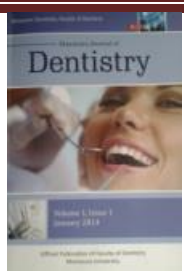
Evaluation of the Effect of Local Melatonin Gel Application in the Treatment of Intrabony Defects in Chronic Periodontitis Patients:



Dina E. AbdAllah[1],Ilham A. Elsaied[2] ,Mohamed M. Anees[3], Una M. Elshinnawi[4]
1-BDS, Faculty of Dentistry, Mansoura university, Egypt
2- Ass.Professor of pharmaceutics pharmaceutical department, Faculty of Pharmacy, Mansoura Uniersity.
3- Ass.Professor of Oral Medicine and Periodontology, Faculty of Dentistry, Mansoura university.
4- Professor of Oral Medicineand Periodontology, Diagnosis and Oral Radiology Faculty of Dentistry, Mansoura university.

Abstract:

Background: Melatonin is a free radical scavenger and has antioxidant and anti-inflammatory properties It is also has osteoinductive properties on bone. GCF osteocalcin levels are more revealing than serum or saliva levels regarding bone turnover in periodontium.
Aim: The aim of this study was to assess the effectiveness of local drug delivery of Melatonin gel as an adjunct to scaling and root planning in the treatment of moderate chronic periodontitis.
Patients and methods: Split mouth design was utilized upon fifteen chronic periodontits patients. Clinical parameters (Gingival Index, Plaque Index, Clinical Attachment Level, probing Pocket Depth) were recorded at baseline and after twelve weeks after treatment. GCF samples were collected at baseline and twelve weeks after treatment. All patients were received scaling and root planning, the test sites only were locally injected with Melatonin gel.
Results: The clinical parameters (PI, GI, PD, CAL) showed highly significant improvement in the test sites (SRP+Melatonin)
Also the test sites showed statistically high significant reduction in GCF OC than in control sites $p<0.001$.
Conclusion: The local application of melatonin gel offers a promising therapeutic approach in periodontal treatment.

Introduction

Periodonitis is a disease of the periodontium characterized by the irreversible loss of connective tissue attachment and supporting alveolar bone. Although bacterial infection and release of toxic bacterial products triggers a series of processes leading to damage of healthy tissues, a number of actions of the host' immune response is also involved. [1]

periodontal tissue destruction via osteoclastic action results in the sequestration of bone specific matrix proteins, like telopeptides type I collagen [2], osteocalcin [3]osteonectin [4], osteopontin [5] and bone phosphoprotein [6] in the gingival crevicular fluid, all of which have been positively associated with the progression of periodontal disease.[7,8]

Melatonin (N-acetyl-5-methoxytryptamine) is one such powerful hormone derived from an essential amino acid tryptophan. Melatonin (N-acetyl-5-methoxytryptamine) is one such powerful hormone derived from an essential amino acid tryptophan.[9]

Melatonin influences fibroblast activity and bone regeneration bypromoting osteoblast differentiation and bone formation and suppression of bone resorption.[10,11] Moreover, it stimulates the synthesis of type I collagen fibers.[12]Moreover, it interferes with osteoclast function, inhibiting bone resorption directly and by reducing RANKL.[13] Furthermore, melatonin was shown to increase the expression of bone sialoprotein as well as other essential bone marker proteins including alkaline phosphatase ALP and osteocalcin.[14]

Melatonin also has been shown to inhibit the inflammatory enzyme cyclooxygenase (COX-2). Melatonin reportedly binds to the active sites of COX-1 and COX-2 indicating that it may act as a natural inhibitor of the function of these enzymes and thereby be an endogenous inhibitor of inflammation.[15,16]

Melatonin could directly neutralize a variety of reactive oxygen species (ROS) including superoxide anion radical O-2, Hydrogen peroxide H2O2 and the hydroxyl radical–OH.[17,18] Increased ROS scavenging by melatonin and its metabolites in the inflamed area would be beneficial in reducing the degree of tissue damage.

The osteocalcin in the gingival fluid appeared to link well with periodontal disease and bone turnover as evidenced by significant elevations in gingival crevicular fluid osteocalcin level during the more active periods of bone loss. [(19)] Osteocalcin is currently an effective marker of bone turnover when resorption and formation are coupled and is a particular marker of bone formation when formation and resorption are uncoupled.[(20)]

Aim of the study

The aim of the study was to investigate the efficiency of local melatonin gel application as adjunct to scaling and root planning in the treatment of intrabony defects (IBDs) in moderate chronic periodontitis patients and to assess the osteocalcin levels in the gingival crevicular fluid (GCF) in those patients .

