CLINICAL EVALUATION OF TOPICAL MELATONIN APPLICATION ON IMPLANT STABILITY OF IMMEDIATE DENTAL IMPLANT IN ANTERIOR & PREMOLAR REGION IN SYSTEMICALLY HEALTHY PATIENTS

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ABSTRACT

Aim: evaluate the effect of topical application of melatonin with immediate implant placement for better implant stability, soft tissue healing and post-operative pain versus immediate implant alone.

Materials & Methods: twenty-four subjects with non-restorable anterior and premolar teeth indicated for immediate implant placement were divided into equal proportions between a study group (A) (Immediate implant with melatonin) and a control group (B) (immediate implant alone). Outcomes for implant stability were measured and recorded at baseline and after 6-months by Ostell, post-operative pain and soft tissue healing.

Results: at the end of the study, a significant difference was shown in the mean of implant stability between the control group (59.5 ± 3.8) and the test group (68.0 ± 2.6) at p = 0.001. The test group showed a significant soft tissue healing 2 (2-3) versus 3 (2-3) in the control group (p = 0.005). The median and range of the VAS scores were 7(6-8) for test group and 8(6-8) for control group with no statistically significant difference between both groups (p= 0.532) in day 0. Nevertheless, there was a statistically significant difference between the test group and control group regarding post-operative pain in day 2 and day 7 after surgery.

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

Clinical significance: when compared to immediate implant alone, topical application of melatonin with immediate implant placement improves implant stability, soft tissue healing, and decrease post-operative pain.

Keywords: Immediate implant, implant stability, melatonin, post-operative pain, soft tissue healing.

I. INTRODUCTION

Millions of people across the world suffer from tooth loss caused by decay, wear, trauma, and periodontal diseases. Numerous studies showed that tooth loss could create an intense emotional distress in a person’s life especially if it involves front teeth or affects the ability to speak and eat (Kisely 2016). However, advances in science and technology have made dental implant a very viable option to fully restore form, function and most importantly esthetics to people who have lost their teeth. Schult and his colleague made a significant progress in the field of implantology as they were the first ones to introduce immediate dental implant placement in recent extraction socket. (Schulte and Heimke 1976) Immediate post extraction implants are widely used in which, a dental implant is placed just after extraction of the teeth in a fresh socket without waiting for any bone or soft tissue healing in order to reduce the treatment periods. (Hämmerle, Araújo, and Simion 2012) In a comparison between immediate
and delayed implant placements in anterior and premolar regions, (Amin et al. 2019) concluded that immediate implant placements would preserve the bone and prevent the collapse of the gingival architecture. They also reduce the treatment cost, time, preserve the gingival esthetics, and increase the comfort of the patients. The main objective of immediate implant placement is to provide an osseointegrated implant fixture suitable for an aesthetic and functional restoration. (Grunder 2011) There are several grafting materials that could be used as autografts, allograft or xenograft to improve bone synthesis and ensure better survival (Campana et al. 2014). However, limitations associated with autografts include limited availability and associated morbidity. Therefore, the potential transmission of disease and immunological response enhanced the use of alternative biomaterials. (Pollock et al. 2008) Recently, a great attention has been directed towards melatonin hormone as a graft material. (Rivara et al. 2015) Melatonin is an important mediator in bone formation and stimulation. Melatonin (N-acetyl-5-methoxytryptamine) was discovered by Lerner 1958. The synthesis of melatonin occurs in bone marrow, pineal gland, and extra pineal tissue that happens during the hours of darkness and with exposure to artificial light at night. Melatonin plasma level concentrations are 50 folds higher in night in comparison to daytime. (Claustrat and Leston 2015) Melatonin would appear to participate in the neo-formation of bone around implants as it stimulates the differentiation of new pre-osteoblasts, which are transported from bone marrow to the alveolar bed via the vascular system. Also, it enhances new bone tissue formation and stimulation of gene expression of certain proteins in the bone matrix. (Radio, Doctor, and Witt-Enderby 2006) Melatonin could be applied to the surface of titanium implants or in the osteotomy site to promote the bone formation at early stages of bone healing, as more bone-to-implant contact is being formed. (Arora and Ivanovski 2017) Therefore, it’s being hypothesized in this research that topical melatonin administration has a lot of potential effects in the dental implants and may contribute to regeneration of alveolar bone through the stimulation of type I collagen fiber production and modulation of osteoblastic and osteoclastic activity, thus promoting osseointegration of dental implant. (Liu, Huang, and He 2013) In this study, we are discovering the effectiveness of the antioxidant properties of melatonin for the treatment of the local inflammatory lesions, modulating pro and anti-inflammatory cytokines in different pathophysiological conditions, and for accelerating the healing process including tooth extraction and other surgical procedures like dental implantation.

