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Comparison of Transdermal and Oral Diclofenac as an analgesic following extraction of Bilateral Impacted Mandibular Third Molar

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Abstract

Objective: To compare and evaluate the efficacy of post-operative diclofenac sodium tablets and the diclofenac transdermal patch in controlling pain, swelling and trismus following removal of mandibular impacted third molar teeth.

Method: The bilateral extraction of mandibular third molars (mesioangular) in 18-40 years of age group patients provided a favourable setting to evaluate the two formulations since identical operative procedures could be performed in the same individuals on two different occasion with the patients acting as their own control in this cross over trial. After removal of impacted mandibular third molars, following parameters were studied: 1. Analgesic Activity, 2. Maximum mouth opening. 3. Swelling.

Results: The scores were recorded preoperatively and on 1st, 2nd and 3rd postoperative day.

Conclusion: Transdermal administration has the advantage of being very easy, simple route of administration and also comparatively fewer side effects and complications.

Keywords: Mesioangular, Analgesic Activity, Swelling.

Introduction

Pain has been so closely associated with surgery that the word pain and surgery become almost synonyms. Proper pain management, particularly postoperative pain management, is a major concern for clinicians as well as for patients undergoing surgery. Patients commonly enquire about the level of pain they may experience after a dental treatment and operation.[1]

Non-steroidal anti-inflammatory drugs (NSAIDs) are amongst the most widely used therapeutic class of

analgesic compounds used to relieve post extraction pain. Diclofenac sodium is a commonly prescribed NSAIDs, which exhibits anti-inflammatory, analgesic and anti-pyretic.[2]

At present, the most common form of delivery of drugs is the oral route. While this has the notable advantage of easy administration, it also has significant drawbacks namely poor bioavailability due to hepatic metabolism (first pass) and the tendency to produce rapid blood level spikes (both high and low), leading to a need for high and/or frequent dosing, which can be both cost prohibitive and inconvenient.[3,4]

Various routes of drugs delivery are presents like oral, mucosal, anal, dermal, topical, inhalation, parenteral (intramuscular, intravenous, intradermal, subcutaneous). The reason for choice of routes of drug administration are governing by various factors:

Condition of the patient

Transdermal patches have in the recent past been developed as innovative topical delivery systems for diclofenac and other NSAIDs, offering the advantage of sustained drug delivery[5] with reduced incidence of systemic adverse effects due to lower plasma concentration.[6,7]

Pharmacology of Diclofenac Sodium

Packaging and Storage- Preserve in light resistant containers, and store at controlled room temperature.[4]

Pharmacokinetics Bioavailability: It is well absorbed following oral administration. It undergoes first-pass metabolism; only 50–60% of a dose reaches systemic circulation as unchanged drug. Peak plasma concentration usually attained within about 1 hour (diclofenac sodium conventional tablets), 2 hours (diclofenac sodium delayed-release tablets), or 5.25 hours (diclofenac sodium extended-release tablets). Absorbed into systemic circulation following topical administration as gel or transdermal system; plasma concentrations generally very low as compared with oral administration. Following application of a single Diclofenac transdermal system to intact skin on the upper arm, peak plasma concentrations occur in 10–20 hours. Moderate exercise does not alter systemic absorption of topically applied diclofenac (transdermal system or 1% gel).[15,18]

Onset: Single 50- or 100-mg doses of diclofenac provide pain relief within 30 minutes.[17]

Duration: Pain relief lasts up to 8 hours following administration of single 50 or 100 mg doses of diclofenac sodium. [3,8]

Food: Food delays time to reach peak plasma concentration but do not affect extent of absorption.

