Innovations

"Comparative Analysis of Analgesic Efficacy Between Ketoprofen Transdermal Delivery and Oral Administration in Postoperative Pain Management Following Multiple Premolar Extractions in Orthodontic Patients: A Randomized Crossover Study"

Dr.Vinod Thangaswamy.S (MDS)
Professor, Department of Oral and Maxillofacial Surgery,JKKN Dental College and Hospital

Dr.Rekha.M (MDS, DNB, MNAMS)
Professor and Head of the department, Department of Oral and Maxillofacial Surgery,JKKN Dental College and Hospital.

Dr.Vijay Thiyagarajan.J (MDS)
Reader, Department of Oral and Maxillofacial Surgery, JKKN Dental College and Hospital

Dr.Venkatesh Praveen. M (MDS)
Senior Lecturer, Department of Oral and Maxillofacial Surgery,JKKN Dental College and Hospital

Dr.Roshini (BDS)
Under Graduate student,JKKN Dental college and Hospital.

CorrespondingAuthor: **Dr.VinodThangaswamy.S**

Abstract

Background:

Orthodontic interventions frequently necessitate therapeutic extraction of premolars to achieve optimal dental occlusion. Adequate management of post-operative analgesia is crucial for patient comfort and adherence to orthodontic treatment protocols. Nonsteroidal anti-inflammatory drugs (NSAIDs) such as ketoprofen are routinely employed for analgesia following these procedures. However, a comprehensive comparison of the efficacy and safety of different ketoprofen delivery systems—oral capsules versus transdermal patches—remains limited. ***Objective:*** *To systematically evaluate and compare the analgesic efficacy of*

oral ketoprofen capsules versus transdermal ketoprofen patches in a cohort of orthodontic patients undergoing multiple premolar extractions. Additionally, the study aims to assess patient compliance and document any adverse events associated with each therapeutic modality. ***Methods:*** *This study will employ a randomized, crossover design involving orthodontic patients scheduled for therapeutic premolar extractions. Participants will be randomly assigned to receive either oral ketoprofen capsules or transdermal ketoprofen patches during one treatment phase, followed by a washout period, and then crossover to the alternate treatment. Pain intensity will be quantified using validated pain assessment scales, and patient adherence will be evaluated through self-reported compliance measures. Adverse events will be systematically recorded and analysed.* ***Results:*** *The primary endpoint will be the comparative assessment of analgesic efficacy between the two ketoprofen delivery methods, as determined by changes in pain scores. Secondary endpoints will include rates of patient compliance and the frequency and severity of adverse effects.Statistical analysis of pain relief scores and pain intensity scores demonstrated similar trends for both oral ketoprofen capsules and transdermal ketoprofen patches. Over the three postoperative days following extraction of premolars in all four quadrants, there was a gradual increase in pain relief scores and a gradual decrease in pain intensity scores observed with both formulations.* ***Conclusion:*** *This investigation aims to elucidate the relative therapeutic benefits and safety profiles of oral versus transdermal ketoprofen in the context of post-operative pain management in orthodontic patients. The findings of this study suggest that both oral ketoprofen capsules and transdermal ketoprofen patches provide effective analgesia following orthodontic extractions. However, patients reported greater comfort and satisfaction with the transdermal patch due to its oncedaily application over three days,compared to the more frequent dosing regimen of oral capsules. Furthermore, the transdermal patch showed advantages in terms of better patient compliance, fewer systemicadverse effects, and reduced incidence of gastric discomfort and burning sensation.*

Keywords: *Orthodontics, Premolar Extraction, Ketoprofen, Oral Administration, Transdermal Delivery, Post-Operative Analgesia, Randomized Crossover Trial*

Introduction

Orthodontic treatments often necessitate therapeutic extractions of premolars to facilitate proper alignment of teeth. Post-operative pain management is crucial for patient comfort and adherence to the treatment plan. Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly employed to manage such pain due to their efficacy in reducing inflammation and pain. Among these, ketoprofen, a well-known NSAID, has been used both orally and transdermally to alleviate post-operative discomfort.

