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RESEARCH ARTICLE

BERBERINE GEL AS LOCAL DRUG DELIVERY AGENT IN CHRONIC PERIODONTITIS.

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Abstract

Background & objectives- It has been well established that berberine extracts has strong anti- microbial effects. So, this study was conducted to evaluate the efficacy of berberine gel as local drug delivery agent for treatment of pockets in chronic periodontitis through clinical assessment.

Materials & methods- A split-mouth designed study was conducted in 20 patients having bilateral mild to moderate periodontal pockets (5-7mm) clinically with radiographic evidence of bone loss.

-Following clinical parameters are recorded on day 0, 7 & 21.

i. Gingival Bleeding Index
Ii. Probing Pocket Depth
Iii. Clinical Attachment Level

Test group (10 patients) –After scaling and root planing, 1 ml of 5% berberine gel placed into the selected sites on day 0,day 7 & day 14.Control group (10 patients) - Scaling and root planingonly.

Results:- There was a statistically significant difference in the gingival bleeding index on both intra-group & inter-group comparisons on day 21 .Periodontal pocket depth reduction was significant in intra-group comparison but inter-group comparisons was not significant. The changes of clinical attachment level was not significant in both intra-group & inter-group comparisons.

Conclusion:- The use of 5% berberine gel resulted in more clinical improvements when compared to control group, but it was not considered as a significant benefit. It may be possible that by increasing the concentration of the berberine drug in the gel, its sustainability & its evaluation with increased sample size ,significant effects can be observed.

Introduction:-

Periodontal disease is recognized as a major public health problem throughout theworld and is the most common cause of tooth loss in adults.[1] The association betweendental plaque and periodontal disease has been well established, and the importance ofeffective plaque control has been emphasized over the years. Periodontal pocket formation results from the accumulation of bacterial plaque on tooth surface in close proximity to the gingival sulcus.[2] Clinical trials have confirmed that plaque control combined with scaling and root planing are effective therapeutic modalities for arresting periodontitis but there are factors that can limit the clinical and microbiological response.[3] To override this, addition of antimicrobials both systemically and locally would enhance a treatment protocol and serve as adjuncts to mechanical therapy. Adverse effects such as drug toxicity, acquired bacterial resistance, drug interaction and patient's compliance limit the use of systemic antimicrobials which led to development of local delivery of anti-microbial agents directly to the periodontal pocket.[4]

Periodontal local delivery devices that have been used for the targeted delivery of antimicrobial agents include: fibers (hollow and monolithic), strips and compacts, films, microparticles, gels and nanoparticles.[5] Despite several chemical agents being commercially available, these can alter oral microbiota and have undesirable side-effects such as vomiting, diarrhoea and tooth staining.[6,7]

Natural compounds can act in a synergetic manner within the human body, and can provide unique therapeutic properties with minimum or no undesirable side effects.Hence, the search for alternative products continues andnatural phytochemicals isolated from plants used intraditional medicine are considered as good alternatives to synthetic chemicals.Berberine is a plant alkaloid with a long history of medicinal use in both Ayurvedic and Chinese medicine. It is present in *Hydrastis Canadensis* (goldenseal), *Coptischinensis*(Coptis or goldenthread), *Berberisaquifolium*(Oregon grape), *Berberis vulgaris* (barberry), and *Berberisaristata*(tree turmeric). The berberine alkaloid can be found in the roots, rhizomes, and stem bark of the plants. Berberine extracts and decoctions have demonstrated significant antimicrobial activity against a variety of micro-organisms including bacteria, viruses, fungi, protozoans, helminths, and chlamydia. The predominant clinical uses of berberine include bacterial diarrhea, intestinal parasite infections, and ocular trachoma infections.[9]Furthermore, studies have demonstrated that alkaloids such as berberine were more effective against oral bacteria such as *A. actinomycetemcomitans*and *P. gingivalis*than against lactobacilli and streptococci.[10]

It has been established that berberine has strong antimicrobial effects but little is known however regarding its activity against potential periodontal pathogenic bacteria. Hence, this pilot study was an attempt to evaluate the efficacy of 5%berberine gel as local drug delivery agent for treatment of pockets in mild tomoderate chronic periodontitis.

Materials and methods:-

The patients were selected from Outpatient Department Of Periodontics, College Of Dental Sciences, Davangere, Karnataka .Informed consent was obtained before the initiation of the treatment.