II. MATERIAL & METHODS

This is a randomized clinical trial study. Its protocol is registered on clinicaltrials.gov under identifier NCT03689998 (https://clinicaltrials.gov/ct2/show/NCT03689998). The present study was approved by the research ethics committee of Faculty of Dentistry, Cairo University (approval number 18-9-59) (approval date 26/9/2018) and complies with the declaration of Helsinki. The detailed surgical procedures and follow up periods were clearly described in detail to all patients participated in this clinical trial. Informed consent was obtained from all participants included in the study and fully agreed to participate in this clinical trial.

Sample size:

Based on the previous paper by Granić et al., 2015,(Granić et al. 2015) the expected difference in stability between groups is 2±1.4 ISQ. Using power 80% and 5% significance level, 9 patients are required in each group. This number is to be increased to a sample size 12 in each group to compensate for possible losses during follow up. Sample size calculation was achieved using PS software.

Randomization

Allocation sequence will be generated using computer-generated random numbers.

List will be created on (https://www.random.org/), the patients will be randomly classified into two groups.

The first group will be the study group (A) and the second group will be the control group (B). This method was done by the main investigator (A. M.) and the main supervisor (M.S.).

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 inserted into opaque envelope.

Eligibility criteria

Inclusion criteria
Age: 18-60, systemically healthy patients indicated for single or multiple immediate implants in anterior and premolar region, non-smoker, patients with adequate bone volume for immediate dental implant procedure, patients with absence of any periapical pathosis, patients with intact buccal plate of bone.

Exclusion criteria

Heavy smokers, systemic disease that contraindicates implant placement or surgical procedures, no or poor patient’s compliance, psychological problems, pathology at the site of intervention, pregnant females, patients refusing to sign the informed consent.

Eligible individuals were divided into two equal groups:

Intervention group (A): twelve patients were participated in the study group indicated for immediate implant placement with topical melatonin application were considered as a (study group).

Control group (B): twelve patients participated in this group and were indicated for immediate implant with placebo gel and were considered as a (control group).

Participants were selected from the outpatient clinic at the department of Periodontology in Cairo University in Egypt. After discussing the treatment plan with the patient and educating the patient with all the data needed and complications that could be met, an Arabic consent form will be signed by the willing participants. A thorough preoperative assessment of all patients was carried out including history taking, clinical examination and radiographic examination. Proper intraoral examination was done to evaluate the following parameters for the tooth of interest: restorability of the tooth, relation to adjacent teeth and the available mesio-distal space and relation to the opposing teeth and the available occluso-gingival space.

Procedures

All eligible patients went through phase I therapy (supra and subgingival scaling with oral hygiene instructions tooth brushing twice daily using modified bass technique and chlorhexidine 0.12% mouthwash twice daily).

After 4 weeks, all patients were re-examined to determine the compliance with oral hygiene procedures.

Pre-operative photographs were taken for eligible patients (Figure 1A) and intraoral periapical radiographs at the time of the initial examination to confirm the diagnosis of the non-restorable tooth and absence of any peri-apical pathosis.

CBCT scan using OnDemand 3D was performed to record preoperative bone height and width measurements used to determine implant diameter, length, position. Minimally invasive extraction was performed using periotome to preserve the alveolar bony integrity figure (1B). Sockets were irrigated by sterile saline and curetted to remove any remnants of the periodontal ligament. In a study group, pure melatonin 5% was purchased from pure-bulk supplements and prepared in a gel form. Then, it was placed around the dental implants in the osteotomy and in jumping gap by a 5ml disposable plastic syringes to ensure equal concentration of melatonin being delivered to each osteotomy site. El-Gamal MY, stated that melatonin in a gel form can be easily applied and retain in osteotomy site. (El-Gammal MY, 2016) Since Calvo-Guirado JL, who studied the pro-osteogenic effect of melatonin on both titanium and zirconia implants used 5% solution of melatonin showed a positive effect on implant at the first week in rabbits. And, at 4 weeks melatonin showed a significantly higher bone implant contact. (Calvo-Guirado et al. 2015) Therefore, a similar concentration of 5% of melatonin was used in this study due to its positive impacts in bone implant contact.

T4 NucleOSS implant was soaked in melatonin before insertion. Implant was inserted as in manufacture instruction by flapless surgery (Figure 1C). Melatonin was inserted in the jumping gap between implant fixture and socket walls. Primary implant stability was measured at the time of implant placement using Osstell.

