"A COMPARATIVE EVALUATION OF TRANSDERMAL KETOPROFEN PATCH WITH ORAL KETOPROFEN FOLLOWING SURGICAL REMOVAL OF MANDIBULAR THIRD MOLAR"

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CONTENT

LIST OF ABBREVIATIONS

Sr no.	Abbreviation	Long form
1.	NICE	National Institute of Clinical Evidence
2.	NSAIDs	Non-steroidal anti-inflammatory drugs
3.	VAS	Visual analogue scale
4.	CAT	Categorical scale
5.	PID	Pain intensity difference
6.	SPID	Sum of Pain intensity difference
7.	TOTPAR	Total pain relief
8.	R- KETOPROFEN	Racemic ketoprofen
9.	SUMPI	Sum of pain intensity
10.	DOMS	Delayed onset muscle soreness
11.	Mg/ml	Milli gram/ Milli liter
12.	TDDS	Transdermal drug delivery system
13.	GIT	Gastrointestinal tract
14.	HS	Highly significant
15.	NS	Non significant / insignificant
16.	CHADD	controlled heat-assisted drug delivery
17.	COX- 1	Cyclo-oxygenase -1
18.	COX -2	Cyclo-oxygenase -2
19.	Hr/h	Hour
20.	TID	Ter in die(Latin) means thrice a day
21.	OD	Omne in die (Latin) means once a day

LIST OF FIGURES

LIST OF TABLES

LIST OF GRAPHS

LIST OF COLOUR PLATES

Introduction

Third molar surgery is one of the most common procedure that is performed by oral and maxillofacial surgeons worldwide. Pain, swelling, trismus are the most common complication after surgical removal of third molar.[1]

According to Archer "a tooth which is completely or partially unerupted and is positioned against another tooth, bone or soft tissue so that its further eruption is unlikely, described according to its anatomic position."[2] According to Kramer and Williams incident of impacted mandibular third molars is found to be 41.13% which is considered very high.[3]

According to National Institute of Clinical Evidence (NICE) indication for removal of impacted third molar includes pathology such as unrestorable caries,

nontreatable pulpal and/or periapical pathology, cellulitis, abscess and osteomyelitis, internal/external resorption of the tooth or adjacent teeth, fracture of tooth, disease of follicle including cyst/tumour.[4]

While treating dental patients, alleviating pain is of utmost importance as it is prevalent and has far-reaching implications, for both the patient and the clinician.[5] When the effects of the local anesthesia subsides, the postsurgical pain begins and reaches peak levels in 6 to 12 hours postoperatively. 37.7% patients reported mild pain on the third post-operative day and 43.4% patients had no pain on the seventh postoperative day.[6]The major cause of pain is thought to be the release of inflammatory mediators that activates sensory nocioceptors surrounding the tooth.[7]

Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most widely prescribed analgesics for management of post-operative pain in dental patients.[8]

However, the use of systemic NSAIDs can result in an increased risk of serious side effects, especially with regard to gastrointestinal, renal and cardiovascular systems[9.]

The use of topical NSAIDs preparations (foam, gel, patch, etc.) may remarkably reduce both intensity and frequency of such side effects, while the pharmacologic action of the active medication remains unaltered. Topical preparations combine the selective and rapid action at the site of application with a good degree of efficacy and limited or absent side effects.[10]

When choosing to administer an anti-inflammatory drug topically, the following considerations should be taken into account: the molecular weight of NSAIDs, the degree of lipophilia and the absorption-rate of active ingredients.

In the case of topical patch, account is also to be taken of the "technology of the transdermic system" in which the drug is placed and whence it spreads into the tissues. A low molecular weight is associated with an elevated transdermic absorption.

Amongst those NSAIDs commonly used, ketoprofen has a low molecular weight (260 dalton) as compared to diclophenac (325 dalton), piroxicam (330 dalton) and indomethacyn (350 dalton). As a result, ketoprofen is especially suited for preparations involving its transdermic molecular passage. In NSAIDs, highest cutaneous permeability is seen with ketoprofen. As a result, ketoprofen spreads through the skin far more quickly and intensely than other NSAIDs do since its percutaneous absorption takes place within 4 hours.[11]

Transdermal systems are an innovative delivery mechanism commonly replacing oral and other traditional routes of administration. The drug contained on the transdermal patch enters the body through the skin in contact with the patch. The drug diffuses across the layers of the skin and ultimately diffuses into the capillaries for systemic delivery.[12]

The ketoprofen patch consists of a micro-domain structure. The major adhesive polymer is realised by an anhydrous matrix made up of styrene-isoprenestyrene (SIS) block, which is an elastic and flexible material. The active

principle is dissolved into oil components and dispersed inside the polymer network. Such a structure adheres gently to the skin, keeps a high drug concentration inside the micro-domain and induces a strong thrust aimed at delivering the drug through the skin into the underlying body structures. Moreover, the supporting flexible and stretchable material of the patch is designed to fit all the body joints.

The development of a new ketoprofen patch appears to be a welcome progress for the therapy of all the inflammatory and rheumatic disorders as well as for a variety of traumatic lesions involving practically all the areas of the body, including the joints. In addition, the use of the ketoprofen patch represents the administration of choice for patients suffering from gastrointestinal disorders, since ulcerogenic effect induced by the patch is minimised as compared with that produced by oral administration of the active principle.[13]

This study is a new way to achieve more effective management after third molar surgeries with minimal occurrence of adverse effects.

Aim And Objectives

Aim of the Study

The aim of the study is comparatively evaluate the effectiveness of transdermal ketoprofen patch against oral ketoprofen for postoperative analgesia after surgical removal of mandibular third molars.

Objectives of the Study

1. To evaluate the effect of transdermal ketoprofen on pain reduction.
2. To evaluate the effect of transdermal ketoprofen on trismus alleviation.
3. To evaluate the effect of transdermal ketoprofen on reduction in swelling.
4. To compare the findings with those of ketoprofen tablets.

Review of Literature

"Those who do not learn from history are doomed to repeat it"

Pederson Anne (1985)[14] evaluated swelling, pain and trismus quantitatively after the removal of mandibular third molars on 30 healthy patients and concluded from the study that the longer the operation takes the more postoperative pain can be expected. However neither swelling nor trismus was correlated with the length of time operation. The size of swelling was not related to the degree of trismus or post-operative pain. A strong interrelation between post-operative pain and trismus indicates pain as the main reason for reduced mouth opening

Cooper S A (1988)[15] conducted three 6-hour double-blind, single-dose, placebo-controlled studies in which patients who had undergone dental impaction surgery took ketoprofen or a comparator drug are reviewed. In the first study, ketoprofen 25, 50,

and 100 mg was compared with aspirin 650 mg and placebo in 153 patients. In comparison with aspirin, significant ($P < 0.001$) differences favoring ketoprofen at each dose level were found for all measures of analgesic efficacy. For the combined ketoprofen groups, 60% of the patients rated treatment as very good or excellent, compared with 16% in the aspirin group. The second study compared ketoprofen 25, 50, and 100 mg with codeine 90 mg and placebo in 129 patients. Ketoprofen appeared to have a more rapid onset, higher peak effect, and longer duration of pain relief than codeine. At least 70% of patients in each of the ketoprofen groups rated the test medication as very good or excellent, compared with only 7% of the patients in the codeine group. The third study compared ketoprofen 25 and 100 mg with ibuprofen 400 mg and placebo in 161 patients. Ketoprofen 100 mg had a faster onset of effect, the highest peak effect, and the longest duration of action over the 6-hour evaluation. Ketoprofen treatment was not associated with any unusual or serious side effects in any of the three studies. These data suggest that ketoprofen is a safe and effective analgesic with a rapid onset and at least a 6-hour duration of action.

Troullos ES et al (1990)[16] compared two nonsteroidal anti-inflammatory drugs (NSAIDs), flurbiprofen and ibuprofen, with a prototype glucocorticoid, methylprednisolone, in two replicate placebo-controlled studies for suppression of inflammation due to the surgical removal of impacted third molars. The results indicate that NSAIDs produce greater initial analgesia than do steroids, whereas steroids result in greater suppression of swelling and less loss of function. Examination of the pooled data from the two studies indicates that NSAID pretreatment results in a modest suppression of swelling in comparison with placebo. Author concluded that the acute analgesic effects of NSAIDs in the oral surgery

model are due to suppression of a nociceptive process, presumably prostaglandin formation, rather than a generalized anti-inflammatory effect.

Willimann H et al (1992)[17] studied a composition useful in the delivery of pharmaceutically active agents through the skin. In one embodiment of the invention, the composition is formulated with a non- steroidal anti-inflammatory agent, such as ibuprofen or ketoprofen; a muscle relaxant, such as cyclobenzaprine; or other active ingredient .In another embodiment of the invention, the composition is formulated with an antineoplastic or other pharmaceutically-active agent. Such formulation is rapidly absorbed through the skin to provide local delivery.

Grahame R (1995)[18] studied transdermal non-steroidal anti-inflammatory agents and concluded that topical NSAIDs as an effective alternative to local steroid injection in cases of soft-tissue rheumatism, either where the injection is not acceptable to the patient or where the doctor has not acquired the necessary techniques. The safety profile of topical NSAIDs is good. Skin reactions are rare, and this apparently applies to all topical NSAIDs currently available. It is logical to treat a local pathological lesion with a local therapy, provided the agent is delivered effectively and sagely to the target organ or tissue. Where this can obviate the risk of life-threatening complications such as gastric hemorrhage, the case for substituting local for systemic medication is overwhelming.

Evans JM et al (1995)[19] evaluate the relation between topically applied non-steroidal anti-inflammatory drugs and upper gastrointestinal bleeding and perforation. A case-control study with 1103 patients admitted to hospital for upper gastrointestinal bleeding or perforation between was carried out. Two different control groups were

used, with six community controls and with two hospital controls for each case. Previous exposure to topical and oral non-steroidal anti-inflammatory drugs and ulcer healing drugs was assessed. Unadjusted and adjusted odds ratios of exposure in those admitted to hospital compared with controls. Significant unadjusted associations were detected between all three classes of drug and upper gastrointestinal complications. The significant association detected for topical non-steroidal anti-inflammatory drugs was no longer evident in analyses which adjusted for the confounding effect of concomitant exposure to oral anti-inflammatories and ulcer healing drugs (odds ratio = 1.45; 95% confidence interval 0.84 to 2.50 with community controls; 1.06; 0.60 to 1.88 with hospital controls). Author concluded that topical non-steroidal anti-inflammatory drugs were not significantly associated with upper gastrointestinal bleeding and perforation after adjustment for the confounding effects of concomitant use of oral anti-inflammatories and ulcer healing drugs.

Levin LM et al (1997)[20] evaluated the analgesic efficacy and safety of ketoprofen 12.5 mg in patients experiencing pain following the removal of impacted third molars. This study was single-dose, double-blind and randomized utilizing a 6-hour in-patient evaluation period. Patients ingested a single dose of ketoprofen 12.5 mg (n = 30), ketoprofen 37.5 mg (n = 32) or placebo (n = 15) when their post-surgical pain reached at least a moderate intensity on a 5-point categorical (CAT) scale and greater than 50 mm on a 100 mm visual analog scale (VAS). Measures of pain intensity and relief were gathered every 20 minutes for the first 2 hours, and then hourly from hours 3 through 6. Adverse drug reactions were also recorded as they occurred. Both dosages of ketoprofen were significantly more efficacious than placebo (two way ANOVAs, $p < 0.05$). For pain intensity difference (PID) and pain relief, the 12.5 mg dose

exhibited statistical superiority from hours 1 through 3, while the 37.5 mg dose exhibited statistical superiority from 40 minutes through 4 hours. Ketoprofen 37.5 mg was significantly more efficacious than the 12.5 mg dose only at 40 minutes for PID (VAS) and relief, and at 60 minutes for PID (VAS). Both ketoprofen dosages displayed significantly greater 3-hr, 4-hr and 6-hr summary analgesic measures (SPID (VAS), SPID(CAT), TOTPAR) than placebo, with the exception of the 6-hr SPID(CAT) measure for ketoprofen 12.5 mg. No serious side effects were observed in this study. We conclude that ketoprofen in a dose range of 12.5 mg to 37.5 mg is a safe and effective analgesic for the relief of post-operative dental pain.

Moore RA el al (1998)[21] reviewed the effectiveness and safety of topical non-steroidal anti-inflammatory drugs in acute and chronic pain conditions. 86 trials involving 10,160 patients were included in the study, In acute pain conditions (soft tissue trauma, strains, and sprains) placebo controlled trials had a relative benefit of 1.7 (1.5 to 1.9), the number needed to treat was 3.9 (3.4 to 4.4). With analysis by drug (at least three trials), ketoprofen (number needed to treat 2.6), felbinac (3.0), ibuprofen (3.5), and piroxicam (4.2) had significant efficacy. Benzydamine and indomethacin were no different from placebo. In chronic pain conditions (osteoarthritis, tendinitis) placebo controlled trials had a relative benefit of 2.0 (1.5 to 2.7); the number needed to treat was 3.1 (2.7 to 3.8). Small trials (< 40 treated patients) exaggerated effectiveness of topical non-steroidals by 33% in acute conditions but not in chronic conditions. There was no relation between trial quality and treatment effect. In both acute and chronic pain local and systemic adverse events and withdrawal from the study related to the drug had a low incidence and were no

different from placebo. Author concluded that topical non-steroidal anti-inflammatory drugs are effective in relieving pain in acute and chronic conditions.

Cooper SA et al (1998)[22] compared the analgesic efficacy and safety of single doses of (R)- ketoprofen 25 mg and 100 mg to that of acetaminophen 1,000 mg and placebo in 177 patients experiencing moderate to severe pain after surgical removal of their impacted third molars. Both (R)- ketoprofen 100 mg and acetaminophen 1,000 mg were significantly ($P < 0.05$) more efficacious than placebo for all summary analgesic measures. Other than a more rapid analgesic onset (45 minutes versus 60 minutes) for acetaminophen 1,000 mg, (R)- ketoprofen 100 mg and acetaminophen 1,000 mg were statistically equivalent to each other. The 25 mg dose of (R)- ketoprofen appeared to approach the analgesic threshold dose, being numerically but not statistically superior to placebo for all summary measures. There were no serious adverse events observed in this study, with the overall incidence of side effects being somewhat less in the (R)-ketoprofen groups than in the acetaminophen 1,000 mg group. (R)- Ketoprofen possesses analgesic activity and an acceptable side-effect profile in the oral surgery pain model.

