Original Article

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COMPARATIVE STUDY OF MANAGEMENT OF POST EXTRACTION PAIN WITH TRANSDERMAL DICLOFENAC VERSUS ORAL DICLOFENAC

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ABSTRACT:

Background: Pre emptive analgesia is administration of analgesia prior to the painful stimuli. NSAIDS are commonly used medication for the post extraction pain. The transdermal NSAIDS have advantages of higher bioavailability, no gastric side effects.

Objectives: The present study was undertaken to compare the efficacy of Transdermal Diclofenac and Oral Diclofenac in management of post operative pain in bilateral extractions.

Methods: Seventeen healthy patients with bilateral extractions were included in this study. During the first extraction the patient was prescribed with Tablet. Diclofenac 50mg thrice daily for three days and after a week, during second extraction the patient was prescribed with Transdermal Diclofenac Diethylamine 100mg patch for three days. The post operative pain was recorded in Visual Analog Scale, Verbal Rating Scale, Pain Intensity Scale, Pain Relief Scale during the post operative period of 2 hours, 6 hours and 12 hours for three consecutive days.

Results: 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 Visual Analogue Scale, Verbal Response Scale, Pain Intensity Scale, Pain Relief Scale for Transdermal patch was lesser than the mean pain scores of diclofenac tablet, the difference was not statistically significant.

Conclusion: From this study we can arrive at a conclusion that both diclofenac tablet and diclofenac transdermal patch are equally effective in management of post extraction pain. And Transdermal patch with its various advantages of transdermal delivery system can be used as an alternative for oral diclofenac in management of post extraction pain.

Keywords: VAS - Visual Analog Scale, VRS - Verbal Rating Scale, PIS - Pain Intensity Scale, PRS - Pain Relief Scale

INTRODUCTION:

Pain is a complex, multifaceted experience which 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

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International Association for the Study of Pain.[1]

Pain is a predictable part of the postoperative experience. If the post operative pain in unrelieved, it may cause clinical as well as psychological changes decreasing quality of life and increasing morbidity and mortality.[2]

Administration of analgesics before a painful stimulus is Preemptive Analgesia. It provides better pain relief better than the same analgesic used after the painful stimuli. In early 1980s the concept of pre emptive analgesia was proposed, when experimental studies showed, that central hypersensitization can be prevented by measures taken prior the onset of painful stimuli, thus reducing the pain post operatively.[3]

Diclofenac is the commonly prescribed NSAIDS which exhibit anti inflammatory, analgesic and anti-pyretic action. When used oral route, however only 50% of absorbed dose of diclofenac becomes available in the systemic circulation after first pass metabolism and also to the high plasma concentration attained, oral diclofenac caries the potential for significant adverse reactions particularly involving gastrointestinal tract.[4]

In 1970s transdermal patches were developed and the first was approved by the FDA in 1979 for the treatment of motion sickness. It was a three-day patch that delivered scopolamine. In 1981, patches for nitroglycerin were approved, and today there exist a number of patches for drugs such as clonidine, fentanyl, lidocaine, nicotine, nitroglycerin, oestradiol, oxybutinin, scopolamine, and testosterone.[5]

Transdermal patches have the following advantages

- non invasive painless parenteral route,
- bypasses gastrointestinal tract, first pass mechanism higher bioavailability,
- no gastric side effects
- it is effective in effective delivery of drug which is extensive broken down in gastric acid and first pass metabolism
- it can extend the duration of action of the drug which has short plasma half life by constant delivery of drug transdermally
- delivery of the drug can be stopped abruptly
- patient friendly for handicapped, patients with cognitive impairment
- The aim of the study is to compare the efficacy of transdermal diclofenac patch with oral diclofenac tablet in management post extraction pain.[6]

MATERIALS AND METHODS:

This study is a cross over inteventional study involving 17 bilateral extraction patients in each group. Group1 – when patients received diclofenac tablet for post operative pain during tooth extraction in one side of the jaw. Group2 – when patients received transdermal diclofenac patch for post operative pain during tooth extraction in opposite side of the jaw. Patients were given the medications preemptively tablet diclofenac 50mg TID one hour before procedure and transdermal diclofenac 100mg (Dicloplast 100mg, Figure 1 shows the Dicloplast pack consisting of three transdermal patch) two hour before procedure
(Figure 2 shows the placement of transdermal pactch on right shoulder). Both extractions in bilateral extraction were performed by same resident under local anesthesia 2%ligonocaine with adrenaline 1:80000 under aseptic precautions with aninterval of one week. For the first extraction when the patients receive tablet diclofenac, tablet Ranitidine 150mg (Rantac 150 - JB chemicals and Pharmacueticals Pvt Ltd) bid for three days were prescribed. Tablet Paracetamol 500mg ten in number given to the patients as a rescue medication and Capsule amoxicillin 500 mg (Mox 500 – Ranbaxy laboratories) tds for five days if needed. Patient are assigned to score the post operative pain three times in a three consecutive days in VAS – Visual analog scale, VRS – Verbal response scale, PIS-Pain intensity scale , PRS – pain relief scale after 2hours, 6 hours and 12 hours and to stop the scoring, if they required the tab paracetamol 500mg for pain control and from then the number of paracetamol tablet required is calculated for both the extractions. Figure 3 shows the data record sheet used for pain scoring.

Statistical analysis

The data were analyzed by Statistical Package for Social Sciences (SPSS 16.0) version. Unpaired t test applied to find the statistical significant between groups. ANOVA (Post hoc) followed by Dunnet t test applied to find statistical significant between the groups. p vale less than 0.05 ($p<0.05$) considered statistically significant at 95% confidence interval.

RESULTS:

In group one, the day one 2 hours , 6 hours and 12 hours mean VAS score were 4.88, 3.47, 2,52 respectively and day two scores were 3.00, 2.64, 2.35 respectively and the day three scores were 1.35, 0.82, 0.00 respectively. In group two, the day one 2 hours, 6 hours and 12 hours mean VAS score were 3.23, 2.41, 2.11 respectively and the day two scores were 2.01, 1.58, 1.23 respectively and day three scores were 0.58, 0.11, 0.00 respectively. Figure 4 shows the graphical representations of mean VAS score.

In group one, the day one 2 hours, 6 hours and 12 hours mean VRS score were 3.00, 2.64, 2.00 respectively and

day two scores were 2.00, 2.00, 1.47 respectively and the day three scores were 1.11, 0.23, 0.00 respectively. In group two, the day one 2 hours, 6 hours and 12 hours mean VRS score were 2.52, 2.00, 1.52 respectively and the day two scores were 2.00, 2.00, 1.47 respectively and day three scores were 0.23, 0.00, 0.11 respectively. Figure 5 shows the graphical representations of mean VRS score

In group one, the day one 2 hours, 6 hours and 12 hours mean PIS score were 3.00, 2.64, 2.00 respectively and day two scores were 2.05, 2.00, 1.52 respectively and the day three scores were 1.23, 0.64, 0.00 respectively. In group two, the day one 2 hours, 6 hours and 12 hours mean PIS score were 2.88, 2.00, 1.47 respectively and the day two scores were 1.47, 1.05, 0.88 respectively and day three scores were 0.23, 0.00, 0.11 respectively. Figure 6 shows the graphical representations of mean PIS score

In group one, the day one 2 hours, 6 hours and 12 hours mean PRS score were 3.00, 2.58, 2.00 respectively and day two scores were 2.05, 1.88, 1.52 respectively and the day three scores were 1.23, 0.58, 0.00 respectively. In group two, the day one 2 hours, 6 hours and 12 hours mean PRS score were 2.88, 1.94, 1.52 respectively and the day two scores were 1.52, 1.11, 0.88 respectively and day three scores were 0.35, 0.00, 0.00 respectively. Figure 7 shows the graphical representations of mean PRS score.