Indications

- Mild to moderate pain
- In sign and symptoms of osteoarthritis
- For acute and long-term use in the relief of sign and symptoms of ankylosing spondylitis.[23,24]

Excretion: Elimination by the hypatic biotransformation followed by renal excreation.[13,14]

Drug Delivery System [33,34]

- Tablets
- Injections
- Transdermal patch
- Gel
- Spray

Diclofenac Tablet

Trade Name

- Defenac 50mg
- Dicloflam 50mg
- Voveran

Advantage

- Easy to take

- Relatively safe as drug does not directly go to the blood.
- Cheap
- Self medication possible no assistance of trained medical staff is needed
- Can be recovered by gastric lavage if over dose occurs

Disadvantage

- Abdominal pain
- Constipation
- Diarrhea
- Nausea and vomiting
- Skin rash
- tinnitus

Transdermal Patch

Transdermal patches have in the recent past been developed as innovative topical delivery for the diclofenac and other NSAIDs, offering the advantage of sustained drug delivery with reduced incidence of systemic adverse effect due to lower plasma concentration within the body and foreign substances out. Diclofenac transdermal patch is a transdermal delivery system (TDS) designed for continuous and systemic release of diclofenac following its application to an intact skin. It contains Diclofenac Diethylmine and a 75sq. cm patch contains 200 mg of the same. Transdermal systems are an innovative delivery mechanism commonly replacing oral dosage forms and other traditional forms of administration. Stratum corneum is the layer most important to transdermal delivery systyem. If the drug is able to penetrate the stratum corneum, it can enter the blood stream. The drug diffuses across the layer of the skin and ultimately diffuses passively into capillaries for systemic delivery.[7]

Components of transdermal patch

Transdermal devices are Adhesive device, Monolithic matrix device and the reservoir system. These devices basically contain-

1. Backing layer
2. Drug reservoir
3. Release control layer (polymer matrix)

Advantage

- Avoid gastrointestinal difficulty.
- Suitable in instances like vomiting, diarrhoea where the oral route is not desirable.
- Avoid first pass metabolism.
- Provide the capacity for multiday therapy with a single application.
- Therapy can be quickly terminated by removal of the patch immediately.

Disadvantage

- Transdermal drug delivery system could be unsuitable for drug that irritate or sensitize skin.
- The natural limit of drug entry imposed by the skin's permeability.
- Only potent drugs are suitable only for transdermal delivery.
- Expensive more than the tablets or oral route.[19]

Materials and Methods

A prospective randomized comparative study was designed to study the effectiveness of diclofenac transdermal patch in management of postoperative pain intensity, pain relief, duration of action and adverse events after surgical extraction of mandibular bilateral third molar (mesioangular) and to compare the effects with those of oral diclofenac tablets with transdermal patch.

Inclusion criteria

1. Systemically healthy subjects aged 17-40 years of age.
2. Patient should have mesioangular bilateral impacted 3rd molar.

3. Patient should not have pericoronitis and periapical abscess at the time of removal.
4. All cases were operated on by single operator.

Exclusion criteria

1. Medically compromised patient.
2. Patient with the history of allergy to local anaesthetic agent were excluded from the study.
3. Patient with serious renal, hepatic, respirational, cardiac ,endocrine or metabolic impairment, persistent mental confusion, active gastrointestinal symptom, pregnant or lactating, asthmatic or alcohol misuse or those who required antibiotic or corticosteroid prophylaxis.

Procedure

- Total 30 patients were participated in the study in the age group of 17-40 years based on inclusive and exclusive criteria.
- The subjects belonged to both sexes and were within the age range of 17 to 40 years.
- All the subjects chosen for the study had a healthy periodontal status with none of them being extensively decayed or periapically involved.
- The ethical clearance for the study was provided by an institutionally approved ethical committee 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 subjects.
- In Group A the left mandibular impacted third molar mesioangular first were surgically extracted and a 200 mg transdermal Diclofenac patch is placed.

Discussion

On the each of the following two days, the patch was changed and a new one placed; thus placing a total of three patches over the three post-operative days. Each successive application of the transdermal patch was made on a different hairless skin area. Each of the patients was given a Visual Pain Intensity chart and Pain Relief Score chart (value from 0 to 10) for assessing pain intensity and pain relief for each of the three postoperative days.

