Comparative Evaluation of Efficacy of 1.2% ATV Gel and 1 % ALN Gel as Local Drug Delivery for the Treatment of Intrabony Defect in Individuals with Chronic Periodontitis – A Randomized Controlled Clinical Trial

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ABSTRACT

Introduction: Atrovastatin (ATV) is a specific competitive inhibitor of 3-hydroxy-2-methyl-glutaryl coenzyme A reductase. Recently, statins have shown pleiotropic effects such as anti-inflammation and bone stimulation. Alendronate (ALN), an aminobisphosphonate, is known to inhibit osteoclastic bone resorption and was proposed to have osteostimulative properties in vivo and in vitro as shown by an increase in matrix formation. The aim of the present study is to compare the efficacy of 1.2% atv gel and 1.2 % aln gel as local drug delivery for the treatment of intrabony defect in individuals with chronic periodontitis.

Material and methods: Sixty six individuals were randomized into two treatment groups : SRP plus 1.2% ATV and SRP plus 1 % ALN gel. At baseline and 3, 6, and 9 months, clinical parameters, which included modified sulcus bleeding index, plaque index, probing depth (PD), and clinical attachment level (CAL), were recorded at baseline. Radiologic assessment of IBD fill was done using computer-aided software at baseline and 6 and 9 months.

Results: No significant difference observed between the two groups in terms of Mean PD reduction and mean CAL gain at 3, 6 and 9 months. Also the radiographic bone fill in both the groups were similar at different time intervals.

Conclusion: Both the drugs (1.2% ATV & 1 % ALN gel) when used as local drug delivery in the intrabony defects in chronic periodontitis patients were equally effective in decreasing all clinical parameters and significant gain in CAL and bone fill.

Keywords: Atrovastatin, Alendronate (ALN), Chronic Periodontitis, Scaling and Root Planing.

INTRODUCTION

Although periodontal diseases are initiated by bacteria that colonize the tooth surface and gingival sulcus, the host response is believed to play an essential role in the breakdown of connective tissue and bone, which are key features of the disease process[1]. As infection progresses there is a disturbance in the balance of host – parasite equilibrium which causes an excessive host response, leading to the destruction of periodontium and periodontal pocket formation[2]. Current techniques to treat bony defect associated with periodontitis or dental implants consists of surgically placing bone particles or substitutes into the defects to stimulate host bone formation[3]. Williams stated that there are datas from the studies in animal and human trials indicating that pharmacological agents that modulate the host responses that are believed to be involved in the pathogenesis of periodontal destruction may be efficacious in slowing the progression of disease[4]. Among several such agents local drug delivery of Bisphosphonate such as alondronate [5] and statins such as simvastatin[6] atrovastatin[7] have shown considerable percentage defect depth reduction and hence increased longevity of previously periodontally compromised teeth. Statins (Hydroxy methyl glutaryl coenzyme A reductase inhibitors) are a group of lipid-lowering drugs that are widely used to prevent cardiovascular events 8. Anti inflammatory and bone stimulating properties are among the action of statins that could positively effect periodontitis[9]. Furthermore, statins have been reported to stimulate the expression of bone anabolic factors, such as VEGF and BMP-2 and to promote osteoblastic differentiation and mineralization in MC3T3-E1 cells[10].

Bisphosphonates were also proposed to have osteostimulative properties as shown by an increase in matrix formation [11]. Previous studies also demonstrated that bisphosphonates induced osteoblasts to secrete inhibitors of osteoclast mediated resorption and stimulated the formation of osteoblast precurssors and mineralized nodules, thereby promoting early osteogenesis[12]. Studies also demonstrated systemic or topical applicationof Alendronate gel was highly effective in reducing the alveolar bone loss and increasing bone density[13].

