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Evaluation of locally delivered 1.2% Atorvastatin gel versus 2% melatonin gel as adjunctive to non-surgical periodontal therapy on GCF osteocalcin level in stage II periodontitis patients: a randomized controlled trial

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ABSTRACT

Objective: Atorvastatin (ATV) and melatonin have antioxidant and anti- inflammatory properties and were suggested to have positive effect when used in periodontitis cases. In periodontitis, osteocalcin (OC) was suggested to be a bone formation marker. Regarding bone turnover in periodontium, gingival crevicular fluid (GCF) osteocalcin levels are more accurate than salivary or serum levels.

Aim: The aim of the present study was to assess the effectiveness of local delivery of ATV gel and melatonin gel as adjuncts to scaling and root planning (SRP) in the treatment of stage II periodontitis patients.

Subjects and method: Thirty-six patients having stage II periodontitis were included in this study. They were divided into three groups: SRP plus placebo gel, SRP plus 1.2% ATV gel and SRP plus melatonin gel. Clinical parameters (Plaque Index (PI), Gingival Index (GI), Probing Depth (PD) and Clinical Attachment Level (CAL)) were recorded and GCF samples to assess the osteocalcin level were collected at baseline and at 3 months follow up.

Results: All three groups showed statistically significant changes in all clinical parameters, PI, GI, PD and CAL. However, these changes were more significant in the ATV and melatonin groups. Reduction in OC was only significant in the ATV and melatonin groups. Melatonin group showed greater mean OC reduction level than the ATV group at 3 months follow up.

Conclusion: The adjunctive use of topical ATV gel and melatonin gel with nonsurgical periodontal therapy have showed to be effective in treatment of stage II periodontitis patients. Melatonin gel proved to be more potent in reducing the OC level in the GCF than the ATV gel.

1. INTRODUCTION

Periodontitis is a chronic inflammatory disease that develops due to a destructive tissue response to protracted inflammation and a disturbed homeostasis in the interaction between the dental biofilm microorganisms and the host.[1] Generation of free radicals and reactive oxygen species from the bacteria and also from neutrophils which are the first line of defense is one of the role factors in worsening the damage to the existing periodontium [2,3].

The purposes of periodontal therapy are primarily to arrest periodontal disease progression and secondly to regenerate lost periodontal tissues. Conventional therapy may result in successful outcomes such as reduction of probing depth and gaining of clinical attachment through formation of a long junctional epithelium not through periodontal regeneration [4,5]. The biological regenerative potential of the periodontium is high, and numerous biomaterials can be applied to improve the periodontal therapy outcome [6].

Melatonin that is defined as a pleiotropic multitasking molecule [7] is an element that is secreted by multiple organs such as the pineal gland, bone marrow, retina, and the gastro-intestinal tract. Its key role is to regulate the circadian rhythm [8]. In addition, it plays an antioxidant [9-11], anti-inflammatory, and immunomodulatory role [12,15]. Furthermore, Melatonin boosts angiogenesis and wound healing through regulating the expression of ROS, MMPs, and growth factors [16,18].

Melatonin is physiologically existing in saliva and in gingival crevicular fluid [19,20] and it was found to influence both bone regeneration and fibroblast activation. Besides, melatonin promotes type I collagen fibers synthesis and was reported to stimulate osteoblasts differentiation, proliferation, and activation while inhibiting bone resorption [21]. In this regard melatonin, helping as a potent radical scavenger and antioxidant, could be depleted in unhealthy periodontal tissues if compared to healthy ones [22]. In addition, periodontitis patients express a statistically significant reduction in salivary melatonin levels [23].

Statins like simvastatin (SMV), atorvastatin (ATV), lovastatin, and pravastatin are inhibitors of the 3- hydroxy-3-methylglutaryl coenzyme A reductase (HMG-CoA reductase), which is a vital enzyme linked to cholesterol synthesis [24].