Ong KS & Seymour RA (2002)[23] states that nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most widely used medications in the world.' Their introduction into clinical practice has improved dramatically the management of acute pain in dentistry. But , due to the widespread use of these drugs, there are concerns about NSAIDs-induced toxicity, which can be a significant health hazard.they also conclude that no drugs are without adverse effects or are perfectly safe, but their safe use in clinical practice would entail maximizing the therapeutic efficacy and

minimizing the adverse effects. An evidence-based approach is used in this review to analyze critically the evidence available about the safe use of NSAIDs in acute postoperative dental pain. The mandibular third molar surgical model is used for the analysis. This is a well-validated, well-documented, and highly sensitive model to assess therapeutic relief of moderate to severe pain by analgesics including NSAIDs.

McGrath C et al (2003)[24] evaluated the performances of patient-centred outcome measures after oral surgery in a prospective cohort study of 100 patients and showed that although minor in nature, pain, swelling and trismus are the most common postoperative complaints and influence the patient's quality of life in days following surgery.

Bjornsson GA et al (2003)[25] carried out a randomized, double-blind, within-patient, crossover study was after bilateral "identical" surgical procedures using local anesthesia only. A 3-day tablet regime of racemic ketoprofen 75 mg or acetaminophen 1000 mg qid (x 4) was given starting 3 hours after surgery. Ketoprofen reduced objectively measured swelling 27.8% ($p < 0.04$) better than acetaminophen 3 days after surgery and 70.8% ($p < 0.02$) better than acetaminophen 6 days after surgery. The pain intensity (PI) was lower after ketoprofen than after acetaminophen from 2 to 6 hours after the first drug intake (all p-values < or = 0.03). Sum PI during the first (SUMPI3.5-6, $p = 0.003$) and second dose intervals (SUMPI6.5-9, $p = 0.007$) was lower for ketoprofen than for acetaminophen but not different for the third dose interval (SUMPI9.5-11, $p = 0.53$). Ketoprofen was a more effective analgesic than acetaminophen on the day of surgery (SUMPI3.5-11, $p = 0.005$). There was no difference ($p > 0.05$) between the treatments with respect to

mouth opening, drug preference, global evaluation, or adverse reports. Adverse reports included stomach pain and diarrhoea in both treatment groups. Ketoprofen 75 mg x 4 for 3 days reduces subjectively assessed pain and objectively measured swelling (i.e., anti-inflammatory effect) following third-molar surgery.

Cannavino CR et al (2003)[26] determined the efficacy of transdermal ketoprofen in reducing delayed-onset muscle soreness (DOMS), limiting systemic absorption, and improving postexercise function following repetitive muscle contract. Thirty-two healthy males 18 to 35 years old are taken for double-blind, placebo-controlled clinical trial subjects performed a leg extension and flexion exercise program designed to create DOMS in quadriceps muscles. Subjects were randomly assigned to receive any combination of transdermal ketoprofen or placebo cream, applied TID, to their right and left quadriceps.Subjective measure of DOMS in quadriceps muscles, serum ketoprofen levels, strength index scores (a measure of postexercise function), and adverse reactions were assessed at baseline, 24 hours, and 48 hours.Within-subjects analysis (n = 16) showed a significant reduction in DOMS scores in legs receiving transdermal ketoprofen compared with legs receiving placebo cream (P = 0.002 at 48 hours and 0.000 at 24 and 48 hours combined). Between-subjects analysis (n = 16) showed a marginally significant reduction in DOMS scores at 48 hours (P = 0.05 in right legs and 0.053 in left legs). Systemic absorption was minimal, with serum ketoprofen levels in the ng/mL range. No differences in strength index scores were observed. No adverse reactions were reported. They concluded that transdermal ketoprofen appears to be effective in reducing self-reported DOMS after repetitive muscle contraction, particularly after 48 hours. Systemic absorption of the drug was

minimal. Treatment did not appear to have any effect on postexercise function, and there were no reported adverse reactions.

Mazières B (2005)[27] discussed the pharmacokinetics, efficacy and tolerability of a new formulation of ketoprofen available as a topical patch. The topical patch containing ketoprofen 100mg as the active principle has been developed using a novel delivery system that dispenses therapeutic doses of the drug directly to the site of injury. Pharmacokinetic data indicate that although plasma levels of ketoprofen are higher when the drug is administered as a patch versus a gel, the total systemic bioavailability of ketoprofen 100 mg administered via a patch is no more than 10% of that reported for ketoprofen 100 mg administered orally. Because the patch facilitates ketoprofen delivery over a 24-hour period, the drug remains continually present in the tissue subjacent to the site of application. High tissue but low plasma ketoprofen concentrations mean that while tissue concentrations are high enough to exert a therapeutic effect, plasma concentrations remain low enough to not result in systemic adverse events caused by elevated serum NSAID levels. Phase III clinical trials in patients with non-articular rheumatism and traumatic painful soft tissue injuries showed that the topical ketoprofen patch was significantly more effective than placebo at reducing pain during daily activities and spontaneous pain after 7 days' treatment. Moreover, the topical ketoprofen patch was well tolerated; adverse events were primarily cutaneous in nature and occurred in a similar number of ketoprofen and placebo recipients suggesting that these events were related to the patch itself rather than the active ingredient. The incidence of gastrointestinal adverse events was low (<8% of all patients), and occurred in a similar proportion of patients receiving

ketoprofen and placebo. Thus, the topical ketoprofen patch appears to be a simple, effective and safe therapeutic option for the treatment of local painful inflammation.

Jung et al (2005)[28] in contrast with previous studies, observed that analgesic effects of NSAIDs administered preoperatively were no more effective than when administered postoperatively for postoperative pain and recommended that scheduling postoperative analgesic dosing before development of pain is adequate for postoperative analgesia without preoperative administration in surgical extraction of third molars.

Agarwal A et al (2006)[29] evaluate the efficacy of a diclofenac transdermal patch placed over the venepuncture site in decreasing the pain of cannulation. Seventy-two adults undergone elective surgery were included in this randomised, prospective, double-blind, placebo-controlled study. Patients were divided into three equal groups. The Control group had a placebo adhesive patch placed on the both the dorsum of hand and the buttock; the Diclofenac-Buttock group had a placebo patch placed on the dorsum of the hand and a diclofenac transdermal patch on the buttock; the Diclofenac-Hand group had a diclofenac transdermal patch placed on the dorsum of hand and a placebo patch on the buttock. The patches were applied 1 h before cannulation. An 18G cannula was used for all venous cannulations. Pain during cannulation was assessed on a non-graduated 10-cm visual analogue scale. Median [interquartile range] pain scores were 3.0 [2.0–4.0] in the Diclofenac-Hand group, 5.0 [4.3–7.8] in the Diclofenac-Buttock group and 6.5 [4.5–7.0] in the Control group, $p < 0.05$. The numbers needed to treat were six and two in the Diclofenac-Buttock and

Diclofenac-Hand groups, respectively. Author concluded that application of a diclofenac transdermal patch at the cannulation site appears to be effective in decreasing cannulation pain.

Kim JC et al (2006)[30] carried out a study to ascertain the incidence of minor complications after mandibular third molar surgery. One hundred and four patients subjected to surgical extraction of horizontally impacted lower third molars were selected and investigated by means of questionnaires and clinical examinations. They concluded that reduced opening of mouth over 10 mm at 1st postoperative day was significantly associated with the degree of tooth impaction. However, the also reported few cases presenting limitations in mouth opening at 7th postoperative day.

Nusair YM (2007)[31] reported that any tissue injury causes an inflammatory response. A typical feature of this response is vasodilatation, which leads to an increased blood flow to the site of injury. This is followed by increased vascular permeability, which results in outpouring of protein rich fluid into the extravascular tissues, causing swelling at the site of injury. These changes take place early after the injury and last for a few days depending on its severity. Because postoperative edema is caused by the extravascular collection of fluid, it seems logical to expect the resultant swelling to extend equally in all directions in a ballooning fashion and become spherical. However, attachments of muscles and fascia, and displacement of swollen tissue by adjacent structures such as bone and teeth, are possibly the reasons why swelling extends in one direction more than another.

In an attempt to minimize the swelling, many oral and maxillofacial surgeons advise the patients to apply cold dressings to the affected side of the face during the first few hours of surgery.

However **Nusair YM** conducted a study to find out what effect the local application of ice bags had on facial swelling after oral operations in rabbits. He found that there was no statistically significant difference between the test and control sides 24 or 48 hours postoperatively.

Esparza F et al (2007)[32] compared the ketoprofen TDS patch with diclofenac gel in the treatment of traumatic acute pain in benign sport-related soft-tissue injuries. Patients aged 18–70 years diagnosed for painful benign sport-related soft-tissue injury (sprains, strains and contusions within the prior 48 h), randomised to either ketoprofen patch 100 mg once daily (n = 114) or diclofenac gel 2–4 g three times daily (n = 109).7–14 days of topical non-steroidal anti-inflammatory drugs treatment to assess the pain intensity changes (daily activities and spontaneous at rest) in a daily diary (100-mm Visual Analogue Scale (VAS)). They found that the ketoprofen patch was not inferior to diclofenac gel in reducing the baseline pain during daily activities (difference of –1.17 mm in favour of ketoprofen patch, 95% CI (–5.86 to 3.52), reducing to the baseline VAS 79%. Ketoprofen patch presented also a higher cure rate (64%) than diclofenac gel (46%) at day 7 (p = 0.004). Patient opinions about the treatment comfort (pharmaceutical shape, application and dosage) were also statistically higher for the ketoprofen patch (.80% of the patients rated as good or excellent the patch removal and skin adherence). So ketoprofen patches are effective

and safe pain relievers for the treatment of sports injury pain with advantages compared with diclofenac gel.

Mendez LL et al (2007)[33] showed statistically significant relationship between duration of surgery and postoperative pain on 1st postoperative day and observed in their patients that pain subsequently declined steadily until 7th postoperative day, when the sutures were removed. They have also mentioned that the differing results obtained in various studies may reflect differences in the type of anaesthetic used and in the analgesic administered after surgery. An ideal study design will involve elimination of postoperative analgesics which is not possible for ethical reasons.

Al khateeb TH & Nusair Y (2008)[34] performed a study on 24 healthy individuals undergoing surgical removal of bilateral impacted third molars to assess the effect of proteolytic enzyme serratiopeptidase on swelling, pain and trismus after surgical procedure. All patients received a combination of either serrapeptase 5mg or placebo tablets and 1000 mg paracetamol tablets at either the 1st or 2nd operation in accordance with the randomization plan. Cheek thickness, pain and interincisal distance were measured preoperatively, and on the 1st, 2nd, 3rd and 7th postoperative days. There was a significant reduction in the extent of cheek swelling and pain intensity in the serrapeptase group at the 2nd, 3rd and 7th postoperative days ($P<0.05$).

Kim K et al (2009)[35]states that use of medication to relieve pain and inflammation after removal of third molars has been explored thoroughly in the literature. Narcotic analgesics, non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and combinations of these all have a role in the postoperative management of pain and

swelling within this group of patients. Author suggested the use of NSAIDs and corticosteroids after third molar surgery.

Bachalli PS et al (2009)[36] performed a study to evaluate the analgesic efficacy of oral Diclofenac against trandermal Diclofenac patch in the management of postoperative pain following surgical removal of impacted mandibular third molars. Twenty healthy subjects belonging to both the sexes in the age group of 18–40 years with bilateral mesioangular impactions of mandibular third molar teeth underwent surgical removal under local anaesthesia on two different occasions with a minimum interval of 1 week in-between the procedures. The postoperative pain was recorded on visual analog scale, a verbal rating scale, a pain relief scale and a pain intensity scale. Readings were taken at 2 hours, 4 hours, 8 hours, 12 hours and 24 hours postoperatively, taking the time at which the surgery was completed as a reference. On the second and third days, the repeat medication was administered at that reference time and recordings taken at the same intervals for a total of 3 days. Patients received the study medication i.e. Diclofenac Sodium 100mg once a day for 3 days after performing surgery on one side and the same patients were given Diclofenac Sodium Transdermal Patch 100mg once a day for 3 days after performing surgery on the contralateral side.Both the statistical analysis and clinical observation showed that on the first postoperative day diclofenac sodium administered orally has slightly more significant efficacy when compared to the drug administered transdermally. However, on the second and third postoperative days there was no statistical or clinical difference in the pain control by either route of administration.

The study concludes that transdermal diclofenac sodium can be used as an alternative form of pain control following removal of impacted mandibular third molars, however considering that the analgesic potency might be lesser in the immediate postoperative period, it might be prudent to use oral diclofenac sodium for immediate postoperative pain relief, following which transdermal route can be used for pain control.

Kumar J A et al (2010)[37] studied that 74% of drugs are taken orally and are found not to be as effective as desired. To improve such characters transdermal drug delivery system was emerged. Drug delivery through the skin to achieve a systemic effect of a drug is commonly known as transdermal drug delivery and differs from traditional topical drug delivery. Transdermal drug delivery systems (TDDS) are dosage forms involves drug transport to viable epidermal and or dermal tissues of the skin for local therapeutic effect while a very major fraction of drug is transported into the systemic blood circulation. The adhesive of the transdermal drug delivery system is critical to the safety, efficacy and quality of the product. Topical administration of therapeutic agents offers many advantages over conventional oral and invasive methods of drug delivery. Several important advantages of transdermal drug delivery are limitation of hepatic first pass metabolism, enhancement of therapeutic efficiency and maintenance of steady plasma level of the drug.

