

A Comparative Study to Evaluate Efficacy of Fentanyl Transdermal Patch VS Ketoprofen Patch in Pain Control after Mandibular Third Molar Surgery

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ABSTRACT

Background: Surgical removal of impacted lower third molars is a common oral surgical procedure, generally followed by moderate to severe postoperative pain. Transdermal drug delivery as a concept offers interesting possibilities for postoperative pain control. **Aims and Objectives:** to evaluate and compare the degree of post-operative analgesia, patient compliance and frequency of adverse events between transdermal ketoprofen patch and transdermal fentanyl patch following third molar extraction. **Methods:** Total 7 patients aged 18-65 years with impacted mandibular third molar teeth were included in the study. The study drugs transdermal patches of fentanyl and ketoprofen was applied one hour before the surgical procedure on the skin, preferably in an area devoid of any hair. The selected mandibular third molar tooth of either of the side was extracted in the first appointment using an aseptic protocol. Every patient was given a Verbal Pain Intensity and Pain Relief chart (both 5- point scales with values 0-4) for assessing pain intensity and pain relief for all the three post-operative days. **Results:** During the first four hours of operative day, the difference observed between the two groups was not found to be statistically significant ($p=0.881$). Whereas during the first eight hours of operative day the difference observed between the two groups was not found to be statistically significant ($p=0.141$). During the first twelve hours of operative day, the difference observed between the two groups was not found to be statistically significant ($p=0.276$). At the end of operative day, the difference observed between the two groups was found to be statistically significant ($p=0.048$). **Conclusion:** Transdermal fentanyl patch was more effective for immediate pain relief than transdermal ketoprofen patch for pain control following removal of mandibular impacted third molars.

Keywords: Analgesia, Fentanyl, Ketoprofen, Mandibular Third Molar, Transdermal Patch.

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INTRODUCTION

Surgery results in damage to local tissue with consequent release of analgesic substances (prostaglandins, histamine, serotonin, bradykinin, 5-hydroxytryptamine, substance P) and generation of noxious stimuli that are transduced by nociceptors and transmission to the neuraxis by A delta and C nerve fibers.^[1]

Post-operative good analgesia improves the quality of life, reduces the morbidity and provides greater comfort, allowing for rapid recovery and early return of patients to daily routine. This may be achieved by use of non-steroidal anti-inflammatory drugs (NSAIDs), opioids, or a combination.^[2]

Some patients present with bilaterally similar impacted third molars provides an opportunity to

carry out two similar surgical procedures on separate occasions. So it is not surprising that the impacted third molar model has been widely used in clinical pharmacology to evaluate a variety of therapeutic measures.^[3]

A relatively new phenomenon, an adhesive skin patch has been formulated that delivers drug systemically. In addition, the drug when applied topically in the form of a transdermal patch, penetrates the skin, subcutaneous fatty tissue, muscle and finally into the blood stream in amounts sufficient to exert therapeutic effects without reaching higher plasma drug concentrations when compared to parenteral or intramuscular route.^[4,5]

NSAIDs and Opioids administered through skin patches include Diclofenac, Ketoprofen and fentanyl transdermal patch. Ketoprofen is a propionic acid derivative which has analgesic and antipyretic effects. Ketoprofen used in IM/IV and oral preparations by several authors for postoperative analgesia for moderate to severe postoperative pain. Ketoprofen transdermal patches in various doses have been found to be more effective in traumatic

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and nontraumatic patients without additional side effects.^[6]

The aim of this comparative pilot study is to assess the efficacy of transdermal fentanyl patch vs Ketoprofen patch in managing postoperative pain after third molar surgery.

MATERIALS & METHODS

Total 7 patients aged 18-65 years with impacted mandibular third molar teeth reporting to the outpatient section of Department of Oral and Maxillofacial Surgery, Army College of Dental Sciences, Secunderabad were selected for the study. The study period was from January 2017 to September 2018. The ethical clearance was obtained from the Institutional Ethics committee of Army college of Dental Sciences. A written informed consent was obtained from all the patients.