Recent studies have explored the efficacy of transdermal ketoprofen compared to other analgesic modalities. For instance, a study by Pandey et al. (2023)

demonstrated that transdermal ketoprofen patches could be as effective as diclofenac patches for postoperative pain management in orthodontic extractions, providing a viable alternative to traditional oral NSAIDs[1]. Similarly, Sharma et al. (2022) investigated the pre-emptive analgesic effects of single-dose transdermal ketoprofen and diclofenac patches for managing postoperative pain following mandibular fracture treatments, highlighting the benefits of transdermal administration in reducing pain effectively[2].

In another clinical trial, Zadsirjan et al. (2023) compared ketoprofen transdermal patches with ibuprofen oral tablets in managing postendodontic pain. Their findings suggested that ketoprofen patches provided comparable or superior pain relief compared to ibuprofen tablets, further supporting the efficacy of transdermal ketoprofen for managing acute pain[3]. Additionally, Porwal et al. (2023) conducted a randomized clinical trial assessing the efficacy of ketoprofen and diclofenac transdermal patches against oral diclofenac tablets in postoperative endodontic pain. This study reinforced the potential of transdermal NSAIDs as effective analgesics for post-surgical pain management[4].

Furthermore, Bhargava et al. (2019) highlighted the efficacy of transdermal ketoprofen and diclofenac patches in patients undergoing therapeutic extractions, emphasizing their role in providing targeted pain relief without the systemic side effects commonly associated with oral NSAIDs[5].

This study aims to further investigate and compare the efficacy of oral ketoprofen capsules versus transdermal ketoprofen patches for postoperative analgesia following multiple premolar extractions in orthodontic patients. By assessing both pain relief and patient compliance, this research seeks to provide additional insights into optimizing pain management strategies in orthodontic practice.

Materials and Methods:

StudyDesign

This investigation utilized a within-subject, randomized, cross-over design to systematically assess and compare postoperative analgesia, adverse events, patient tolerability, and compliance betweentransdermal ketoprofen patches with oral ketoprofen capsules. The study was conducted on young orthodontic patients requiring therapeutic extraction of premolars in all four quadrants. Each participant served as their own control, receiving both treatment modalities in separate phases of the study to minimize variability and enhance the reliability of the results.

Participants

A total of 25 young orthodontic patients were recruited for the study. The following criteria were applied for participant selection:

Inclusion Criteria:

- **Age**: Patients aged between 12 and 18 years.

- **Orthodontic Need**: Indication for pre-orthodontic therapeutic extraction of premolars in both maxillary and mandibular quadrants.
- **Health Status**: No significant medical conditions that would contraindicate the use of NSAIDs or affect the study outcomes.
- **Informed Consent**: Ability to provide informed consent (or assent, with parental consent for minors) and adhere to the study protocol.

Exclusion Criteria:

- **Contraindications**: History of gastrointestinal disorders, renal impairment, or other conditions contraindicating NSAID use.
- **Allergies**: Known hypersensitivity or adverse reactions to ketoprofen or any components of the study medications.
- **Non-Compliance**: Inability or unwillingness to comply with the study protocol, including adherence to prescribed treatment regimens and follow-up requirements.
- **Concurrent Medications**: Use of other analgesic or anti-inflammatory medications that could interfere with the study outcomes.

