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Comparison of Diclofenac Transdermal Patch Against Oral Diclofenac for Pain Control Following Removal of Mandibular Impacted Third Molars: A Systematic Review

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***Abstract*: *Background:* Diclofenac sodium is the most prescribed NSAID for postoperative pain management after third molar surgery. It can be administered through various routes. A transdermal patch, one of the newer routes to administer drugs, has fewer adverse effects and better patient compliance. *Aim:* To assess the effectiveness of a diclofenac transdermal patch against oral diclofenac for postoperative pain management after third molar surgery. *Methods:* This literature study used PubMed, Elsevier science direct, Wiley online library, Ovid Medline, Cochrane, Prospero, and CINAHL using MeSH terms- diclofenac sodium, transdermal patch, third molar surgery. Of the total 197 articles screened, 113 were full-text articles assessed for eligibility, and 5 were taken for the qualitative analysis. This search was reported according to the PRISMA guidelines. In addition, five randomized controlled trials were included in the review process. *Results:* The transdermal patch was compared with the oral group in all the studies, and the transdermal patch showed statistically significant results compared to the oral route. No Meta-analysis was performed due to clinical heterogeneity and differences in data reporting among the included studies. *Conclusion:* Transdermal patch was effective in improving postoperative pain and equally effective in the oral group and had lower adverse effects and better patient compliance.**

***Keywords*: Diclofenac sodium, transdermal patch, third molar surgery.**

1. Introduction

At the posterior end of the mandibular arch, the mandibular third molar is the most common unerupted or impacted tooth. This causes pain, bone loss, root resorption of the adjacent teeth, pericoronitis, distal caries, cyst and tumour formation and periodontal diseases, which indicates surgical removal of mandibular third molars. It is also indicated in orthodontic treatments. It is the most common routinely performed oral surgical procedure globally. [1]-[3] Even when the surgery is performed with the most care, it can result in pain, swelling, and trismus due to loose connective tissue and high vascularity. These postoperative discomforts are triggered by inflammatory processes initiated by trauma during surgery, causing great distress to the patients. [4]

"An unpleasant sensory or emotional experience caused by, or reminiscent of, actual or potential tissue damage" by the international association for the study of pain. [6] It is often said to be a protective process that usually manifests when an environmental change occurs that causes tissue injury [7]. Pain caused by the injured tissue modulates the somatosensory system, which increases the responsiveness of central and peripheral pain pathways. [8] The most commonly elicited symptom by a dentist is pain. Effective pain management after postoperative procedures plays an important role in patients comfort. If the pain is not relieved or recurring, it may cause physical discomfort and psychological distress, decreasing the quality of treatment and increasing morbidity and mortality [9].

The most prioritized and commonly used class of drugs for postoperative pain management are NSAIDs [non-steroidal anti-inflammatory drugs] which have effective anti-inflammatory, anti-pyretic, and analgesic properties. [10] These drugs can be administered in various routes such as oral, parenteral, inhalation, and transdermal patches. [5] Diclofenac sodium, an aryl-acetic acid derivative, acts by blocking COX-1 and COX-2 enzymes, inhibiting the synthesis of chemical mediators such as prostaglandin E2, D2, F2, and thromboxane A2. [9] The overuse of oral NSAIDs (diclofenac) leads to untoward adverse reactions in cardiac, renal, and gastrointestinal toxicity. When diclofenac is administered orally, half the dose of diclofenac reaches the circulation due to first-pass metabolism with the potential adverse effect of gastric irritation due to high concentration. [5]

Research in alternative or newer drug delivery systems is

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emerging to minimize the adverse effects. One such drug delivery system is the transdermal system. A transdermal drug delivery system is a local drug delivery system that is a non-invasive and painless way to deliver drugs directly into the body. Adverse reactions of the transdermal system are mild with better compliance. Transdermal patches ensure simple, painless procedures that have better compliance in patients with needle phobia. They are on par or equally with sustainable plasma concentrations comparable with oral medication. With the local drug delivery system, hepatic first-pass metabolism is bypassed, and no gastric irritation offers increased flexibility in placing and removing the patch; better compliance is achieved. They deliver the drug over a controlled long period and can terminate the delivery of the drug abruptly. Transdermal patches are an alternative for patients with cognitive impairment and handicaps who cannot self-medicate. [11], [12]. This review attempts to assess and compare diclofenac sodium through two different drug delivery systems (oral and transdermal patch routes) in managing postoperative pain following surgical removal of impacted third molars.

2. Materials and Method

Study design:

A systematic review of clinical trials was done using diclofenac transdermal patches as an alternative for oral diclofenac to manage postoperative pain during surgical removal of the impacted mandibular third molar.

Search strategy:

The electronic databases were used to find published articles comparing diclofenac transdermal patch against oral diclofenac for postoperative pain management during surgical removal of the impacted mandibular third molar.

Eligibility criteria:

1) Inclusion criteria:

1. Studies published in English
2. Articles on the comparison of diclofenac transdermal patch against oral diclofenac for management of postoperative pain during surgical removal of impacted mandibular third molar.
3. Clinical trial studies.
4. Full-text articles.
5. Publications over the years.

