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EVALUATION AND COMPARISON BETWEEN LOCALLY AND SYSTEMICALLY ADMINISTERED NSAIDs USED IN GINGIVITIS AND PERIODONTITIS

Faiza Hasan*[1] and Rahila Najam[2]

[1]Department of Pharmacology, Fatima Jinnah Dental College, Karachi, Sindh, Pakistan.

[2]Department of Pharmacology, University of Karachi, Sindh, Pakistan.

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***Correspondence for Author**
Dr. Faiza Hasan
Department of Pharmacology, Fatima Jinnah Dental College, Karachi, Sindh, Pakistan.

ABSTRACT

The aim of the study was to develop an NSAID gel which was applied topically into the periodontal pockets along with the conventional treatment to improve the clinical variables as well as minimize the adverse effects associated with the systemic use of the NSAIDs. A total of 30 subjects were included in the study. The patients of gingivitis and periodontitis were recruited from Crown Dental Clinic, Karachi, Pakistan (private practice) between the periods of February 2015 to October 2015. 1% Aspirin gel was prepared and their physicochemical properties were also evaluated before the application in to the periodontal pockets.The results were compared statistically to its control using Student's T test. The results were also compared using ANOVA followed by multiple comparisons with Dunnet's T test and Bonferroni's test. There is a statistically significant difference in the clinical variables between untreated and treated 1% ASA gel groups from baseline and 30 days after treatment ($p<0.05$). Thus, this research support the local use of NSAIDs to avoid the adverse effects associated with its systemic use.

KEY WORDS: Aspirin, gel, gingivitis, periodontitis.

INTRODUCTION

The two main forms of inflammatory diseases affecting the periodontium are gingivitis and periodontitis. The main cause of these diseases is bacterial plaque which is responsible for initiating the destruction of gingival tissues and periodontal attachment loss.[1,2]

Gingivitis and periodontitis shares the same clinical features of inflammation but in periodontitis there is clinical attachment loss, periodontal pocketing and alveolar bone loss. Common clinical features include erythema, edema, tissue enlargement and bleeding. Sometimes the disease may occur as a result of hormonal changes in the body[3], due to medications[4] and may be associated with systemic disease.[5]

The common form of periodontitis is chronic periodontitis and there is host tissue destruction which is dependent on local etiological factors such as plaque and calculus as well as variable microbial pattern. The disease usually follows a slow to moderate rate of progression but sometimes rapid progression may also occur. Variety of bacteria found in periodontal tissue but only few species have been associated with the disease. These include P. gingivalis, P. intermedia, T. forsythia, C. rectus, E.coorodens, E nucleatum, A. actinomycetemcomitans, P. micros, E.coli, E faecalis, Staphyloccocus aureus and T. denticola.[6,7] The number of the organisms decreases with the treatment of the disease.

In response to inflammation of periodontal tissue the remodeling of connective tissues leads to the loss of soft tissues, bone and periodontal attachment apparatus. The conversion of gingivitis to periodontitis occurs as a result of loss of soft tissue attachment to the tooth followed by the loss of alveolar bone. Bacteria lead to tissue destruction and in response to bacteria production of mediators occurs that also contributes to tissue destruction that includes proteinases, cytokines and prostaglandins.

Prostaglandins are arachidonic acid metabolites generated by COX-1 and COX-2 enzymes. Arachidonic acid is found in plasma membrane of most cells. COX-2 is upregulated by IL-1 beta, TNF- alpha and bacterial lipopolysaccharides and responsible for the production of PGE2 associated with inflammation.[8] In periodontium macrophages and fibroblasts are responsible for PGE2 production which results in inflammation and attachment loss. PGE2 also induce MMPs and bone resorption by osteoclasts. Studies showed that PGs inhibitors prevent the inflammation and bone loss associated with advanced periodontitis in humans.[9] As the periodontal disease progresses, there is a substantial increase in the concentration of PGE2. There is a strong relationship between PGE2 levels in gingival crevicular fluid and periodontal pocket depths, plaque index, gingival index and clinical attachment loss.[10]

NSAIDs are one of the extensively recommended drugs for most of the diseases associated with pain, inflammation and fever. Although these agents are harmless but it increases the

risk of gastrointestinal and cardiovascular problems as compared to those who are not using NSAIDs. Salvi and Lang in 2005 reviewed different literatures on the use of selective and non-selective NSAIDs which have an influence on periodontal disease.[11] They discussed that the effects of NSAIDs decreases rapidly after the withdrawal of the drug. But it stabilizes the disease by reducing the rate of bone resorption as a result of inhibition of both COX-1 and COX-2 enzymes. Some studies showed good results but no data and clinical trials are available that these effects are long termed. Salvi and Lang (2005) also evaluated that flurbiprofen which is a selective COX-2 inhibitor is absorbed rapidly through gingival tissues. So they suggested that topical formulation of NSAIDs developed in different formulations such as gels, toothpastes and rinses which will not only produce the local anti-inflammatory effects at the infected sites but can also reduces the systemic adverse effects of non-selective NSAIDs in long term modulation of gingivitis and periodontitis-susceptible patients.[11]

The aim of the study was to develop an NSAID gel which was applied topically into the periodontal pockets along with the conventional treatment to improve the clinical variables as well as minimize the adverse effects associated with the systemic use of the NSAIDs.

MATERIALS AND METHODS

The participants in this study obtained information about the research proposal and all of them signed the consent form.

Subjects

A total of 30 subjects were included in the study. The patients of gingivitis and periodontitis were recruited from Crown Dental Clinic (private practice) between the periods of February 2015 to October 2015.

Inclusion criteria

- Patients more than 20 years
- Patients with gingivitis and periodontitis with history of no systemic disease

Exclusion criteria

- Patients who were taking medicines since six months
- Patients with known systemic disease

Drugs and chemicals

Aacetylsalicylic acid was obtained from Kaizen Pharmaceutical (Pvt) Limited, Karachi. The remaining chemicals were obtained from Nighebaan Pharmacy, Karachi.

Formulation of 1% aspirin gel

5 gram of acetylsalicylic acid (ASA) was dissolved in tween 80 on a basic magnetic stirring hot plate (IKA Works Inc.) at 100°C with continuous stirring until a clear solution was obtained.[12] Triethanolamine was added to adjust the pH of the solution.[13] 1 gm of methylparaben sodium, 0.75 mg of propylparaben sodium and 0.5 mg of ethylenediaminetetraacetic acid were dissolved in warm water with continuous stirring in a separate beaker.[14] The solution containing the preservatives was then added to 2% carboxymethyl cellulose gel with continuous stirring to prevent the lump formation. The solution containing 1% ASA was then added to CMC gel at room temperature with continuous stirring and distilled water was added to make 500 gram of ASA gel. The physico-chemical properties were also evaluated before the application of the gel.

Pharmacological treatment procedure

Initially detailed medical and dental histories of patients were taken. Clinical examination and clinical parameters were observed when the participant was sitting on a dental chair. The clinical parameters were measured by using WHO (CPTIN) probe. The data was recorded in a special Performa sheet which was specially designed before conducting the study.[15]

The patients were grouped in three categories

- Group 1: patients with no treatment at all (positive control group)
- Group 2: patients given only scaling and root planning (negative control group)
- Group 3: patients given scaling and root planning with intercrevicular 1% aspirin gel

Group 1 did not receive any treatment and clinical variables were recorded on day 0 and then after 30 days. Group 2 received scaling and root planning every week in each mouth quadrant. This treatment was done once a week for four consecutive weeks. Group 3 also received scaling and root planning in four sessions every week in each mouth quadrant and intra-crevicular gel was applied after 48 hours of each sitting.

Method of application of gel in periodontal pockets

After finishing of scaling and root planning the oral cavity was isolated with cotton rolls to prevent the contamination of saliva. A disposable syringe of 5 ml having 25 gauge blunted needle was used for the application of the gel. The needle was bent along its shank. The quadrant was cleaned and dried with air get and gel was applied with the needle. [15]

Estimation of clinical parameters

Clinical parameters were recorded at baseline and post base line i.e. 30 days. The readings of post-base line were recorded after one week of last treatment session. The following clinical parameters were studied:

- **Probing depth**

Probing depth is measured as the distance from the gingival margin to the base of the sulcus or periodontal pocket. The measurement was done using WHO (World Health Organization) probe also called as CPTIN probe.[15,16]

