Open Access Journal

Indian Journal of Medical Research and Pharmaceutical Sciences

September 2018;5(9) ISSN: ISSN: 2349-5340

DOI: 10.5281/zenodo.1437222 Impact Factor: 4.054

EVALUATION OF MELOXICAM TRANSMUCOSAL PATCHES IN DENTAL PAIN MANAGEMENT. A RANDOMIZED, DOUBLE BLINDED, PLACEBO-CONTROLLED PRELIMINARY STUDY

Dr. Nimesh Jain*, Dr. Pratik R Pipliya, Dr. Rajeshwari G Annigeri, Dr. Rajita Mehta & Dr. Manisha Jadhav

*Senior Lecturer, Department of Oral Medicine & Radiology, College of Dental Sciences, Rau, Indore

Dental Surgeon, Refrral Hospital &CommintyHealt Center, Lodhika, Rajkot, Gujrat

Professor & Head, College of Dental Sciences, Davangere, Karnataka

Senior Lecturer, Seema Dental College, Rishikesh, Uttrakhand

Private Practitioner, Dombivali, Maharashtra

Keywords:
Transmucosal Patch, Mucoadhesion, Dental Pain, Meloxicam, Pulpitis.

Abstract

Introduction:

The present study aimed to evaluate the effectiveness of Meloxicam transmucosal patches in dental pain management.

Materials and Methods:

Patientswith symptomatic irreversible pulpitis withoutany other pathology and experiencing moderate to severe pain on Verbal Rating Scale (VRS-4) and 4 to 10 pint score on Numerical Rating Scale (NRS-11) were included. Transmucosalpatches, containing the meloxicam/no drug,of 1x1cm^{2}were prepared and applied over the attached gingiva and alveolar mucosal region of offending tooth.Pain was measured before and 5, 10, 15, 20, 25, 30 mins, 1hour and 6 hours after the application of patch.

Results:

A total of 51 participants completed the study i.e. Meloxicam group had 26 and placebo group had 25 participants. On VRS-4 pain scale, at the end of the study 1(4%) participantin meloxicam group had moderate pain, while in the placebo group 2(8%) participants had severe pain and 10(40%) participants had moderate pain. On NRS-11 scale, meloxicam group showed 86.65% (5.29 ± 0.94point) pain reduction compared to placebo group which had 45.10% (2.76 ± 0.18point) pain reduction ($P<0.01$). Three participants reported bitter taste of very mild intensity during the patch application for few mins. No other discomfort were reported.

Conclusion:

The application of meloxicam containing transmucosal patch, is safe and efficacious alternate to oral administration, for the management of dental pain.

Introduction

Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage(1).The estimated overall prevalence for orofacial pain ranges from 7–66%(2). Among the orofacial pain, pulpitis is the most commonly reported painful condition(3, 4), that brings patients to seek dental appointment. A survey of non-institutionalized civilian residents of the United States showed that 28% of the population reported experiencing orofacial pain, with the most common report being odontalgia(5). Even in Indian population, 43% of the complaint to seek the dental attention is pulpitis(4). Considering this fact, the pulpitis pain model was considered in the present study.

Indian Journal of Medical Research and Pharmaceutical Sciences
September 2018;5(9) ISSN: ISSN: 2349-5340
DOI: 10.5281/zenodo.1437222 Impact Factor: 4.054

Irreversible pulpitis generally originates as a localized inflammatory response to bacterial invasion of the pulp-dentin complex. The mechanisms for this pain are thought to be caused by sensitization and activation of pulpal nociceptors because of local release of inflammatory mediators(6).

Nonsteroidal anti-inflammatory drugs (NSAIDs) come into play to manage such inflammatory pain conditions.The use NSAIDs reduces the chemical inflammatory mediators that activate or sensitize peripheral nociceptors and the related subsequent events involved in pain perception(7). Among the NSAIDs, meloxicam are routinely prescribed drug now a days. Meloxicam, of oxicam class, is given at the dosage of 7.5 to 15 mg daily to confer its analgesic effect(8). Meloxicam posses strong anti-inflammatory spectrum and are potent analgesics. Considering these facts, meloxicam was used as interventional drug in the present study.

One of the most important medical and social-economic problem associated with use of NSAIDs is Gastro-intestinal (GI) toxicity(9) and this GI toxicity is dose dependent(10).In addition, the parenteral route has the same risks of GI toxicity as the oral route(11). However, the topical routes of NSAIDs administration are not associated with any of the gastrointestinal effects seen with other routes(12) of drug delivery. Transmucosal route is also one such topical route through which NSAIDs can be administered.

Transmucosal route is one of the preferred topical route, which gets special attention in dentistry. There are many reports(13-17) on the transmucosal delivery system. It offers distinct advantages over peroral delivery including reduced dosage, rich blood supply, robustness of the epithelium, suitable patient compliance and improved bioavailability due to avoidance of degradation in the GI tract and hepatic first-pass metabolism (18) .Transmucosal patches are highly flexible and thus much more readily tolerated by the patient than tablets. Patches also ensure more accurate dosing of the drug compared to gels and ointments(19). To attain these advantages , the transmucosal patches were used in the present study.