Inclusion criteria

1. Patients with bilateral partially impacted mandibular third molars
2. Bilateral symmetrical / similar partially impacted third molar
3. Symptomatic and asymptomatic patients

Exclusion criteria

1. Patients with history of NSAIDS allergy.
2. Patients with active peptic ulcer within 6 months.
3. Patients with systemic diseases like bronchial asthma, epilepsy, psychological disease.
4. Bilateral asymmetrical partially impacted third molar.
5. Pregnant patients.
6. Extreme age patients (<18 years to >65 years).

Parameters evaluated

1. Pain intensity recorded using 5 point verbal pain intensity score chart.
2. 5 point pain relief score chart.
3. Adverse drug reactions- Local irritation, gastric irritation, euphoria, dysphoria
4. Need for additional analgesic(number of patients who had taken rescue analgesic as soon as pain reached a moderate level)
5. Time elapsed until pain perceived

Categories:

1. Drug A: Fentanyl transdermal patch 25mcg (FENSTUD PATCH)
2. Drug B: Ketoprofen transdermal patch 20mg (KETOPLAST).

Methodology:

The selected patients were double blind randomized using a paired sample clinical trial for this study. Study drug and the surgical site was chosen randomly. The study drug was applied one hour before the surgical procedure on the skin, preferably in an area devoid of any hair [Figure 1 and 2].



Fig 1: Transdermal Ketoprofen Patch



Fig 2: Transdermal Fentanyl Patch

The selected mandibular third molar tooth of either of the side was extracted in the first appointment using an aseptic protocol. Standardization of the study was maintained by either removing both the teeth in the same patient in toto or both the teeth were sectioned and removed. Post-operative antibiotics were prescribed to all the patients.

Every patient was given a Verbal Pain Intensity and Pain Relief chart (both 5- point scales with values 0-4) for assessing pain intensity and pain relief for all the three post-operative days. On each of the following two days, the patch was replaced by a new one, thus a total of three patches were placed over the first operative day, 1st and 2nd postoperative days for ketoprofen and for fentanyl there is no need of replacement as its duration of action is for 72 hours. Each successive application of the

transdermal patch was made on a different hairless skin area. Paracetamol 650 mg tablets were permitted to be used as rescue medication and a total of ten tablets were provided to each patient for three days post operatively. The patients were asked to assign scores for each parameter at intervals of 2 hours, 4, 8, 12 and 24 hours postoperatively.

The subjects were asked to report the intensity and pain relief on the verbal pain score chart for the First operative day, 1st and 2nd postoperative days, following which they were asked to submit the 5-point pain intensity scale chart and the 5-point pain relief scale chart for evaluation. The rescue medication tablets taken, if any, were noted and the patients were asked if they experienced any adverse effects such as gastric discomfort, nausea, vomiting, gastric acidity or burning sensation euphoria/dysphoria and dyspepsia, diarrhea, dizziness, pruritis etc on all post-operative days. The same procedure was done on the contralateral side by the same operator.

Methods of Statistical Analysis:

The collected data was analyzed using Statistical package for Social Sciences (SPSS for Windows, version 20.0; IBM Corp, Chicago, IL, USA). The normality of the data was evaluated using Shapiro-Wilk test and the data was found to be normal ($p > 0.05$). Categorical variables were analyzed by chi-square test and quantitative data comparison was carried out using independent t-test. P values < 0.05 were considered to be statistically significant.

RESULTS

Among the seven study subjects, two (28.6%) of them belonged to 18-25 years age group and the remaining five (71.4%) subjects belonged to 26-35 years age group. During the first two hours of operative day, the difference observed between the two groups was not found to be statistically significant ($p = 0.112$).

