Assessment of implant stability in immediate post-extraction implants with and without the application of Hyaluronic acid and Melatonin mixture: A randomized clinical trial

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Abstract:

Background: Replacement of missing teeth using dental implants is a successful and reliable treatment option. A variety of substances have been used to enhance the peri-implant bone response, including hyaluronic acid and melatonin. Aim: Assessing the effect of adding a mixture of hyaluronic acid and melatonin to the implant surface in immediate implants; regarding implant stability and post-operative pain, in comparison to immediate implant placement without adding any materials.

Materials and methods: Twenty- four patients with teeth scheduled for extraction and implant replacement in the inter-bicuspid region were divided equally between a study group (Immediate implant with hyaluronic acid and melatonin mixture) and a control group (only immediate implant). Outcomes for implant stability were measured and recorded at baseline and after 6-months and post-operative pain for 10 days after implant placement.

Results: No significant difference was shown in the mean of implant stability between the test group and the control group. With regard to the post-operative pain scores, test group recorded
lower median NRS score in comparison to a greater median NRS score in control group. This difference was statistically significant.

Conclusions: Within the limitations of this study, immediate implant placements with topical application of melatonin and hyaluronic acid mixture would be a valuable option in comparison to immediate implants alone.

**Keywords:** Immediate implants, Hyaluronic acid, Melatonin, implant stability, post-operative pain.

**Introduction:**

For decades, dental implants have been considered a reliable and successful approach for oral rehabilitation. Installation of implants in extraction sockets was promoted to reduce the number of surgical procedures, time between tooth removal and placement of a fixed restoration and to preserve the dimensions of alveolar ridge (Buser et al. 2012). In 2001, Paolantonio et al. reported that the degree of bone to implant contact was high, between 62-71%, both in implants installed in fresh extraction sockets (test sites) and in implants placed in healed bony sites (control site). Implant stability is directly related to the percentage of the bone to implant contact area (BIC) (Scarano et al. 2006).

Different approaches have been introduced lately to positively enhance the healing around dental implants (Schulz et al. 2014). One of these approaches is coating the implant surface with organic components of the extracellular matrix. Recent studies have shown promising results using different organic surface modifications on dental implants such as glycosaminoglycans, collagen, hyaluronic acid (Juodzbalys and Wang 2007; Stadlinger et al. 2008; Schliephake et al. 2009) and melatonin (Gomez-Moreno et al. 2016).

Hyaluronic acid (HA) is a natural, non-sulfated glycosaminoglycans which plays a role in the inflammatory process and wound healing of mineralized and non-mineralized tissues of the periodontium including granulation tissue formation and tissue remodeling (Casale et al. 2016). In a study by (Schulz et al. 2014) found that coating of implant surface with low sulfated HA increased peri-implant bone formation around implants in maxillary bone compared to uncoated implants in early healing period.
Melatonin (N-acetyl-5-methoxy tryptamine) plays an anti-inflammatory, anti-oncotic, and immunomodulatory role by scavenging free-radicals and by interacting with cell membrane and intracellular proteins (Guardia et al. 2011). It has a positive effect on new bone formation around implants as it promotes osteoblast differentiation and bone formation (Cutando et al. 2006; Gomez-Moreno et al. 2007; Calvo-Guirado et al. 2010; Guardia et al. 2011; Munoz et al. 2012). Experimental evidence suggests that topical application of melatonin may be useful in oral surgery and implant dentistry, increasing BIC values and new bone formation, and so improving the success and long-term survival of the implants (Cutando et al., 2008).

There is a strong belief that if both melatonin and hyaluronic acid are having such a positive impact on improving the quality of osseointegration and decreasing inflammation of the tissues (Cutando et al. 2006; de Brito Bezerra et al. 2012; Muñoz et al. 2012; Casale et al. 2016), it is expected that both materials if combined together may have a synergistic effect. To the best of our knowledge, the effect of combining melatonin and HA in a complex active compound was insufficiently investigated. Therefore, our study aims at investigating the effect of adding HA and melatonin mixture to immediate implants’ stability and postoperative pain.

**Subjects and methods:**

**Study design:**

Single center, single-blinded, randomized two-arm controlled clinical trial with parallel group set up and 1:1 allocation ratio. The study protocol was approved by the Ethics Committee of Scientific Research, Faculty of Dentistry, Cairo University and registered in U.S. National Institutes of Health Clinical Trials Registry (ClinicalTrials.gov Identifier: NCT03692026). Informed consent was obtained from all participants included in the study after agreement of participation. The primary outcome of the current study is implant stability; the secondary outcome was assessment of post-operative pain.

**Sample size calculation:**
According to the previous paper by (Granic et al. 2015), the expected difference in stability between groups was 2±1.4 ISQ. Using power 80% and 5% significance level, 9 patients were required in each group. This number was to be increased to a sample size of 12 patients in each group to compensate for possible dropouts during study follow up. Sample size calculation was achieved using PS: Power and Sample Size Calculation Software\textsuperscript{1} Version 3.1.2

Patients’ selection:
Twenty-four participants with non-restorable teeth in the inter-bicuspid region were enrolled in this study (15 females and 9 males), of age range from 20-60 years. Patients were recruited from the outpatient clinic of Oral Medicine, Oral Diagnosis and Periodontology department, Faculty of Dentistry, Cairo University. The following inclusion criteria were applied: adequate bone width and height, and adequate inter-occlusal distance for implant placement, an intact socket buccal plate of bone (type I extraction socket) after tooth extraction, primary stability of the implant is achieved at the time of implant placement.

The patients were excluded on the basis of: uncontrolled diabetes mellitus or any systemic disease that might contraindicate implant placement, no or poor patient’s compliance, psychological problems, pregnant females, patients taking any medication that might affect bone metabolism, patients with any parafunctional habits and any pathological condition at site of intervention.

Allocation concealment and randomization:
Each experimental site was randomly assigned to either test (immediate implant with hyaluronic acid and melatonin mixture) or control (Immediate implant only) group using computer generated randomization list (www.randomizer.org)\textsuperscript{2} with 1:1 allocation ratio to ensure a balanced allocation of treatments. Allocation concealment was performed using opaque sealed envelopes opened just before the surgical procedures. The two groups were equally prepared for both surgical procedures. Then the decision to which group the site was assigned was taken

\textsuperscript{1} SSPS ®Software. Vanderbilt University, Nashville, Tennessee, USA.

\textsuperscript{2} Research Randomizer computer software (Version 4.0), from http://www.randomizer.org/.
according to the randomized numbers placed in the opaque sealed envelope. The number was picked by the supervisor after local anesthesia was administrated at the surgical site.

Treatment Protocol:
Each patient was interviewed to obtain a comprehensive medical and dental history through a questionnaire (Cornell Medical Index). Intraoral periapical radiographs\(^3\) were taken for proper diagnosis of the non-restorable tooth. All subjects passed through initial phase of therapy which consisted of supragingival scaling, subgingival debridement and oral hygiene instructions (teeth brushing twice daily using modified bass technique and chlorhexidine 0.12% mouth wash\(^4\) twice daily). After 4 weeks, all subjects were recalled for examination of their compliance to the given oral hygiene instructions. CBCT scan using OnDemand 3D\(^5\) was done to record preoperative bone height and width measurements used to determine implant ideal size and position.

Surgical procedures were performed under local anesthesia\(^6\) using a local infiltration technique for maxillary teeth and nerve block technique for mandibular teeth. Atraumatic extraction of the intended teeth was done using Periotome\(^7\) to preserve the alveolar bone integrity. Periotome was inserted between the tooth/root and surrounding bone in a wedging action, then a small straight elevator was used for root luxation, and a remaining root forceps was used to remove the tooth/root. Irrigation of the socket was done followed by curettage of the socket walls using a Lucas\(^8\) curette to remove any granulation tissue. Then a standardized periodontal probe\(^9\) was used to explore the alveolar bone integrity (Figure 1.c).

Sequential drilling was done for the preparation of implant \(^{10}\) osteotomy which extended at least at least 3-5 mm apical to the socket for proper immediate implant bone engagement and sufficient primary stability. The implant osteotomy was directed more in a palatal direction of the socket to allow for correct implant three dimensional position; which is placing the implant

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\(^3\) Kodak D speed films. Carestream ® USA
\(^4\) Hexitol mouthwash 100ml, ADCO, Alexandria, Egypt
\(^5\) OnDemand 3D. Cybermed Inc., Technoville, Gasan-dong, Geumcheon-gu, Seoul, South Korea
\(^6\) Ubistesin forte 3M ESPE AG, ESPE Platz, D-82229 Seefeld, Germany
\(^7\) Nordent,REPC N15, USA
\(^8\) Helmut Zepf Medizintechnik GmbH, Germany
\(^9\) CP-15UNC, Hu-Friedy Inc., Chicago, IL. USA
\(^10\) NucleOSs ™, ŞANLILAR Tibbi Cihazlar Medikal Kimya San. Tic. Ltd. Şti. Turkey
center along with the cingulum of the adjacent teeth in case of anterior teeth and with the central fossa in case of premolars.

For the test group, Melatonin and hyaluronic acid mixture were prepared by mixing gels of both Melatonin with Hyaluronic acid (1 c.c. of each) (Figures 1.d & 1.e), while for the control group, no materials were added around implants placed in extraction sockets. Melatonin gel was made by mixing pure melatonin powder added to the carrier propylene glycol (1.2/ml). While the Hyaluronic acid gel used was ‘Gengigel® Hyaluronic Acid’. The prepared mixture was locally applied around the implant, inside the socket and in the jumping gap using a sterile plastic syringe (Figure 1.f). Primary implant stability was measured immediately after implant placement using Osstell device with its corresponding SmartPegs which were directly attached to the implant with no tissue interposition and placement of the Osstell probe approximately 2mm from the SmartPeg (Figure 2.b). The ISQ value was recorded, then cover screw was tightened in place. Internal criss-cross suture with a 5-0 silk suture for approximation of the tissues (Figure 2.d). Immediate post-operative CBCT scans were performed to confirm proper implant position (Figure 2.e).

Post-operatively, patients were informed to avoid any hard brushing and rinse with antiseptic mouth rinse (0.12% Chlorhexidine oral rinse) twice daily for two weeks. Mechanical tooth cleaning was resumed after sutures were removed at the treated sites using a soft tooth brush and roll technique. They were also instructed to report any excessive pain, bleeding, or swelling to the main investigator.

Post-operative pain was assessed using Numerical rating scale for pain (NRS) (Scarano et al. 2011) for 10 days following the day of surgery. Values were recorded by patients in a specially designed form given to each patient after implant placement procedure and retrieved on the day of sutures removal (10 days after surgery).

Patients were recalled every month to check on the implantation site without any complications (dehiscence, inflammation, excessive pain), and to check for their compliance.

Six months postoperatively, implant exposure was then done, a full thickness flap was raised in order to visualize the implant head and secondary implant stability was measured again for all

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11 Pure melatonin, Bulk supplements
12 Gengigel Gel®, 20ml, Ricerfarma, Milano, IT
13 Osstell Integration Diagnostics AB, Gamlestadsvägen 3B - SE 415 02 Göteborg – Sweden
14 Assut sutures of Switzerland
patients in both groups using Osstell (Figure 3.b). A healing cap was then placed and 2 single interrupted 5/0 silk sutures were used for papilla stabilization around the healing cap (Figure 3.c). Two weeks later, healing caps were removed and rubber base impressions were taken, jaw relation registration (Wax Wafer technique) and proper shade selection were done for fabrication delivery of the final implant supported porcelain-fused-to metal (PFM) crowns. (Figure 3.d).

Figure 1: a) occlusal view showing non-restorable upper left lateral incisor, b) extraction socket following the remaining root removal and socket debridement, c) Checking the integrity of the buccal plate using a 15-UNC periodontal probe. d) preparation of HA and melatonin mixture, e) 2 cc of HA and melatonin mixture, f) HA and melatonin mixture applied to the implant surface before its insertion in the prepared osteotomy

15 Express, 3M ESPE, 3M Corporate Headquarters, Maplewood, Minnesota. USA
Figure 2: a) paralleling pin inserted in the prepared osteotomy, b) placement of 3.4/14 mm implant into the extraction socket in a palatal direction, c) Installation of SmartPeg and measurement of primary implant stability using OSSTELL device, d) Closure of the extraction socket with 5/0 silk suture (internal criss-cross suture), e) Immediate postoperative CBCT showing implant in correct position

Figure 3: a) Healed alveolar ridge 6 months following implant placement (occlusal view), b) Installation of SmartPeg and measurement of secondary implant stability with OSSTELL device, c) Placement of a healing collar and suturing of the flap using two single interrupted sutures, d) Cementation of the final porcelain-fused-to-metal (PFM) crown.

Outcome measurements:

Primary outcome, Implant stability quotient (ISQ) was measured using Osstell, immediately after implant placement and after 6 months during the prosthetic phase. Readings were recorded for each patient and comparison was done between values for test group and control group.

Secondary outcome, Postoperative pain was recorded for all patients using the Numerical Rating Scale (NRS) of pain (Scarano et al. 2006). Patients were instructed to record the level of pain they experience daily from the day following surgery for 10 days where 0 refers to no pain at all and 10 refers to worst pain. Values were recorded and comparison was done between values for test group and those for the control group.

Statistical analysis:

Data were analyzed using IBM SPSS advanced statistics (Statistical Package for Social Sciences), version 24. Values were presented as mean and standard deviation (SD) values, or median and range. Data were explored for normality using Kolmogorov-Smirnov test of

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16 SPSS Inc., Chicago, IL. USA

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normality. The results of Kolmogorov-Smirnov test indicated that NRS pain data were not normally distributed (non-parametric data), therefore Mann Whitney U test was used for comparison between both groups, while Friedman test and Wilcoxon signed Rank test were used for intra-group comparison. Values of age and implant stability were normally distributed and were compared using independent t test between groups and paired t test for intra-group comparison. Fisher exact test was used for comparison of gender distribution in the tested groups. The significance level was set at $p \leq 0.05$. Statistical analysis was performed with SPSS 18.0 for Windows.

Results:

Twenty-four patients, aged 20-60 years were included at first. No patients dropped out during the follow-up period. Thus, 12 patients in the test group, and 12 patients in the control group completed the study and their data were used for statistical analysis.

Demographic results:

The mean age of patients in test group was 39.58±12.35, while in control group it was 36.08±10.94. The difference between both groups was not statistically significant ($p=0.47$)

Test group consisted of 8 females and 4 males, while control group consisted of 7 females and 5 males, with no significant difference in gender distribution of groups ($p=0.99$).

Implant stability:

Within treatment groups, the mean primary implant stability for test group was 56.50±3.61, while in control group, it was 56.92±5.55. A statistically significant increase was recorded in secondary stability to reach 71.33±3.65 for test group and 70±5.06 for control group ($P =0.00$); as shown in (Table 1).

When comparing the two groups after 6 months from implant placement, the mean primary implant stability in test group was 56.50±3.61, compared to 56.92±5.55 in control group. The difference between both groups was not statistically significant ($p=0.83$); as shown in (Table 1).