Paracetamol 500 mg tablets were permitted to be used as rescue medication and a total of nine tablets were provided to each of the patients for the three postoperative days. The patients were asked to maintain a record of the number of paracetamol tablets consumed on the pain assessment charts and to return the remaining tablets to operator on their next visit.

After three post operative days, another day was given to allow for the complete wash out of drug from the body and the patients were recalled and their verbal pain score charts were evaluated.

In Group B the right mandibular impacted third molar were first extracted successively in the same appointment using a standardized armamentarium. Following which 50mg oral diclofenac sodium tablets were prescribed to be taken thrice a day on every 4 to 6 hourly for a period of three days .

The patients were permitted to use paracetamol 500 mg tablets as rescue medication during the post operative period.

The subjects were asked to report the intensity and pain relief on the verbal pain score chart for the three post operative days along with adverse effect questionnaire chart. Then ask for the rescue medication tablets taken.

All the surgical extractions were performed by the same operator. Thus removing any operator-induced bias from the study. Since all the mandibular third molar were extracted in the same patient were of comparable periodontal status. Study bias was further negated.

Measurements of following parameters pain intensity, pain relief, swelling and trismus postoperatively on 1st , 2nd , and 3rd day along with onset of pain was done. [10,11]

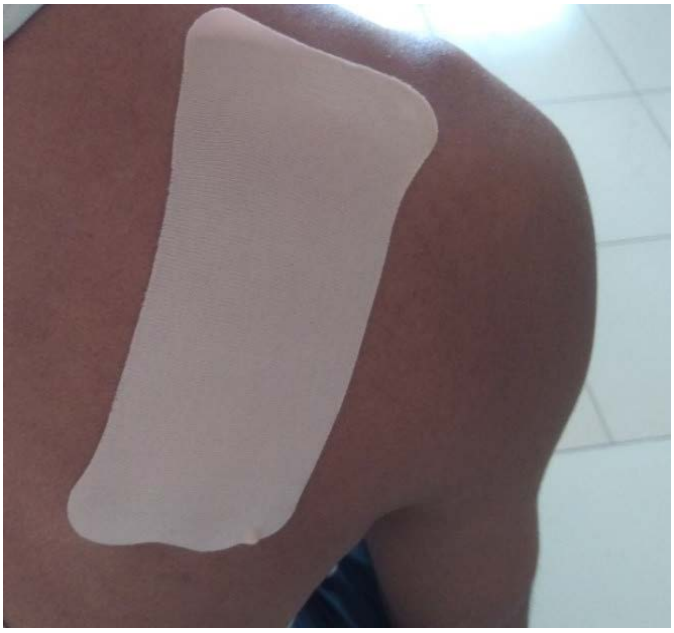

Figure 1: The Placement of Patch on Patient's Forearm

Assessment of Swelling And Trismus

Surgical removal of third molar generally produce pain, trismus and facial swelling in postoperative period. Inflammatory process initiated by the surgical trauma.

To evaluate swelling marking with permanent marker were made on the following facial region-

Swelling

Preoperatively, the swelling was measured by taking a horizontal distance from the corner of the mouth to the lobe of the ear and a vertical distance between outer canthus of the eye and angle of lower jaw using silk suture following the natural convexity of the patient's face. The procedure was repeated on first, second and third postoperative days.[6]

Trismus

Maximum mouth opening was recorded preoperatively between the incisal edges of upper and lower central incisors by using vernier calliper. Patients were reexamined and mouth opening was recorded on first, second and third postoperative days.

