Development And Clinical Evaluation Of Transmucosal Mucoadhesive Patch Of Lornoxicam For The Odontogenic Pain Management -A Preliminary Study.

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Abstract: Background: Pain is the most common complaint of the patient that brings him to the dentist, often occurring in conjunction with inflammation and which considerably reduce patient quality of life. Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly prescribed for the dental pain management. The GI complications associated with NSAIDs can be effectively overcome if they are delivered by transmucosal route in the form of buccal patch. Aim: To evaluate the efficacy of mucoadhesive lornoxicam patches in odontogenic pain management. Materials and Method: The study was conducted in 60 adult patients of either sex, diagnosed with odontogenic pain and were attending the outpatient department. Informed consent was obtained from all the patients. A 1×1 cm mucoadhesive patch containing 4 mg of lornoxicam was applied on the attached gingival region of the tooth with pain. Pain was recorded using a ten point visual analogue scale (VAS) score before and every 5 min till 30 min after the application of the patch. Statistical analysis was done using repeated measure ANOVA with $p<0.05$. Results: The results of the study revealed a significant drop in the pain scores from baseline to the score recorded after 30min ($p<0.05$). Conclusion: The results of the present study conclusively suggested the suitability, safety and efficacy of the transmucosal delivery of lornoxicam in the form of mucoadhesive patch for the management of odontogenic pain. [Thriveni R Natl J Integr Res Med, 2019; 10(4):26-30]

Key Words: : Odontogenic pain; Lornoxicam; Transmucosal mucoadhesive patches; Pain scores

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Introduction: Pain is an unpleasant, subjective, sensational and emotional experience associated with actual or potential tissue damage. The level of pain perception, threshold and response varies under different conditions [1]. Pain is the most common reason for patients to come to the dental clinic; this pain usually originates in the tooth itself or its supporting structures [2]. Literature survey suggests that the overall estimated prevalence for dental pain ranges from 07–66% [3].

Dental pain may be defined as pain that originates from the innervated tissues within the tooth or immediately adjacent to it and it has an impact on the individuals quality of life [4].

The drugs most commonly used to manage dental pain are nonsteroidal anti-inflammatory drugs (NSAIDs) and mostly they are administered through peroral route. Diclofenac, meloxicam, etc., are the most commonly used medications in the world because of their demonstrated efficacy in reducing pain and inflammation. Numerous studies have clearly documented that the risk of upper gastrointestinal complications increases with increasing doses as well as increasing frequency of use of NSAIDs [5].

Lornoxicam, a congener of tenoxicam, is a new NSAID belonging to the oxicam class. It is a strong analgesic and anti-inflammatory NSAID as compared to other NSAIDs. Its analgesic activity is comparable to that of opioids. Studies have shown that it is more effective than 10 mg morphine when used at doses > or = 8 mg to control pain after oral surgery. Lornoxicam combines the high therapeutic potency of oxicams with an improved gastrointestinal toxicity profile .Clinical investigations have established it as a potent analgesic with excellent anti-inflammatory properties in a range of painful and/or inflammatory conditions, including postoperative pain and Rheumatoid Arthritis.[6]

In oral transmucosal drug delivery, drugs are directly exposed to the oral (buccal and sublingual) mucosa and permeate across the mucosal tissues to reach the systemic circulation. Mucoadhesion is a new emerging concept in drug delivery. Buccal drug delivery provides a numerous advantages over peroral delivery such as abundant blood supply, robustness of the epithelium, more accurate dosing of the drug, short duration, satisfactory patient compliance and bioavailability is improved due to the avoidance of degradation in the GIT and hepatic first pass metabolism [7]. Buccal patches are greatly pliable and easily tolerated by the patient than tablets and more accurate than gels and ointments because of poor retention.

Lornoxicam binds extensively to plasma albumin (99%), and has a relatively short plasma half-life (3 to 5 hrs) [8] which makes it a good candidate for local delivery. Literature survey, revealed the absence of any work on transmucosal delivery of lornoxicam for the treatment of odontogenic pain. Hence, the present work has been undertaken with an aim to develop mucoadhesive transmucosal lornoxicam patches for the rapid and effective pain relief of odontogenic pain.

