TO COMPARE ANALGESIC AND ANTI-INFLAMMATORY EFFICACY OF SUBLINGUAL TABLET TRAMADOL VERSUS SUBLINGUAL TRAMADOL PLUS KETOROLAC AFTER THE SURGICAL EXTRACTION OF IMPACTED MANDIBULAR THIRD MOLARS: A RANDOMIZED, DOUBLE BLIND PROSPECTIVE STUDY

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LIST OF ABBREVIATIONS

Abbreviations	Full Form
IASP	International association for the study of pain
NSAID'S	Non-steroidal anti-inflammatory drugs
COX	Cyclooxygenase
AMP	Adenosine monophosphate
INDO	Indomethacin
DS	Diclofenac sodium
IL	Interleukin
Tx	Thromboxane
PGE2	Prostaglandin

INTRODUCTION

Introduction

Oral surgery encompasses a set of surgical procedures that often requires the incision of soft tissue and excision of mineralized tissue, such procedure may cause some injury and loss of the constitutional integrity of the anatomical structures involved at the surgical site, thereby leading to the occurrence of pain.[1]

International society of study of pain (ISSP) has defined pain as unpleasant sensory or emotional experience associated with actual or potential tissue damage or described in terms of such damage. [2]

Understanding of the pathophysiology of pain began more than a century ago, but the progress that has been made in the last few decades is phenomenal. This has resulted in better appreciation of the mechanisms of pain and development of innovative treatment modalities and drugs. There was a time in the history, where unexplained pain was a cardinal feature of hysteria, then considered as the commonest chronic disease.[3]

The surgical removal of the impacted mandibular third molar is one of the commonly performed operations by the oral and maxillofacial surgeons. Removal of tooth results in considerable pain, swelling and discomfort to the patient and is an inevitable sequel of inflammation. Proper surgical technique will minimize the squelae of inflammation but will not prevent them completely. [4]

Therefore, there has to be some pharmacological intervention that is needed to control the extent of inflammation and squelae of it such as pain, swelling and trismus in the immediate postoperative period.

The research in control of pain and inflammation is vast and a never ending process where new drugs are introduced , administered and analysed upon for their merits and demerits.

The anti-inflammatory agents aid to alleviate pain, reduction of edema and promotion of healing of the immediately adjacent tissue with minimal or no side effects. The drug should target unwanted inflammatory process which causes pain and edema. Once inflammation is brought under control the factors associated with it are reduced thereby providing relief to the patient.

In an attempt to overcome these problems, steroids, non-steroidal anti-inflammatory drugs (NSAIDs), opioids, enzymes, anti-histaminics, long acting local anesthetics and antibiotics have been tried with varying degrees of success.

Non-steroidal inflammatory drugs (NSAID's) in oral surgery

Inflammation produced by trauma at the surgical site and surrounding tissues is directly proportional to tissue damage, and directly involved in tissue healing; therefore, a meticulous surgical technique is essential to attenuate such condition. Classical signs of inflammation include pain, swelling, erythema, redness and loss of function, and several inflammatory mediators are involved, such as: prostaglandin, histamine, bradykinin and serotonin. [5]

During inflammation, prostaglandin and histamine levels are increased. Bradykinin plays a vast role in pro-inflammatory pharmacology, including a strong potential in pain production (**Gersema & Baker**). Prostaglandins are derived from arachidonic acid, which originates from the cellular membrane phospholipids. These are released through the action of phospholipase, activated by mechanical, chemical or physical stimuli.[5]

The metabolism of arachidonic acid follows through two main pathways: the cyclooxygenase (COX) or the lipoxygenase. COX is responsible for the production of prostaglandins (PGE2, PGD2, and PGF2), prostacyclin and thromboxane A2; on the other hand the lipoxygenase leads to the formation of a family of compounds collectively named leukotrienes. The byproducts of these two pathways play a key role in the inflammatory process.[6]

Two isoforms of COX have been identified, COX-1 and COX-2, which have specific mechanisms of action, COX-1 is mainly constitutive of several organs and tissues, such as the gastric mucosa and kidneys, while COX-2 besides being constitutive

of organs such as the brain, pancreas and kidneys, highly inducible such as in the inflammatory processes and cancer .COX- 2 also influences ovulation, medullary bone synthesis, osteoblasts and osteoclasts activities and regulation of endothelial and platelet response. Non-steroidal anti-inflammatory drugs can suppress the COX pathway.[6]

Ketorolac Tromethamine is a pyrrolizine carboxylic acid derivative and a non-steroidal anti-inflammatory agent used for analgesia for postoperative pain and inhibits cyclooxygenase activity. Ketorolac Tromethamine, a non-selective inhibitor of the cyclooxygenase (COX), inhibits both COX-1 and COX-2 enzymes. The anti-inflammatory effect of this agent is exerted by preventing conversion of arachidonic acid to prostaglandins at inflammation site mediated through inhibition of COX-2.

Opioids drugs in oral surgery

Opioids are derived from opium and therefore are included in the class of the group of drugs that act on neuronal opioidergic receptors. Such receptors are implied in regulation of the pain sensation, producing analgesia sensation. They are used primarily in therapy of high intensity pain, from chronic to acute. The modulation is made by endogenous opioids (physiological) such as endorphins and encephalin, which are neurotransmitters.

The three types of opioid receptors are: mu, kappa and delta. The pharmacological effects of opioids may be useful or adverse, according to the dose and situation; each drug can produce effects of different intensity, depending on their specificity for one or other receptors as well as other characteristics. Opioids, through

their G protein coupled receptors, inhibit adenylate cyclase and thereby reduce the content of intracellular cyclic-AMP. They also have effect on cationic channels, as they promote the opening of potassium channels and inhibit the opening of voltage-dependent calcium channels. This reduces both neuronal excitability and neurotransmitter release. However, they do not show any anti-inflammatory activity.

The side effect of opioids is in the central nervous system, opioids can produce analgesia, euphoria and dysphoria (at doses greater than those used for analgesia), respiratory depression, sedation, miosis, cough suppression, and nausea. Peripherally, in high doses, may also act in the gastrointestinal tract, causing constipation and biliary constriction.

In the cardiovascular system they can cause hypotension and in smooth muscle it is observed to cause an anti-diuretic effect and bronchoconstriction.

The works studied, showed that certain associations of anti-inflammatory and analgesics may be more effective than with the use of these medications alone. Opioids can be a good choice for patients who do not tolerate the use of NSAIDs. The prescription of pharmacological methods of analgesia should follow some principles that include: selection of a drug with sufficient potency to control the anticipated pain, the medication should be administered before the onset of pain, using the lowest doses necessary at regular and frequent intervals.[6]

Tramadol is increasingly being used for the management of pain associated with acute and chronic inflammatory conditions. It is neither a non-steroidal anti-inflammatory drug (NSAID) nor a true opioid. Tramadol exerts a unique dual mechanism of action. It binds weakly to μ opioid receptors and inhibits neuronal

reuptake of norepinephrine and 5-hydroxytryptamine (serotonin).Recently, anti-inflammatory effect has been demonstrated. Tramadol inhibits different types of experimental inflammation in rats and reduces the amount of inflammatory exudates, as well as the concentration of prostaglandin E_2.[8, 9,10,11,12]

Several recent studies have reported that the combined use of Tramadol and NSAID provides superior effect and therefore reduction in drug dosage reduces the associated complications.

Sublingual drug delivery

A preferable route is provided by the oral mucosa for the local and systemic administration of certain drugs and for the treatment of some diseases. This route provides several distinct advantages over the enteral and parenteral routes of drug delivery due to its rich blood supply, rapid onset of action, enhanced bioavailability, avoidance of the first pass metabolism and food effects, increased patient compliance, and ease of self-medication.[13]

The postoperative pain after surgical removal of third molars is so predictable and because of its consistency and intensity the removal of impacted third molars is often used to assess the quality of analgesics.

This randomized clinical trial was designed to compare the analgesic and anti-inflammatory effect of Tramadol Hydrochloride and Tramadol Hydrochloride with Ketorolac Tromethamine in combination in mandibular third molar surgery.