Sarzi-Puttini P et al (2010)[38] states that ketoprofen is a drug belonging to the family of non-steroidal anti-inflammatory drugs (NSAIDs). They suggested that present review examines the main available clinical evidence of ketoprofen in the treatment of acute and chronic pain, of both rheumatic and traumatic origin, as well as

postoperative pain. Ketoprofen has shown to be an excellent choice of drug for the treatment of chronic pain in patients with osteoarthritis, rheumatoid arthritis or gout, demonstrating a high level of efficacy with good tolerability also in elderly patients. Even in the treatment of acute forms of pain such as bursitis, tendinitis and back pain, ketoprofen compares favourably to other NSAIDs (e.g., ibuprofen and diclofenac) in terms of efficacy. Ketoprofen has been shown to be effective also for the treatment of post-operative pain, particularly in the orthopaedic field, with an efficacy similar to opioids in some studies. In this setting, some evidence indicates that ketoprofen exhibits additional important benefits, showing to be effective in the prophylaxis of heterotopic calcification following hip or pelvic major intervention, without affecting the bone healing process. Moreover, the use of ketoprofen in elastomeric pump in combination with opioids or other NSAIDs has proven to be effective and safe. In conclusion, available data confirm that ketoprofen is effective and well tolerated, through different administration routes, for the treatment of various forms of rheumatic, traumatic and post-surgical pain, and may therefore be considered as a valid therapeutic option for these patients.

Bhaskar H & Pranav Kapoor R (2010)[39] carried out a study to compare the degree of postoperative analgesia, patient compliance and frequency of adverse effects with the use of oral diclofenac tablets and transdermal patch following multiple premolar extractions in 20 young patients undergoing orthodontic treatment.

Statistical analyses revealed that there was a gradual increase in pain relief scores and gradual decrease in pain intensity scores with the use of diclofenac tablets as well as patch. However, patient reported a good compliance with the use of patch basically

due to once a day application and lesser frequency of systemic adverse effects. These results indicate that transdermal diclofenac patch provides as potent analgesia as diclofenac tablets with the added advantage of better patient compliance.

Kaczmarzyk T et al (2010)[40] conducted a study to examined whether ketoprofen administered 60 min before surgical extraction of the lower wisdom teeth provides effective postsurgical analgesia and reduces rescue analgesic intake compared with ketoprofen administered 60 min after surgery or placebo. The 96 patients were placed into three groups: pre-group (ketoprofen 60 min preoperatively); post-group (ketoprofen 60 min postoperatively); and no-group (placebo). Study interventions had a significant effect on pain sensations in the 12 h after surgery. The initial onset of pain was significantly delayed only in the post-group. Pain intensity at the first onset of pain was significantly lower only in the post-group. Patients in the pre- and postgroups required significantly less rescue analgesic than those in the no-group. Ketoprofen administered after third molar surgery provides more effective pain control than ketoprofen administered before the surgery or placebo.

Adachi H et al (2011)[13] discussed the mechanism of action of non-steroidal anti-inflammatory drugs (NSAIDs), to which ketoprofen belongs and reviewed that it is based on their cyclo-oxigenase (COX) inhibiting action, concerning both subtype COX-1 constitutive isoform and COX-2 inducible isoform. Ketoprofen administration may be carried out by oral and parenteral routes as well as by topical application, which includes transdermic patch use. Following a synthetic description of the results obtained by several investigators on ketoprofen use, the Authors present a new formulation of the ketoprofen patch obtained by the so called Derma Light

Technology. The Authors concluded by stating that ketoprofen patch is both a good alternative and a safe modality of administration, with special reference to patients who are prone to gastrointestinal disorders.

Bortoluzzi MC et al (2011)[41] evaluated the pain course after surgical removal of third molars in 100 consecutive patients. Pain intensity was assessed by means of a Visual Analogue Scale (VAS). At day 1, moderate and severe pain were observed predominantly in patients who had surgery in the mandible ($p < 0.001$) and for patients younger than 24 years ($p = 0.009$), while more patients who weekly consumed mate tea (Ilex paraguariensis) showed pain classified as none or light ($p = 0.017$). At day 2, the profile of pain moderate/severe was more prevalent for patients who had surgery in the mandible ($p < 0.001$) with the report of difficult surgery ($p = 0.042$) and with odontotomy performed ($p = 0.033$). In the third postoperative day, severe/moderate pain was associated with surgery in the mandible ($p < 0.001$) and with odontotomy ($p = 0.021$) and ostectomy ($p = 0.028$) performed, with report of long and difficult procedure ($p = 0.023$), surgeries which last more than sixty minutes ($p < 0.026$), and for those patients who developed postoperative inflammatory complications ($p < 0.001$).they concluded that third molar surgery performed in maxilla and mandible is also unequal concerning pain response. Higher pain complains could be expected for patients who have difficult mandibular surgery and that means increase of trauma and procedure time spent. Regular mate tea consumption may have an anti-inflammatory and/or analgesic effect.

Rana M et al (2011)[42] carried out a study to assess the beneficial effects of cold treatment on postoperative swelling, pain, and inflammation and to compare

postoperative cooling therapy using cooling compresses with that using the water-circulating cooling face mask by Hilotherm. They reported regarding the vascular effects of cold therapy that cold therapy constricts the blood vessels and the intensity of vasoconstriction reaches the greatest value at a temperature of 15°C. Furthermore, a decrease in body temperature slows down peripheral nerve conduction. For temperatures less than 15°C, nerve conduction is completely disabled, and vasoconstriction becomes vasodilation. Ice packs or similar conventional cooling methods use a temperature of about 0°C. Such a low temperature constrains lymph drainage and cell metabolism. Thus, they concluded that application of a temperature around 15^{o} C, during early postoperative period follweing surgical removal of impacted lower third molar, is beneficial.

Dhiman S et al (2011)[43] suggested that transdermal drug delivery system was introduced to overcome the difficulties of drug delivery through oral route. A transdermal patch is medicated adhesive patch that is placed on the skin to deliver a specific dose of medication through the skin and into the bloodstream. Often, this promotes healing to an injured area of the body. An advantage of a transdermal drug delivery route over other types of medication delivery such as oral, topical, intravenous, intramuscular, etc. is that the patch provides a controlled release of the medication into the patient, usually through either a porous membrane covering a reservoir of medication 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 in this method.

Prabhakar V (2012)[44] evaluated that transdermal delivery provide a leading edge over injectable and oral routes by increasing patient compliance and avoiding first pass metabolism respectively. Transdermal delivery not only provides controlled, constant administration of the drug, but also allows continuous input of drugs with short biological half-lives and eliminates pulsed entry into systemic circulation, which often causes undesirable side effects. Thus various forms of Novel drug delivery system such as Transdermal drug delivery systems, Controlled release systems, Transmucosal delivery systems etc. emerged. Several important advantages of transdermal drug delivery are limitation of hepatic first pass metabolism, enhancement of therapeutic efficiency and maintenance of steady plasma level of the drug. The first Transdermal system, Transderm-SCOP was approved by FDA in 1979 for the prevention of nausea and vomiting associated with travel, particularly by sea. The evidence of percutaneous drug absorption may be found through measurable blood levels of the drug, detectable excretion of the drug and its metabolites in the urine and through the clinical response of the patient to the administered drug therapy.

Krishna R & Nataraj MS (2012)[45] compared the analgesic efficacy of a transdermal diclofenac patch 100 mg (NuPatchR 100, Zydus Cadila, Ahmedabad, India) and intramuscular diclofenac sodium 75 mg (VoveranR, Novartis, India) for postoperative analgesia, and the associated side-effects of the transdermal diclofenac patch. Sixty participants in the study were randomly allocated to two groups of 30 each, by a computer-generated randomisation table. The anaesthetic procedure was standardised. A transdermal diclofenac patch 100 mg was applied to the participants in the study group at the beginning of the surgery. In the control group, 75 mg of diclofenac sodium was given intramuscularly half an hour before the end of surgery. Pain was

assessed postoperatively at two-, six-, and 12-hour intervals using a visual analogue scale (VAS). An injection of tramadol 2 mg/kg was administered intramuscularly as rescue analgesia. The study ended when the patients asked for rescue analgesia, or when the VAS score was > 5. Results indicated that the mean duration of analgesia in the control group was 7 hours 28 minutes, and in study group, it was 8 hours 6 minutes, which was comparable (p-value < 0.341). Authors concluded that intraoperative application of a single dose of 100 mg transdermal diclofenac patch is as effective as a single dose of intramuscular diclofenac (75 mg) for acute postoperative pain, without any significant side-effects.

Rastogi V (2012)[46] suggested that transdermal drug delivery system has been accepted as potential noninvasive route of drug administration, with advantages of prolonged therapeutic effect, reduced side effects, improved bioavailability, better patient compliance and easy termination of drug therapy. Non-steroidal anti-inflammatory drugs (NSAIDs) represents the most commonly used medications for the treatment of pain and inflammation, but numerous well described side effects can limit their use. Therefore transdermal delivery of NSAIDs has advantages of avoiding hepatic first pass effect, gastric irritation and delivering the drug for extended period of time at a sustained level. The present article gives the brief view on the work been done on various NSAIDs by formulated and delivered as transdermal patches to decrease the side effects associated with the oral delivery. The various NSAIDs included in this article include Ketoprofen, Ibuprofen, Naproxen, Fluribrofen, Diclofenac, Aceclofenac, Ketorolac, Indomethacin, Meloxicam, Nimesulide, Celecoxib, Etoricoxib.

Komatsu T & Sakurada T (2012)[47] compared the efficacy and skin permeability of nine topical preparations of nonsteroidal anti-inflammatory drugs (NSAIDs) (ketoprofen, diclofenac, flurbiprofen, and piroxicam patches; and ketoprofen, diclofenac, piroxicam, niflumic acid, and ibuprofen gels) available in the European Union. The anti-inflammatory effect of these NSAID preparations was evaluated in rat models of acute inflammation (carrageenan or yeast treatment) and chronic inflammation (collagen or adjuvant treatment). Skin permeability of the preparations was evaluated in vitro using mouse skin. In rats with acute inflammation, both ketoprofen preparations significantly inhibited carrageenan-induced edema and yeast-induced hyperalgesia. Flurbiprofen and diclofenac preparations also showed a significant anti-inflammatory effect, but the ketoprofen products were the most potent among the four patch preparations and five gel preparations. With repeated application, the ketoprofen patch significantly decreased edema from day 3 in collagen-treated rats, while other preparations (ketoprofen gel, diclofenac patch, and diclofenac gel) decreased edema from day 7. In rats with adjuvant-induced arthritis, only the ketoprofen patch significantly decreased edema after 2 weeks of application. In the skin permeation study, the ketoprofen preparations showed higher skin permeability compared with the other NSAID preparations. These results suggested that ketoprofen preparations had the most potent anti-inflammatory and analgesic activity related to good skin permeability. Efficacy of the ketoprofen patch was comparable to or better than that of ketoprofen gel at a lower dose and frequency of administration. Ketoprofen products, especially the patch preparation, could be useful for treating inflammatory pain in diseases like osteoarthritis and rheumatoid arthritis.

Santosh K & Jyoti M (2013)[48] concluded that most inflammatory diseases occur locally and near the body surface, transdermal drug delivery of non-steroidal anti-inflammatory drugs (NSAIDs) may be an interesting strategy for delivering these drugs directly to the diseased site. Ketoprofen (KP), a potent non-steroidal anti-inflammatory drug (NSAID) inhibits arachidonic acid metabolism by cyclo-oxigenase and lipoxygenase. The compound has been widely used in the treatment of rheumatoid arthritis, osteoarthritis, as well as a mild to moderate painkiller.

Velásquez GC et al (2014)[49] evaluate the preemptive analgesia of ketoprofen in comparison with diclofenac after mandibular third molar surgery. This study was a double-blind, randomized clinical trial. Forty patients were randomized into two treatment groups (each with 20 patients) by using a series of random numbers: group A received ketoprofen 100 mg and group B received diclofenac 75 mg, all intramuscularly. Surgery was done 30 minutes after analgesic treatments. The durations of analgesia, pain intensity, analgesic consumption, and side effects were evaluated.The duration of analgesia was longer in the ketoprofen group when compared with the diclofenac group. The number of patients taking the first rescue analgesic at 6 hours was lower in the ketoprofen group in comparison with the diclofenac group. Patients who received ketoprofen had lower pain intensity compared with patients who received diclofenac. So they concluded that Intramuscular ketoprofen 100 mg is more effective than intramuscular diclofenac 75 mg after mandibular third molar extraction when used as a preemptive analgesic.

Koray M et al (2014)[50] recently performed a study to compare the efficacies of two oral sprays in reducing swelling, pain, and trismus after the extraction of impacted

mandibular third molars. This prospective double-blind, randomized, crossover clinical trial included 34 patients with bilateral symmetrically impacted mandibular third molars of similar surgical difficulty. Hyaluronic acid or benzydamine hydrochloride spray was applied (two pumps) to the extraction area, three times daily for 7 days. Swelling was evaluated using a tape measure method, pain with a visual analogue scale (VAS), and trismus by measuring the maximum inter-incisal opening. Assessments were made on the day of surgery and on days 2 and 7 after surgery. On the second postoperative day, facial swelling was significantly increased in both groups when compared to preoperative measurements; however, the facial swelling in the Hyaluronic acid group was lower than that in the Benzydamine hydrochloride group and the differ-ence between the two groups was statistically significant (P 0.002). By the seventh postoperative day, facial swelling in both groups was minimal and there was no statistically significant difference between the two groups. Thus, they concluded that hyaluronic acid appears to offer a beneficial effect in the management of swelling during the immediate postoperative period following impacted third molar surgery.

Pouchain EC et al (2015)[51] compared the effect of nimesulide and ketoprofen on inflammatory parameters related to the surgical removal of third molars. A splitmouth, prospective, randomized, doubl e-blind study was conducted in patients undergoing removal of four third molars. Eighteen eligible patients were allocated to one of two groups to receive treatment two times a day with either ketoprofen 100 mg or nimesulide 100 mg for a period of 3 days. The rescue medication intake (number) and pain intensity were evaluated at 6, 12, 24, and 48 h, and at 7 days postoperatively. Swelling and maximum mouth opening were evaluated at 24 h, 72 h, and 7 days

postoperatively. The peak pain score occurred at 6 h after surgery in the nimesulide group and at 12 h in the ketoprofen group. There was no statistically significant difference between the groups, although pain relief was observed after 48 h in the nimesulide group and after 7 days in the ketoprofen group. For each group, there was a statically significant difference in pain scores among the studied periods ($P < 0.0001$). None of the patients required rescue medication. There was a statistically significant difference in maximum mouth opening between the preoperative and postoperative periods ($P < 0.0001$). Ketoprofen and nimesulide were effective at controlling pain, swelling, and trismus after the surgical removal of third molars.

