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Original Article

The comparative evaluation of 1% alendronate gel as local drug delivery system in chronic periodontitis in smokers and non smokers: Randomized clinical trial

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ABSTRACT

Introduction: Periodontitis is a progressive disease of microbial origin involving the loss of supporting tissues of the teeth resulting from host inflammatory and immunologic reactions. The standard approach to the prevention and treatment of periodontal diseases for a number of years has been mechanical therapy and if required surgical intervention Researcher thought of creating a treatment modality where by altering the host response, the destructive host mechanisms could be interfered affecting the final outcome of the disease process.

Aim: The present study aims to explore the efficacy of local delivery of a 1% Alendronate (ALN) gel as an adjunct to scaling and root planing (SRP) for the treatment of infrabony periodontal pockets in smokers and non-smoker with Chronic Periodontitis.

Materials and method: 60 infrabony periodontal pockets in patients with chronic periodontitis between the age group of 30–50 years were selected. The study consisted of 2 groups smoker and nonsmoker. A gel based drug delivery system of Alendronate was formulated. 0.1 ml alendronate gel and 0.1 ml placebo gel was placed at the experimental and control sites respectively following root planing. Clinical and radiographic parameters were recorded at baseline, three months and six months.

Results: Alendronate was effective in improving clinical and radiographic parameters compared to placebo. Alendronate showed better result in non smoker group when compared with smoker group.

Conclusion: This Study showed improvements in clinical parameters both at the control and experimental sites. However, the experimental sites (Alendronate) showed greater improvement as compared to the control sites (Placebo). A significant gain in alveolar crest height and defect fill was measured radiographically at non smoker Alendronate group.

1. Introduction

Periodontitis is a chronic progressive disease of bacterial origin involving the loss of supporting tissues of the teeth. It results from host inflammatory and immunologic reactions to one or more bacterial pathogens and is characterized by the loss of periodontal attachment on the root surface and alveolar bone.[1] The standard approach to the prevention and treatment of periodontal diseases for a number of years has been mechanical therapy and if required surgical intervention for regeneration of the structures lost due to periodontal disease.[2,3,4]

The concept of reducing the plaque bacteria by standard approaches as the only treatment of periodontal disease was changed when investigators began to document the host's contribution to disease pathogenesis.[5]

Host response is a protective mechanism but concomitantly induce tissue damage, alveolar bone resorption viz breakdown of connective tissue fibers in the periodontal ligament. Consequently, Researchers thought of creating a treatment modality where in by altering the host response, the destructive host mechanisms could be interfered by altering the outcome of the disease process. A great interest has been generated in this field with the development of host modulatory therapy against periodontal disease. Host modulation reduces bone resorption by modifying the destructive aspects of the host response.[4,5] A number of host modulatory agents have been investigated in clinical trials. Among those, bisphosphonates are a unique class of pharmacological agents which are potent inhibitors of bone resorption and have

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been effectively used to treat metabolic bone diseases in humans such as Paget's disease, hypercalcaemia of malignancy, osteoporosis and estrogen deficiency.[6,7] It is logical to hypothesize that any therapeutic agent that can cause suppression of bone resorption can protect against alveolar bone loss in periodontitis. Bisphosphonates suppress osteoclast- mediated bone resorption as it is well taken up by the skeleton. Among the various bisphosphonates, Alendronate (4 - amino 1 - hydroxybutylidine bisphosphonate), is a very persuasive inhibitor of bone resorption.[8] A number of animal and human studies have proved the efficacy of bisphosphonates in treating metabolic bone diseases.[9,10] Smoking is one among those confounding factors that affect the treatment outcome.[11] Since chronic Periodontitis is more prevalent and resistant to treatment in smokers, a chemotherapeutic agent such as Alendronate could be a breakthrough in treating such resistant cases.

Present study was undertaken with the aim to explore the efficacy of a 1% Alendronate (ALN) gel as a local drug delivery system in smokers and non-smokers as an adjunct to scaling and root planing (SRP) for the treatment of infrabony periodontal pockets in patients with chronic periodontitis and to evaluate the periodontal tissue response in smokers and non-smokers both clinically and radiographically.

2. Material and methods

A total of 60 sites with infrabony defects from 17 patients (age range 30–50 yrs) with chronic periodontitis were selected from the outpatient section of Department of Periodontics, Manav Rachna Dental College, Faridabad, India. An equal number of smokers and non-smokers were included. Allocation of the patients into various subgroups was done with the help of flip of a coin. The research protocol was approved by institutional ethical committee and review board and a written informed consent was taken from all the participants in the study.

