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Original Article

Histopathological comparison of the effect of 5% melatonin gel and 1.2% rosuvastatin gel on bone regeneration in the rat model

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ABSTRACT

Background: This study aimed to histopathologically compare the efficacy of 5% melatonin (MEL) gel and 1.2% rosuvastatin (RSV) gel on bone regeneration in rat calvarial defects.

Materials and Methods: In this animal study, 8-mm defects were created in the calvaria of 24 adult male Wistar rats weighing 200 g. The rats were randomly assigned to three groups (n = 8). The defects were filled with placebo gel (methylcellulose with no active ingredient) in Group I, 5% MEL gel in Group II, and 1.2% RSV gel in Group III. The rats were sacrificed after 4 weeks. Hematoxylin and eosin (H and E) staining was used to prepare histological sections. Statistical analysis was performed using the ANOVA and Tukey tests (α =0.05).

Results: Osteogenesis was significantly higher in the MEL and RSV groups than in the control group ($P < 0.05$). However, the difference between the MEL and RSV groups was not significant ($P > 0.05$).

Conclusion: Osteogenesis was significantly higher in the MEL and RSV groups than in the control group ($P < 0.05$). Local administration of MEL and RSV can be used as a stimulant of bone formation. However, more investigations are required to evaluate the bone regeneration capacity of MEL and RSV gels.

Key Words: Bone regeneration, histopathology, melatonin, rats, rosuvastatin

INTRODUCTION

Successful implantation requires sufficient alveolar ridge dimensions. These dimensions are necessary for housing the implant and providing esthetics and function.[1] Various materials and membranes are utilized to augment the ridge.[2]

Statins are competitive inhibitors of hydroxyl-2-methylglutaryl coenzyme A (HMG-CoA) reductase, which limits the mevalonate pathway. Therefore, they are widely employed because they reduce the cholesterol level. Further, statins have anti-inflammatory, antioxidant, antitumor, anticoagulant, bone growth stimulation, and transplant antirejection properties.[3]

It has also been reported that statins prohibit the differentiation of osteoclasts and enhance the production of bone anabolic factors. These factors include vascular endothelial growth factor and bone

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morphogenetic protein 2 (BMP-2), which elevate bone formation and osteoblastic differentiation.[4-6]

Rosuvastatin (RSV) is a synthetic statin with desirable pharmacologic characteristics such as hepatic selectivity, minimal metabolism, and HMG-CoA reductase inhibition.[7] Like other statins, RSV enhances the expression of BMP-2 and differentiation of osteoblast *in vitro*.[8,9] Recent research has indicated that, as hydrophilic statins, RSV and pravastatin are more effective than lipophilic ones regarding mineralization and proliferation.[10] Moreover, the local administration of RSV can possibly trigger bone formation.[8,11-13]

Melatonin (MEL) (N-acetyl-5-methoxytryptamine) is an indoleamine synthesized and secreted by the pineal gland and other organs such as bone marrow, retina, and intestines in a circadian pattern.[14] MEL has many physiological properties in various body parts, including circadian rhythm control, body temperature regulation, and immune system activation.[14] Moreover, MEL has different biological functions, including anti-angiogenic, antioxidant, and antitumor activities.[14,15] It is also involved in bone resorption reduction and bone formation.[15-17]

Osteoblastic cell formation induced by MEL takes place due to the enhanced expression of BMP-2 and BMP-4, which play a role in osteoblast differentiation.[18]

MEL promotes the differentiation of osteoblasts by activating bone morphonegenetic protein (BMP), Extracellular Signal-Regulated Kinase (ERK) and Wnt signaling pathways. Yet, it prohibits osteoclast differentiation by elevating the osteoprotegerin expression in osteoblast, an antagonistic agent for Receptor Activator of Nuclear Factor κB Ligand (RANKL).[19] *In vivo* research has demonstrated that the topical administration of MEL can trigger osteogenesis around titanium implants, thereby contributing to osseointegration.[18,20]

The positive impact of MEL and RSV on bone growth has been investigated. However, a comparative study on these two medications is lacking. The current research conducted a histopathological evaluation to compare the effect of 5% MEL gel and 1.2% RSV gel on bone formation in rat calvarial defects.