R. Shenoi & H. Neha (2015)[52] evaluate the effectiveness of transdermal diclofenac patch for postoperative analgesia in maxillofacial trauma patients. : 64 patients of maxillofacial trauma, undergone an open reduction and internal fixation, were divided into 4 groups according to the pattern of fractures. All the patients were subjected to transdermal diclofenac patch (100 mg) once a day for management of postoperative pain. The patients were asked to score on the pain intensity scale and the pain relief scale charts every day for three postoperative days. Statistical analysis showed that there was a gradual decrease in pain intensity score and a gradual increase in pain relief score in all four groups after application of transdermal diclofenac patch ($p < 0.001$). Author concluded that transdermal diclofenac patches provide an effective way of post-operative pain management in patients of maxillofacial trauma with negligible side effects and good patient compliance.

Deliverska EG & Petkova (2016)[53] addresses the incidence of specific complications and, where possible, offers a preventive or management strategy. Complications, such

as pain, dry socket, swelling, paresthesia of the lingual or inferior alveolar nerve, bleeding, and infection are most common. Factors thought to influence the incidence of complications after third molar removal include age, gender, medical history, oral contraceptives, presence of pericoronitis, poor oral hygiene, smoking, type of impaction, relationship of third molar to the inferior alveolar nerve, surgical time, surgical technique, surgeon experience, use of perioperative antibiotics, use of topical antiseptics, use of intra-socket medications, and anaesthetic technique.

Leya Mathews AR (2016)[54] state that Transdermal delivery is a non-invasive route of drug administration through the skin surface that can deliver the drug at a predetermined rate across the dermis to achieve a local or systemic effect. It is potentially used as an alternative to oral route of drugs and hypodermic injections. Analgesics are mostly used for various diseases as most of them are associated with severe or mild pain. The use of analgesics as a pain relief patch is now being used commonly. A transdermal analgesic or pain relief patch is a medicated adhesive patch used to relieve minor to severe pain. Currently, the patches are available for many opioids, non-opioids analgesics. local anesthetics, and antianginal drugs. The drugs include fentanyl, buprenorphine ketoprofen, diclofenacepolamine, piroxicam, capsaicin, nitroglycerine, and lignocaine. They are available as both matrix and reservoir patches. They aiso explores the various drugs used to manage pain and their route of administration in terms of frequency, complications, and effects.

Verma R et al (2016)[55] compare the efficacy and safety of transdermal patch of ketoprofen in comparison to diclofenac patch for postoperative analgesia. Sixty patients were randomly allocated to receive either ketoprofen or diclofenac patch at

the end of surgery under spinal anaesthesia. In diclofenac group the post-operative VAS was 2.4±0.72 and in ketoprofen group, post-operative VAS was 1.4±0.3 which was significantly low when compared to group D ($p<0.05$ value). 11 patients in group D and 3 patients in group K required rescue analgesia (Inj. tramadol) in the first 24 hours which was statically significant ($p<0.05$). Both ketoprofen and diclofenac transdermal patch are effective for postoperative analgesia but less number of patients required rescue analgesic in ketoprofen group.

Jadhav P et al (2017)[56] compared the analgesic efficacy of Diclofenac vis-a-vis Ketoprofen transdermal patch, in the management of immediate post-operative pain following orthognathic procedures. They conducted a prospective, double-blinded, randomised controlled study among 50 subjects, between 2012 and 2015. These patients were diagnosed clinically and cephalometrically as skeletal and dental class II malocclusion and underwent bi-jaw surgical procedure. In total, 25 Diclofenac and 25 Ketoprofen transdermal patches, sealed in envelopes and numbered, were administered to subjects. The patches used, contained 100 mg of either Diclofenac or Ketoprofen and administered by a nurse prior to induction. Duration of analgesia, severity of pain using Visual Analogue Scale, necessity of rescue analgesia (spontaneous pain > 5 on a 10-cm scale) and any other adverse effect associated with the drug were evaluated. They found that mean duration of analgesia was significantly higher in the Ketoprofen group (20 h), compared to Diclofenac group (13 h) ($p = 0.001$). Rescue analgesia was required in 12% of subjects who received Diclofenac patch, compared to 4% in Ketoprofen group. None of the subjects showed any allergic reactions. They concluded subjects in both groups were comfortable and returned to early function. However, Ketoprofen transdermal patch

had an edge over the Diclofenac transdermal patch with respect to analgesic efficacy.

Materials And Method

An experimental study was designed to study the effectiveness of ketoprofen transdermal patch in management of postoperative pain, swelling and trismus after surgical removal of impacted mandibular third molar and to compare the effects with those of oral ketoprofen tablets.

Sample Size –

30 patients (60 sites) visiting the Department of Oral & Maxillofacial Surgery requiring surgical removal of impacted mandibular third molar were selected for the study.

Study design –

An experimental study was designed with randomized selection of patients.

Duration of study -

The study was performed for a period of 18 months from January'2016 to June' 2017.

Inclusion Criteria –

- Patients needing surgical removal of impacted lower third molars.
- Patients above 18 years of age without any systemic conditions.

Exclusion Criteria –

- Patients with known allergy to ketoprofen or local anesthetic agent.
- History of GIT bleeding or ulceration.
- Pregnant/lactating women.
- Patients taking systemic steroids

Materials –

- Surgical instrument kit for removal of impacted mandibular third molar
- Local anesthetic solution consisting of 2% lignocaine with a vasoconstrictor (adrenaline 1:2,00,000)
- Ketoprofen transdermal patch containing 30mg of ketoprofen (Infen plaster, Emcure)
- Tablet ketoprofen containing 50 mg of drug (Tablet Infen, Emcure)
- Tablet paracetamol containing 650 mg of drug (Tablet Dolo, GSK pharmaceuticals)
- VAS chart
- Metallic scale
- Non-elastic thread

- Vernier caliper

Method –

- An experimental study was designed with random selection of patients.
- Total 30 (60 sites) patients requiring surgical removal of mandibular third molars were divided into two equal groups A and B.
- Patients of group A were given oral ketoprofen (50 mg) in tablet form; while transdermal ketoprofen patch (30 mg) was applied on any non-hairy area of upper torso and limbs in patients of group B, 1 hour prior to surgery.
- Surgical removal of third molar was performed in a proper aseptic manner and with minimal trauma to surrounding structures.
- Postoperatively, tablets Infen, Amcure (50 mg) were prescribed to the patients of group A to be taken TID; while Infen transdermal patch, Amcure (30 mg) was prescribed to be used OD for 3 days in patients of group B. Patients in group A were advised to take the tablets after meals. Patients in group B were advised to apply the transdermal patch on any non-hairy area of upper torso or limbs such as neck, supraclavicular region, upper arm or back and to change the site while applying the next patch.
- Rescue medications containing paracetamol were prescribed to be taken as and when needed in the form of tablet Dolo 650 mg, GSK pharmaceuticals.
- Measurements of following parameters were made preoperatively and on 1^{st}, 3^{rd} and 7^{th} postoperative days:

  Pain – By VAS i.e. Visual Analogue Scale (100mm)

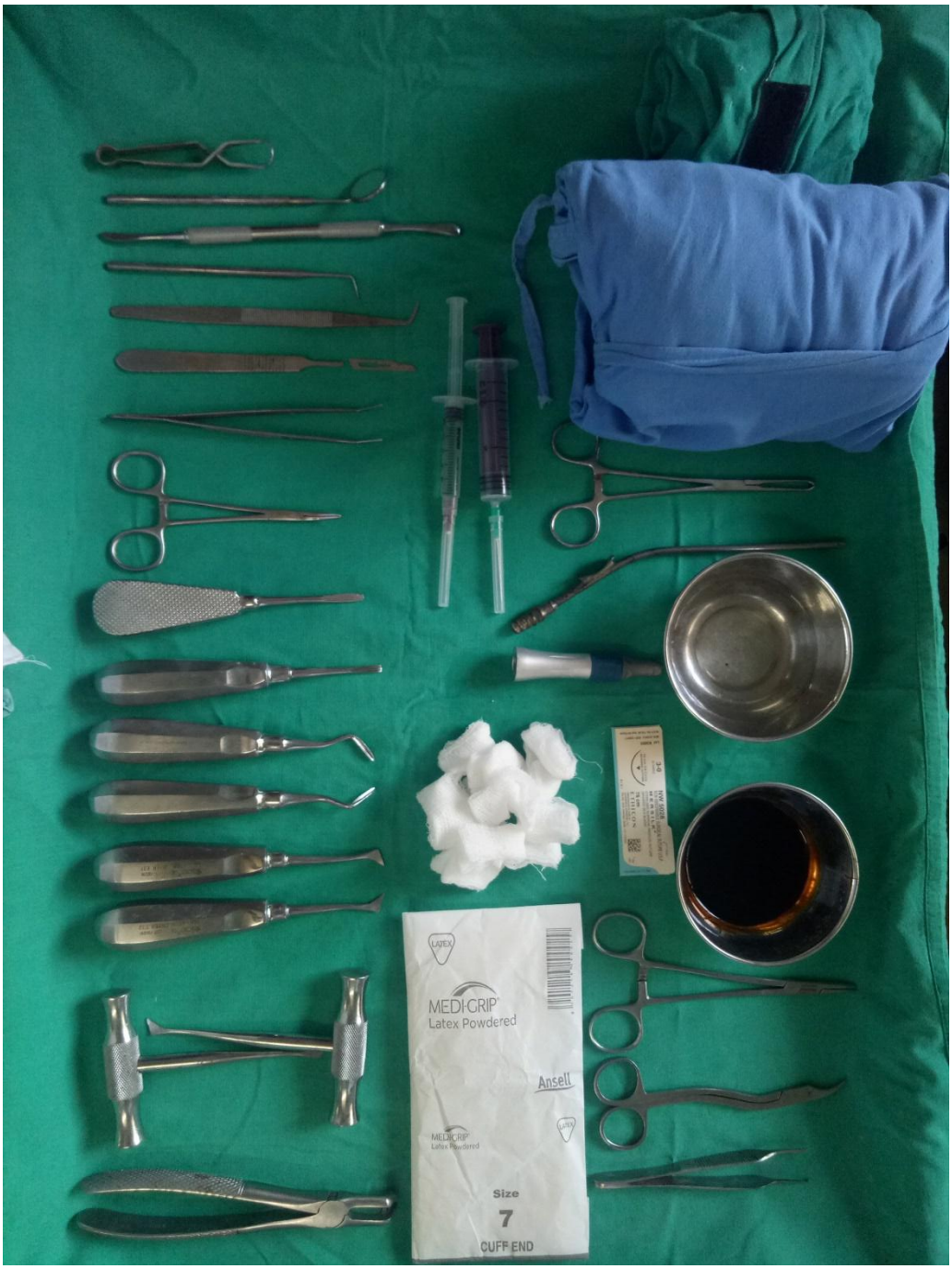
  Swelling – With the help of non-elastic thread and scale

  Trismus – With the help of caliper
- Results of one group were compared with those of another on 1^{st}, 3^{rd} and 7^{th} postoperative days.

Statistical methods

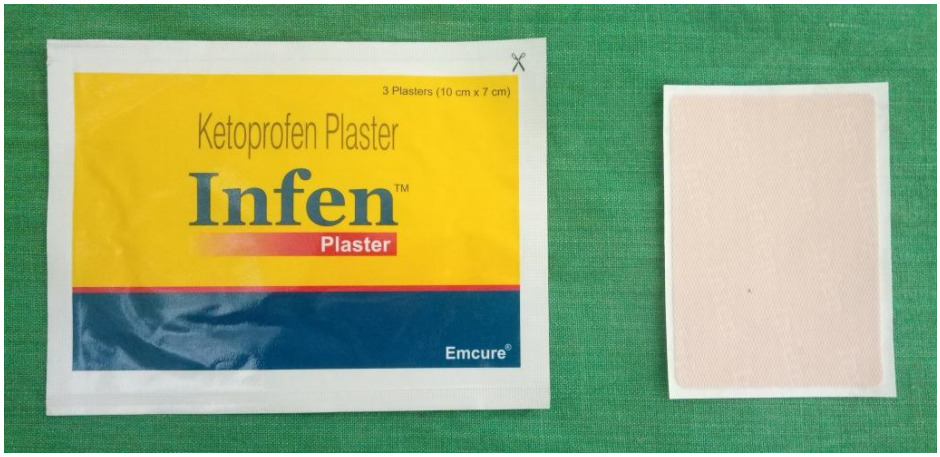
The data on VAS pain score, facial swelling measurement and trismus alleviation distance were obtained pre-operatively and post-operatively at 1st, 3rd and 7th day on each patient from Tablet and Patch groups. Descriptive statistics like mean, median, standard deviation, minimum and maximum were obtained for each parameter with time. The difference of VAS scores across times in each group was tested for statistical significance using Friedman test. Pair wise comparison of VAS scores between times was done using Wilcoxon signed rank test. Further, the comparison of VAS scores between two groups at each time point was carried out using Wilcoxon rank sum test. The comparison of facial swelling measurements and trismus alleviation distance across times in each group was performed using repeated measure analysis of variance. The paired comparison was done using Tukey's post-hoc test. The significance of difference in the proportion of patients requiring rescue medication as well as showing adverse GIT effect in two groups was determined using Pearson's chi-square test. All the analyses were performed using SPSS ver 20.0 (IBM Corp) and the statistical significance was evaluated at 5% level.

