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Efficacy Of Supplementary Melatonin as Adjunct to Surgical Periodontal Therapy on Periodontal Parameters: A Pilot Study

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ABSTRACT

Aim: To evaluate the effect of two dosages of systemically administered melatonin compared to a placebo on clinical parameters in adjunct to regenerative surgical periodontal therapy.

Material And Methods: 30 subjects with Stage III Grade A/B periodontal disease indicated for surgical periodontal therapy were recruited. Group I received 3mg melatonin (n=10), group II received 6 mg melatonin (n=10) and the control group received a placebo (n=10), once a day, for one month. Clinical parameters assessed: Probing Depth (PD), Clinical Attachment Levels (CAL), Gingival Index (GI) and Plaque Index (PI) evaluated at 3 months from baseline. Obtained data analysis done using SPSS software version 23 (Statistical Package for the Social Sciences, SPSS, version 21). Data normality tested using Shapiro-Wilk and Kolmogrov Smirnov tests. One way Anova test was done for intergroup analysis, paired-t test was used to compare all the parameters between different time intervals within each group. In all the tests, the p value of < 0.05 was considered to be statistically significant.

Results: All groups showed significant improvement at follow up in the intra-group analysis on all clinical outcomes. A one-way ANOVA test was performed to evaluate the effect on clinical outcomes between each group. Tukey's HSD comparisons found a statistically significant difference in both intervention groups compared to placebo in PD reduction and gingival index values ($p< 0.05$). However, 6 mg melatonin was seen to have higher differences compared to 3mg melatonin and placebo group in CAL outcomes.

Conclusion: Oral administration melatonin after surgical periodontal management resulted in significant improvement in clinical parameters. 6mg melatonin was more effective in improving clinical parameters compared to 3mg melatonin. However, further studies involving a longer follow up period would be desirable to substantiate the current results.

Keywords *Dysbiosis, Inflammation, Melatonin, Periodontal disease*

INTRODUCTION

A chronic inflammatory condition known as periodontitis is the result of a number of bacterial and host factors that were previously only thought to be pathogen-induced 1. Dysbiosis between the host and the pathogen includes disproportionate immune responses, the breakdown of the periodontium and its supporting structures, release of reactive oxygen species (ROS) , reactive nitrogen species (RON), and enzyme imbalances 2. Scaling and root planing are two mechanical nonsurgical periodontal therapy methods for treating periodontal disease 3. However, these methods alone are insufficient to reduce bacterial loads and do not guarantee the resolution of inflammation in the periodontal pocket.4 As a result, systemic, local, and topical adjuncts have been developed to enhance the effectiveness of mechanical periodontal therapy 5.

Melatonin is one such alternative being used to treat periodontal disease alongside nonsurgical and surgical periodontal therapy 6. Pineal gland, situated in the midline of the brain, is responsible for producing this endogenous hormone 7. It is connected to the third ventricle and is mediated by the suprachiasmatic nucleus. Melatonin is also secreted by extra pineal organs, including the retina, spleen, bone marrow, testicles, and ovaries. Melatonin does not have a specific target organ; instead, because of its lipophilic properties, it affects all cellular components, including the mitochondria and nucleus 8. Melatonin is therefore essential for many physiological processes, including the control of the circadian rhythm, immune response, ovarian physiology, etc.

Melatonin's antioxidant abilities have been extensively researched. Strong free radical scavengers, melatonin and its metabolites trigger mechanisms that activate enzymes with antioxidant activity 9. Melatonin being a potent antioxidant, is concentrated in the mitochondria, playing a protective role against DNA damage, protein oxidation, and lipid peroxidation 10. Other characteristics of the indoleamine hormone include stimulation of transcription activity and inhibition of the formation of the hydroxyl free radicals. By lowering levels of ROS and RANKL, which promote osteoclastogenesis and oxidative stress within the tissue and result in local destruction, melatonin hormone reduces bone resorption. In addition to promoting angiogenesis at sites of bone resorption, melatonin also increases the chondrogenic and osteogenic differentiation, proliferation, migration of mesenchymal stem cells 11. These actions together with the action of increasing VEGF levels promote healing and the avoidance of ischemic injuries. Hence, melatonin supplementation could be used as adjunctive therapy during the treatment of periodontal disease management.12–21

The effectiveness of systemically administered melatonin on the outcome periodontal disease management as an adjunct in the treatment of periodontal disease is yet to be studied, hence the aim of this study was to evaluate the effects of using two dosages of systemically administered melatonin compared to a placebo on clinical parameters in adjunct to regenerative surgical periodontal therapy.