MATERIALS AND METHODS

Study design

This animal study was conducted on 24 adult male Wistar rats weighing 200 g that were obtained from the Animal Room of Isfahan University of Medical Sciences. The study was approved with the ethics code of IR.AJUMS.ABHC.REC.1401.007 and in accordance with the guidelines for the care and use of laboratory animals.

The rats were randomly divided into three groups of eight rats each: Group I – Control, Group II – MEL, and Group III – RSV.

A single defect was created in the calvarial bone of each animal, and rats were then euthanized with an injection of potassium chloride into their heart 4 weeks later.

Preparation of melatonin and rosuvastatin gels

Preparation of the 5% MEL gel: a solution of methylcellulose was made by slowly adding the specified amounts of the polymer while stirring into one-third of the needed volume (33 mL out of a total of 100 mL) of freshly prepared distilled water at 80°C. The final volume was achieved by adding the remaining water volume (approximately 67 mL), in which the desired amount of MEL was dispersed while stirring. The resulting mixture was subjected to a vacuum to eliminate trapped air before being stored at 4°C until needed.[21]

To prepare RSV gel, the desired amount of methylcellulose was dissolved in distilled water to synthesize methylcellulose gel for later use as an RSV carrier after cooling. Sodium methylparaben and sodium propylparaben at specified concentrations were added to methylcellulose gel, respectively. RSV was then added to create a suspension with 1.2 mg/0.1 mL concentration. The suspension was stored at 4°C.[22] The placebo gel included methylcellulose with no active ingredient for use in the control group.[19]

Surgical protocol

The rats were kept in separate metal cages at optimal temperature and humidity and 12-h light/12-h dark cycles for the purpose of acclimation. At the time of surgery, general anesthesia was induced by injection of 2% xylazine (10 mg/kg) and 10% ketamine (10 mg/kg) intraperitoneally. Furthermore, the rats underwent antibiotic therapy for 3 days by subcutaneous injection of enrofloxacin (10 mg/kg). All surgical phases were conducted under sterile conditions.

The calvarial area of the rats was first shaved and then prepped and draped using alcohol and betadine. A 1.5-cm incision was made by a #15 scalpel from the nasal bone extending caudally to the mid-sagittal

crest, and a full-thickness flap was elevated. A hole was then drilled by a trephine surgical bur with an 8-mm diameter at low speed under copious irrigation [Figure 1].[23] To prevent injury to the dura mater and brain tissue, the bone was thinned and detached from the underlying dura mater by a blunt instrument.

The cranial defects were reconstructed using 0/1 ml of 1/2% RSV in Group I, 0/1 ml of 5% MEL gel in Group II, and 0/1 ml of the placebo gel in Group III. The incisions were sutured in one layer with simple single sutures and 3-0 nonabsorbable nylon sutures.

After the surgical procedure, the animal received a subcutaneous injection of sterile saline at a rate of 10 mL/kg/h of surgery and remained on pure oxygen until it regained consciousness from anesthesia. Subsequently, the rats were transferred to a room with a constant temperature of 21°C and kept in separate soft-bedded plastic cages. Throughout the postoperative period, the animals had unrestricted access to food and water and received 2.5 mg/kg morphine daily for 3 days for pain control.[23]

After a period of 4 weeks (28 days), the rats were euthanized by administering an overdose through intraperitoneal injection, combining 2% xylazine (10 mg/kg) and 10% ketamine (100 mg/kg). Following euthanasia, samples of the reconstructed cranial bones were collected using a surgical saw.