Plate I

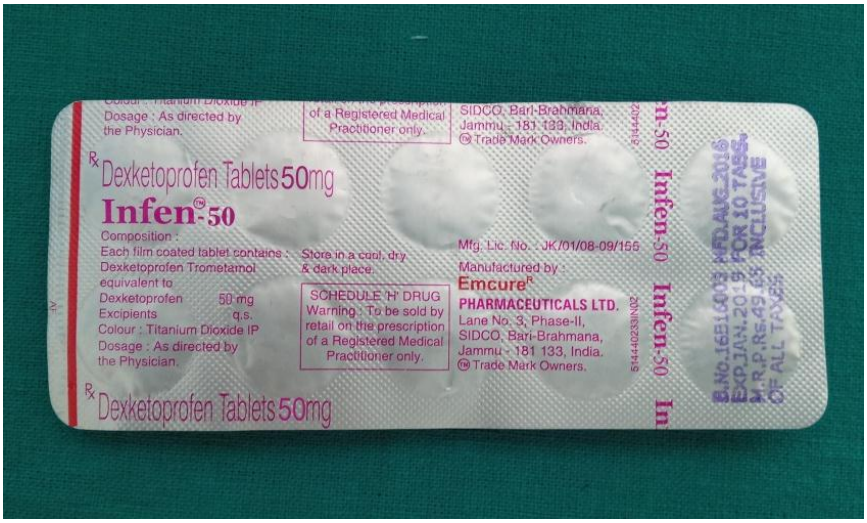


Instrument for surgical removal of mandibular third molar (figure 1)

Plate II

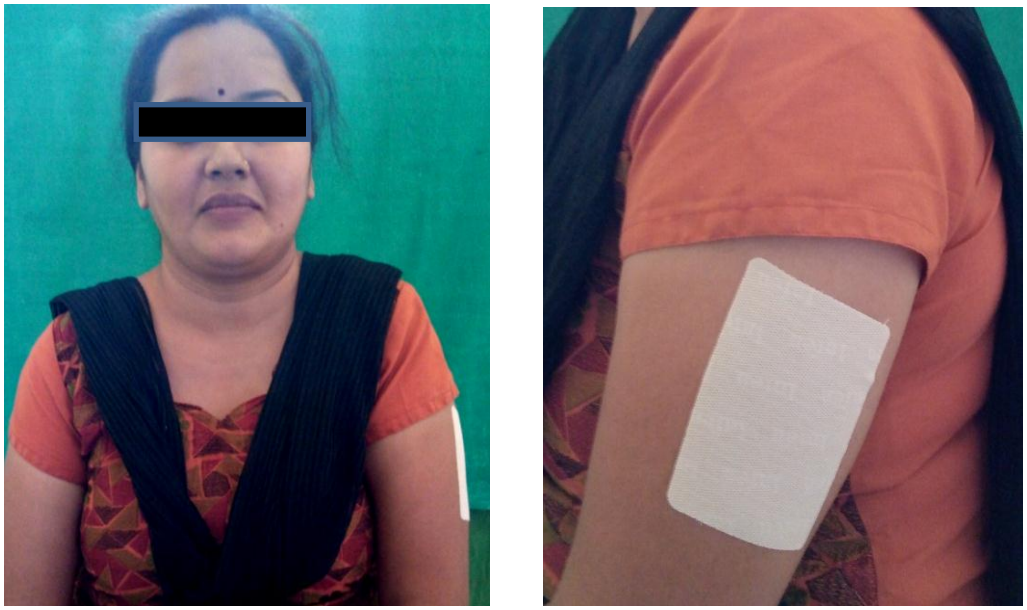


Transdermal ketoprofen patch 30 mg (InfenEmcure) (figure 2)

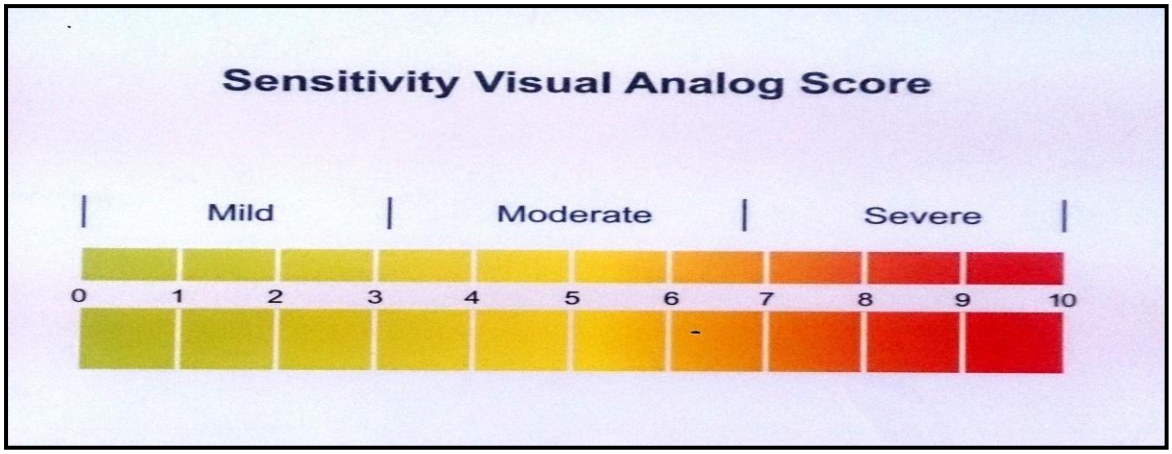


Tablet ketoprofen 50mg (Infen 50 mg Emcure) (figure 3)

Plate III

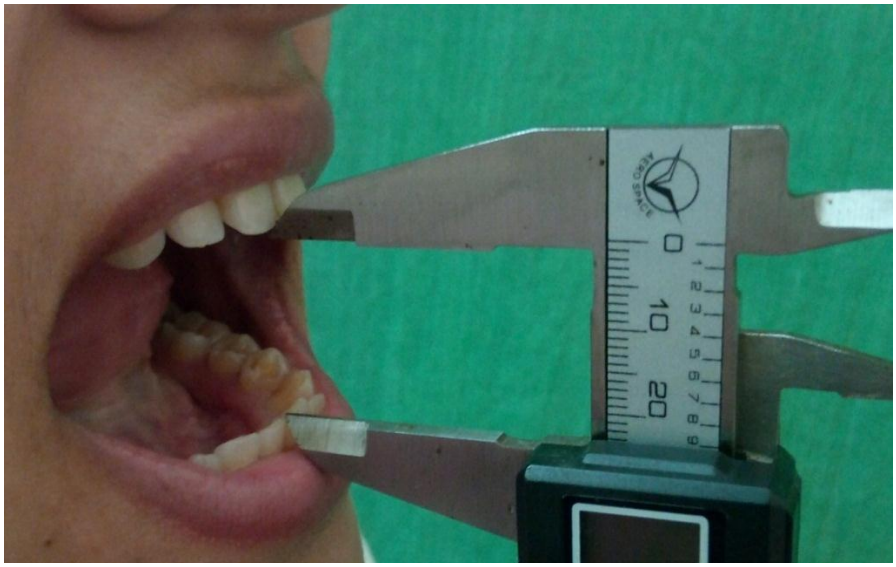


Transdermal ketoprofen patch 30 mg applied on non-hairy area (figure 4)



Visual Analog Scale(figure 5)

Plate IV

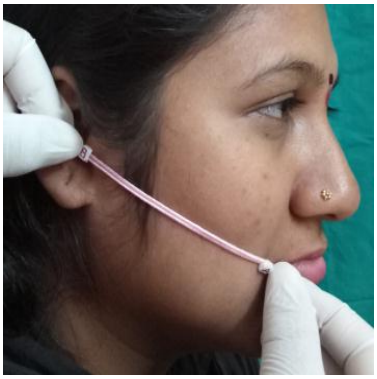


Measurement of Inter-incisal distance for Trismus using Vernier Caliper (figure 6)

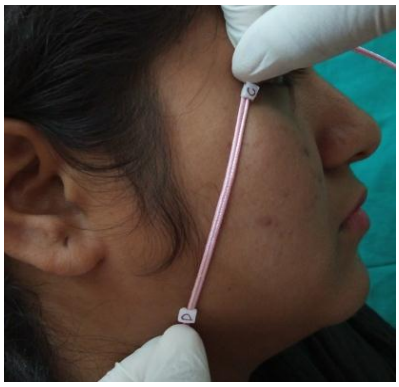
Vernier Caliper (figure 7)

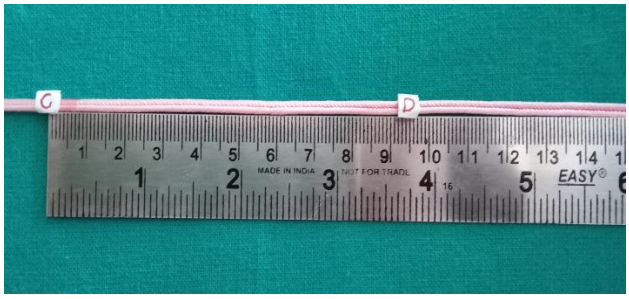
Plate V

Measurement of facial swelling with non- elastic thread and metallic scale



AB- distance from angle of mouth to lobe of ear just below the tragus(figure 8)





CD- distance from lateral canthus of eye to angle of mandible(figure 9)

Results

Table 1 provide the distribution of patients as per age. The maximum i.e. 20(66.7%) were in the age range of 23-27 years, followed by 6(20%) in range of ≤ 22 and 4(13.3%) were in range of ≥ 28. A graphical representation of the mean is depicted through column chart in graph 1. A graphical representation of the mean is depicted through column chart in figure 1. Table 2 provide the distribution of patients according to gender.19 male patients (63.33%) and 11 female patients (36.67%). A graphical representation of the mean is depicted through column chart in figure 2. A graphical representation of the mean is depicted through column chart in graph 2.

Table 3 gives the comparison of VAS scores between tablet and patch groups at different time points using Wilcoxon rank sum test. Pre-operatively, the difference between the VAS score distribution between two groups was statistically insignificantly different, as indicated by p-value of 0.5275. However, at 1^{st} and 3^{rd}

day, the mean VAS score was statistically highly significant with $p < 0.0001$. Further, at 7th day, the difference was statistically insignificant with p-value of 0.1431. A graphical representation of the mean is depicted through line chart in graph 3.

Table 4 shows that in tablet group, the pre-operative VAS scores differed significantly from that of 1st post-operative day ($p < 0.0001$), whereas pre-operative VAS was insignificant from 3rd and 7th post-operative day as indicated by p- value 0.7630 in both. Moreover, VAS scores at 1st post-operative day and 3rd post-operative day, 1st post-operative day and 7th post-operative day also differed significantly with $p< 0.0001$. However when VAS scored compared between 3rd and 7th post-operative day it was statistically insignificant with p- value 0.1573.

Similarly, in patch group, the pre-operative VAS scores differed significantly as compared to 1st day after post-operative, as well as 3rd day after post-operative ($p < 0.0001$). Further, the scores between 1st day and 3rd day, 1st day and 7th day, 3rd and 7th day postoperative, also differed significantly as indicated by p-values 0.0089 and $p < 0.0001$ and $p < 0.0001$ respectively (table 5).

Table 6 gives the comparison of facial swelling measurements between tablet and patch group at each time point. At pre-operative stage, the difference in the mean measurements between two groups was statistically insignificant with p-value of 0.9459. At 1st post-operative day, the difference in the means was statistically significant with p-value of 0.0027, which continued to be significant at 3rd day with p-value of 0.0001 and on 7th day with p-value of 0.001. A graphical representation of the mean is depicted through line chart in graph 4.

Table 7 gives the paired comparison of facial swelling measurements between different time points in tablet group. It is evident that the pre-operative measurements differed significantly from that of 1st, 3rd and 7th post-operative days with p-values 0.0025, 0.0003 and 0.0003 respectively. Further, the difference in the measurements of 1st and 7th, as well as 3rd and 7th days were also statistically significant with $p < 0.0001$.

On similar lines, the paired comparisons were performed in patch group between different times. The mean difference of measurements between pre-operative and post-operative 1st day, as well as 3rd and 7th day were statistically highly significant with $p < 0.0001$. The difference between 1st day and 3rd day was significant with p-value of 0.0324. Further, the difference between 1st and 7th was insignificant with p-value 0.0324 and between 3rd and 7th day was highly significant with $p < 0.0001$. (table 8)

Table 9 gives the comparison of mean trismus alleviation distance between tablet and patch groups at different time points. Pre-operative, the difference of means between two groups was statistically significant with p-value of 0.0093. Further at 1st post-operative day, the difference was statistically significant with p-value of 0.0006, which became highly significant at 3rd day with p-value < 0.0001 and then again significant with p-value of 0.0007 at 7th day. A graphical representation of the mean is depicted through line chart in graph 5.

Table 10 shows the pair wise comparison of trismus alleviation distance between different time points for tablet group using Tukey's post-hoc test. The mean difference of distance between pre-operative and 1st post-operative day as well as 3rd post-operative day were statistically highly significant with p-value < 0.0001. Further, the mean difference of distance between 1st day and 3rd day was statistically significant was p-value of 0.0067. Further, the difference between 1st day and 7th day, as well as 3rd day and 7th day were statistically highly significant with p-value < 0.0001.

Table 11 shows the pair wise comparison of trismus alleviation distance between different time points for patch group using Tukey's post-hoc test. The mean difference of distance between pre-operative and 1st post-operative day as well as 3rd post-operative day were statistically highly significant with p-value < 0.0001, and between pre-operative and 7th post-operative day it was insignificant with p- value 0.5797. Further, the difference between the 1st and 3rd post-operative day is in significant with p -value 0.9999, but the difference between 1st day and 7th day, as well as 3rd day and 7th day were statistically highly significant with p-value < 0.0001.

Table 12 provides details of rescue medication required in both the study groups. In tablet group, out of 30, only 2 (6.67%) patients required medication, while in patch group, 15 (50%) patients needed the medication. The difference between the two groups as regards need for medication was statistically significant with p-value of 0.0006 using Chi-square test. A graphical representation of the mean is depicted through bar chart in graph 6.

Table 13 gives the number of patients with adverse GIT effects in two groups. In tablet group, 10 (33.3%) cases showed adverse effect, while in patch group, 2 (6.67%) cases showed the effect. The difference in the proportion of cases showing effect was statistically significant with p-value of 0.0238 using Chi-square test. A graphical representation of the mean is depicted through bar chart in graph 7.

