International Journal of Science and Research (IJSR)
ISSN: 2319-7064
SJIF (2022): 7.942

Comparative Evaluation of Transdermal Diclofenac and Oral Diclofenac in Management of Post - Operative Pain in Bilateral Premolar Orthodontic Extractions - A Comparative Interventional Study

Running title: *Comparison of Transdermal and Oral Diclofenac*

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Abstract: ***Aim: This study was performed to compare the efficacy of transdermal diclofenac patch and oral diclofenac tablet in management of post - extraction analgesia and adverse effects following bilateral first premolar extractions in patients undergoing orthodontic treatment. Materials and Methods: Thirty young pre - orthodontic patients requiring bilateral first premolar orthodontic extractions were selected and divided into 2 groups. Group1 – diclofenac tablet for post operative pain during first premolar extraction in one side of the jaw. Group2 – transdermal diclofenac patch for post operative pain during premolar extraction on opposite side of the jaw after one week of first extraction. Pain relief with both diclofenac tablet and diclofenac patch was recorded for each of the three postoperative days using Visual Analog Scale, Verbal Rating Scale and Pain Relief Scale charts. Results: Statistical analysis showed that both diclofenac tablet and diclofenac transdermal patch caused the significant reduction in pain scores with time. Though mean pain scores of various scales used like VAS, VRS, PRS for Transdermal patch was lesser than the mean pain scores of diclofenac tablet, the difference was not statistically significant. However, patients were more comfortable with transdermal patch because of lesser frequency of side effects and once a day application of the patch. Conclusions: Transdermal diclofenac patch seems to be a promising analgesic modality for the management of pain following dental extractions, given the evidence of its established analgesic potency with a lower incidence of systemic adverse effects.***

Keywords: Diclofenac tablets, transdermal patch, bilateral extraction.

1. Introduction

Pain is defined as “an unpleasant sensory and emotional experience associated with either actual or potential tissue damage, or described in terms of such damage” by the International Association for the Study of Pain[1]. Pain is a predictable part of the postoperative experience. If the post - operative pain is unrelieved, it may cause clinical as well as psychological changes decreasing quality of life and increasing morbidity and mortality.[1]Nonsteroidal anti - inflammatory drugs (NSAIDs) are most commonly used pain medications in dentistry.[2]Analgesic drugs can be administered in a variety of routes, including oral, parenteral, inhalation as well as transdermal. Diclofenac is most commonly prescribed NSAIDS which exhibits anti - inflammatory, analgesic and anti - pyretic action.[2]

Transdermal administration has been proposed as a very easy, simple route of administration without the disadvantages of the routes mentioned above and also comparatively fewer side effects and complications.[1, 4] Furthermore, it has been proposed that the transdermal drug delivery system can deliver the drugs through the skin portal to systemic circulation at a predetermined rate and maintain clinically the effective concentrations over a prolonged period of time.[1]

This study was necessary to compare the efficacy of analgesia, occurrence of side effects and patients compliance during the drug usage after first premolar extraction on one side of jaw with oral diclofenac sodium 50mg given as twice daily medication for three consecutive days and diclofenac sodium transdermal patch 100mg applied once daily for three consecutive days after extraction of contralateral first premolar. Pain score was noted for both groups after 2 hours, 6 hours and 12 hours of oral diclofenac sodium administration and diclofenac sodium transdermal patch application for three consecutive days using linear VAS, VRS and PRS Scales.

Aim and objectives

Aim
The aim of the study is to compare the efficacy of transdermal diclofenac patch with oral diclofenac tablet in management post extraction pain.

Objective
To evaluate post extraction pain relief in patients with transdermal diclofenacpatch and oral diclofenac tablet.

2. Materials and Methods

Study design:
This is a comparative interventional study for comparing the efficacy of transdermal diclofenac and oral diclofenac in management of post operative pain in bilateral extraction.

Sample size

Total Sample: 60 surgical sites (30 bilateral extractions)
A total sample size of 30 patients (60 surgical sites) of either gender, between 18 - 35 years attending Department of Oral and Maxillofacial Surgery requiring bilateral first premolar orthodontic extraction of same teeth in adjacent quadrants were included and divided into two groups, Group 1 – diclofenac tablet for post operative pain during tooth extraction in one side of the jaw (30 surgical sites). Group 2 – transdermal diclofenac patch for post operative pain after tooth extraction in contralateral side of the jaw (30 surgical sites). Randomization was done by coin toss.