Preparation of specimens

The specimens were placed in 10% formalin for 5 days at 20°C.[18] For demineralization, the specimens were immersed in EDTA for 2 days and were then placed in a neutral solution for 12 h. The blocks were then rinsed and dehydrated in 70% ethanol and were then embedded in paraffin. A total of 5–6 slices with 5-μm thickness were obtained from each specimen and stained by hematoxylin and eosin (H and E) staining.

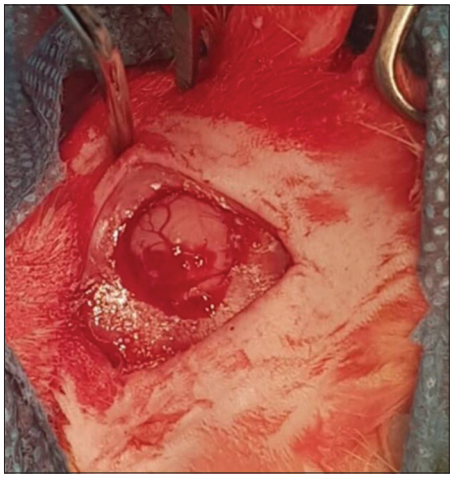

Figure 1: Created defect in the calvaria of a rat.

Histological analysis

The best slide was used for this purpose. For qualitative and quantitative assessment of bone, the slides were inspected by an experienced pathologist using an optical microscope (BX41, Olympus Co., Tokyo, Japan). The slides were coded, and the pathologist was blinded to their group allocation.

Color analysis was employed to assess the quantity of newly formed bone, and the percentage of bone tissue in the images was quantified using QuickPhoto Micro software version 2.3(Promicra, Prague, Czech Republic), followed by detailed analysis. The type of newly formed bone (cancellous, lamellar, or a combination of both) was also recorded.

Statistical analysis

Considering the normal distribution of data shown by the Kolmogorov–Smirnov test ($P > 0.05$) and homogeneity of variances confirmed by Levene's test ($P > 0.05$), one-way and two-way ANOVA were applied to compare osteogenesis among the three groups. Pairwise comparisons were conducted by the Tukey test. All statistical analyses were carried out by SPSS software (version 21) was provided by IBM Corp. (Armonk, NY, USA) at 0.05 significance level.

RESULTS

Microscopic histological findings

One rat in the RSV group expired during the surgical procedure. Furthermore, one rat was excluded from the MEL and one from the control group since a suture thread as a confounder was found at the defect site. Tissue healing occurred uneventfully in the remaining rats.

Microscopic assessment of the specimens after 28 days in the control group revealed the formation of callus tissue, including connective tissue fibers, along with the newly formed vasculature and several inflammatory cells such as macrophages, lymphocytes, and neutrophils along the defect site [Figure 2]. Hemorrhage was seen in some areas due to loose new vessel walls. Osteogenesis started at the defect sites, and the newly formed bone mass (cancellous bone) was expanding toward the center.

Several masses of newly formed cancellous bone were seen in the MEL group at the defect site. The formed lamellae had an irregular arrangement and different directions. Osteocytes were seen within the lacunae. Furthermore, osteoblasts were noted around them. Large vessels containing erythrocytes and several leukocytes were seen between the cancellous bone masses [Figure 3]. In the RSV group, several foci of newly formed cancellous bone were seen in the callus connective tissue [Figure 4]. The amount of newly formed bone in the MEL and RSV groups was highly similar.

Results of the quantitative and semi-quantitative assessment of histopathological parameters

The amount of newly formed bone was 22.41% in the MEL, 23.16% in the RSV, and 8.41% in the control group. The ANOVA test revealed a significant difference in the amount of newly formed bone among the three groups ($P < 0.05$). Thus, pairwise comparisons were carried out by Tukey test [Table 1], which showed that the percentage of newly formed bone was significantly higher in the MEL and RSV groups than in the control group ($P < 0.05$), but the difference was not significant between the MEL and RSV groups ($P > 0.05$).

