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RESEARCH ARTICLE

EVALUATION OF EFFECTS OF 1.2% ATORVASTATIN AS A LOCAL DRUG DELIVERY: A RANDOMIZED CONTROLLED CLINICAL STUDY

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Abstract

Aim: The aim of this randomized controlled clinical trial was to assess the clinical and radiographic effects of 1.2% Atorvastatin (ATV) gel as an adjunct to scaling and root planing in treating chronic periodontitis patients with and without Type II diabetes.

Materials and Methods: 40 subjects ageing between 30 to 50 years were included in the study and were divided into two groups: Group A (chronic periodontitis) and Group B (Type II diabetics with chronic periodontitis). Periodontal status was assessed by using plaque index, modified sulcular bleeding index(mSBI), probing pocket depth and clinical attachment level(CAL) at baseline and 6 months. Intrabony defect depth fill was assessed by comparing periapical radiographs taken at baseline and at 6 months.

Results: Both the groups showed significant improvements in all the parameters from baseline to 6 months with no significant difference during the intergroup comparison. However, in Group A, there was greater fill in mean intrabony defect compared to Group B with statistical significance during intra and intergroup comparison

Conclusion: Local delivery of 1.2% ATV showed beneficial effects on periodontium with improvement in all clinical parameters. Within the limits of this study, it can be concluded that ATV, can be used for periodontal regeneration in angular defects due to chronic periodontitis.

Introduction:-

Periodontitis is a chronic inflammatory disease of periodontium occurring as a result of an interplay between bacteria, host immune response, and environmental factors. It involves a continuous destruction of periodontal ligament, cementum, alveolar bone and connective tissue[1]. In an attempt to regenerate the lost periodontal structures including alveolar bone, a magnitude of therapies have been tried with varying

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degrees of success. Amongst them, local drug delivery is a non-surgical treatment modality that employs continuous release of the desired agent at a specific site.

A variety of agents have been tried for LDD with varying and promising results among which statins are a group of hyperlipidaemic drugs that act by inhibiting 3-hydroxy 2-methyl glutaryl coenzyme-A reductase (HMG-coA) in Mevalonate pathway analogous to bisphosphonates. Statins as a LDD agent augment the expression of BMP-2, VEGF, osteocalcin, BSP, etc. The pleiotropic effects of statins include decreasing platelet aggregation, thrombus deposition, and angiogenesis by increased production of VEGF which drive their usage in the treatment of periodontitis.

Two subtypes of statins are in use (a) Natural and (b) Synthetic. Simvastatin (SMV) is a fermentation-derived lipophilic statin, whereas Atorvastatin (ATV) is a synthetic lipophilic statin. Although the plasma half-life of statins is typically short, their reduction in the concentration of low-density lipoprotein (LDL) is gradual and more sustained, with maximal effects seen after several weeks of the therapy. Plasma LDL concentrations are reduced more effectively by recently developed ATV compared to SMV[2].

Topical administration of SMV invitro in cultured rat calvarial cells and in vivo in periodontitis-induced rats by Sato. H et al[3] yielded that SMV has the potential to stimulate the osteoblastic function and it may be effective for the recovery of alveolar boneloss in rats. Saxlin.T[4] investigated the association between statin medication and periodontal infection in an adult population of 2032 samples and concluded that statin medication affects the periodontium based on its inflammatory condition. Fajardo.M.E studied the effects of ATV treatment on boneloss prevention in subjects with chronic periodontitis results suggested that systemically administered ATV might have beneficial effects on bone loss and tooth mobility in subjects with periodontal disease[5].

Considering the above facts the current study is designed as a single center randomized controlled clinical trial to evaluate the efficacy of 1.2% ATV as a local drug delivery agent in adjunct to scaling and root planing for the treatment of intrabony defects in individuals with chronic periodontitis in comparison to Type II diabetics with chronic periodontitis.