Allocation ratio of different groups: 1: 1

Inclusion criteria: -
1) Patient in the age group of 14 to 35 years will be selected irrespective of sex, caste, religion and socio - economic status.
2) Bilateral orthodontic extraction of first premolars in adjacent quadrants.
3) Patients who agreed to follow the study protocol.

Exclusion criteria: -
1) Uncontrolled systemic diseases.
2) Patient with anti - coagulant therapy and Pregnant females.
3) Patient allergic to diclofenac or any NSAIDS
4) Patient with history of peptic ulcer.
5) Tender teeth, central incisors, lateral incisors, second premolars, molars and periodontally compromised teeth.
6) Uncooperative patients not willing to commit to an appropriate post - procedure follow - up.

Ethical clearance: The ethical clearance for the study was provided by an institutionally approved ethical committee (IEC Ref No.: SDDHDC/IEC/2020/SS - 03) on 25 - 01 - 2020 and all subjects were informed about the nature of the study and the probable side effects from the drugs being administered. A written informed consent was obtained from all the patients. The study adhered to the ethical guidelines of Declaration of Helsinki.

3. Procedure

After proper case recording and selecting the patients, the procedure was thoroughly explained to the patient. Under aseptic precautions, armamentaria were prepared for extraction. Of the two teeth to be extracted in two quadrants, extraction of first premolar was performed in one side of the jaw under local anesthesia 2% Lignocaine with adrenaline 1: 80000 with Tablet diclofenac sodium 50mg BD for three days. Patients were assigned to score thepost operative pain for three consecutive days after drug delivery in VAS – Visual analog scale, VRS – Verbal response scale and PRS – pain relief scale after 2hours, 6 hours and 12 hours, post - operatively.

Patient was recalled for the next extraction after one week of the first extraction. Under aseptic precautions, extraction of first premolar in opposite jaw was performed under local anesthesia 2% with adrenaline 1: 80000. Patient was instructed to apply the diclofenac patch once daily over the non - hairy area of the same side shoulder of the tooth extracted. Patients were asked to score the post operative pain similarly as after first extraction.

The rescue medication tablets - Paracetamol 500mg bd for 3 days taken, if any, were noted and the patients were asked if they experienced any adverse effects such as gastric discomfort, nausea, vomiting, gastric acidity, burning sensation, dyspepsia, diarrhea, dizziness, pruritis, etc. Side effects were noted as present or absent, postoperatively. All the bilateral extractions were performed by the same operator, thus removing any operator - induced bias from the study. Since all the bilateral teeth extracted in the same patient were of comparable periodontal status, study bias was further neglected.

The statistician was not aware of the groups**,** thus removing the analytical bias of the study. The data was analysed by Statistical Package for Social Sciences (SPSS 16.0) version. Unpaired t - test was applied to find the statistical significant between groups. ANOVA (Post hoc) followed by Dunnel t - test was applied to find statistical significance of Visual Analog Scale (VAS), Verbal Rating Scale (VRS) and Pain Relief Scale (PRS) between the two groups. p value less than 0.005 ($p<0.05$) was considered statistically significant at 95% confidence interval.

4. Results

In group A and B, male and female patients constituted of 46.7%, 53.3% and 60%, 40% respectively. The mean age was calculated to be 28.53±5.67 and 30.93±6.54 years respectively**.**

Mean VAS scores between the groups at different time periods (Table 1). p - value between the groups, for the day one 2 hours, 6 hours and 12 hours were 1.34, 0.33, 0.44 respectively and p - value for day two were 1.43, 2.44, 0.44 respectively and the day three p - value were 0.43, 0.34, 0 respectively. The differences in mean VAS scores were not statistically significant between Group I and Group II ($p>0.05$).

Mean VRS scores between the groups at different time periods (Table 2). p - value between the groups, for the day one 2 hours, 6 hours and 12 hours were 1.56, 1.03, 1.24respectively and p - value for day two were 0.44, 1.56, 1.43 respectively and the day three p - value were 1.23, 1.56, 1.67 respectively. The difference in mean VRS scores were not statistically significant between Group I and Group II ($p>0.05$).