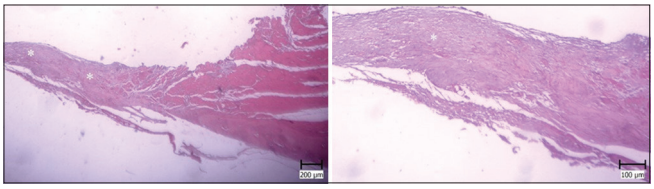

Figure 2: Calvarial bone defect in the control group after 28 days. Soft callus (white star) indicating immature fibrous connective tissue at the defect site (H and E, ×100).

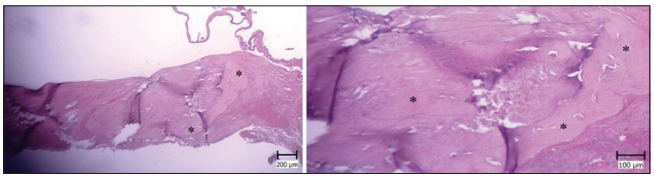

Figure 3: Calvarial bone defect in the melatonin group after 28 days. Newly formed bone masses (black star) can be seen at the defect site (H and E, ×100).

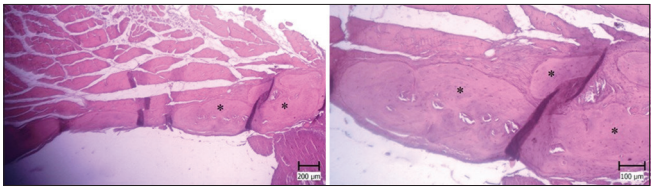

Figure 4: Calvarial bone defect in the rosuvastatin group after 28 days. Newly formed bone masses (black star) can be seen at the defect site (H and E, ×100).

DISCUSSION

Because grafting autogenous bone has several limitations, there is a growing demand for the application of alloplastic materials. Alloplastic substances are blended with osteoinductive materials such as BMPs to produce more efficient bone graft substances with promoted osteogenic characteristics.[24]

Research has indicated that statins trigger BMP-2 gene expression and enhance osteoblast differentiation during the early and middle phases of osteoblast cell culture.[7,8] MEL can also promote osteoblast differentiation by activating BMP/ERK/Wnt signaling pathways.[19] On the other hand, these agents can be applied locally to promote bone graft treatment.

Therefore, this study was performed to histopathologically compare the effect of 5% MEL gel and 1.2% RSV gel on bone formation in calvarial defects in rats. The results showed higher new bone formation in the 5% MEL group than in the control group. Newly formed bone had occupied a larger percentage of the defect compared with the control group and was mainly cancellous type on day 28. This finding indicates the stimulation of a higher number of bone cells by MEL and their early differentiation and subsequently enhanced mineralization of the osteoid matrix. MEL directly induces the osteoblasts and results in faster differentiation of preosteoblasts to osteoblasts and subsequent production of bone matrix and its calcification. The osteoblastic properties of MEL have been previously documented as well. For instance, Shino *et al*.[17] showed that the local application of MEL enhanced bone regeneration in rat calvaria. Furthermore, Cutando *et al*.[20] found that local application of MEL enhanced peri-implant bone and dental implant osseointegration in beagle dogs. Calvo-Guirado *et al*.[25] demonstrated that MEL significantly induced angiogenesis in the first 4 weeks and preserved capillary homeostasis under normal conditions such that a high number of endothelial

Table 1: New bone rate (%)

Variable	Control group (*n*=7)	MEL group (*n*=7)	RSV group (*n*=7)	*P*
New bone rate (%)	8.41±3.73	22.41±4.35	23.16±7.16	<0/05

MEL: Melatonin; RSV: Rosuvastatin

sprouts and capillaries were seen. The penetration of blood vessels allowed the migration of osteogenic and angiogenic cells. In the meta-analysis conducted by Lopez-Valverde *et al*., which explores the role of MEL in the osseointegration of titanium dental implants, it was found that in animals, bone-implant contact of titanium implants increases 2–6 weeks after placement when accompanied by MEL. However, bone crystal analysis in humans decreases over 6 months.[26] Their results were in line with those of the present study.