Pain intensity was assessed by using 10 level visual analog scale (VAS scale)

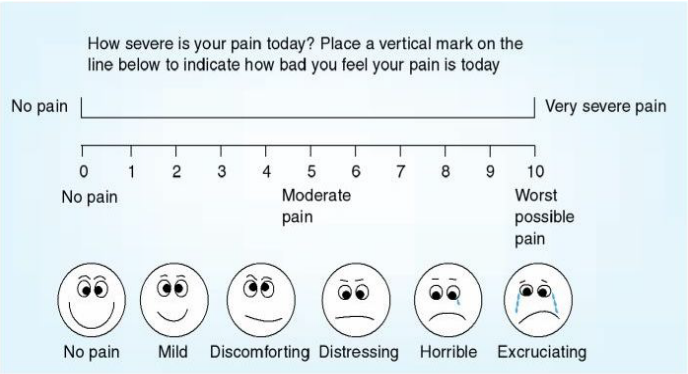

Figure 2:

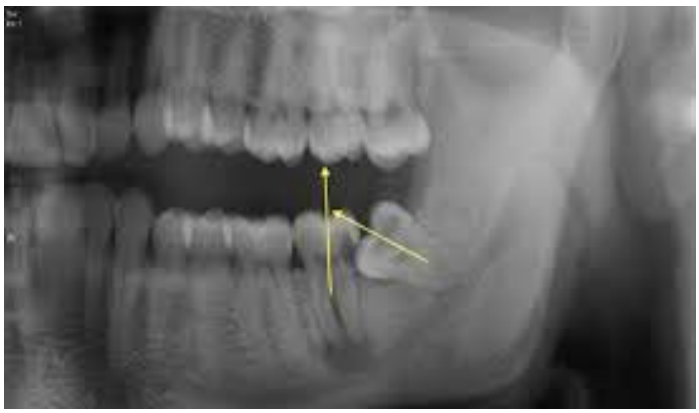

Figure 3: OPG Showing Mesioangular Impacted Third Molar

Figure 4 : Intraoral photograph of mesioangular third molar

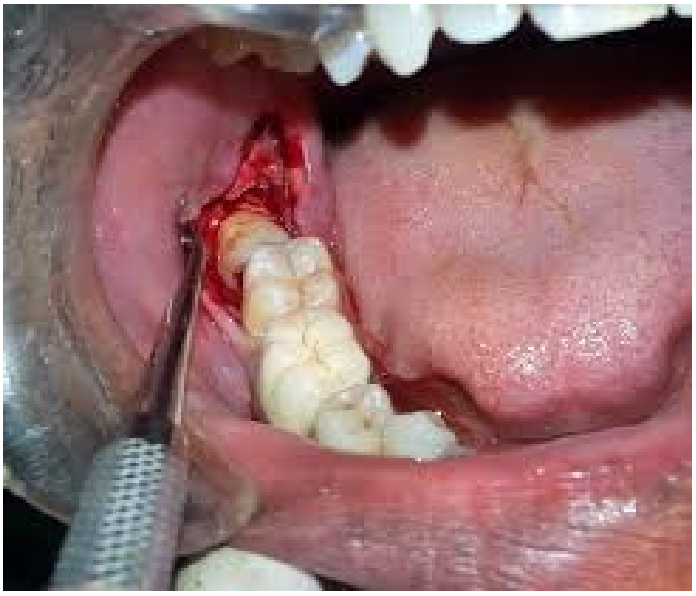

Figure 5: Bone guttering and exposure of the tooth

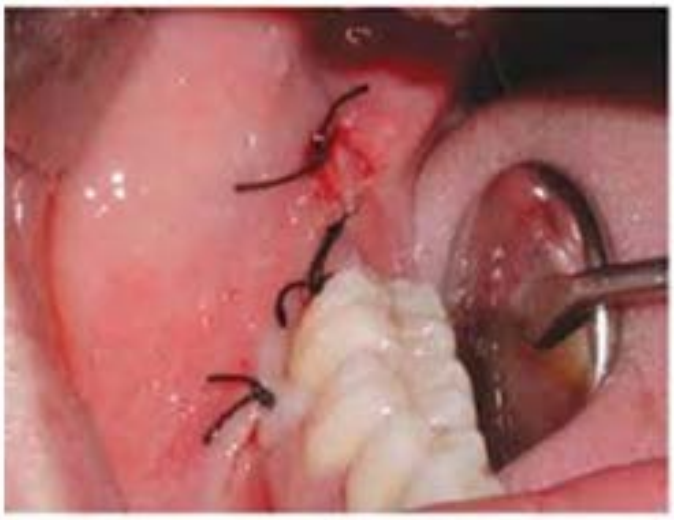

Figure 6: Interrupted sutures placed

Observation and Results

The study was done to compare transdermal and oral diclofenac as an analgesic following extraction of bilateral impacted mandibular third molar. Thirty patients requiring extraction of bilateral third molars were recruited for the study and divided into two groups based on the method of giving analgesic i.e. oral and transdermal patch group. Post-operative Pain, Swelling and Mouth opening was measured on 1st , 2nd and 3rd post-operative day.[16]

Statistical Analysis

The data was transformed from pre-coded survey form to computer. The job of data entry, validity checks and formation of desired results (as per analysis plan) was done using statistical package of social sciences (SPSS version 22.0). The level of statistical significance was set at $P \leq 0.05$. The comparison between shear strength of the different unit was done by using ANOVA test while the intergroup comparison was done with t test.

One-Way Anova: The one-way analysis of variance (ANOVA) is aced to determine whether there are any significant differences between the means of three or more independent groups.

$$F = \frac{explained\ Variance}{Unexplained\ Variance}$$

Or

$$F = \frac{Between\ group\ variability}{within\ group\ variability}$$

p -VALUE: (Probability of difference)

$p > 0.05$ = Difference is not significant (NS)

$p \leq 0.05$ Difference is significant (SIG)

Student t test

$$t = \frac{\bar{x}_1 - \bar{x}_2}{\sqrt{S^2}\left(\frac{1}{n_1} + \frac{1}{n_2}\right)}$$

S_d = Standard deviation .

$\bar{D}$ = Mean of samples

