

Transdermal drug delivery for post operative analgesia in oral & maxillofacial surgery-diclofenac patch or nicotine patch

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Abstract

Introduction: Pain control following removal of impacted tooth is always a challenging task for the surgeons due to differences in patient’s perception to the pain. Oral analgesics of course help in pain management, but have its own side effects like gastritis, vomiting and other GI disturbances. Hence, transdermal analgesic patches are easily available in the market, which disables

all the GI disturbances caused due to oral analgesics during its metabolism. This article is a prospective, split mouth study which enables the comparison and efficacy of transdermal diclofenac 100mg patch and transdermal nicotine 14mg patch in post operative period following removal of bilateral impacted mandibular third molar.

Objective: The objective of this study was to evaluate subjectively the analgesic efficacy of Transdermal

Diclofenac Sodium against Transdermal Nicotine patch in the management of postoperative pain following surgical removal of impacted bilateral mandibular third molars with a time interval of 21 days on each side.

Materials & Methods: 20 patients who require removal of bilateral impacted mandibular third molar under local anaesthesia with adrenaline were randomly divided into 2 groups. Patients in both the groups were treated one side at one time by giving a time interval of 21 days for the removal of the other side. (Group- A) advised transdermal diclofenac 100mg patch (Group-B) advised transdermal nicotine 14mg patch and assessed for post operative pain, edema, trismus and reduced mouth opening.

Results: Among both the groups, (Group-A) Diclofenac group showed good results in post operative analgesia, maintaining anti-inflammatory property by reducing edema, fewer chances of trismus and reduced mouth opening.

Conclusion: Based on our study, Transdermal Diclofenac 100mg patch (Group- A) is superior than compared to Transdermal Nicotine 14 mg patch. Still further studies are required to give a definitive conclusion.

Keywords: Tooth, Pain, PCA.

Introduction

Pain has been defined as an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage¹. Despite the widespread adoption of patient-controlled analgesia (PCA) and its superiority over intermittent IM injection of analgesics, acute postoperative pain continues to be poorly controlled. As many as 70%–80% of patients experience moderate to severe pain in the postoperative period despite pharmacological management^{2,3}. The use of analgesics such as

nonsteroidal anti-inflammatory drugs can improve pain control and decrease opioid-related side effects, but carries serious pro- and anticoagulant side effects.⁴

There need to be a new era in analgesics to prevent all these side effects, as the analgesics play a major role in the medical field in day-to-day life. Transdermal route of drug administration has gained a tremendous acceptance by the patients due to its potent therapeutic action with decreased side effects which were caused by oral route of drug administration.

A transdermal patch is a medicated adhesive patch that is placed on the skin to deliver a specific dose of medication through the skin and into the bloodstream. An advantage of a transdermal drug delivery route over other types of medication delivery is that it provides a controlled release of the medication into the patient, usually through either a porous membrane covering or through body heat melting thin layers of medication embedded in the adhesive. The main disadvantage to transdermal delivery systems stems from the fact that the skin is a very effective barrier; as a result, only medications whose molecules are small enough to penetrate the skin can be delivered by this method.

Diclofenac being a Non-Steroidal Anti Inflammatory drug acts as a potent analgesic than compared to other group of analgesics. It acts by inhibiting Cyclooxygenase enzyme in arachidonic acid pathway and promotes analgesia. Diclofenac Diethylamine 100mg is commercially and easily available as a transdermal patch.

Nicotine is a naturally produced alkaloid predominantly from tobacco and *Duboisia hopwoodii*.⁵ It is widely used recreationally as a stimulant and anxiolytic. As a pharmaceutical drug, it is used for smoking cessation to relieve withdrawal symptoms.^{6,7} Nicotine is used as a tool for quitting smoking has a good safety

history.⁸ Animal studies suggest that nicotine may adversely affect cognitive development in adolescence, but the relevance of these findings to human brain development is disputed.⁹ At low amounts, it has a mild analgesic effect.¹⁰

Nicotine produces antinociception in preclinical models,^{11,12} and cigarette smoking rates are elevated in patients with chronic pain.¹³ Accordingly, nicotine has been examined as an analgesic for postoperative pain; the most common modalities have been nicotine patch and nasal spray. However, a recent review and meta-analysis found that the use of nicotine as an analgesic increased postoperative nausea and did not reduce pain in a statistically significant fashion.¹⁴

This article compares the post operative clinical efficacy of Diclofenac 100Mg transdermal patch and Nicotine 14 Mg transdermal patch in bilateral impacted mandibular molar removal.

