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COMPARATIVE EVALUATION OF DICLOFENAC AND MELOXICAM AS TABLETS AND AS TRANSMUCOSAL MUCOADHESIVE PATCHES IN DENTAL PAIN REDUCTION

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Keywords:

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ABSTRACT: Aims and Objectives: To evaluate and compare diclofenac and meloxicam as tablets and as mucoadhesive patches in the control of odontogenic pain. **Materials and Methods:** 60 patients of either sex with acute dental pain were included in the study. Informed consent was obtained from each patient and they were randomly divided into 4 groups. Group A1 received meloxicam tablets, A2 meloxicam mucoadhesive patches, B1 diclofenac tablets, and group B2 was allotted diclofenac mucoadhesive patches. A 10 cm Visual Analogue Scale (VAS) was used to record pain scores at baseline, 20 and 30 min post-administration. Patients were also given the allotted tablets and patches to be used for 2 days, along with a pain diary to record their VAS scores at 30 min post-administration. Diary was collected and data analyzed on the 4th day. **Results:** Statistically significant reduction in pain was seen in all 4 groups from baseline to the end of the study period. Overall pain reduction was greater with the mucoadhesive patches than with tablets. Diclofenac patches showed a greater reduction in pain as compared to meloxicam patches ($p > 0.05$). Diclofenac tablets also showed a statistically significant reduction as compared to meloxicam ($p<0.05$). **Conclusion:** The results of this study indicate that mucoadhesive patches resulted in a greater reduction in pain as compared to the tablets. Hence, they can be considered as feasible alternatives to conventional methods of drug delivery and can be used in daily practice.

INTRODUCTION: The most common complaint with which patients report to dentists is tooth pain. It has the potential to severely affect the quality of life, motivating patients to take immediate treatment. Individuals may also report additional symptoms such as difficulty in chewing food, radiating pain to the head and ears and also reduced sleep.

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For relief of such odontogenic pain, clinicians most frequently prescribe non-steroidal anti-inflammatory drugs (NSAIDs). NSAIDs act by blocking the cyclooxygenase enzymes, COX-1 and COX- 2. Diclofenac and meloxicam, belonging to the NSAID family, are prescribed routinely for control of pre and post-operative odontogenic pain because of their established efficacy in reducing pain and inflammation.

They are given most commonly through the peroral route. Diclofenac is an acetic acid derivative and a non-selective COX inhibitor. Meloxicam belongs to the oxicam group of NSAIDs, which preferentially inhibits COX-2 enzyme.

Despite their efficacy in pain relief, NSAIDs are known to cause several adverse effects, primarily on the gastrointestinal system. It has also been established that the risk of upper gastrointestinal complications increases with increasing the dosage and frequency of administration of these drugs [1]. Over the years, various alternative routes of drug administration have been developed to circumvent these side effects. One such route is transmucosal drug delivery which offers distinct advantages over the oral route such as elimination of hepatic first-pass metabolism, avoidance of pre systemic elimination, prolonged contact with the mucosal surface, and rapid and sustained release of the drug [2]. This will, therefore, ensure less dosing frequency with shorter dosing periods, improved patient compliance, and reduced intensity of local and systemic side effects [3].

A variety of transmucosal drug delivery systems have been developed such as patches, wafers, films, sprays, tablets, lozenges, gels and creams [4]. These transmucosal delivery systems work on the principle of bioadhesion, defined as, "the state in which two materials, at least one biological in nature, are held together for an extended period of time by interfacial forces." When the adhesive attachment is to a mucous coat, the phenomenon is referred to as mucoadhesion. Mucoadhesion occurs in two stages, the contact stage and the consolidation stage [3] **Fig. 1**.

In the first stage, there is close contact between the mucoadhesive substance and the mucous membrane and swelling of the formulation. In the next step, the mucoadhesive substances (polymers) within the system are activated by the presence of moisture, allowing the molecules to break and form weak links with the mucosa through Van der Waal forces and hydrogen bonds [5]. The drug is slowly released and enters into the bloodstream, bypassing oral-systemic absorption. Mucoadhesive delivery systems can thus be considered as effective alternatives to conventional drug delivery such as tablets, by providing the desired action with little or no adverse effects.

The aim of this study was therefore, to evaluate and compare the efficacy of tablets and mucoadhesive patches of meloxicam and diclofenac in the management of odontogenic pain.