17 Statistical Package for Scientific Studies, SPSS, Inc., Chicago, IL, USA
The mean secondary implant stability (after 6 months) in test group was 71.33±3.65, compared to 70±5.06 in control group. The difference between both groups was not statistically significant (p=0.468); as shown in (Table 1).

The mean difference between primary and secondary implant stability in test group was 14.83±2.98, compared to 13.08±4.74 in control group. The difference between both groups is not statistically significant (p=0.293); as shown in (Table 1).

The mean percent change from primary to secondary implant stability in test group was 26.48±6.17, compared to 23.56±9.99 in control group. The difference between both groups was not statistically significant (p=0.4); as shown in (Table 2).

Post-operative pain score (NRS):
Comparison within the same group overtime showed that in test group, NRS score showed a statistically significant decrease overtime (P=0.00). In control group, NRS score showed a statistically significant decrease overtime (p=0.00), as shown in (Table 3).

Comparison between groups showed that test group recorded lower median NRS score at days 1, 3, 5, 7 and 10 in comparison to a greater median NRS score in control group. This difference was statistically significant (p=0.010), as shown in (Table 4).

### Table 1: Mean, standard deviation (SD), inter and intragroup comparison of implant stability of the studied groups (t test)

<table>
<thead>
<tr>
<th>Stability</th>
<th>Group A</th>
<th>Group B</th>
<th>P-value (Between groups)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
</tr>
<tr>
<td>Primary</td>
<td>56.50</td>
<td>3.61</td>
<td>56.92</td>
</tr>
<tr>
<td>Secondary (After 6 months)</td>
<td>71.33</td>
<td>3.65</td>
<td>70.00</td>
</tr>
<tr>
<td>P-value (Within group)</td>
<td>0.00*</td>
<td></td>
<td>0.00*</td>
</tr>
</tbody>
</table>

Significance level P ≤ 0.05, *significant, ns: non-significant

### Table 2: Mean, standard deviation (SD) of difference and percent change of implant stability of the studied groups (t test)

<table>
<thead>
<tr>
<th>Stability</th>
<th>Group A</th>
<th>Group B</th>
<th>P value (between groups)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
</tr>
<tr>
<td>Difference</td>
<td>14.83</td>
<td>2.98</td>
<td>13.08</td>
</tr>
<tr>
<td>Percent change (%)</td>
<td>26.48</td>
<td>6.17</td>
<td>23.56</td>
</tr>
</tbody>
</table>
Significance level $P \leq 0.05$, ns: non-significant

Table 3: Median and range of NRS pain score at different time points and comparison between the tested groups (by Mann Whitney U test) and overtime in each group (by Friedman test)

<table>
<thead>
<tr>
<th>Groups</th>
<th>Test group</th>
<th>Control group</th>
<th>P-value (between groups)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median</td>
<td>Min</td>
<td>Max</td>
</tr>
<tr>
<td>Post Operative Pain</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Day1)</td>
<td>6</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>(Day3)</td>
<td>4</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>(Day5)</td>
<td>1</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>(Day7)</td>
<td>1</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>(Day10)</td>
<td>0</td>
<td>0</td>
<td>3</td>
</tr>
</tbody>
</table>

P-value (Within group over time) 0.00* 0.00*

Significance level $p \leq 0.05$, *significant, ns=non-significant

Table 4: P value of NRS pain score pairwise comparison at different time points in each group (by Wilcoxon signed Rank test)

<table>
<thead>
<tr>
<th>Groups</th>
<th>Day 1 Versus Day 3 Versus Day 5 Vs Day 7 Vs Day 10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day3</td>
<td>Day5</td>
</tr>
<tr>
<td>Test</td>
<td>0.002*</td>
</tr>
</tbody>
</table>
Discussion:

Immediate implant placement has become a widely used strategy for replacing non restorable teeth. Nonetheless, there are some drawbacks of this technique that may decrease its success rate, including technique sensitivity, inability to achieve primary implant stability and inadequate soft tissue closure particularly with thin gingival biotype (Chen et al., 2009; Ortega-Martinez et al., 2012).