MATERIALS AND METHODS

Patient selection

In this prospective, single blinded, single center, randomized placebo controlled clinical trial, 30 systemically healthy patients with Stage III Grade A/B periodontal disease were recruited within the periodontics department of Saveetha Dental College and Hospitals, Chennai, India. These 30 subjects were randomly allocated into intervention (melatonin 3mg n1= 10, melatonin 6 mg n2= 10) and placebo group (n=10) by coin toss method. The research protocol was approved by the institution research board (Saveetha Research Board). All the subjects recruited were informed about the treatment and follow up protocol and an informed written consent was taken prior to intervention.

Inclusion and exclusion criteria

The inclusion criteria was as follows: systemically healthy males and females (n=14 and 16 respectively) between 20-50 years of age; Stage III Grade A/B periodontal disease (according to the 2017 American Academy of

Periodontology classification). Less than 6 missing teeth, probing depth (PD) of ≥ 5 mm and clinical attachment loss (CAL) of ≥ 4 mm.

Subjects were excluded if they had systemic diseases like: diabetes, hypertension, cardiovascular disease and thyroid disorders, smokers, pregnant and lactating women, subjects on immunosuppressants, insulin, antibiotics, antiresorptive drugs such as bisphosphonates, mood modulators and sedatives. Previous history of periodontal surgery, use of antioxidants, antiinflammatory drugs and any dietary changes over the past six months.

Study design

30 Stage III Grade A/B subjects with periodontal disease and completed phase 1 therapy (non-surgical periodontal therapy) indicated for phase 2 (surgical periodontal therapy) were divided into 3 groups. Group I received 3mg of melatonin supplementation, Group II received 6 mg of melatonin supplementation (Health vit, West Coast Pharmaceutical Works, India) containing calcium carbonate, dibasic calcium phosphate, anhydrous lactose, maize starch and 3/6 mg melatonin respectively. Group III received a placebo tablet containing starch, cellulose, silicon dioxide and magnesium stearate (Herbalife, India). The patients asked to take each of the tablets once a day one hour before bedtime for one month.

Subjects were asked to report side effects from the drug allocated to them during the course of the study. The patients were asked to report one month after flap surgery to assess the compliance of the subjects. At the follow up visit, if less than 90% of the prescribed tablets were consumed, the subject was excluded from the study.

Outcome Measures

At the start of treatment and after three months, periodontal charting was performed. At baseline and after three months, the operator (IR)measured the gingival index (GI), plaque index (PI), probing depth (PD), and clinical attachment levels (CAL). Measurement of PD and CAL done with UNC-15 probe.

Clinical Procedure

After an initial examination and treatment planning, all of the individuals received oral hygiene instructions on how to control plaque, and scaling and root planing (SRP) was carried out. Following SRP for two weeks, patients were instructed to use a 0.2% chlorhexidine mouthwash twice daily. Subjects of both groups underwent full mouth open flap debridement, both the groups received Amoxicillin 500 mg - three times a day.

Patients in the first two groups were prescribed 3 and 6 mg of melatonin respectively, once daily an hour before bedtime and a placebo tablet was given to patients in group III similarly.

Three months following surgery, clinical findings were assessed. The following measurements were made: clinical attachment levels, plaque index, gingival index and probing depth.

Statistical analysis

The entire set of data was entered into a Microsoft Excel spreadsheet and examined with SPSS for Windows (version 21 of the Statistical Package for the Social Sciences). With the application of the Shapiro-Wilk and Kolmogorov-Smirnov tests, the data's normality was determined. Parametric tests were chosen because the data was normally distributed. Paired t-tests were conducted to compare Group I, Group II, and Group III within each group for PD, CAL, GI, and PI at baseline and three months after intervention.

One-way ANOVA was used to compare baseline and follow-up intergroup analyses for all the specified parameters between Group I, Group II, and Group III. A p value of <0.05 was regarded as statistically significant for all tests.

RESULTS

a. Overview

In this clinical trial, 30 patients with periodontal disease were divided into three groups and given either melatonin (3 mg), melatonin (6 mg), or a

placebo. The patients were monitored throughout the study which consisted of 16 females and 14 males between the ages of 20 and 50. None of the subjects reported any negative outcomes.

Clinical parameters assessed were Probing Depth (PD), Clinical Attachment Level (CAL), Gingival Index (GI) and Plaque Index (PI) measured at baseline and 6 months.

b. Clinical outcomes

In the intra-group analysis, all three groups displayed statistically significant improvements from the baseline to the follow-up period (mean parameter change ± standard deviation) (table 1). At three months, the mean of the clinical parameters (PD, CAL, GI, and PI) in the intervention groups (Group I and Group II) significantly decreased when melatonin supplementation was combined with surgical periodontal therapy. Clinical parameters improved in subjects receiving RSPT in the placebo group as well; 3 months following the intervention, the mean levels of PD, CAL, GI, and PI considerably increased. Significant differences were seen between Groups I, II, and III when comparing the mean changes in PD, CAL, and GI from the baseline to the follow-up period. Between the two groups, there were no significant variations in PI ($p>0.05$).

i. Probing depth

In order to compare the impact on Probing depth levels, a one-way ANOVA was used. When the placebo group was contrasted with both intervention groups, Tukey's HSD Test for multiple comparisons revealed a significant difference in the mean value of PD ($p = 0.00$) (Table 2). When compared to each other, there was no statistically significant difference between 3 mg and 6 mg of melatonin ($p=0.16$).

ii. Clinical Attachment Levels

The effect on CAL levels was compared using a one-way ANOVA. When 6mg of melatonin was compared to either 3mg or placebo, Tukey's HSD Test for multiple comparisons revealed that the mean value of CAL was significantly different ($p = 0.00$). (Table 2) Comparing 3mg melatonin with placebo control, there was no statistically significant difference observed ($p=0.98$).

iii. Gingival and Plaque Indices

A one-way ANOVA was performed to compare the effect on GI. Tukey's HSD Test for multiple comparisons found that the mean GI was significant when 3 and 6mg melatonin was compared to placebo ($p = 0.00$). (Table 3)

A one-way ANOVA was performed to compare the effect on PI levels. Tukey's HSD Test for multiple comparisons found that there was no statistically significant difference between either groups when compared to each other ($p=0.98$). (Table 3)

TABLE 1: Intragroup comparison of clinical parameters from baseline to follow up (3 months).

Parameter	Groups	Baseline (mean ± std. deviation)	Followup (mean ± std. deviation)	p Value
PD	Melatonin (3mg)	7.66 ± 0.74	3.020 ± 0.39	0.000*
	Melatonin (6mg)	7.63 ± 1.22	2.427 ± 0.45	0.000*
	Placebo	7.51 ± 0.97	4.765 ± 1.05	0.001*
CAL	Melatonin (3mg)	7.60 ± 1.26	5.37 ± 0.72	0.001*
	Melatonin (6mg)	7.54 ± 1.40	3.64 ± 1.15	0.000*
	Placebo	7.48 ± 1.23	5.45 ± 1.04	0.030*
GI	Melatonin (3mg)	3.85 ± 0.54	1.80 ± 0.32	0.000*
	Melatonin (6mg)	3.97 ± 0.58	2.05 ± 0.59	0.000*
	Placebo	3.72 ± 0.56	2.45 ± 0.24	0.000*
PI	Melatonin (3mg)	3.82 ±0.55	2.53 ± 0.22	0.000*
	Melatonin (6mg)	4.07 ± 0.65	2.57 ± 0.51	0.003*

	Placebo	3.58 ± 0.42	2.45 ± 0.25	0.050*

PD:Probing Depth (mm), CAL: Clinical Attachment Level (mm), GI: Gingival Index, PI: Plaque Index *Significance: p<0.05

TABLE 2: Comparison of Probing Depth and Clinical Attachment Levels between group I, II and III at follow-up.

Clinical Parameter: (PD)	Groups	Mean difference (at 3 months)	p Value
Melatonin (3 mg)	Melatonin (6mg)	0.593	0.162
	Placebo	-1.745*	0.000*
Melatonin (6mg)	Melatonin (3mg)	-0.593	0.162
	Placebo	-2.338*	0.000*
Placebo	Melatonin (3mg)	1.745*	0.000*
	Melatonin (6mg)	2.338*	0.000*
Clinical Parameter: (CAL)	Groups	Mean difference (at 3 months)	p Value
Melatonin (3 mg)	Melatonin (6mg)	1.730*	0.002*
	Placebo	-0.080	0.982
Melatonin (6mg)	Melatonin (3mg)	-1.730*	0.002*
	Placebo	-1.810*	0.001*
Placebo	Melatonin (3mg)	0.080	0.982
	Melatonin (6mg)	1.810*	0.001*

PD- Probing Depth (mm), CAL- Clinical Attachment Levels (mm); *Significance: p<0.05

*Significance: p<0.05

TABLE 3: Comparison of Gingival and Plaque Index values between group I, II and III at follow-up (3 months).