DISCUSSION:

Pain is a highly subjective phenomenon to an individual. Factors like age, sex, precious experience affect the experience of pain, which is tempered by individuals' tolerance threshold. The Assessment of pain can either be unidirectional or multidirectional. The multidirectional scales lead us to the cause of the pain, it is used for a chronic setting. For assessment of post operative pain, unidirectional pain scales are useful as the reason for pain is the trauma form surgery.[7]

The VAS consists of a l0 cm horizontal or vertical line with the two endpoints labeled 'no pain' and 'worst pain ever.' The patient is required to mark the l0 cm line at a point that corresponds to the level of pain intensity he or she presently feels, The distance in centimeters from the low end of the VAS and the patient's mark is used as a numerical index of the severity of pain.[8] The Verbal Rating Scale is a four point scale with values assigned ranging from 0–3. Comfortable, Mild, Moderate and Severe were the corresponding interpretation for the above scores.[9] The Pain Intensity Scale is a scale which is similar to the Verbal Rating Scale. In this scale, the interpretation for the values was 'none, mild, moderate and severe' for corresponding scores between 0–3. The Pain Relief Scale is also a four point scale, again with values from 0–3. In this scale,

the interpretation for the values was complete relief for a score of 0 and no relief for a score of 3.[10]

In our study, in day one, the mean pain scores in all the scales reduced with time in both the groups and the reduction were statistically significant in both groups.In day two, the mean pain score in all the pain scales reduced with time in both the groups and the reduction of mean VAS score was significant in both groups. Where as in like VRS, PIS, PRS the difference in the pain score between 2hour and 6 hour were not significant but the difference in scores between 6hour and 12 hour were significant in both groups. In day three, the mean pain scores in all the pain scales reduced with time in both the groups and the reduction were statistically significant in both groups.

Though the mean pain scores of Diclofenac transdermal patch group were lesser than Diclofenac tablet group in all the evaluated days, the difference was not statistically significant respective to the time intervals. Thus leading to the conclusion of equal efficacy of the two medication in management of post operative pain. Patients neither had gastric irritation due to tablet diclofeanac nor allergic reaction of diclofenac patch,as the patients allergic to diclofenac were excluded from the study and tablet Rantidine 150mg BD was prescribed along with tablet Diclofenac 50mg TID.

Previous studies comparing transdermal Bachalli PS, Nandakumar H, Srinath N in 2009 and Krishnan S in 2015. Bachalli PS, Nandakumar H, Srinath N used the transdermal diclofenac patch 100mg against oral diclofenac 100mg OD for pain control following surgical extraction of mandibular impacted third molar in 20 subjects. They evaluated the post operative pain in 2 hour, 4 hour, 8 hour, 12 hour, 24 hours in three consecutive days on VRS, VAS, PIS and PRS. They concluded that the oral diclofenac 100mg was slightly more significant efficacy than transdermal diclofenac patch in the first post operative day. But in second and third days both transdermal diclofenac patch and oral diclofenac were equally effective in post operative pain management.[8] Krishnan S in 2015 compared the efficacy of transdermal diclofenac and oral diclofenac in post extraction pain management in extraction in 40 patients with unsalvageable non tender molar teeth. The post operative pain was evaluated in 6 hours and 12 hours in VAS. He concluded that the transdermal diclofenac patch showed neither statistical nor clinical difference from the efficacy of diclofenac sodium oral tablet in management of post operative pain in non tender molar extractions.[11]

No patients in our study required an emergency medication in both Group I-diclofenac tablet and Group II - diclofenac patch.this was unlikely to the study done by Bhaskar H, Kapoor P, Ragini in 2013 which compared the

transdermal diclofenac patch 100mg with oral diclofenac as an analgesic modality for orthodontic extraction in a cross over efficacy trial and evaluated post operative pain in three consecutive days in PIS, PRS in 20 subjects. One patient with transdermal patch required emergency medication tab paracetamol. The results showed that the pain intensity scale of both transdermal diclofenac patch 100mg and diclofenac tablet showed a gradual decrease from day 1 to day 3. The pain relief score showed gradual decrease in both transdermal diclofenac patch and oral diclofenac in three days of time. They concluded that the transdermal diclofenac 100mg provides as potent analgesia as the oral diclofenac tablets with added benefits better patient compliance.[12]