Patients and Methods

Patient selection*:*

Fifteen patients diagnosed with moderate chronic periodontitis were chosen from the Deparetment of Oral Medicine and Periodontology Clinic, Faculty of Dentistry, Mansoura University. Patients with history of antibiotic administration or periodontal therapy in the last six months or suffering from any relevant systemic disease were excluded from this study.

Study design:

A split mouth design was utilized as follow; in each patient, one site was randomly assigned to study group and the other contra lateral site to control group. Gingival crevicular fluid (GCF) samples were collected at the beginning of the study before treatment. Thorough SRP was performed using both hand scalers and ultrasonic scalers. The root surfaces adjacent to the defects were conditioned for 2 min with EDTA gel according to the instructions given by the manufacture. The defects and root surfaces were then rinsed thoroughly with sterile saline to remove EDTA remnants. Melatonin gel local drug delivery (LDD) in study sites were performed once a week for a month. Placement of placebo gel in control sites was performed. After 12 weeks GCF samples were collected from both sites.

Clinical Examination:

In order to determine the periodontal condition, a full periodontal evaluation was made for each patient including the following clinical parameters (PPD, CAL, PI, GI) at the baseline of the study and after 12 weeks follow-up period.

GCF sample collection:

*All the clinical samples were collected the following morning after patients had fasted overnight. Participants were asked to avoid brushing and drinking anything in the morning except water before sample collection**.** Two samples were collected for each patient one at baseline and the other at the end of the study.*

Laboratory assessment*:*

Enzyme linked immuno-sorbent assay (ELISA): GCF samples were assayed using ELISA technique for estimation of the level of osteocalcin.

Results:

At baseline there was no significant difference between the two sites regarding clinical parameters and laboratory investigations. Where mean and standard deviation of PD, CAL, GI, PI and OC of study site 4.56±0.62, 2.75±0.59, 1.78±0.65, 2.18±0.58 and 0.95±0.43 where on the control site 4.28±0.45, 2.54±0.38, 1.70±0.5, 2.0±0.56 and 0.84±0.32.

At the end of our study there was statistically significant difference between both sites as the PD, CAL, GI, PI and OC in the study site 2.75±0.59, 1.51±0.38, 0.38±0.19, 0.40±0.21 and 0.31±0.25 respectively where on the control site 3.19±0.51, 2.14±0.45, 1.03±0.27, 1.12±0.43 and 0.60±0.36.

Discussion:

Periodontitis is a multifactorial disease, with participation of bacterial, environmental, and host factors. We used local drug delivery system in our study which offers the controlled release of the therapeutic agent at specific subgingival sites, thus translating into high concentrations at the target site with reduced dosage for an extended period.[21]Melatonin a noval indolamin has been found to be an important modulator of the metabolism of calcium, and prevents osteoporosis and hypocalcemia in certain cases, probably due to its interaction with other bone regulatory factors, such as parathormone, calcitonin or prostaglandins.[22,23]

A key advantage of the split mouth design used in our study is due to the fact that each patient acts as his/her own control, so much of the inter-subject variability is removed, resulting in increased study power.[24] The osteocalcin in gingival fluid appeared to link well with periodontal disease and bone turnover as evidenced by significant elevations in gingival crevicular fluid osteocalcin during the more active periods of bone loss. [25]

At baseline of our study there was no statistically significant difference in all clinical parameters (PD, CAL, GI, PI) in both sites (test and control). The clinical findings of the present study reflected significant improvement of previously mentioned clinical parameters in chronic periodontitis patients after scaling and root planning in both sites.

At the end of our study the test sites showed a greater reduction in PD, and gain in CAL, a decrease in the gingival index more than in control sites. ***Cutando et al.2014,****;this study was designed to assess the effect of topical application of melatonin on the gingival on salivary RANKL, OPG and melatonin levels as well as plasma melatonin. They found that after topical melatonin application that there was a statistically significant decrease of the gingival index and proping pocket depth in the treatment of chronic periodontitis.[26]*

At baseline there was no statistical significant difference between both sites. After 12 weeks our results showed the study sites showed a statistically significant decrease in mean OC on the other hand there was no statistically significant decrease in mean OC in the control sites.

