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CLINICAL AND BIOCHEMICAL EVALUATION OF CHLOROHEXIDINE GEL VERSUS PROPOLIS GEL IN NON-SURGICAL MANAGEMENT OF PERI-IMPLANTITIS (RANDOMIZED CLINICAL TRIAL)

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ABSTRACT

Background: Peri-implantitis is an inflammatory disease induced by microorganisms affecting the tissues around an osseointegrated dental implant, causing bone loss.

Objectives: The purpose of this work was to evaluate the clinical and biochemical outcome of local application of two different types of gel (Propolis gel or chlorohexidine gel) without surgical intervention.

Methods: 23 patients of both sexes, aged between 34 and 57y, suffering from peri-implantitis were included in this study aged between 34-57 years old. These implants had implant probing depth (IPD) of ≥ 5 mm, bleeding and/or suppuration on probing and evidence of radiographic of bone loss of at least 3 mm. Patients were divided randomly into two groups to receive either propolis gel (group I) or chlorhexidine gel (group II) following debridement without surgical intervention. Clinical assessment includes modified plaque index (MPI), modified gingival index (MGI), and implant probing depth (IPD) were recorded at baseline (prior to treatment) and at 3 and 6 months after treatment and biochemical assessment, include bone morphogenic protein-2 (BMP-2), and interleukin-1beta (IL-1β) were collected from Peri-implant crevicular fluid (PICF) at baseline (prior to treatment), 7 and 14 days after treatment.

Results: The two treatment modalities were effective in reducing the clinical parameters associated with peri-implantitis. Regarding biochemical parameters, BMP-2 level showed no significant difference intra or inter groups at baseline, 7, or 14. On the other hand, IL-1 β level showed intragroup significant improvement in both groups from baseline to 7 and 14 days, however, no significant difference was observed between the two groups.

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Conclusions: Both Chlorhexidine and propolis gel, when used in combination with mechanical debridement of peri-implantitis, can reduce inflammation, plaque accumulation, implant pocket depth, and (IL-1β) levels and increasing BMP levels. However, there was no statistically significant difference in biochemical parameters between the two groups.

KEYWORDS: Chlorhexidine, propolis, peri-implantitis

INTRODUCTION

Peri-implant diseases are inflammatory conditions of the tissues surrounding an osseointegrated dental implant caused by an imbalance between the bacterial biofilm and the host response to the biofilm, resulting in dysbiosis and tissue destruction **(Giovanni et al., 2021).** According to the classification of periodontal and peri-implant diseases in consensus report of the World Workshop in 2017, peri-implantitis is a plaque-associated pathological condition occurring in tissues around dental implants, characterized by inflammation in the peri-implant mucosa and associated with progressive loss of supporting bone **(Berglundh et al., 2018).**

Peri-implantitis is a biofilm-associated pathologic condition characterized by inflammation of the soft tissues surrounding an implant combined with progressive loss of marginal bone, redness, swelling, suppuration, and pocket probing depths (PPD) ≥ 5mm are often observed in implants diagnosed with peri-implantitis **(Schwarz et al., 2018)**.If left untreated, peri-implantitis may lead to implant loss, therefore, it appears essential to monitor the conditions of the peri-implant tissues at regular intervals by means of peri-implant probing and treat peri-implant mucositis and initial peri-implantitis. Measures in treating peri-implant diseases must include anti-infective approaches to remove supra- and sub-mucosal biofilm deposits, thereby resolving inflammation and preventing disease progression **(Giovanni et al., 2021)**.

If peri-implant diseases are detected early, non-surgical therapy may yield a successful outcome. Therefore, non-surgical treatment should always be the first step of treatment including optimal patient-administered biofilm control (**Salvi & Ramseier., 2015)** and professionally administered mechanical debridement **(Schwarz et al., 2015).**

Non-surgical treatment approaches may be divided according to the method of biofilm removal including mechanical debridement with hand- and power-driven instruments, laser irradiation, antimicrobial photodynamic therapy, adjunctive delivery of antiseptic and antimicrobial agents, use of probiotics or combinations. Moreover, implant materials, surface characteristics, and topography may also impact biofilm formation and the selection of decontamination methods **(Giovanni et al., 2021).**