Materials & Methods:-

Source of data

In this intervention study with a 6-month follow-up, a total of 40 individuals (21 males and 19 females, aged 30 to 50 years) were recruited based on inclusion and exclusion criteria. The study population (mean age 42.34 ± 3.6 years) was divided into two groups: Group A (12F, 8M; chronic periodontitis) and Group B (13M, 7F; Type II diabetics with chronic periodontitis). The study was conducted in agreement with the principles embodied in the 1964 Declaration of Helsinki, as revised in 2000, and was approved by the institutional ethical committee. All individuals were verbally informed and written consent was taken for participation in the study.

Inclusion Criteria

1. Systemically healthy individuals with probing depth >5mm, CAL >4mm, and vertical bone loss >3mm.
2. Patients with no history of periodontal and antibiotic therapy in the preceding 6 months.
3. Type II diabetics in Group B were selected based on HbA1C diagnostic test criteria given by ADA

Exclusion Criteria

1. Patients who are on statin therapy
2. Patients with aggressive periodontitis
3. Pregnant and lactating females
4. Smokers and alcoholics
5. Immunocompromised individuals.

Clinical Parameters

1. Plaque index(PI)
2. Modified Sulcular Bleeding Index(mSBI)
3. Probing Pocket Depth(PPD)

4. Clinical Attachment Loss(CAL)
5. Intra Bony Defect Depth fill(IBD)

All the parameters were measured by using the University of North Carolina (UNC)-15 probe. To standardize the direction of probing, an individual customized clear acrylic stent was prepared for each patient.

Method Of Collection of Data

During the first visit of the subject,

1. An individualized custom-made acrylic stent was used to record all the periodontal parameters and full mouth SRP was completed
2. A preoperative radiograph of the test site was taken and 1.2% ATV was delivered with a blunt cannula till it overfilled the test site.

- All subjects were reevaluated for plaque index at 3 months.
- mSBI, PI, PD, CAL, and radiographs of the test site were evaluated at baseline, 3 months and 6 months.

Radiographic Examination

The periapical radiographs (IOPA) were taken in paralleling angle technique using a film holder device, Rinn XCP, Dentsply. The dental X-ray machine was Satelec X mind, films used were Carestream Dental (E speed). An IOPA of the test site, both in Groups A & B were taken by using an X-ray mesh gauge (Dentech, Tokyo, Japan) and individual customized bite blocks were prepared using rubber-based putty impression material.

The defect site was measured on a periapical radiograph for each site as follows

1. The height of the alveolar crest(AC) - measured from the CEJ to the AC
2. The depth of the defect - measured from the CEJ to the bottom of the defect

When two levels of AC were observed (lingual/palatal and buccal surfaces), the deepest point was considered[7].

Formulation of 1.2% Atv Gel

3%w/v methyl cellulose (low viscosity) was dissolved in distilled water under magnetic stirring to form a gel which was allowed to stand for 6hrs for complete solubilization of methylcellulose and air bubbles were removed by sonication. A weighed amount of Atorvastatin calcium was dissolved in 2ml of ethanol and was added to the gel using magnetic stirrer. Uniform mixing was ensured by mixing for about 30 minutes.

The pH of the gel was adjusted to neutral (pH7.0) by adding a dilute solution of triethanolamine (10%w/v solution in distilled water). Benzalkonium chloride (0.01%w/v) is added as a preservative. The final volume was made up by adding distilled water and prepared gels were transferred to glass vials and screw-capped till further use.

Sterilization Of 1.2% Atv Gel

The sterilization was done by exposing it to 10 kilograys (Co60 source) of γ-radiation for 20 minutes at room temperature (25°C) and 60% relative humidity at CFTRI, Mysore.

Local Drug Delivery into the Site

During the first visit, all clinical parameters were recorded followed by scaling and root planning (SRP) at the test site. After 2 weeks, a preoperative IOPA of the test site was taken and delivery of 1.2% ATV gel into the test site was done using a 2ml disposable syringe (24 gauge needle). Post-operative instructions include refraining from chewing hard or sticky foods, brushing near the treated areas or using any interdental aids for 3days. All pre and post-treatment clinical parameters were recorded by an examiner, who was masked to the treatment while another clinician provided treatment to both groups.