Materials & Methods

Aim of the study was to assess the clinical outcome between Diclofenac transdermal patch and Nicotine patch during post operative bilateral impacted mandibular third molar surgery.

Subjects

20 patients who require removal of bilateral impacted mandibular third molar under local anaesthesia with adrenaline were randomly divided into 2 groups. Patients in both the groups were treated one side at one time by giving a time interval of 21 days for the removal of the other side.

Both the patients were first given with Diclofenac 100 mg patch for one side and the next visit the same patient was given Nicotine 14 mg patch.

Group-A: (Diclofenac group) includes patients who underwent removal of impacted tooth on one side followed by Diclofenac Diethylamine 100 mg

transdermal patch application on left deltoid region for 48 hours post operatively.

Group-B: (Nicotine group) includes patients who underwent removal of impacted tooth on one side followed by Nicotine 14 mg transdermal patch application on left deltoid region for 48 hours post operatively.

Inclusion Criteria

- Patients with bilateral impacted mandibular third molars requiring surgery.
- The third molars included were to have symmetrical impaction topography according to the classifications proposed by winter and by Pell and Gregory.
- Patients with age ranging from 19 to 40 years both male and female.
- Patients with no other systemic problems.
- Non-pregnant and non-lactating females were included.

Exclusion Criteria

- Patients who are allergic to NSAID's
- Patients with underlying systemic problems
- Patients with unilateral impacted mandibular third molar.

A prospective, randomized, double-blind clinical trial with a split-mouth design was conducted, where surgeon and patient were blinded about the patch advised. All procedures were performed under local anaesthesia (lignocaine 2% and adrenaline 1:80,000) and an equivalent dose of anaesthetic was used for both sides. Each surgical procedure was timed and a 21-day interval was observed between interventions. All the patients were explained about the study and taken their consent and advised to apply the patch over left deltoid region for the next 24 hours immediately after the surgery.



Fig. 1: Site of application of transdermal patch in both the groups (A & B)

The patients were prescribed rescue analgesics for the postoperative period (Aceclofenac 100mg+ Paracetamol 325mg+ Serratiopeptidase 15 mg) one tablet orally every 6- 8 hourly, as needed). The number of analgesics taken was recorded on a specific chart.

Parameters Assessed

Post operative pain was measured on five consequences: 2 hours (after the effect of the anaesthesia had worn off), 8 hours (time of peak pain), 12 hours, 24 hours (removal of adhesive), and 72 hours recorded by the patients using a visual analogue scale (VAS) ranging from 0 (absence of pain) to 10 (worst pain imaginable). Oedema and trismus were also evaluated at post operative 1st day, 2nd day, and 3rd day and at 7th day after the surgery.

Post operative swelling was measured on day 1, 3 and 7 with a measuring tape, with 3 reference points, Corner of

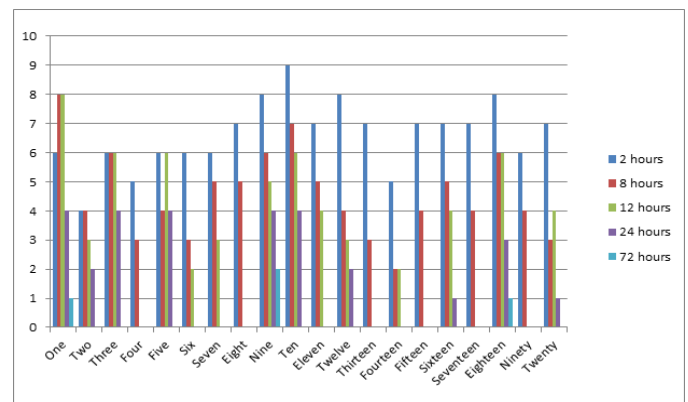
angle to corner of eye (1), Tragus to corner of the mouth (2), Tragus to pogonion (3).

Post operative trismus and mouth opening by measuring interincisal distance were assessed for after 2nd and 7th day post operative day in both the groups. All the parameters were recorded and evaluated statistically.

