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Effect of Adjunctive Supplementation of Melatonin in Periodontal Therapy in Patients with Periodontitis

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Abstract

Introduction: Association between periodontitis and obesity has been evidenced both in experimental and epidemiological studies which share common risk factors. Melatonin is a natural hormone secreted in the pineal gland. It is suggested that melatonin may be useful in treatment of periodontal diseases through reducing the oxidative stress, stimulating immune response and reducing progressive loss of alveolar bone. Therefore, it is suggested that melatonin supplementation along with non-surgical periodontal therapy may play an important role in control of both diseases. There are no human studies on the effect of melatonin in these two diseases simultaneously, so the aim of the study was to evaluate the effect of melatonin supplementation adjunctive to non-surgical periodontal therapy in periodontitis patients with obesity.

Materials and Methodology: A total of 30 subjects (Group 1 - 15 periodontitis subjects and Group 2 - 15 periodontitis with obesity subjects) were included in this study. Clinical periodontal parameters including probing pocket depth, clinical attachment loss, gingiva index and plaque index were recorded at baseline, 1 months and 3 months of therapy.

Results: In the obese-periodontitis group, adjunctive melatonin administration resulted in stastically significant reduction in periodontal clinical parameters at 3 months of therapy.

Conclusion: Within the limitations of the present study, it can be concluded that melatonin supplementation might serve as a viable adjunct to periodontal therapy that yielded statical significant reduction in clinical parameters in periodontitis with obesity. Hence, melatonin can be used as an adjunct in the treatment of periodontitis and obesity.

Keywords: Melatonin, Periodontitis, Probing pocket depth, Clinical attachment loss

Introduction

Periodontal disease is a chronic form of inflammation. Damage of periodontal tissues is caused by the direct effect of the toxic products released by bacteria and from the action of the immune system stimulated by the bacterial infection. A notable feature of periodontal diseases is the generation of free radicals, some derived from the bacteria themselves, and others as a consequence of the immune responses. The increased reactive oxygen and nitrogen species that occur in periodontal disease are responsible for the oxidative damage to the periodontal tissues. Also, the increase in free radical generation co-exists with a decrease in the antioxidant defence mechanisms. This imbalance between the pro-oxidant and antioxidant systems may lead to a further oxidative attack and a marked deterioration of the periodontal tissues.[1,2]

Melatonin (N-acetyl 5-methoxytryptamine) is a well-studied endogenous indoleamine that regulates the sleep/waking cycle and is largely released by the pineal gland. In general, about 30% of adults in various nations reported one or more symptoms of insomnia, including difficulties falling asleep, problems staying asleep, getting up too early, and, in some cases, non-restorative or poor quality sleep[3,4]. In elderly persons with insomnia, exogenous melatonin supplementation was demonstrated to increase sleep quality and morning alertness.

Melatonin also has anti-inflammatory, antioxidant, on costatic, as well as neuroprotective properties.[5, 6] Salivary melatonin levels were found to be considerably lower in periodontal disease patients, suggesting that melatonin could be employed as a biomarker for periodontal diagnosis and as a potential therapy in various periodontal illnesses. Melatonin is seen to employ its effect on the oral cavity as an antioxidant and free radical scavenger, an immune modulator and promote bone formation. It is released during night and diffuses passively into saliva through the bloodstream, and can be reliably examined.[7]

Melatonin appears to be a significant modulator of the immune system as it improves the natural and acquired immunity in vivo, and activates monocytes and neutrophils. Melatonin has an anti-inflammatory effect and is chemotactic for cultured chick retinal pigment epithelial cells. It also encourages type I collagen synthesis and stimulates bone formation.[8, 9] The relationship between periodontal status and melatonin levels is still indistinct and inconclusive.

Obesity plays a role in modulating the initiation and progression of periodontal disease. Recent meta-analyses have demonstrated a positive link between overweight/obesity with periodontitis[10] Melatonin is an indoleamine that is synthesized and secreted in pineal gland. It is difficult to allocate a single specific function to melatonin as it is involved in various physiological and behavioural processes.[11,12]

However, the relationship between periodontal diseases and melatonin level remains unknown. There are limited studies in the literature that evaluate the effect of melatonin in periodontal disease. Hence, the present study was conducted to evaluate the effect of melatonin supplementation adjunctive to non-surgical periodontal therapy in periodontitis patients with obesity.