In the present study, several foci of newly formed cancellous bone in callus connective tissue were noted in the RSV group. Areas of newly formed bone were significantly higher in the control group, indicating that RSV can significantly enhance osteogenesis. Türer *et al*.[11] reported that local administration of 1 mg RSV along with autogenous bone grafting enhanced bone regeneration in critical-size defects in rat calvaria. Their results were in line with the present findings although autogenous bone grafting was not performed in the present study. Türer *et al*.[12] also assessed the effect of local application of RSV on mandibular fractures and showed that the newly formed bone was significantly higher in the RSV group than in the control group after 2 weeks. Nonetheless, the difference between the two groups was no longer significant after 28 days. They concluded that local RSV enhanced early bone regeneration in mandibular fractures in rats. Differences between their results and the present findings after 28 days may be due to different locations of defects in the two studies. Özer *et al*.[27] evaluated the effect of local RSV along with xenograft on new bone formation in rabbits and showed significantly higher new bone formation after 12 weeks in the RSV group than in the control group; however, the difference between the two groups was not significant after 6 weeks.

Furthermore, in the study by Pankaj *et al*., which investigated the use of 1.2% RSV gel and 1% metformin gel as a supplement in the treatment of chronic periodontitis infra-bony defects, it was revealed that the complementary use of 1.2% topical RSV and 1% metformin gel after 6 and 12 months leads to a reduction in probing depth and an increase in clinical attachment level and bone fill. Moreover, the improvement in indices in the group using 1.2% RSV gel was significantly higher compared to the group using 1% metformin gel.[28]

In the present study, the amount of newly formed bone was highly close in the MEL and RSV groups. The formed bone masses were cancellous bone in both groups. In contrast, the defects in the control group were mainly filled with connective tissue.

In a study conducted by Koç *et al*. to investigate the synergistic effect of a combination of simvastatin and MEL on bone regeneration, 48 male Wistar rats were divided into four groups. In Group 1, only human allograft was applied, while in Group 2, human allograft was combined with 10 mg MEL. Group 3 received human allograft and 0.1 mg simvastatin, and Group 4 received human allograft along with 10 mg MEL and 0.1 mg simvastatin. The results after 4 and 8 weeks indicated that local application of MEL and simvastatin leads to increased new bone mass and improved bone microstructure quality. Simvastatin reduces the regeneration time more than MEL, and the combined use of simvastatin and MEL shows a synergistic effect on bone regeneration, especially in the final phase of repair.[3]

Only one dose of MEL and RSV was evaluated in the present study. Future studies on different doses are required to find the most effective dose for the enhancement of bone regeneration. Furthermore, this study evaluated the results only at one postoperative time point, so further longitudinal studies are recommended. Different forms of medications and other drug carriers should also be tested to find the most suitable drug form and carrier for this purpose. Moreover, future studies should create several defects in each calvaria in a larger animal to compare the effects of different medications on the same host. The impacts of many host-related confounders on the results would be eliminated as such. Bone grafts can also be used in combination with medications to assess their possible synergistic effects. Finally, clinical trials are required to obtain results with higher generalizability to the clinical settings.

CONCLUSION

Within the limitations of this study, our findings revealed that osteogenesis was significantly higher in the MEL and RSV groups than in the control group ($P < 0.05$) and MEL and RSV gels can be used as a stimulant of bone formation. However, further research is required to assess the bone regeneration capacity of MEL and RSV gels.

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Conflicts of interest

The authors of this manuscript declare that they have no conflicts of interest, real or perceived, financial or non-financial in this article.

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