone quantity and interocclusal space (23).

Exclusion criteria

Immune-compromised patient with reduced defensive capacity such as patient on immunosuppressive drugs or with acquired immunodeficiency disease (HIV infection or AIDS), patient with any blood coagulation disorders which affect the coagulation process, pregnant women, smokers and patients with any parafunctional habit were excluded from the study. Patients with bone diseases i.e. osteoporosis were excluded.

Patient grouping

Group I (Study group): 17 immediately placed dental implants (10 female, 7 male) where the gap were filled with bone graft & CGF and covered by collagen membrane.

Group II (Control group): 17 immediately placed dental implants (12 female, 5 male) where the gap had been filled with bone graft only & covered by collagen membrane.

MATERIALS

Superline Implant system*

OneXeno Graft**.

* Dentium Co., Korea

Hypro-Sorb***.

METHODS

1- Presurgical phase

The preoperative data were collected & recorded in full details containing name, years old, sex, occupation, address, telephone number. A chart including past medical history, family history, drug history and past dental history were fulfilled. Intra oral & extra oral Inspection was done to identify any swelling, asymmetry, malocclusion, & texture of mucosa, occurrence of any ulceration, hypertrophy & draining sinuses. Palpation of buccal, labial & palatal mucosa & site of implant placement. Cone beam computed tomography were done for evaluation of bone height, width & suitable implant size and location. (Figure 1a, b and Figure 4a, b)

2- Surgical phase

Before surgery, antiseptic mouth wash were used as prophylaxis and local anaesthesia was administered. Atraumatic extraction were performed to the desired decayed lower posterior teeth followed by drilling of implant site were done according to the principles and guidelines of the Dentium System. Implants were placed using handpiece carrier with maximum torque of 30Ncm. any extra torque needed were done using a hand ratchet.

Periimplant defect ≥ 2mm were filled with CGF, bone graft & covered by collagen membrane in the study group and it was filled with bone graft & covered by collagen membrane in the control group. (Figure 1c,d,e,f,g,h, Figure 2a,b,c,d,e,f,g, Figure 4c,d,e,f,g,h, Figure 5a)

*Concentrated growth factors preparation protocol*

Intravenous blood samples were collected from studied cases & located in centrifuge tubes without anticoagulants & were speeded for thirty sec centrifuged at 2700rpm, for 4min/2400rpm, for4min/2700, for4min/3000rpm and decelerated for 36 sec. A haemostatic clamp were used to hold layer in form of membrane including CGF and separate it from red blood cells. The layer is then pressed to form membrane. (Figure 1c,d,e,f,g,h and Figure 2a,b,c,d,e,f,g)

3- Post-surgical phase

*1. Postoperative instructions*

Oral hygiene instructions, soft diet for two weeks, cold fomentation for 1st day, warm mouth wash next day, anti-inflammatory NSAID two times a day for 3 days and antibiotic two times a days for 5 days.

*2. Postoperative medication*

NSAID: Diclofenac potassium fifty mg tablets, Cataflam (Novartis, Switzerland)

Antibiotic: oral tablet of amoxicillin trihydrate corresponding to 875 mg amoxicillin & potassium clavulanate equivalent to 125 mg of clavulanic acid, Augmentin (GlaxoSmithKline, UK).

Mouth wash: 0.12 percent chlorhexidine HCL, Hexitol (Arab Drug Company, Cairo, Egypt).

*3. Radiographic evaluation*

CBCT was done preoperatively for implant tracing, immediate postoperatively, after two months and after four months after prosthesis. (Figures 1b, 3a, 3b,3h, 4a, 5b, 5c, 5e)

Peri implant bone loss was evaluated through study and control group after four months of implant insertion (24).

Peri implant bone density was evaluated through hounsefield units collected from CBCT measurement tools immediately post operatively, two months and 4th month for both groups (25).