n -1 = Degree of freedom

p -VALUE: (Probability of difference)

$p > 0.05$ = Difference is not significant (NS)

$p \leq 0.05$ Difference is significant (SIG)

Table 1(a): Mean Pain score at different time interval after extraction of bilateral mandibular third molars in Oral medication group

Days	Oral		F value	p value
	Mean	S.D.		
Day 1	5.7	1.54		
Day 2	2.8	1.12		
Day 3	1.8	0.65	35.06	0.01

Pain was measured on the Visual Analog Scale (VAS scale) ranging from 1 to 10. The pain was measured among both the groups on day 1, 2 and 3. An assessment of the intensity of pain following third molar extractions revealed that there was a gradual decrease in the pain intensity scores from first day to third day in the oral diclofenac tablets and there was significant difference in pain score with maximum score on day 1 and minimum score on third day after extraction.

Table 1(b): Post Hoc Tuckey test for comparing pain at different time interval in oral Group

Days		Mean Difference	P value
Day 1	Day 2	2.9	0.01
	Day 3	3.9	0.01
Day 2	Day 3	1.0	0.01

The Post Hoc test was used to analyze the intergroup comparison found that there was significant decrease in pain from day 1 to day2 and day3. There was also significant decrease in pain from day 2 to day 3 after taking oral analgesic.

Graph 1: Mean Pain score at different time interval after extraction of bilateral mandibular third molars.

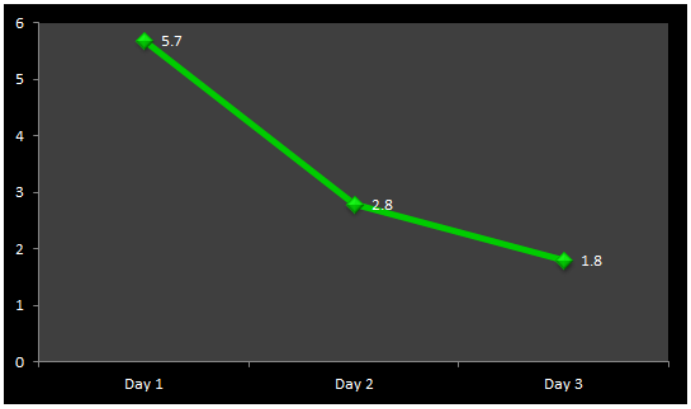

Table 2: Mean Pain score at different time interval after extraction of bilateral mandibular third molars

Days	Oral		F value	p value
	Mean	S.D.		
Day 1	6.9	1.66		
Day 2	3.9	1.23		
Day 3	2.7	0.54	37.06	0.01(s)

An assessment of the intensity of pain following third molar extractions revealed that there was a gradual decrease in the pain intensity scores from first day to third day in the transdermal diclofenac patch and there was significant difference in pain score with maximum score on first day and minimum score on third day after extraction.