Results

Post-operative pain

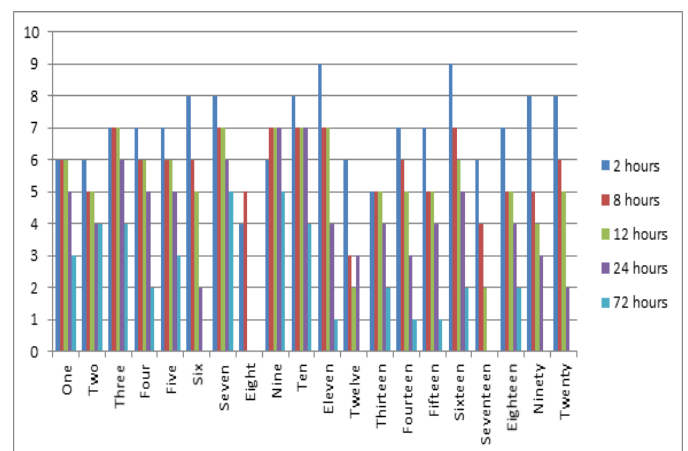
Group: A (Diclofenac transdermal patch)



Graph 1

Among 20 patients in diclofenac group, by the end of 2 and 8 hours post operatively, all the patients given scores other than 0, 12 hours post operatively 6 patients gave a score 0, 24 hours post operatively 10 patients gave a score of 0, 72 hours post operatively 17 patients gave a score of 0.

Group: B (NICOTINE 14 Mg)



Graph 2

Among 20 patients in nicotin group, by the end of 2 and 8 hours post operatively all the patients gave score other than 0, 12 hours post operatively only 1 patient gave a score 0, 24 hours post operatively 2 patients were gave a score of 0, 72 hours post operatively 5 patients were gave a score of 0. Even at the end of 3rd day, 15 patients were scored other than score 0.

Post-Operative Oedema

Oedema was greater at the different evaluation times among both the groups. The difference ranged from 13.09 cm in Group A and 13.01 cm in Group B on day 1. 12.06 cm in Group A and 12.68 CMS in Group B on day 2. 2.6 CMS in Group A and 6.3 CMS in Group B on day 7. With significant differences between the groups at 24, 48, and 72 hours.

In Group A (Diclofenac group), mean oedema at the 7-day evaluation was different than compared preoperative period, and the value ranged from 13.09 cm to 2.6 cm from the mentioned reference points.

In Group B (Nicotine group), mean oedema at the 7-day evaluation was the same as that found in the preoperative period, and the value ranged from 13.01 cm to 6.3 cm.

Post Operative Trismus & Mouth Opening

Mouth opening and trismus were assessed on day 2nd and 7th post operative day by measuring the interincisal distance. Among both the groups, mouth opening was better in Group A (Diclofenac group) than in Group B (Nicotine group). Mean value of mouth opening in Group A ranges from 13.4 to 28.6 CMS on post operative day 2 and 7, whereas in Group B it ranges from 10.2 to 23.4 CMS on post operative day 2 and day 7.

Discussion

Managing tooth pain management is an important aspect in the dental practice. Most importantly for tooth extraction, proper analgesia is always mandatory which

brings a positive reinforcement in patient throughout the procedure. Intra operative analgesia anyway taken care by anaesthesia and conscious sedation. The management of postoperative pain is an aspect where attention has to be directed.

Transdermal analgesic patches seem to have been in routine use in various medical fields for a significant period of time now. Its use ranges from pain control during intravenous cannulation¹⁵, post breast augmentation pain relief¹⁶, chronic/acute muscular pain relief¹⁷, sports injury¹⁸ and post-intubation pharyngeal pain¹⁹.

Diclofenac a commonly used drug used in dentistry and oral surgery for the management of postoperative pain in the form of tablets, suppositories, or injectable preparations. Even though commonly used it has its own side effects during its metabolism. It is a Non-Steroidal Anti-inflammatory drug. Acts by inhibiting cyclooxygenase during arachinoid acid pathway. The transdermal diclofenac has usually the tendency to be subjected to absorption interferences due to the presence of anatomical barriers such as the epidermis, dermis, and the underlying muscle tissue.

The drug is usually retained or may undergo metabolism during its journey to the nearest vascular supply, hence, the amount of drug that reaches the circulation establishes a minimum plasma concentration. This low concentration hence leads to a lesser incidence of systemic adverse effects; however, a larger dosage may have been incorporated onto the patch but still the mean plasma diclofenac concentration remains lower than that of the other modes of administration²⁰.

The second drug in the article was Nicotine 14 mg. Davis et al. first described the analgesic properties of nicotine in 1932 in a feline visceral pain model²¹. More recently, the anti-nociceptive mechanism induced by

nicotine has been related to the modulation of the pain process in the central nervous system through the selective agonist effect on $\alpha 4\beta 2$ nicotinic receptors located in the brain and spinal cord^{22, 23}.