Comparative studies between diclofenac injection and diclofenac transdermal patch based the requirement of emergency medication was done by Krishna R, Natraj MS in 2012 and Bhargava GS, Sidhu AS, Bansal D, Bhatia AS in 2015. Krishna R, Natraj MS compared the efficacy of single dose of diclofenac patch 100mg with diclofenac injection 75mg as pre emptive analgesia in lower limb surgeries under subarachnoid block on 60 patients. The transdermal diclofenac 100mg was given at the beginning of the surgery for the study group and intramuscular diclofenac 75mg was given half an hour before the end of the surgery for the control group. Post operative pain was evaluated in two hours and six hours in VAS. The mean time for rescue analgesia of injection tramadol 2 mg/kg in control group was 7 hours 28 minutes and in study group was 8 hours 6 minutes.[13] Bhargava GS, Sidhu AS, Bansal D, Bhatia AS compared their difference in post operative pain management, after abdominal surgeries in 100 subjects. Transdermal diclofenac patch was placed one hour before the end of surgery and Diclofenac injection 75mg was given intramuscularly half an hour before the end of surgery. They observed that the mean time first supplement of analgesia for transdermal diclofenac group was 7.21 hours and for oral diclofenac it was 7.43 hours. They concluded that Diclofenac patch is as effective as Diclofenac intramuscular injection in providing post operative analgesia.[14]

Transdermal Diclofeanc patch is effective in post operative pain management in general surgical procedure according to Alessandri et al in 2006, Reddy RP et al in 2015, Narzaree P, Griwan MS, Sign J in 2016, Verma R, Kumar S, Goyal A, Ajay C. Alessandri et al studied the efficacy of transdermal diclofenac in management of laparoscopic gynaecological surgeries. The authors noted that the rate of discharge in patients receiving a transdermal diclofenac patch with a standard analgesic was comparable to a standard analgesic alone in patients undergoing laparoscopic benign gynaecologic surgery.[15]

Reddy RP et al compared the efficacy of transdermal diclofenac with intramuscular diclofenac in ingunal hernia mesh repair surgeries in 60 randomised patients. The intramuscular diclofenac 75mg and transdermal diclofenac diethylamine was given one hour after initiating spinal anesthesia. The post operative pain was evaluated in visual analog scale in 2hours, 4hours, 6hours, 12hours, 18hours and 24hours after surgery and rescue medication was inj butrophanol 2mg. The mean time of rescue medication for intramuscular diclofenac group was 7.45 hours and for transdermal patch group it was 17.76 hours. Thus concluded that transdermal diclofenac is more efficient in post operative pain management in hernia repair surgeries.[16]

Narzaree P, Griwan MS, Sign J compared the efficacy of transdermal diclofenac and intramuscular diclofenac for management of post operative pain in inguinal hernia surgery. The transdermal patch was applied 3hours prior to surgery and two doses of diclofenac intramuscular injection was given at 2hours and 12 hours after the surgery. The post operative pain was evaluated in VAS and VRS every six hours for 24 hours and the pain score of 5 was decided to be treated with tramadol 50mg slow intravenous infusion. The VAS score obtained at 24 hours showed statistically significant difference between the two groups. They concluded that when applied three hour before surgery transdermal diclofenac was found to be equally efficient with intra muscular diclofenac.[17]

Verma R, Kumar S, Goyal A, Ajay C compared the efficacy of transdermal diclofenac diethylamine 100mg with transdermal ketoprufen 20mg for post operative pain management in lower limb surgeriesThey concluded that transdermal diclofenac and transdermal ketoprufen have equal efficacy in managing post operative pain in lower limb surgeries.[18]

The effective post operative pain control by transdermal diclofenac patch depend on critical factors like initiation of action of transdermal diclofenac inturn depending on its penetration and plasma level obtained when trandermal diclofenac patch is applied.

