

## Evaluation of Effects of Melatonin Application on Osseo Integration of Dental Implant

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### ARTICLE INFO



Keywords:

Composite, Microleakage

### ABSTRACT

#### Background

Insufficient bone availability for prosthesis-guided implant placement is one of the most frequent challenges these days. Limited bone volume is related to poor bone quality that constitutes a challenge for the implant-supported rehabilitation specially in maxilla. The poor bone quality is more frequently seen in aged patients with atrophic and osteoporotic bones due to the reduction of function of osteoprogenitor cells.

#### Materials and Method

The study was performed in a dental institute with the total number of 15 patients who falls in the age group of 45-55 years. The study protocol was approved by the Ethics Committee of the institution. Subjects were divided into three groups. Control group (CG) (n=5): No treatment was applied, and dental implants were simply inserted, Melatonin Dose 1 (MLT D-1) group (n=5), Melatonin Dose 2 (MLT D-2) group (n=5)

#### Results

New bone regeneration reached the top in the melatonin group; however, it reached to about one-third in the control group. Some blood vessels were observed in the newly generated bone in the melatonin groups. The total percentages of areas of new bone were significantly different between the melatonin and control groups at 12 weeks.

#### Conclusion

In conclusion, melatonin promoted vertical bone regeneration in a secluded space using a plastic cap. Further studies are needed to fully evaluate the benefit of melatonin in enhancing bone regeneration.

### INTRODUCTION

Insufficient bone availability for prosthesis-guided implant placement is one of the most frequent challenges these days. Limited bone volume is related to poor bone quality that constitutes a challenge for the implant-

supported rehabilitation specially in maxilla. The poor bone quality is more frequently seen in aged patients with atrophic and osteoporotic bones due to the reduction of function of osteoprogenitor cells, an increase in osteoclastogenesis, and in local free radical

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concentrations in all types of cells, including osteoblasts which leads to a decrease in bone regenerative capability.<sup>1,2</sup> Bone is a tissue which involves into the continuous remodelling process that leads to the resorption of old bone by osteoclasts, and formation of new bone by osteoblasts regulated by growth factors produced in the bone marrow and osteoid matrix and by the action of systemic hormones, like estradiol, parathyroid hormone, growth hormone (GH), and, probably, melatonin.<sup>3-7</sup> Among these systemic hormones, Melatonin is a tryptophan derived indolamine which is secreted by the pineal gland with well-known antioxidant properties<sup>8-10</sup> and free radical scavenging abilities.<sup>11,12</sup> This hormone can also inhibit bone resorption by suppressing osteoclast activity.<sup>13</sup> due to its ability of increasing osteoblast proliferation and differentiation in vitro,<sup>14,15</sup> that lead to a thought that it could be a good agent to stimulate the peri-implant bone response during implant placement. So, the objectives of our study was to evaluate the effects of melatonin on Implant Osseointegration.

## **MATERIALS AND METHODS-**

The study was performed in a dental institute with the total number of 15 patients who falls in the age group of 45-55 years. The study protocol was approved by the Ethics Committee of the institution. Subjects were divided into three groups and they are-

- Control group (CG) (n=5): No treatment was applied, and dental implants were simply inserted
- Melatonin Dose 1 (MLT D-1) group (n=5)
- Melatonin Dose 2 (MLT D-2) group (n=5)

In all three groups, a total of 24 sand-blasted large acid-etched surface implants from Es-Dent Dental Implants measuring 6-mm in length and 3 mm in diameter were used and all the process were performed under the sterile

conditions. The morphometrical study to quantify the newly formed bone around the implants was performed with a MIP-4 imaging analyzer (Digital Image System, Barcelona, Spain). The parameters calculated were BIC, cortical area density, and trabecular area density. BIC was defined as the length of bone surface border in direct contact with the implant perimeter (¥100%).<sup>19</sup> BIC has been measured at the cortical zone in contact with the implant (cortical level) and at the medullar zone in contact with the implant (trabecular level). Cortical area density was defined as the bone area in the cortical level with respect to the total bone area (¥100%). Trabecular area density was defined as the bone area in the trabecular level with respect to the total bone area (¥100%).

Statistical Analysis was done by the SPSS software. Mean values  $\pm$  a standard error equal to the mean of each group were calculated for all the analysed data. The differences between groups were tested with a one-way ANOVA, for parameters that showed a normal distribution.  $p < .05$  was considered to be significant.