*4. Clinical evaluation*

Peri implant stability was measured by osstel device immediate postoperatively, at first week and at fourth week (26). (Figures 3e, 5f)

Pain was evaluated at the day of procedure and after one week throughout the study and the control group through visual analogue scale. As follows: zero = no pain, one= midl, two moderate and three = severe (27).

Edema was evaluated at 24 hours after procedure and one week throughout the study and control group through a scale as follows: 0 no edema, 1 mild (2 mm depth with immediate rebound time) and 2 moderate (3 to 4 mm depression with 15 second or less rebound time). Presence of infection was evaluated throughout follow up (28).

*5. Prosthetic phase*

Prosthetic phase begins after 4 months of implant insertion. Porcelain fused to metal was the material of choice for final prosthesis (29). (Figures 3c, 3d, 3f, 3g, 5d)

*6. Follow up period*

A total of two months follow up period was considered.

Statistical analysis of the data

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp). Categorical data were represented as numbers and percentages. Chi-square test was applied to compare between two groups. For continuous data, Quantitative data were expressed as mean and standard deviation for normally distributed quantitative variables Student t-test was used to compare two groups while ANOVA with repeated measures was used to compare between more than two periods and followed by Post Hoc test (adjusted Bonferroni) for pairwise comparisons. On the other hand for not normally distributed quantitative variables Mann Whitney test was used to compare two groups

** One graft Company, Germany

*** Bioimplon GmbH. Germany

while Friedman test. Was used to compare between more than two periods and Post Hoc Test (Dunn's) for pairwise comparisons Significance of the obtained results was judged at the 5% level.

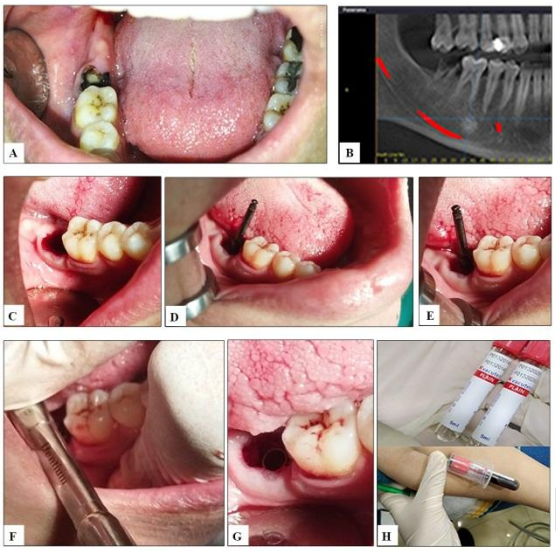

**Figure (1):** A: Before extraction, B: Pre operative CBCT and implant tracing, C: After extraction, D: Socket drilling, E: Cheking paralillsm, F: Implant insertion, G: Implant inside socket, H: Blood collection

**Figure (2):** A: Compression, B: Medifuge centrifuge, C: Cover screw inserted, D: Mixing CGF with bone graft, E: Preparing CGF membrane, F: Insertion of the mix inside socket, G: Collagen membrane overall,

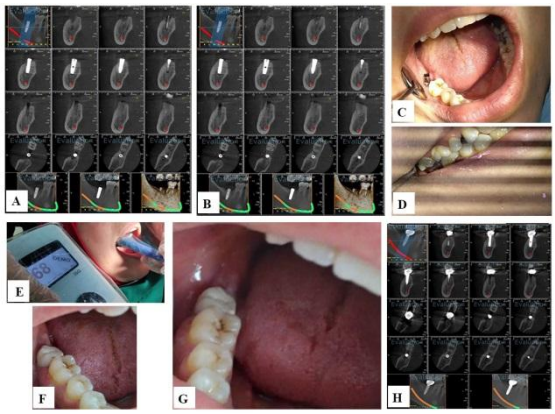

**Figure (3):** A: Immediate postoperative CBCT, B: CBCT after 2 months1, C: Final abutment, D: Final abutment1, E: ISQ measurements, F: Final prothesis 1, G: Final prosthesis, H: CBCT after final prothesis1