AIMS & OBJECTIVES

Aims And Objectives

Aim of the Study

To compare the clinical efficacy of sublingual Tramadol Hydrochloride alone versus a combination of sublingual Tramadol Hydrochloride and Ketorolac Tromethamine in the management of post operative pain, swelling and trismus after surgical removal of mandibular third molar.

Objectives of the Study

1. To evaluate the analgesic and anti inflammatory efficacy of sublingual Tramadol hydrochloride.
2. To evaluate the analgesic and anti inflammatory efficacy of sublingual combination of Tramadol Hydrochloride and Ketorolac Tromethamine.
3. Comparative evaluation of pain control and anti-inflammatory effect of sublingual Tramadol Hydrochloride alone with combination of Ketorolac Tromethamine and Tramadol Hydrochloride administered by sublingual route.

REVIEW OF LITERATURE

Review of Literature

Anti-inflammatory drugs

NSAIDs and corticosteroids are commonly used as anti-inflammatory agents.

Wilder-Smith et al reported that a combination of different analgesic mechanisms can reduce postoperative pain.[14] NSAIDs exert analgesic and anti-inflammatory effects through inhibition of cyclooxygenase and the biosynthesis of prostaglandins.[15] Recent studies have demonstrated that, in addition to its well-recognized stimulation of μ-opioid receptors and inhibition of biogenic amine reuptake, Tramadol reduces prostaglandin E2 concentrations in inflammatory exudates.[11,12] Actually, this anti-inflammatory effect of Tramadol could stem from the afore mentioned effect on serotonergic and noradrenergic transmission, which reduced inflammatory edema in experimental conditions.[16] In addition, the pharmacodynamic profile of Tramadol is different from that of NSAIDs that facilitate its gastric and renal tolerability.[17]

Ketorolac Tromethamine

Ketorolac Tromethamine is a pyrrolizine carboxylic acid derivative structurally related to Indomethacin. It is a non-steroidal anti-inflammatory agent used for analgesia for postoperative pain and inhibits cyclooxygenase activity.[18]

Ketorolac Tromethamine is the Tromethamine salt of Ketorolac, a synthetic pyrrolizine carboxylic acid derivative with anti-inflammatory, analgesic and antipyretic properties. Ketorolac Tromethamine, a non-selective inhibitor of the cyclooxygenase

(COX), inhibits both COX-1 and COX-2 enzymes. The agent exerts its anti inflammatory effect by preventing conversion of arachidonic acid to prostaglandins at inflammation site mediated through inhibition of COX-2, which is undetectable in most tissues but is up-regulated at the inflammation sites. Since COX-1 is expressed virtually in all tissues, this agent prevents normal state production of prostaglandins by inhibiting the COX-1 enzyme, which plays housekeeping roles in the protection of the gastrointestinal tract, renal blood flow regulation, and functioning in platelet aggregation. As a result, inhibition of COX-1 is usually associated with adverse effects such as gastrointestinal toxicity and nephrotoxicity.[18]

Mary-Frances Jett et al in 1999 did study in rats to evaluate the pharmacology of Ketorolac enantiomers (R,S)-, (S)-, and (R) in vivo and in vitro to elucidate possible mechanism underlying its analgesic efficacy using the nonselective cyclooxygenase (COX) inhibitors [Indomethacin (INDO) and Diclofenac sodium (DS)] as well as the selective COX-2 inhibitor, Celecoxib, as references and found that the potency of racemic (R,S)-Ketorolac was similar in tests of acetic acid-induced writhing, carrageenan induced paw hyperalgesia, and carrageenan-induced edema formation in rats; ID50 values 5 0.24, 0.29, and 0.08 mg/kg, respectively. (R,S)- Ketorolac's actions were stereo specific, with (S)-Ketorolac possessing the biological activity of the racemate in the above tests. The analgesic potencies for (R, S)-, (S)-, and (R)-Ketorolac, INDO, and DS were correlated highly with their anti-inflammatory potencies, suggestive of a common mechanism. (R, S)-Ketorolac was significantly more potent than INDO or DS in vivo. Neither difference in relative potency of COX inhibition for (R, S)-Ketorolac over INDO and DS nor activity of (S)-Ketorolac at a number of other enzymes, channels, or receptors could account for the differences in observed potency.

The distribution coefficient for (R, S)-Ketorolac was approximately 30-fold less than for DS or INDO, indicating that (R, S)- Ketorolac is much less lipophilic than these NSAIDs. Therefore, the physicochemical and pharmacokinetics properties of (R, S)-Ketorolac may optimize the concentrations of (S)-Ketorolac at its biological target(s), resulting in greater efficacy and potency in vivo.[19]

Trombelli L et al (1996) [20] conducted a double-blind, randomized, single-dose clinical trial to evaluate the analgesic efficacy of preoperative Ketorolac Tromethamine administration on periodontal postoperative pain. Two groups were formed of which one received Ketorolac immediately before periodontal flap surgery, and the other group received placebo. Results showed that a significant reduction in pain was observed when treated with Ketorolac as compared to placebo with no adverse reactions related to the drug.

Zackova M et al (2001)[21] reported a study which aimed to assess the best analgesia following oral surgery by using Ketorolac or Tramadol or their association and to know the associated side effects.51 patients were enrolled in the study and randomly assigned into Group K, Group T and Group KT. Group K received Ketorolac intravenously and Group T received Tramadol in the same way. Group KT received first Tramadol during surgery and then Ketorolac. Results seen were, no statistical difference statistically observed between K, T and KT groups in the pain scores. 64.8% in T group, 41.2% in K group and 58.8% in KT group achieved excellent analgesia. Side effect observed in all the groups was vomiting. It was concluded that Ketorolac and Tramadol resulted in effective postoperative analgesia during oral surgery.

Perez-Urizar J et al (2002)[22] conducted a randomized cross-over trail on 13 female volunteers to compare the bioavailability of Ketorolac after sublingual and intramuscular administration. First all the 13 volunteers were given Ketorolac sublingually followed by intramuscular route after washout period. Pharmacodynamic and pharmacokinetics of the drug with different routes were studies. Results showed that sublingual tablet was absorbed more rapidly than the intramuscular injection. Moreover, the onset on action of Ketorolac is slow via intramuscular route but duration of activity of the two routes was found same. The study concluded that sublingual route can be a better choice over intramuscular route.

De Franceschi L et al (2004)[23]conducted a study to evaluate the impact of a new analgesic regimen, with continuous infusion of Ketorolac and Tramadol in relieving pain associated with associated sickle cell disease.7 adults with sickle cell disease were enrolled in the study and were treated with Ketorolac plus Tramadol . The results showed that administration of Tramadol and Ketorolac was effective in pain relief and showed significant improvement in patient's mood and sleep. Thus it was concluded that a combination of Ketorolac and Tramadol proved to be a good analgesic in sickle cell patients.

Lopez Munoz FJ et al (2004)[24] conducted a pre clinical trial on rats to assess synergistic antinociceptive interactions between Ketorolac Tromethamine and Tramadol Hydrochloride. The drugs were given alone or in combination doses and the interaction was determined using a rat model of arthritic pain. Female rats received orally Ketorolac alone, Tramadol alone or 24 different combinations of Ketorolac plus Tramadol. The results showed that 10 combinations revealed

antinociceptive effects while other 14 combinations showed additive antinociceptive effects. Three combinations of Ketorolac and Tramadol (1.0+17.78, 1.78+10, and 1.78+17.78, mg/kg respectively) showed maximum antinociceptive effects. The study concluded that the combination of Tramadol and Ketorolac have a clinical utility in pain and prove to be better than a single drug.

Lepri A et al (2006)[25] conducted a double-blinded, randomized controlled trial to compare the clinical advantages and disadvantages with Tramadol alone versus a combination of Tramadol plus Ketorolac in the management of pain after major abdominal surgery.60 patients were randomly divided into Group T and Group TK to receive Tramadol and Ketorolac plus Tramadol respectively. Visual analogue scale was used for pain score assessment. Sedation score and the occurrence of adverse effects were assessed at 3 hours and 18 hours. It was found that no significant differences was present between the groups in terms of pain and side effects thus concluding that combination of Ketorolac plus Tramadol is an safe and effective treatment for postoperative analgesia in abdominal surgery.