- **Attachment level**

Clinical attachment loss (CAL) is measured by using the periodontal probe. CAL occurs as a result of destruction of periodontal ligament and adjacent alveolar bone and it identifies the severity of the disease. It is measured from the base of the pocket to the cementoenamel junction. The measurements were done using the WHO probe.[15,16]

- **Tooth mobility**

Assessment of tooth mobility is essential for research purposes. The following criteria were used to assess the tooth mobility[15,16]

Grade 0= Physiological mobility (no mobility)

Grade 1= Increased mobility but less than 1mm in horizontal direction

Grade 2 = Increased mobility but more than 1mm in horizontal direction

Grade 3= More than 1 mm displacement combined with displacement in vertical direction

Silness and Loe plaque index

The following criteria were used to score the plaque index:

0 = No plaque

1= A film of plaque adhering to the free gingival margin and adjacent area of the tooth, which cannot be seen with the naked eye. But only by using disclosing solution or by using probe.

2 = Moderate accumulation of deposits within the gingival pocket, on the gingival margin and/ or adjacent tooth surface, which can be seen with the naked eye.

3 =Abundance of soft matter within the gingival pocket and/or on the tooth and gingival margin.

The scores of the four areas of the tooth was summed and divided by four which gave the plaque index for the tooth and the plaque index of the individual was obtained by adding the values of each tooth and divided it with the number of teeth. [15, 16]

Loe and Silness gingival index

The following criteria were used to score the plaque index:

0 = No inflammation.

1= Mild inflammation, slight change in color, slight edema, no bleeding on probing.

2 = Moderate inflammation, moderate glazing, redness, bleeding on probing.

3. Severe inflammation, marked redness and hypertrophy, ulceration, tendency to spontaneous bleeding.

A score from = 0.1 -1 Mild gingivitis; 1.1- 2 = Moderate gingivitis; 2.1- 3 = Severe gingivitis. The scores of the four areas of the tooth was summed and divided by four which gave the gingival index for the tooth and the gingival index of the individual was obtained by adding the values of each tooth and divided it with the number of teeth. [15, 16]

Bleeding on probing

Bleeding on probing was assessed by probing gently along the wall of the gingival tissue of the sulcus.[15,16]

The following criteria were used to score bleeding on probing:

0 = Negative (No bleeding on probing)

1 = Positive (Bleeding on probing)

STATISTICAL ANALYSIS

The results were compared statistically with control using Student's T test. The results were also compared using ANOVA followed by multiple comparisons with Dunnet's T test and Bonferroni's test. P value of< 0.05 was considered statistically significant.

RESULTS

Table 1: Comparison of the reduction in the clinical variables between untreated and treated 1% ASA gel groups from base-line to 30 days

	ASA 1% (group=1 , n=10		Positive Control (group=2), n=10		Negative Control (group= 3), n=10	
	Baseline	**30 days**	**Baseline**	**30 days**	**Baseline**	**30 days**
Probing Depth	3.8871 ± 0.78	2.8438 *!♯ ± 0.406	3.8966 ± 0.83	3.9118 ± 0.83	3.6892 ± 1.07	3.72 ± 0.849
Plaque Index	2.7927 ± 0.203	0.1577*!♯ ± 0.17	2.8693 ± 0.351	2.6730 ± 0.76	2.7978 ± 0.174	0.7* ¥ ± 0.478
Gingival Index	2.5963 ± 0.331	0.2677*!♯ ± 0.083	2.4490 ± 0.363	2.4710 ± 0.349	2.6311 ± 0.365	1.8927*¥ ± 0.774
Probing Bleeding	1.0000 ± 0.00	0.1164*! ± 0.137	0.9000 ± 0.3162	0.9000 ± 0.316	1.0000 ± .000	0.3699* ¥ ± 0.375
Attachment Level	4.2818 ± 0.9640	2.9645*!♯ ± 0.574	3.9584 ± 0.813	3.9748 ± 0.808	4.0385 ±1.22	3.6645* ± 0.289
Tooth mobility	0.6000 ± 0.699	0.5000 ± 0.52705	0.7000 ± 0.674	0.7000 ± 0.674	0.6000 ± 0.699	0.5000 ± 0.527

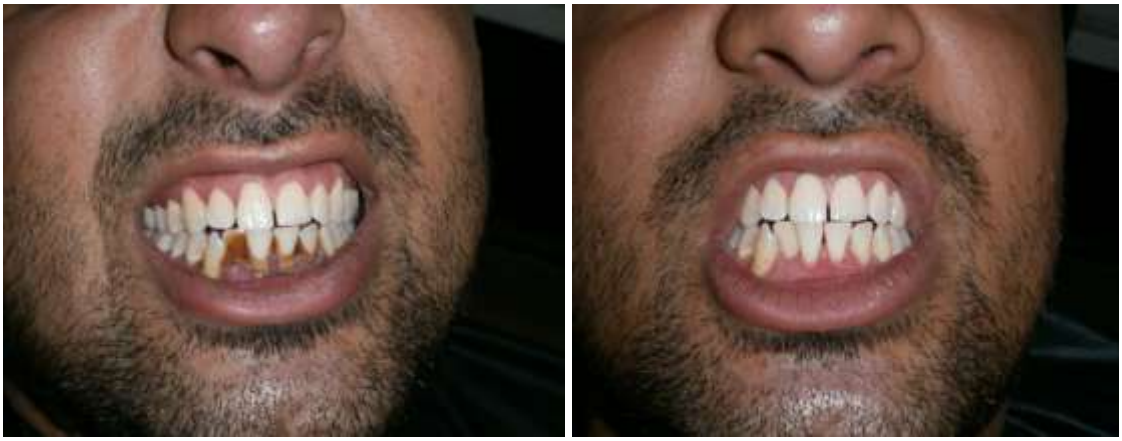
*Statistically significant difference between baseline and 30 days after treatment (Student t test, $p<0.05$) and Bonferroni's test to compare means among groups

#statistically significant difference between 1% ASA and Negative control group ($p<0.05$)

!statistically significant difference between 1% ASA and Positive control group ($p<0.05$)

¥statistically significant difference between Negative and Positive control group ($p<0.05$)

Table 1 indicates statistically significant difference in the clinical variables between untreated and treated 1% ASA gel groups from baseline and 30 days after treatment. The clinical variables including gingival index, plaque index, probing depth, attachment level and bleeding on probing showed marked reduction in group received 1% ASA gel with mechanical therapy as compared to positive and negative control group. The negative control group only showed significant reduction in plaque index, gingival index and bleeding on probing ($p<0.05$) from base-line to 30 days, whereas no reduction in any clinical variables were observed ($p>0.05$) in positive control group.



Base Line **30 Days**

Figure1: 1% ASA gel clinically reduced the signs and symptoms of inflammation after 30 days of treatment.

Table 2: Effects of 1% ASA gel on the clinical variables studied 30 days post-administration among groups

	Probing depth	Plaque Index	Gingival Index	Probing Bleeding	Attachment Level	Tooth Mobility
ASA 1% (group=)	1.04330* ± 0.386	2.48540* ± 0.234	2.32860* ± 0.233	0.88360* ± 0.218	1.01730* ± 0.414	0.100 ± 0.312
Positive	0.1520 ± 0.36	0.19630 ± 0.305	0.0220 ± 0.251	0.00 ± 0.244	0.01640 ± 0.365	0.00 ± 0.327
Negative	0.5420 ± 0.51	2.269* ± 0.344	0.73840 ± 0.370	0.63 ± 0.312	1.06530 ± 0.555	0.100 ± 0.37

*Significant difference in the reduction of clinical variables for each group (ONE WAY ANOVA followed by Dunnet's test). ASA, Acetylsalicylic acid.

Table 2 indicates the effects of 1% ASA gel on the clinical variables studied 30 days post-administration. The group received 1% ASA gel with mechanical therapy showed notable decrease in probing depth, attachment level, plaque index, gingival index and bleeding on probing ($p<0.05$), but no changes were found in tooth mobility ($p>0.05$). There is also in the reduction of plaque index, gingival index and bleeding on probing in the negative control group which received only mechanical treatment ($p<0.05$), but no significant changes were observed in probing depth, attachment level, and tooth mobility ($p>0.05$), whereas no significant changes were observed in the positive control group after 30 days ($p>0.05$).