The adjunctive use of local delivery of antiseptics /antibiotics into peri implant pockets were shown to improve tissue response when compared with non-surgical debridement **(Renvert et al., 2008).** A broad-spectrum antiseptic, chlorhexidine digluconate (C34H54Cl2N10O14) belongs to the biguanide class and acts topically on bacteria, fungi, and viruses. Its cationic component targets the cell wall of microorganisms by acting upon direct contact with their negatively polarized surfaces **(Gartenmann et al., 2016).** As it is the most often used antiseptic following surgical periodontal therapy; the majority of research has shown that utilizing mouthwash containing chlorhexidine (CHX) is essential for the therapy of periodontal patients **(Solderer et al., 2019).**

Propolis is a resinous substance collected by bees from the buds and bark of plants (**Zaccaria V et al., 2017**). It has many different forms and uses, there are toothpaste and mouthwash preparations used in caries prevention and treatment of oral infections such as gingivitis and stomatitis (**Castal-**

do S and Capasso F., 2002). In addition, propolis can be used as a local delivery system for its antibacterial **(Zaccaria V et al., 2019),** anti-inflammatory, and antioxidant activities.The antimicrobial activity of propolis against various periodontal pathogens has been largely demonstrated, including Porphyromonas gingivalis, Aggregatibacter actinomycetemcomitans, Fusobacterium nucleatum and Prevotella intermedia **(Cinzia et al., 2021).**

Thus, the purpose of this study was to assess and compare the local application of Propolis gel versus chlorhexidine gel into the peri-implant pockets affected by peri-implantitis following non-surgical debridement in terms of their adjunctive effects, both clinically and biochemically.

PATIENTS AND METHODS:

Sample size calculation:

For the purpose of applying a statistical test to the null hypothesis that there is no difference between clinical parameters of the two groups, a power analysis was created. With an alpha threshold of 0.05, a beta of 0.2, meaning power of 90%, and an effect size (d) of 1.1557022, the estimated sample size (n) was fifteen samples in total. To account for follow-up loss, 10% of the total sample size was added. As a result, the final sample size for the entire study consisted of 32 cases, 16 for each group. G*Power version 3.1.9.7 was used to calculate the sample size **(Maniani et al., 2016)**.

Ethical regulations:

Before beginning the study, all patients were given a thorough explanation of the treatment plan, including all the steps, risks, and anticipated outcomes. Their signed consent was also obtained. The research adhered to the guidelines established by the Helsinki Declaration (2008), the International Conference on Harmonization Good Clinical Practice Guidelines, and the Research Ethics Committee, Faculty of Dentistry-Minia University Committee No. (99), Decision No. (812).

Inclusion and exclusion criteria:

This study was operated on 23 male and female patients (7 males and 16 females) with 32 implants affected by peri-implantitis with age ranged 34-57 years old. Nine patients had 2 implants affected by peri-implantitis, and the other fourteen patients each contributed one implant with peri-implantitis, and all the implants had to be in function with cement retained fixed prostheses for more than 2 years. The patients were chosen from the outpatient's clinic of the Oral Medicine ,Oral Diagnosis ,and Periodontology Department, Faculty of Dentistry ,Minia University .

All patients were devoid of any systemic disorder and had not be given any type of periodontal treatment , antibiotics, or even anti-inflammatory drugs within the last six months. The study excluded females who were pregnant or nursing as well as smokers.

According to the American Academy of Periodontology and the European Federation of Periodontology, the primary inclusion criterion was the existence of peri-implantitis around one or more implants per patient **(Berglundh et al., 2018)**. depending on the following combination: probing depths of ≥ 5 mm; bleeding and/or suppuration upon gentle probing; bone levels more than or equal to 3 mm apical of the most coronal portion of the intra-osseous part of the implant.

Study design and Randomization:

This clinical study of six-month duration was designed as a randomized clinical trial and conducted on 23 patients of both sexes with 32 implants affected by peri-implantitis. A computerized algorithm of random numbers created with the SAS program was used to divide the 32 implants into two groups randomly:

- Group I (propolis group): include 10 patients with 16 implants affected by peri-implantitis.
- Group II (chlorohexidine group): include 13 patients with 16 implants affected by peri-implantitis.

Treatment protocol:

- All patients undergo phase I periodontal therapy, which includes four sessions of root planning and supra-and sub-gingival scaling over the course of two weeks, using ultrasonic scalers and hand instruments.
- All implant surfaces were mechanically debrided by means of plastic scalers and curettes where all soft and hard deposits were removed.
- In group I (propolis group): propolis gel was used locally in peri-implant pocket.