2.1. Selection criteria

Selection criteria included pocket depth ≥ 5 mm, clinical attachment loss ≥3 mm and radiographic evidence of vertical osseous defects 3–6 mm were selected. The distribution of which has been summarized in Fig. 1. Smokers were classified by using criteria established by the Centers for Disease Control and Prevention (CDC)[12] Patient with known systemic disease, history of use of antibiotics 6 months prior to the study, suspected allergy to ALN/bisphosphonte therapy, Alcoholics, Immunocompromised patients and lactating females were excluded from the study.

2.2. Preparation of the gel[13]

The Alendronate gel was prepared in accordance with the method described by Reddy et al.

200 mg of Alendronate sodium was dissolved in 100 ml of distilled water. To get a concentration of 1% 200gms of Carbopol 934 P was added as a viscosity increasing agent The mixture was then stirred gradually and Carbopol was allowed to soak for 2 h. Thereafter, 0.5 ml of triethanolamine and 30 mg of Methyl paraben was added to the gel. 10 mg of Propyl paraben dissolved in 2 ml of Ethanol was added to the preparation. Triethanolamine neutralizes the acidic ph of carboxylic acid in carbopol 934-P and methyl paraben and propyl paraben act as preservatives.The gel formulations were sterilized by autoclaving for 30 min at 121 °C. The same procedure was followed for the placebo gel except for the addition of Alendronate sodium.

3. Methods

All the patients received a full mouth scaling and root planing and were randomly assigned to either the Alendronate gel or placebo gel subgroups. Since it was a single blind study, the identity of the gel being placed in the patients was not revealed to the clinician who was placing the gel. These gels were labelled as gel 1 and gel 2 and provided to the clinician. The identity of the gel was revealed to the examiner only after the end of the study.

The experimental area was dried properly with gauze and well isolated. The pocket wall was then separated from the tooth surface with the help of an air syringe. 0.1 ml of the Alendronate gel was carefully injected into the pocket with the help of a syringe and needle (the tip of which was made blunt). (Figs. 2 and 3) Pocket was pressed firmly for 5 min after delivery. Due to it carbopol 934p content, the gel swells upon hydration,thus forming a colloidal dispersion. The insoluble ingredients as a result were permanently trapped in the interstitial spaces between the hydrogel particles.

3.1. Clinical assessment

Clinical parameters including Plaque index (PI) (Silness and Loe)[14] Gingival index (Loe and Silness),[14] Pocket depth (PD), Clinical attachment level were recorded at baseline, 3 and 6 months.Measurement were standardized by custom-made acrylic stent and a colour-coded periodontal probe (UNC-15) were used to record clinical parameters.

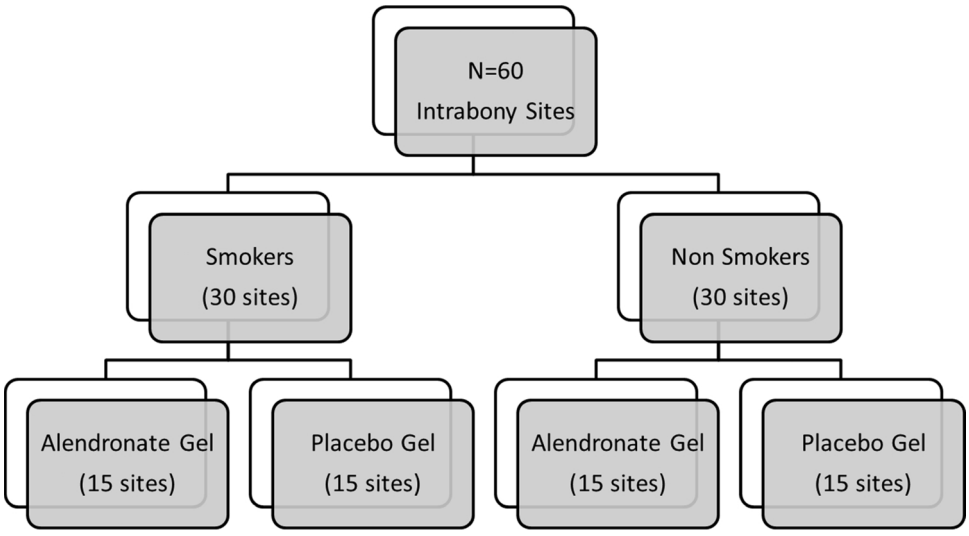

Fig. 1. Distribution of sample into different group.

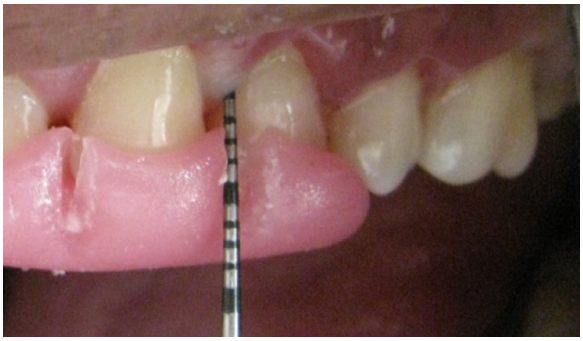

Fig. 2. Measuring the periodontal pocket.

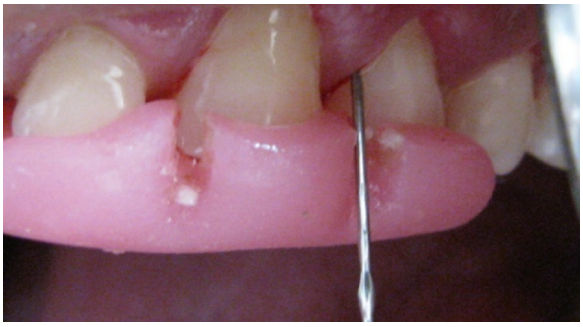

Fig. 3. Placing the gel with blunt needle.

3.2. Radiographic assessmentof infra bony defects (IBDs)

Bone fill was evaluated at baseline and 6 months using a computer aided software. An intraoral periapical radiograph of each defect site was taken by using the Long Cone Paralleling technique. All the radiographs were then scanned and digitized by using Epson perfection V700 photo scanner. Linear measurements were then made on the digitized images using Adobe photo shop 7.0 computer software. Landmarks for radiographic assessment were marked on the digitized image of the radiograph which included, Cemento-enamal-junction (CEJ),Alveolar crest (AC), Base of the defect (BD) (Fig. 4)

The calculations for radiographic parameters were done as described ahead. Percentage of original defect resolved (ODR) was calculated as the percentage change in distance from alveolar crest to base of defect over six months [(B0–B6) × 100/ B0]. Amount of defect fill (DF) was determined by change in mm from CEJ to BD over 6 months (A0-A6). Percentage fill of original defect (OD) was assessed by dividing Defect fill with distance from AC to BD at baseline in percentage (DF/ B0 × 100). Change in alveolar crest (ACH) was determined by change in distance from CEJ to AC from baseline to 6 months in mm (C0-C6). Percentage change in alveolar crest height was assessed by dividing ACH by distance from alveolar crest to base of defect at baseline (ACH × 100 / B0)

3.3. Primary and secondary outcome measures

Complete bone defect fill was ascertained to be the primary outcome of our study where PD,CAL,PI and GI were the secondary outcomes.

3.4. Statistical analysis

Plaque index, Gingival Index, Probing depth and Clinical Attachment Level was summarized as mean values, and standard deviation using SPSS 21software graphs were prepared on Microsoft Excel. Inferential statistics were performed using Repeated Measures of Analysis of Variance (ANOVA) Test and student t-test

4. Results

Sixty sites, with 30 sites each in smokers and non-smokers were randomly treated with either Alendronate gel or the placebo gel. The periodontal status of all test sites was assessed at baseline, three months and six months. The PI in all the subgroups significantly reduced from baseline to six months ($p < 0.001$) (Table 1). Although there was no significant difference in PI scores ($p < 0.05$) between Alendronate and placebo groups in both smokers and non-smokers. Similar results were observed for GI also (Table 2).

Clinical parameters PD and CAL showed no difference ($p < 0.05$) at baseline in both the groups. At 3 months the reduction in PPD and CAL gain was maximum with respect to Alendronate non smoker group. Although there was significant PD reduction and CAL gain at 6months in both subgroups smoker and non smoker ($p < 0.001$). Overall the result achieved was better with non smoker group whether Alendronate or placebo was used (Tables 3 and 4). All the radiographic parameters (ODR,DF,OD,ACH,%age change in alveolar crest height)showed a highly significant difference between the Alendronate and placebo groups in both smokers and non smokers with highly significant contribution of Alendronatet defect fill and resolution.Also, the Alendronate gel was significantly more effective in non smokers than smokers for all the radiographic parameters of bone defect resolution.

Percentage of original defect resolved was seen maximum in cases of Alendronate nonsmoker group. ODR was stastically highly significant in Alendronate smoker and nonsmoker($p < 0.001$) and Alendronate group also showed stastically significant ODR when compared to placebo ($p < 0.001$).ODR in placebo smoker showed moderately significant amount of defect resolved. Same findings were observed in Alendronate group wrt to defect fill. The placebo group did not show any significant defect fill between smoker and non smoker ($p = 0.348$) when compared to ALN group. Alendronate non smoker showed the highest amount the highest amount of defect fill(2.48 ± 0.46) when compared to ALN smoker group($p < 0.001$) and placebo smoker group ($p < 0.001$) and placebo non-smoker. Percentage of original defect resolved, change in alveolar crest and percentage change in alveolar crest height showed similar result as obtained in case of defect fill. Maximum percentage of defect fill, change in alveolar crest and

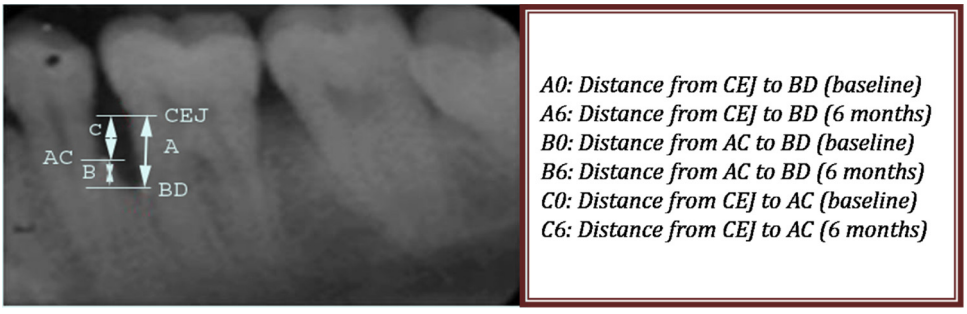

Fig. 4. The radiographic parameters depicted in figure were recorded at baseline and 6 months post treatment.

Table 1
Comparative evaluation of Plaque index at baseline, 3 and 6 months between Alendronate and Placebo and in smokers and non smokers.

PLAQUE INDEX									
	BASELINE			3 MONTHS			6 MONTHS		
	ALENDRONATE	PLACEBO	P VALUE	ALENDRONATE	PLACEBO	P VALUE	ALENDRONATE	PLACEBO	P VALUE
SMOKER	1.55 ± 0.39	1.55 ± 0.32	0.99	1.18 ± 0.42	1.17 ± 0.35	0.90	0.60 ± 0.16	0.55 ± 0.14	0.36
NON SMOKER	1.93 ± 0.49	1.93 ± 0.54	0.99	1.35 ± 0.44	1.33 ± 0.44	0.91	0.50 ± 0.34	0.62 ± 0.40	0.39
P VALUE	0.024,S	0.02,S		0.29	0.26		0.31	0.54	

Table 2
Comparative evaluation of Gingival index at baseline, 3 and 6 months between Alendronate and Placebo and in smokers and non smokers.

GINGIVAL INDEX									
	BASELINE			3 MONTHS			6 MONTHS		
	ALENDRONATE	PLACEBO	P VALUE	ALENDRONATE	PLACEBO	P VALUE	ALENDRONATE	PLACEBO	P VALUE
SMOKER	1.55 ± 0.32	1.50 ± 0.39	0.70	1.17 ± 0.35	1.10 ± 0.42	0.64	0.55 ± 0.14	0.58 ± 0.15	0.54
NON SMOKER	1.93 ± 0.49	1.88 ± 0.51	0.78	1.35 ± 0.44	1.22 ± 0.57	0.48	0.57 ± 0.33	0.63 ± 0.41	0.62
P VALUE	0.016,S	0.028,S		0.217	0.530		0.860	0.662	

Table 3
Comparative evaluation of Pocket probing depth at baseline, 3 and 6 months between Alendronate and Placebo and in smokers and non smokers.

POCKET PROBING DEPTH									
	BASELINE			3 MONTHS			6 MONTHS		
	ALENDRONATE	PLACEBO	P VALUE	ALENDRONATE	PLACEBO	P VALUE	ALENDRONATE	PLACEBO	P VALUE
SMOKER	7.07 ± 0.96	7.00 ± 0.93	0.85	5.87 ± 0.74	5.47 ± 0.99	0.23	4.60 ± 0.83	4.73 ± 0.88	0.43
NON SMOKER	7.33 ± 0.98	6.93 ± 0.80	0.23	5.47 ± 0.99	4.53 ± 0.83	0.009,S	3.07 ± 0.70	3.27 ± 0.27	0.17
P VALUE	0.45	0.834		0.22	0.009,S		< 0.001,S	< 0.001,S	

Table 4
Comparative evaluation of Clinical attachment level at baseline, 3 and 6 months Between Alendronate and Placebo and in smokers and non smokers.

CLINICAL ATTACHMENT LEVEL									
	BASELINE			3 MONTHS			6 MONTHS		
	ALENDRONATE	PLACEBO	P VALUE	ALENDRONATE	PLACEBO	P VALUE	ALENDRONATE	PLACEBO	P VALUE
SMOKER	7.80 ± 1.15	7.60 ± 1.24	0.65	6.60 ± 0.91	6.00 ± 1.13	0.12	5.33 ± 1.05	5.73 ± 0.88	0.21
NON SMOKER	8.13 ± 1.13	7.80 ± 1.01	0.40	6.27 ± 1.10	5.40 ± 0.99	0.03,S	3.87 ± 0.83	4.13 ± 0.83	0.36
P VALUE	0.42	0.633		0.37	0.133		< 0.001,S	0.002,S	

Table 5
Comparative evaluation of Radiographic indices at baseline and 6 months in Alendronate and Placebo.

	Percentage of original defect resolved (ODR)			Differences in amount of defect fill (DF)		
	Alendronate	Placebo	P Value	Alendronate	Placebo	P Value
Smokers	14.84 ± 6.26	8.06 ± 5.18	< 0.002,S	1.66 ± 0.53	0.73 ± 0.39	< 0.001,S
Non Smokers	25.51 ± 8.26	14.80 ± 8.06	< 0.001,S	2.48 ± 0.46	1.12 ± 1.55	< 0.003,S
P Value	< 0.001,S	< 0.008,S		< 0.001,S	0.348,NS	

Intragroup and intergroup comparisions- student's t –test. $p \leq 0.05$ (significant).

percentage change in alveolar crest height was obtained in Alendronate non smoker group and minimum change in radiographic indices was observed in placebo smoker group (Tables 5 and 6).

5. Discussion

Periodontal disease is a multifactorial, infectious disease that results from the interaction of the host defense systems with the microorganisms in plaque, causing destruction of the supporting structures of the teeth.[4] A better understanding of the role of host immune inflammatory mediators in the progression of the disease has directed investigations towards the potential use of modulating agents as adjuncts to routine periodontal treatment.[5] Bisphosphonates are a unique class of pharmacological agents that are potent inhibitors of bone resorption by

Table 6
Comparative evaluation of Radiographic indices at baseline and 6 months in Alendronate and Placebo.

	Percentage fill of original defect (OD)			Change in alveolar crest (ACH)			Percentage change in alveolar crest height		
	Alendronate	Placebo	P Value	Alendronate	Placebo	P Value	Alendronate	Placebo	P Value
Smokers	33.24 ± 12.46	18.13 ± 10.18	< 0.001,S	0.24 ± 0.51	−0.16 ± 0.29	< 0.013,S	5.16 ± 10.37	−3.07 ± 5.95	< 0.014,S
Non Smokers	52.84 ± 13.71	21.13 ± 26.37	< 0.001,S	1.34 ± 0.55	−0.33 ± 0.41	< 0.001,S	28.61 ± 12.79	−0.50 ± 6.87	< 0.001,S
P Value	< 0.001,S	0.685,NS		< 0.001,S	0.339,NS		< 0.001,S	0.283,NS	

Intragroup and intergroup comparisions- student's t –test. $p \leq 0.05$ (significant).

osteoclasts. They have an affinity to bind to hydroxyapatite crystals, to increase osteoblast differentiation. Several animal and human studies reported the effectiveness of Alendronate in preventing alveolar bone destruction associated with periodontal disease when administered systemically or locally to the target site.[15,16,17,18] Literature has shown that systemic use of Alendronate sodium in medically compromised patients is associated with osteonecrosis of the jaw bone. However, when used topically no cytotoxic effects have been seen.[19] The role of smoking in periodontal disease has been well documented, it being considered a major risk factor, affecting the prevalence, extent and severity of disease and also affects the mineral content of bone tissues.[20] Also,it has been observed that smoking induces an acceleration of the periodontal bone height reduction rate.[21] A plethora of evidence suggests that surgical and non-surgical treatments are less successful in smokers than in non-smokers.[22] It is evident from the mean values that a proportionate decrease in Gingival and Plaque indices was observed in the Alendronate and placebo sites from baseline to 3 and then to 6 months post treatment. These reductions were statistically significant and possibly attributable to a large extent to the non surgical therapy itself.When the Alendronate and placebo subgroups were compared in smokers and non-smokers the reduction in Gingival Index and Plaque Index scores was not significant, but a comparatively greater reduction was seen in the non-smoker Alendronate subgroup. This may be explained by the different immune response of smokers and non-smokers which has been established in several previous studies.[23,24]