The perception of pain is influenced by many factors(20) and several scales are proposed to measure the pain level i.e. Numerical Rating Scale (NRS), Verbal Rating Scale (VRS) and Visual Analogue Scale (VAS). The NRS can bea 11, 21 or 101 point scale where the end points are the extremes of no pain and pain as bad as it could be, or worst pain. The NRS can be graphically or verbally delivered(21). The VRS comprises a list of adjectives used to denote increasing pain intensities. The most common words used being: no pain; mild pain; moderate pain; and severe or intense pain(21). The VAS is presented as a 10-cm line, anchored by verbal descriptors, usually ‘no pain’ and ‘worst imaginable pain’ (Fig. 1). The patient is asked to mark a 100 mm line to indicate pain intensity. The score is measured from the zero anchor to the patient’s mark(21-24).

It is believed the NRS is preferred when the sensitivity is required, whereas the VRS is preferred by patients because of its and high compliance rate(25).So in the present study, the NRS-11 was used to quantitatively analyse pain reduction, and the VRS-4 was used to qualitatively analyse patients’ perception of pain reduction.

Materials and methods

The study protocol was reviewed and approved by Institution Review Board of College of Dental Sciences, Davangere(Certificate no. CODS/487/2014-2015). The study was conducted in accordance to Declaration of Helsinki. Eligibility of the participant was assessed by clinical and radiographic examinations. Participants who had moderate to severe pain on VRS–4 scale and 4 to 10 score on NRS–11 scale were further assessed for radiographic examination. And whose periapical radiographs confirmed the absence of any periapical pathology were considered suitable and invited to participate in this study.

The minimum sample size to detect difference between the 2 groups with 5% type I error and 95% confidence interval, is 189 per group.However, for the preliminary study, the sample size can/should be 10% of original calculated parent study(26, 27), so the number obtained was (n=) 19 participants per group. Then the sample size was increased to (n=) 30 per group, to account for refusal to participate, loss of follow up, displacement of patch or damaged medication.

Indian Journal of Medical Research and Pharmaceutical Sciences
September 2018;5(9) ISSN: ISSN: 2349-5340
DOI: 10.5281/zenodo.1437222 Impact Factor: 4.054

The participants of either sex attending department were included based on following inclusion andexclusion criteria.

Inclusion criteria:

(i) Participants of both sexes aged above 18 years.
(ii) Participants with symptomatic irreversible pulpitis and normal periapical appearance of radiograph.
(iii) Participants having moderate to severe pain on VRS–4 scale and 4 to 10 points score on NRS–11 scale.
(iv) Participants with American Society of Anesthesiologists I or II medical history (28).
(v) Mentally sound enough to answer the VRS-4 and NRS-11 pain scale.
(vi) Participants who had not taken any type of analgesic drugs, anti-inflammatory drugs or tranquilizers for 72 hours before the study.
(vii) Participants who are willing to follow the strict instructions i.e. Not to do any tongue movement that can dislodge the patch etc.

Exclusion criteria:

(i) Participants with American Society of Anesthesiologists III or IV medical history (28).
(ii) Participants allergic to the drugs (NSAIDs) or patch material.
(iii) Pregnant or nursing.
(iv) Participants with persistence mental confusion.

Preparation of the transmucosal patches and the randomization method

Transmucosal patches were prepared at Department of Pharmaceutics, Bapuji Pharmacy College, Davangere. Drug used in the study was meloxicam (Dr Reddy Labs, Hyderabad). The patches were prepared by Anders and Merkle's solvent casting technique(29) using film Hydroxypropyl methyl cellulose (HPMC) polymer, acetone, ethanol, and drugs(30). After preparing the patches, they were cut into 1x1cm^2 pieces, secured with protective covering and preserved in desiccator till the evaluation tests were performed. Then the patches were tested for all quality control measures such as drug content uniformity, thickness uniformity, weight uniformity, sterility, folding endurance, tensile strength and stability by the third author. The single meloxicam patch contained an average of0.50mg of drug while the placebo patch contained no drug. Following all quality control measures, the patches were packed into60 identical opaque sachets, 30 per group.

These sachets were coded following a simple randomization sequence assisted by computer, which was prepared in advance by someone who was not directly involved in the any steps of the study. Following coding, the sachets were placed in black bag to camouflage it both from participants and the investigatorat sachet drawingstage. The rationale being that, every participant will have equal opportunity of being included on treatment group or placebo group(31).

Pain assessment:

First author was assigned for the for assistance and collection of the data on a detailed proforma where in the pain scores and other related information were recorded. Participants were asked to make entry on NRS-11 scale as well as VRS-4 scale at pre-defined interval during the study.

After screening and enrolment according to inclusion and exclusion criteria, all participants were asked to draw one sachet from the black bag and the serial number of that sachetwas recorded. Following that, patch from the drawn sachet was recovered and applied over the attached gingiva and alveolar mucosa of the offending tooth. Before applying the patch, the area was mopped with cotton pallet. Following patch application, participants were advised not to talk, swallow or do any tongue movement which can dislodge the patch.The key to breaking code was delivered to principal investigator after the study was complete at data analysis stage.

For pain score, the participants were assessed before the application of patch as well as after the application of patch, at every 5 mins for 30 mins. After 30 mins, patches were removed and discarded. Then participants were followed

Indian Journal of Medical Research and Pharmaceutical Sciences
September 2018;5(9) ISSN: ISSN: 2349-5340
DOI: 10.5281/zenodo.1437222 Impact Factor: 4.054

up over telephonic medium to assess the pain score at 1 hour and 6 hours time point.Methodology in illustrative form is represented in Figure 1.

Statistical Analysis was done using Software SPSS version 21.0 (SPSS, Chicago, IL, USA). MS Excel 2015(Microsoft Corporation, Washington, DC, USA) was used to generate tables and chart. Descriptive data that included means, numbers and percentages, were calculated for each group and were used for analysis. One-way ANOVA was done followed by Post Hoc Tuckey's test for the analysis. P value < 0.05 was considered as statistically significant.

Results

There were 60 intervention medication/placebo sachets prepared, 30 for each group. Out of 60, 5 participants had their sachets fall on the floor so these samples were considered damaged (because of cross infection and contamination) and excluded. They were given another chance to draw another sachet from the bag. Moreover, one participant had his patch displaced because of tongue movements and hence excluded. Oneparticipants didn't complete the follow-up because of not answering the phone call, hence excluded. And another two participants discontinued the intervention because of personal reasons, hence excluded. Thus final sample size consisted of 51 participants i.e. n=26 for meloxicam and n=25 for placebo group. All 51 participants' demographic characteristic are shown in Table 1.

Overall pain assessment on VRS-4 scale among both the groups are shown in table 2. At 3rd time interval i.e. 15 mins after the patch application, more number of meloxicam group participants had mild to moderate pain, however placebo group participants had moderate to severe pain,at the same time point – Table 2.

The pre-intervention NRS-11 score for meloxicam group was 4 for 6 (23%) participants, 5 for 4(15%) participants, 6 for 6 (23%) participants, 7 for 4 (15%) participants, 8 for 3 (12%) participants, 9 for 1 (4%) participant and 10 for 2 (8%) participants. Similarly, for placebo group, the pre-intervention NRS-11 scale pain score was 4 for 4 (16%) participants, 5 for 8 (32%) participants, 6 for 1 (4%) participant 7 for 5 (20%) participants, 8 for 5 (20%) participants, 9 for 1 (4%) participant and 10 for 1 (4%) participant – Table 3.

After the intervention 12 (46%) participants had score 0, 9(35%)participants had score 1, 4 (15%) participants hadscore 2 and 1 (4%) participant hadpain score 4 in Meloxicam group. For placebo group, the post-intervention pain scores were 0 for 2 (8%) participants, 1 for 2 (8%) participants, 2 for 4 (16%) participants, 3 for 5 (20%) participants, 4 for 3 (12%) participants, 5 for 5 (20%) participants 6 for 2 (8%) participants and 7 for 2 (8%) participants. It showed that after the intervention, more number of the participantsin meloxicam group had low pain score compared to placebo group.The mean pre-intervention and post-intervention NRS-11 score for meloxicam and placebo group are shown in table 3. Meloxicam group participants showed 88.64% (5.44±1.18) reduction in mean NRS-11 score ($p<0.01$) while placebo group participants had 49.67% (3.04 ± 0.16) mean pain reduction ($p<0.01$) – Table 3, Figure 2.

To evaluate the validity and reproducibility of the pain scales used in the present study i.e. VRS-4 and the NRS-11, Pearson correlation test was used to correlate the readings, and the correlation found significantly positive (0.945).

Discussion

The commonly used dental pain model is extraction model however in this preliminary study,pulpitis was selected as a pain model. The extraction pain models are mainly used because of its ease of availability(32) and inflammation, being the dominant pain producing component(33). Similarly, pulpitis is also inflammatory in nature and being the most common complaint of patients, to seek a dental appointment(3, 4), considering this fact pulpitis was selected.

The drug delivery route used in the present study was transmucosal, which is based on phenomenon of bioadhesion. Bioadhesion is 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(34-36). Many theories have been postulated to describe mechanism of

Indian Journal of Medical Research and Pharmaceutical Sciences
September 2018;5(9) ISSN: ISSN: 2349-5340
DOI: 10.5281/zenodo.1437222 Impact Factor: 4.054

bioadhesion, namely adsorption theory, wetting theory, diffusion theory, electronic theory, and fracture theory(37, 38) . The term mucoadhesion is used instead of bioadhesion when mucosa is one of the adhesion material, however these terms are interchangeable.Mucoadhesion is one of the way of targeted drug delivery to an active site of choice. For this, the pharmacological formulation is prepared in which the active pharmaceutical ingredient (API) is incorporated within bioadhesive hydrophilic polymers. The rationale being that the formulation will be ‘ held ’ on or at the biological surface and the API will be released close to the absorptive membrane, thereby achieving increased bioavailability (34, 39).