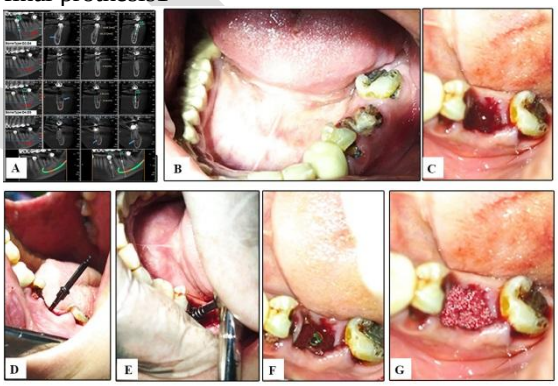

**Figure (4):** A: Preoperative CBCT, B: Before extraction, C: After extraction, D: Drilling, E: Implant insertion, F: Implant insitu, G: Bone graft,

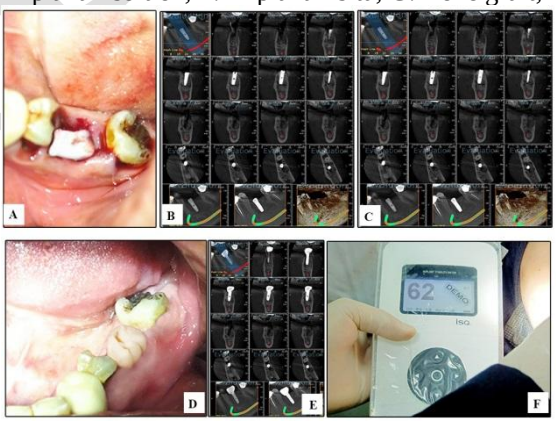

**Figure (5):** A: Collagen membrane overall, B: Immediate postoperative CBCT, C: CBCT after 2 month, D: Crown insertion, E: 12-CBCT after prosthesis, F: ISQ measurements

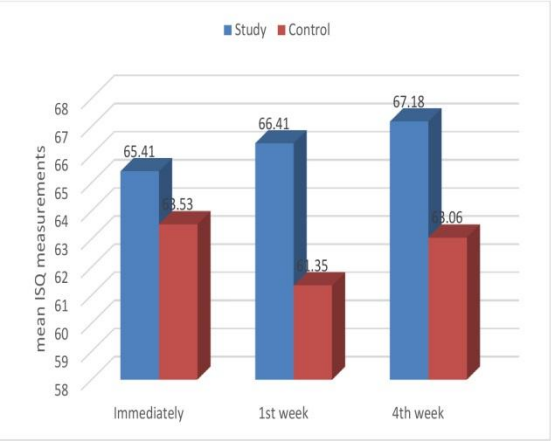


**Figure (6):** Comparison between the two studied groups according to ISQ measurements

## RESULTS

The study included male or female patient ranging from 20-45 years old. Total of 34 implants had been located, 17 of these contained in study group (50%), & other 17 contained in control group (50%). There was no variation among control group & study group in terms of sex distribution, installed implant diameter, or bone quality. Throughout healing process, there were no issues.

Clinical evaluation

*Implant stability evaluation*

Regarding the ISQ measurements, immediately postoperative, study group was 65.41 ± 3.79 and control group was 63.53 ± 4.49. There was no variation among groups (p=.196). After 1st week, Study was 66.41 ± 3.92 and control group was 61.35 ± 3.84. There was variation among groups (p=0.001*). Study group found greater mean ISQ measurements than control group. After 4th week, Study was 67.18 ± 2.88 and control group was 63.06 ± 4.13. There was variation among groups (p=0.002*). Study group found a greater mean ISQ measurements than control group. (Table 1, Figure 6)

When comparing the three periods according to ISQ measurements in each group, the study group was 65.41 ± 3.79 immediately, 66.41 ± 3.92 at 1st week and 67.18 ± 2.88 at 4th week. There was rise in mean ISQ measurements (p=0.012*) at first week & fourth week. Regarding control group, mean ISQ measurements was 63.53 ± 4.49 immediately, 61.35 ± 3.84 at 1st week and 63.06 ± 4.13 at 4th week. There was also rise in mean ISQ measurements (p=0.021*) at first week & fourth week.

