

Efficacy of Diclofenac Transdermal Patch in Maxillofacial Surgeries

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Abstract

Background: Surgical interventions in maxillofacial and oral regions elicit an immense inflammatory response, which leads to post-operative pain. Pain management following maxillofacial surgeries has been a challenge to surgeons for many years. Surgeons have used either opioids or non-opioids to control the post-operative pain. To overcome, this post-operative pain diclofenac transdermal patch (TP) was used in this study. Transdermal drug delivery systems always had the advantage of controlled drug delivery. They also ensure simple and painless procedures with better patient compliance. **Materials and Methods:** This study chooses diclofenac TP for post-operative analgesia in oral and maxillofacial surgeries. This study was done on 44 patients who have undergone oral and maxillofacial surgeries to access the efficacy of diclofenac TP for post-operative analgesia. **Results:** The results have shown that the diclofenac TP has been effective in providing analgesia postoperatively in maxillofacial surgeries. **Conclusion:** This study can be concluded that TP containing diclofenac diethylamine shows a good control of post-operative pain following oral and maxillofacial surgeries.

Keywords: Diclofenac, Post-operative pain, Transdermal patch.

INTRODUCTION

Maxillofacial and oral surgeries lead to high inflammatory response, which causes post-operative pain. To prevent the post-operative pain, most of surgeon's advices opioids or non-steroidal anti-inflammatory drugs (NSAIDs).^[1] The complications associated with opioids make the NSAIDs the drug of choice.^[2,3] NSAID's exercise anti-inflammatory and analgesic effects as they impede prostaglandin synthesis by blocking the activity of cyclooxygenase.

In transdermal drug delivery system (TDDS), drugs penetrate through the skin, subcutaneous tissue, and muscle, which diffuse into the bloodstream to exert the necessary action without an increase in plasma drug concentration. This helps in a decrease of systemic toxicity, which is the main advantage over the other drug delivery routes. Better compliance was achieved in patients with needle prick phobia due to increased flexibility in placing and removing the transdermal patch (TP).^[4]

Topical administration of NSAIDs is advantageous over other delivery systems by their local, enhanced drug delivery to the tissues. The transdermal route offers supremacy as it evades the need for intravenous or intramuscular (IM) drug delivery,

extended duration of onset and offset (typically 12–24 h), patient acceptability, lower systemic adverse effects, and shorter analgesic consumption and hospital stay, thus figuring themselves out as therapeutic analgesic modalities with proven welfare being.^[5]

Bhaskar *et al.*, in their study, compared the viability of TP with oral diclofenac following the extraction and expressed that TP was progressively agreeable due to once-a-day application with lesser foundational antagonistic impacts. TDDSs are intended to convey a foreordained measure of medication through the stratum corneum, and subsequently, the systemic circulation.^[6]

Diclofenac is the most commonly used NSAIDs to control inflammation and pain. Oral and parenteral routes have disadvantages such as gastric irritation, increased blood pressure,

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peptic ulcers, generalized swelling, and renal problems.^[7] The most available form of topical administration is a combination of diclofenac and diethylamine. It bypasses the hepatic metabolism so that the total amount of administered drug reaches the circulatory system. Diclofenac diethylamine possesses certain features such as reduced bioavailability and biological half-life. They work by diffusion, which is an indication of usage as a TDDS. Sustained release of the drug, water insolubility, and self-application and removal are the advantages of the transdermal route.^[8]

The most commonly used non-selective NSAID is diclofenac sodium, which is available in various forms to treat pain. The diclofenac TP is a newly introduced delivery system for post-operative pain management. Hence, this study is undertaken to observe the efficacy of diclofenac TP for post-operative analgesia in oral and maxillofacial surgeries.

MATERIALS AND METHODS

A prospective study was done on 44 patients who have undergone oral and maxillofacial surgeries to access the efficacy of diclofenac TP for post-operative analgesia.

Method of collection of data

Patients undergoing surgeries in the Department of Oral and Maxillofacial Surgery at GITAM Dental College and Hospital, Visakhapatnam.