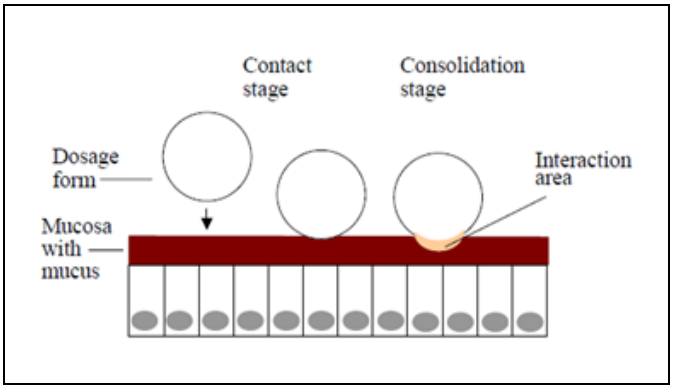


FIG. 1: STAGES OF MUCOADHESION

MATERIALS AND METHODS: The study was conducted on patients visiting the out-patient department of Oral Medicine and Radiology. The study was approved by the institutional review board and informed consent was obtained from each patient. 60 patients of either sex presenting with odontogenic pain, were involved in the study.

Patients included in the study were those presenting with acute odontogenic pain who had not taken analgesics in the past 24 h, those who were not indicated for antibiotic therapy and who were able to follow the instructions given clearly. The exclusion criteria were, patients with a history of allergy to NSAIDs, with inflammatory swellings, who were currently on antibiotic therapy, lacking manual dexterity, pregnant patients and those with severe hepatic, renal and respiratory illness as well as patients with active peptic ulcerations within the last 6 months.

Diclofenac sodium tablets (Divon 50) were obtained from Micro Labs Ltd. and meloxicam tablets were procured from Sun Pharma (Muvera 7.5). Mucoadhesive patches of the same drugs were prepared in the Pharmacy College by solvent casting technique [6].

Preparation of Patches: Hydroxyl polymethyl cellulose (HPMC) was weighed accurately (1000 mg) and dissolved in 5 ml of acetone and kept aside for 5 min for swelling of the polymer. 3 ml of acetone was then added to this solution and stirred followed by the addition of 10 drops of glycerine. 480 mg of meloxicam powder was accurately weighed and dissolved in1 ml of methanol in another beaker. The drug solution was then added to the polymer solution and mixed thoroughly using a magnetic stirrer.

A glass mold was placed over a flat surface. The entire solution was poured into this glass mold over which an inverted funnel was placed to avoid sudden evaporation. The apparatus was kept for 12 h at room temperature for drying. After drying, films were checked for possible imperfections. They were cut into sizes of 1 × 1 cm^2, covered with wax paper and preserved till usage. A similar procedure was used to prepare diclofenac patches using 1300 mg of the drug. The amount of drug present in each 1 × 1 cm^2 patch was 2 mg and 8mg of meloxicam and diclofenac respectively.

Clinical Assessment: 60 patients reporting with acute dental pain were included in the study. Clinical examination was done and a structured proforma regarding chief complaint and history of presenting illness was filled to establish a working diagnosis. Evaluation was done by a single examiner to reduce bias. Patients were divided randomly into 4 groups.

Group A1: Meloxicam tablet.

Group A2: Meloxicam mucoadhesive patches.

Group B1: Diclofenac tablet.

Group B2: Diclofenac mucoadhesive patches.

Patients in the tablet groups were given the respective medications to be taken orally, following examination. For patients who were allotted the mucoadhesive patches, the patches were placed on the alveolar mucosa at the site of pain. In all 4 groups, the degree of pain was assessed at baseline, 20 and 30 min post-administration, on a 10 cm Visual Analogue Scale (VAS); 0 representing no pain and 10 for worst imaginable pain. Patients were then given the tablets or patches according to their allotted group, to take back with them and use for a period of two days. Patients receiving meloxicam were instructed to use the tablets or patches once daily in the mornings.

Those receiving diclofenac were asked to use the tablet or patch twice daily, once in the morning and once at night. The tablets were to be swallowed after food and the patches were to be placed by the patient in the alveolar mucosa at the site of pain after meals. The method of application of the patches was demonstrated to the patients at the first visit **Fig. 2**. Those patients using the mucoadhesive patches were instructed to place the patches at the same site every time, to avoid eating or drinking for half-hour after placement of the patches, and to also avoid vigorous movements of the mouth which may displace the patch. Dental treatment was deferred until after the period of study when patients were recalled and appropriate treatment was carried out. Rescue medication in the form of paracetamol (500 mg) was allowed.