Clinical Parameter: (GI)	Groups	Mean difference at 3 months	p Value
Melatonin (3 mg)	Melatonin (6mg)	-0.250	0.038
	Placebo	-0.650*	0.005*
Melatonin (6mg)	Melatonin (3mg)	0.250	0.038
	Placebo	-0.400	0.101
Placebo	Melatonin (3mg)	0.650*	0.005*
	Melatonin (6mg)	0.400	0.010*
Clinical Parameter: (PI)	Groups	Mean difference at 3 months	p Value
Melatonin (3 mg)	Melatonin (6mg)	-0.040	0.965
	Placebo	0.080	0.870
Melatonin (6mg)	Melatonin (3mg)	0.040	0.965
	Placebo	0.120	0.732
Placebo	Melatonin (3mg)	-0.080	0.870
	Melatonin (6mg)	-0.120	0.732

GI- Gingival Index, PI- Plaque Index; *Significance: p<0.05

DISCUSSION

A chronic inflammatory condition called periodontitis results in the breakdown of the periodontium's attachment network.2 Pathologic biofilm and subgingival microbiota are the main indicators of this condition, and an accentuated

host immune response is what causes it to progress.22 Reactive oxygen and nitrogen species, proinflammatory cytokines, and inflammatory mediators were released as a result, causing tissue damage and alveolar bone loss.23 Complete mechanical debridement with both non-surgical and surgical periodontal therapy was able to reduce the bacterial burden. Drugs that are administered systemically and have the dual effects of being an antioxidant and an anti-inflammatory are prescribed.

Because of its anti-inflammatory and antioxidant properties, immunomodulation abilities, and osteogenic potential, the hormone melatonin, which is produced endogenously, could serve as adjunct to both nonsurgical and surgical therapy for chronic periodontal disease.24,25 Furthermore, the gingiva itself is an extrapineal site of melatonin biosynthesis. The presence of MT1 (melatonin 1) receptors in gingiva exerts receptor-mediated effects in the oral cavity.26 Different concentrations of melatonin have been studied in order to determine its diverse range of actions, relative safety, and low incidence of negative effects.27 As shown in the current experiment, melatonin was well tolerated by all patients and had no negative side effects, in contrast to other adjuncts.

To the best of our knowledge, this is the first study examining the effects of melatonin administration as a supplementary treatment for patients with severe periodontal disease who are undergoing surgical periodontal therapy. Melatonin's application as an adjuvant in patients receiving non-surgical periodontal therapy has been researched. 28,29

In the current study, melatonin supplementation with 3 and 6 mg melatonin tablets along with surgical periodontal therapy significantly decreased clinical parameters (probing depth, clinical attachment level, gingival index and plaque index) at followup. Out of which, 6 mg melatonin showed statistically significant differences in clinical attachment levels. Correspondingly, significant differences were seen with respect to clinical parameters in the placebo group after RSPT at follow up. Similar findings were the association of melatonin with non-surgical periodontal therapy exerted statistically significant improvements, in periodontal parameters (PD and CAL), with a significant decrease in periodontal disease severity was observed. In the current trial no significant difference in mean plaque index was observed at follow-up between group I and group II. 29,30

The effect of melatonin supplementation on clinical periodontal parameters are due to anti-inflammatory, anti-oxidant properties and osteoblast promotion.27 Melatonin's anti-inflammatory properties are related to its capacity to scavenge exogenous and endogenous ROS) and RNS and to suppress the production of pro-inflammatory cytokines in periodontal tissues.31

Researchers have found that Porphyromonas gingivalis (Pg) and other periodontal pathogens produce virulence factors (lipopolysaccharides, fimbriae, and outer membrane vesicles) that cause the host to produce cytokines and chemokines, which causes bone loss.32 Melatonin was found to suppress COX-2 expression and nuclear factor kappa B (NF-B) activation, which were both induced by Pg fimbriae. This, combined with the stimulation of type I collagen fiber production and the modulation of osteoblastic and osteoclastic activity mediated by cellular proteins, results in the regeneration of alveolar bone. 32,33

To the best of our knowledge, none of the existing literature studies have evaluated clinical outcomes of comparing the outcomes of two dosages of melatonin supplementation versus a placebo in the treatment of periodontal disease. The current study reported that oral administration of melatonin after surgical periodontal therapy in patients with periodontal disease, resulted in significant improvement in clinical parameters compared to that of a placebo. Therefore, melatonin could be used as an effective adjunct to surgical periodontal therapy.

CONCLUSION

Oral administration of both the dosages of melatonin after Regenerative Surgical Periodontal Therapy in patients with periodontal disease, resulted in statistically significant

improvement in clinical parameters compared to that of a placebo. 6mg of melatonin showed significant improvements in clinical parameters. However, further studies with a longer follow up period would be desirable to substantiate the current results.

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