## **RESULTS**

### **MORPHOMETRICAL EVALUATION**

New bone regeneration reached the top in the melatonin group; however, it reached to about one-third in the control group. Some blood vessels were observed in the newly generated bone in the melatonin groups. The total percentages of areas of new bone were significantly different between the melatonin and control groups at 12 weeks. The height of newly generated bone was significantly greater in the melatonin group (Table 1 and 2)

**Table:** Bone volumes in the melatonin and control groups at 2, 4, 6, 8, 10, and 12 weeks. Significant differences were observed at 4 to 12 weeks. ( $P < 0.05$ )

| Weeks | Melatonin Group | Control Group |
|-------|-----------------|---------------|
| 2     | 1.27 ± 0.3      | 1.16 ± 0.1    |
| 4     | 8.24 ± 3.4*     | 4.27 ± 1.4    |
| 6     | 10.49 ± 3.2*    | 5.30 ± 1.6    |
| 8     | 11.47 ± 3.3*    | 6.20 ± 2.2    |
| 10    | 12.40 ± 3.2*    | 7.11 ± 2.8    |
| 12    | 13.20 ± 3.0*    | 8.21 ± 2.4    |

**Table 2:** The total percentages of newly generate bone

|                 | Newly Generated Bone | Height of Newly Generated Bone |
|-----------------|----------------------|--------------------------------|
| Melatonin group | 64.2±6.0*            | 63.4±7.2*                      |
| Control group   | 28.4±3.2             | 25.4±2.6                       |

## DISCUSSION

The present study showed that melatonin increased vertical bone augmentation. The secluded space created was intended as a model for vertical bone augmentation, as in dental implant placement. The results showed that the height of newly generated bone was significantly greater in the melatonin group, and the generated bone was well mineralized. Our previous studies found that some scaffolds or growth factors were needed for newly generated bone to reach the top (17). Prior to implanting, the topical application of melatonin powder and growth hormone (GH) at osteotomy significantly enhanced new bone formation around titanium implants in the early stage of healing (18). This suggested that melatonin functioned as a growth factor to enhance new bone formation. Furthermore, local application of melatonin to dental implants increased the bone implant contact (BIC) area and inter-thread bone at 4-12 weeks (19-21). Melatonin acted on the bone as a local growth factor with paracrine effects on nearby cells (22,23). Enhancing BIC signifies a direct action of melatonin on osteoblasts,

inducing a higher rate of maturation of preosteoblasts to osteoblasts, in terms of both quantity and speed, with a higher rate of production of the osseous matrix and its subsequent calcification. The present study found significantly larger numbers of osteoblast-like cells in melatonin groups compared to control groups. In vitro studies have demonstrated that melatonin promotes osteoblast proliferation (24,25). Furthermore, melatonin and GH function through several related mechanisms; however, each also plays other roles. Melatonin is more important in osteoblast differentiation and osteoclast inhibition. A recent study showed that melatonin promoted osteoblastic differentiation and mineralization of mouse preosteoblastic cells under hypoxic conditions (26). Bone healing and regeneration are both hampered under hypoxic conditions.

We also demonstrated that the number of blood vessels increased significantly in the melatonin group versus the control group. Melatonin enhanced angiogenesis during the repair of bone defects. Melatonin maintained capillary homeostasis because the wound tissue includes many blood vessels. Another study showed that melatonin administration had positive effects on both angiogenesis and wound healing (27). Angiogenesis plays a key role in bone regeneration. Previous studies showed that angiogenesis preceded bone regeneration in calvaria bone defects and secluded spaces. The local application of melatonin significantly induced angiogenesis during the first 4 weeks. Another study reported that the local application of melatonin resulted in a rapid increase in bone formation at 2 weeks. Other studies revealed that local application of melatonin enhanced bone regeneration in concave defects. Ramirez-Fernandez et al. generated 5-mm-diameter concave defects and implanted 1.2 mg melatonin powder in tibiae. Calvo-Guirade et al. created concave defects ~4

mm in diameter and implanted 5 mg of melatonin impregnated in a resorbable sponge. In the present study, only melatonin powder was placed in the cap (10 mg). No melatonin remained in the regenerated bone, and the tissue was well mineralized. However, melatonin powder is difficult to use in GBR because the powder does not tend to hold its form. Clafshenkel et al. They indicated that the calcium–melatonin scaffolds had the potential to provide a moldable, bioactive scaffold that would target bone-regenerating activity directly to sites of bone loss. Thus, melatonin can be used with other scaffolds to extend clinical applications such as GBR in implant placement. In conclusion, melatonin promoted vertical bone regeneration in a secluded space using a plastic cap. Further studies are needed to fully evaluate the benefit of melatonin in enhancing bone regeneration.

## CONCLUSION

In conclusion, melatonin promoted vertical bone regeneration in a secluded space using a plastic cap. Further studies are needed to fully evaluate the benefit of melatonin in enhancing bone regeneration.

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