During the first four hours of operative day, the difference observed between the two groups was not found to be statistically significant ($p = 0.881$). Whereas during the first eight hours of operative day the difference observed between the two groups was not found to be statistically significant ($p = 0.141$). During the first twelve hours of operative day, the difference observed between the two groups was not found to be statistically significant ($p = 0.276$). At the end of operative day, the difference observed between the two groups was found to be statistically significant ($p = 0.048$).

During the first two hours of post-operative day one, the difference observed between the two groups was found to be statistically significant ($p = 0.020$). During the first four hours of post-operative day one, the difference observed between the two groups was

not found to be statistically significant ($p = 0.842$). During the first eight hours of post-operative day one, the difference observed between the two groups was not found to be statistically significant ($p = 0.280$). During the first twelve hours of post-operative day one, the difference observed between the two groups was not found to be statistically significant ($p = 0.223$). At the end of post-operative day one the difference observed between the two groups was not found to be statistically significant ($p = 0.213$).

During the first two hours of post-operative day two, the difference observed between the two groups was not found to be statistically significant ($p = 0.287$). During the first four hours of post-operative day two, the difference observed between the two groups was not found to be statistically significant ($p = 0.270$). During the first eight hours of post-operative day two, the difference observed between the two groups was not found to be statistically significant ($p = 0.299$). During the first twelve hours of post-operative day two, the difference observed between the two groups was not found to be statistically significant ($p = 0.299$). At the end of post-operative day two, the difference observed between the two groups was not found to be statistically significant ($p = 0.311$).

Table 1: Summary of pain relief scores on post-operative day one

Time	Pain relief score	Test Drug		P value
		Fentanyl N (%)	Ketoprofen N (%)	
2 hours	A little	0 (0)	7 (100)	0.049
	Some	0 (0)	0 (0)	
	A lot	3 (42.8)	0 (0)	
	Complete	4 (57.2)	0 (0)	
4 hours	Some	0 (0)	1 (14.2)	0.574
	A lot	2 (28.6)	2 (28.6)	
	Complete	5 (71.4)	4 (57.2)	
8 hours	A little	2 (28.6)	1 (14.2)	0.613
	Some	1 (14.3)	2 (28.6)	
	A lot	1 (14.3)	0 (0)	
	Complete	3 (42.8)	4 (57.2)	
12 hours	None	0 (0)	1 (14.3)	0.261
	Some	0 (0)	2 (28.6)	
	A lot	1 (14.2)	1 (14.3)	
24 hours	Some	0 (0)	1 (14.2)	0.213
	A lot	2 (28.6)	0 (0)	
	Complete	5 (71.4)	6 (85.8)	

During the first two hours of operative day, the difference observed between the two groups was found to be statistically significant ($p = 0.041$). During the first four hours of operative day, the difference observed between the two groups was not found to be statistically significant ($p = 0.630$). During the first eight hours of operative day, the difference observed between the two groups was not found to be statistically significant ($p = 0.675$). During the first twelve hours of operative day, the difference observed between the two groups was not

found to be statistically significant ($p=0.475$). At the of operative day, the difference observed between the two groups was not found to be statistically significant ($p=0.368$).

Summary of pain relief scores on post-operative day one is showed in [Table 1].

Summary of pain relief scores on the post-operative day two is shown in [Table 2].

Table 2: Summary of pain relief scores on the post-operative day two

Time	Pain relief score	Test Drug		P value
		Fentanyl N (%)	Ketoprofen N (%)	
2 hours	A little	0 (0)	2 (28.6)	0.370
	Some	1 (14.2)	0 (0)	
	A lot	4 (57.2)	3 (42.8)	
	Complete	2 (28.6)	2 (28.6)	
4 hours	None	0 (0)	1 (14.2)	0.574
	Some	1 (14.2)	2 (28.6)	
	A lot	2 (28.6)	4 (57.2)	
	Complete	4 (57.2)	0 (0)	
8 hours	A little	2 (28.6)	0 (0)	0.127
	Complete	5 (71.4)	7 (100)	
12 hours	A lot	0 (0)	1 (14.2)	0.299
	Complete	7 (100)	6 (85.8)	
24 hours	Some	0 (0)	1 (14.3)	0.311
	A lot	0 (0)	1 (14.3)	
	Complete	7 (100)	5 (71.4)	

