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CLINICAL AND RADIOGRAPHIC ASSESSMENT OF IMMEDIATELY PLACED DENTAL IMPLANTS WITH ENAMEL MATRIX DERIVATIVE (EMDOGAIN): A SPLIT MOUTH RANDOMIZED CONTROLLED CLINICAL TRIAL

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ABSTRACT

INTRODUCTION: The osseointegration of immediately placed implants remain challenging prerequisites to successful implant integration. Enamel matrix protein derivative (EMD) is composed of growth factors extracted from piglet teeth, which has shown to have regenerative capacity. Several studies have suggested that EMD improves the regeneration of bone. However, its effect around immediately placed implants has not been fully investigated.
AIM: determine the effect of EMD on osseointegration and healing potential.
Methods: Twelve patients with hopeless bilateral maxillary anterior teeth who need dental implant rehabilitation were recruited, without the need for bone augmentation. After atraumatic tooth extraction, immediate implants were installed; one side received an implant with an 0.15 mm EMD injected into the osteotomy site, while the contralateral side received an implant without EMD. Stability of implants at immediately postoperative, 2 and 6 months were measured, radiographic changes at the bone implant contact were assessed; by taking cone beam computed tomography image at postoperative and at 6 months, besides assessing wound healing at 4 and 15 days using the wound evaluation scale.
RESULTS: The application of EMD into the implant bed showed comparable results to immediately placed implants without EMD, in terms of secondary stability, and bone changes. There was a significant difference between the two groups regarding wound healing at 4 days favoring the application of EMD, however, the difference was insignificant at 15 days.
CONCLUSION: EMD is equally beneficial in enhancing implant stability, marginal bone level, and bone density, and has shown an enhanced potential to wound healing.
KEYWORDS: Emdogain, osseointegration, implant stability, immediate placement.
RUNNING TITLE: Effect of Emdogain on immediately placed dental implants.

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INTRODUCTION

Immediate implant placement (IIP) or placing implants into fresh sockets has been a favored treatment modality by dental practitioners and patients (1). Several studies reported vertical and horizontal alveolar ridge reduction arising after tooth extraction, and the changes were more noticeable on the coronal aspect of the ridge, they were principally attributed to bone resorption, affecting both biologic and aesthetic properties of the site (2), this has increased the demand for placing augmentative / regenerative materials for buccal hard and soft tissue preservation. (3)

Emdogain (enamel matrix protein derivative- EMD) is a tooth bud derivative extracted from porcine teeth buds, it is composed of amelogenin, a functional protein that has shown to have a regenerative potential by the activation of fibroblasts and osteoblasts, resulting in the formation of new collagen fibers, periodontal ligament, and alveolar bone (4). Several studies have concluded that Emdogain is successful in the treatment of intrabony defects (5), recession (6), implant mucositis (7), and wound complications (8). However, the effect of Emdogain on bone surrounding dental implants is not fully understood (9), the product was found to be effective in the treatment of peri-implantitis and promotive to bone formation in maxillary anterior

ridge preservation when conjugated with deproteinized bovine bone mineral (7).

It is noted that the effect of the material on implant biological stability, and the functional integration of immediately placed has not been investigated (9). In addition, there seem to be conflicting results between the invitro studies compared to human clinical trials in terms of determining the regenerative capacity of EMD on bone, this is possibly attributed to the different protocols and concentrations of using Emdogain and the difficulty in determining the solitary effect of the material without the adjunct effect of a bone graft substitute (9).

Therefore, the purpose of this present split-mouth clinical study was to determine whether Emdogain is a regenerative therapeutic alternative, by measuring the secondary stability of the immediately placed dental implants, assessing the peri-implant bone and the healing capacity.

The null hypotheses tested will be that after placing the product, there will be no significant difference in the secondary stability between the test and control groups, and there will be no significant difference in the bone-implant interface or the implant clinical success.

MATERIALS AND METHODS

MATERIALS

Materials included:

- Enamel matrix derivative- Emdogain [1]
- Osstell device (Resonance Frequency Analysis – RFA). [2]
- Implant fixture (Vitronex- V-line). [3]
- Cone beam computed tomography (CBCT) scans [4]
- 3 D fabricated surgical guide
- Surgical curettes [5]

1. Institut Straumann, Basel, Switzerland.
2. Integration Diagnostics Ltd. Company (Sävedalen, Sweden)
3. Vitronex Milano, Italy.
4. Vatech, Green X, Korea.
5. Surgical curette lucas #CL85 #4, GDC Fine Crafted Dental Pvt. Ltd, Pakista

- Articaine 4% 1:100,000 epinephrine. [6]

METHODS

An ethical approval by the Ethical committee of Alexandria University was acquired from the faculty of dentistry. All patients were granted full knowledge of the procedure's risks and benefits, and each provided an informed consent.