Statistical Analysis
The Statistical software namely SAS 9.2, SPSS 15.0, Stata 10.1, MedCalc 9.0.1,Systat 12.0, and R environment ver.2.11.1 were used for the analysis of the data, and Microsoft word and Excel have been used to generate graphs and tables.

The results were subjected to statistical analysis by the Mann-Whitney U test and Wilcoxon matched pairs test to find the significant mean difference between study parameters.

Result:-

A total of 40 patients were enrolled in the study with no dropout and no adverse effect ofthe drug. In the intergroup comparison of PI, from baseline to 3 months and from baseline to 6 months in Group A and Group B is 0.64 ± 0.21 and 1.08 ± 0.30 which is statistically significant (p=0.0004). (Table 1)

The mSBI mean score of GroupA from baseline to 6 months in Group A is 0.85 ± 0.37 which is statistically significant (p=0.0003) whereas the mean difference in Group B is 0.94 ± 0.25 which is statistically significant (p=0.0007). (Table 2)

The mean probing depth value of Group A from baseline to 6 months has shown a mean difference of 2.15 ± 0.59 mm which is statistically significant (p=0.0001). Whereas in Group B the score from baseline to 6 months is 2.00 ± 0.63 which is statistically significant (p=0.0004). (Table 3)

The mean clinical attachment level score of Group A from baseline to 6 months is 2.15 ± 0.59 mm which is statistically significant (p=0.0001). The mean difference in score from baseline to 6 months in Group B is 2.06 ± 0.68 mm which is statistically significant (p=0.0004). (Table 4)

The mean intrabony defect depth value of Group A from baseline to 6 months in is 2.15 ± 0.59 mm which is statistically significant (p=0.0001). The mean difference in score from baseline to 6 months in Group B is 2.06 ± 0.68 mm which is statistically significant (p=0.0004). (Table 5)

Discussion:-

Nonsurgical periodontal therapy has evolved over the years and has become a gold standard of periodontal therapy.[8] A strategy against biofilm infection has been proposed recently in which the dental plaque community is disrupted by targeting the easy-to-remove key members, leaving rest that cannot support pathogenic species. However, evidence shows that conventional mechanical debridement alone cannot eradicate all periodontopathic bacteria from the subgingival environment, especially those in inaccessible areas such as furcations, grooves, concavities, and intrabony defects. Advances in understanding the etiology and pathogenesis have led to the development and subsequent acceptance of the use of pharmacological agents in the management of periodontal diseases[9].

Local drug delivery systems can deliver the antimicrobial agents to the target sites, and achieve a sufficient concentration over the desired duration to be effective.[10] Non-surgical therapy has covered a new dimension by the addition of yet another newer group of drugs for periodontal regeneration i.e., Statins, to the family of local drugs. The purpose of this study was to investigate the efficacy of sub-gingivally delivered 1.2% ATV in the treatment of Chronic Periodontitis patients with and without Type II diabetes mellitus by evaluating clinical and radiographical parameters.

In the present study, both groups maintained satisfactory levels of oral hygiene throughout the study. The reduction in the mean plaque scores (Table 1) of both the groups from baseline to 3 months and 6 months is statistically significant during intragroup comparison. This can be due to complete scaling and root planing procedures done preoperatively. This can also be attributed to increased patient awareness and reinforcement of oral hygiene instructions at every 3 months visits.

During the intergroup comparison, the mean reduction in full mouth plaque scores of Group B is satisfactory compared to Group A from baseline to 3 and 6 months with statistical significance (P=0.01,

0.02). This can be explained by the inter-relationship between periodontitis and diabetes which may provide an example of a two-way relationship of a systemic disease predisposing to oral infection and vice versa.[11] The worsened periodontal status in Group B subjects has responded well to SRP and showed a statistical significance compared to Group A.