*Pain evaluation*

Regarding mean pain score, the study group at the day of procedure was 2.00±0.79 and after 1 week was 0.00, although in control group mean pain at day of procedure had been 2.11±0.78 and after 1 week was 0.00.

*Edema evaluation*

Regarding edema,12 patients showed mild edema and 5 patients showed moderate edema in study group, while the control group, 9 patients showed mild edema and 8 patients showed moderate edema. No edema was observed after one week in both groups.

Radiographic evaluation

*Peri-implant bone loss evaluation*

Mean crestal bone loss in study group at 4 months was 0.31 ± 0.15 while in control group it was 0.36 ± 0.13. (Table 1)

*Peri-implant bone density evaluation*

Mean peri-implant bone density in study group immediately post-operative was 402.5 ± 58.4 and after 2 months was 535.8 ± 47.5, and at 4 months was 788.2 ± 55.6 while in control group the mean density was 421.6 ± 49.1 and after 2 months was 527.5 ± 32.5, and at 4 months was 663.8 ± 66.7. The difference was statistically significant at 4 months (p<0.001*). (Table 1)

**Table (1):** Comparison between the two studied groups according to different measurement

| | Study (n = 17) | Control (n = 17) | p |
|---|---|---|---|
| ISQ measurements | | | |
| Immediately | 65.41$^{b}$ ± 3.79 | 63.53$^{a}$ ± 4.49 | $^{t}$p=0.196 |
| 1$^{st}$ week | 66.41$^{ab}$ ± 3.92 | 61.35$^{b}$ ± 3.84 | $^{t}$p=0.001$^{*}$ |
| 4$^{th}$ week | 67.18$^{a}$ ± 2.88 | 63.06$^{ab}$ ± 4.13 | $^{t}$p=0.002$^{*}$ |
| Pain | | | |
| Day of procedure | 2.00 ± 0.79 | 2.11 ± 0.78 | $^{U}$p=0.665 |
| 1 week | 0.0 ± 0.0 | 0.0 ± 0.0 | $^{U}$p=1.000 |
| Edema 24 hr. | | | |
| Mild | 12 (70.6%) | 9 (52.9%) | $\chi^2$p=0.290 |
| Moderate | 5 (29.4%) | 8 (47.1%) | |
| Crestal bone loss after 4 months | 0.31 ± 0.15 | 0.36 ± 0.13 | $^{U}$p=0.330 |
| Density | | | |
| Post-operative | 402.5$^{c}$ ± 58.4 | 421.6$^{c}$ ± 49.1 | $^{U}$p=0.193 |
| 2 months | 535.8$^{b}$ ± 47.5 | 527.5$^{b}$ ± 32.5 | $^{U}$p=0.563 |
| 4 months | 788.2$^{a}$ ± 55.6 | 663.8$^{a}$ ± 66.7 | $^{U}$p<0.001$^{*}$ |

Quantitative data was expressed using Mean ± SD.SD: **Standard deviation**
**t: Student t-test**
**U: Mann Whitney test** $\chi^2$: **Chi square test**
p: p value for comparing between **Study** and **Control**
*: Statistically significant at p ≤ 0.05

## DISCUSSION

In current research, according to exclusion criteria, we excluded patients with bone disease like osteoporosis, due to their negative effect on implant stability and oseointegration. Gibreel et al., assessed impact of bone disease on osseointegration,
24 cases of osteoporotic patients had dental implants. After 1 year of follow up failure in 12 cases occurred which is 50% of the cases (30).
Primary stability is crucial prerequisite for success of osseointegration, according to numerous writers. At present study, we measured the stability after 1st week, and after 4th week. There aren't many papers on CGF's impact on dental implants' stability throughout healing process. Due to this, we examined in research how CGF affected durability of dental implants (18,31).