Study design: This was a split mouth randomized clinical trial that was set up according to the CONSORT guidelines, it included 2 groups in each patient.

Settings and location: Twelve participants were selected from the oral and maxillofacial surgery department's outpatient clinic at Alexandria University's faculty of dentistry, Egypt. Patients in need for immediate bilateral implant placement replacing hopeless maxillary anterior teeth were recruited.

The inclusion criteria of patients included the presence of hopeless bilateral teeth in the maxillary inter canine aesthetic region in need of tooth rehabilitation, with a fully intact facial bone wall at the extraction site, likewise, systemically healthy, with adequate quantity of bone; mesiodistal space for implant placement (≥6.5 mm (10), after assessing with a cone beam computed tomography (CBCT) (11). Participants completed periodontal treatment so full mouth plaque and bleeding scores were ≤ 25% at the study baseline. The exclusion criteria included systemic conditions that would prevent successful healing or implant osseointegration, patients who received no head and neck radiation for cancer treatment, non smoker, and teeth devoid of any periapical pathologies, or suppuration, previously guided bone regeneration (GBR) or dental implant placement in the anterior region of the maxilla, cysts or neoplasms at the anterior part of the maxilla, or severe bruxism (12).

6. Artinibsa 40 mg/0.1 mg/mL—epinephrine 1:100.000, Spain.

Pre-Surgical

Motivational interviewing and full mouth scaling were performed. Thorough medical and dental histories were taken, in addition to clinical and radiographic examination. A preoperative CBCT and intraoral scan were both obtained to aid in the fabrication of a 3D constructed tooth supported surgical guide.

Surgical

All participants were pre-medicated with 2 g of amoxicillin-clavulanic acid (or an alternative for patients allergic to Penicillin) (Augmentin – GlaxoSmithKline, by Medical Union Pharmaceuticals (MUP)) and 50 mg of diclofenac (or 500 mg of paracetamol), one hour prior to surgery. Upon starting the procedure, A 0.2% chlorhexidine mouthwash utilized for 60 s, followed by checking the seating of the 3D fabricated surgical guide. The patient received the local anesthesia in preparation for implants installation. Administration of local anesthesia (4% articaine with 1:100,000 epinephrine) (Alexadricaine anesthetic solution, Egypt) was performed followed by loosening of teeth using periotomes that severe the periodontal tissue to gently loosen and remove teeth (atraumatic extraction), and socket debridement. The surgical guide is then seated and successive drilling in the tooth socket was performed to engage in a correct three-dimensional position buccally, palatally, and apically to achieve high primary stability for both groups. Group A received a prefilled single use sterile packed 0.15 syringe of EMD gel injected into the osteotomy bed, followed by placing the fixture, while Group B received a fixture without EMD. All implants were seated with the aid of a manual ratchet and the primary implant stability quotient was measured using the Osstell device for

both groups. ISQ values between 55–80 are optimal for implant success, with ISQ values higher than 54 considered acceptable for early loading. (13) The appropriate size healing abutments were then placed. All patients received post-operative instructions; with recommendations to maintain the appropriate soft tooth brushing, and oral hygiene measures, and to continue the medication regimen for five days.

Post-surgical phase

Follow up phase

An immediate postoperative CBCT image was done to insure the implant position.

At the first 2 weeks:

The wound evaluation scale (WES) was measured on days 4, and 15, to assess wound healing by giving a score to 6 variables; visually (clinically) assessing the presence or absence of the step-off borders, contour irregularities, scar width, overall cosmetic appearance, edge inversion, and inflammation or discharge. The score is then derived with the presence or absence of the mentioned signs. If absent; a score of 1 corresponds to absent signs while zero corresponds to present signs; by adding the score of all variables; a score of 6 is optimal, and less than 5 is suboptimal. (14)

A prefabricated acrylic crown was seated provided that the primary stability was found optimum. The provisional restoration was free of any contact in both centric and eccentric positions. Patients were advised to avoid placing any pressure on the crown during the healing period. (15)

At 2 months: Secondary stability was measured, followed by loading and receiving the final prosthesis.

At 6 months: Stability of dental implant was measured the radiographic evaluation was undertaken to assess bone changes at the bone-implant interface by dividing the implant into 3 imaginary lines tangent to a line running down the long axis of the implant, the following was measured:

- Marginal bone level: The distance from the most coronal margin of the implant collar to the most coronal point of the bone implant.
- Length of the bone covering the implant on both buccal and palatal surfaces; measured from the alveolar crest to the apex of the implant in the sagittal section.
- The bone density was measured in Hounsfield units (HI) at 3 referenced points at the buccal, palatal, and marginal bone.

RESULTS

Twelve patients were enrolled in this study, their age ranged from 26 to 55 years, the mean age 40.7 ± 10.02 years, 66.7% were patients aged over 40 years, while 33.3 % were under 40 years. All implants were successfully osseointegrated.

As for the implant stability quotient, there was an intergroup significant difference between the primary stability and the data extracted at 2 and 6 months; the mean difference between the primary stability of the control and test group were 55.3 =3.2, and 53.8=3.1, respectively. At 2 months, the secondary stability values increased to 63.4+3.8 for the control group and 62.8=4.7 for the test group.

At 6 months, the mean difference for the control group was 65.6 ± 4.3, while the study group was 64.5 ± 5.0, resulting a statistically negligible t-test ($p \leq 0.05$) when both groups were compared. (Table 1)

Regarding marginal bone level, the mean difference for the control group taken at postoperative was 0.96+ 0.26 and 0.16+0.31 for the test group. At 6 month there was an intergroup significant difference; the values of the control group were 0.33±0.21, while the test group mean was 0.26±0.32, with an overall non-significant P value of 0.197. (Table 2)

Similarly, the results of bone density measured in (Hounsfield units) showed a mean difference of 853.2+368.1 for the control group and 747.3+248.4 for the test group at the postoperative phase, while at 6 months the results showed a significant difference for the same groups with mean value for the control group 1002.7 ± 233.3, and 958.4 ± 313.1 for the test group; resulting no significant difference in terms of bone gain when both groups were compared. (Table 2)

With respect to wound healing scale (WES), the mean difference of the control group was 4.2 ± 1.0 and the test group was 5.8± 0.5 resulting in a significant difference at day 4, P value was 0.001, however, the values of both groups were comparable at day 15 giving no statistically values between the groups as the mean difference of the control group was 5.8 ± 0.5, and the test group was 5.9 ±0.3. (Table 3)

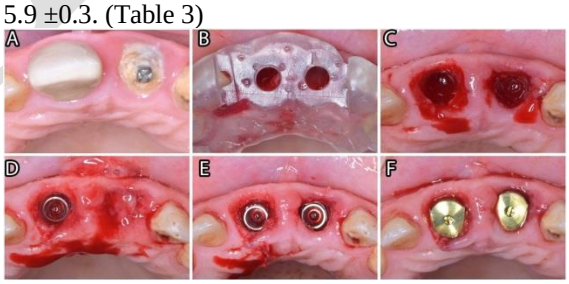

Figure (1) A: Preoperative image for tooth "8" and "9" in need for prosthetic solution **B:** Tooth supported surgical guide placement to guide the implant direction.

C: extraction sockets of teeth "8" and "9" after atraumatic extraction. **D:** Placement of Emdogain at the socket of tooth "9". **E:** Immediate Implant placement in sockets. **F:** placement of healing abutments over implants.

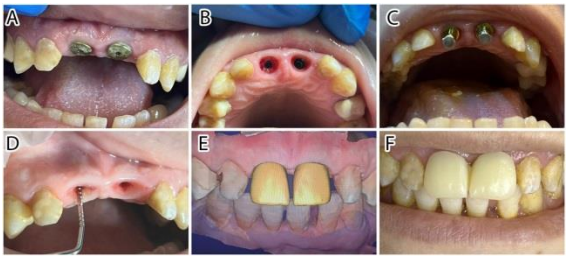

Figure (2): A: Immediately postoperative image showing healing abutments for tooth "8" (control group) and "9" (test group). **B:** Image showing peri-implant tissue for both groups after the removal of healing abutments one week after surgery **C:** Image showing stock abutments fixed on implants. **D:** Periodontal probe measuring distance from implant collar to the mucosa DIM. **E:** Image showing crown prosthetic designing for loading the implants. **F:** Image showing crown fixation over abutments.

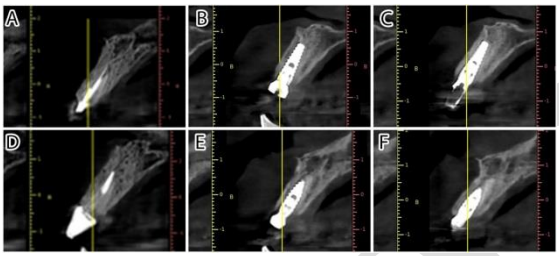

Figure (3): A: Preoperative sagittal CBCT scan image of tooth "9". **B:** Immediately postoperative image showing implant placement (test group). **C:** Six months follow-up image of implant replacing #9 of EMD group. **D:** Preoperative sagittal CBCT scan image of tooth "8". **E:** Immediately postoperative image showing implant placement (control group). **F:** Six months follow-up image of implant replacing #9 of control group.

Table (1): Comparison between the two studied group according to Implant stability.

Implant Stability Quotient (ISQ)	Control group	Test group	Mean Percent difference	T test P value
Post operative			-2.7	1.07 0.128 N.S.
Range	50-60	50-61		
Mean	55.3	53.8		
SD	3.2	3.1		
2 months			-0.9	0.985 0.353 N.S.
Range	59-73	58-74		
Mean	63.4	62.8		
SD	3.8	4.7		
6 months			-2.0	0.259 N.S.
Range	61-77	60-77		
Mean	65.6	64.3		
SD	4.3	5.0		
ANOVA P value	25.21 0.003*	29.7 0.004*		

T= student t-test
P was significant if ≤ 0.05
N.S. = Not significant
* Significant difference

The mean percent difference was calculated as a percent of change of test group in relation to control group.
ANOVA – One way analysis of variance; to compare between the interval times in the same group.

Table (2): Comparison between the two studied groups according bone changes, including (marginal bone level and bone density).

Marginal bone level	Control group	Test group	Mean Percent difference	T test P value
Post operative			33.3	1.98 0.056 N.S.
Range	0.7-1.31	0.64-1.5		
Mean	0.96	1.16		
SD	0.26	0.31		
6 months			-33.3	1.331 0.197 N.S.
Range	0.1-0.64	0-0.78		
Mean	0.33	0.26		
SD	0.21	0.32		
T-test (2) P value	4.64 0.001*	7.1 0.001*		
Bone density (measured in HU)	**Control group**	**Test group**	**Mean Percent difference**	**T test P value**
Post operative			-12.4	1.55 0.212 N.S.
Range	414-1596	410-1199		
Mean	853.2	747.3		
SD	368.1	248.4		
6 months			-4.41	1.38 0.251 N.S.
Range	538-1350	388-1410		
Mean	1002.7	958.4		
SD	233.3	313.1		
T-test (2) P value	3.11 0.009*	3.81 0.006*		

T= student t-test
P was significant if ≤ 0.05
N.S. = Not significant
* Significant difference
t-test-2 comparison between post operative and 6 months in the same group.

Table (3): Comparison between the two studied groups according to wound evaluation scale (WES)

WES	Control	Test	Mean Percent difference	T test P value
4 days			38.1	3.85 0.001*
Range	3-6	5-6		
Mean	4.2	5.8		
SD	1.0	0.5		
15 days			1.7	0.68 0.184
Range	5-6	5-6		
Mean	5.8	5.9		
SD	0.5	0.3		

T= student t-test
P was significant if ≤ 0.05
N.S. = Not significant
* Significant difference
t-test-2 comparison between post operative and 6 months in the same group.

DISCUSSION

Placing immediate implants has become one of the prosthetic rehabilitation approaches to overcome tooth loss. The technique has high survival and

success rates reaching 95.7%, which is comparable to delayed implant placement (16) and has proved satisfactory results in hard and soft-tissue preservation, it has also shortened chair time, and omitted the need for a second stage implant surgery. (17) Furthermore, it offers predictable outcomes especially in the anterior maxillary aesthetic zone. (18)

It is recommended that meticulous atraumatic extraction of the hopeless teeth helps avoid gingival recession and marginal bone loss leading to favourable esthetics, and postoperative comfort to the patient, as recommended by Lee et al, (19) especially when immediate implant placement is adopted.

The immediate flapless placement of implants in fresh sockets of the esthetic zone is a technique recommended by Buser (20), who highlighted the importance of placing implants in a non-pathologic extraction sockets, and in intact walls of bone, using a flapless technique to overcome crestal bone loss at the facial bone. The flapless technique is found to preserve gingival papillae and reduce postoperative pain. (21) This comes more with a more predictable outcome when a 3D surgical guide is fabricated, as it offers high accuracy when compared to implants inserted by free-hand. (22)

Prescribing a prophylactic antibiotics regimen has always been a dilemma to practitioners, however, they were found valuable to overcome implant failures as reported by Romandini et al in a systematic review and metanalysis. (23)

The use of regenerative hydrogels has been gaining popularity as they are considered alternative therapeutic substances that enhance cell proliferation and the formation of mesenchymal cells, both that act as precursors for the formation of new essentials cells in the peridontium. (24) Emdogain is one of the prefilled regenerative preparations extracted from piglet teeth; used in most periodontal surgeries, and osseous defects, as concluded by the meta-analysis conducted by Esposito and his colleagues. (25) Its regenerative capacity has not been fully understood, however, it has shown promising results in wound care and intraosseous defects as well as periimplantitis as reported by Kashefimehr et al when EMD was used in the non-surgical treatment of periimplantitis. (6)

dental implant placement: Which is the best protocol? A systematic review and network meta-analysis.
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In our study, we have explored the effect of EMD on the stability of dental implant and the bony changes that occur around the implant fixture, as well as the capacity of wound healing.

Implant stability is known to be a vital element for the implant survival even though the clinical outcomes of the implant are influenced by factors such as the implant's body, the surgeon's skill, and the oral environment. (26)

The RFA device (Osstell device) is one of the widely used devices for implant stability measurement. There is evidence that there is a strong correlation between RFA measurement and implant success as reported by clinical studies. (27, 28)

In this current study we have inserted two immediately placed bilateral implants after gently removing hopeless anterior teeth in the maxilla, one side received EMD around the implant fixture, and the contralateral side received an implant without EMD. Primary and secondary stability were both measured, our values showed that EMD group had similar ISQ values to those of control after two months; the mean values have increased overtime for both groups which could have been attributed to the gradual bone remodeling. This comes in agreement with Alkam et al and his colleagues, who confirmed EMD didn't affect the readings of ISQ values. (29)

It was noted that the stability quotients measured in one of the cases that rendered buccal bone resorption did not show any different values when compared to the other cases that showed no resorption, it is likable to say that the RFA test was not determinative enough to correlate to the bone tissue and implant fixture contact in this particular case; this comes with accordance to Zanetti et al. and Rittel et al. results (30,31) which concluded that the RFA test is not highly sensitive, nor does it reflect an actual predictive assessment.

The marginal bone height around implant fixture is an indicative measure for implant maintenance and a criterion to evaluate success. This is measured by cone beam computed topography (32), which best displays the quality and quantity of peri-implant bone that is essential for the process of osseointegration.(33) In our study we have measured bone density, marginal bone height to establish whether EMD has an effect on the quality and quantity of bone.

Our results showed no significant difference upon comparing the control group to the test group with respect to marginal bone levels; this is consistent with a study conducted by Isehed et al that studied the radiographic changes around implants for 3- 5-years follow-up; (34) which concluded that the sole

application of EMD did not cause positive changes at bone level. Moreover, Froum et al and Matarasso and colleagues, suggested that the combination of Emdogain with other grafting materials enhanced bone level, when compared to the sole application of EMD. (35,36) Similar results were observed with respect to bone density around dental implants, both groups showed comparable results in our study, this complies with Parodi et al's work that also concluded that there was no difference in bone density after a 36 months study following up on the sole application of Emdogain. (37) While Fakheran et al used EMD as an adjunct to alveolar preservation, and found insignificant difference with respect to new bone formation and type of tissue. (38)

Concerning wound healing; our results showed significant difference during the first week between the two groups favoring the application of EMD, this comes in agreement with a peer review that affirmed that Emdogain causes an increase in the vascularization, and angiogenesis, resulting in a fast healing process, (39) however, at the end of the test period there was an insignificant difference between the two groups, possibly attributed to the immune response, presence of saliva, increased anti-inflammatory cytokine release, cleavage of chemokines, that resulted in normal wound healing in the oral mucosa (40)

CONCLUSION

According to our study, it was concluded that EMD is equally beneficial in enhancing implant stability, periimplant bone formation and osseointegration, and provides a rapid healing to the peri-implant tissue.

CONFLICT OF INTEREST

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