In the present study, there was a significant decrease in the mSBI index from baseline to 6 months (Table 3), suggesting an anti-inflammatory effect of ATV. A similar anti-inflammatory effect of SMV was observed by Lindy et al[13] using systemic statin therapy in patients with chronic periodontitis. Patients with periodontitis taking statins had 37% fewer pathologic periodontal pockets than those not taking statin medication.

The mean difference in probing depth (Table 4) and clinical attachment scores (Table 5) from baseline to 6 months in both groups is statistically significant. This magnitude of difference can be explained by the pleiotropic effects of Atorvastatin. In a study by Mandosi. E et al 8-week treatment with ATV reduced CD36 expression and decreased nuclear NFκB levels which are known to be involved in TNF-α production, in circulating monocytes in patients with Type II diabetes. Since, NFκB activation seems to be part of the stress response to oxidative stimuli, the reduction of the nuclear-active and the increase of the cytosolic-inactive NFκB form observed in these patients, after ATV treatment, might indicate reduced oxidative stress.[14]

The results obtained in this study are similar to the study carried out by Pradeep et al[12] where the effectiveness of 1.2% ATV as an adjunct to scaling and root planning in the treatment of intrabony defects was evaluated and Fajardo et al[5] who studied the effect of Atorvastatin treatment on bone loss prevention in subjects with chronic periodontitis.

Saxlin et al[4] found dual effects of statin medication on the periodontium and showed that in individuals with no gingival bleeding, statin medication was found to be associated with an increased likelihood of having deepened periodontal pockets. On contrary, the present study showed a significant decrease in PD and CAL in both the test groups.

A significant decrease in IBD, in present study from baseline to 6 months (Table 6) in both the groups suggests a role for ATV in radiographic defect fill. Previously Fajardo et al[5] found that the crestal alveolar bone to the cementoenamel junction distance increased in the control group but decreased in the ATV group after 3 months. The more bone gain seen in the current study can be due to subgingival delivery of ATV directly into the pocket rather than systemic administration.

Majima et al[15] suggested the beneficial effect of ATV, on bone metabolism by reducing bone resorption rather than by stimulating bone formation in hypercholesterolaemic patients treated for 3 months. Additionally, ATV has been reported to increase the number of circulating endothelial progenitor cells. ATV increases the secretion of OPG, a potent inhibitor of bone resorption in human osteoblasts. Secondly, statins directly affect osteoclasts through mechanisms, which closely resemble the mode of action of nitrogen-containing bisphosphonates and a paracrine pathway, which acts through osteoblast-osteoclast interaction and involves the RANKL/OPG system.

Morris et al[16] studied the effect of injectable SMV in three-walled periodontal IBDs, Grade II furcation defects, and edentulous alveolar ridges in beagle dogs by histomorphometric analysis. 29% greater ridge thickness was found with SMV, but the bone loss was detected in the interproximal and furcation defects. In contrast, the present study showed effective IBD fill and a greater decrease in PD and CAL in both the test groups.

In the present study, the bone fill is slightly more (44.58%) in Group A compared to a similar study by Pradeep et al[17] where the efficacy of 1.2% SMV in chronic periodontitis was 32.54% at 6 months. Whereas the bone fill in Group B from baseline to 6 months is 29.39%, compared to 27.63 ± 13.14% bone fill by 1.2%subgingivally delivered simvastatin in the treatment of Type II diabetes subjects with chronic periodontitis by Pradeep et al[18]. This difference in bone fill can be explained as ATV being more

efficacious than SMV. ATV 10, 20, and 40mg produced greater ($p < 0.01$) reductions in total cholesterol than the milligram equivalent doses of SMV, pravastatin, lovastatin, and fluvastatin.

During the intergroup comparison, the reduced bone fill percentage in Group B compared to Group A can be explained by the severity of the deterioration of lipid metabolism, and the worsening hyperlipidaemic state is associated with periodontal inflammation by increasing the serum and GCF proinflammatory cytokines[18].