Melatonin is used in bone-grafting procedures, in reversing bone loss due to osteopenia and osteoporosis, and in treating periodontal diseases. Melatonin increases pre-osteoblast/osteoblast /osteoblast-like cell proliferation, promotes the expression of collagen type I and bone marker proteins (e.g osteocalcin), and induces the mineralized matrix formation in these cells. As a result of the direct action of melatonin on the osteoblasts cells as it induces a higher rate of maturity of pre-osteoblasts to osteoblasts, both in quantity and velocity, with a higher rate of production of the osseous matrix and its equivalent calcification.[27,28,29,30]

Conclusions:

1. *Local drug delivery of melatonin gel can be effective in the treatment of chronic periodontitis as adjunctive to SRP.*

2. *Osteocalcin level in GCF may be used as a biomarker in chronic periodontitis.*

Recommendations:

1. *Trial of melatonin gel in the treatment of periodontal diseases in surgical and non surgical modes of treatment.*
2. *Further studies should be accomplished with greater number of patients and with different treatment modalities.*

Reference:

1. *Pihlstorm BL, Michalowicz BS, Johnson NW. Periodontal diseases. Lancet 2005; 366:1809-1820.*
2. *Talonpoika JT, HÃmÃlÃinen MM. Type I collagen carboxyterminal telopeptide in human gingival crevicular fluid in different clinical conditions and after periodontal treatment. J Clin Periodontol.1994; 21:320–6.*
3. *. Lee AJ, Walsh TF, Hodges SJ, Rawlinson A. Gingival crevicular fluid osteocalcin in adult periodontitis. J Clin Periodontal. 1999; 26:252–6*
4. *Eley BM, Cox SW. Advances in periodontal diagnosis. 10. Potential markers of bone resorption. Br Dent J. 1998; 184:489–92.*
5. *Kido J, Nakamura T, Asahara Y, Sawa T, Kohri K, Nagata T. Osteopontin in gingival crevicular fluid. J Periodontal Res. 2001; 36:328–33.*
6. *. Bowers MR, Fisher LW, Termine JD, Somerman MJ. Connective tissue-associated proteins in crevicular fluid: potential markers for periodontal diseases. J Periodontal. 1989; 60:448–51.*
7. *. Bullon P, Goberna B, Guerrero JM, Segura JJ, Perez-Cano R, Martinez-Sahuquillo A. Serum, saliva, and gingival crevicular fluid osteocalcin: their relation to periodontal status and bone mineral density in postmenopausal women. J Periodontal. 2005; 76:513–9.*
8. *. Sharma CG, Pradeep AR. Gingival crevicular fluid osteopontin levels in periodontal health and disease. J Periodontal. 2006; 77:1674–80.*
9. *. KalsbeekA and Buijs R M."Output pathways of the mammalian suprachiasmatic nucleus: coding circadian time by transmitter selection and specific targeting," Cell and Tissue Research, 2002; 309:109–118.*
10. *. Koyama H, Nakade O, Takada Y, Kaku T, Lau KH. Melatonin at pharmacologic doses increasesbone mass by suppressing resorption throughdown-regulation of the RANKL-mediatedosteoclast formation and activation. J. Bone Miner.Res. 2002; 17(7):1219–1229*
11. *Cutando A, Gómez-Moreno G, Arana C, et al.Melatonin: Potential functions in the oral cavity. J.Periodontal. 2006; 78(6):1094–1102.*
12. *Nakade O, Koyama, H, Ariji H, et al.Melatonin stimulates proliferation and type I collagen synthesis in human bone cells in vitro. J. PinealRes. 1999; 27(2):106–110.*
13. *. Calvo-Guirado JL, Gómez-Moreno G, López-Marí L, Guardia J, Martínez-González JM, Barone A, et al. Actions of melatonin mixed with collagenized porcine bone versus porcine only on osteointegration of dental implants. J Pineal Res. 2010; 48:194-203.*
14. *Roth JA, Kim, BG, Lin WLet al.Melatonin promotes osteoblast differentiation and bone formation. J. Biol. Chem. 1999; 274 (31):22041–22047.*
15. *. Deng W-G, Tang S T, Tseng H P, and Kenneth K. Melatonin suppresses macrophagecyclooxygenase-2 and inducible nitric oxidesynthase expression by inhibiting p52 acetylationand binding. BLOOD, 2006; 108: 519-524*
16. *- De la Rocha N, Rotelli A, Aguilar C, et al.Structural basis of the anti-inflammatory activityof melatonin. Arzneimittelforschung. 2007;56:782-786*
17. *Lanas O, Olinescu R, and Badscu I. Melatonin involvement at oxidative processes. Endocrinology. 1991; 29: 147-153.*
18. *- Reiter R J, Manchester L C, and Dun-XianTan. Neurotoxins: Free Radical Mechanisms andMelatonin Protection. Current Neuropharmacol, 2010; 8: 194-210.*
19. *Lynch SE Giannobile WV, Denmark RG, Paquette DW, Fiorellini JP, Williams RC. ,Crevicular fluid osteocalcin and pyridinoline cross¬linked carboxyterminal telopeptide of type I collagen (ICTP) as markers of rapid bone turnover in periodontitis. A pilot study in beagle dogs. . J Clin Periodontol 1995; 22: 903-910*
20. *Sweta Vilas Kulkarni, Suruthi Meenatchi, R Reeta, Ramasamy Ramesh, A R Srinivasan, and C Lenin Association of Glycemic Status with Bone Turnover Markers in Type 2 Diabetes Mellitus doi: 10.4103/ijabmr.IJABMR_35_17 Int J Appl Basic Med Res. 2017 Oct-Dec; 7(4): 247–251.*