DISCUSSION

There is an increase prevalence of eating pan and chalia (dried areca nut) among Pakistani population. There is also common use of tobacco in Pakistan in different forms. A study

reported that there is an increase in the consumption of cigarettes among Pakistani population and was approximately 90,000,000,000 cigarettes in 2005.[17] Due to these habits and lack of awareness of oral hygiene there is an increased risk of developing gingivitis and periodontitis among Pakistanis.[18]

NSAIDs play a very important role in the gingivitis and periodontitis and in the inhibition of disease progression. Periodontal researchers start evaluating the effects of NSAIDs on periodontal tissues since 1970's.[19] Although it decreases the inflammation and extent of the disease, the adverse effects associated with its oral use cannot be denied. Oral NSAIDs have been associated with significant problems particularly in the gastrointestinal system. [20] Recently in 2015 Scheiman reported the serious cardiovascular effects of these drugs along with gastrointestinal effects. [21] Hsu and Tsai (2015) reported that the low dose aspirin (75-325 mg/day) is associated with dyspnea, gastrointestinal erosions, and endoscopic peptic ulcers leading to symptomatic or complicated ulcers.[22] Even the use of buffered preparations and enteric coated tablets did not reduce the risk of these complications. Aspirin use is also associated with the complication of diverticular disease.[23] Long and his research team in 2015 observed that there is an association of NSAIDs and acetaminophen with active Crohn's disease.[24] In addition to adverse effects associated with its oral use, the patient's compliance is also important with recommended doses and there are certain factors that may affect the absorption of the drug.[25]

Nowadays, the use of local drug delivery system in the treatment of periodontal disease is appreciated to bypass the systemic adverse effects. The first local drug delivery system for periodontal disease was Actisite fiber system. These are non-absorbable tetracycline fibers. The fiber was placed into the periodontal pockets and a periodontal dressing was placed to prevent the dislodgement of the fiber.[25] NSAIDs are the drugs which inhibit the response of host in periodontal disease and prevent prostanoid formation. Krayer et al. (2010) performed a quantitative analysis and found out that when NSAIDs were combined with mechanical therapy, it showed alveolar bone maintenance.[25] Our research showed that when 1% ASA gel was placed in periodontal pockets it reduced pocket depth, plaque index, gingival index and bleeding on probing. There is controversy about the reduction in attachment loss associated with the use of NSAIDs. Shiloah et al. (2014) found that smoker patients with periodontitis when treated with systemic NSAIDs showed reduction in attachment loss[26] whereas, Heasman and Seymour (1990) showed in their study that systemic use did not

reduce the attachment loss.[27] Funosas et al. (2009) also reported that there is no gain in attachment levels when different concentrations of intracrevicular gels were applied.[16] The results of our study showed a significant reduction in attachment loss in patients with periodontal disease who received 1% ASA gel with mechanical debridement ($p<0.05$).

Thus, local drug administration of NSAIDs is more beneficial as compared to systemic administration which will decrease the systemic gastrointestinal, cardiovascular, and renal adverse effects. This method of drug delivery also has other advantages such as it is retained in the pocket for longer time than irrigants, take less time for preparation and application as compared to fibers and strips, can be applied only to those specific areas which requires treatment, and ensure adequate concentration at the target sites. [28]

There is also reduction in plaque index, gingival index and bleeding on probing ($p< 0.05$) in the group received only mechanical therapy but no changes in pocket depth and attachment levels were found ($p>0.05$). No significant changes in tooth mobility were found in both the negative control group and the group who received the gel treatment ($p>0.05$).

Because of the poverty and inflation all over Pakistan, people usually do not visit the dentist until it is necessary for them such as in severe toothache and in tooth infections. They usually take NSAIDs for longer period of time without the dentist's advice which may lead to minor to major ulcers of the gastrointestinal tract and kidney cancers as these drugs are easily available over- the- counter.[29]

CONCLUSION

The results of this research support the local use of NSAIDs along with the debridement of root surface by scaling and root planning. However, the recovery from the disease also depends upon the oral hygiene, brushing technique, and eating habits of the individual. Therefore, it is required to educate people on community basis, emphasize the importance of dental treatment, and the adverse effects associated with the prolong use of these drugs without prescription.

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ETHICAL APPROVAL

All procedures accomplished in this study which involved human participants were according to the ethical standards. The ethical approval was taken from the Karachi University ethics committee.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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