Adverse effects:

None of the subjects who received either transdermal Fentanyl patch or Ketoprofen patch had gastric irritation, local irritation or allergy up to post-operative three days. None of the subjects in the two groups had euphoria till post-operative two days [Table 3].

Table 3: Adverse effects reported by the subjects on post-operative day two

Characteristic	Category	Test Drugs		P value
		Fentanyl N(%)	Ketoprofen N(%)	
Euphoria	Present	1 (14.2)	0 (0)	0.299
	Absent	6 (85.8)	7 (100)	

Subtle difference was observed between the two groups and it was found to be statistically insignificant ($p=0.299$: [Table 4]).

Table 4: Comparison of mean elapsed time to pain perceived in two groups (in minutes)

Group	Elapsed time Mean $\pm$ SD	P value
Fentanyl	247.5 $\pm$ 10.6	0.213
Ketoprofen	308.5 $\pm$ 202.2	

The difference observed between two groups was not found to be statistically significant ($p=0.017$).

DISCUSSION

The present study was conducted to evaluate efficacy of transdermal fentanyl over ketoprofen patch after third molar surgery in patients with

bilaterally symmetrical/similar impacted mandibular third molars. Such patients provide an opportunity to carry out two similar surgical procedures on separate occasions. They can thus act as their own controls in crossover trials or evaluate different treatments in a 'split mouth' study when similar bilateral extractions are performed at the same visit.^[2,3]

High incidence/probability of mesioangular lower third molar impaction, the age group most commonly involved was 15–30 years, left side was more common with female predominance and recurrent pericoronitis was observed as the most common reason the distribution comparatively more in favor of females which is explained by Hellman's theory, that the jaws of females stop growing when the third molars just begin to erupt, whereas in males the growth of the jaws continues beyond the time of eruption of third molar resulting in decreased incidence in males compared to females.^[7]

However in our study we found that males are predominant with 57.1%, this finding is not in accordance with Hellmans theory and dominant age group is ranging from 26-35 years which is around 71.4% and in agreement with studies conducted earlier, This can be explained by more no of males reporting to the hospitals, females staying back at home due to cultural and social customs There is general consensus that the main factor for impaction of mandibular third molar is lack of space for eruption, the way in which shortage arises has been explained in various ways.^[8]

In a study done by Velasquez GC et al, they evaluated the pre-emptive analgesic effect of intramuscular ketoprofen (100 mg) with i.m. diclofenac (75 mg) after mandibular third molar surgery. Results showed that patients with ketoprofen had lower pain intensity scores as compared to diclofenac group.^[9] Sarzi-Puttini P et al also observed in their meta-analysis that orally administered ketoprofen (50-200 mg/day) relieved moderate to severe pain and improved functional status and general condition better than diclofenac (75- 150 mg/day).^[10]

The side effect of opioids is in the central nervous system, Opioids could produce analgesia, euphoria and dysphoria (at doses greater than those used for analgesia), respiratory depression, sedation, miosis, cough suppression, and nausea. Peripherally in high doses, may also act on the gastrointestinal tract causing constipation and biliary constriction. In the cardiovascular system they can cause hypotension and in smooth muscle it is observed an antidiuretic effect and bronchoconstriction.^[11]

Verma et al have assessed the efficacy of ketoprofen patch for postoperative analgesia in lower limb orthopaedic surgery and compared it with diclofenac patch. Although the usual dose of ketoprofen used in various studies through various routes varied from 20 to 150 mg for post-operative analgesia, they used commercially available 20 mg ketoprofen patch.