Till date no study has been conducted comparing the effect of bisphosphonates and statins as a local drug delivery in the treatment of intrabony defect in individuals with chronic periodontitis. Considering the above facts the current study is designed as a single – center , randomized , controlled clinical trial to compare the efficacy of 1.2 % ATV and 1 %

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ALN as local drug delivery for the treatment of intrabony defect in individuals with chronic periodontitis.

MATERIAL AND METHODS

Source of data : in this longitudinal interventional study with 9 month follow up a total of 70 individuals (35 females and 35 males age 34-50) who was diagnosed with severe chronic periodontitis were selected from outpatient department of M.G.M. Medical college and hospital , Jamshedpur. The research protocol was initially submitted to ethical comitee of M.G.M. Medical college. After ethical approval , all individuals were verbally informed and written informed consent was taken for participation in the study.

Selection of Participants

Systemic healthy patients were selected using the following inclusion criteria

1. Participants with site showing PD ≥ 5 mm, CAL ≥ 4 mm and vertical bone loss ≥ 3 mm (on intra-oral periapical radiograph)and those with no history of periodontal therapy in the last 6 months.

Participants using antibiotics therapy 3 months prior to and during the 1st 3 months of study were excluded.

Exclusion criteria also included following :

1. Participants allergic to ATV and ALN.
2. Participants with aggressive periodontitis.
3. Immunocompromised participants
4. Patient with heavy alcohol and smoke use.
5. Lactating / pregnant females

After patient enrollment by an examiner individuals were randomly assigned to either ATV group or ALN group. In the ALN group , sites were treated with SRP followed by a 1% ALN gel (10 mg/ml) local drug delivery , whereas in the ATV group sites were treated with SRP followed by 1.2 % ATV gel (1.2mg/0.1ml) local drug delivery. Only one site per patient was enrolled for either ATV or ALN group. Individuals were masked for allocation into ATV or ALN group. SRP was performed at base line until the root surface was considered smooth and clean by the operator. Clinical parameters include Plaque index (PI), modified sulcular bleeding index (mSBI), probing depth (PD), and clinical attachment level (CAL), were recorded at base line (before SRP) and at 3, 6 and 9 months. A custom made acrylic stent and a colour coded periodontal probe were used to standardize the measurement of clinical parameters. All pre and post treatment clinical parameters were recorded by an examiner (ARP) who was masked to the treatment received whereas another clinician (AS) provided the treatment to both the group.

Radiographic assessment of intrabony defect depth (IBDs)

The depth of IBDs (bone fill) was evaluated at base line, and at 6 month using an image analyzer. IBDs were measured on the radiographs by measuring the vertical distance from the crest of the alveolar bone to the base of the defect. Individually customized bite block and a parallel-angle technique were used to obtain films as reproducible as possible. All radiographs were reviewed in a single reference center by a masked evaluator (SSM). For assessment, radiographs were scanned with a 6,400-dpi scanner‖ by the evaluator (SSM) who was masked to treatment group. The radiographic IBD depth was measured by computer-aided software as in previous studies.

Formulation of 1% ALN gel AND 1.2% ATV gel

The ALN gel was prepared as described by Reddy et al[14] and ATV gel was prepared as described by Pradeep et al[15].

Local drug delivery

For standardization 10µL prepared ALN gel (10mg/ml) and 10µL prepared ATV gel (1.2 mg/0.1ml) was injected into the periodontal pocket using a syringe with blunt cannula. Individuals were instructed to refrain from chewing hard or sticky foods near the treated areas or using interdental aids for 1 week.