21. *Vandana Srikrishna Chadha ,Kapil Arora, Manjunath B C, Sarika Kalra LOCAL DRUG DELIVERY IN PERIODONTICS: CURRENT CONCEPTS AND TRENDS [INTERNATIONAL JOURNAL OF ADVANCED RESEARCH ON ORAL SCIENCES 1:1 (2012): 1 -9].*
22. *Hakanson D O, Penny R, and Bergstrom W H, "Calcemic responses to photic and pharmacologic manipulation of serum melatonin," Pediatric Research. 1987; 22: 414– 416*
23. *Z. Ostrowska, B. Kos-Kudla, M. Nowak et al., "The relationship between bone metabolism, melatonin and other hormones in sham-operated and pinealectomized rats," Endocrine Regulations, vol. 37, no. 4, pp. 211–224, 2003.*
24. *Lynch SE Giannobile WV, Denmark RG, Paquette DW, Fiorellini JP, Williams RC. ,Crevicular fluid osteocalcin and pyridinoline cross¬linked carboxyterminal telopeptide of type I collagen (ICTP) as markers of rapid bone turnover in periodontitis. A pilot study in beagle dogs. . J Clin Periodontol 1995; 22: 903-910*
25. *Nikolaos Pandis Tanya Walsh Argy Polychronopoulou Christos KatsarosTheodore Eliadessplit-mouth designs in orthodontics: an overview with applications toorthodontic clinical trials ,EuropeanJournal of Orthodontics, Volume 35, Issue 6, 1 December 2013, Pages783–789 doi.org/10.1093/ejo/cjs108.*
26. *Cutando A, Lopez-Valverde A, de Diego RG, de Vicente J, Reiter R, Fernandez MH, et al. Effect of topical application of melatonin to the gingiva on salivary osteoprotegerin, RANKL and melatonin levels in patients with diabetes and periodontal disease. Odontology 2014;102:290e6.*
27. *Satomura K[1], Tobiume S, Tokuyama R, Yamasaki Y, Kudoh K, Maeda E, Nagayama M. Melatonin at pharmacological doses enhances human osteoblastic differentiation in vitro and promotes mouse cortical bone formation in vivo.J Pineal Res. 2007 Apr;42(3):231-9*
28. *Maria S, Witt-Enderby PA. Melatonin effects on bone: potential use for the prevention and treatment for osteopenia, osteoporosis, and periodontal disease and for use in bone-grafting procedures. J. Pineal Res. 2014; 56:115–125.*
29. *Radio, N.M.; Doctor, J.S.; Witt-Enderby, P.A. Mela tonin enhances alkaline phosphatase activity in differentiating human adult mesenchymal stem cells grown in osteogenic medium via MT2 melatonin receptors and the ME K/ERK (1/2) signaling cascade. J. Pineal Res. 2006; 40: 332–342.*
30. *Sethi, S.; Radio, N.M.; Kotlarczyk, M.P.; Chen, C.T. ; Wei, Y.H.; Jockers, R.; Witt- Enderby, P.A. Determination of the minimal melatonin exposure required to induce osteoblast differentiation from human mesenchymal stem cells and these effects on downstream signaling pathways . J. Pineal Res. 2010; 49: 222–238*