Discussion

Third molars extraction is one of the most common procedures performed by oral & maxillofacial surgeons.[57] There are several postoperative complications encountered with the removal of third molar.[58] Commonly associated post-operative sequelae involve pain, trismus, and swelling. These are directly related to the difficulty factor associated with impacted teeth, duration of surgery, age of the patient & expertise of the surgeon. Trismus following surgical extraction is secondary due to pain and swelling.[59] Post-operative pain control is one of the most important aspects of management of surgical patients. Several drugs, which are used to regulate the postoperative pain, are mainly divided into two groups, i.e., non-steroidal anti-inflammatory drugs (NSAIDs) and opioids.[60] Non-steroidal anti-inflammatory drugs (NSAIDs) are an important category of drugs widely used in treating musculo-skeletal disorders, such as rheumatoid arthritis and osteoarthritis, as well as some of the symptoms due to traumatic lesions. **Pouchain EC et al in 2015** [51] compared the effect

of nimesulide and ketoprofen on inflammatory parameters related to the surgical removal of third molars. They concluded that Ketoprofen and nimesulide were effective at controlling pain, swelling, and trismus after the surgical removal of third molars. However, the use of systemic NSAIDs can result in an increased risk of serious side effects, especially with regard to gastrointestinal, cardiac, neurological system etc.[61]

Adachi H et al in 2011[13] concluded by stating that ketoprofen patch is both a good alternative and a safe modality of administration, with special reference to patients who are prone to gastrointestinal disorders.

Hence in this study we tried to find out more appropriate and comfortable route for drug administration in managing post-operative pain, swelling and trismus after surgical removal of mandibular third molar. We compared the transdermal ketoprofen patch with that of oral ketoprofen tablet for management of post-operative complication after surgical removal of mandibular third molar. Observations were made by evaluating the patients on the basis of VAS score for pain, measurement of facial swelling and that of inter-incisal distance for assessing trismus.

During post-operative period when the effects of the local anesthesia subsides, pain begins and reaches peak levels in 6 to 12 hours post-operatively.[6]

Pain after the removal third molar is because of trauma-induced inflammation. Various author have stated different scales for studying the intensity of pain. **Marcelo Carlos Bortoluzzi in 2011**[41] studied the intensity of pain after surgical removal of third molars by using Visual Analogue Scale (VAS).

Similarly in our study we measured the intensity of pain by the mean of VAS scale. The findings of the present study showed that both ketoprofen tablet and transdermal patch effectively lead to reduction in postoperative period from day 1 to day 7, but the mean VAS score in patch group was much higher (5.40) than that in tablet group (3.00) on 1st postoperative day which is highly significant. On 3rd postoperative day, it was still higher in patch group (4.83) than that in tablet group (1.20), which is also highly significant, but on 7th postoperative day the VAS score difference was less between patch group (1.50) and tablet group (1.27) which is non-significant (table 3). A graphical representation of the mean is depicted through line chart in graph 3.

However, the change in VAS score from day 1 to day 3 and day 7 was observed to be more in patients treated with patches than those treated with tablets (ref. table 4 & 5).

A similar study was performed by **Bachalli PS et al in 2009**[36] to evaluate the analgesic efficacy of oral Diclofenac against trandermal Diclofenac patch in the management of post-operative pain following surgical removal of impacted mandibular third molars. The results of the study, both clinically and statistically showed that diclofenac sodium when administered orally showed slightly better pain control in the first 24 hours as compared to the transdermal form. However, over the next two post-operative days, there was no difference was observed in either form of administration

Post-surgical edema is an expected complication after third molar surgery. It can be caused by the response of the tissues to manipulation and trauma caused during surgery. Its onset is gradual and maximum swelling is present during 48 hours after

surgery.[62] Regression of the swelling is expected by the 4th day and completely resolution occurs in 7days.[6]

Troullos et al in 1990 also observed that swelling was maximum 48 hours after surgery[16]

King Kim et al in 2009 reviewed the literature and elaborated on the role of corticosteroids, NSAIDs and combination of these drugs in management of postoperative pain and swelling.[35]

On 1st postoperative day, mean facial swelling noted in patch group (11.18) was more than that noted in tablet group (10.81) which is significant. The swelling increased in both the groups upto 3rd post-operative day according to its natural course. It was still higher in patch group (11.38) than that in tablet group (10.86) which is also significant. The swelling showed a gradual decrease in both the groups till 7th post-operative day and the mean values for both the groups was 10.68 for tablet group and 11.13 for patch group (table 6) which is significant. A graphical representation of the mean is depicted through line chart in graph 4. Further, the difference in the measurements of 1st and 7th, as well as 3rd and 7th days were also statistically significant with $p < 0.0001$ in tablet group (table 7). In patch group the difference between 1st day and 3rd day was significant with p-value of 0.0324, the difference between 1st and 7th was insignificant with p-value 0.0324 and between 3rd and 7th day was highly significant with $p < 0.0001$ (ref table 8). Although the results pertaining to post-operative swelling were statistically significant on 7th post-operative day, showing that oral route was better but clinically both the routes proved effective and patient showed reduction in swelling.

Dental trismus means a limited mouth opening. It is a temporary condition commonly encountered after third molar surgeries. Trismus might result from some kind of insult to the muscles of mastication, restriction in jaw opening for a period of time. Trismus may also be due to post-operative swelling and pain and it influences patient's quality of life in the days following surgery. According to **Pederson A et al in 1985**[63] trismus in post-operative period is because the patient avoids maximum mouth opening due to pain.

Yu XM et al in 1995[64] suggested that trismus, in the postoperative period, is the result of a protective reflex against inflammatory states of orofacial tissues.

Trismus i.e. limitation in opening the mouth, may also affect the patient's quality of life in postoperative period after removal of impacted mandibular third molar. In the present study, trismus was measured by measuring inter-incisal distance (in millimeter) between upper and lower arch. On 1st postoperative day the inter-incisal distance in tablet group is more (34.83 mm) compared to patch group (28.13mm) which is significant. on 3rd postoperative day inter-incisal distance between tablet group (36.33 mm) and patch group (28.20 mm) was highly significant. On 7th postoperative it again increased in both group ie. tablet group (42.93 mm) and patch group (37.13 mm) which is significant (table 9). A graphical representation of the mean is depicted through line chart in graph 5.

Between 1st & 3rd postoperative day there is significant increase in inter-incisal distance in tablet group and between 1st & 7th postoperative day it is highly significant, similarly between 3rd & 7th it is highly significant (table 10). In patch group on 1st & 3rd postoperative day the inter-incisal distance is statistically non-

significant but difference between 1st & 7th postoperative day is highly significant and similarly it is highly significant between 3rd & 7th postoperative day (table 11).

We had found that in management of postoperative pain, swelling and trismus transdermal ketoprofen patch were comparatively less effective than ketoprofen tablets. It is reported that 15 out of 30 patients (50%) in transdermal ketoprofen patch group consumed rescue medication from the day of surgery to 1st and 2nd postoperative day and rarely on 3rd day. In contrast only 2 out of 30 patients (6.67%) in ketoprofen tablet group required rescue medications on the day of surgery (table 12). A graphical representation of the mean is depicted through bar chart in graph 6. The difference between the two groups as regards need for medication was statistically significant with p-value of 0.0006 using Chi-square test.

David Borenstein in 2015[65] conducted a study to evaluate the safety and efficacy of a transdermal ketoprofen patch with CHADD heat versus a placebo patch with dummy heat in patients with mild to moderate pain associated with osteoarthritis of the knee. Throughout the study, patients were allowed to take up to 2000 mg acetaminophen per day as rescue medication.

When ketoprofen used alone showed good results**. Mazières B** et al in 2005[66] test the efficacy and tolerability of a 100-mg patch of ketoprofen applied once a day for ankle sprain, and suggested that a 7-day course of treatment with a ketoprofen patch is useful in benign ankle sprain, without revealing unexpected adverse events.

But in our study when we compared oral ketoprofen with that of transdermal ketoprofen patch, it is found that oral keroprofen tablets are more effective than

transdermal ketofrofen patch in management of postoperative pain, swelling and trismus. On the other hand we had also considered the gastrointestinal side effect of the ketoprofen tablets and found that 10 out of 30 patients suffered from the gastrointestinal side effects such as abdominal pain etc in ketoprofen tablet group whereas only 2 out of 30 patients in transdermal ketoprofen patch group suffered from gastrointestinal side effect may be due to rescue tablets or antibiotics. The difference in the proportion of cases showing effect was statistically significant with p-value of 0.0238 using Chi-square test (table 13). A graphical representation of the mean is depicted through bar chart in graph 7.

Evans et al in 1995[19] evaluated the relation between **topical**ly applied non-steroidal anti-inflammatory drugs and upper gastrointestinal bleeding and perforation. In this study, the authors found that the **topical** non-steroidal anti-inflammatory drugs were not significantly associated with upper gastrointestinal bleeding and perforation, hence concluding that the topically applied NSAIDs have a safe systemic profile

Vaile JH et al in 1998[67] conducted a study to review the existing literature regarding systemic and topical NSAIDs and found the high incidence of serious gastrointestinal adverse events associated with the use of systemic NSAIDs, and the premise that minimization of plasma concentrations of active drug may result in fewer systemic adverse effects. Topical NSAIDS shows less plasma concentration in human and animal when compared to systemically given drugs. They noticed that the adverse event profile of topical agents is reasonable: minor cutaneous effects occur in up to 2% of patients but tend to be self-limiting. They concluded that it appears likely that

the lower plasma concentrations achieved with topical administration are likely to be associated with reductions in serious systemic adverse effects.

Moore RA et al in 1998[21] reviewed literature on the effectiveness and safety of topical non-steroidal anti-inflammatory drugs in acute and chronic pain conditions. 86 trials involving 10160 patients were studied. They found that topical NSAIDs were significantly more effective than placebo for pain relief. Local skin reactions were rare (3.6%), and systemic effects were rarer (less than 0.5%). They also reported that topical NSAIDs have a lower incidence of gastrointestinal adverse effects than the same drugs when they are taken orally. They concluded that the systemic adverse effect of topical NSAIDS is less in lower plasma concentration, while comparing the similar doses given orally and topically.

Various studies showed the occurrence of an erythematous rash, pruritus, etc. as common local adverse effects of the transdermal patch.[29] In contrary **Bhaskar H et al in 2010**[39] compare analgesic modility of transdermal diclofenac patch with oral diclofenac following multiple premolar extractions in orthodontic patients and they did not found any local adverse effect of transdermal patch. Similarly these events were not reported in any patient in our study.

Thus, transdermal patch provide less control of postoperative pain and inflammation as seen with oral tablets but had a safer systemic profile than tablet group. On the other hand tablet provide better pain control initially but the gastrointestinal adverse effects are more compared to patch group.

Summary And Conclusion

Third molar surgery is one of the most common procedure that is performed by oral and maxillofacial surgeons worldwide. Pain, swelling, trismus are the most common complication after surgical removal of third molar.[1]

The results of the study, both clinically and statistically showed that ketoprofen when administered orally showed better pain control in the immediate postoperative period when compared to the transdermal form. Transdermal patch was not seen to be adequate to relieve the symptoms like pain, swelling and trismus and most of the patients required rescue medications. However, in the following postoperative days, the results were comparable to those of the oral tablets. Though better in pain control, ketoprofen tablets were frequently associated with adverse gastrointestinal effects in which trandermal patch proved significantly better and safer.

Transdermal administration of ketoprofen has its role in pain control following minor surgical procedures, especially in patients who are susceptible to gastritis and in whom compliance is a problem. Looking at the findings of this study, it can be suggested that ketoprofen can be used in tablet form in the immediate postoperative period along with the drugs to control gastrointestinal symptoms such as antacids followed by use in the form of transdermal patch for prolonged management after surgical removal of impacted mandibular molars. However, ketoprofen transdermal patch can be the first choice in relatively less traumatic procedures, involving no or less trauma to hard tissues e.g. intra-alveolar or even trans-alveolar extraxtions of teeth.

Considering the small size of the sample, it would need a larger study to validate the above findings.

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Table 1

Descriptive statistics for age of patients

Age	No.	%
≤ 22	6	20
23-27	20	66.7
≥ 28	4	13.3
Mean	24.73	
SD	2.61	
Median	24.5	

Table 2

Gender distribution

Gender	No.	%
Male	19	63.33
Female	11	36.67

Table 3

Comparison of VAS scores between tablet and patch group at each time point

Statistical parameter	Pre-operative		1st day		3rd day		7th day	
	Tablet group	Patch group	Tablet group	Patch group	Tablet group	Patch group	Tablet group	Patch group
Mean	1.23	1.33	3.00	5.40	1.20	4.83	1.27	1.50
Median	1.00	1.00	3.00	6.00	1.00	6.00	1.00	1.00
Standard Deviation	0.50	0.61	1.14	1.77	0.41	2.26	0.45	0.63
Minimum	1.00	1.00	2.00	2.00	1.00	1.00	1.00	1.00
Maximum	3.00	3.00	6.00	8.00	2.00	8.00	2.00	3.00
P-value*	0.5275 (NS)		< 0.0001 (HS)		< 0.0001 (HS)		0.1431 (NS)	

*Obtained using Wilcoxon rank sum test

Table 4

Pairwise comparison between different time points in tablet group

Groups	P-values*
Pre-operative vs. 1st day	< 0.0001 (HS)
Pre-operative vs. 3rd day	0.7630 (NS)
Pre-operative vs. 7th day	0.7630 (NS)
1st day vs. 3rd day	< 0.0001 (HS)
1st day vs. 7th day	< 0.0001 (HS)
3rd day vs. 7th day	0.1573 (NS)

*Obtained using Wilcoxon signed rank test and adjusted using Bonferroni correction

Table 5

Pairwise comparison between different time points in patch group

Groups	P-values*
Pre-operative vs. 1st day	< 0.0001 (S)
Pre-operative vs. 3rd day	< 0.0001 (S)
Pre-operative vs. 7th day	0.3345 (NS)
1st day vs. 3rd day	0.0089 (S)
1st day vs. 7th day	< 0.0001 (S)
3rd day vs. 7th day	< 0.0001 (S)

*Obtained using Wilcoxon signed rank test and adjusted using Bonferroni correction

Table 6

Comparison of facial swelling measurements between tablet and patch group at each time point