Significant difference in gingival index and plaque index scores between the Alendronate and placebo groups was seen in previous studies also which could be attributed to the action of Alendronate on bone tissues alone.[25,9,10,26]

On intergroup comparison significant reductions in probing pocket depth and gain in clinical attachment level were observed at the Alendronate subgroup at 3 months in non-smokers only. Similar results were obtained by Rocha M et al.[27] Veena H.R et al.[13] and Sharma A et al,[26] who reported a trend towards decreased pocket depth after treatment with Alendronate compared to a placebo. In the present study, when smokers and non-smokers were compared, Non-smokers showed a statistically significant greater reduction in pocket depth and gain in clinical attachment level at the end of 6 months as compared to smokers as seen in study.[24]

On assessment of radiographic parameters the percentage of original defect resolved showed a significant change over 6 month duration in the Alendronate and placebo sites. Similar findings were seen in studies done by Kaynak D et al,[28] Rocha M et al, [27] Veena H.R et al.[13] and Sharma A et al.[26]

When all the Alendronate and placebo sites were compared, the Alendronate subgroups in both smokers and non-smokers showed a greater percentage of original defect resolved as compared to the placebo subgroups. Therefore, additional benefit may be derived by the application of Alendronate in the presence of a risk factor such as smoking for the treatment of Periodontitis.

A highly significant change in amount of defect fill was observed in the Alendronate sites over 6 months duration. A mean defect fill of 2.07 mm was observed at the Alendronate sites, while the placebo sites showed a mean defect fill of 0.93 mm only. The post operative percentage of defect fill was greater in the Alendronate sites (43.04%) compared to the placebo sites (19.63%). These findings were in accordance with the findings of Meraw SJ et al, [29] Reddy MS et al,[9] Brunsvold MA et al,[30] Veena H.R et al[13] and Sharma A et al[26] who demonstrated that Alendronate clearly reduced loss in bone density as measured radiographically.

This may be explained by the affinity of Alendronate for binding to the hydroxyappetite crystals of bone and their promotion of osteoblast differentiation. The percentage increase in alveolar crest height from baseline to 6 months was 16.89% for the Alendronate subgroup ($p < 0.001$). The placebo subgroup showed a percentage reduction of -1.79% in alveolar crest height thus indicating a statistically highly significant ($p < 0.001$) difference in alveolar crest height between the Alendronate and placebo sites. This data was in accordance with the findings of Binderman I et al,[31] Kaynak D et al[28] and Yaffe A et al,[32] who demonstrated that Alendronate was effective in reducing alveolar bone loss. Rocha M et al,[27] also demonstrated that Alendronate increased alveolar bone height.

5.1. Conclusion

In the present study, the Alendronate is used as an adjunct to mechanical non surgical periodontal therapy in Chronic Periodontitis patient who are having a risk factor of smoking. Alendronate administration showed a gain in bone density and improved bone mass when used to treat periodontal defects. Mechanical non-surgical periodontal therapy results in a significant reduction in plaque scores, gingival inflammation and pocket depth, and gain in clinical attachment. All patients tolerated the gels well, without any complications or adverse reactions throughout the study period. However, Smokers also showed the improvement in the Alendronate subgroup as compared to placebo group. In future Alendronate gel can be used as a chemotherapeutic agent to reduce bone loss.

To the best of our knowledge, this study is one of the first of its kind on the efficacy of Alendronate incorporated into a local drug delivery system for direct placement in the periodontal pocket of smokers with Chronic Periodontitis.

5.2. Limitations

Firstly, the study was limited in its design as 2 dimensional images i.e. intraoral radiographs were used to check changes in a 3 dimensional structure i.e. alveolar bone. Secondly, the clinical results obtained would be better explained if the drug release profile from local drug delivery system had also been assessed. Thirdly long term studies, with a larger sample size will be required.

Conflict of interest

There is no conflict of interest.

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