Mean PRS scores between the groups at different time periods (Table 3). p - value between the groups, for the day one 2 hours, 6 hours and 12 hours were 0.89, 0.24, 0.54 respectively and p - value for day two were 0.23, 1.56, 0.35 respectively and the day three p - value were 0.53, 0.52, 0 respectively. The difference in mean PRS scores were not statistically significant between Group I and Group II ($p>0.05$). Chi square test analysis reported there is a significant difference in proportion of the participants in taking the drugs between the groups ($p<0.05$)

Both the diclofenac tablet and diclofenac transdermal patch caused the significant reduction in pain scores with time. Though mean pain scores of various scales used like VAS, VRS, PRS for Transdermal patch was lesser than the mean pain scores of diclofenac tablet, the difference was not statistically significant.

5. Discussion

The management of post operative pain is a never ending field of research, which changes continuously. Evaluation of pain is always subjective, but can be evaluated in various scales like Visual Analog Scale, Verbal Rating Scale and Pain Relief Scale. The Visual Analog Scale is a 11 pointed scale from values 0 - 10 referring to no pain and worst pain respectively. The other scale like Verbal Rating Scale is similar to Visual Analogue Scale in short4 pointed scale 0 - 3 indicating “no pain” to “severe pain” respectively. The Pain relief scale is the Pain intensity scale in reverse with the values 0 - 3 corresponding to complete relief and no relief respectively.

Oral route carries the risk of first pass metabolism and loss of substantial quantities of the drug before it is absorbed systemically. Parenteral administration of drugs can be extremely painful and sudden increase in drug concentration in the plasma could lead to certain adverse effects.[2]

Diclofenac is most commonly prescribed NSAIDS which exhibits anti - inflammatory, analgesic and anti - pyretic action. When used by oral route, however only 50% of absorbed dose of diclofenac becomes available in the systemic circulation after first pass metabolism. Also high plasma concentrations attained by oral route caries the potential for significant adverse reactions particularly involving gastrointestinal tract.[1]

Transdermal administration has been proposed as a very easy, simple route of administration without the disadvantages of the routes mentioned above and also comparatively fewer side effects and complications. Furthermore, it has been proposed that the transdermal drug delivery system can deliver the drugs through the skin portal to systemic circulation at a predetermined rate and maintain clinically the effective concentrations over a prolonged period of time.[7]

In this comparative interventional study, the efficacy of Diclofenac tablet and Diclofenac transdermal patch in management of post operative pain was compared in patients with bilateral orthodontic teeth extractions. This study being a cross over study, all the participants were exposed to both the form of drugs (Diclofenac tablet and diclofenac patch) within the interval of one week. Emergency medication used was Tab paracetamol 500mg, the parameters evaluated were postoperative pain score at intervals of 2 hour, 6 hours and 12 hours in following scales like VAS, VRS and PRS in three consecutive days and if the patient required the emergency medication, the number of paracetamol tablet consumed wascalculated. The mean pain scores in all the pain scales like VAS, VRS and PRS reduced with time in both the groups and the reduction was statistically significant in both groups. In day one, two and three, though the mean 2 hour, 6 hour and 12 hour pain scores in all the scales seems to be lesser in group II (diclofenac patch) when compared to group I (diclofenac tablet) but the p value was not statistically significant. This result is in accordance with **Bhaskaret al**[1], where he showed that on comparing post operative pain, the mean pain score reduced with time in both the groups.

In this study no patients required any emergency medication in either Group I - diclofenac tablet or Group II - diclofenac patch. In this study, only one patients had mild skin irritation at the patch site on third day of diclofenac patch application. Six patients had side effects like gastric irritation from the tablet diclofeanac. This is in accordance with the study of **Bhaskar et al** [1] where he reported that two of twenty patients had gastric irritation. The results of the present study are also in accordance with the study conducted by **Divan V**[5] et al in 2019 in which it was concluded that the diclofenac administered transdermally has equal potency in relieving postoperative pain as compared to orally administered diclofenac sodium following modified flap surgery and also stated that transdermal patch has an added advantage of better patient compliance as it does not cause gastric disturbance.