The pre-synaptic activation of these neuronal receptors induces the release of neurotransmitters involved in the control of pain and the modulation of the pain process, such as acetylcholine, dopamine, gamma-aminobutyric acid, and noradrenaline, besides minimizing the production of tumour necrosis factor and oedema after surgical procedures on soft tissues^{24, 25}.

Flood and Daniel²⁶ et al concluded that Nicotine administration led to the significant control of pain in both the first hour and on the first day after the procedure and reduced the need for morphine in the postoperative period by half compared to the placebo group.

Habib et al.²⁷ also demonstrated the effectiveness of a nicotine patch for the control of pain in patients submitted to radical retropubic prostatectomy under general anaesthesia, reporting that the nicotine group required significantly less morphine in 24 hours than the placebo group.

But in contrast to the other studies, present study shows significantly none of the patient had reduced pain after the procedure. Only 1 patient had 0 pain according to VAS post 12 hours after the surgery.

Many evidences results described in the literature on the use of nicotine in surgical procedures under general anaesthesia, But, the present study assess the use of nicotine in procedures performed under local anaesthesia. This is involved in the evaluation of clinical outcomes after a hard tissue surgery and employed a split-mouth design with randomization, blinding of the interventions, and the evaluation of variables at standardized time intervals over the course

of 1 week, which is considered compatible with the regression of symptoms following oral surgery. This study makes an important counterpoint with regard to possible biases in the results obtained from individuals submitted to general anaesthesia, as some drugs compete for nicotinic receptors and may alter the expected clinical outcomes for the control of pain with the use of nicotine, especially when the general anaesthetic is isoflurane²⁸.

This possible interaction was reported by Martins-Filho et al²⁹, who used a nicotine patch with 14 mg for the treatment of pain following laparoscopic cholecystectomy in comparison to a placebo patch and found that the highest pain scores 6 hours after the procedure were in the nicotine group. The authors attributed this undesirable effect to the interaction with the drugs used for general anaesthesia. The intervention group had significantly lower pain levels compared to the placebo group after 24 hours, suggesting that the time required for clearance of the drugs used for general anaesthesia during the operation may mask the true therapeutic effectiveness of nicotine.

The efficacy of NSAIDs in reducing the post operative pain depends on their ability to inhibit cyclooxygenase's which are key in prostaglandin synthesis³⁰. Transdermal drug administration bypasses first-pass metabolism in the liver, and overcomes concerns regarding drugs that are poorly absorbed in the gastrointestinal tract³¹. It offers several advantages as it avoids the need for intravenous or intramuscular drug administration, prolonged duration of onset and offset, typically 12–24 h, patient compliance, shorter analgesic consumption and hospital stay, reduced systemic adverse effects due to lower plasma concentrations³² thus carving out a niche for themselves as therapeutic analgesic modalities with established benefits.

In a study done by Krishna et al.³³ intraoperative application of a single dose of 100 mg transdermal diclofenac patch is as effective as a single dose of intramuscular diclofenac for acute postoperative pain, without any side-effects.

In a study done by Alessandri et al.³⁴ the authors had administered transdermal diclofenac sodium and a placebo into the incision area in postoperative period and observed that there was significantly less analgesic consumption and a shorter duration of hospital discharge.

Bruhlmann et al.³⁵ in their study evaluated effectiveness of transdermal diclofenac sodium on 103 patients with knee osteoarthritis and reported that transdermal diclofenac sodium application to the placebo group is an effective and reliable method. The results of our study suggest that application of diclofenac transdermal patch is more effective than transdermal nicotine 14 mg prolonging the requirement of postoperative analgesia and

Conclusion

The introduction of transdermal analgesic system of drug delivery in the field of oral and maxillofacial surgery got a tremendous change in the pharmacotherapy in post operative analgesia. As, almost every patient requires a proper analgesia after a minor oral surgical procedure to the complex ablative and reconstruction procedures. In our study, we had compared the efficacy of transdermal diclofenac patch with transdermal nicotine 14 mg patch in a bilateral lower wisdom tooth extraction for a time interval of 21 days each side. We assessed few parameters which are troublesome for both the patient and operating surgeon post operatively. Based on our study and its results, we conclude that transdermal diclofenac 100mg patch was superior in providing good post operative analgesia, less intake of

rescue analgesics, maintains and balances post operative edema and very fewer chances of trismus and limited mouth opening than compared with the transdermal nicotine 14mg patch. Further studies with more sample size are required for a definitive conclusion.

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