Table 2(b): Post Hoc Tuckey test for comparing pain at different time interval in Transdermal Patch Group

Days		Mean Difference	Sig
Day 1	Day 2	3.0	0.01
	Day 3	4.2	0.01
Day 2	Day 3	1.2	0.01

The Post Hoc test was used to analyze the intergroup comparison found that there was significant decrease in pain from day 1 to day 2 and day 3. There was also

significant decrease in pain from day 2 to day 3 after taking transdermal patch analgesic.

Graph 2: Mean Pain score at different time interval after extraction of bilateral mandibular third molars in transdermal patch group

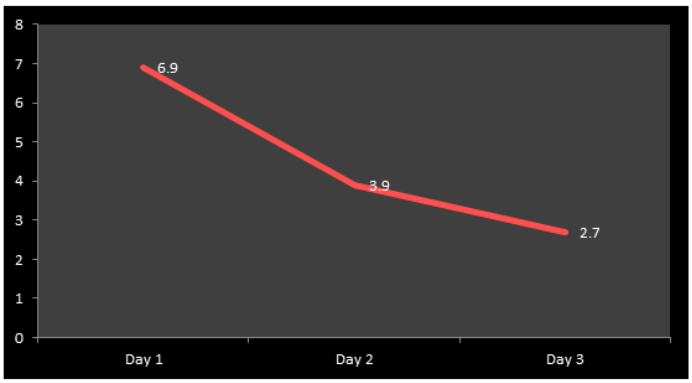

Table 3: Comparison of mean Pain score at different time interval after extraction of bilateral mandibular third molars

Days	Oral		Transdermal		t value	P value
	Mean	S.D.	Mean	S.D.		
Day 1	5.7	1.54	6.9	1.66	2.07	0.02(s)
Day 2	2.8	1.12	3.9	1.23	1.07	0.01(s)
Day 3	1.8	0.65	2.7	0.54	0.89	0.04(s)

The pain measurement was compared between Oral tablet and Transdermal patch group found that there was a gradual decrease in the pain intensity scores from first to third day with both the oral diclofenac tablets as well as with the transdermal patch. The mean pain scale shows statistically significant difference in mean pain score among oral diclofenac group in comparison to the transdermal patch group.

Graph 3: Comparison of mean Pain score at different time interval after extraction of bilateral mandibular third molars

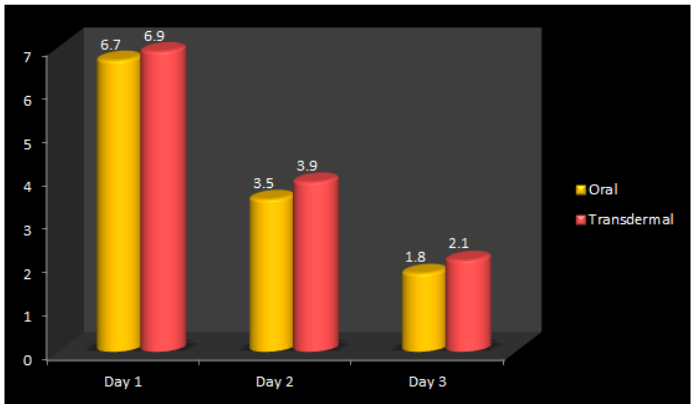

Table 4: Maximum mouth opening at different time interval after extraction of bilateral mandibular third molars in Oral Medication group

Days	Oral		F value	p value
	Mean	S.D.		
Day 1	15.4	4.6	56.17	0.01
Day 2	22.5	5.7		
Day 3	28.3	8.7		

The maximum mouth opening increases from day one to day three in oral medication group with mean maximum mouth opening on day 1 was 15.4 ±4.6 mm, day 2 was 22.5± 5.7 mm and day 3 was 28.3 ± 8.7 mm There was significant differences in terms of maximum mouth opening from first day to third day post extraction.