Anabolic and anti-resorptive bone effects were demonstrated in both in vitro and in vivo studies [25,26]. Accordingly, statins were considered an almost idyllic candidate of anti- osteoporotic drugs family [27]. Statins show pleiotropic effects on the expression of bone morphogenetic protein-2 (BMP-2) gen in bone cells[25], representing an anabolic effect on bone [24], and modulating inflammation and alveolar bone loss [28]. In addition, several animal studies stated promising bone regeneration effects when statins were applied either locally or orally [29-31] besides its optimistic effect in increasing osteogenesis around dental implants [32-34].

Atorvastatin was found to be more effective when compared to simvastatin and pravastatin in patients with hyperlipidemia [35]. In addition, locally delivered atorvastatin in the treatment of periodontitis was evaluated in an animal study that showed decrease in the release of pro-inflammatory (IL-1β, IL-6 and IL-8) and anti- inflammatory (TGF-β1 and TGF-β2) cytokines subsequent to its administration [36]. Significant improvement in alveolar bone healing and tooth mobility was also concluded several studies [37-39].

Periodontal diseases progression and bone turnover markers in periodontitis patients gingival crevicular fluid (GCF) samples were investigated in multiple studies (40-44). Markers of bone resorption mirror the osteoclastic activity that are probably the breakdown products of type I bone collagen, the key component of the organic bone matrix [45-47].

The GCF analysis is valuably diagnostic in both periodontology and orthodontics (48). Various host GCF biomarkers that are corelated to the levels of periodontal diseases have been extensively studied [49-52].The biomarkers found in GCF are different interleukins, prostaglandin E2, osteocalcin, tumor necrosis factor-alfa, RANK, RANKL, matrix metalloproteinases, acid, and others [53].

Osteocalcin (OC) is a major non collagenous components of bone [48]. It is primarily synthesized and secreted by osteoblasts, odontoblasts, and chondrocytes (54). OC plays a significant role in bone remodeling and is commonly considered as bone formation biomarker but in periodontitis where bone hemostasis is disturbed due to higher resorption rate, it recruits osteoclasts to the site of bone degradation with promoting their differentiation into active osteoclasts. Hence, OC is now broadly accepted as a bone turnover rather than a bone formation marker [55].

To our knowledge, there is no human study that compared the effect of both melatonin and atorvastatin on osteocalcin levels in periodontitis patients. Therefore, the aim of this study was to assess the effects of topical melatonin and atorvastatin as an adjunct to non-surgical periodontal therapy in the treatment of patients with stage II periodontitis.

2. SUBJECTS AND METHODS

This controlled double-blinded, randomized study was carried out on Thirty-six non-smoking patients with stage II periodontitis (13 men, 23 women) from the outpatients' clinic in Faculty of Oral and Dental Medicine, Future university in Egypt.

The patients were selected according to the following criteria:

- Patients' age range from 21-55 years.
- Patients with stage II periodontitis were diagnosed as having interdental CAL is detectable at ≥2 nonadjacent teeth, or buccal or oral CAL ≥3 mm with pocketing

>3 mm is detectable at ≥2 teeth and CAL 3-4 mm and maximum probing depth ≤5 mm [56]

The criteria for exclusion were as follows:

- Individuals with known or suspected allergy to melatonin or ATV/statin group.
- Individuals on systemic drug affecting metabolic bone diseases and medically compromised patients.
- Users of tobacco in any form & alcoholics.
- Pregnant or lactating women.

Study design:

At the beginning of the treatment, all selected patients were motivated about the benefit of plaque control and periodontal treatment. They received detailed instruction about the purpose of the study, steps, and predictable benefits or hazards that may arise. At baseline, proper case history, clinical examination and radiographic evaluation were done to selected subjects. GCF samples were collected at the beginning of the study before treatment and two months later from all participants in the study.

Following GCF collection, thorough SRP was performed for all patients using both hand scalers and ultrasonic scalers for meticulous removal of subgingival and supragingival plaque and calculus.