6. Summary and Conclusion

The purpose of the study was to compare the efficacy of transdermal diclofenac and oral diclofenac in management of postoperative pain in bilateral premolar extraction. Considering the experience of the present study, it could reasonably be concluded that the transdermal diclofenac patch seems to be a promising analgesic modality for the management of pain following dental extractions, given the evidence of its established analgesic potency with a lower incidence of systemic adverse effects.

Strength: This study is different from previous published dental procedures as it included the pre - orthodontic patients requiring bilateral first premolar orthodontic extractions removing the bias of difference in anatomical form. This study being a cross over study, all the participants

were exposed to both the form of drugs (Diclofenac tablet and diclofenac patch) within the interval of one week.

Limitations: The statistician was not aware of the groups**,** thus removing the analytical bias of the study. However, there may be possible limitations in this study as the blinding/placebo drug was not possible and small sample size of the study resulting in p - value greater than 1. This limitation can be overcome by larger sample size to be included before the real scope of the transdermal diclofenac patch can be clearly defined.

Conflict of interest: The authors declare that they have no conflict of interest. Larger sample need to be conducted before the real scope of the transdermal diclofenac patch can be clearly defined

Source of Funding: NIL

CTRI declaration: NIL

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Table 1: Mean VAS scores between the groups at different time periods

Groups	VAS score (MEAN±SD)		
Day one	**2 hours**	**6 hours**	**12 hours**
Group - I	4.88±0.60	3.47±0.71	2.52±0.51
Group - II	3.23±0.43	2.41±0.50	2.11±0.60
p value	**1.34**	**0.33**	**0.44**
Day two	**2 hours**	**6 hours**	**12 hours**
Group - I	3.00±0.01	2.64±0.49	2.35±0.49
Group - II	2.01±0.50	1.58±0.50	1.23±0.43
p value	**1.43**	**2.44**	**0.44**
Day three	**2 hours**	**6 hours**	**12 hours**
Group - I	1.35±0.49	0.82±0.52	0.00±0.00
Group - II	0.58±0.50	0.11±0.33	0.00±0.00
p value	**0.43**	**0.34**	**0**

(p>0.05 no significance compared Group - I with group - II)

Table 2: Mean VRS scores between the groups at different time periods

Groups	**VRS score (MEAN±SD)**		
Day one	**2 hours**	**6 hours**	**12 hours**
Group - I	3.00±0.02	2.64±0.49	2.00±0.01
Group - II	2.52±0.51	2.00±0.01	1.52±0.62
p value	**1.56**	**1.03**	**1.24**
Day two	**2 hours**	**6 hours**	**12 hours**
Group - I	2.00±0.01	2.00±0.01	1.47±0.52
Group - II	1.47±0.51	1.35±0.49	0.52±0.51
p value	**0.44**	**1.56**	**1.43**
Day three	**2 hours**	**6 hours**	**12 hours**
Group - I	1.11±0.33	0.23±0.43	0.00±0.00
Group - II	0.23±0.43	0.00±0.00	0.11±0.33
p value	**1.23**	**1.56**	**1.67**

(p>0.05 no significance compared Group - I with group - II)

Table 3: Mean PRS scores between the groups at different time periods

Groups	PRS score (MEAN±SD)		
Day one	**2 hours**	**6 hours**	**12 hours**
Group - I	3.00±0.01	2.58±0.50	2.00±0.01
Group - II	2.88±0.33	1.94±0.42	1.52±0.51
p value	**0.89**	**0.24**	**0.54**
Day two	**2 hours**	**6 hours**	**12 hours**
Group - I	2.05±0.24	1.88±0.33	1.52±0.51
Group - II	1.52±0.51	1.11±0.33	0.88±0.32
p value	**0.23**	**1.56**	**0.35**
Day three	**2 hours**	**6 hours**	**12 hours**
Group - I	1.23±0.43	0.58±0.50	0.00±0.00
Group - II	0.35±0.49	0.00±0.00	0.00±0.00
p value	**0.53**	**0.52**	**0**

(p>0.05 no significance compared Group - I with group - II)