Dealing with post-operative pain remains an arena for never ending research with better formulations and modalities continuously replacing obsolete ones. Post extraction pain has often been a nemesis for dental surgeons and patients alike due to the considerable degree of inflammatory response involved.

NSAIDs have the ability to reduce both pain and inflammation as a result they, are the ideal analgesic agents for the control of pain in the event of surgical removal of mandibular third molar impactions. Surgical tooth removal causes a typical type of pain which reaches

peak values in the immediate extraction period and thereafter reaches moderate levels.[1] In that respect for the procedure of surgical removal of mandibular third molars, anesthesia during the procedure is important; however, adequate pain control is also important in the immediate post-operative period as the pain from surgical removal of third molar reaches its peak level in the immediate post-operative period.[2]

The efficacy of NSAIDs in reducing pain is largely a result of their capacity to inhibit cyclo-oxygenases 1 and 2 (COX-1 and COX-2), key enzymes in prostaglandin (PG) biosynthesis.[26]

Oral administration of NSAIDs, however, carries a risk of first pass metabolism with significant amount of the drug being lost before it is systemically absorbed. Oral NSAIDs are also known to cause several adverse effects, particularly gastro intestinal effects, which are dose dependant. Topical formulations of NSAIDs have been developed as alternate routes of drug administration, offering the advantage of local, enhanced drug delivery to the affected tissues with a lower incidence of systemic adverse effects. Topical NSAIDs have thus carved out a niche for themselves as therapeutic analgesic modalities with established benefits and lower incidence of adverse events.[20,24,25,29]

Transdermal systems for NSAIDs are an innovative delivery mechanism replacing oral and other traditional forms of drug administration. The drug contained in the transdermal patch enters the body through skin and ultimately diffuses into capillaries for systemic delivery. The steady permeation of drug across the skin allows for more consistent serum drug levels, often a goal of therapy [20,21]

In the present study, diclofenac was used as analgesic, both in its oral and transdermal form, following extraction of bilateral impacted mandibular third molar. Diclofenac is an NSAID, which exhibits anti-inflammatory, analgesic, and anti-pyretic activity and has been routinely used as an analgesic following dental extractions.[42]

The two formulations of diclofenac used in this study were oral diclofenac 50 mg tablets to be taken thrice a day and 100 mg transdermal diclofenac patch (Zydus-Cadilla labs), which is designed to remain at the site of application for 24 hours. The 50-sq. cm patch used in the study contains 100 mg of Diclofenac Diethylamine as its active agent and allows for sustained release of the drug.[22]

The transdermal diclofenac patch 100 mg used once daily was found to be as potent as oral diclofenac 150 mg daily for post dental extraction analgesia. These findings are similar to those of **Funk *et al***,[35]

In terms of safety, the patch was well tolerated and did not cause any local or systemic adverse effects whereas two patients on oral diclofenac therapy reported with gastric acidity and nausea. **Agarwal *et al***,[39] when using the transdermal diclofenac patch for the attenuation of venous cannulation, reported the occurrence of a localized erythematous rash or pruritis at the site of application of the transdermal patch. Although this finding is contrary to those in the present study perhaps due to the fact that each successive application of the diclofenac patch was done at a different site.