Inclusion criteria

The following criteria were included in the study:

- Individuals who are fit and indicated for maxillofacial surgeries
- Patients who are willing to participate in the study.

Exclusion criteria

The following criteria were excluded from the study:

- Patients with liver dysfunction
- Patients not willing to participate in the study
- Patients allergic to NSAIDs
- Patients having bronchial asthma
- Patients with renal pathology
- Patients with active peptic ulceration
- Patients underwent cardiac surgeries.

Study design

A prospective study was to evaluate the analgesic efficacy of diclofenac TP in maxillofacial surgeries.

Pain was assessed using a Visual Analog Scale (VAS) at 2, 5, 10, 24, and 48 h postoperatively. This study was undertaken in 44 subjects between age groups 13–56 years. A transdermal diclofenac patch was placed on any non-hair-bearing area such as deltoid region, chest for females, and abdomen for males after obtaining institutional ethical committee clearance and informed consent from the patients.

The armamentarium used:

- Diclofenac TP (Figures 1-3)
- VAS



Figure 1: Application of transdermal diclofenac patch



Figure 2: Diclofenac transdermal patch with diclofenac diethylamine

Statistical analysis

- Data were entered in MS Excel and analyzed in SPSSV22
- Descriptive statistics were represented with percentages
- McNemar's and Cochran's Q tests were done to find significance.

RESULTS AND FINDINGS

This study was designed to evaluate the efficacy of diclofenac TP for post-operative analgesia in oral and maxillofacial surgeries. The pain was measured by VAS on the 2nd, 5th, 10th, and 24th post-operative hours.

Pain

Post-operative pain scores at 2nd, 5th, 10th, and 24th h are illustrated in Table 1.

Among the total 44 patients, there was a pain score of 0 for 79.6%, 86.4%, 93.2%, and 81.8% at the 2nd h, 5th h, 10th h, and 24th h, respectively. There was a statistical significance ($P < 0.01$) when the post-operative analgesic efficacy was evaluated for the diclofenac TP at 2nd, 5th, 10th, and 24th h postoperatively.

It can be inferred from the above observations that the diclofenac TP at the 10th h has shown its most significant



Figure 3: Diclofenac transdermal patch

Table 1: Post-operative pain scores at 2nd, 5th, 10th, and 24th h

VAS score	2 h		5 h		10 h		24 h	
	Count	%	Count	%	Count	%	Count	%
0	35	79.6	38	86.4	41	93.2	36	81.8
2	6	13.6	4	9.1	1	2.3	7	15.9
3	1	2.3	0	0.0	0	0.0	1	2.2
4	2	4.5	2	4.5	2	4.5	0	0
Total	44	100.0	44	100.0	44	100.0	44	100.0

VAS: Visual Analog Scale

post-operative analgesic effect when compared with 2nd, 5th, and 24th h in maxillofacial surgeries.

In conclusion, the results have shown that the diclofenac TP has been effective in providing analgesia postoperatively in maxillofacial surgeries.

DISCUSSION

Pain is an unpleasant, inevitable, and protective function post-surgery. The post-operative pain remains a challenge for both the patients and the operator due to the inflammatory response.^[5,9] Tissue injury results in the triggering of nociception, which results in the activation of chemical mediators, initiating the chemosensory nerve endings which result in pain.^[10,11] Alleviating the pain becomes the cynosure for the operative surgeon. There are different routes available in the armamentarium of maxillofacial surgeons to control pain ranging from parental, oral, rectal, and topical; each route having its own advantages and disadvantages.