A randomized controlled trial with split-mouth designed study was conducted in 20 patients having bilateral mild to moderate periodontal pockets (5-7mm) clinically with radiographic evidence of bone loss.

Selection Criteria:-

Inclusion Criteria:

1. Age group: 25- 50 yrs
2. Patients with periodontal pockets (5-7mm) clinically with radiographic evidence of bone loss.
3. No systemic history

Exclusion Criteria:

1. Patients who have received any surgical/non-surgical therapy 3months prior to the study
2. Patients under any antibiotic therapy in last 3 months or using any anti-bacterial mouthwashes
3. Pregnant females & lactating mothers
4. Patients who were alcoholic/smokers

Preperation Of 5% Berberine Gel: (Fig-1)

200 g of the ground particles fromdried roots of barberry plant were extracted followed reflux protocol over a 24-hour period with 96% ethanol using Soxhletinstrument.The alcohol extract was concentrated to yield 40 g using vacuum evaporation.The 5% aqueous gel specimens were prepared by geometrically triturating 5 g of the extract with 95 g of gel base(Hydroxypropyl methylcellulose- HPMC).Glycerin as plasticizer and Cetylpyridinium chloride as preservative were also added.

The selected sites were categorised into test group and control group.

Test Sites Group- Scaling& root planing was performed and followed by local application of 5% berberine gel .

Control Sites Group- Scaling& root planing only

Clinical Parameters:-

-Following clinical parameters are recorded at baseline, Day 7 & Day 21.

I. Gingival bleeding index (GBI) (Ainamo& Bay,1975)
II. Probing pocket depth (PPD) (Syed et al,1980)
III. Clinical attachment level (CAL) (Syed et al,1980)

Complete scaling and root planing was done using ultrasonic & hand instruments.
1 ml of 5% BERBERINE GEL was administered sub-gingivallywith the help of a syringe in all selected sites at Day 0,7,14 & 21.(Fig-2)

Statistical analysis:-

Results were expressed as Mean± standard deviation for each parameter at different intervals. Repeated measures ANOVA &Unpaired 't' test were used for intra-group & inter-group comparisons respectively.

Results:-

A total number of 60 sites from 20 chronic periodontitis patients were selected using clinical parameters. There was a statistically significant difference in the GBI on both intra-group & inter-group comparisons.(Table-1)
Periodontal pocket depth reduction was significant in intra-group comparison but inter-group comparisons was not significant.(Table-2).
The changes of CAL gain was not significant in both intra-group & inter-group comparisons(Table-3)

Discussion:-

Traditionally, periodontal disease therapy has been directed at altering the periodontal environment to one which is less conducive to the retention of bacterial plaque in the vicinity of the gingival tissues, in particular, the marginal attachment apparatus[10]Scaling and root planing (SRP) is one of the most commonly utilized procedures forthe treatment of periodontal diseases and has been used as the "gold" standard therapy in comparison to other therapeutical procedures.[11]

However, numerous investigations have demonstrated that SRP alone ineffectivelyeliminates microorganisms in deep pockets including Aggregatibacteractinomycetemcomitans,Porphyromonasgingivalis, Prevotellaintermedia and Tannerellaforsythus due to its ability to invade the periodontium[12] and dentinal tubule [13] or because they reside in sites inaccessible for periodontal instruments, root concavities or in furcations, thereby resulting in renewal of inflammatory state.

Goodson (1989) pointed out that successful control of periodontal microflorarequires delivery of an intrinsically effective antimicrobial agent according to fundamental pharmacokinetic principles, reaching the site of action that is periodontal pocket and its surrounding tissues and thus, maintaining minimum effective concentrations for sufficient duration to produce the therapeutic effect[14]

Natural compounds contained in the herbal cocktail can act in a synergetic manner within the human body, and can provide unique therapeutic properties with minimum or no undesirable side effects[15] .Barberry is a plant that grows in different parts of the world, including parts of Europe, Africa and in Asia.Berberine is the most effective alkaloid derived from barberry plants and has been added to toothpastes and mouthwashes due to its antimicrobial activities. Makarem et al had demonstrated thatberberine gel reduces both PI and GI in gingivitis patients.[16] The present study was carried out to evaluate the clinical effects of berberine gel as local drug delivery agent in mild to moderate type periodontitis patients.