In the study by **Bhaskar *et al***.[3] they also concluded in his study that diclofenac transdermal patches were well tolerated by the patients, 2 patients had reported gastric irritation and nausea following the intake of oral diclofenac tablets. In a meta analyses by **Mason *et al***.,[36] it has been shown that topical NSAIDs do not show any serious gastrointestinal injury or increased chances of renal failure. Also in a study by **Naesdal *et al***.,[40] it has been shown that the overall gastrointestinal complications such as ulcer and dyspepsia were statistically significantly lower with the use of topical NSAIDs due to their lower

systemic concentrations. Apart from the discomforts, the patients who had taken transdermal drug delivery had shown better compliance and also were enthusiastic of the prospect of achieving pain control without the need for oral medications, as was previously experienced in the study by **Bhaskar *et al***.[3,30,31]

In the present study, patients using the transdermal patch reported a statistically and clinically significant reduction in pain scores, from the level of 6.9 to 2.7 on the VAS scale from day 1 to day 3 but it is significantly less as compared to those achieved with oral diclofenac tablets at first, second and third day. The result was similar to **Bhaskar** H **et al** who finds 50% of the patients who were prescribed oral diclofenac tablets reported of significant pain relief, while amongst those with the transdermal patch, 65% reported of significant pain relief in the first two postoperative days.

There was significant increase in mouth opening seen among the treatment groups from 15.4 mm to 28.3mm in the oral medication group while 13.2 to 27.5 from first day to third day in the transdermal patch group. There was no significant reduction in swelling among both the groups.

There was significant reduction in post operative swelling seen among the treatment groups. It is measured by comparative increase in distance between the treated and control sides from gonion to tragus from pre operative day. The result shows the decrease from 0.22 mm to 0.08 mm in the oral medication group while 0.25mm to 0.10mm from first day to third day in the transdermal patch group. There was no significant reduction in swelling among both the groups.

Our result was similar to the other study who finds that NSAIDs are effective in reducing pain and swelling following oral surgeries due to their potent analgesic and anti-inflammatory properties.[38,41]

The transdermal diclofenac patch seems to be a promising analgesic modality for the management of mild to moderate pain following dental extractions however, it is less potent in reducing pain as compared to the oral analgesic so limited use in the treatment of patients with severe pain.[31,32]

Topical diclofenac patches offer an efficacious, safe, well-tolerated, patient-compliant treatment modality that is an effective alternative to conventional oral diclofenac treatment.[27,28,37]

Conclusion

This study " Comparison of diclofenac as transdermal patch with oral diclofenac as an analgesic following extraction of bilateral mandibular impacted third molar : A Prospective Randomized Controlled trial." was conducted in the Department of Oral and Maxillofacial surgery, Modern Dental College and Research Centre, Indore for 30 patients who required surgical extraction of impacted bilateral third molar . Following split mouth technique, each patient was randomly divided into 2 equal groups. Group A patients were prescribed diclofenac transdermal patch while Group B patients were prescribed oral diclofenac tablet. Parameters observed were pain relief, trismus and swelling in both the group at 1st, 2nd, and 3rd post operative day .

The following differences were observed from the present study

Pain intensity on 1st day after extraction is more, while intensity is less in 2nd and 3rd day with transdermal patch compare to oral tablet. This difference Pain was measured on the Visual Analog Scale (VAS scale) ranging from 1 to 10. The pain was measured among both the groups on day 1, 2 and 3. An assessment of the intensity of pain following third molar extractions revealed that there was a gradual decrease in the pain intensity scores from first day to third day in the oral diclofenac tablets and there was

significant difference in pain score with maximum score on day 1 and minimum score on day 3 after extraction is statically significant.

The maximum mouth opening increases from day one to day three in transdermal patch group with mean maximum mouth opening on day 1 was 13.2 ± 3.3 mm, day 2 was 20.3 ± 4.7 mm and day 3 was 27.5 ± 8.3 mm There was significant differences in terms of maximum mouth opening from day one to third day post extraction The amount of swelling was measured by finding increased volume of the skin from the gonion to tragus. For Oral Medication group, the mean amount of swelling was 0.22 ± 0.13 mm standard deviation (SD) cm first day after extraction, 0.15±0.08 on the second day and 0.08±0.04 mm on third day post extraction. There was significant decrease in swelling from first to third day after extraction.

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