Assandri et al. in 1993 evaluated tolerability and pharmacokinetic profile for transdermal Diclofenac Hydroxy ethyl pyrolidone in both animals and human volunteers revealed that flexor patch delivered diclofenac at constant level into plasma up to 12 hours after application. He also reported that the peak plasma concentration of diclofenac after plaster application was about 15 $ngml^{-1}$, much lower than that reached by oral administration (approximately 1500 ng ml^{-1}).[19] Thus according to above study, the onset of action in transdermal diclofenac is 2 hours and thus the transdermal diclofenac is used in post operative situation where pain is anticipated. Thus in our study and in studies by Narzaree P et al, Reddy RP et

al, Krishna R et al. Agarwal et al., the transdermal diclofenac patch was placed 2-3 hours prior to the period to which pain is anticipated.

Agarwal et al., in 2006 compared the efficacy of EMLA patch and transdermal diclofenac patch for intravenous cannulation pain reported that using transdermal diclofenac patch for attenuation of venous cannulation.[20] A similar study by Khalili S et al., in 2014 compared transdermal diclofenac and EMLA in double blinded placebo controlled study for venous cannulation in 90 patients undergoing elective surgery.[21] Thus they concluded that EMLA and diclofenac patch are equally efficient in controlling the venous cannulation pain with transdermal patch having advantage of having minimal local side effects.

Bookman AAM et al. in 2004 studied the effect of transdermal diclofenac in osteoarthritis pain in 248 patients. It was a randomized double blinded placebo controlled study in which group one was diclofenac with permeation enhancer dimethyl sulfoxide second group with only enhancer and third group with placebo.[22]

A similar study by Funk et al., in 2008 compared the efficacy of transdermal diclofenac hydroxyl pyrolidone with oral diclofenac in management of post arthroscopic pain in shoulder joint. Thus concluded the transdermal diclofenac was effective in management of osteo arthritis.[23] The above studies state that the transdermal diclofenac is used extensively in osteoarthritis of shoulder and knee joints and it is effective for completely relieving the anticipated pain like pain of cannulation prior elective surgeries.

CONCLUSION:

From our study we conclude that the transdermal diclofenac and oral diclofeanc are equally efficacious in management of post extraction pain. However trials with larger sample and longer duration are required for the further evaluation. Though Transdermal diclofenac cannot be used in emergency management of pain to disadvantage of late onset of action, the advantages like painless parentral system, nil gastric side effects, effective delivery at constant rate, patient friendly dosing outweighs the disadvantages and permits its usage in management of post operative pain elective surgical procedures.

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FIGURES:

Figure 1

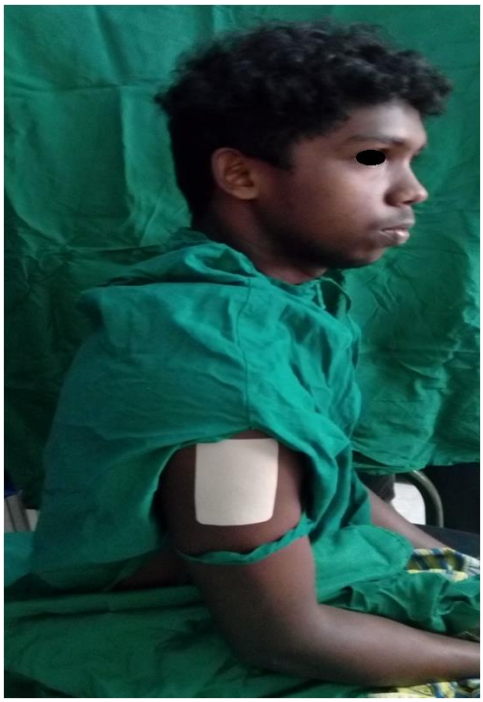


Figure 2

DATA RECORD SHEET

Reference no :
Age :
Sex :

Date:

Op.No:

DAY ONE :	VAS (0-10)			VRS (0-3)			PIS (0-3)			PRS (0-3)		
TIME	2 hrs	6 hrs	12 hrs	2 hrs	6 hrs	12 hrs	2 hrs	6 hrs	12 hrs	2 hrs	6 hrs	12 hrs
GROUP 1												
No. of paracetamol tablets consumed												
GROUP 2												
No. of paracetamol tablets consumed												

Day two	VAS (0-10)			VRS (0-3)			PIS (0-3)			PRS (0-3)		
TIME	2 hrs	6 hrs	12 hrs	2 hrs	6 hrs	12 hrs	2 hrs	6 hrs	12 hrs	2 hrs	6 hrs	12 hrs
GROUP 1												
No. of paracetamol tablets consumed												
GROUP 2												
No. of paracetamol tablets consumed												

Day three	VAS (0-10)			VRS (0-3)			PIS (0-3)			PRS (0-3)		
TIME	2 hrs	6 hrs	12 hrs	2 hrs	6 hrs	12 hrs	2 hrs	6 hrs	12 hrs	2 hrs	6 hrs	12 hrs
GROUP 1												
No. of paracetamol tablets consumed												
GROUP 2												
No. of paracetamol tablets consumed												

Group1-diclofenac 50mg tablet . Group2- diclofenac transdermal patch 100mg.
VAS - visual analogue scale. VRS - Verbal rating scale (0-3) PRS - Pain relief scale PIS - Pain intensity scale

Participant's Signature
Date:

Investigator's Signature,

Figure 3

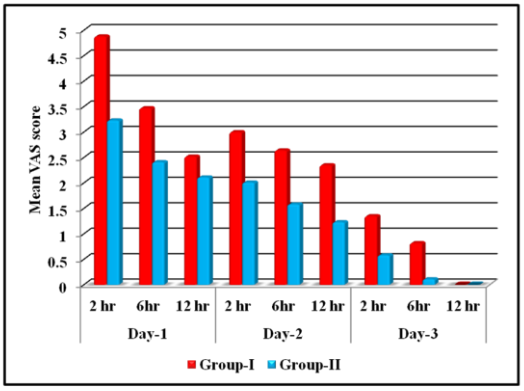
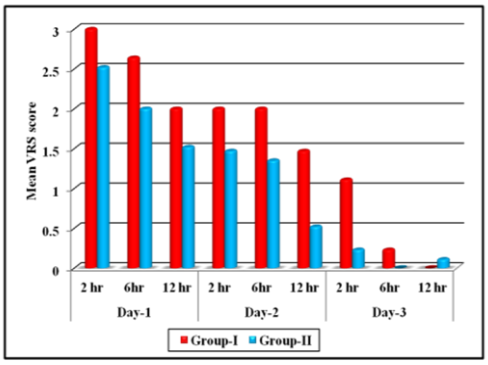


Figure 4



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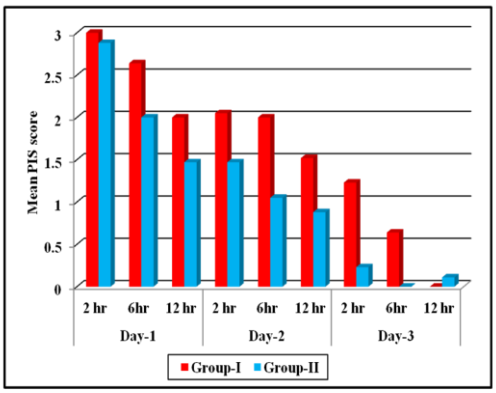

Figure 6:

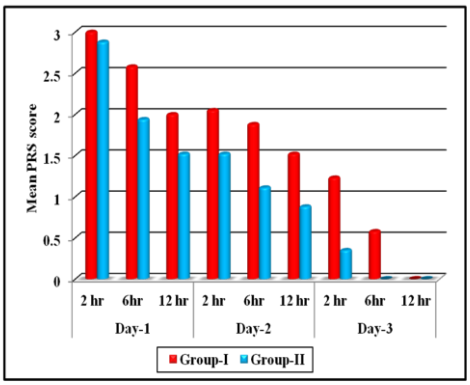

Figure 7: