AL-AZHAR
Assiut Dental Journal

The Official Publication of The Faculty of Dental Medicine, Al-Azhar Assiut University, Egypt

AADJ, Vol. 6, No. 1, April (2023) — PP. 55:62
ISSN 2682-2822

Measurement of Interleukin-1β Level in Gingival Crevicular Fluid in Periodontitis Patients Treated by Non-Surgical Periodontal Therapy Combined with Topical Application of Melatonin Gel

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Codex : 06/2023/04

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ABSTRACT

Aim: The present study was performed to evaluate the efficacy of topical application of melatonin gel on clinical parameter and biochemical level of IL-1-β in gingival crevicular fluid in patients with periodontitis treated by non-surgical periodontal therapy. **Subjects and methods:** In this study, forty periodontitis patients with stage I, Π grade A, were divided randomly into two groups: Group I: Twenty periodontitis patients with stage I, II grade A treated with conventional periodontal treatment (scaling and root planing) combined with intra pocket application of 2% melatonin gel. Group Π: Twenty periodontitis patients with stage I,II grade A treated with conventional periodontal treatment alone (scaling and root planing). All patients were evaluated clinically at; base line and after 3 and 6 months. Also, biochemical evaluation of IL-1β using ELISSA at; base line and after 2 weeks, 1and 3 months. Results of the present study were recorded, tabulated and statistically analyzed. **Results:** clinical findings showed a statistically significant difference in all groups at the different intervals when compared to the baseline, biochemical evaluation of IL-1β was a statistically significant difference between group I and group II at 2 weeks and after 1 month only during the period of application. **Conclusion:** Adjunctive use of topically applied melatonin gel 2% appeared to be has beneficial effect on both clinical and biochemical parameters in patients with stage I, Π, grade A periodontitis, with a statistically significant difference between group I and group II at 2 weeks and after 1 month of treatment (during the period of melatonin application) however, this effect is not significant when compared with scaling and root planning alone after 3 months of treatment

KEYWORDS

Melatonin gel 2%, Periodontitis, gingival crevicular fluid, biochemical level.

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INTRODUCTION

Periodontal disease is an oral inflammatory process affecting the alveolar bone, the gingiva and the periodontal ligament. Disease status ranges from gingivitis to advanced periodontitis with destruction of connective tissue attachment and alveolar bone which can lead to tooth loss. The pathological mechanisms of periodontal disease are still not completely understood. Microbial organisms in dental plaque are considered the primary pathogens in periodontal disease[(1)].

There is overwhelming evidence that bacteria cause periodontitis by extending apically along the surfaces of the tooth roots and creating pockets. A very complex mixture of microbial species, mostly although not exclusively gram-negative, anaerobic and motile is involved. Local oral condition such as tooth position plays an etiologic role by affecting plaque accumulation and retention [2].Periodontitis is a mixed infection in which the host response to bacterial biofilms is associated with high level of pro-inflammatory mediators. These mediators trigger a cascade of events which, in some individuals, culminates in irreversible degradation of bone tissues and consequent periodontal attachment loss [3].Clinical evidence suggests that; periodontitis is associated with raised serum level of systemic inflammatory markers [4]. Sever form of periodontitis that has been associated with increased serum level of pro-inflammatory cytokines and pro-inflammatory mediators, including several interleukins (IL), such as interleukin-1 beta (IL-1β). Pro-inflammatory mediators including IL-1β are associated with periodontal disease progression and alveolar bone resorption. Reduction in gingival crevicular fluid cytokines following initial periodontal therapy has also been reported [5].The primary goal of periodontal therapy is to eliminate sub-gingival microbes and to remove their deposits from the root surfaces, thereby controlling the progression of periodontal destruction, reducing etiologic agents and creating a healthy sub-gingival environment [6].Scaling and root planing (SRP) is the basic periodontal treatment [7] which has proven clinical effectiveness in terms of reducing inflammation, decreasing the probing pocket depth and improving the clinical attachment level (CAL) [8]. However, SRP has some limitations, such as difficulties in accessing deeper pockets, furcation areas and root concavities [9].To overcome these limitation; antiseptics, antibiotics and immuno-modulatory agents delivered locally or systemically had been used as adjunct to SRP procedures in order to control the sub-gingival microbes and thereby improve the treatment outcome [10].Melatonin is an endoleamine secreted by pineal gland in a circadian manner also produced in several organs and melatonin-forming enzymes which are found in tissues, including the retina, ovaries, the gastrointestinal tract and immune system cell, among others [11].