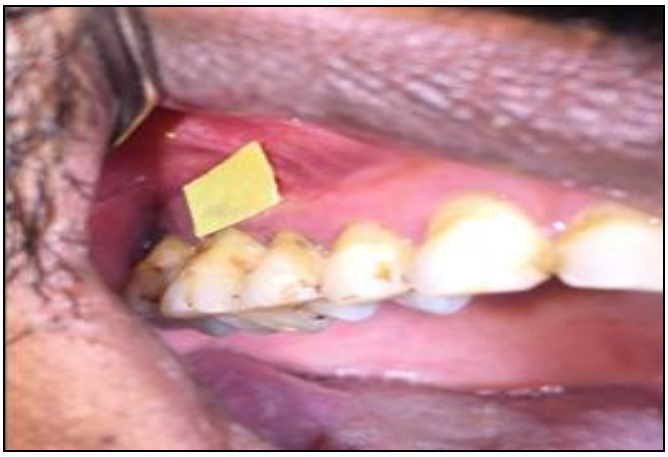


FIG. 2: MUCOADHESIVE PATCH APPLICATION

Prior to enrolment in the study, 4 patients out of 30 in the tablet groups had a history of gastritis for which they were prescribed pantoprazole (40 mg) before food, along with the study tablet. Patients were also given a pain diary to record their pain scores at 30 min following ingestion of tablet or placement of the patch, every day for two days on a VAS scale.

They were also instructed to note down the time of recurrence of pain after the intake of the drug and to note any adverse effects such as gastritis, itching, erythema, burning sensation or ulcers after using the medications. Follow up was done after two days, on the fourth day when the pain diary was collected and data analyzed **Fig. 3**. The mucosa of patients receiving patches was analysed for any reactions or changes at the site of application.

Statistical Analysis: SPSS software (version 21.0) was used for statistical analysis. Descriptive analysis was carried out along with a one-way analysis of variance (ANOVA) for intragroup comparison, independent t-test for intergroup comparison and Mann-Whitney U test to assess the level of significance. A P-value of less than 0.05 was considered statistically significant.

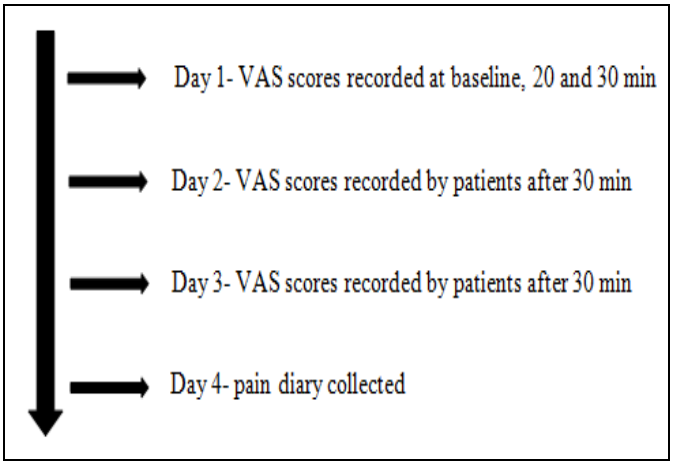


FIG. 3: FLOW DIAGRAM SHOWING STAGES OF STUDY

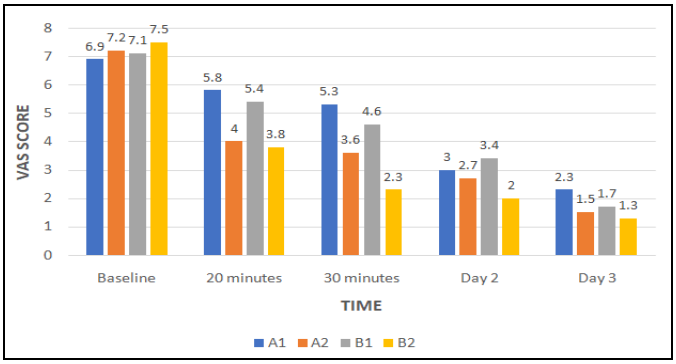
RESULTS: 73 patients meeting the criteria were considered eligible for the study, of which 13 were lost to follow up. The remaining 60 patients were included. The study population included 28 females and 32 males with age ranging from 19-50 years, and mean of 36.05 ± 12.00 years. The mean age of patients in the 4 groups was not statistically significant. A gradual reduction in pain was seen in all four groups with statistically significant results from the baseline to the end of the third day. A maximum reduction in pain at the end of the study period was seen in diclofenac mucoadhesive patch group **Table 1**, **Graph 1**.

TABLE 1: INTER AND INTRA GROUP COMPARISON OF MEAN VAS SCORES AT BASELINE, 20 min, 30 min, DAY 2 AND DAY 3

GROUP	Baseline	20 min	30 min	Day 2	Day 3
A1 (meloxicam tablet)	6.93 ± 1.70	5.8 ± 2.47	5.3 ± 2.19	3.0 ± 2.40	2.3 ± 2.58
A2 (meloxicam patch)	7.26 ± 1.16	4.5 ± 1.45	2.7 ± 1.83	3.6 ± 1.34	1.8 ± 1.01
B1 (diclofenac tablet)	7.13 ± 1.92	5.4 ± 1.76	4.6 ± 1.45	3.46 ± 2.27	1.73 ± 1.74
B2 (diclofenac patch)	7.23 ± 1.06	3.3 ± 1.11	1.0 ± 0.88	2.3 ± 0.83	1.3 ± 0.74

In the diclofenac groups, the mucoadhesive patches showed a greater reduction in pain as compared to the tablets, with the reduction being statistically significant ($p = 0.02$). In the meloxicam group, the patches showed a greater reduction in pain than the tablet although the reduction in pain intensity was not statistically significant ($p = 0.06$). On comparing the results between the tablets, diclofenac showed a significantly better reduction in pain than meloxicam ($p < 0.05$). Diclofenac patches also showed improved results as compared to meloxicam, however it was not significant statistically ($p > 0.05$).

Pain of varying intensity recurred in patients of all groups, although the time of recurrence of pain was observed to be different. The earliest recurrence was seen after using the diclofenac mucoadhesive patches (4 h), whereas meloxicam tablets exhibited reappearance of pain after the longest time (7 h). If the pain that recurred was intolerable patients were allowed to take the rescue medication. 5 patients in group A1, 6 in group A2, 3 in group B1 and 4 in group B2 took the rescue medication (paracetamol 500 mg). 2 patients in each of the tablet groups, with no history of gastritis, complained of mild gastric irritation after taking the analgesic tablets. In the patch groups, pantoprazole was not prescribed for those with a history of gastritis, due to local mode of administration and none of the patients complained of any gastric symptoms after using the patches. Patients using mucoadhesive patches reported that the patch stayed in contact with the mucosa for approximately a period of 25 min after which they slowly started to dissolve, with complete dissolution by 40 min. 5 patients reported difficulty in the placement of the patches in the posterior regions of the oral cavity. None of the patients reported of any side effects of itching or burning sensation at the site of placement and no mucosal changes (erythema or ulcerations) was observed at the end of the study period.



GRAPH 1: COMPARISON OF REDUCTION IN VAS SCORES

DISCUSSION: Gastrointestinal and respiratory tracts in the body are lined by mucous membranes. These membranes are made moist by the continuous secretion of mucus, which is a gel-like substance that is adherent to the epithelium.

Mucous consists of glycoproteins, lipids, inorganic salts and more than 95% water, making it a highly hydrated system. The thickness of the mucous layer varies in different mucosal surfaces, from 50 to 450 μm in the gastric lining to less than 1 μm in the oral cavity [4]. The phenomenon of adhesion of polymers to this mucous layer is termed as mucoadhesion. Despite tremendous advances in drug delivery systems, the oral route remains ideal because of low cost, ease of administration and high patient compliance. Significant barriers, however, are imposed on oral administration including hepatic first-pass metabolism and degradation of the drugs within the digestive tract before absorption. Hence, other potential sites for administering drugs such as mucosal linings of the nasal, rectal, vaginal, ocular, and oral cavity have been investigated. In such transmucosal delivery systems, the drug is transferred directly into the bloodstream *via* mucous membranes avoiding pre systemic elimination.

The lining mucosa of the oral cavity which includes the buccal mucosa, labial mucosa, sublingual mucosa and the ventral surface of the tongue possesses higher overall permeability as compared to other mucosae. This is because the mucosa in this region is thinner and highly vascularized and therefore drugs diffusing across the membranes have direct access to the systemic circulation via the abundant blood supply. The overall permeability of the oral mucosa has been estimated to be greater than that of the epidermis, in the range of 4-4000 times, varying across different regions of the oral cavity and with the chemical substances penetrating the barrier [5]. The oral mucous membrane can, therefore, be considered as a viable alternative to efficiently deliver drugs for both local and systemic actions.