It has been proven that berberine evoked bactericidal activity against oral bacteria, with substantial activity against A. actinomycetemcomitans(MIC = 13 μg/mL) and Porphyromonasgingivalis (MIC = 20 μg/mL).Studies conducted to evaluate the antimicrobial mechanism and efficacy of berberine alsodemonstrated that it inhibited the collagenase activity of A. actinomycetemcomitans and P. gingivalis.[17]

A study was conducted by Amir Moeintaghavi et al(2012) to evaluate the efficacy of a berberine-derived topical gel on periodontal inflammation through both clinical and histological analysis. The results demonstrated thatthe use of a barberry-derived gel reduced the degree of inflammatory cell infiltrates in the gingiva.[18]

There was a statistically significant difference in the GBI on both intra-group & inter-group comparisons & this finding is attributed to the anti-inflammatory effect of berberine drug similar to the study conducted by Makaremet al[16]. Periodontal pocket depth reduction was significant in intra-group comparison but inter-group comparison was not significant. The changes of CAL gain was not statistically significant in both intra-group & inter-group comparisons. These findings suggest the insignificant role of 5% berberine gel as local drug delivery agent in periodontal regeneration.

To our knowledge, The Medline search reveals no studies reporting the use of 5% berberine gel as local drug delivery in the treatment of patients with chronic periodontitis. Therefore, a direct comparison with other studies to evaluate the clinical results is not possible.

Figures:-

Fig-1

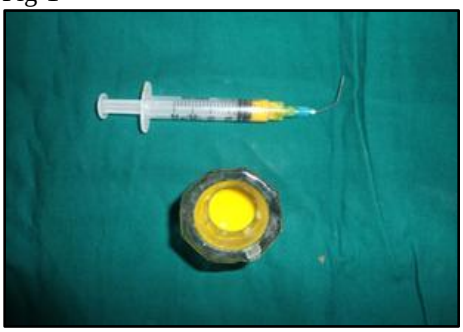
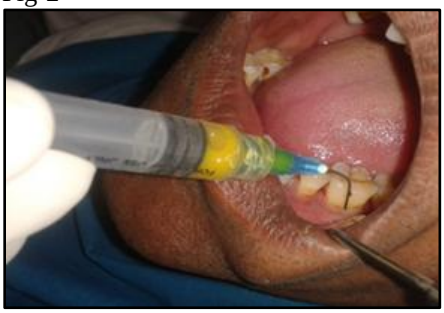


Fig-2



Tables:-

Table 1- Comparison Of Mean Gingival Bleeding Index Between Two Groups At Different Intervals

TIME INTERVAL	TEST GROUP	CONTROL GROUP	UNPAIRED 't' TEST
BASELINE	1.21 ± 0.18	0.96 ± 0.19	P=0.001
DAY 7	0.99 ± 0.15	0.78 ± 0.1	P=0.001
DAY 21	0.73 ± 0.14	0.67 ± 0.10	P=0.001
Repeated measures ANOVA	P = 0.001 (HS)	P = 0.001 (HS)	

Table 2-Comparison Of Mean Pocket Depth Between Two Groups At Different Intervals

TIME INTERVAL	TEST GROUP	CONTROL GROUP	UNPAIRED T-TEST
BASELINE	5.37 ± 0.48	5.4 ± 0.53	p= 0.107(NS)
DAY 7	4.42 ± 0.38	4.62 ± 0.39	p=0.164(NS)
DAY 21	3.62 ± 0.56	4.15 ± 0.43	p=0.877(NS)

Table 3-Comparison Of Mean Cal Between Two Groups At Different Intervals

TIME INTERVAL	TEST GROUP	CONTROL GROUP	UNPAIRED t-TEST
BASE LINE	4.2 ± 0.3	4.27 ± 0.52	P=0.102(NS)
DAY 7	3.7 ± 0.44	3.92 ± 0.41	P=0.165(NS)
DAY 21	3.37 ± 0.78	3.67 ± 0.54	P=0.583(NS)

P value - <0.01- Significant(S); P value <0.001 – highly significant (HS); P value > 0.05 – Non significant (NS)

Conclusion:-

The use of 5% berberine gel demonstrated significant anti-inflammatory effect in test group but no significant benefit was observed in relation to pocket depth reduction and CAL gain. It may be possible that by increasing the effective concentration of the berberine drug in the gel, its sustainability & its evaluation with increased sample size ,significant effects can be observed.

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Conflict of interest:-
None Declared.
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