Melatonin has revealed itself to be pleiotropic multitasking molecules playing an immuno-modulatory role, in addition to powerful antioxidant activity and anti-inflammatory effects which is preventing over-expression of pro-inflammatory mediators and inhibiting the effects of several of pro-inflammatory cytokines [12]. The immuno-modulatory effects of melatonin have already been established in patients with and without periodontal disease. Systematic review has stated that melatonin may suppress the inflammation of the gingiva and periodontium. It was found that; topical application of melatonin improves peridental biochemical parameters which are useful in adjunctive treatment in periodontal diseases [13]. The present study tried to evaluate the efficacy of topical application of 2%melatonin gel on clinical parameters and biochemical level of IL-1-β in gingival crevicular fluids in periodontitis patients treated by non-surgical periodontal therapy (SRP).

PATIENTS AND METHOD

The present study is randomized, controlled clinical trial study carried out on 40 patients of both sex (aged from 26-47 years) with stage I, Π grade A periodontitis. All patients were selected from outpatient of Oral Medicine and Periodontology Department clinic, Faculty of Dentistry, Al-Azhar University, Assiut Branch

The inclusion criteria:

All patients should be free from any systemic diseases according to criteria of Cornell medical index and its modification. [14-16]. All patients with stage I, II grade A with probing pocket depth (PPD) not more than 5 mm, CAL 1-4mm and mostly horizontally radiographic bone loss ≤ 33 % at coronal third.

The exclusion criteria:

Patients on an antibiotic, immunosuppressive, anti-inflammatory and antioxidants drug regimen within the 6 months preceding the beginning of the study, and patients working in night shifts or received any drug that known to alter melatonin levels (e.g., for sleeping disorders). Smokers and pregnant or lactating women. Patients were subjected to previous periodontal therapy during at least 6months.

Patients grouping and randomization:

Group I: Twenty periodontitis patients with stage I, II grade A treated with conventional periodontal treatment (scaling and root planing) combined with intra pocket application of 2% melatonin gel. **Group II:** Twenty periodontitis patients with stage I,II grade A treated with conventional periodontal treatment alone (scaling and root planing).

Melatonin oral gel preparation: Thick and muco-adhesive buccal gel containing 2% w/w melatonin was prepared using methylcellulose as gel base in department of pharmaceutics and industrial pharmacy; Faculty of Pharmacy Al-Azhar University, Assuit Branch, plain gel was obtained be dissolving 10 grams of methylcellulose in 100 ml of distilled water. The medicated gel was prepared by dissolving 2 grams of melatonin powder in 100 grams of plain gel under low stirring to avoid the entrapment of air bubbles until homogenous gel was obtained. The prepared gel was stored in tightly closed container in the refrigerator until use. The prepared melatonin gel supplied as a syringe of gel, contained melatonin 2%.With special needles that are designed for application of gel inside the periodontal pocket.

Evaluation of periodontal status: All patients were evaluated clinically at; baseline, 3 and 6 months using plaque index, gingival index, probing depth and clinical attachment level. Biochemical evaluation was done at; baseline, 2 weeks, 1 and 3 months to evaluate the IL-1β level.

Gingival crevicular fluid samples collection: GCF samples were obtained from the site which showed the highest probing depth not more than 5 mm score and CAL 1-4 mm

Conventional periodontal treatment: All patients were received initial periodontal treatment consisted of scaling and root planning.

Supra-gingival Scaling: Supra-gingival scaling was performed by sickle scaler.

Sub-gingival scaling and root planing: were accomplished with either universal or area specific (Gracey) curettes.

Intra-pocket application of melatonin gel: Firstly areas of application were isolated by cotton roll. Application was accomplished by inserting the needle to the base of the periodontal pocket firstly and then placing the gel while working the way up, until the gingival margin

IL1β analysis: The samples were assayed for IL1 β levels using commercially available enzyme-linked immune-sorbent assay (ELISA) according to the manufacturer's instructions. Highly sensitive ELISA kit was used to detect the IL1β level in the sample of GCF in periodontitis patients.

Statistical analysis:

The data were collected, tabulated and statistically analyzed using recent software.

RESULTS

Changes in plaque index: A statistically significant differences in all groups at the different intervals when compared to the baseline. No statistical significant difference in group I when compared with group II at different intervals.

Changes in gingival index: A statistically significant differences in all groups at the different intervals when compared to the baseline. Statistically significant differences in group I when compared with group II at 3 and 6 months after treatment.

Probing pocket depth measurements: A statistically significant difference in both groups at the different intervals when compared to the baseline. No statistical significant difference in group I when compared with group II at different intervals table (1).

Clinical attachment level measurements: A statistically significant differences in all groups at the different intervals when compared to the baseline. No statistical significant difference in group I when compared with group II at different intervals table (2).

Interleukin 1-beta assessment: A statistically significant difference in all groups at the different intervals when compared to the baseline. No statistically significant difference between group I and group II at base line, but there was a statistically significant difference between group I and group II at 2 weeks and after 1 month. No a statistically significant difference between group I and group Π at 3 months table (3).