For the transmucosal drug delivery, various mucous devices including tablet, ointment and gels have recently been developed. However transmucosal patch offer greater flexibility and comfort than other devices, in addition a patch can circumvent the problem of the relatively short residence time of oral gels on mucosa, since gels are easily washed away by saliva(40, 41). So transmucosal patches containing the drug were formulated and used in this intervention.

NSAIDs are the most commonly prescribed drugs in dentistry to manage tooth pain. Amongst NSAIDs, meloxicam was selected in the present study because, along with otheroxicam derivatives, theseare routinely used in the unit of Endodontics.

The present study was designed as randomized, double-blind and placebo controlled.Randomization and double blinding was done to eliminate the potential of matching variables, increaseinternal validity and generatereliable results. In addition, the placebo was used to eliminate any potential bias in the study outcomes.

In this preliminary study, VRS-4 and NRS-11 were used as pain management tool. There are many pain rating scales proposed and evaluated (i.e. VAS, VRS and NRS), none is consistently more superior to the other (42-44). Basically they are subject to patients’ and practitioners’ preferences. Moreover, VRS and NRS are reportedly preferred by patient because of its ease of use and better psychometric properties(45). Hence, the present study used both VRS-4 and NRS-11 pain rating scale to measure the pain.

Table 3 shows the mean NRS-11 pain score over the study period starting from base line i.e. the time before patch application, to 6 hours after the intervention.In general, there has been progressive decline in the level of pain within the timeframe of intervention for both groups. Meloxicam group showed 86.75% (5.29± 0.94 point) reduction in pain ($p<0.01$) and placebo group showed 45.10% (2.760±0.18 point) reduction in NRS-11 pain score. It showed that participants treated with meloxicam patches showed trend towards a greater pain reduction score compared to those treated with placebo – Table 3.

The pain scores using VRS-4 and NRS-11 scale, were recorded at every 5 mins interval for 30 mins and after that the patch was removed from the mouth and discarded. However, to avail data for the analysis of duration of action, 1 hour and 6 hours time frames were selected. At 1 hour and 6 hour, participants were asked over telephonic medium to provide the pain score data and also to provide information if they had taken any other medication (i.e. analgesics, opioids etc.) or not. At those point of time, 4 people lost follow up (meloxicam group n=2, placebo group n=2) because to technical and personal reasons, hence excluded from the analysis – Figure 1.

In the meloxicam group using VRS-4 scale, 38% (n=10) participants had severe pain & 62% (n=16) participants had moderate pain before the application of patch. After 10 mins of patch application 38% (n=10) had moderate to sever pain while the rest 62% (n=16) had their pain reduced to mild intensity in VRS-4 scale and after the completion of the study (at 6 hours), no participants had severe pain, 4% (n=1) participants had moderate pain, 54% (n=14) had mild pain while 42% (n=11) had no pain. There was continuous reduction in number of moderate to sever pain participants upto 1 hour, but at 6 hours reading 4% (n=1) participant reported moderate pain on VRS-4 scale, it may be due to wearing of the drug action.

Similarly, for the placebo group, 48% (n=12) had sever pain and 52% (n=13) had moderate pain before the intervention. After the patch application, 8% (n=2) had sever pain, 40% (n=10) had moderate pain, 44% (n=11)

Indian Journal of Medical Research and Pharmaceutical Sciences
September 2018;5(9) ISSN: ISSN: 2349-5340
DOI: 10.5281/zenodo.1437222 Impact Factor: 4.054

participants had mild pain & 8% (n=2) had no pain. It showed that after the intervention, placebo group had more (n=12) number of participants with moderate to sever pain compared to meloxicam group which had (n=) 1 participant with moderate pain. Thus, meloxicam group showed significant pain reduction compared to placebo group in the present study.

Using NRS-11 scale, post intervention assessment showed 25 (96%) participants in meloxicam group had 0 to 2 pain score, compared to placebo group which had 8 (32%) participants had 0-2 pain score. It reflects greater pain score reduction with meloxicam group compared to placebo.

In the present study, author tried to evaluate the efficacy as well as safety of the transmucosal patches containing NSAIDs, for dental pain management.Similar study reported from Assiut university hospital maxillofacial unit, in which the author studied pain management of 40 patients, underwent minor and major surgery, using single patch ($1x5cm^2$) containing 4mg of lornoxicam daily for 3 days. Here, pain intensity was measured using100mm VASscale. The author achieved significant analgesic effect using mucoadhesivepatches of lornoxicam(46). Another study done in Teikyo University Japan, wherein mucoadhesive indomethacin patches used at 0.5% and 1% concentration in 65 patients diagnosed with various oral conditions associated with pain. The author stated that effects were the greatest in the 1% indomethacin group (47).

Twelve participants (46%) in meloxicam group showed maximum (100%) pain reduction compared to 2 (8%) participants in placebo group. The over all pain reduction achieved with meloxicam group and placebogroup was 86.75% and 45.10% respectively. Thus meloxicam patch performed significantlybetter in pain management compared to placebo patch.