Mucoadhesive formulations are available in a variety of forms such as tablets, patches, wafers, gums, lozenges, ointments and gels. Patches allow greater modification of shape, flexibility, thinness, ease of application, and patient comfort as compared to other formulations [6] and hence were the preferred mode of delivery in this study. NSAIDs are amongst the most commonly used agents for managing pain prescribed primarily for odontogenic and arthritic pain. Oral administration of tablets is the standard mode of carrying these drugs into the body. However, because of hepatic first-pass metabolism, large amounts of the drugs are eliminated pre systemically. This requires that the dosage and frequency of administration must be increased to achieve therapeutic quantities of the analgesics in serum. The results of this study showed that mucoadhesive patches of meloxicam and diclofenac resulted in a significant reduction in pain at the offending site. These results are similar to a study conducted in 2015 which compared the analgesic effects of meloxicam and diclofenac mucoadhesive patches along with placebo for management of odontogenic pain.

The study concluded that there was a significant reduction in pain in the diclofenac and meloxicam patch groups at the end of the 20^{th} and 30^{th} min as compared to the placebo group [7]. Similar results with transdermal analgesic patches were seen in a crossover study comparing oral and transdermal diclofenac for postoperative pain following periodontal flap surgery. Pain reduction was more with transdermal than oral diclofenac of the same dose [8]. Peak action of diclofenac sodium is reached at 1.5-2 h after oral ingestion and meloxicam at 5-6 h. In this study, although there was a reduction in pain with both tablets and patches, the mucoadhesive patches showed a consistently better reduction in pain as compared to the tablets beginning in the 20^{th} min. This could be attributed to the direct and targeted delivery of the drugs to the site of action. A study was conducted to compare oral diclofenac sodium with transdermal diclofenac patches in twenty orthodontic patients undergoing premolar extractions.

In the cross over study, patients were first given 50 mg diclofenac orally three times a day for three days. Following extraction of contralateral premolars, 100 mg diclofenac transdermal patch was placed on the shoulder once daily for three days. Pain reduction was seen in both groups, the transdermal patch group showing better results [9]. Cyclooxygenase enzymes help protect the gastric mucosal lining, by the synthesis of prostaglandins (prostaglandin E2). By inhibiting the enzymes and prostaglandin synthesis, NSAIDs can cause severe gastric effects such as inflammation, ulcerations, erosions, and perforation of the gastric mucosal lining. Prolonged usage of NSAIDs also results in renal damage. The severity of these effects is also

seen to increase with the dosage and frequency of administration of NSAIDs [1]. In this study, 2 patients in each of the tablet groups had mild gastric irritation after taking the tablets.

None of the patients in the patch groups complained of gastritis during or after the period of study, which could be attributed to the local system of drug delivery. The patients using the mucoadhesive patches did not complain of any mucosal reactions in the area after the placement of patches. Similar results were seen in a study conducted using lornoxicam buccal patches on 40 patients who underwent maxillofacial surgeries. Patients were evaluated using a VAS scale 4 h after application of the first dose, then on the second, third and fourth days, when a significant reduction in pain was observed with no side effects after using the patches [10].

The overall reduction in pain observed in this study was greater with the mucoadhesive patches as compared to the tablets. However, there were some limitations in this study in evaluating the effect of the patches on alleviating pain. The amount of drug that penetrated the mucosa from the transmucosal patches could not be estimated. The evaluation was also done on a relatively small population presenting with only acute odontogenic pain. Future studies are recommended where other transmucosal drug delivery systems such as gels, wafers, sprays, etc can be tried for the management of odontogenic pain. It also imperative to create awareness among clinicians about such drug delivery methods which can be incorporated into routine practice, reducing the systemic side effects and at the same time providing a substantial reduction in pain.

CONCLUSION: This study showed that trans-mucosal patches of meloxicam and diclofenac provided effective relief of acute odontogenic pain when compared with tablets of the same drug. No side effect was reported by any of the patients after using the patches. Transmucosal mucoadhesive patches can hence, be considered as alternatives to systemic administration of NSAIDs, providing an effective reduction of local pain.

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CONFLICTS OF INTEREST: There are no conflicts of interest.

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