With the current availability of many sub-gingival drug delivery systems containing antimicrobials for periodontal therapy, questions can be raised about their efficacy in periodontal regeneration. The findings of this study using 1.2% Atorvastatin as a local drug delivery system has been encouraging in terms of periodontal regeneration despite the presence of systemic disease in one of the test groups.

Conclusion:-

Statins have a broad therapeutic effect beyond their use in cardiovascular diseases and potentially have shown great promise in regenerative therapies as a result of their pleiotropic effects on bone metabolism. Within, the limitations of this study, this clinical trial demonstrates that local delivery of 1.2% ATV into intrabony defects in individuals with chronic periodontitis resulted in a significant decrease in pocket depth, clinical attachment level gain, and improved bone adjunct to SRP, despite the presence of systemic disease in one of the test groups. Though, not comparable to the bonefilling test group with healthy subjects, this can provide a new direction in the management of intrabony defects in chronic periodontitis with Type II diabetes. The improved results can be due to better half-life and increased efficacy in lowering LDL-C suggesting its role in regenerative therapy.

The limitations of the present study include a histologic study to assess the quality of bone formed and a short-term study with less number of subjects. But, within these limitations, it can be proposed that statins are effective drugs in the treatment of hyperlipidemia and prevention of cardiovascular events can be used to treat chronic periodontitis with proven efficacy.

Tables

Table 1:- Comparison of group A and group B with respect to full mouth plaque scores at baseline, 3 months and 6 months by Mann-Whitney U test.

Groups	Baseline		3 months		6 months		Changes from baseline			
							3 months		6 months	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Group A	1.09	0.70	0.73	0.46	0.39	0.35	0.36	0.34	0.70	0.50
Group B	1.49	0.52	0.85	0.48	0.41	0.35	0.64	0.21	1.08	0.30
P-value	0.1264		0.7138		0.7023		0.0129*		0.0219*	

*p<0.05, # applied Wilcoxon matched pairs test

Table 2:- Comparison of group A and group B with respect to modified sulcular bleeding index scores at baseline and 6 months by Mann-Whitney U test.

Groups	Baseline		6 months		Changes from 6 months	
	Mean	SD	Mean	SD	Mean	SD
Group A	1.45	0.51	0.60	0.60	0.85	0.37
Group B	1.25	0.45	0.31	0.48	0.94	0.25
P-value	0.2209		0.1383		0.4131	

*p<0.05, # applied Wilcoxon matched pairs test

Table 3:- Comparison of group A and group B with respect to probing depth scores at baseline and 6 months by Mann-Whitney U test.

Groups	Baseline		6 months		Changes from 6 months	
	Mean	SD	Mean	SD	Mean	SD
Group A	5.85	0.59	3.70	0.73	2.15	0.59
Group B	5.38	0.50	3.38	0.72	2.00	0.63
P-value	0.0174		0.1445		0.4663	

Table 4:- Comparison of group A and group B with respect to clinical attachment levels at baseline and 6 months by Mann-Whitney U test.

Groups	Baseline		6 months		Changes from 6 months	
	Mean	SD	Mean	SD	Mean	SD
Group A	6.25	0.91	4.10	1.07	2.15	0.59
Group B	6.06	0.85	4.00	0.73	2.06	0.68
P-value	0.5284		0.7880		0.7003	

Table 5:- Comparison of group A and group B with respect to angular defect depth scores at baseline and 6 months by Mann-Whitney U test.

Groups	Baseline		6 months		Changes from 6 months	
	Mean	SD	Mean	SD	Mean	SD
Group A	3.06	0.91	1.69	0.98	1.36	0.88
Group B	2.85	1.03	2.01	1.07	0.84	0.78
P-value	0.4538		0.4258		0.0668	

*p<0.05, # applied Wilcoxon matched pairs test.

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