Materials and methods

Patients reporting to the outpatient Department of Periodontology, Faculty of Dental Sciences, Ramaiah University of Applied Sciences, Bangalore were recruited for this study and ethical clearance for the present study was obtained from the institutional ethics committee. Patients reporting to the Department of Periodontology diagnosed with periodontitis were selected for this study. The aim of the study and the

sample collection method were explained in detail to the patients before collecting sample. Written informed consent was obtained from the patients who agreed to participate in this study. The study was carried out after obtaining ethical clearance from the ethics committee of Ramaiah University of Applied Sciences, Bangalore.

Subjects with age 18 to 65 yrs. Patients with periodontitis should have at least 20 teeth having pocket depth ≥5 mm and at least three sites in each quadrant with clinical attachment loss ≥4 mm (CAL) and radiographic evidence of bone loss. Patients with periodontitis and obesity having Body mass index BMI (≥25) were included and patient with diabetes mellitus, Smokers, patients with autoimmune diseases or osteoporosis, users of antibiotics or non- steroidal anti-inflammatory drugs within the last 3 months and patients who were subjected to any periodontal therapy during the last year were excluded from the study

Demographic details that included name, age, gender and occupation were recorded for all the patients. Medical history and Body Mass Index (BMI) were also recorded. BMI was calculated by measuring the height (in centimeters) and weight (in kilograms) of the patient. If the BMI of the patient was >25, then the patient was said to be obese and were included in Group 2.

Patients were included in groups 1 and 2 if they were diagnosed with periodontitis. The clinical periodontal parameters Gingival Index (GI), Plaque Index (PI), Probing Pocket Depth (PPD), Clinical Attachment Level (CAL) were recorded at six sites per tooth using a UNC-15 periodontal probe for all the 2 groups.

Body Mass Index (BMI) were also recorded. BMI was calculated by measuring the height (in centimeters) and weight (in kilograms) of the patient. If the BMI of the patient was >25, then the patient was said to be obese and were included in the study.

Patients who underwent SRP were supplemented with tablet melatonin 3 mg daily at night for 4 weeks. Clinical parameters were recorded at baseline, 1 months and 3 months of therapy.

Statistical Analysis

Statistical Package for Social Sciences [SPSS] for Windows, Version 22.0 Released 2013 Armonk, NY: IBM Corp., will be used to perform statistical analyses. The frequency distribution for categorical data will be expressed in terms of number & percentage, whereas for continuous data, it will be expressed in frequency, mean, and standard deviation (SD).Independent Student t test will be used to compare mean Clinical parameters [PI, GI, PPD & CAL] between two groups at different time intervals [Baseline, 3 & 6 months post treatment intervals].Repeated measures of ANOVA followed by Bonferroni Post hoc Analysis will be used to compare the mean clinical parameters between different time intervals in each study group. The level of significance will be set at $P<0.05$

Results

Gingival Index at baseline, of group 1, where mean of 15 and mean value is 2.40 with a standard deviation of 0.28 and in group 2, mean of 15 mean value 2.30 with a standard deviation of 0.24 with mean difference of 0.10 showed p-value of 0.31 which is not stastically significant. Comparison was done using independent student t test. At 1 month, GI of group 1, where mean of 15, mean value is 1.49 with an standard deviation of 0.23 and in group 2, where mean of 15 mean value is 1.29 with an standard deviation of 0.25 with mean difference of 0.20 showed p-value of 0.03 which is not stastically significant. Similarly, At 3 month, GI of group 1, where mean of 15, mean value is 0.83 with a standard deviation of 0.36 and in group 2, where mean of 15, mean value is 0.57 with a standard deviation of

0.24 with a mean difference of 0.26 showed P-value of 0.03 which is not stastically significant.

Intergroup comparison of GI among 2 groups was done using Bonferroni's post hoc test. Statistically significant results were observed on comparing Group 1 versus Group 2 (p<0.001).

Plaque Index at baseline, PI of group 1, where mean of 15 and mean value is 2.73 with a standard deviation of 0.20 and in group 2, mean of 15 mean value 2.64 with a standard deviation of 0.17 with mean difference of 0.09 showed p-value of 0.21 which is not stastically significant. Comparison was done using independent student t test.