Thirty-six patients were randomly divided into three groups:

Group (A): 12 patients received SRP in addition to placebo gel.

Group (B): 12 patients received SRP in addition to ATV gel that was injected in the pocket site using a syringe with a blunt cannula once weekly for four weeks.

Group (C): 12 patients received SRP in addition to melatonin gel that was injected in the pocket site using a syringe with a blunt cannula once weekly for four weeks.

Gel Preparation:

ATV gel was prepared as described by Thylin et al.(57) Briefly, preparation of the methylcellulosegel was done by adding the required amount of distilled water to an precisely weighed amount of methylcellulose. The vial was then heated to 50ºC -60ºC and agitated using a mechanical shaker to gain a clear solution. A weighed amount of ATV was added to that solution and dissolved completely to obtain a homogeneous phase of polymer, solvent, and drug. Consequently, the ATV gel was set with aconcentration of 1.2%. The placebo gel contained the same methylcellulose gel without the ATV added.

The melatonin gel was prepared using melatonin drug 2% w/w that was isolated uniformly in double distilled water and added to the gel with stirring till homogenous distribution. The weight of gel was adjusted to 100 gm, and then packed in sterile and dry glass containers until used.

Clinical evaluation:

The following periodontal parameters were recorded at baseline and after 3 months:

- **Gingival Index (GI):** the status of the gingiva was evaluated to assess the presence or absence of gingival inflammation (58).
- **Plaque Index (PI):** the sum of dental plaque was assessed in order to screen the oral hygiene performance by the patient (59).
- **Probing Pocket Depth (PPD):** the distance between the gingival margin and the deepest part of the pocket was measured using William's graduated periodontal probe.
- **Clinical Attachment Level (CAL):** was measured from the cemento-enamel junction to the deepest part of the pocket using William's graduated periodontal probe.

Biochemical Analysis:

Evaluation of changes in the GCF level of osteocalcin was done using enzyme-linked immunosorbent assay (ELISA).

Collection of GCF samples:

GCF samples were collected from the sites with the deepest PD at baseline and 3 months follow up. GCF samples were obtained as follows: All supragingival plaque was detached and the tooth surfaces were cleaned from

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blood or any debris, dried by air syringe and isolated from saliva using cotton rolls. Sterile filter paper strip (1.5 × 20 mm) was inserted into the pocket until minimal resistance was felt and left in the place for 45 seconds. Strips contaminated by blood or saliva were discarded. After GCF collection, the strips were placed immediately in sterile Eppendorf tubes that were stored in liquid nitrogen (−80°C) until biochemical analysis [60].

3. STATISTICAL ANALYSIS

Statistical package, IBM SPSS Statistics 22.0™, was utilized for the analysis of this study. T-test was used for the comparison between the means of each two levels of each group. While the one-way ANOVA test was used for the comparison between the means of the different levels of each of the 3 groups. All statistical analyses were calculated at a 0.05 significance level (P-value of 0.05 and a confidence level of 0.95).

4. RESULTS

Thirty-six patients (23 females -13 males) with age ranging from 21 to 55 years old and mean age of 41.25 (±8.84) were included in the present study and continued the 3 months follow up evaluation. The patients who received melatonin gel or ATV gel reported no adverse effects.

The results of the clinical and biochemical parameters at baseline and 3 months following treatment are shown in Tables 1 and 2. Regarding PI & GI there was a statistically significant reduction in all groups, however this reduction was more significant in the groups B and C compared to group A.

PD & CAL readings showed a statistically significant post treatment changes in all three groups, though PD and CAL readings were statistically different in favor of groups B and C compared to group A in the 3 months follow up period. Osteocalcin level displayed a significant reduction only in groups B and C in the follow up period in addition to significant reduction in group C compared to group B.

Table (1) — Effect of post-operative duration time on the mean change on all clinical variables during the follow-up period within each group.