Table (1) *The mean, ±standard deviation (±SD), minimum, maximum and p-values of probing pocket depth in mm in both groups at different intervals.*

	PPD												
	Baseline				After 3m				After 6m				p-value
	Mean	SD	Min	Max	Mean	SD	Min	Max	Mean	SD	Min	Max	
Group I	3.74	0.16	3.50	4.00	3.00	0.29	2.50	3.37	2.91	0.29	2.75	3.75	**<0.001***
Group II	3.45	0.46	2.75	4.50	2.82	0.22	2.50	3.12	2.74	0.31	2.25	3.25	**<0.001***
p-value	**0.061ns**				**0.109ns**				**0.185ns**				

**; significant (p<0.05) ns; non-significant (p>0.05)*

Table (2) *The mean, ±standard deviation (±SD), minimum, maximum and p-values of clinical attachment level in mm in both groups at different intervals***.**

	CAL												
	Baseline				After 3m				After 6m				p-value
	Mean	SD	Min	Max	Mean	SD	Min	Max	Mean	SD	Min	Max	
Group I	1.97	0.29	1.75	2.50	1.27	0.36	1.00	2.25	1.10	0.26	0.75	1.62	**<0.001***
Group II	1.83	0.43	1.00	2.50	1.34	0.38	0.50	1.87	1.31	0.36	0.50	1.75	**0.005***
p-value	**0.401ns**				**0.656ns**				**0.121ns**				

**; significant (p<0.05) ns; non-significant (p>0.05)*

Table (3) *The mean, ±standard deviation (±SD), minimum, maximum and p-values of interleukin-1β (IL-1β) levels in pg/ml in both groups at different intervals.*

	IL-1β								
	Group I				Group II				p-value
	Mean	SD	Min	Max	Mean	SD	Min	Max	
Baseline	32.50	2.06	28.50	35.50	34.13	2.49	31.50	39.00	**0.105ns**
After 2w	26.64	4.37	19.00	32.00	30.58	4.51	22.50	37.50	**0.045***
After 1m	25.55	5.10	16.50	30.00	29.38	3.72	21.50	34.00	**0.049***
After 3m	26.45	5.08	17.00	34.00	27.67	6.18	17.00	36.50	**0.614ns**
p-value	**0.025***				**0.021***				

**; significant (p<0.05) ns; non-significant (p>0.05)*

DISCUSSION

In the present study periodontitis patients were selected because this condition is considered as one of the most common bacterial infection worldwide with prevalence in mild to moderate (stage I, Π, grade A) forms ranging from 13% to 57% in different populations depending on oral hygiene and socio-economic status [17]. Melatonin by its effects could be used as a novel support to modulate host response in patients affected by periodontitis [13]. Several studies were conducted evaluating the melatonin effect on periodontal disease but as oral supplementation or in the topical forms other than the gel form used in the present study [18] Furthermore, topical administration of melatonin with conventional periodontal therapy could enhance the treatment outcomes [13]. It had been found that IL-1β crevicular fluid levels were closely linked with periodontal disease severity, when comparing the amount of inflamed and non-inflamed pockets the average amount of IL-1β collected was three times higher in inflamed pockets than from non-inflamed pockets yet IL-1β level decreased after initial therapy, So the present study select IL1β as a biochemical marker to detect the response of periodontitis to treatment with scaling and root planning versus with scaling and root planning plus melatonin gel [19]. In this study, smokers, pregnant, medically compromised patients and patients under an antibiotic, immunosuppressive and /or anti-inflammatory drug regimen at/ or prior to the study which could affects results of this research were excluded, this in agreement with the criteria established by Cornell Medical Index and it's modification [14-16].. The present clinical trial was designed by whole mouth technique due to a potential disadvantage of split mouth design which may lead to bias due to carry across effects that occur when the treatment performed in one part of mouth can affect the treatment response in the other parts of mouth [20,21]. Time period for clinical evaluation was 6 months since this time was considered enough for clinical evaluation of cases included in this clinical trial, moreover no measurements were taken from the baseline up to 3 months post treatment because the healing in the sulcus begins at the bottom of the pocket in an attempt to avoid adverse effect on healing tissues which is fragile and could be damaged with probing process [22]. Gingival crevicular fluid (GCF) analysis has been used in this study to assess the activity of periodontitis and to clarify the outcome of periodontal treatment; GCF is suitable for detection of biochemical marker as an indicator of periodontal disease activity [23]. In addition, there is positive relationship between the level of inflammatory mediator in GCF and clinical periodontal parameter [24, 25].