Two participants in meloxicam group and 1 participant in placebo group reported bitter tasteof very mild intensity during the patch application for few mins. These can be due to the dissolution of the drug/patch material in the saliva, followed by reception on the taste receptors. In addition, no any other adverse effects or discomfort reported.

In the present study, the meloxicam patch contained average drug of approximately 0.50mg however the single oral dosage is 7.5mg for meloxicam. Thus dosage of the drugs used in present study, were very low. It is similar to a reported study from Teikyo University Japan, wherein mucoadhesive indomethacin patches used at 0.5% and 1% concentration(47). Moreover, commercially available analgesic gel preparation, aimed for local pain management, also contains less dosage of the drug i.e. 1 w/w% diclofenac gel. This can be argued as the present study wasdesignedusingtargeted drug delivery system, so the drug concentration was kept low.

Short comings and future recommendations:

- The present study was designedusing 6 hours time frame only. Longer the duration of observation with between readings can provide more information regarding the duration of action.
- No biochemical parameters were assessed in the present study. Future studies can correlate the serum drug concentration with its clinical effect.
- The smaller sample size was also anothershort fall here.Further studies with large sample size can be taken.

Conclusion

The findings of this randomized, double-blind, placebo controlled study opens new panorama in the field of safer and faster pain relief systems and it recommends the application of meloxicam containing transmucosal patch, is safe and efficacious alternate to oral administration, for the management of dental pain.

Acknowledgement: The authors gratefully thank Dr N Narendra,DrGarima J, Dr Manisha Jadhav, MrMailappa and Mr Shankar for their contribution towards this study, and DrParth Thakkar for statistical analysis.

Conflicts of interest: The authors deny any conflicts of interest related to this study.

Indian Journal of Medical Research and Pharmaceutical Sciences
September 2018;5(9) ISSN: ISSN: 2349-5340
DOI: 10.5281/zenodo.1437222 Impact Factor: 4.054

Source of funding: The authors gratefully thank Divine HealthtechPvt Ltd – Rajkot, for providing funds and other support.

References

1. Sharav Y. Oral facial pain. In: Wall PD, Melzack R, editors. Text Book of Pain. 2nd ed. New York: Churchill Livingston; 1999. p. 712-3.
2. Pau AK, Croucher R, Marcenes W. Prevalence estimates and associated factors for dental pain: a review. Oral health & preventive dentistry 2003;1(3):209-220.
3. Horst OV, Cunha-Cruz J, Zhou L, Manning W, Mancl L, DeRouen TA. Prevalence of pain in the orofacial regions in patients visiting general dentists in the Northwest Practice-based REsearch Collaborative in Evidence-based DENTistry research network. Journal of the American Dental Association 2015;146(10):721-728 e723.
4. Shetty A, James L, Nagaraj T, Abraham M. Epidemiology of orofacial pain: A retrospective study. Journal of Advanced Clinical & Research Insights 2015;2(1):13.
5. Lipton JA, Ship JA, Larach-Robinson D. Estimated prevalence and distribution of reported orofacial pain in the United States. Journal of the American Dental Association 1993;124(10):115-121.
6. Byers MR, Narhi MV. Dental injury models: experimental tools for understanding neuroinflammatory interactions and polymodal nociceptor functions. Crit Rev Oral Biol Med 1999;10(1):4-39.
7. Holstein A, Hargreaves KM, Niederman R. Evaluation of NSAIDs for treating post-endodontic pain. . Endodontic Topics 2002;3:3-13.
8. Euller-Ziegler L, Velicitat P, Bluhmki E, Turck D, Scheuerer S, Combe B. Meloxicam: a review of its pharmacokinetics, efficacy and tolerability following intramuscular administration. Inflamm Res 2001;50 Suppl 1:S5-9.
9. Becker JC, Domschke W, Pohle T. Current approaches to prevent NSAID-induced gastropathy--COX selectivity and beyond. Br J Clin Pharmacol 2004;58(6):587-600.
10. Lanza FL, Royer GL. NSAID-induced gastric ulceration is dose related by weight: an endoscopic study with flurbiprofen. Am J Gastroenterol 1993;88(5):683-686.
11. Ong CK, Lirk P, Tan CH, Seymour RA. An evidence-based update on nonsteroidal anti-inflammatory drugs. Clin Med Res 2007;5(1):19-34.
12. Moore RA, Tramer MR, Carroll D, Wiffen PJ, McQuay HJ. Quantitative systematic review of topically applied non-steroidal anti-inflammatory drugs. Bmj 1998;316(7128):333-338.
13. Albertini B, Passerini N, Di Sabatino M, Monti D, Burgalassi S, Chetoni P, et al. Poloxamer 407 microspheres for orotransmucosal drug delivery. Part I: formulation, manufacturing and characterization. Int J Pharm 2010;399(1-2):71-79.
14. Christrup LL, Christensen CB, Friis GJ, Jorgensen A. Improvement of buccal delivery of morphine using the prodrug approach. International Journal of Pharmaceutics 1997;154(2):157-165.
15. Hassan N, Ali M, Ali J. Development and evaluation of novel buccoadhesive wafers of nimodipine for treatment of hypertension. Drug Deliv 2010;17(2):59-67.
16. Lee J, Kellaway IW. Combined effect of oleic acid and polyethylene glycol 200 on buccal permeation of [D-ala2, D-leu5]enkephalin from a cubic phase of glyceryl monooleate. Int J Pharm 2000;204(1-2):137-144.
17. Tsutsumi K, Obata Y, Takayama K, Loftsson T, Nagai T. Effect of cod-liver oil extract on the buccal permeation of ergotamine tartrate. Drug Dev Ind Pharm 1998;24(8):757-762.
18. Campisi G, Paderni C, Saccone R, Di Fede O, Wolff A, Giannola LI. Human buccal mucosa as an innovative site of drug delivery. Current pharmaceutical design 2010;16(6):641-652.
19. Nafee NA, Ismail FA, Boraie NA, Mortada LM. Mucoadhesive buccal patches of miconazole nitrate: in vitro/in vivo performance and effect of ageing. Int J Pharm 2003;264(1-2):1-14.
20. Wandner LD, Scipio CD, Hirsh AT, Torres CA, Robinson ME. The perception of pain in others: how gender, race, and age influence pain expectations. J Pain 2012;13(3):220-227.
21. Williamson A, Hoggart B. Pain: a review of three commonly used pain rating scales. Journal of clinical nursing 2005;14(7):798-804.
22. Guyatt GH, Townsend M, Berman LB, Keller JL. A comparison of Likert and visual analogue scales for