Simple interrupted suture with a 5-0 silk suture was used for approximation of buccal and palatal tissue. In control group, immediate implant placement only after extraction. Simple interrupted suture using (5-0) silk suture.
Post-operative care
Sutures were removed after 10 days. Soft tissue healing was assessed using likert scale (Galli et al. 2008). Post-operative pain was assessed by visual analogue scale at day 0, 2, 7.(Al-Khabbaz, Griffin, and Al-Shammari 2007)

Second stage:
After 6 months, periapical radiograph was performed. The implant exposure procedure was performed under local anesthesia, implant stability was measured, and the healing collar was screwed for promoting soft tissue healing. (figure 1E)

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

Figure 1 (A-F)
Figure (1A) pre-operative photo (Study group). Figure (1B) Extraction Socket. Figure (1C) Implant in position & 3mm jumping gap. Figure (1D) Immediately post-operative peri-apical Radiograph. Figure (1E) Emergency Profile. Figure (1F) Crown Delivery.
Outcomes:

Primary outcome (implant stability): was measured in the day of surgery and after 6 months.

Secondary outcomes: Post-operative pain was measured at days 0, 2 and 7 after surgery 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 sever pain "10" (Al-Khbabaz, Griffin, and Al-Shammari 2007). Soft tissue healing was measured at the day of suture removal, which was 10 days after surgery and assessed as the following: 0 would be complete wound closure without presence of fibrin; 1 would be complete wound closure with a thin line of fibrin present; 2 would be complete wound closure with presence of fibrin; 3 would be incomplete wound closure (dehiscence); and 4 would be incomplete wound closure (necrosis). (Galli et al. 2008)

Result

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. Percent change, pain score and healing score 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.

The mean age of patients in group (A) was 37.6±7.4 years and range (29-42) while in group (B) patients were 38.3±5.2 and range (29-42). This was statistically not significant, p=0.546. Gender distribution in group (A) involved 6 females and 6 males, while in group (B) involved 8 females and 4 males. (Table 1)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group</th>
<th>Group A</th>
<th>Group B</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group</td>
<td>No</td>
<td>%</td>
<td>No</td>
</tr>
<tr>
<td>Age (years)</td>
<td>Mean± SD</td>
<td>37.6±7.4</td>
<td>38.3±5.2</td>
<td>0.546</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>29-42</td>
<td>29-42</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>Female</td>
<td>6</td>
<td>50.0</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>6</td>
<td>50.0</td>
<td>4</td>
</tr>
</tbody>
</table>

SD: standard deviations, P≤0.05 is significant

The mean primary implant stability in group A was 53.6±4.3 and was 51.0±2.8 in group B. This was statistically not significant; p=0.092

The mean secondary implant stability of group A was 68.0±2.6 compared to 59.0±3.8 in group B. This was statistically significant; p <0.001. (table 2)
Table (2): 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></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
<td>P value</td>
<td></td>
</tr>
<tr>
<td>Primary</td>
<td>53.6</td>
<td>4.3</td>
<td>51.0</td>
<td>2.8</td>
<td>0.092</td>
<td></td>
</tr>
<tr>
<td>Secondary</td>
<td>68.0</td>
<td>2.6</td>
<td>59.0</td>
<td>3.8</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

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

The median and range of the VAS scores in day (7) was 2 (0-3) for group A and 2(0-3) for group B with statistically significant difference between both groups (p= 0.015). (table 3)

Table (3): Median and range of VAS score 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 (12)</th>
<th></th>
<th>Group B (12)</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median</td>
<td>Min.</td>
<td>Max.</td>
<td>Median</td>
<td>Min.</td>
<td>Max</td>
</tr>
<tr>
<td>Day (0)</td>
<td>7</td>
<td>6</td>
<td>8</td>
<td>8</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>Day (2)</td>
<td>4</td>
<td>3</td>
<td>5</td>
<td>6</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Day (7)</td>
<td>2</td>
<td>0</td>
<td>3</td>
<td>3</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>P value 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P value 2</td>
<td>&lt;0.001</td>
<td></td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SD: standard deviations, P≤0.05 is statically significant; P1: for comparison between 2 groups. P2: for comparison over time in each group separately

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 statistically significant difference between both groups (p= 0.005).

Complete closure was in 75% of patients in group A in comparison to 16.7% in group B; this was statistically significant (p=0.004) (table 4).

Table (4): Soft tissue healing of the tested groups (Group A:; Group B: ).