Buccal patches offers several advantages over peroral delivery of NSAIDs like rapid onset of action, decreased local or systemic side effects, improved drug utilization thereby reducing the total of the drug administered and also improves patient compliance and tolerance [9].

Clinical implications of the study includes Rapid pain relief, No adverse effects, No allergenic effects, Beneficial in treatment of odontogenic pain. Hence, developed transmucosal patches are safe in management of odontogenic pain.

Literature survey, revealed the absence of any work on transmucosal delivery of lornoxicam for the treatment of odontogenic pain. Hence, the present work deals with the development of mucoadhesive buccal patches of lornoxicam for rapid and effective pain relief.

Materials and Methods: This study was conducted in 60 adult patients of either sex, who were diagnosed with odontogenic pain and were attending the outpatient department of oral medicine and radiology, A.M.E's Dental College & Hospital, Raichur, Karnataka, India. Ethical clearance was obtained from the Institutional Review Board, A.M.E's Dental college & Hospital, Raichur. The informed consent from the patients was obtained before the study.

Clinical trial registry has done with a registration number-REF/2019/01/023371. Inclusion criteria: Adult patients of either sex of age group between 18-55 years, clinically diagnosed with odontogenic pain (apical periodontitis, acute and chronic periapical abscess), mentally sound to answer the VAS score and who had not taken any type of analgesic/anti-inflammatory drugs, or tranquilizers for one day before the study. Exclusion criteria: Patients allergic to the drug or patch material, pain due to ulcerated lesion or carcinomatous conditions, patients with any serious systemic diseases, patients with persistence mental confusion, or women who were pregnant and lactating.

Preparation of patches: The mucoadhesive patches were prepared by solvent casting method. The known quantity of lornoxicam (1.2%w/v) was dissolved in 10 ml of alkalinized water (5ml of 0.15 NaOH in 100ml water). To this solution HPMC K15M (4% w/v) and glycerol (0.5%w/v) were added as a mucoadhesive polymer and plasticizer respectively under stirring. The films were casted on a glass petridish and placed in the hot air oven maintained at 40 °C for 24hours. The patches were cut into appropriate sizes (1x1cm), packed in aluminium foil and stored in a glass dessicator till further use [10]. The patches were evaluated for drug content uniformity, weight uniformity, thickness and folding endurance [11].

Clinical Evaluation: The patients were explained about the procedure and the VAS scores (0-10). The patient data were collected on a detailed proforma wherein the chief complaint, diagnosis, detailed medical history, VAS scores and side effects in the next 24hours were also recorded through telephonic conversation. Pain intensity was measured by 10mm VAS score with 0 being no pain and 10 being worst pain.

The patients were asked to describe the intensity of pain they experienced at baseline and every 5min for 30 mins (Figure 1). The area with pain was mopped with cotton pallet and then mucoadhesive patch was placed over the attached gingiva and alveolar mucosa of the offending tooth as shown in (Figure 2). The patients were advised to avoid talking, spitting and to leave the applied area undisturbed for next 30 mins and VAS score was recorded for every 5mins. After 30mins patch was removed and discarded [12].

Figure 1:Assessment of pain (visually)

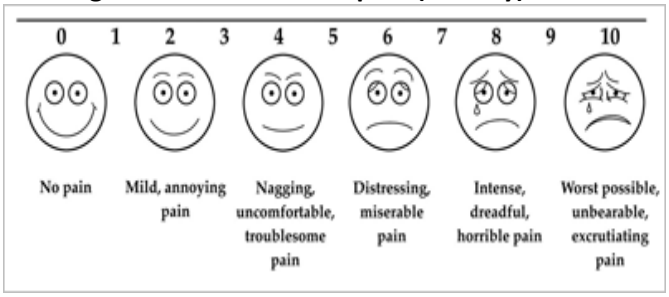
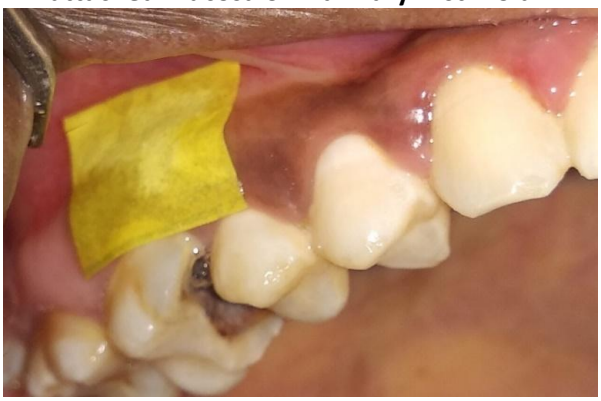