September 2018;5(9) ISSN: ISSN: 2349-5340
DOI: 10.5281/zenodo.1437222 Impact Factor: 4.054

measuring change in function. J Chronic Dis 1987;40(12):1129-1133.
23. Jensen MP, Karoly P, Braver S. The measurement of clinical pain intensity: a comparison of six methods. Pain 1986;27(1):117-126.
24. Kremer E, Atkinson JH, Ignelzi RJ. Measurement of pain: patient preference does not confound pain measurement. Pain 1981;10(2):241-248.
25. Jensen MP, Karoly P, O'Riordan EF, Bland F, Jr., Burns RS. The subjective experience of acute pain. An assessment of the utility of 10 indices. Clin J Pain 1989;5(2):153-159.
26. Connelly LM. Pilot studies. Medsurg Nurs 2008;17(6):411-412.
27. Treece EW, Treece JW. Elements of research in nursing. 3rd ed. St. Louis: Mosby; 1982.
28. ASA. New classification of physical status. Anesthesiology 1963;24:111.
29. Anders R, Merkle HP. Evaluation of laminated muco-adhesive patches for buccal drug delivery. International Journal of Pharmaceutics 1989;49(3):231-240.
30. Thimmasetty J, Pandey G, Babu P. Design and in vivo evaluation of carvedilol buccal mucoadhesive patches. Pakistan journal of pharmaceutical sciences 2008;21(3):241-248.
31. Altman RD, Moskowitz R. A randomized clinical trial of intra-articular sodium hyaluronate in patients with osteoarthritis of the knee: a summary. Am J Orthop (Belle Mead NJ) 1999;28(11 Suppl):3-4.
32. Cooper SA, Desjardins PJ. The value of the dental impaction pain model in drug development. Methods in molecular biology 2010;617:175-190.
33. Urquhart E. Analgesic agents and strategies in the dental pain model. J Dent 1994;22(6):336-341.
34. Ahuja A, Khar RK, Ali J. Mucoadhesive Drug Delivery Systems. Drug Develop Indus Pharm 1997;23:489-515.
35. Andrews GP, Laverty TP, Jones DS. Mucoadhesive polymeric platforms for controlled drug delivery. European journal of pharmaceutics and biopharmaceutics : official journal of Arbeitsgemeinschaft fur Pharmazeutische Verfahrenstechnik e.V 2009;71(3):505-518.
36. Henriksen I, Green K, Smart J, Smistad G, Karlsen J. Bioadhesion of hydrated chitosans: an in vitro and in vivo study. Int J Pharm 1996;145:231-240.
37. Huang Y, Leobandung W, Foss A, Peppas NA. Molecular aspects of muco- and bioadhesion: tethered structures and site-specific surfaces. Journal of controlled release : official journal of the Controlled Release Society 2000;65(1-2):63-71.
38. Miller N, Chittchang M, Johnston T. The use of mu- coadhesive polymers in buccal drug delivery. Advanced drug delivery reviews 2005;57:1666-1691.
39. Woodley J. Bioadhesion: new possibilities for drug administration? Clin Pharmacokinet 2001;40(2):77-84.
40. Squier C. The permeability of oral mucosa. Critical Reviews in Oral Biology & Medicine 1991;2(1):13-32.
41. Rathbone MJ, Tucker IG. Mechanisms, barriers and pathways of oral mucosal drug permeation. Advanced drug delivery reviews 1993;12(1–2):41-60.
42. Hartrick CT, Kovan JP, Shapiro S. The numeric rating scale for clinical pain measurement: a ratio measure? Pain practice : the official journal of World Institute of Pain 2003;3(4):310-316.
43. Lara-Munoz C, De Leon SP, Feinstein AR, Puente A, Wells CK. Comparison of three rating scales for measuring subjective phenomena in clinical research. I. Use of experimentally controlled auditory stimuli. Arch Med Res 2004;35(1):43-48.
44. Lund I, Lundeberg T, Sandberg L, Budh CN, Kowalski J, Svensson E. Lack of interchangeability between visual analogue and verbal rating pain scales: a cross sectional description of pain etiology groups. BMC Med Res Methodol 2005;5:31.
45. Brunelli C, Zecca E, Martini C, Campa T, Fagnoni E, Bagnasco M, et al. Comparison of numerical and verbal rating scales to measure pain exacerbations in patients with chronic cancer pain. Health and quality of life outcomes 2010;8:42.
46. Habib F, Shaltout SED, Azeem MA, Fetih G, Safwat M. Mucoadhesive buccal patches of lornoxicam: in-vivo evaluation and clinical efficacy, Bull. Pharm. Sci., Assiut University, 2011, 34(1)21-30.
47. Takeuchi K, Watanabe M, Yanagi M, Murakami I, Hosono H, Nishizawa S, et al. In-vitro and clinical evaluation of an oral mucosal adhesive film containing indomethacin. Yakugaku Zasshi 2008;128(12):1791-1795