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group</th>
<th>Group A</th>
<th></th>
<th>Group B</th>
<th></th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>No</td>
<td>%</td>
<td>No</td>
<td>%</td>
<td></td>
</tr>
<tr>
<td>Soft tissue healing</td>
<td>Complete wound closure</td>
<td>9</td>
<td>75.0</td>
<td>2</td>
<td>16.7</td>
<td>0.004</td>
</tr>
<tr>
<td>presence of fibrin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incomplete wound closure</td>
<td>(dehiscence)</td>
<td>3</td>
<td>25.0</td>
<td>10</td>
<td>83.3</td>
<td></td>
</tr>
</tbody>
</table>

SD: standard deviations, P≤0.05 is significant
III. DISCUSSION

Modern dentistry aims to return patients to normal oral health and function in a predictable fashion. Osseointegrated implants have been utilized with great success for many years as full mouth rehabilitations with fixed prosthesis by implants significantly increase the quality of life in fully or partial edentulous patients when compared with other conventional technique. (Prithviraj and Gupta 2008)

The success of the implant depends on the primary stability as achieved when implant is placed 2-3 mm apical to the socket. The overall reduced in treatment time and surgical visits makes immediate implants a treatment of choice over the conventional approach of tooth extraction and waiting up-to 4-6 months. (Chavan and Chavan 2016)

In conjunction with immediate implant placement, there are a variety of available techniques that had been established. The dental implant placement using flapless surgery is a minimally invasive technique that improves blood supply and reduces bone loss and recession after tooth extraction compared with flapped surgery. (Lin et al. 2014) However, other experimental studies determined that even with flapless approach the amount of bone loss and the dimensional changes of the alveolar process following tooth extraction were similar with flap elevation. (Jané-Salas et al. 2018)

In the present study, Osstell Mentor was used for recording Implant Stability Quotient (ISQ) measurement at the time of implant placement and after 6 months in both groups. The higher the ISQ value, the more stable the implant. (Park et al. 2011). Many studies have shown that implants whose ISQ values exceed 65 before functional loading have 99% survival rate and ISQ values of 57 to 82 have been used as threshold values for implant success, ISQ values less than 45 indicate failure of the implant. (Bornstein et al. 2009)

The discrepancy in size and form between the extraction socket and the implant usually leaves a gap or bone defects especially around the coronal portion of the implant. (Jyothi et al. 2013) It was reported by (Pluemsakunthai, Kasugai 2015) that the bone gap around the immediate dental implants may endanger the success of osseointegration process due to migration of the surrounding soft tissues into the gaps.

Multiple materials have been proposed to regenerate the living bone around immediate dental implants. Melatonin is considering one of the most common materials that would enhance new bone formation around dental implant and improves osseointegration. Thus, improving stability of the dental implant and survival rates. (Salomó-Coll et al. 2016)

In a recent clinical study showed that, immediate implants augmented with autogenous bone/melatonin composite graft would be a valuable option in the esthetic zone. (Hazzaa et al. 2019) Furthermore, another study showed that local application of melatonin at the osteotomy site is associated with good stability and minimal bone resorption. (El-Gammal et al. 2016)

Topical application of melatonin may act as a biomimetic agent in the placement of dental implant. (Guardia et al. 2011) Significant improvement in the soft tissue healing scores compared to the control group was attributed to that melatonin has a free radical scavenger, anti-inflammatory, antioxidant effects and angiogenesis by the proliferation of fibroblast. It scavenges reactive oxygen and nitrogen species and increases antioxidant defenses. Thus, it prevents tissue damage and blocks transcriptional factors of pro-inflammatory cytokines. (Hacışevki and Baba 2018)

Also, melatonin significantly decreased the pain intensity, as evidenced by the pain scores. Moreover, melatonin administration also reduced the proportion of patients with analgesic requirements. (Zhu et al. 2017) It was important to note the majority of the studies showed that there was a direct correlation between melatonin and implant stability, and soft tissue healing and pain.

To the best of our knowledge, this was the first study that evaluated topical application of melatonin only with immediate implant placement on implant stability, soft tissue healing and pain scores.
IV. CONCLUSION

Topical application of melatonin could be used as a valuable agent with immediate implant placement. Topical application of melatonin with immediate implant placement significantly improves the implant stability, soft tissue healings and reduces the (VAS) scores level.

Clinical Significance

Clinical significance: when compared to immediate implant alone, topical application of melatonin with immediate implant placement improves implant stability, soft tissue healing and decreases post-operative pain.

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Declaration of interests

The authors declare no conflict of interest.

REFERENCE