Figure 2: Mucoadhesive patch applied to the attached mucosa of Maxillary first molar



Statistical analysis: Data obtained in the study were analysed by the SPSSv 19 statistical package software for the social sciences (SPSS Inc., Chicago, IL, USA).Descriptive statistics such as mean, standard deviation and percentage was used (Table 1). Comparison of mean VAS score at different time intervals was carried out using Repeated measures ANOVA.

Table 1. Mean Pain Scores at different time intervals.

Time Interval	N	Mean	Standard Deviation
Baseline	60	6.07	2.875
05 minutes	60	3.73	3.635
10 minutes	60	2.13	2.703
15 minutes	60	1.20	2.530
20 minutes	60	0.73	1.604
25 minutes	60	0.33	1.174
30 minutes	60	0.07	0.362

Results : In the present study, out of 60 patients, 28 were females and 32 were males. The cases consisted of acute and chronic periapical abscess, apical periodontitis and other pain of odontogenic origin. The baseline score was ranged from 2-10 with a mean of 6.07±2.87 indicating the higher pain levels in most of the patients.

Pain reduction was noted starting from the first 5min after the application of patch. The maximal pain reduction was seen in the first 10min. Quick analgesic effect was achieved with the patch in all the patients and symptoms were also relieved with no adverse effect.

The mean VAS scores recorded at baseline was 6.07 which dropped down to 0.07 at the end of 30mins. The difference observed in VAS score between all the time intervals was found to be statistically significant (p<0.05). The results of the VAS scores are given in (Table 2) and depicted in (Figure 1).

Table 2: Pairwise comparison of visual analogue scale scores between all-time intervals.

Time Interval	Baseline	5 min	10 min	15 min	20 min	25 min	30 min
Baseline		<0.001[a]	<0.001[a]	<0.001[a]	<0.001[a]	<0.001[a]	<0.001[a]
5 min			<0.001[a]	<0.001[a]	<0.001[a]	<0.001[a]	<0.001[a]
10 min				<0.001[a]	<0.001[a]	<0.001[a]	<0.001[a]
15 min					0.106[c]	<0.05[b]	<0.05[b]
20 min						<0.05[b]	<0.05[b]
25 min							0.412[c]
30 min							

Statistically significant at p<0.001, Statistically significant at p<0.05, Statistically non-significant (p>0.05)

Discussion: Lornoxicam has an improved gastrointestinal toxicity profile with the high therapeutic potency as compared to naproxen [3].Although the usual oral dose of (4-8) mg of lornoxicam is well tolerated by the patients, yet several side effects have been reported such as stomach ache, nausea, vomiting, dizziness, somnolence, drowsiness, headache and flushing [13].

The parenteral route has its own flaws and thus in recent years there has been tremendous interest in the development of transmucosal delivery systems. One of the most common adverse effects of the most prescribed NSAID's is gastritis, which could be changed with the help of newer techniques like transmucosal drug delivery systems.

Buccal drug delivery provides a numerous advantages over peroral delivery such as abundant blood supply, robustness of the epithelium, more accurate dosing of the drug, short duration, and satisfactory patient compliance [14].

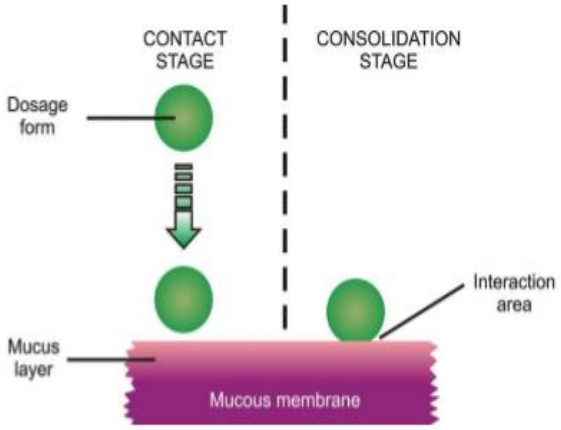
It is estimated that the permeability of the buccal mucosa is 4-4000 times greater than that of the skin. The vessels drain absorbed drug along with the blood into the major veins, which ultimately open into the jugular vein. Thus buccal route of drug delivery provides a direct access to the

systemic circulation painlessly and with a steady rate of delivery bypassing the stomach environment and first pass metabolism, leading to high bioavailability [15].