When they compared this dose of ketoprofen with 100 mg diclofenac patch, ketoprofen was found to be better.^[6]

Vladimir S Todorvic et.al have assessed the efficacy of fentanyl transdermal patch in third molar surgery concluding that transdermal system with fentanyl significantly reduced postoperative pain after third molar surgery.^[12]

The mean PIS recorded by the patients was more for fentanyl patch than for ketoprofen patch. On the operative day, 2 hours after the completion of procedure patients had less intense pain with fentanyl patch than ketoprofen patch. Ketoprofen started showing reduction of pain from the 4th hour onwards. At the end of day four patients from both the groups showed no pain, where as three patients from fentanyl group experienced very mild pain and three patients from ketoprofen group experienced mild pain explaining statistically significant difference in efficacy of fentanyl over ketoprofen patch.

On the first post-operative day, a new ketoprofen patch given to the patients, where as in fentanyl group same patch was continued. Patients had less intense pain with Fentanyl patch in its 26th hour in comparison to ketoprofen patch in its first 2 hours. In the 8th hr of first post-operative day one patient with ketoprofen patch presented with moderate pain intensity, where as none of the patients who received fentanyl reported moderate pain intensity throughout the day explaining its efficacy. Five patients from the fentanyl group and six patients from ketoprofen group experienced no pain at the end of the day.

On second post-operative day, a new ketoprofen patch given to the patients, where as in fentanyl group same patch was continued. Two patients from both the groups on 2nd post-operative day experienced no pain at all in first 2 hrs of ketoprofen patch and 50th hr of fentanyl patch. At the end of the day all the 7 patients from fentanyl group and 5 patients from ketoprofen group experienced no pain at all. The mean PRS recorded by the patients was more for Fentanyl patch than for Ketoprofen patch.

The time elapsed until pain perceived was also calculated. Out of all the seven patients, two patients from the fentanyl group experienced moderate pain after 4hrs. Whereas in ketoprofen group all the patients experienced moderate intensity of pain at some point of time. On statistical analysis mean time elapsed until pain perceived for fentanyl was 247 ± 10.6 in min (for 2 patients) and for ketoprofen it was 308.5 ± 202.2 in min (for 7 patients). This result is in similitude with the Vladimir S todorvic et.al study of efficacy of transdermal fentanyl patch in mandibular third molar surgery, where the mean time elapsed until pain perceived for fentanyl is 4 ± 0 in hrs which is around 240 min and for diclofenac group it is 7.7 ± 4.3 in hrs. Other parameters that were evaluated in the study were gastric discomfort, local irritation and

anaphylaxis, euphoria/dysphoria. None of the patients presented with any of those adverse effects until postoperative day two. One of the patients presented with euphoria on 2nd postoperative day three with Fentanyl patch, but this difference is not statistically significant.

These transdermal patches can be safely given to patients especially those suffering from peptic ulcers. Additionally Drug bioavailability is better with transdermal system as first pass metabolism is avoided. Serious complications associated with Oral NSAIDS such as hepatotoxicity and acute renal failure could be avoided. Moreover, the fact that these patches are cost-effective and do not require oral intake of any medication makes the patients more compliant towards them.

Limitations of the study:

The sample size of the study was very small and as a result, the observations cannot be generalized for large population. This study was a patient-dependent study where the results were based on the subjective score values recorded by the patients. Thus, participant's bias could not be eliminated from the study.

Further studies incorporating more number of participants and comparing other pharmacological agents can be carried out in future.

CONCLUSION

Transdermal fentanyl patch was more effective for immediate pain relief than transdermal ketoprofen patch for pain control following removal of mandibular impacted third molars. Because of longer duration of action of transdermal fentanyl patch, there is no need to change to the patch repeatedly which increased the patient compliance. Transdermal patches can be given as an effective alternative to oral medications as they minimise the systemic side effects.

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