Statistical parameter	Pre-operative		1st day		3rd day		7th day	
	Tablet group	Patch group	Tablet group	Patch group	Tablet group	Patch group	Tablet group	Patch group
Mean	10.65	10.66	10.81	11.18	10.86	11.38	10.68	11.13
Median	10.75	10.80	10.88	11.25	10.88	11.40	10.78	11.13
Standard Deviation	0.51	0.47	0.53	0.37	0.50	0.45	0.54	0.47
Minimum	9.60	9.60	9.85	10.50	10.05	10.50	9.50	10.30
Maximum	11.60	11.25	11.65	12.00	11.90	12.20	11.60	12.00
P-values*	0.9459 (NS)		0.0027 (S)		0.0001 (S)		0.0010 (S)	

*Obtained using independent sample t-test; S: Significant; NS: Non-significant

Table 7

Pairwise comparison of facial swelling measurements between different time points in tablet group

Groups	P-values*
Pre-operative vs. 1st day	0.0025 (S)
Pre-operative vs. 3rd day	0.0003 (S)
Pre-operative vs. 7th day	0.0003 (S)
1st day vs. 3rd day	0.5382 (NS)
1st day vs. 7th day	< 0.0001 (HS)
3rd day vs. 7th day	< 0.0001 (HS)

*Obtained using Tukey's HSD test; S: Significant

Table 8

Pairwise comparison of facial swelling measurements between different time points in patch group

Groups	Adjusted P-values
Pre-operative vs. 1st day	< 0.0001(HS)
Pre-operative vs. 3rd day	< 0.0001(HS)
Pre-operative vs. 7th day	< 0.0001(HS)
1st day vs. 3rd day	0.0324 (S)
1st day vs. 7th day	0.9999 (NS)
3rd day vs. 7th day	< 0.0001(HS)

*Adjusted P-values obtained using Tukey's HSD test

Table 9

Comparison of trismus alleviation distance between tablet and patch group at each time period

Statistical parameter	Pre-operative		1st day		3rd day		7th day	
	Tablet group	Patch group	Tablet group	Patch group	Tablet group	Patch group	Tablet group	Patch group
Mean	43.77	39.40	34.83	28.13	36.33	28.20	42.93	37.13
Median	44.00	40.00	35.00	28.00	35.00	28.00	42.50	36.50
Standard Deviation	5.75	6.77	7.75	6.52	7.59	6.54	5.56	6.83
Minimum	32.00	24.00	20.00	20.00	22.00	18.00	32.00	25.00
Maximum	53.00	50.00	50.00	45.00	50.00	47.00	52.00	50.00
P-values*	0.0093 (S)		0.0006 (S)		< 0.0001 (HS)		0.0007 (S)	

*Obtained using independent sample t-test

Table 10

Pairwise comparison of trismus alleviation distance between different time points in tablet group

Groups	P-values*
Pre-operative vs. 1st day	< 0.0001 (HS)
Pre-operative vs. 3rd day	< 0.0001 (HS)
Pre-operative vs. 7th day	0.1886 (NS)
1st day vs. 3rd day	0.0067 (S)
1st day vs. 7th day	< 0.0001 (HS)
3rd day vs. 7th day	< 0.0001 (HS)

*Adjusted P-values obtained using Tukey's HSD test

Table 11

Pairwise comparison of trismus alleviation distance between different time points in patch group

Groups	P-values*
Pre-operative vs. 1st day	< 0.0001 (HS)
Pre-operative vs. 3rd day	< 0.0001 (HS)
Pre-operative vs. 7th day	0.5797 (NS)
1st day vs. 3rd day	0.9999 (NS)
1st day vs. 7th day	< 0.0001 (HS)
3rd day vs. 7th day	< 0.0001 (HS)

*Adjusted P-values obtained using Tukey's HSD test

Table 12

Rescue medication required in two study groups

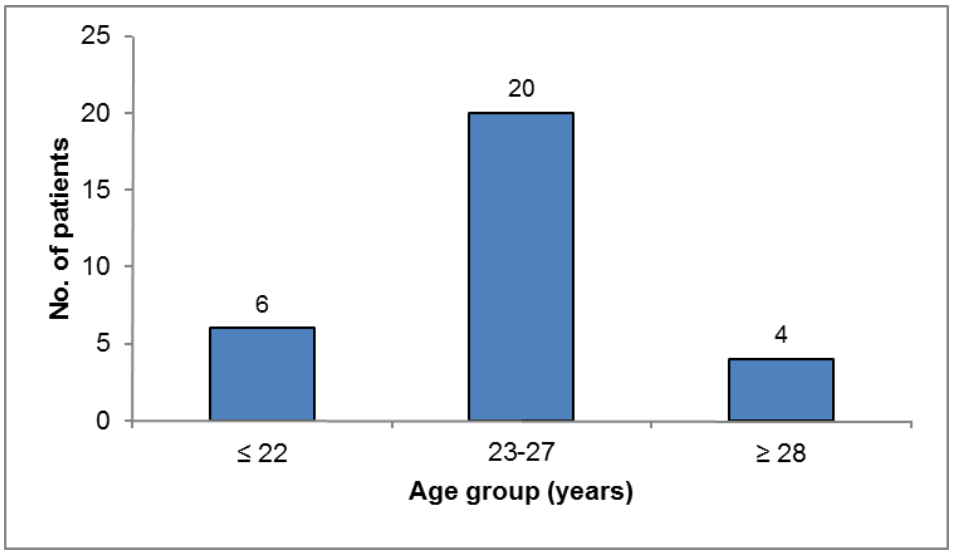
Rescue medication	Tablet group (n=30)	Patch group (n=30)
Yes	2 (6.67%)	15 (50%)
No	28 (93.3%)	15 (50%)

Table 13

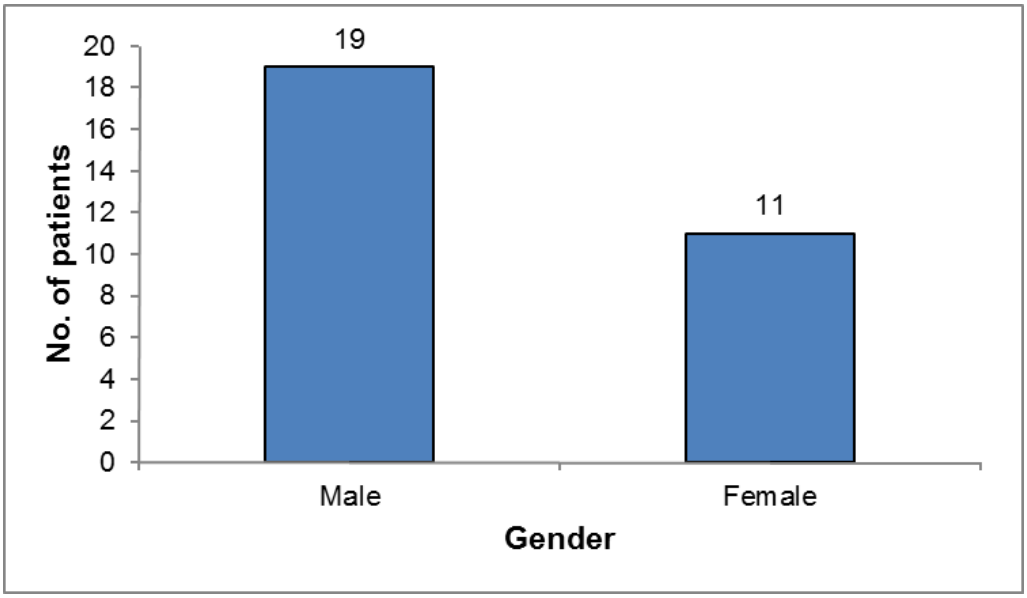
Adverse GIT effect noted in two study groups

Adverse GIT effect	Tablet group (n=30)	Patch group (n=30)
Yes	10 (33.3%)	2 (6.67%)
No	20 (66.7%)	28 (93.3%)

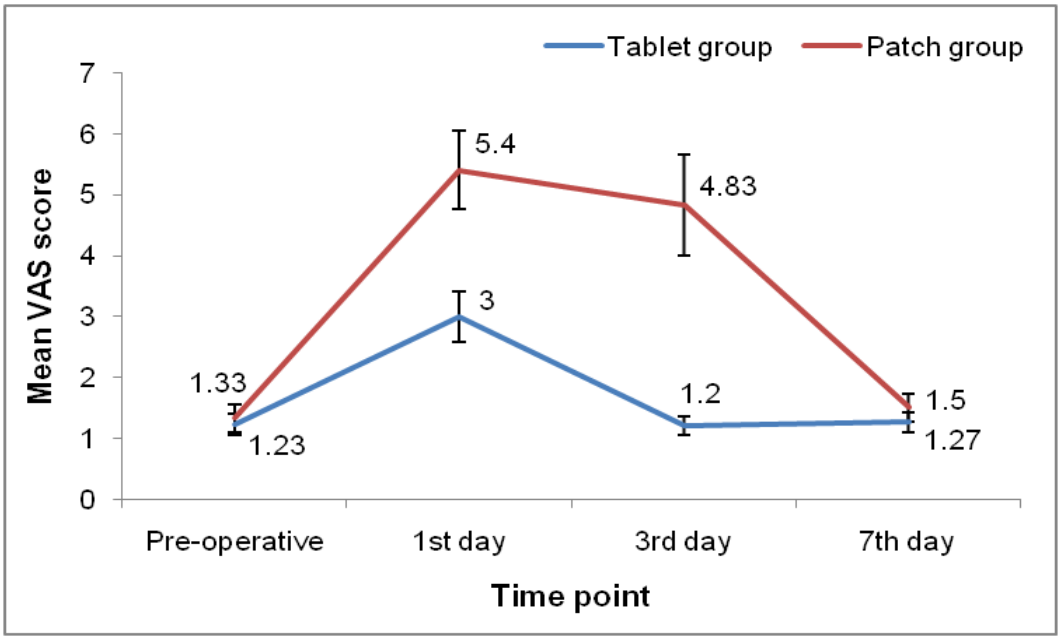
GRAPHS



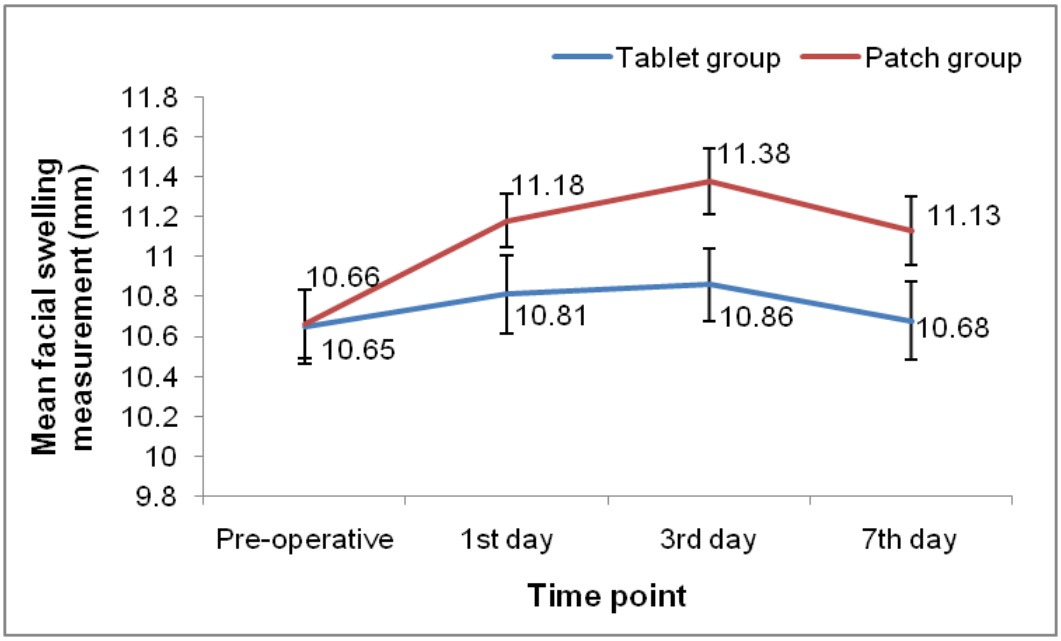
Graph 1: Column chart showing number of patients as per age group



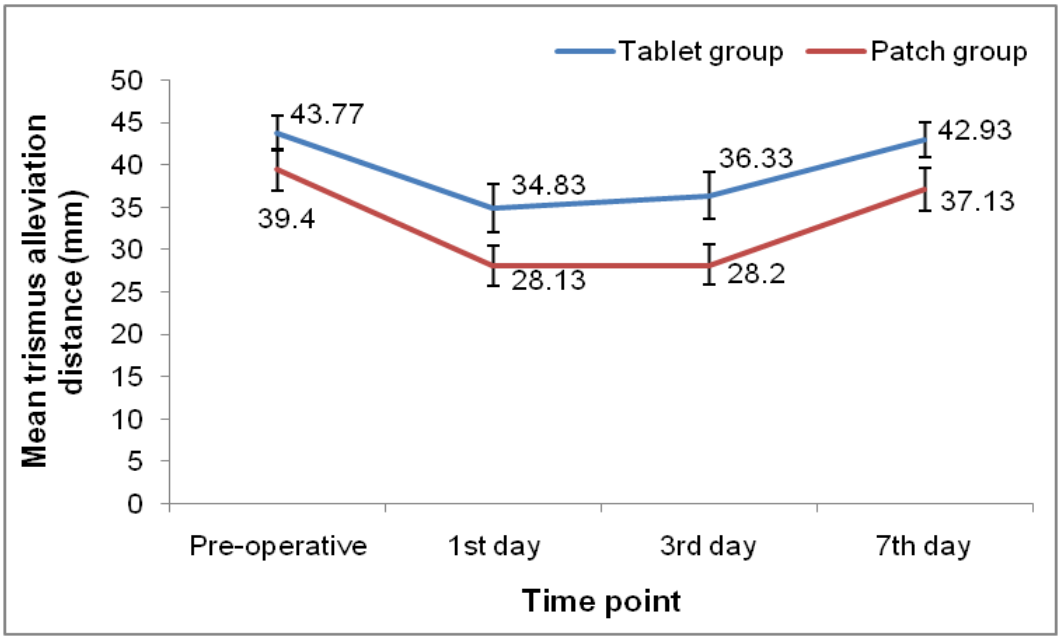
Graph 2: Column chart showing number of patients as per gender