StudyProcedure:

- **Ethical clearance** for the study was provided by an approved ethical committee, and all subjects were informed about the study and potential side effects, with written informed consent obtained.
- To avoid operator-induced bias, all Premolar extractions were performed by the same operator.
- **Initial Extraction Phase:** In the first phase, left maxillary(Figure 1) and mandibular(Figure 2) premolars were extracted under local anaesthesia. Following these extractions, a 30 mg transdermal ketoprofen patch was applied. The patch was changed daily for three consecutive post-operative days.The transdermal ketoprofen patch (Ketoplast) is a flat, transparent matrix-controlled system(Figure6) that provides continuous and systemic release of ketoprofen. It was applied to a dry, flat, hairless skin area, such as the upper arm(Figure7), upper chest, or lower abdomen. Each 10x7 cm patch contains 30 mg of ketoprofen IP as its active ingredient(Figure 5)The patch features a polymer matrix that controls drug release and an impermeable backing membrane to prevent drug leaching. It delivers a slow,sustained release of ketoprofen,ensuring long-term effectiveness and convenience.
- **Subsequent Extraction Phase:** After an adequate recovery period from the initial extraction, right maxillary and mandibular premolars were extracted. During this phase, patients were prescribed oral ketoprofen capsules (50 mg) to be taken four times daily for three consecutive post-operative days.

Outcome Measures

- **Pain Intensity:** Pain intensity was assessed using the Wong-Baker FACES Pain Rating Scale, where patients selected a facial expression that best represented their level of pain. The scale ranges from 0 (no pain) to 10 (worst possible pain). Patients completed this assessment daily for three days following each extraction.
- **Pain Relief:** Pain relief was evaluated using the Verbal Pain Relief Scale, where patients described their pain relief on a scale from 0 to 4, with 0 indicating no relief and 4 indicating complete relief. Daily ratings were recorded for three days following each extraction
- **Patient Adherence**: Adherence to the prescribed treatment regimen was evaluated through self-reported compliance measures. Patients reported their adherence to the application of the transdermal patches and the oral medication schedule, which was monitored and recorded daily for the duration of each treatment phase.

The data were then evaluated and tabulated.

Results:

Patients were monitored for three days postoperatively to assess pain intensity and relief through a standardized questionnaire. Pain levels and relief were evaluated using the Wong-Baker FACES Pain Rating Scale (Figure3)and the Verbal Pain Relief Scale(Figure4). In cases of severe pain, paracetamol 750 mg tablets were planned to be administered as a rescue medication although none of the patients in the study required it.

Patients were also assessed for any adverse effects, such as nausea, vomiting, gastric acidity, or burning sensations. The frequency and severity of these adverse effects were systematically recorded to determine the safety and tolerability of the treatments.

The data collected from the subjects were evaluated using the statistically significant Mann-Whitney U test (table 3).

Observations

1. **Pain Intensity Scores**
    - A gradual reduction in pain intensity scores(table 1) was observed from day one to day three following orthodontic therapeutic premolar extractions.
    - Both transdermal ketoprofen patches and oral ketoprofen capsules demonstrated a significant decrease in pain intensity over the three-day assessment period(graph 1).

2. **Pain Relief**
    - By the third day of treatment, all patients reported either complete or near-complete pain relief with both transdermal ketoprofen patches and oral ketoprofen capsules.
    - There was a modest but consistent increase in pain relief scores(table 2) throughout the postoperative days for both treatment modalities(graph 2).
    - Notably, no additional analgesia was required with the ketoprofen patch.

3. **Side Effects**
    - Five patients using oral ketoprofen capsules (50 mg) reported adverse effects including gastric acidity and a burning sensation.
    - Two patients utilizing the transdermal ketoprofen patch experienced mild rashes and pruritus.

Discussion

Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely utilized as analgesic agents for postoperative dental pain, primarily exerting their effects through the inhibition of cyclooxygenases COX-1 and COX-2, which are critical enzymes in the biosynthesis of prostaglandins. While oral NSAIDs are effective, they are associated with various adverse effects and significant drug loss due to first-pass metabolism. This limitation has led to the exploration of innovative delivery systems, such as transdermal NSAIDs, which offer a promising alternative. Transdermal systems facilitate drug permeation through the skin and diffusion into the capillary system, achieving more consistent serum drug levels—a key therapeutic objective.

Our study indicates that patients using the transdermal ketoprofen patch achieved comparable reductions in pain intensity scores to those using oral ketoprofen capsules. The transdermal delivery system demonstrated advantages over oral administration in terms of patient compliance and drug delivery efficiency.

Previous research supports the efficacy of topical NSAIDs in managing acute pain conditions. For instance, a systematic review by Mason et al. (2023) validated the effectiveness of topical NSAIDs in pain relief in the UK context. Additionally, studies have documented the successful application of ketoprofen patches for treating endodontic pain (Mason et al., 2023) (Dove Medical Press),in lower limb orthopaedic surgery (Reetu Verma et al, 2016)(MSJ Online)(Kawai et al., 2010). Ketoprofen, similar to diclofenac, inhibits both COX-1 and COX-2 enzymes, disrupting the synthesis ofprostanoids, including prostaglandins (PGE2, PGD2, PGF2), prostacyclin (PGI2), and thromboxane (TXA2) Prostaglandin E2 (PGE2), a predominantprostanoidin inflammation, is a primary target for NSAIDs, contributing significantly to their analgesic and anti-inflammatory effects.

Beyond COX inhibition, ketoprofen also affects the lipoxygenase pathway in the arachidonic acid cascade, reducing leukotriene synthesis (Esparza et al., 2007). It further inhibits bradykinin and stabilizes lysosomal membranes, thereby minimizing the release of lysosomal enzymes and reducing inflammatory responses. Ketoprofen's robust anti-inflammatory activity extends to conditions such as rheumatoid arthritis (Kawai et al., 2010).

Supporting this, Metry et al. (2022) demonstrated that transdermal ketoprofen patches are effective and safe for managing pain during venous cannulation. Additionally, ketoprofen lysine salt has shown substantial efficacy in controlling inflammation in rheumatoid arthritis patients. This formulation rapidly crosses the blood-brain barrier, inhibiting prostaglandin synthesis centrally and in joint spaces (Esparza et al., 2007) Notably, ketoprofen lysine salt significantly improved tenderness and reduced synovial PGE2 levels more effectively than naproxen after one week of treatment (Kawai et al., 2010)

The transdermal patch offers consistent drug absorption across the dermis, maintaining steady serum drug levels. Pharmacokinetic studies suggest that transdermal delivery results in increased tissue concentrations with minimal systemic side effects, underscoring the clinical advantages of transdermal NSAID delivery. Notably, no additional analgesia was required with the ketoprofen patch, in contrast to the study by Bhargava et al. (2023), which noted a need for supplementary analgesia with the diclofenac patch (Verma et al., 2016)

Conclusion

Both ketoprofen capsules and transdermal ketoprofen patches present effective analgesic options for managing mild to moderate pain following dental extractions. The transdermal ketoprofen patch, in particular, offers advantages such as improved drug delivery and a lower incidence of systemic adverse effects, including gastrointestinal disturbances. The transdermal route's reduced frequency of administration and minimized gastrointestinal side effects make it a promising alternative to oral NSAIDs.

The superiority of transdermal ketoprofen over oral administration is supported by studies indicating better pain control and reduced need for rescue medication (Esparza et al., 2007). Moreover, transdermal patches provide sustained release and stable serum drug levels, which are crucial for consistent pain management (Kawai et al., 2010). However, further research with larger sample sizes and longer study durations is necessary to comprehensively evaluate the efficacy and safety of transdermal ketoprofen patches, not only for dental extractions but also for other minor surgical procedures where anti-inflammatory and postoperative analgesic effects are required (Verma et al., 2016).

Based on these results, the ketoprofen transdermal patch emerges as a viable option for routine post-extraction analgesia in orthodontic practice. Its ability to provide potent analgesia comparable to oral ketoprofen capsules,coupled with enhanced patient comfort and reduced side effects, supports its consideration as

a preferred choice for managing postoperative pain in orthodontic patients undergoing premolar extractions. Future research could explore broader applications and long-term outcomes to further validate these findings and optimize pain management strategies in dental and orthodontic settings.

References

1. *Pandey K, Shettar V, Kale T (2023). Efficacy of transdermal ketoprofen patch in comparison to transdermal diclofenac patch in postoperative analgesia for orthodontic extractions: A randomized split-mouth study. Cureus.* ***15****(4).*
2. *Zadsirjan S, Toghrolian A, Zargar N (2023). Analgesic efficacy of ketoprofen transdermal patch versus ibuprofen oral tablet on postendodontic pain in patients with irreversible pulpitis: A randomized clinical trial. Pain Res Manag.* ***2023****:8549655.*
3. *Porwal P, Shah N, Singh Rao A, Jain I, Maniangat Luke A, Shetty KP, Reda R, Testarelli L, Pawar AM (2023). Comparative evaluation of efficacy of ketoprofen and diclofenac transdermal patches with oral diclofenac tablet on postoperative endodontic pain: A randomized clinical trial. Patient Prefer Adherence.* ***17****:2385-2393.*
4. *Bhargava D, Thomas S, Beena S (2019). Comparison between efficacy of transdermal ketoprofen and diclofenac patch in patients undergoing therapeutic extraction: A randomized prospective split-mouth study. J Oral Maxillofac Surg.* ***77****(10):1998-2003.*
5. *Sharma AA, Jadhav AA, Bhola ND, Gupta AA, Gupta CS (2022). Pre-emptive analgesic efficacy of single-dose transdermal ketoprofen and diclofenac patches in post-operative pain management following open treatment of mandibular fractures: A randomized controlled study. Cureus.* ***14****(8)*
6. *Mason L, Moore RA, Edwards JE, Derry S, McQuay HJ. Topical NSAIDs for acute pain: a meta-analysis. BMC FamPract. 2004 May 17;5:10.*
7. *Verma, R., Kumar, S., Goyal, A., & Chaudhary, A. (2016). Comparison of single dose transdermal patches of diclofenac and ketoprofen for postoperative analgesia in lower limb orthopaedic surgery. International Journal of Research in Medical Sciences, 4(3), 718–721.*
8. *Kawai S, Uchida E, Kondo M, Ohno S, Obata J, Nawata Y, Sugimoto K, Oribe M, Nagaya I. Efficacy and safety of ketoprofen patch in patients with rheumatoid arthritis: a randomized, double-blind, placebo-controlled study. J ClinPharmacol. 2010 Oct;50(10):1171-9.*
9. *Esparza F, Cobián C, Jiménez JF, García-Cota JJ, Sánchez C, Maestro A; Working group for the acute pain study of SETRADE. Topical ketoprofen TDS patch versus diclofenac gel: efficacy and tolerability in benign sport related soft-tissue injuries. Br J Sports Med. 2007 Mar;41(3):134-9.*
10. *Metry AA, Kamal MM, Ragaei MZ, Nakhla GM, Wahba RM. Transdermal Ketoprofen Patch in Comparison to Eutectic Mixture of Local*

AnestheticCream and Subcutaneous Lidocaine to Control Pain Due to Venous Cannulation. Anesth Essays Res. 2018 Oct-Dec;12(4):914-918.

11. *Bhargava D, Thomas S, Beena S. Comparison Between Efficacy of Transdermal Ketoprofen and Diclofenac Patch in Patients Undergoing Therapeutic Extraction-A Randomized Prospective Split Mouth Study. J Oral Maxillofac Surg. 2019 Oct;77(10):1998-2003.*

Figures:

Figure 1: The figure 1 shows thearmamentarium for maxillary premolar extraction

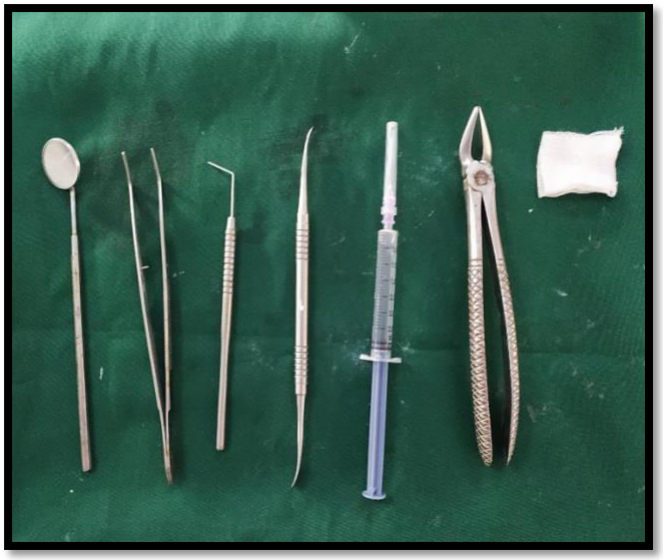


Figure2: The figure 2 shows the armamentarium for mandibular premolar extraction

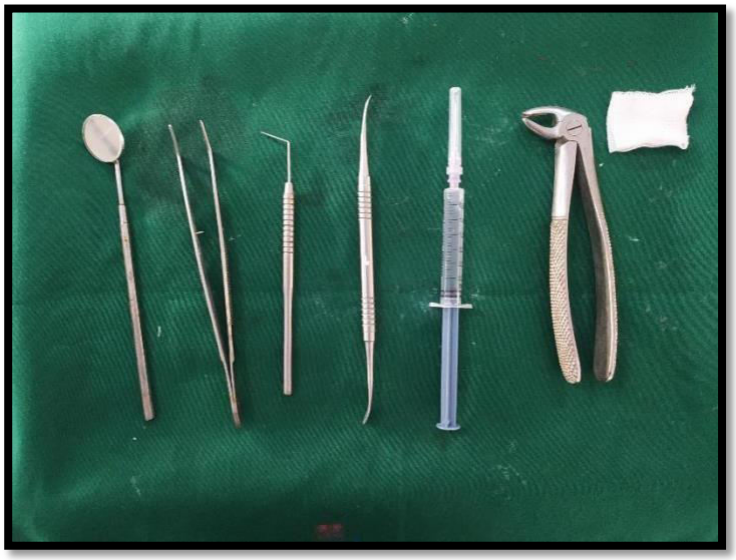


Figure3: The figure 3 shows the Wong Baker pain intensity scale used for pain intensity measurement

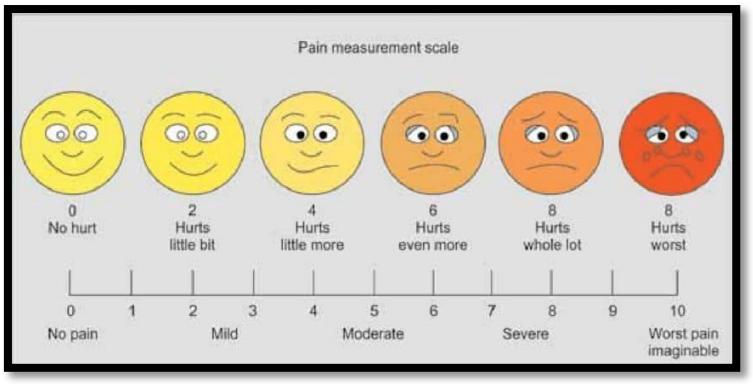


Figure4: The figure 4 shows the Verbal pain relief scale used for measuring pain relief.