Results of this study showed that with respect to change in the plaque index scores there is statically significant difference in both groups at the different intervals when compared to baseline, while no statically significant difference in group I when compared with group II. Similarly the results of gingival index showed statically significant difference at the different intervals as compared to baseline, while in group I it was statically significance difference when compared with group II at 3and 6 months. This is in agreement to the findings of similar study [13] and the most recent performed study [26].With reference to the probing pocket depth measurement of this study showed a statically significant difference in group I and group II at 3 and 6 months when compared to baseline, while there was no statically significant difference in group I when compared with group II at 3 and 6 months. These results are in contrary to another finding which recorded that statically significant difference between two groups at 3 and 6 months. This may be attributed to the difference of number and frequency of application of melatonin according to recent study, injection applied twice weekly for four weeks, but in this study injection repeated once weekly for one month [13, 26]. This study observed a statically significant difference in the gain in clinical attachment level at 3 and 6 months in group I and group II when compared to baseline. But, no significant gain in clinical attachment level in group I when compared to group II at 3 months and 6 months, these results are in contrary to the results of similar researches which found there is was statically significant difference between two groups at 3 and 6 months [13,26]. As regard to IL-1β which used as biochemical marker in this study, the present study showed marked decrease in the level of IL-1β measurement with statically significant difference in group I and group II at 2 weeks, 1 and 3 months when compared to baseline, with statically significant difference in group I when compared with group II at 2 weeks and after 1 month with no statically significant difference at 3 month after the end of the application of the gel, this is in consistent with study that found that as the severity of inflammation increases, there is a significant increase in IL-1β level suggesting a direct relationship between IL-1β level in GCF and periodontal destruction [13].

CONCLUSIONS

Adjunctive use of topically applied melatonin gel 2% appeared to be has beneficial effect on both clinical and biochemical parameters in patients with stage I, Π, grade A periodontitis, with a statistically significant difference between group I and group II at 2 weeks and after 1 month of treatment (during the period of melatonin application) however, this effect is not significant when compared with scaling and root planning alone after 3 months of treatment.

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AADJ, Vol. 6, No. 1, April (2023) — PP. 62

فياس مستوى انترليكون 1بيتا فى السائل اللثوى فى مرضى اربطة الاسنان المعالجة بعلاج اللثه الغير جراحى المصحوب بوضع جيل الميلاتونين موضوعيا

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الملخص:

الهدف: تم إجراء هذه الدراسة لتقييم فعالية التطبيق الموضعي لجيل الميلاتونين على المعلمة السريرية والمستوى الكيميائي الحيوي لـ IL-1-في السائل الخزامي اللثوي في مرضى التهاب دواعم السن الذين عولجوا بالعلاج اللثوي غير الجراحي.

المواد والأساليب : في هذه الدراسة ، تم تقسيم أربعين مريضًا من مرضى التهاب دواعم السن في المرحلة ، من الدرجة A ، بشكل عشوائي إلى مجموعتين: المجموعة: عشرون مريضًا بالتهاب دواعم السن في المرحلة I ، و II من الدرجة A تم علاجهم بعلاج دواعم الأسنان التقليدي (التحجيم وكشط الجذر) جنبًا إلى جنب مع الجيب الداخلي تطبيق 2٪ هلام الميلاتونين. المجموعة II: عشرون مريضًا مصابًا بالتهاب دواعم السن في المرحلة I ، من الدرجة الثانية A يعالجون بالعلاج التقليدي للثة وحده (التحجيم وكشط الجذر). تم تقييم جميع المرضى سريريًا في : خط الأساس وبعد 3 و 6 أشهر. أيضًا ، التقييم الكيميائي الحيوي لـ IL-1B باستخدام ELISSA في : خط الأساس وبعد أسبوعين ، 1 و 3 أشهر. تم تسجيل نتائج الدراسة الحالية وجدولتها وتحليلها إحصائياً.

النتائج: أظهرت النتائج السريرية وجود فرق معتد به إحصائيًا في جميع المجموعات على فترات مختلفة عند مقارنتها بخط الأساس ، كان التقييم الكيميائي الحيوي لـ IL-1B فرقًا مهمًا إحصائيًا بين المجموعة الأولى والمجموعة الثانية في أسبوعين وبعد شهر واحد فقط خلال فترة التطبيق.

الخلاصة: يبدو أن الاستخدام المساعد لجيل الميلاتونين المطبق موضعياً 2 ٪ له تأثير مفيد على كل من المعايير السريرية والكيميائية الحيوية في المرضى الذين يعانون من التهاب دواعم السن من الدرجة I و A ، مع وجود فرق معتد به إحصائيًا بين المجموعة الأولى والمجموعة الثانية في أسبوعين وبعد 1 شهر من العلاج (خلال فترة تطبيق الميلاتونين) ومع ذلك ، فإن هذا التأثير ليس مهمًا عند مقارنته مع التحجيم وتخطيط الجذر فقط بعد 3 أشهر من العلاج

الكلمات المفتاحية: جل الميلاتونين 2٪ ، التهاب دواعم السن ، سائل الخزامى اللثة ، مستوى الكيمياء الحيوية