THE EFFECT OF HYALURONIC ACID ON IMPLANT STABILITY AFTER IMMEDIATE IMPLANT PLACEMENT IN ANTERIOR AND PREMOLAR REGION IN SYSTEMICALLY HEALTHY PATIENTS

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ABSTRACT

Aim of the study: To evaluate the efficacy of topical application of hyaluronic acid on implant stability, soft tissue healing, and post-operative pain after immediate implant placement. Material and Methods: 24 patients indicated for immediate implants were randomly allocated into 2 equal groups. Intervention group (Immediate implant with topical application of HA) and control group (Immediate implant with topical application of placebo gel). Implant stability was evaluated at baseline and after 6 months, soft tissue healing was assessed after 10 days during suture removal and pain intensity was assessed at days 0, 2, and 7 after the surgery. Results: The mean secondary implant stability shows no significant difference between both groups (P=0.656). The median and range of the soft tissue healing scores show no statistically significant difference between both groups (P=0.424). Regarding post-operative pain, there was only a significant difference at day 2 (P=0.001). Conclusions: Topical application of hyaluronic acid around immediate implants does not seem to improve implant stability or soft tissue healing. However, it could have a short-term effect on post-operative pain reduction.

Keywords: Hyaluronic acid, Immediate implant, Implant stability, Soft tissue healing, Visual Analogue scale, Post-operative pain.

I. INTRODUCTION

In 1976 Schulte and Heimke (1) first described implant placement immediately after tooth extraction. In the systematic review by Lang et al., 2012 (2) the results showed that after a follow-up period of 2.08 years, the annual failure rate of immediate implants was 0.82% (95% CI: 0.48-1.39%), which means a 2-year survival rate of 98.4% (97.3-99%). Immediate implant placement is now considered an increasingly common strategy for the replacement of hopeless teeth; this approach aims to reduce the post-extraction alveolar bone resorption, the treatment time, and the number of visits (3). Consequently, improves the patient acceptance and the esthetic outcomes in terms of achieving natural gingival contouring and better papillae height (4). However, immediate implants may have some disadvantages that could affect the success rate, which includes unexpected post-extraction alveolar bone resorption, inadequate primary implant stability when compared with delayed implants, and inadequate soft tissue closure which leads to healing by secondary intention (3).

Implant stability plays the most important role in successful osseointegration, which is usually evaluated at two different intervals: Primary and secondary (5). Primary implant stability develops from the mechanical interlocking of the implant fixture with the alveolar bone (6). Secondary implant stability is established from regeneration and remodeling of the bone around the implant fixture (7).

Resonance frequency analysis (RFA) was initially introduced by Meredith, 1998 (8). RFA is based on vibration and structural analysis principles by utilizing a small transducer that is screwed to the implant. This transducer is composed of two ceramic components, one of them generates vibration by a sinusoidal signal ranges from 5 to 15...
kHz, while the other acts as a receptor. The vibrated transducer shakes the implant with a constant amplitude, initiating with low frequency, then increasing till the implant resonates (9). The RFA values are usually expressed as implant stability quotient (ISQ) which is an objective worldwide standard measuring unit for implant stability. ISQ values range from 0 to 100, as the ISQ value increases, implant stability increases (10).

Hyaluronic acid is a glycosaminoglycan, which is mainly found in the extracellular matrix, but also can be present in the pericellular matrix and intracellular (11). HA may be found in many tissues such as the skin, synovial joints, and periodontal tissues (12). HA is a biocompatible molecule that can promote wound healing (13), induce osteogenic differentiation (14) also shows anti-inflammatory (15), anti-edematous (16), and bacteriostatic (17) effects.

In a review article by Carolina & Hernandez, 2019 (18) it was concluded that hyaluronic acid may have a favorable effect on bone and soft tissue healing around dental implants. However, there is a need for further studies to be done to support this conclusion.

II. MATERIAL AND METHODS:

Trial design:
This study is a double-blinded, randomized clinical trial. Which was approved by the Ethics Committee of Scientific Research - faculty of Dentistry, Cairo University (approval number 18-9-60) (approval date 26/9/2018) and complies with the declaration of Helsinki. The study protocol was registered in ClinicalTrials.gov Identifier: NCT03691467

Participants:
This study was carried out on 24 patients (every patient was treated as a separate examination unit) with non-restorable tooth in the anterior or premolar regions attending outpatient clinics in the Department of Periodontology - Faculty of Dentistry, Cairo University-Egypt. After discussing the treatment plan with the patient and informing the patient of all the data needed and complications that could be met, informed consent was signed by the willing participants.

Eligibility criteria
Inclusion criteria include: Age ranges from 18 to 60, systemically healthy patients indicated for immediate implant in the anterior and premolar region, absence of any periapical pathosis, patients with intact buccal plate of bone, patients with adequate bone volume for the dental implant procedure, and informed consent approval and signing.

Exclusion criteria include: Smokers, systemic disease that may affect the outcome of the surgical procedure, no or poor patient’s compliance, patients with psychological problems, pathology at the site of intervention, pregnant patients, and patients who refuse to sign an informed consent.

Eligible individuals were divided into two equal groups:
Intervention group: 12 patients received an immediate implant with topical application of hyaluronic acid.

Control group: 12 patients received an immediate implant with topical application of placebo gel.

Procedures:
All eligible patients undergo phase I therapy with oral hygiene instructions including tooth brushing twice daily using modified bass technique and chlorhexidine 0.12% mouthwash twice daily). Eligible patients take pre-operative photographs (Fig.1A) and intraoral periapical radiographs at the time of the initial examination.

CBCT scan using OnDemand 3D was performed to record preoperative bone height and width measurements to determine the size of the implant.

All procedures were performed under local anesthesia (4% articaine with 1/200 000 adrenaline solution). 1 gm. Amoxicillin + Clavulanic acid (Augmentin 1gm) will be given orally 1 hour before the procedure.
Atraumatic extraction was performed using periotome to maintain the integrity of the buccal plate of bone (Fig.1B).

T4 nucleoss implant was inserted by flapless surgery. Gengigel (0.8% Hyaluronic acid)/placebo gel was inserted in the jumping gap between implant fixture and socket walls using a plastic syringe (Fig.1C). Primary implant stability was measured at the time of implant placement. Interrupted sutures were done to close the socket (Fig.1D). Patients take the visual analogue scale to assess the pain intensity.

Post-operative care
After 10 days, sutures were removed, soft tissue healing was assessed using Likert scale (Fig.1E), and visual analogue scales (VAS) were collected.

Second stage
After 6 months, periapical radiograph was performed, an implant exposure procedure was performed under local anesthesia, implant stability was measured, and the healing collar was screwed.

Prosthetic phase
Healing collars were replaced by permanent abutments, impressions were taken and porcelain fused to metal fixed prosthesis were fabricated (Fig.1F).

Figure 1 (A-F).

Figure (1A) non-restorable upper left 2nd premolar and missing upper left 1st premolar. Figure (1B) atraumatic extraction socket. Figure (1C) immediate implant placement with topical application of HA gels in the jumping gap. Figure (1D) flapless immediate implant replacing upper left 2nd premolar and flapless implant placement for upper left 1st premolar. Figure (1E) soft tissue healing after 10 days. Figure (1F) crowns cementation.

Outcomes:
Primary outcome (implant stability):
It was measured using resonance frequency analysis (RFA) [measuring unit implant stability quotient (ISQ)]:

1. Immediately after implant placement.
2. After 6 months during the prosthetic phase.

Secondary outcomes:
A. Soft tissue healing:
Assessments were done at suture removal 10 days after implant placement by the investigator (I.S.K.) who performed the surgical procedure using Likert scale by Galli et al., 2008 (19).

Assessment of soft tissue healing was done according to the following scoring system:

0: Complete wound closure without the presence of fibrin.

1: Complete wound closure with a thin line of fibrin present.

2: Complete wound closure with the presence of fibrin.

3: Incomplete wound closure (dehiscence).

4: Incomplete wound closure (necrosis).

B. Post-operative pain:

Pain intensity was assessed using a 10-point visual analogue scale (VAS), with the patient placing a mark on the scale to indicate an intensity range from no pain ‘0’ to severe/unbearable pain ‘10’ The severity of the pain was evaluated on the operation day 0 and postoperative days 2 and 7.

III. RANDOMIZATION:

Allocation - sequence generation:

The allocation sequence was generated using computer-generated random numbers. A list was created on (https://www.random.org/); the patients were randomly classified into two groups. The first group was the intervention group (A) and the second group was the control group (B).

Allocation concealment mechanism:

According to the allocation sequence obtained from the computer software, the numbers that were generated randomly from the software were written in small folded opaque papers then insert into an opaque envelope.

Implementation

The main investigator (I.S.K.) referred all participants' numbers to the supervisor (M.S.D.) who generated the random sequence and assigned the patients for intervention or control group.

Blinding:

Double-blinded "both operator and participants were blinded".

Statistical methods

Data management and statistical analysis were performed using the Statistical Package for Social Sciences (SPSS) version 24. Numerical data were summarized using means, standard deviations, median and range. Data were explored for normality using Kolmogrov-Smirnov test and Shapiro-Wilk test. Comparisons between the 2 groups were done using the independent t-test. Pain scores and healing scores were compared by Mann Whitney test. For categorical variables, differences were analyzed with Fisher’s exact test. All p-values are two-sided. P-values ≤0.05 were considered statistically significant.

Results

The mean primary implant stability in group A was 53.1±2.8 and 52.8±3.0 in group B. This was statistically not significant; P=0.836.

The mean secondary implant stability in group A was 72.3±4.8 compared to 71.5±4.3 in group B. This was statistically not significant; P=0.656.
Table (1) Mean, SD, and independent t-test of implant stability in the studied groups.

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th></th>
<th>Group B</th>
<th></th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
<td></td>
</tr>
<tr>
<td>Primary</td>
<td>53.1</td>
<td>2.8</td>
<td>52.8</td>
<td>3.0</td>
<td>0.836</td>
</tr>
<tr>
<td>Secondary</td>
<td>72.3</td>
<td>4.8</td>
<td>71.5</td>
<td>4.3</td>
<td>0.656</td>
</tr>
</tbody>
</table>

SD: standard deviations, P≤0.05 is considered statistically significant.

The median and range of the soft tissue healing scores was 2 [2-3] for Group A and 3 [2-3] for Group B with no statistically significant difference between both groups (P = 0.424).

Table (2) Median and range of soft tissue healing scores at day 10 in the tested groups.

<table>
<thead>
<tr>
<th>Soft tissue healing at Day(10)</th>
<th>Group A</th>
<th></th>
<th>Group B</th>
<th></th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median</td>
<td>Min.</td>
<td>Max.</td>
<td>Median</td>
<td>Min.</td>
</tr>
<tr>
<td>Soft tissue healing at Day(10)</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>3</td>
<td>2</td>
</tr>
</tbody>
</table>

P≤ 0.05 is statically significant; min: minimum, max: maximum, analysis done by Mann Whitney test.

Comparison of median VAS scores in the studied groups at 0, 2, and 7 days:

Day 0: The median and range of the VAS scores was 8 [7-8] for both groups with no statistically significant difference between them (P= 1).

Day 2: The median and range of the VAS scores was 4 [3-6] for Group A and 6 [5-6] for Group B with statistically significant difference between both groups (P=0.001); being higher in control group.

Day 7: The median and range of the VAS scores was 3 [1-4] for Group A and 3 [2-4] for Group B with no statistically significant difference between both groups (P= 0.794).

Comparing median pain score over time in each single group was statistically significant (P<0.001)

Table (3) Median and range of VAS scores at different time points in the tested groups by Mann Whitney test and overtime in each group by Friedman Test.