2) Exclusion criteria:

1. Articles published in other languages
2. Only abstracts available
3. Unrelated articles
4. Animal studies
5. In-vitro studies

Search engine:

- PubMed
- Elsevier science direct
- Wiley online library
- Ovid Medline
- Cochrane
- Prospero
- CINAHL

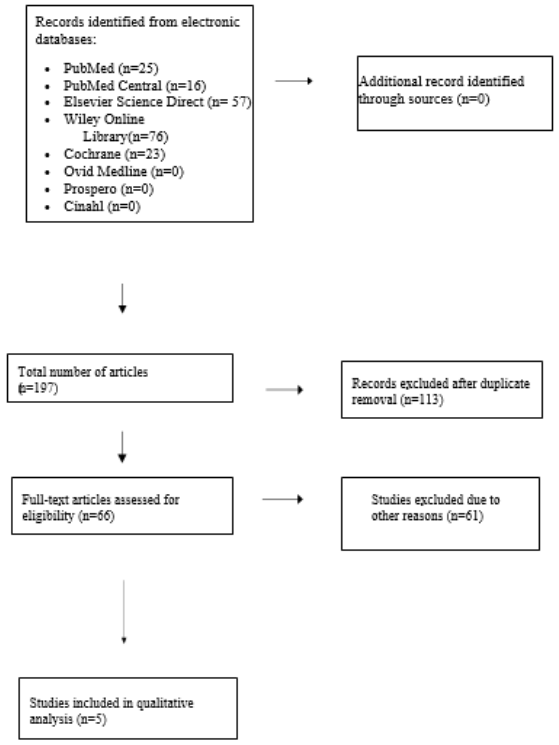

Fig. 1. Flow diagram shows the number of studies identified, screened, assessed for eligibility, excluded and included in the systematic review

After searching the appropriate mesh terms, 197 articles were found from the online databases. After duplicates removal, 113articles were screened, and 66 full-text articles were available. Applied inclusion-exclusion criteria and the final five related articles were selected for further assessment. Figure 1

Table 1
Characteristics of the included study in the systematic review

Author Name	Year	Sample Size	Patient Characteristics	Duration	Number (Case/Control)
Prithvi S Bachalli et al [12]	2009	20	anesthesia	3 days	Test 1 (day 1) – Oral group (one side of the jaw) Test 2 (day 3) - transdermal group (contralateral side of the jaw)
Fauziya dastagir et al [13]	2019	100	Patients who underwent mandibular third molar extraction	3 days	Group I (patch group)-50 subjects GROUP II (oral group)- 50 subjects
Prajakta wankhade et al [14]	2020	40	A patient who reported to third molar removal surgery	3 days	GROUP A Oral – 20 subjects GROUP B Transdermal- 20 subjects
Aimuamwosa OD et al [15]	2020	68	Patients with mild Pederson index mandibular tooth impaction who had their teeth surgically removed	7 days	GROUP I (Patch group)- 34 subjects GROUP II (Oral group)- 34 subjects
Ramvihari thota et al [16]	2021	40	Patients who reported for third molar removal surgery	3 days	GROUP I Oral group- 20 subjects GROUP II Transdermal patch – 20 subjects

Table 2
Outcome data as reported in included studies

Author Name	Year	Sample Size	Patient Characteristics	Duration	Number (Case/Control)
Prithvi S Bachalli et al [12]	2009	20	Patients with bilaterally impacted mesioangular mandibular third molars	3 days	Test 1 (day 1) – Oral group (one side of the jaw) Test 2 (day 3) - transdermal group (contralateral side of the jaw)
Fauziya dastagir et al [13]	2019	100	Patients who underwent mandibular third molar extraction	3 days	Group I (patch group) -50 subjects GROUP II (oral group) - 50 subjects
Prajakta wankhade et al [14]	2020	40	A patient who reported to third molar removal surgery	3 days	GROUP A Oral – 20 subjects GROUP B Transdermal - 20 subjects
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Table 3
Bias assessment as included in the studies

Author name	Random sequence generation	Allocation concealment	Blinding of outcome	Incomplete outcome data	Blinding of participants and personnel	Selective reporting
Prithvi s bachalli et al [12], 2009	+	-	+	-	-	+
Fauziya dastagir et al [13], 2019	+	+	+	+	+	+
Prajakta wankhade et al [14], 2020	+	+	+	+	+	+
Aimuamwosa OD et al [15], 2020	+	+	-	+	+	+
Ramvihari thota et al [16], 2021	+	+	+/?	+	+	+

+= Low risk of bias; -= high risk of bias; = unclear risks of bias

shows the flow diagram of several studies identified, screened, assessed for eligibility, excluded, and included in the systematic review.

Table 1 shows the characteristics of the intervention in the included studies. In all the above studies, diclofenac transdermal patch efficacy was compared to oral diclofenac for pain management after surgical removal of an impacted third molar. Trials were conducted on patients who underwent third molar surgery. Therefore, trial duration and preparations used varied in each.