Clinical variable	Plaque index (PI)	Gingival index (GI)	Probing depth (PD)	Clinical Attachment Level (CAL)	Osteocalcin (OCT)
Group A (BL- 3 months)	1.56 ± 0.1 P= < 0.0001*	1.33 ± 0.1 P= < 0.0001*	0.93 ± 0.06 P= < 0.0001*	0.79 ± 0.08 P= < 0.0001*	0.05 ± 0.06 P=0.3776
Group B (BL- 3 months)	2.00 ± 0.1 P= < 0.0001*	1.89 ± 0.1 P= < 0.0001*	1.72 ± 0.09 P= < 0.0001*	2.52 ± 0.1 P= < 0.0001*	0.35 ± 0.03 P= < 0.0001*
Group C (BL- 3 months)	1.70 ± 0.1 P= < 0.0001*	1.66 ± 0.1 P= < 0.0001*	1.88 ± 0.07 P= < 0.0001*	1.75 ± 0.2 P= < 0.0001*	0.89 ± 0.1 P= < 0.0001*

*: significant at P ≤ 0.05

Tables 2: Descriptive statistics and one-way ANOVA results for the effect of the 3 groups on all clinical variables during the follow-up period.

Clinical variable	Group A	Group B	Group C	F-value	P-value
Plaque index					
(PI) Baseline	2.47 ± 0.6	2.47 ± 0.6	2.08 ± 0.5	1.57205	0.222773
Posttreatment	0.91 ± 0.3^{a}	0.47 ± 0.2^{b}	0.37 ± 0.1^{b}	12.8973	0.000073*
Gingival index					
(GI) Baseline	2.62 ± 0.4	2.62 ± 0.4	2.35 ± 0.5	1.09935	0.344978
Posttreatment	1.29 ± 0.4^{a}	0.72 ± 0.3^{b}	0.68 ± 0.2^{b}	11.12725	0.000202*
Probing depth					
(PD) Baseline	4.66 ± 0.5	4.75 ± 0.3	4.60 ± 0.6	0.242	0.7860
Posttreatment	3.73 ± 0.5^{a}	3.03 ± 0.5^{b}	2.72 ± 0.5^{b}	12.2197	0.0001*
Clinical Attachment Level (CAL)					
Baseline	4.32 ± 1.0	4.67 ± 1.1	4.03 ± 0.93	1.14076	0.331857
Posttreatment	3.53 ± 0.8^{a}	2.15 ± 0.6^{b}	2.28 ± 0.6^{b}	13.35041	0.000056*
Osteocalcin					
(OC) Baseline	2.44 ± 0.5	2.20 ± 0.2	2.04 ± 0.4	2.50302	0.097255
Posttreatment	2.41 ± 0.6^{a}	1.84 ± 0.2^{b}	1.14 ± 0.4^{c}	21.2971	<0.0001*

N.B. Different letters mean statistically significantly different means.

*: significant at P ≤ 0.05

5. DISCUSSION

Chronic periodontitis is considered as a multi-factorial infectious disease that arises because of host immune inflammatory response to pathogenic microorganisms, leading to periodontal tissues destruction, bone resorption and ending up with tooth loss [61]. Besides the effective non- surgical periodontal therapy, local drug delivery in the periodontal pocket is one of the best treatment options[62], as substantial drug levels can be maintained in the GCF for prolonged time [63].

Various studies have suggested that ATV, and other statins could induce bone formation and suppress bone resorption [64-68]. ATV is supposed to have potent antioxidant and anti-inflammatory properties when compared to SMV[61]. In addition, it inhibits the secretion of cytokines in chronic inflammatory diseases [69], and could predominantly increase bone formation via differentiation of mesenchymal stem cells into differentiated osteoblasts, by inducing expression of BMP-2 [70].