It is documented that both HA and melatonin possess good properties in promoting bone healing and osseointegration between implant and bone. This can be attributed to the fact that HA is used mainly as a carrier for growth factors and bone grafts in bone defect models to enhance bone regeneration, and the fact that melatonin is an important mediator for bone formation by stimulation of osteoblast differentiation together with inhibition of osteoclastic activity (Conti et al., 2000; Cardinali et al., 2003; Maldonado et al., 2007). Since both hyaluronic acid and melatonin are potent biomimetic materials which may enhance hard and soft tissue healing; hence, the resulting mixture of both materials can be efficiently used in implant dentistry. That was supported by the results of a study by (Corina et al., 2018) who found out that no structural changes happened at the level of functional groups of both HA and melatonin when mixed together and thus a possible synergic effect of the two substances may be expected.

The rationale behind using a melatonin and HA mixture around immediately placed implants in the current trial was to gain a beneficial synergistic effect from adding both materials together, in terms of increased implant stability and less postoperative pain. To the best of our knowledge, this is the first clinical trial to evaluate the effect of HA and melatonin mixture application around immediately placed implants on implant stability and post-operative pain.

Requirements for immediate implant placement that had been shown through the results of many clinical studies; including atraumatic extraction of the tooth to-be replaced, aseptic environment of the whole procedure, minimally invasive surgical approach and the ability to achieve

| Control | 0.002* | 0.002* | 0.002* | 0.003* | 0.002* | 0.002* | 0.180 ns | 0.109 ns | 0.083 ns |

Significance level $p \leq 0.05$, *significant, ns=non-significant
satisfactory primary implant stability (Vanden Bogaerde et al., 2005; Siegenthaler et al., 2007; Rebeiro et al., 2008; Canullo et al., 2009; Siciliano et al., 2009).

In the present study, flapless extraction was done for participants in both groups in order to maintain the periosteal blood supply to the facial bone plate reducing the risk of its resorption with consequent gingival recession (Novaes et al., 2011; Jung et al., 2013). Moreover, studies by (Raes et al., 2011; Buser et al., 2017) concluded that flapless technique had been linked to less recession of soft tissue, shorter treatment duration, less trauma to the patient with increased comfort, faster healing and better esthetic results.

Engagement of apical bone is clinically vital to ensure both favorable implantation and to attain sufficient primary stability of the implant. Smith and Tarnow, 2013, stated that at least 3-5mm of periapical bone is important for an intimate bone to implant contact. Osteotomy was prepared in a way that allowed the implant to engage in the bone for about 3mm apical to the extraction socket in order to achieve sufficient primary implant stability (Cavallaro and Greenstein, 2014).

Regarding the implant stability, results of the present study showed no statistically significant difference between secondary implant stability (ISQ) values after 6 months from implant placement between test group (71.33±3.65) and the control group (70±5.06) (p = 0.468). This is in agreement with the study by (Awwad et al., 2019) who investigated the effect of local application of melatonin gel mixed with beta-tri calcium phosphate around immediate implants in maxillary anterior teeth. The measurements of implant stability using Osstell device after 3 months showed a higher mean value in melatonin group (60±4.61) than control group with no melatonin (54.7±4.02), with a significant difference (p = 0.041) in favor of the test group. Meanwhile, after 6 months, a higher mean implant stability value was recorded in test group (77.7±10.3) than in control group (70.8±12.68) with no statistically significant difference between both groups (p = 0.286) as reported in our present study. Also, our results are in line to what (Kaya et al., 2019) mentioned in their 1-year-follow up comparing the use of HA with xenograft and collagen membrane (test group) to xenograft and collagen membrane alone (control group) to treat small and medium-size peri-implant defects. The mean ISQ values at the 6 months after intervention showed that test groups showed higher ISQ values (78.15 ± 4.8 in small-sized defect, and 77.41 ± 4.4 in medium-sized defect) than the control groups (77.27 ± 4.68 in small-sized defect, and 75.15 ± 3.09 in medium-sized defect). However, the difference was not statistically significant.
On the other hand, (El-gammal et al., 2016) reported better implant stability values in the test group which received one-piece implants with application of topical 1.2% melatonin gel in the osteotomy site compared to the control group with no melatonin added. The difference between the two groups was statistically significant only at 1 month of implant loading (1.28±0.76 for test group versus 0.85±1.77 for control group), and not statistically significant at 3, 6 and 12 months. This difference from our study results may be explained by the different implant placement protocol in healed bony sites in contrast to our study where we placed implants in fresh extraction sockets.