Table 2 shows the outcome and result of the efficacy of the diclofenac transdermal patch against oral diclofenac for pain management following surgical removal of the impacted third molar in the studies mentioned above. The outcome and results were positive in the above studies showing the diclofenac transdermal patch as a potent analgesic in reducing the postoperative pain following surgical removal of the impacted third molar.

Table 3 shows the bias analysis of all the included studies. It is categorized as high-risk bias "-", low-risk bias "+" and unclear "?". Categorization was done according to the Cochrane risk of bias tools for randomized controlled trials.

3. Discussion

This review aimed to compare two different drug delivery systems, oral and transdermal routes, using diclofenac sodium as a standard drug for postoperative pain management following impacted third molar surgery.

NSAIDs are the most commonly used analgesics. It can reduce both pain and inflammation. The principal interest behind this study was to compare the pain at different levels, adverse effects, and patient compliance. When administered systematically, diclofenac sodium, an aryl acetic acid derivative, has various side effects due to the mechanism of inhibiting prostaglandin synthesis, thus affecting general physiology. [9]

Transdermal drug delivery system is the newly advancing system of local drug delivery that enters the body non-invasively through the skin and diffuses into the capillaries for systemic delivery over several hours to days after the application. Generally, the transdermal patch consists of five components: liner- a protection for the patch during storage, which is removed before application to the skin; drug reservoir where the drug is contained; drug release membrane, which controls drug release from the reservoir through the multi-layers and into the skin; contact adhesive, serves to adhere the patch components to the skin; clear backing protects the patch from outside contamination.

Transdermal patches are highly beneficial and suggested for patients who are unable to take oral medication due to adverse effects. Compared to traditional drug delivery systems, the transdermal patch has many advantages. Drugs taken orally show low bioavailability as a result of poor gastrointestinal absorption. Consequently, high doses and frequent administration are required to achieve more concentration. Transdermal patches also offer a longer duration of action and consequent low dose frequency, easy non-invasive administration, and flexibility in discontinuing the drug. Transdermal offers a more uniform plasma concentration which reduces the adverse effects of the drugs.

When diclofenac is administered trans-dermally, a local delivery system of drugs provides an advantage of reducing

unfavourable adverse effects such as gastric irritation and has direct access to the area of interest, drug release to the body is controlled, limited plasma concentration and prolonged duration of action. Diclofenac transdermal patch is administered once a day when compared to diclofenac tablet, which is administered three times a day makes the patient less compliant.

This systematic review found results of using Diclofenac transdermal patch as a potent analgesic against oral diclofenac for post-surgical pain management following impacted third molar surgery. Among the five included studies, four studies reported statistically significant effects with diclofenac transdermal patch as a potent analgesic against oral diclofenac, which reduced the potential adverse effects such as gastric irritation and better patient compliance.

Prithvi S Bachalli et al., evaluated pain using a visual analogue scale, pain relief scale, pain intensity scale, and verbal rating scale at intervals of 2,4,8,12,24, and 72 hours reported, diclofenac administered orally provides slightly better pain relief than when administered transdermally within 24 hours. However, after 24 hours, there is no significant clinical or strategical difference observed [12]. This gives conflicting results against all the other included studies where the transdermal patch provided a better analgesic effect in 24 hours post-surgery and had better patient compliance.

Fauziya dastagir et al., assessed pain using a 10cm visual analogue scale at the intervals of 12, 24, 48, 72 hours post-surgery reported the intensity of pain has significantly reduced in the transdermal patch when compared to the oral route. Prajakta Wankhade et al., [14] assessed pain using a 10cm visual analogue scale at intervals of 12, 24, 48 and 72 hours post-surgery reported, after 12 hours, the pain relief was better in group II [transdermal patch] when compared to group I [oral route] [13].

Aimuamwosa OD et al evaluated pain using a 10cm visual analogue scale at the intervals of 6 hours, 1, 2, and7 days post-surgery reported, after seven days, the intensity of pain was significantly less in the transdermal group compared to oral diclofenac. Ramvihari Thota et al [16] evaluated pain using a 10cm visual analogue scale, verbal rating scale, pain relief scale and pain intensity scale at intervals of 2, 4, 8, 12 and 24 hours post-surgery reported, after diclofenac sodium, when taken orally, provides comparatively less relief than oral diclofenac. After three days, there is no significant statistical difference in pain relief between the two modes of drug delivery [15].

The conflicting result of Prithvi s bachalli et al is due to improper allocation of subjects to test for pain relief. All the 20 subjects were given oral diclofenac after removing the third molar from one side. After three days, the removal of the third molar on the contralateral side is given a transdermal patch. Unfortunately, this gave incorrect and inadequate results to support the efficacy of transdermal patches over the oral route.

There is conclusive evidence that diclofenac sodium transdermal patch is a potent analgesic that can be used as an alternative to oral diclofenac sodium with better patient compliance. It is also evident that there is an effective reduction in gastric irritation compared to oral diclofenac.

4. Conclusion

The local drug delivery of the diclofenac transdermal patch is effective in postoperative pain management following the removal of the impacted third molar. Additionally, being safer than oral diclofenac provides better patient compliance than oral diclofenac without the adverse effects of gastric irritation.

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