Indian Journal of Medical Research and Pharmaceutical Sciences
September 2018;5(9) ISSN: ISSN: 2349-5340
DOI: 10.5281/zenodo.1437222 Impact Factor: 4.054

Table 1: Demographic and clinical characteristics of subjects who participated in study

Groups	Count	Mean age ± s.d. in years	Male: Female
Meloxicam	n=26	36.35 ± 13.27	14:12
Placebo	n=25	35.24 ± 11.40	14:11
Total	n=51	35.80 ± 12.34	28:23

Table 2: Pre and post-treatment pain score on VRS-4 scale at different time interval

		Meloxicam group		Placebo group	
Time	**Pain score**	n=	%	n=	%
Pre-treatment	Severe	10	38	12	48
	Moderate	16	62	13	52
	Mild	0	0	0	0
	No pain	0	0	0	0
After 5 mins	Severe	4	15	12	48
	Moderate	13	50	13	52
	Mild	9	35	0	0
	No pain	0	0	0	0
After 10 mins	Severe	2	8	12	48
	Moderate	8	31	11	44
	Mild	16	62	2	8
	No pain	0	0	0	0
After 15 mins	Severe	0	0	11	44
	Moderate	10	38	12	48
	Mild	16	62	2	8
	No pain	0	0	0	0
After 20 mins	Severe	0	0	11	44
	Moderate	7	27	12	48
	Mild	19	73	2	8
	No pain	0	0	0	0
After 25 mins	Severe	0	0	10	40
	Moderate	7	27	13	52
	Mild	19	73	2	8
	No pain	0	0	0	0
After 30 mins	Severe	0	0	10	40
	Moderate	5	19	13	52
	Mild	21	81	2	8
	No pain	0	0	0	0
After 1 hour	Severe	0	0	3	12
	Moderate	0	0	16	64
	Mild	18	69	6	24
	No pain	8	31	0	0
After 6 hours	Severe	0	0	2	8
	Moderate	1	4	10	40
	Mild	14	54	11	44
	No pain	11	42	2	8

Indian Journal of Medical Research and Pharmaceutical Sciences
September 2018;5(9) ISSN: ISSN: 2349-5340
DOI: 10.5281/zenodo.1437222 Impact Factor: 4.054

Table 3: Pre and post-treatment mean pain score on NRS-11 scale at different time interval

Time	Meloxicam group	Placebo group
Pre-treatment	6.10 ± 1.92	6.12 ± 1.72
After 5 mins	4.85 ± 1.83	5.96 ± 1.55
After 10 mins	3.52 ± 1.95	5.78 ± 1.65
After 15 mins	3.17 ± 1.68	5.56 ± 1.70
After 20 mins	2.60 ± 1.51	5.32 ± 1.98
After 25 mins	2.44 ± 1.34	5.28 ± 2.01
After 30 mins	2.27 ± 1.25	5.28 ± 2.01
After 1 hour	1.27 ± 1.04	4.44 ± 1.82
After 6 hours	0.81 ± 0.98	3.36 ± 1.90
	p<0.01	p<0.01