At 1 month, PI of group 1, where mean of 15, mean value is 1.83 with a standard deviation of 0.14 and in group 2, where mean of 15 mean value is 1.71 with a standard deviation of 0.16 with mean difference of 0.12 showed p-value of 0.03 which is not stastically significant. Similarly, At 3 month, PI of group 1, where mean of 15, mean value is 1.29 with a standard deviation of 0.30 and in group 2, where mean of 15, mean value is 1.03 with a standard deviation of 0.21 with a mean difference of 0.27 showed P-value of 0.009 which is not stastically significant.

Intragroup comparison of PI was done for 2 groups using One-way ANOVA test where the mean values at baseline were 2.73+-0.20, 2.64+-0.17 and at 1 month were 1.83+-0.14, 1.71+-0.16 and at 3 month 1.29+-0.30, 1.03+-0.21 for periodontitis and periodontitis with obesity group respectively which was statistically significant. Intergroup comparison of GI among 2 groups was done using Bonferroni's post hoc test. Statistically significant results were observed on comparing Group 1 versus Group 2 (p<0.001).

At baseline, PD of group 1, where mean of 15 and mean value is 5.80 with a standard deviation of 0.56 and in group 2, mean of 15 mean value 5.53 with a standard deviation of 0.52 with mean difference of 0.27 showed p-value of 0.19 which is not stastically significant. Comparison was done using independent student t test.

At 1 month, PD of group 1, where mean of 15, mean value is 3.53 with a standard deviation of 0.52 and in group 2, where mean of 15 mean value is 3.07 with a standard deviation of 0.26 with mean difference of 0.46 showed p-value of 0.004 which is not stastically significant. Similarly, At 3 month, PD of group 1, where mean of 15, mean value is 3.20 with an standard deviation of 0.56 and in group 2, where mean of 15, mean value is 2.40 with an standard deviation of 0.51 with an mean difference of 0.80 showed P-value of <0.001 which is stastically significant.

Intragroup comparison of PD was done for 2 groups using One-way ANOVA test where the mean values at baseline were 5.80±0.56, 5.53±0.52 and 1 month were 3.53+-0.52, 3.07+-0.26 and at 3 month 3.20+-0.56,2.40+-0.51 for periodontitis and periodontitis with obesity group respectively which was statistically significant. Intergroup comparison of PD among groups was done using Bonferroni's post hoc test. Statistically significant results were observed on comparing Group 1 versus Group 2 (p<0.001).(Table:1 & Graph :1)

At baseline, CAL of group 1, where mean of 15 and mean value is 7.80 with a standard deviation of 0.56 and in group 2, mean of 15 mean value 7.53 with a standard deviation of 0.52 with mean difference of 0.27 showed p-value of 0.19 which is not stastically significant. Comparison was done using independent student t test.

At 1 month, CAL of group 1, where mean of 15, mean value is 5.53 with a standard deviation of 0.52 and in group 2, where mean of 15 mean value is 5.07 with a standard deviation of 0.46 with mean difference of 0.46 showed p-value of 0.01 which is stastically significant.

Similarly, at 3-month, CAL of group 1, where mean of 15, mean value is 5.20 with a standard deviation of 0.56 and in group 2, where mean of 15, mean value is 4.53 with a standard deviation of 0.52 with a mean difference of 0.67 showed P-value of 0.002 which is not stastically significant.

Intragroup comparison of CAL was done for 2 groups using One-way ANOVA test where the mean values at baseline were 7.80+-0.56, 7.53+-0.52 and at 1 month 5.53+-0.52, 5.07±0.46 and at 3 month were 5.20+-0.56, 4.53+-0.52 for periodontitis and periodontitis with obesity group respectively which was statistically significant. Intergroup comparison of CAL among 2 groups was done using Bonferroni's post hoc test. Statistically significant results were observed on comparing Group 1 versus Group 2($p<0.001$).(Table:2 & Graph:2)

Discussion

The goal of this study was to see how well melatonin supplementation worked in conjunction with non-surgical periodontal therapy in periodontitis patients. The combination of melatonin and SRP increased clinical attachment gain and reduced Probing pocket depth. It was previously established that SRP alone as the cornerstone of conventional periodontal therapy has the potential to improve all periodontal parameters in periodontitis patients. However, SRP alone as a therapeutic standard modality failed to halt progressive attachment loss in some patients. Thus, adjunctive therapeutic agents to SRP were explored and yielded better clinical improvements in the treatment of periodontal disease. In the present study, there was an appreciable effect of melatonin combined with SRP on PD reduction and CAL gain after 3 months. Further indicating that melatonin is a potential adjunctive therapy for improving periodontitis.[13,14]

In this study, the melatonin effect on the clinical periodontal parameters appears to be dependent on its anti-inflammatory and antioxidant properties. This might be explained as the anti-inflammatory property of melatonin is linked to its ability to act as a scavenger of exogenous and endogenous reactive oxygen species (ROS) and reactive nitrogen species (RNS) and subsequently, down-regulating the pro-inflammatory cytokines released in the periodontal tissues.[15]

The adopted melatonin dose in the present study seems to be an effective and safe adjunctive therapy to SRP in obese people with periodontitis. As anticipated, SRP alone was effective in reducing BOP score, PD and increasing CAL gain compared to baseline measurements.[16]. In our results, the obese group exhibited greater PD reduction and more CAL gain compared to periodontitis group. Of interest, topical application of melatonin as an adjunctive oral hygiene measure produced similar findings and decreased systemic inflammation.

In our study, daily oral melatonin intake before bedtime has improved gingival index and plaque index for periodontitis patients. Our findings showed improvement in clinical periodontal parameters. More importantly, the used regimen of 3 mg melatonin once daily for 2 months in our study has a maintained effect in improving clinical parameters for 3 months without any observed rebound effect after discontinuation of melatonin intake during the whole study period. However, they used melatonin with vitamin c in their study.[17,18]

Based on data of future clinical trials, systemic melatonin might be used as a reliable adjunctive therapy for periodontitis in patients with obesity.[19,20,21] In conclusion, our data indicate that dietary melatonin supplementation of 3 mg capsule once daily for 2 months when used as an adjunctive therapeutic agent to

SRP significantly improved periodontal treatment outcomes in individuals with obesity and periodontitis.

While our findings indicate stastically significant reduction in periodontal clinical parameters by systemic administration of dietary melatonin supplementation in conjunction with SRP in periodontitis patients and obesity, important limitations of this study are sample size is not large enough to be generalizable for larger population. However, melatonin showed no detectable adverse effects in this study, studies for a minimum of 1 year are warranted to test different doses, safety, and efficacy of melatonin to be prescribed for obese patients with periodontitis. In light of the above finding, within the limitation melatonin can be prescribed as an adjunct to SRP for periodontitis with obesity.

Conclusion

Melatonin is a neuroendocrine hormone, which plays not only an important antioxidant role, but also an immune modulatory role.in the present stastically significant reduction is seen in clinical parameters and pocket depth reduction in periodontitis and obesity group. Hence, melatonin can be used as an adjunct with SRP in the treatment of periodontitis with obesity.

To the best of our knowledge, this is the first study to be conducted to evaluate the effect of melatonin supplementation in periodontitis and obesity. Within the limitations of the present study, it can be concluded that the melatonin supplementation might serve as a viable adjunct to SRP that yielded stastically significant reduction in periodontal clinical parameters in periodontitis and obesity. Further longitudinal studies need to be conducted with a larger sample size. Multi Centre studies with larger samples are required to confirm the findings of this study.

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Legend Tables and Figures

Table 1: Comparison of mean PD values b/w time intervals in each study group**.**

Comparison of mean PD values b/w time intervals in each study group using Repeated Measures of ANOVA Test followed by Bonferroni's Post hoc Test							
Groups	Time	N	Mean	SD	P-Value [a]	Sig. Diff	P-Value [b]
Group 1	Baseline	15	5.80	0.56	<0.001*	BL vs 1M	<0.001*
	1 Month	15	3.53	0.52		BL vs 3M	<0.001*
	3 Months	15	3.20	0.56		1M vs 3M	0.04*
Group 2	Baseline	15	5.53	0.52	<0.001*	BL vs 1M	<0.001*
	1 month	15	3.07	0.26		BL vs 3M	<0.001*
	3 Months	15	2.40	0.51		1M vs 3M	<0.001*

Graph 1: Mean PD levels between different time intervals in each group.

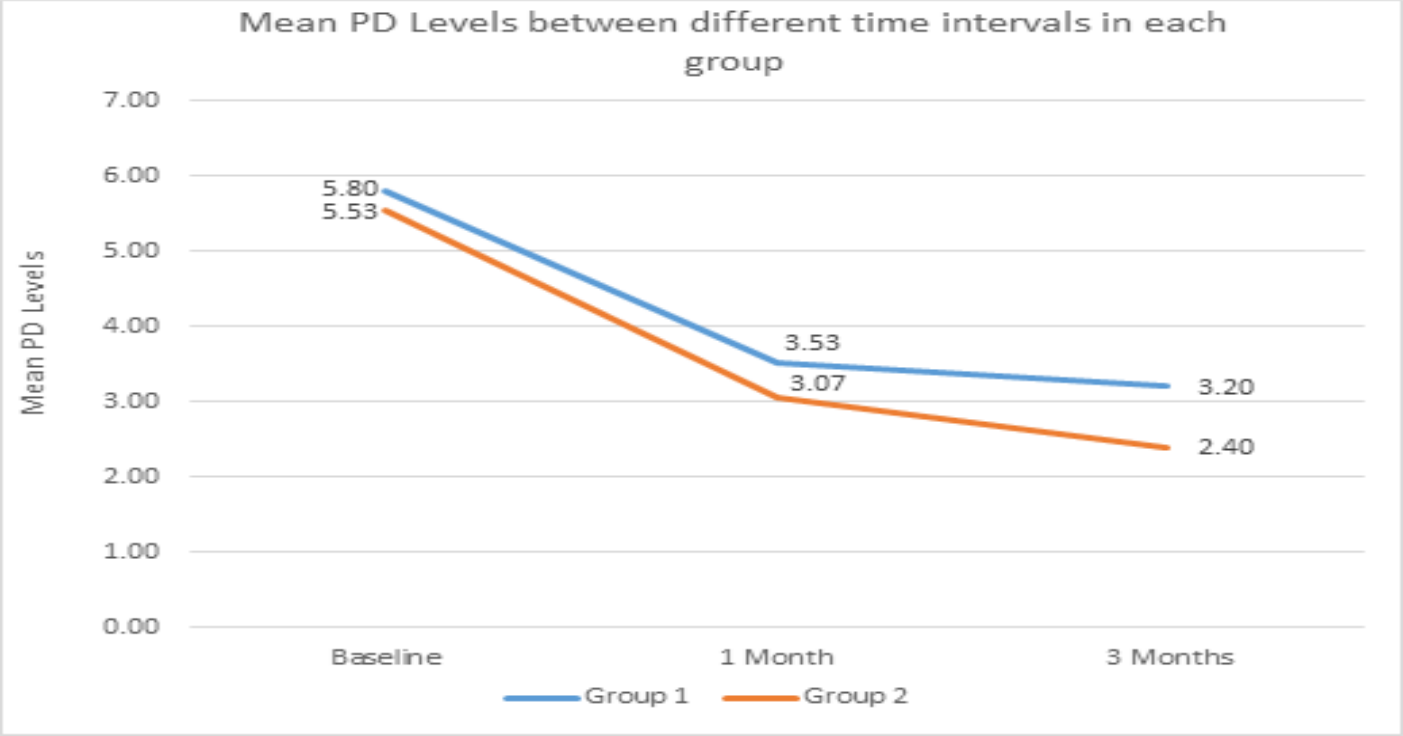

Table 2: Comparison of mean CAL values b/w time intervals in each study group.

Comparison of mean CAL values b/w time intervals in each study group using Repeated Measures of ANOVA Test followed by Bonferroni's Post hoc Test							
Groups	Time	N	Mean	SD	P-Value [a]	Sig. Diff	P-Value [b]
Group 1	Baseline	15	7.80	0.56	<0.001*	BL vs 1M	<0.001*
	1 Month	15	5.53	0.52		BL vs 3M	<0.001*

	3 Months	15	5.20	0.56		1M vs 3M	0.04*
Group 2	Baseline	15	7.53	0.52	<0.001*	BL vs 1M	<0.001*
	1 Month	15	5.07	0.46		BL vs 3M	<0.001*
	3 Months	15	4.53	0.52		1M vs 3M	<0.001*

Graph 2: Mean CAL values between different time intervals in each group.