Melatonin has been observed as a multifaceted molecule. In the oral cavity, melatonin is produced by gingival tissues [71] and salivary glands [72]. Melatonin characterized by an anti-inflammatory and immunomodulatory effects, in addition to acting as a free radical scavenger at the same time[73]. Despite its short half-life [74], Melatonin is still considered as a natural antioxidant gift to living organisms [75].

Due to the antioxidant effects of both ATV and melatonin, the present study was hence planned to evaluate the outcome of locally delivered ATV gel and melatonin gel in addition to the nonsurgical periodontal therapy on the clinical parameters (PI, GI, PD, and CAL) as well as osteocalcin levels in the GCF of stage II periodontitis patients. In the current study, ATV and melatonin were applied in a gel form inside the pocket in order to increase the bio adhesion properties of the material and therefore prolonging their biological effects[76]. Results of this study highlight the promising benefits of the local delivery of ATV gel and melatonin gel on the periodontal disease, and this was reflected by the satisfactory results obtained concerning the clinical parameters including PI, GI, PD, and CAL. Following scaling and root planning all three groups showed significant decrease in all clinical parameters however this reduction was more significant in the groups B and C.

Concerning the ATV group, the results of the present study showed significant reduction in the PD with mean of 1.72 ± 0.09 and significant gain in the CAL with mean of 2.52±0.13 at the 3 months follow up. These results goes in accordance with Pradeep 2016 [39] and Santosh 2017 [61] who showed reductions in the PD with means of 3.92±0.87 and 3.46±1.47 and gaining of 1.96±0.85 and 3.46 ± 1.47 respectively. In addition, Akram et al., 2018 [77] in their meta-analysis study concluded that ATV showed significant PD reduction and CAL gaining. Despite the difference in the melatonin gel concentration, the results obtained from the present study regarding the PI, GI, PD and CAL were similar to those obtained by Ahmed et al., 2021[76] who used a concentration of 5% and showed reduction in PI, GI and PD by means of 0.7±0.6, 0.6±0.5 and 2.9±0.7 respectively, and gain in CAL 3.5±0.6 after 3 months follow up. Montero et al., 2017[73] mentioned that topical melatonin in treatment of diabetic patients with periodontal disease was associated with a significant improvement in the gingival index and in pocket depth. In a very recent systematic review, Oliveira et al., [78] mentioned that the use of either topical or systemic melatonin in periodontal disease treatment presented satisfactory results, revealing that nevertheless of the administration route, melatonin can act as an adjunctive therapy in periodontal disease treatment.

Osteocalcin is a bone formation marker but owing to its role in osteoclastsis recruiting to the bone resorption sites, it is now broadly accepted as a vital marker of bone turnover [55]. Detection of osteocalcin in GCF is vital in treatment of periodontitis cases. In their case-control study, Bullon et al., mentioned that saliva and serum osteocalcin concentrations were not statistically different, however, GCF osteocalcin concentrations were significantly raised in post- menopausal women following periodontal treatment [79].

Conclusively, osteocalcin, could be used as a prognostic marker to predict the probable outcome of the disease [80]. In this study, the laboratory assessment of OC level in GCF was detected at baseline and at 3 months follow up in all study groups. Changeable osteocalcin GCF levels between health and disease may highlight the abnormal bone turnover occurring in periodontitis [55].

In both study groups (B & C), OC level was significantly decreased in the follow up assessment, however there was no statistically significant difference in OC level in group A versus its level at baseline. This indicates the positive effect of both ATV gel and melatonin gel in treatment of stage two periodontitis as an adjunct to SRP.

6. CONCLUSIONS

The results of the current study revealed a significant decrease in OC after intra-pocket application of ATV gel and melatonin gel reflecting their powerful antioxidant potential. With this study outcomes, it can be concluded that the effect of locally delivered ATV gel and melatonin gel as an adjunctive to nonsurgical periodontal therapy have an optimistic effect on periodontitis patients conferring a new feature to the management of periodontitis.

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