Transmucosal patch prepared soft and thin owing a comfort to the patient during application and the treatment period. Mucoadhesive formulations readily attached to buccal cavity and retained for a longer duration and can be discarded at any time. The pain intensity was remarkably reduced within the first 5mins.

The mechanism of mucoadhesion is divided in two stages, the contact stage and the consolidation stage. In Contact stage there is a contact between the mucoadhesive and the mucous membrane, along with spreading and swelling of the formulation, initiating deep contact with the mucus layer [12]. In the consolidation stage, due to the presence of moisture the mucoadhesive materials are activated. Moisture plasticizers in the system, allow the mucoadhesive molecules to break freely and to make bonds by weak van der Waals and hydrogen bonds and after which the drug percolation occurs(figure 3) [16].

Figure 3: Two steps of mucoadhesion process

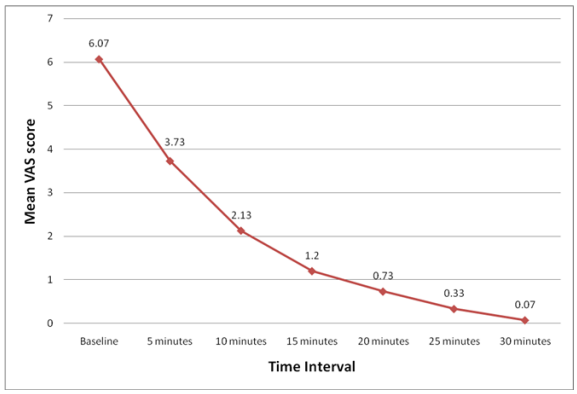


In this study baseline pain score was 6.07 and gradually decreases to 0.07 at different time of intervals i.e. after 5min-3.73, after 10min-2.13, after 15min-1.2, after 20min-0.73, after 25 min-0.33 and after 30 min- 0.07 found statistically significant($p<0.001$).

In this study Maximum decline was observed within the first 10mins after which it became more gradual. Also, the difference in VAS score between all time intervals was found to be statistically significant.

On telephonic conversation, a maximal of 4-6 hours of analgesic effect was noted before the Patient had taken next analgesic and this effect was noticed in all patients.

Figure 4: Mean pain (VAS) scores at different time intervals



The results of the present study were in accordance with another study wherein mucoadhesive indomethacin patches used showed rapid and effective analgesic effect in 65 patients diagnosed with various oral conditions associated with pain [17], and mucoadhesive meloxicam patches in 55 patients diagnosed with dental pain and had the analgesic effect for about 4-5hours [12]. Future studies can be conducted with larger sample size this research open a new panorama in the field of pain relief.

Advantages: Mucoadhesive patch Prolongs the residence time of the dosage form at the site of absorption. Hence the therapeutic efficacy of the drug is also increased. It avoids the first pass metabolism. It has excellent accessibility, rapid onset of action. Rapid absorption because of enormous blood supply and good blood flow rates. Drug is protected from degradation in the acidic environment in the GIT. Patient compliance is improved and ease of drug administration. It also has increased residence time, which enhances absorption and hence the therapeutic efficacy of the drug.

Disadvantages: One of the major limitations in the development of oral mucosal delivery is the lack of a good model for in vitro screening to identify drugs suitable for administration. Patient acceptability in terms to taste, irritancy and mouth feel is to be checked.

Conclusion: Our study established the efficacy of lornoxicam mucoadhesive patch in dental pain

management with no side effects and patient had the analgesic effect for about 4-6 hours. The study revealed statistically significant results suggested that the transmucosal drug delivery system can be safe, promising, therapeutic system for buccal delivery to avoid disadvantage of parenteral and oral route.

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