In the oral route, 50% of the drug metabolizes in the liver and is partly absorbed in the GIT, so considerable therapeutic levels can't be achieved in the circulation.^[12] First-pass metabolism generally lessens the effect of the drug because of the metabolization of the drugs in the liver and gut wall, sometimes the amount of the drug reached into systemic circulation will be less than the medicine absorbed. Due to this wastage of

medication, there is a need to give much larger doses in the oral route, so it can be said that in the oral route, the bioavailability is unpredictable.^[13] Chaitanya *et al.* have conducted a study to assess the efficacy of oral diclofenac sodium tablets, IM diclofenac sodium injection, and diclofenac sodium TP.^[14] He found that the TP has been efficient in reducing moderate oral pain and with fewer adverse effects. Other disadvantages of the oral route are GI disturbances, renal insufficiency, hepatic toxicity, aggravating asthma, and hypertension.^[7]

In recent decades transdermal bio-adhesive routes or patches have been increasing in popularity as an alternative to the oral and parenteral route and having the advantage of pre-determined administered dosage and prolonging the drug release over a period of time. The TPs refer to the drug delivery systems intended to be applied to healthy skin to deliver the active form of the drug into the systemic circulation.^[15]

The transdermal route proved to be efficient when compared with other routes of administration in terms of sustained release of drug, bypassing the first-pass metabolism in the liver, and absence of systemic adverse effects. The transdermal route also has the advantages of being simple painless; better patient compliance, enhanced efficacy, better bioavailability, and shorter half-life. The elimination half-life of the transdermal route is 12 h, and of oral route, it is 1–2 h. In this study transdermal route is chosen for reasons such as it avoids the need of specific training for the administration of IM or intravenous routes and decrease in plasma concentrations. The transdermal route limited adverse effects by maintaining low plasma levels of the drug, that is, <5% of the oral administration.^[16]

In TDDS the drugs penetrate the skin, subcutaneous tissue, and muscle and diffuse into the bloodstream to exert the necessary action without an increase in plasma drug concentration, thereby decreasing the systemic toxicity which is the main advantage over other routes such as parenteral and IM Patch.^[7,17,18] The absorption process continuous to a depth of 3–4 mm.^[17] Plasma levels vary from 20 to 50 mg/mL, which is of lesser amounts than the oral route but can release the drug throughout the day that is why it should be applied for every 24 h.^[19] as in this study.

There are two essential designs of TPs, a membrane-controlled reservoir system and a monolithic matrix system both acts by passive absorption. The four-layered reservoir system, which has both the impermeable and semi-permeable sides acts by storing the medication in liquid or gel form and controlling the drug absorption through the semi-permeable side. The three-layered system contains the medicine in solid form without a semi-permeable membrane.^[20] The transdermal drug delivery route works by crystal reservoir technology and has been introduced as a potential analgesic, it is superior to the oral route because of its sustainable drug release for 24 h and reduced adverse effects.^[21] The onset of time, systemic absorption of the drug, and analgesic action can be enhanced by adding certain additional agents onto the patch.^[3]

Recently, multiple techniques are being tried to improve the penetrating drug capacity of the TP by penetration enhancers and iontophoresis.^[16]

As the transdermal diclofenac patches are also used as an analgesic postoperatively for laparoscopic surgeries, kidney disease, gallbladder surgeries, gynecology, tooth extraction, venous cannulation, and root coverage procedure.^[23,24] Hence, in this present study, TP is chosen for the administration of the drug.

The transdermal drug delivery route works by crystal reservoir technology and has introduced as a potential analgesic, and it is superior to the oral route because of its sustainable drug release for 24 h and reduced adverse effects.^[21] The onset of time, systemic absorption of the drug, and analgesic action can be enhanced by adding certain additional agents onto the patch.^[22] Recently, multiple techniques are being tried to improve the penetrating drug capacity of the TP by penetration enhancers, and iontophoresis.^[18]

Biopolymers such as cellulose and methylcellulose have been introduced as membranes for the transdermal delivery system because of their non-toxicity, biodegradable nature, straightforwardness, and effectiveness. Drug-loaded B cellulose membranes show sustained release when compared with cellulose patches.^[25]

Liner, adhesive, release liner, and backing are the four layers of the TP. The liner protects the patch, the adhesive layer helps with the attachment of the patch to the skin, the drug is released from the patch by the release liner, and the patch is protected from the outer environment by the backing layer. The efficiency of the patch is because of the saturation of the medicament to the adhesive layer, thus forcing a partial transformation of the drug.^[21] the fundamental feature that determines the ability of an adhesive to form the initial bond is called tack. Shear adhesion or holding power refines the resistance of a matrix to flow. Peel adhesion is the force required to peel away the patch.