STATISTICAL ANALYSES

To achieve 90% power and detect mean differences of the clinical parameters between groups, 30 sites in each group were required. The categoric variable (site-specific PI) was expressed as percentage and continuous variables (full-mouth PI, mSBI, PD, CAL, and IBD depth) as mean – SD. Site-specific PI was compared by using the x2 test or a Fisher exact test when the expected frequency was <5. Normality assumption was tested using the Shapiro-Wilk W test. Between-group comparison was carried out using Student t test if continuous variables followed a normal distribution. Statistical significance was defined as P <0.05. Statistical analysis was performed with statistical software.¶

RESULTS

Sixty six (one site per patient) of 70 participants completed the study. All individuals tolerated the drug well without any

	Visit	ATV group	ALN group	p-value
Plaque index (PI)	Base line	1.9 ± 0.02	1.85 ± 0.28	0.87
	3 months	1.1 ± 0.17	1.16 ± 0.42	0.07
	6 months	0.5 ± 0.14	0.6 ± 0.15	0.01
	9 months	0.6 ± 0.15	0.7 ± 0.15	0.048
Mean sulcular bleeding index (m-SBI)	Base line	2.1 ± 0.61	2.1 ± 0.69	0.85
	3 months	1.1 ± 0.68	1.50 ± 0.80	0.02
	6 months	0.9 ± 0.73	1.30 ± 0.82	0.04
	9 months	0.7 ± 0.56	1.3 ± 0.86	0.002

Table-1: Full mouth plaque score and m-SBI for ATV group and ALN group at different time interval.

Parameters	ATV group	ALN group	p value
PD (mm)			
Base line	7.77 ± 1.30	7.73 ± 1.14	0.916
3 months	5.57 ± 0.77	5.45 ± 1.45	0.001
6 months	4.33 ± 0.88	4.20 ± 0.95	0.07
9 months	4.07 ± 0.07	4.02 ± 1.17	0.87
CAL (mm)			
Base line	7.03 ± 1.43	7.40 ± 0.91	0.87
3 months	4.33 ± 1.06	4.60 ± 0.06	0.08
6 months	2.83 ± 0.87	2.60 ± 0.97	0.96
9 months	2.57 ± 0.86	2.50 ± 0.87	0.78
IBD depth (mm)			
Base line	5.0 ± 0.64	4.79 ± 0.84	0.772
6 months	3.70 ± 0.72	3.15 ± 0.46	0.85
9 months	3.5 ± 0.46	3.09 ± 0.40	0.96

Table-2: PD (probing depth) , CAL (clinical attachment level), and IBDs depth (intra bony defect depth) in ATV group and ALN groups at different time interval.

Parameters	ATV group	ALN group	p value
PD (mm)			
3 months	2.20 ± 0.54	2.28 ± 0.45	0.916
6 months	3.40 ± 0.56	3.53 ± 0.47	0.723
9 months	3.70 ± 0.59	3.71 ± 0.49	0.845
CAL (mm)			
3 months	2.70 ± 0.54	2.80 ± 0.54	0.721
6 months	4.20 ± 0.60	4.80 ± 0.97	0.687
9 months	4.46 ± 0.60	4.90 ± 0.67	0.897
IBD depth (mm)			
6 months	1.30 ± 0.46	1.64 ± 0.57	0.87
9 months	1.50 ± 0.35	1.70 ± 0.67	0.96
Radiographic defect fill (%)			
6 months	34.05 ± 5.79	34.65 ± 4.79	0.96
9 months	35.49 ± 5.50	35.55 ± 4.40	0.72

Table-3: Change from base line of mean PD , CAL , IBD & Bone fill (±SD) in ATV and ALN group at different time intervals.

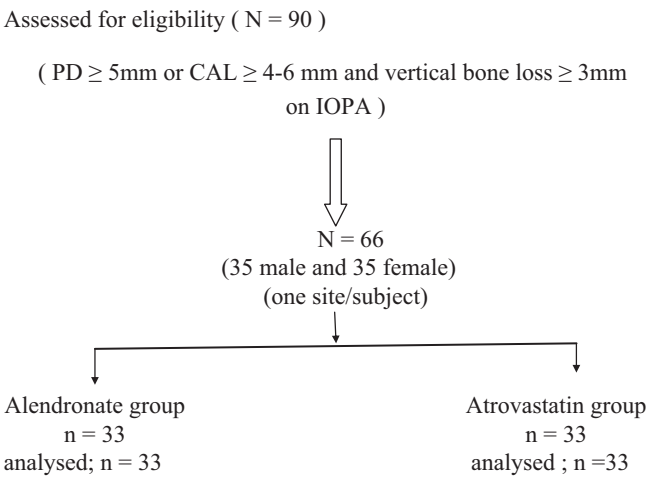
complications or adverse reactions. Soft tissue healed within normal limits. Both the groups showed improvement in site specific and full mouth PI scores but there was no statistically significant difference at any visit indicating that both the groups maintained comparable level of oral hygiene through out the study. mSBI in both the group showed no significant difference at base line and it decreased significantly in both the groups at 3 , 6 , and 9 months but there was no significant difference between the group ($p>0.05$).

Clinical parameters PD and CAL also showed no difference between the two groups at base line. However, both the group showed significantly greater PD reduction and CAL gain at 3, 6, and 9 months ($p < 0.001$) , but there was no statistically significant difference between the two groups ($p > 0.05$) .

Radiographic parameters IBD showed a statistically significant mean reduction of 1.60 ± 0.24 and 1.70 ± 0.24 at 6 and 9 months respectively in ATV group and 1.45 ± 0.46 and 1.60 ± 0.60 at 6 and 9 months respectively in ALN group. But the difference between the two groups is not statistically significant ($p > 0.001$).

ATV group sites as well as ALN group sites showed a significantly greater vertical radiographic defect fill, (34.05 % ± 5.79 % and 35.49 % ± 5.50 % in ATV group and 40.01 % ± 4.45 % and 41.02 % ± 4.56 % in ALN group).

Study flow chart



DISCUSSION

The current study compares the clinical efficacy of 1.2%

ATV and 1% ALN gel in adjunct to SRP for the treatment of IBD in chronic periodontitis patients and the result showed that both the drugs are equally competant and shows significant radiographic bone fill and improvement in clinical parameters.

Fajardo et al [16] foun that ATV administration during a period of 3 months increased alveolar bone height, decreases the distance of CEJ to alveolar bone and had a beneficial effect on tooth mobility in individuals with periodontal disease. ATV has also been reported to inhibit inflammatory cells and matrix metalloproteinases (MMPs) , which play a role in the connective tissue breakdown in periodontal disease[17]. MMPs level have been reported to be highly correlated to probing depth and bleeding on probing. In the present study there is a significant decrease in mSBI index from base line suggesting an anti-inflammatory effect of ATV. Also there is significant mean decrease in IBD depth from base line to 6 and 9 months in ATV group. Which is according to Majima et al [18] . ATV increases the secretion of osteoprotegrin (OPG), a potent inhibitor of bone resorption in human osteoblasts [19]. Also , statins directly affect osteoclasts through mechanism closely resemble the mode of action of nitrogen containing bisphosphonates and a third paracrine pathway , which acts through osteoblast – osteoclast cross talk and involves the receptor activator of NF-Kß ligand/OPG system [20].

ALN, an aminobisphosphonate is a potent inhibitor of osteoclast mediated bone resorption and it is used for the treatment of bone disorders, osteoporosis and paget's disease of bone [21]. ALN appears to affect protein prenylation in osteoclasts through inhibition of mevalonate pathway which is involved in cholesterol synthesis[22]. Previous studies reported that ALN was highly effective in reducing alveolar bone resorption.

The present study found a significant decrease in all clinical parameters PI, SBI, PD with a significant gain in CAL, in both the group, but there is no significant difference between the groups, when compared with each other. Also there is a significant bone fill in intrabony defect depth in both the group, but when compared with each other , the difference between the two group is non-significant.

CONCLUSION

On the basis of the present study we can conclude that both the drugs when used as local drug delivery in intrabony defects are equally effective in decreasing the clinical parameters and significant gain in CAL and bone fill.

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