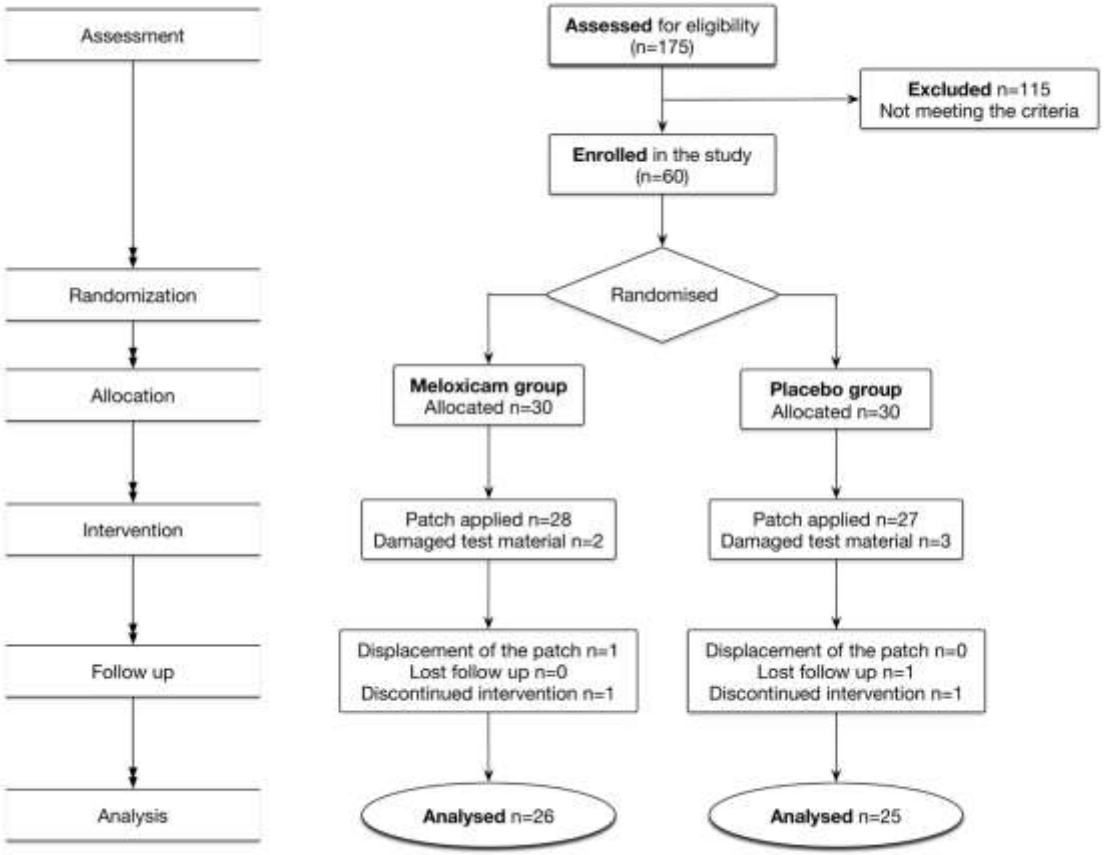

Figure 1: Flow diagram showing overall phases of this preliminary study design

Indian Journal of Medical Research and Pharmaceutical Sciences
September 2018;5(9) ISSN: ISSN: 2349-5340
DOI: 10.5281/zenodo.1437222 Impact Factor: 4.054

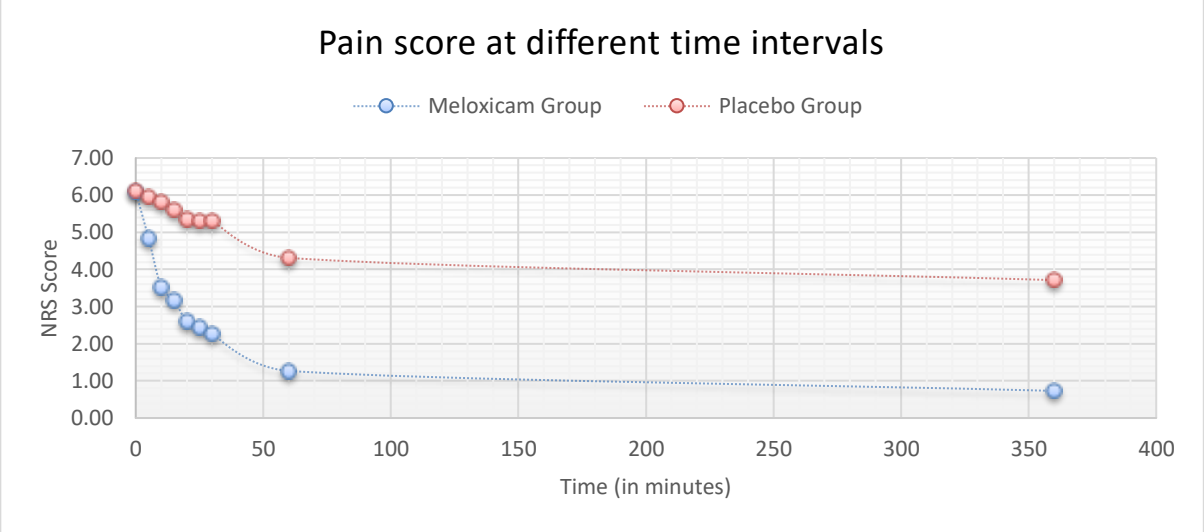

Figure 2: Line diagram showing mean NRS-11 pain score at different time intervals