The tack is the initial bonding of the pressure-sensitive adhesives (PSA), which is used in this study merely, depends on two factors that are viscous elastic properties of the adhesive material (the rate of wetting) and surface energy of the skin. It is said that a patch requires low tack values as it is applied to the skin. The surface energy of the skin ranges from 25 dyne/cm for dry skin to 56 dyne/cm for wet skin. Hence, the adhesiveness of the PSA not only depends on gender and age but also on the physiopathological conditions.

Shear adhesion or holding power of the PSA is the resistance to the perpendicular stress applied to the patch. As the thickness of the adhesive and shearing layer increases, there is a decrease in matrix cohesion, which would lead to adhesive failure leaving the adhesive on the skin. Hence, the holding power is directly related to matrix thickness.

Peel adhesion is the overall force required to peel away the patch, and it should be higher than the shear adhesion or holding power. In general, when the patch is peeled off, it is

expected to leave a clean area with no noticeable residues. An increase in the thickness of the patch decreases the peel force; therefore, it is advisable to keep an elevated thickness at one of the corners of the patch so that there is a reduction of force while peeling.

There are four types of failures while peeling away the patch:

When the adhesive is not strictly attached to the backing layer, the adhesiveness shifts to the adherence. It will cause the peeling apart of the matrix from the backing layer. There is a chance of failure if there is poor cohesion even when there is excellent adhesion. It is a combination of both adhesive and cohesive failures at a time. Adhesive failure was the PSAs does not strictly adhere to the skin which was seen in all the cases in this study.^[26]

The following are the ideal properties of the PSA

1. To adhere to the skin
2. Should not cause itching or irritation
3. To allow easy removal
4. They should be comfortable to wear
5. They should not leave any residues on the skin after removal.

TP (Nupatch) used in this study has fulfilled all the above qualities of the ideal PSA.

There are different pathways for the diffusion of drugs through the skin. They are:

1. Distribution of drug into the deeper tissues through capillaries or lymphatics
2. Diffusion of the drug into the deeper tissues through interconnecting vessels
3. Diffusion of the drug by partial movement from the vessels to the deeper tissues.

The drug can be penetrated from the skin to the deeper layers through three routes.

- a. Transcellular
- b. Intercellular
- c. Direct penetration.^[27]

Skin absorbs the molecular solute; the crystal contents dissolve to maintain the concentration of the drug at the site of skin contact by which sustainable levels were maintained in the circulation.^[21] Drugs to be absorbed into the deeper layers should have to cross the stratum corneum, which is the effective barrier both chemically and physically, which is made up of squamous cells.

There are physicochemical properties of the drug which dictates the transfer of the drug into the systemic circulation:

1. Liposolubility
2. Molecular weight
3. Molecular charge
4. Water solubility
5. The functional group attached to the molecule.^[27]

Peripheral tissue injury caused due to surgery evokes a considerable inflammatory tissue response, which provokes

the nervous system. This results in the hypersensitive state in the post-operative period. Pre-emptive analgesia is of utmost importance in preventing the effects of this hypersensitivity state or pain. Various drugs that are used to control pain, like steroids with the disadvantage of immunosuppression, and opioids with the disadvantage of addiction, one of the most commonly used analgesics in cancer patients, are narcotics, which act on the central nervous system (CNS). The most commonly used opioid is morphine with various disadvantages such as drowsiness, mood alterations, mental clouding, respiratory depression, bradycardia, and hypotension.^[28]

NSAIDs are the drug of choice with minimal adverse effects. NSAIDs are the commonly used drugs for the management of pain; by inhibiting the enzyme cyclooxygenase, which is the precursor for prostaglandins.^[5] Among the NSAIDs, diclofenac, which is a derivative of arylacetic acid, has an anti-inflammatory and mild antipyretic action.^[29] It acts by inhibiting the cyclooxygenase enzyme, thereby decreasing the synthesis of prostaglandins and thromboxanes.^[4] It can be administered through gel, ointment, cream, paste, oral, parenteral, or transdermal route,^[7] suppositories.^[22]

Diclofenac is superior to other NSAIDs by lesser gastrointestinal, CNS symptoms, allergy, and local reactions. The ideal qualities of a drug to be used as a transversal patch should have specific attributes such as low molecular weight, and highly potent; it should be hydrophobic and hydrophilic. The ideal drug delivery system should release the drug into the skin at a slower rate than the maximum speed of skin transport. The plasma levels achieved with the transversal route were 100 times lower when compared to oral administration.^[30] This above thinking can lead to the use of diclofenac through a transdermal route.

Carboxylic acid present in diclofenac attached to the amine-phenyl ring which is lipophilic, offers a great deal of penetration through the corneum. So diclofenac, which has expensive biotransformation by this route, can be helpful in the usage of a transversal patch. Even though the proteoglycan components are hydrophilic, they can uptake a measurable amount of water and aqua-soluble drugs. This is the reason diclofenac was the drug of choice in this study through the transdermal route.

Diclofenac, along with diethylamine, is the most available combination for topical administrations to bypass the hepatic metabolism so that the total amount of administered drug reaches the circulatory system. Diclofenac diethylamine possesses certain features such as reduced bioavailability, biological half-life, and works by diffusion, which is an indication for use in a TDDS.^[8] Diethylamine is an organic compound with the formula $(\text{CH}_3\text{CH}_2)_2\text{NH}$. It is a secondary amine. It is a flammable, weakly alkaline liquid that is miscible with most solvents. Hence, in this study, diclofenac diethylamine was used as a drug in the TP.

In this study, the results show that the diclofenac TP has been efficient in providing analgesia postoperatively in oral

and maxillofacial surgeries in accordance with the research done by Perepa *et al.*^[5] In the study, no local adverse effects of the TP were observed, such as itching, erythema, and hyperpigmentation, which is contrary to the study done by Agarwal *et al.*^[31] Specific adverse effects are associated with topical routes (EMLA cream) such as methemoglobinemia, erythema, urticaria, allergic contact dermatitis, irritant contact dermatitis, hyperpigmentation, and purpura,^[18] are not seen in this study. During the plasma half-life, about 60% of the drug is excreted through kidneys, minute quantities from the urine, and bile.^[12]

NSAIDs can affect the renal system by inhibiting the vasodilation prostaglandins as a result of this sodium, and water retention occurs, and arterial blood pressure increases. Due to this, GFR decreases, which leads to renal failure.^[10] NSAIDs inhibit prostaglandin-induced vasodilation which will lead to diminished renal perfusion.^[32] There will be a rise in serum urea and serum creatinine ratios as the renal blood flow reduces.^[33] In this study, additional observation was done to evaluate kidney function by measuring serum urea and serum creatinine levels, there were no changes in levels in accordance with the study done by Perepa *et al.*^[5]

This study can be concluded that TP containing diclofenac diethylamine shows a good control of post-operative pain following oral and maxillofacial surgeries. None of the cases in this study required the application of a second patch after 24 h postoperatively. Mild-to-moderate pain after 24 h postoperatively was managed by oral NSAIDs. Diclofenac TP can be advised as post-operative analgesia for the advantages of better patient compliance, sustained drug release, and no adverse effects. Further studies can be done with more numbers and segregating them into different types of surgeries.

This study was undertaken in 44 patients to assess the post-operative analgesic efficiency of the Diclofenac TP by evaluating pain scores at 2nd, 5th, 10th, and 24th h postoperatively.

Results recorded in the study have shown that the post-operative analgesic effect of the Diclofenac TP has been efficient in controlling post-operative pain in maxillofacial surgery.

The analgesic action of the diclofenac TP has been most efficient in 5th and 10th h postoperatively.

CONCLUSION

This study concludes that transdermal patch containing Diclofenac diethylamine shows good control of postoperative pain following oral and maxillofacial surgeries.

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