• **Preparation of the Propolis gel:**

Propolis gel was prepared using Chitosan as follows: a predetermined amount of water was added to 1% v/v aqueous acetic acid. The precalculated amount of chitosan was weighed then bit by bit added to aqueous acetic solution which was kept for 30 minutes to swell. A final concentration of 1.8 % of chitosan gel was prepared by adding calculated amount of water to the swollen gel (Mostafa, M et al., 2018) . The prepared gel was kept for (24) hours at room-temperature. Then, about 5 ml of alcoholic propolis extract (30% w/v) was scattered into 5 gm of chitosan gel to make a terminal propolis concentration of 0.15 % (w/w).

- In group II (chlorohexidine group): EZ- cure gel® (periodontal local delivery system– EZ-Pack company, Egypt) 10mg chlorohexidine Digluconate was used locally in peri-implant pocket.
- Peri-implant pockets were isolated using cotton roll then filled with the gel using a sterile blunt needle starting from the bottom of the pocket and the gel injected until it could be noticed at the margin of the gingiva as showed in **Figure 1**.

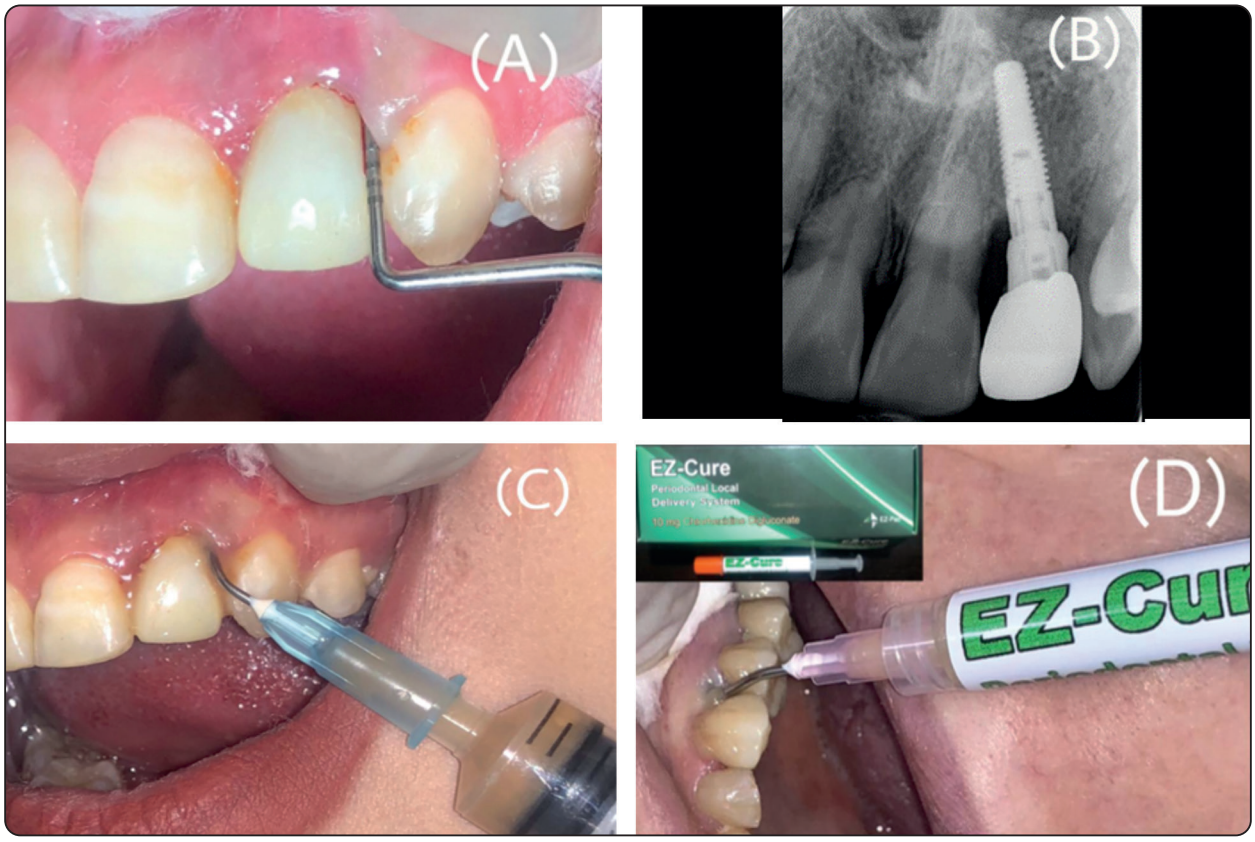

Fig. (1) A: pre-operative measurement of peri-implant pocket depth equal 7mm, B: Peri-apical x-ray showing bone loss around the implant, C: Application of propolis gel (group I), D: Application of chlorohexidine gel (group II)

- Each gel was putted in once more 48 hours later for each group and the gel-applied areas were sealed with a periodontal pack for a duration of seven days.
- To allow the gel to stay in the pocket as long as possible, the patients were told not to eat, drink, or rinse for at least three hours.

Assessment method:

- **Clinical parameters:**
- Modified plaque index (MPI), modified gingival index (MGI), and implant probing depth (IPD) represent the clinical parameters that were measured in both groups at baseline (before treatment), three and six months after treatment.
- **Biochemical parameters:**
- The biochemical parameters include bone morphogenic protein-2 (BMP-2), and interleukin-1beta (IL-1β) were collected from Peri-implant crevicular fluid (PICF) at baseline (before treatment), 7 and 14 days after treatment in both groups.
- To prevent PICF volume interference, all patients were instructed to refrain from eating or brushing their teeth for at least one hour prior to PICF collection.
- PICF samples were collected from a determined site (e.g., site with the deepest IPD at the baseline examination).
- The implants were initially segregated using cotton rolls and a saliva ejector, followed by air drying. At baseline, seven, and fourteen days following treatment, PICF samples were taken using absorbent filter paper strips from Whatman3MM Chromatography (Wh.3MM).
- The paper strip was inserted up to 1 mm or until a slight resistance was felt into the Peri-implant crevice. It was then left there for 30 seconds, and any strips corrupted with blood or exudate were thrown out.
- Before being used for the laboratory analysis, each strip was individually stored in a plastic Eppendorf container and kept at -80C.
- One day prior to analysis, the samples were eluted at 4°C for the entire night into 700 µl of phosphate-buffered saline containing proteinase inhibitors (Sigma-Aldrich, St Louis, MO/USA). Following a 4-minute centrifugation at 400 × g, the paper strips were taken out, and 100 µl aliquots of the supernatant were utilized. Commercially available enzyme-linked immunosorbent assay kits (R&D Systems Europe Ltd., Abingdon, UK) were used to measure the level of IL-1β and BMP-2.

RESULTS

This study was conducted on 23 patients of both sexes (7 males and 16 females) with 32 implants affected by peri-implantitis with ages ranging from 34-57 years old. The 32 implants were randomly grouped into two groups, Group I (propolis group): including 10 patients with 16 implants affected by peri-implantitis. Group II (chlorohexidine group): including 13 patients with 16 implants affected by peri-implantitis. Data were expressed as mean ± standard deviation of the parameters evaluated. The student-paired t-test was used to compare intragroup and intergroup measurements. For all clinical parameters, there was a significant difference observed from baseline to 3 months and 6 months, while in comparison between the two groups, no significant difference was found.

Regarding biochemical parameters, BMP-2 level showed no significant difference in intra or inter-groups at baseline, or 7 and 14 days after treatment. On the other hand, IL-1 β level showed intragroup significant improvement in both groups from baseline to 7 and 14 days after treatment, while in comparison between group I and group II, no significant difference was found.

TABLE(1): Comparison between clinical and biochemical parameters of group I (Propolis) and group II (Chlorhexidine)

Clinical Parameters	Group (I) propolis	Group (II) Chlorhexidine	p-value
Modified Plaque index			
PI-0	2.44 ± 0.22	2.58 ± 0.19	0.406
PI-3	0.71± 0.21	0.67 ± 0.27	0.301
PI-6	0.58 ± 0.29	0.48 ± 0.22	0.055
Modified bleeding index			
BI-0	2.50 ± 0.25	2.57 ± 0.20 0.65±0.15	0.852
BI-3	0.56± 0.26	0.49±0.13	0.341
BI-6	0.44 ± 0.24		0.210
Implant Probing depth			
PD-0	5.58 ± 0.87	5.37 ± 0.89	0.506
PD-3	4.9 ± 0.9	4.75 ± 0.82	0.638
PD-6	3.89 ± 0.85	3.72 ± 0.76	0.269
Biochemical parameters:			
BMP-2			
Day-0	207.36±12.08	211.65±7.17	0.959
Day-7	232.62±25.00	224.44±16.68	0.935
Day-14	248.00±18.73	235.15±11.62	0.896
IL-1 β			
Day-0	218.24±15.11	215.89±22.73	0.667
Day-7	125.54±19.21	118.26±19.75	0.741
Day-14	98.36±17.34	87.72±13.21	0.632

P-value <0.001* (significant)

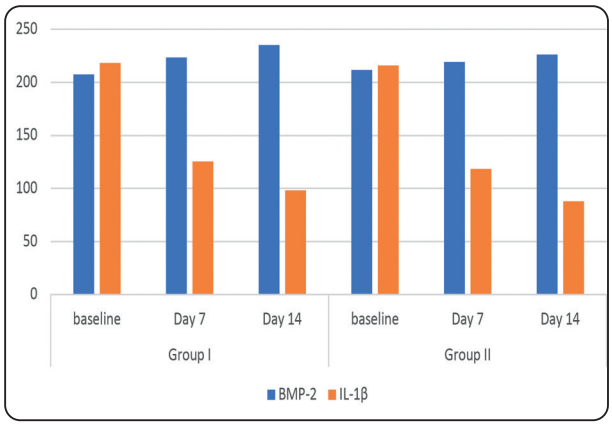

Fig. (2) Bar chart showing biochemical parameters (BMP-2 &IL-1β) at baseline, 7 and 14 days in group I and group II.

DISCUSSION

According to **Lee et al. (2017),** peri-implantitis is an irreversible, progressive disease of the hard and soft tissues surrounding the implant. It is characterized by purulence, pocket formation, osseointegration loss, and progressive bone resorption.

To reduce the pathogen load and treat peri-implantitis, various mechanical instruments such as air powder abrasive, metal or non-metal curettes, an ultrasonic scaler with a metal or plastic tip, and implantoplasty are used to reduce plaque biofilm **(Valderrama et al., 2014)**. The use of mechanical

debridement alone may not be adequate to suppress the microflora to a level associated with healing and healthy clinical situations around implants because threads and rough surface structure impede mechanical cleaning **(Prathapachandran et al., 2012)**.

This study was operated on 23 male and female patients (7 males and 16 females) with 32 implants affected by peri-implantitis with age ranged 34-57 years old. The aim of this randomized controlled trial was to evaluate and compare clinically and biochemically the adjunctive effect of local application of Propolis gel versus chlorhexidine gel after non-surgical management of peri-implantitis cases.

Because peri-implantitis lesions are typically well defined, our study relies on the local application of propolis and chlorohexidine gel. Local delivery devices may also prove to be effective in treating peri-implantitis. These devices can release a high-concentration antimicrobial or anti-inflammatory agent precisely into affected sites over a period of several days. It may also be able to destroy bacteria that are shielded by an inadequately removed biofilm. **(Mombelli et al., 2001).** Machtei et al., reported that the adjunctive use of local delivery of antiseptics /antibiotics into peri implant pockets were shown to improve tissue response when compared with non-surgical debridement alone **(Machtei et al., 2021).**

The current study assessed the levels of IL-1β and BMP-2 in the PICF before and after treatment for 7, 14, and 21 days. A non-invasive liquid biopsy could be performed by identifying and estimating particular inflammatory biomarkers that are predictive of bone resorption in PICF **(Izzotti et al., 2016)**. Liquid biopsy has applications in peri-implant disease as early detection, risk assessment, diagnosis, prognosis, and monitoring. Actually, it is a quick, painless, minimally invasive, and site-specific sampling process that can be carried out over time on many times **(Delucchi et al., 2023)**. To prevent additional variables that could affect the outcomes, such as sulcus bleeding and saliva from the surrounding area, the implants during PICF collection need to be carefully isolated, and blood-contaminated paper strips were not included in the analysis.

An essential mediator for the development of bone is BMP-2. According to **Suárez-López et al. (2015)**, BMP-2 stimulates PDL cells to become osteoblasts and upregulates the expression of markers for mineralized tissue. Conversely, IL-1 β is a strong pro-inflammatory cytokine that contributes significantly to both inflammation and bone resorption; for this reason, it is an essential variable in periodontal studies **(Bergmann A and Deinzer R., 2008).**

The two treatment modalities were effective in reducing the clinical parameters associated with peri-implantitis. The reported results clearly showed that the reductions in MPI, MBI, and IPD were significantly greater in both treatment modalities. This is in accordance with Nart et al., who reported that non-surgical management of peri-implantitis was effective in reducing suppuration and peri-implant pocket depth, but had no effect on bleeding on probing **(Nart et al., 2019).** In the other hand, Del Amo et al., reported in a systematic descriptive review that non-surgical management of peri-implant mucositis produce notable positive outcomes in contrast to peri-implantitis lesions which can't be resolved completely with only non-surgical management **(Del Amo et al., 2016).**

Although BMP-2 level showed improvement in both groups, it was non-significant improvement in both intra and inter groups at the whole study intervals. It could be related to the duration of assessment which extends only to 14 days after treatment. Increase in the level of BMP-2 is an indicator for bone formation, BMP-2 stimulated ALP activity, promoted mineralization, improve adhesion, and mediated the production and activation of specific related osteogenic markers, which helped

bone mesenchymal stem cells differentiate into osteoblasts **(Sun et al.,2015).**

Regarding IL-1 β level, it showed intragroup significant improvement in both groups from baseline to 7 and 14 days after treatment, while in comparison between group I and group II, no significant difference was found. According to our results, we found that IL-1β levels increase in peri-implantitis and significantly decrease in both treatment modality. This is in accordance with Gündoğar et al., whose studies the effect of periodontal and peri-implanter health on the level of IL-1β and TNF-α in both gingival crevicular and peri-implanter sulcus fluid **(Gündoğar et al., 2021).**

According to our results, in spite of non-significant improvement in group I on the level of the clinical and biochemical parameters in comparison to group II, it may be explained by the anti-inflammatory and anti-oxidative properties of propolis, suppressing mitogen-activated protein kinases and NF-kB pathway and upregulating the expression of antioxidant enzymes through Nrf2 signalling activation, respectively (**Song MY et al., 2020).**

Additionally, Propolis significantly reduced the levels of TNF-α and IL-1β in the rat model, indicating that this may be one of the mechanisms by which Propolis counteracts immunological and anti-inflammatory responses by preventing mononuclear macrophage activation and differentiation. Propolis may have anti-inflammatory properties by blocking prostaglandin E2 synthesis, inducible cyclooxygenase-2 expression, and nitric oxide (NO) production **(Burdock et al., 1998; Tan-no et al., 2006).**

The effect of propolis on bone formation had been studied by Altan et al., in 2012. They found that bone formation in the expanded premaxillary suture could be accelerated when propolis is systemically applied **(Altan et al., 2012)**. The effects of propolis on fracture healing were investigated in a study by Guney et al., and the beneficial effects of propolis were studied in relation to time **(Guney et al., 2011)**. According to a different study, applying a layer of propolis together with an allograft improved and sped up osseointegration while also reducing the consolidation period **(Boudra et al., 2014)**. It has been demonstrated that propolis can promote bone formation on the surface of titanium implants **(Al-Molla et al., 2014).**

Regarding the results of group II, chlorohexidine acts as an adjunctive therapy to non-surgical management of peri-implantitis (**Crespi et al., 2019).** chlorohexidine binds to the proteins in the saliva and exfoliated epithelial cells block the acidic valences of the glycoproteins in saliva, and decrease glycoprotein integration, preventing pellicle formation. Also, it inhibits the growth of bacterial plaque, and competes with calcium ions to stop the binding of mature plaque. **(Qiu, W et al.,2020).**

This is in contrast with the studies of (**Machtei et al., 2021**) and **(Levin et al.,2015)** which reported no significant difference in results between CHX and control which was non- surgical debridement only. The variation in outcomes may be explained by the different treatment methodology or difference in chlorohexidine concentration.

Our results in agreement with a systematic review and Bayesian network meta-analysis of complementary treatment for peri-implantitis made by Faggion et al., who found that both singular and combined non-surgical modalities, such as chlorhexidine chips, produced higher IPD reductions than debridement alone **(Faggion et al., 2014)**.

CONCLUSIONS

Despite the limitations (limited sample size, follow-up period and standardization) of our study. The use of either chlorhexidine or propolis gel with the mechanical debridement of peri-implantitis has a role in decreasing inflammation, plaque accumulation, and reduction in probing pocket depth and level of IL-1β as a proinflammatory cytokine and increasing BMP-2 level which is an indicator of bone formation.

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