0	None
1	A Little
2	Some
3	A Lot
4	Complete

Figure5: The figure 5 shows Transdermal ketoprofen patch 30mg

Figure6: The figure 6 shows Design ofmatrix- controlled delivery system

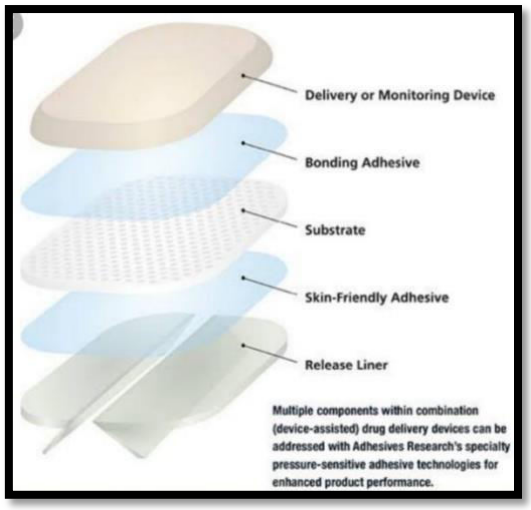


Figure7: The figure 7 shows Transdermal patch placed over upper arm

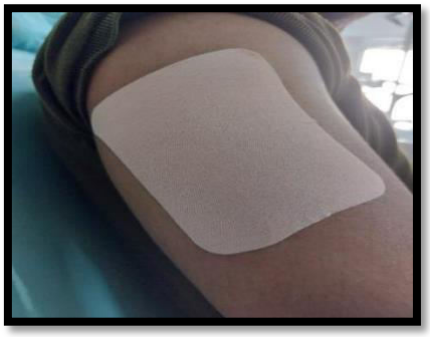


Table 1: The Table 1 shows tabulation of Painintensity Score:

	Transdermal			Oral		
	Day1	Day2	Day3	Day1	Day2	Day3
Mean	4.040	2.120	0.400	6.040	3.960	1.680
SD	1.135	0.832	0.500	1.240	0.675	0.852

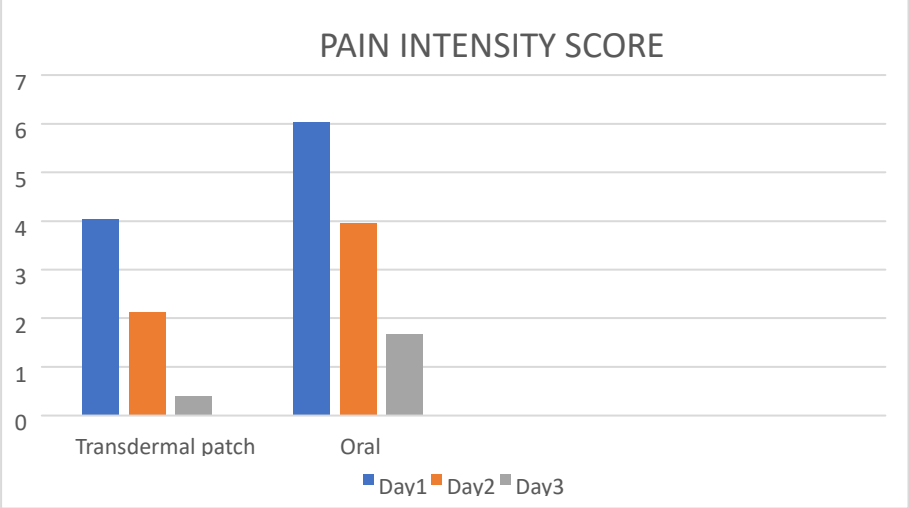
Table 2: The Table 2 shows tabulation of Painrelief Score:

	Transdermal			Oral		
	Day1	Day2	Day3	Day1	Day2	Day3
Mean	2.640	3.320	3.560	1.120	1.680	2.960
SD	0.637	0.556	0.583	0.781	0.556	0.611

Table 3: This table shows statistical analysis (Mann whitney u test values) for pain intensity and pain relief when comparing transdermal and oral ketoprofen formulations

	Pain Intensity			Pain Relief		
Mann Whitney	Day1	Day2	Day3	Day1	Day2	Day3
U value	0.912	1.027	0.994	1.007	1.048	1.117
P value	0.361	0.304	0.319	0.919	0.916	0.911

Graph 1: This graph shows Variation in mean intensity from day 1 to day 3



Graph 2: This graph shows variation in mean Pain relief from day 1 to day 3