Also, in contrast to the current study’s results, there is a clinical study by (Rostom et al., 2019) who reported that the effect of melatonin on increasing bone implant contact and bone density, which contribute to better implant stability, is unclear throughout one year of function. This contradiction may be because they used short implants rather than standard implants, they placed implants in posterior mandible which has different bone morphology and quality than anterior/premolar region in our study. Also, exposure and restoration of implants was done after 3 months followed by 9 months period of implant loading in function which would affect the amount of peri-implant bone resorption.

Concerning postoperative pain measured for 10 days after implant placement, in the present study there was a statistically significant decrease overtime (P=0.00) of the NRS score values for both test and control groups. Also, there was a statistically significant difference between test and control groups in favor of the test group in all time intervals except at day 5 recording less pain values after implant placement. This is in agreement with the meta-analysis by (Wang et al., 2021) who assessed the effect of melatonin on postoperative pain and pre-operative opioid consumption. They concluded that melatonin significantly reduced the need for analgesic requirements and prolonged the time to first analgesic requirement. Melatonin was significantly associated with decreased VAS score (24 hours postoperatively) compared to placebo (mean difference -0.86; 95% CI -1.38, -0.34; P = 0.001) which is in accordance to our results where test group recorded median NRS score 6 [range 4; 8], in comparison to control group score 8 [range 6; 9] at day 1 (p=0.010), and median NRS score at day 10 was 0 [range 0; 3] for test group and 2 [range 0; 3] for control group.

On the contrary, in their study to assess the anti-inflammatory and analgesic effect of melatonin, (Cobo-Vázquez et al., 2014) found that after applying 3 mg melatonin to post-extraction sockets
of extracted third molars, an increase in the concentration of interleukin-6 and nitrotyrosine was detected in the samples of blood clot in the extraction socket tested by ELISA kit with the application of melatonin without statistical significance (361.32 ± 235.22 pg/ml) when compared to control group with application of placebo (262.58 ± 233.92 pg/ml). This could be explained by the little amount of melatonin used at the site of tooth extraction.

Moreover, the current study results are in contrast to the results by (Koray et al., 2014) who studied the effect of 0.2% hyaluronic acid spray three times daily for seven days after surgical extraction of impacted mandibular molars, they evaluated pain with a visual analogue scale (VAS), swelling and trismus. HA seemed to offer a desirable effect in the treatment of swelling and trismus, yet there was no evidence reported on the efficiency of HA in reduction of pain levels. This study may be different from the present study due to the increased surgical trauma caused by the third molar extraction procedure.

Conclusion:
Within the limitations of the current study, we can conclude that topical application of hyaluronic acid and melatonin mixture around immediate implants led to the following: Statistically non-significant increase in implant stability compared to immediate implants alone. A statistically significant decrease of post-operative pain was related to application of HA and melatonin mixture around immediate implants.

Recommendations:
Further studies are needed to fully understand the specific mechanism of action of Hyaluronic acid and Melatonin mixture and its cellular activity. Thorough investigations are required to identify the ideal delivery method, concentrations and possible biomaterials to be added to the mixture to improve bone formation.

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