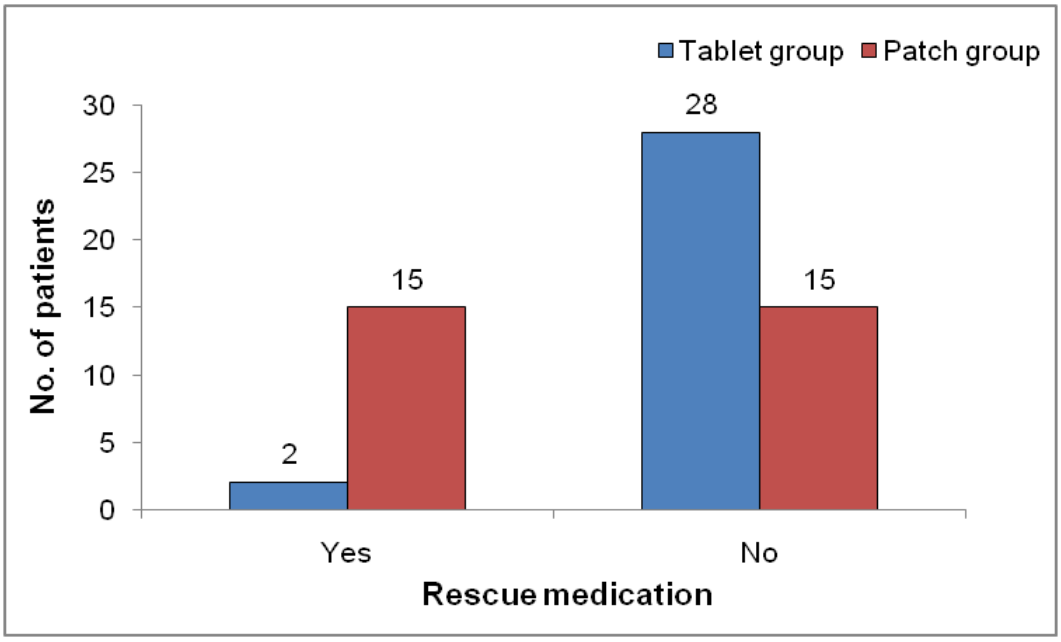
Graph 3:Line chart showing mean VAS scores of pain across times in two groups



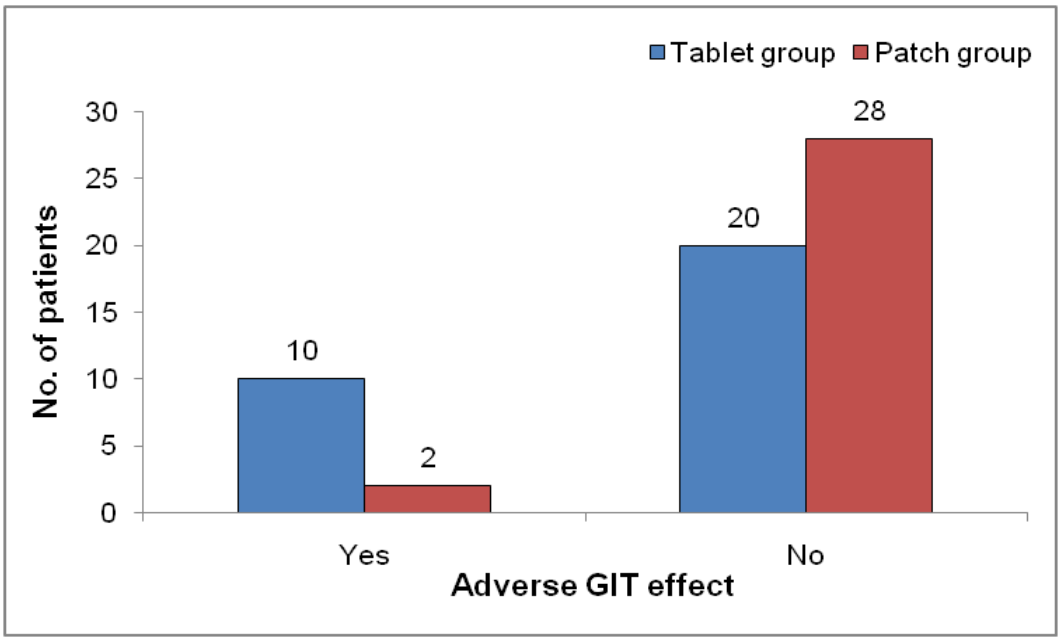
Graph 4: Line chart showing mean facial swelling measurements at different times in two groups



Graph 5: Line chart showing mean trismus alleviation distance across times for two groups



Graph 6: Bar chart showing number of patients requiring rescue medication in two groups



Graph 7: Bar chart showing number of patients with adverse GIT effects

ANNEXURE-I

DEPARTMENT OF ORAL & MAXILLOFACIAL SURGERY

CASE HISTORY PROFORMA

Case number-

Date-

Name-

Age/Sex-

Registration No-

Address-

Education-

Occupation-

Chief Complaint-

History of present illness –

Cause of tooth extraction-

Past Medical History-

Past Dental History-

Drug Allergy History-

Family History-

Personal History-

- Diet
- Habits

Examination-

Extraoral examination:

- Facial Symmetry
- TMJ
- Lymph nodes

Intraoral Examination**:**

- Teeth present
- Missing teeth
- Root piece
- Occlusion
- Caries/attrition/abrasion/erosion/abfraction
- Mobility
- Others

Diagnosis-

Radiographic investigations: IOPA-

OPG-

Other investigations-

Advice-

ANNEXURE-II

Assessment form

Group - A/B

Name: **OPD No:**

Age: **Sex:** **Occupation:**

Address:

Impacted molar for surgical removal –

VAS score for pain

Preop	1st day	3rd day	7th day

Swelling (In cm)

	Preop	1st day	3rd day	7th day
AB				
CD				
Facial (AB+CD) / 2				

AB – Distance from angle of mouth to midpoint of tragus of ear

CD – Distance from outer canthus to angle of mandible

Trismus (In mm)

Preop	1st day	3rd day	7th day

Rescue medications required – Yes / No

(If yes, number of tablets)

Adverse effects encountered - Yes / No

ANNEXURE-III

DEPARTMENT OF ORAL & MAXILLOFACIAL SURGERY

INFORMED CONSENT FORM

(Confidential)

"A Comparative evaluation of transdermal Ketoprofen patch with oral Ketoprofen following surgical removal of mandibular third molar."

I _____resident of _____aged_____years.
Exercising my free will, without any pressure/lure of incentive in any form, hereby give my consent to be included as subject in the said clinical study.

The doctor has informed me about this research project suitably and sufficiently to my satisfaction. I agree to allow my photographs to be drawn as required. I agree to take part in this project and will not mix any other projects during the period of this trial. I shall report to the dental hospital or other place where called on given appointment dates and time. I shall inform the doctor on any adverse effect or unusual symptom noticed by me. I shall co-operate with the doctors in all respects. I permit publishing the results of my participation in this study. I shall not be given any reimbursement or compensation. I have been informed about my right to withdraw from the research project at any given time.

I hereby record my consent for participation in the said trial.

1. _____	_____	_____	_____
Patient's name	Signature	Date	Time
2. _____	_____	_____	_____
Witness name	Signature	Date	Time
3. _____	_____	_____	_____
Investigator's name	Signature	Date	Time

ANNEXURE – IV

MASTER CHART

Sr no.	Comparison of pain VAS score							
	Tablet group				Patch group			
	Pre op	1st day	3rd day	7th day	Pre op	1st day	3rd day	7th day
1	8	2	1	1	1	4	3	2
2	1	2	1	1	1	2	1	1
3	1	4	2	2	1	2	1	1
4	1	4	1	1	2	4	4	1
5	1	4	2	2	1	2	1	1
6	2	4	2	2	1	6	7	1
7	2	2	1	1	1	6	6	2
8	1	2	1	1	1	4	2	1
9	1	3	1	1	1	6	7	1
10	1	5	2	2	1	4	2	2
11	1	3	1	1	1	7	6	1
12	1	2	1	1	1	5	4	2
13	1	2	1	1	1	7	8	3
14	2	3	1	2	1	6	6	2
15	1	2	1	1	2	7	6	2
16	1	4	1	2	1	4	3	2
17	1	4	1	1	1	7	7	2
18	3	3	1	1	3	6	7	1
19	1	3	1	1	1	6	3	1
20	1	2	1	1	1	6	6	1
21	1	5	2	2	2	8	7	2
22	1	2	1	1	3	5	3	1
23	1	2	1	1	1	8	7	1
24	2	6	2	2	2	8	7	3
25	1	2	1	1	2	4	2	1
26	1	2	1	1	1	6	7	1
27	1	3	1	1	2	5	4	2
28	2	4	1	1	1	7	7	2
29	1	2	1	1	1	7	7	1
30	1	2	1	1	1	3	4	1

Sr.no	Comparison of facial swelling							
	Tablet group				Patch group			
	Pre op	1st day	3rd day	7th day	Pre op	1st day	3rd day	7th day
1	10.4	10.45	10.5	10.4	11	11.15	11.15	11.15
2	9.6	9.85	10.05	9.5	10.8	11.3	11.22	10.9
3	10.4	10.5	10.5	10.4	11	11.25	11.5	11.2
4	10.5	11.65	11.65	11.4	10.25	10.8	10.5	10.3
5	10.8	11.05	11.05	10.8	10.76	11.2	11.2	10.8
6	11.25	11.5	11.5	11.25	11.25	11.5	11.85	11.675
7	10.76	11.05	11.05	10.8	10.4	10.75	11.5	10.6
8	10.25	10.4	10.4	10.3	9.9	10.65	10.9	10.5
9	11.35	11.35	11.35	11.35	11.15	12	12.2	11.9
10	10.25	10.4	10.45	10.25	11	11.2	11.6	11.1
11	9.95	10.1	10.2	9.95	10.8	11.55	11.6	11.3
12	11.15	11.25	11.25	11.15	10.9	11.35	11.4	11.2
13	10.2	10.5	10.55	10.2	11	11.35	11.8	11.575
14	10.75	10.4	10.85	10.75	9.8	10.5	10.5	10.5
15	10.75	11	11.05	10.65	10	10.85	10.95	10.6
16	10.9	11.1	11.1	10.9	9.6	10.55	10.75	10.65
17	9.9	10.05	10.05	9.9	10.15	10.95	11.9	11.425
18	10.8	10.85	10.85	10.8	10.8	11.25	12	11.625
19	10.85	10.9	10.9	10.85	11	11.35	11.1	11
20	11.6	11.6	11.6	11.6	11.1	11.3	11.4	11.2
21	10	10.15	10.15	10	10.76	11.15	11.15	11
22	11.5	11.65	11.9	11.45	10.4	11.3	11.35	11.1
23	10.6	10.75	10.75	10.6	11	11.25	10.85	11.05
24	10.25	10.3	10.45	10.25	10.15	10.8	12	11.8
25	11.05	11.1	11.1	11.05	10.9	11.2	11.2	11.2
26	11.4	11.5	11.05	11.45	10.9	11.5	11.8	11.65
27	10.2	10.3	10.3	10.2	10	10.65	10.9	10.3
28	10.9	11.2	11.2	10.9	11.15	12	12	12
29	11	11.1	11.4	11	11.25	11.55	11.6	11.575
30	10.2	10.4	10.6	10.2	10.6	11.3	11.4	10.9

Sr.no	**Comparison of trismus (interincisal distance in mm)**							
	Tablet group				Patch group			
	Pre op	1st day	3rd day	7th day	Pre op	1st day	3rd day	7th day
1	50	48	48	52	40	23	23	36
2	49	35	36	45	43	28	28	45
3	40	30	32	38	43	21	20	42
4	44	26	32	42	46	33	33	42
5	46	37	37	46	35	32	32	35
6	40	32	35	40	35	25	25	40
7	42	26	26	43	30	30	25	25
8	52	50	50	52	35	30	32	34
9	53	38	35	49	35	28	29	30
10	45	40	45	40	45	43	40	45
11	40	25	25	42	30	20	25	40
12	49	47	47	49	35	30	30	37
13	39	33	33	37	35	30	32	32
14	47	35	35	45	24	20	18	30
15	53	32	40	50	48	45	47	50
16	41	35	38	42	40	30	30	38
17	45	30	35	40	44	22	22	45
18	44	40	40	44	48	40	41	46
19	37	30	30	37	50	22	22	25
20	40	30	33	40	48	30	30	46
21	32	29	30	32	40	23	23	36
22	39	35	35	37	43	28	28	43
23	38	35	35	40	43	21	20	40
24	34	25	27	32	46	33	33	42
25	50	45	47	50	35	32	32	35
26	47	28	28	45	35	25	25	36
27	50	47	50	50	36	30	25	29
28	44	37	39	43	35	28	29	30
29	35	20	22	37	30	20	25	35
30	48	45	45	49	50	22	22	25

Rescue medications required		**Adverse GIT effects noted**	
Tablet group	Patch group	Tablet group	Patch group
0	0	No	No
0	0	**Yes**	No
0	0	No	No
0	0	No	No
0	0	**Yes**	No
0	1 tablet	No	No
0	1 tablet	No	No
0	0	**Yes**	No
0	1 tablet	No	No
0	0	No	No
0	2 tablets	**Yes**	No
0	0	No	No
0	2 tablets	No	No
0	0	No	No
0	1 tablet	**Yes**	No
0	0	No	No
1 tablet	2 tablets	No	**Yes**
0	1 tablet	**Yes**	No
0	0	No	No
0	1 tablet	No	No
0	1 tablet	No	No
1 tablet	0	**Yes**	No
0	2 tablets	No	No
0	2 tablets	No	No
0	0	**Yes**	No
0	3 tablets	No	**Yes**
0	0	**Yes**	No
0	1 tablet	No	No
0	2 tablets	**Yes**	No
0	0	No	No