<table>
<thead>
<tr>
<th>Post-operative pain</th>
<th>Group A</th>
<th></th>
<th>Group B</th>
<th></th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median</td>
<td>Min.</td>
<td>Max.</td>
<td>Median</td>
<td>Min.</td>
</tr>
<tr>
<td>Day(0)</td>
<td>8</td>
<td>7</td>
<td>8</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>Day(2)</td>
<td>4</td>
<td>3</td>
<td>6</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Day (7)</td>
<td>3</td>
<td>1</td>
<td>4</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>P-value 2</td>
<td>&lt;0.001</td>
<td></td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

P≤0.05 is statically significant; P1: for comparison between 2 groups. P2: for comparison over time in each group separately.
IV. DISCUSSION

To the best of our knowledge, this is the first clinical trial evaluating the effect of hyaluronic acid on immediate implant stability, soft tissue healing, and postoperative pain.

All implants were placed utilizing minimally invasive flapless surgery, the rationale of this technique is to avoid disturbance of the periosteum by flap elevation, thus preserving the blood supply to the bone and reducing bone resorption (20). D.Buser et al., 2017 (21) stated that flapless surgery is associated with a fewer mucosal recession, less surgical trauma and less time consuming, increase patient comfort, have fewer complications, faster soft tissue healing and resulting in more esthetically accepted outcomes.

The mean secondary implant stability showed no significant difference between the intervention and control groups. The results of this study coincide with the result of an animal split-mouth study by Yazan et al., 2018 (22) who reported that topical application of HA has no additional benefit on implant osseointegration. On the other side, Lee et al., 2014 (23), Shamma et al., 2017 (24), and Lorenz et al., 2018 (25) reported improvement in implant osseointegration and new bone formation with topical application of HA. However, in the former studies, HA gel was used as a carrier for different bone grafts and growth factors to allow for sustained release over an extended period.

Regarding soft tissue healing, the results revealed that there was no significant difference between the two groups. The results also showed that no patient in both groups showed complete soft tissue healing with or without fibrin line formation (grade 0 or 1) after 10 days follow up. This could be attributed to the fact the healing after immediate implant is done via secondary intention, even if the soft tissue was approximated by interrupted sutures.

The results of the present study coincide with the results of a pilot multicenter randomized clinical trial by Galli et al., 2008 (19) who studied the effect of topical application of 0.8% HA on soft tissue healing after any incision in the oral cavity and reported no significant difference in soft tissue healing between HA and placebo gel.

On the other hand, Romeo et al., 2013 (26), Yıldırım et al., 2018 (27), and Marin et al., 2020 (28) reported significant improvement in soft tissue healing after topical application of HA gel. However, these studies were not assessing soft tissue healing around dental implants and were using different soft tissue healing indices.

Regarding post-operative pain assessment, the results indicate that hyaluronic acid has a short-term effect on post-operative pain after 2 days. The results of this study coincide with the results of the study by Yıldırım et al., 2018 (27) who reported a significant reduction of post-operative pain at 3 and 7 days after the use of different concentrations of HA (0.2 and 0.8%) when compared with a periodontal dressing after harvesting free gingival graft.

In contrast, the studies by Koray et al., 2014 (29), Gocmen et al., 2015 (30), and Marin et al., 2020 (28) found that the topical application of HA had no significant effect on post-operative pain after tooth extraction. Also, Romeo et al., 2013 (26) showed that a gel containing amino acids and 1.33% HA used after laser-induced wounds does not appear to affect pain perception.

Generally, the delivering method of HA might play an important role. Different delivering methods of HA can lead to different physiochemical properties and HA-cell interaction time, consequently different biological effects on cell proliferation and osteogenic differentiation. However, until now there are no definitive recommendations or guidelines for the optimal molecular weight, concentration, and delivering methods of HA.

V. CONCLUSION

It was concluded that topical application of hyaluronic acid around immediate implants does not seem to improve implant stability or soft tissue healing. However, it could have a short-term effect on post-operative pain reduction when compared with immediate implants alone.

Further studies are required to identify the ideal delivering method, molecular weight, and concentration of HA and to evaluate the clinical efficacy of HA in the field of implantology.
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Declaration of interests
The authors declare no conflict of interest.

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