One of crucial factors in determining loading time & success of dental implants is implant stability. After 1st week, the ISQ in the study group was 66.41 ± 3.92 and the control group was 61.35 ± 3.84. At the 4th week, the study group was 67.18 ± 2.88 and control group was 63.06 ± 4.13. There was greater mean ISQ measurements in study group at 1st and 4th weeks.

In accordance with our results, Pirpir et al. (26), assessed effect of CGF on implant stability&osseointegration. Mean ISQ values showed to be 79.40 ± 2.604 for study group&73.50 ± 5.226 for control group at first week, 78.60 ± 3.136 for study group&73.45 ± 5.680 for control group at fourth week. Statistics showed that there were variations among groups ($p < 0.05$). They noticed that concentrated growth factor improved implant stability & appeared to hasten early osseointegration.

Furthermore, in experiment involving animals, CGF, PRF, & PRP were each individually injected into rabbit skull defects in study group while control group's flaws were left empty. Histomorphometric analysis found statistically significant variations in growth of new bone formation at six & twelve weeks among control & study groups. Study group's CGF-treated group contained most bone development (32). Moreover, in rat research by Takeda et al., it showed that cell culture from CGF-treated group had considerably greater cell proliferation & osteoblastic differentiation than other groups (33).

In the present research, pain and edema evaluation in study & control group did not find any variations proving that CGF has no effect on pain and edema reduction immediately postoperative or after one week.

Other studies evaluating impact of CGF on the quality of life of studied cases undergoing implant treatment, we had 52 studied cases with 1 missing mandibular molar, divided into to 2 groups. Control group received standard implant therapy & the Test group received CGF with implant treatment. Daily pain was evaluated through visual analogue scale for one weak postoperatively. Postoperative pain with visual analogue scale score was significantly lower with test group on day one, two and three compared to control. The result of this study mismatches our results (34).

Moreover, in research assessing impact of CGF on postoperative sequel of completely impacted lower 3rd molar extraction. Total of seventy four sides of thirty seven patients who had bilateral impacted lower 3rd molars were enrolled in this split mouth trial where a side was filled with CGF and the other without. Test sides had fewer values than control sides regarding facial edema and swelling. Application of CGF in this study has reduced postoperative swelling which contradicts our results (35).

In our study, mean peri implant bone loss evaluated through study and control group found no statistical variations among 2 groups after four months showing that CGF has no effect on decreasing peri implant bone loss around the implant.

Karthik et al. (36) in research measuring effect on CGF on crestal bone level in dental implants stated that there was no variation in crestal bone level between study &control groups which coincides with our results.

Regarding peri implant bone density evaluation in research, there was a statistical variation among two groups with higher bone density in study group after four months of implant insertion proving that CGF has a positive effect on increasing bone density and osseointegration around the implants.

Other studies suggest the same results. Karthik et al. (36) in research measuring effect on CGF on crestal bone level in dental implants reported that CGF is good in regeneration of bone around implants when compared with non CGF group. Also CGF found development in bone formation and marked rise in density values around implants in the study group was noticed showing variation among both groups starting from as early as first month.

## CONCLUSIONS

Concentrated growth factor accelerated implant osseointegration procedure & impacted implant stability values positively especially at 1st week & 4th week. Additional researches should be done according to impact of CGF on implant stability & osseointegration with longer follow up period & larger sample size.

CONFLICT OF INTEREST

Authors affirm that they have no conflicts of interest.

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