Cassinelli EH et al (2008)[26] did study to study to assess the efficacy of Ketorolac in reducing postoperative pain and morphine requirements following primary multilevel lumbar decompression surgery. 25 patients who underwent a primary multilevel lumbar decompression procedure were assigned randomly to receive either Ketorolac or placebo in a double-blinded fashion. All the patients were allowed to receive intravenous morphine on an as needed basis after the surgery. Then the morphine requirements were recorded immediately postoperative, at 6, 12, and at 24 hours postoperative. A patient's overall hospital course morphine requirement was assessed as well. The pain levels of the patient postoperatively, were determined using the Visual

Analog Pain Scale and were documented at 4, 8, 12, 16, 24, and 36 hours postoperative. **Cassinelli EH et al** concluded that Intravenous Ketorolac seems to be a safe and effective analgesic agent following multilevel lumbar decompressive laminectomy. The patients can expect lower morphine requirements and better pain scores throughout their postoperative course.

Villegas-Gomez RM et al (2009)[27] conducted a randomized controlled trial to evaluate the best dose of the combination of Tramadol and Ketorolac to control postoperative pain secondary to open cholecystectomy. A total of 258 patients were recruited for the study and randomly dived into three groups with Group 1 receiving 50 mg Tramadol plus 20 mg Ketorolac, Group 2 receiving 100 mg and 40 mg and Group 3 receiving placebo. Pain intensity and quality along with adverse effects were assessed every 4 hours for 24 hours. Results showed that pain intensity in the Group 1 was 4.62 ± 0.67, Group 2 was 2.97 ± 0.91, and Group 3 was 8.36 ± 0.80 which was statistically different among all the groups. Pain free time was highest with Group 2 followed by Group 1 and 3.Vomiting and nausea were common side effects reported in all the groups apart from this Group 1 and 2 also reported drowsiness. It was concluded that 100 mg Tramadol 40 mg Ketorolac every 8 hours for first 24 hours post-surgery of cholecystectomy is safe and prove to be an effective pain control dose.

Al-Hezaimi K et al (2011)[28] conducted a randomized trial to evaluate the analgesic effect of a Ketorolac Tromethamine (KT) adhesive film for pain management after periodontal surgery. 68 patients were randomly assigned into treatment and control group. In the treatment group, adhesive film with KT was applied over the surgical site, whereas in the control group adhesive film without KT was placed initially. The KT

adhesive film was applied on the surgical site two hours after the surgery, in the control group. The results reported that a significant difference was found between pain reductions in two groups during first two hours but after applying KT film on control group no such difference between the groups was noted. It was concluded that adhesive film containing KT was effective in controlling post-surgical pain with no side effects.

Shankariah M et al (2012)[29] conducted an interventional study which recruited 50 patients undergoing surgery under general anaesthesia. 25 patients were given Ketorolac while other 25 were given Tramadol .Results observed were, both the drugs showed significant decrease in pain intensity from the 2nd to 24th post-operative hour. Tramadol resulted to be better than Ketorolac in relieving pain with a statistical significant difference. It was concluded that Tramadol was useful in pain control over Ketorolac with its intramuscular administration. But, side effects were observed with both the drugs.

Gashi Gecaj A et al (2013)[30] conducted a randomized clinical study to assess analgesic efficacy of Ketorolac and Tramadol when administered intravenously for pain relief postoperatively. 64 patients were randomly assigned into Group KTR who received Ketorolac and Group TMD who received Tramadol . Drug was administered at the time of skin closure and 8 hrs. Results demonstrated no significant differences between the groups with respect to pain scores. 54% in Group TRD and 8% in Group KTR reported side effects. Patients were more satisfied with Ketorolac than Tramadol. It was concluded that Ketorolac and Tramadol produced comparable effective postoperative analgesia, but Ketorolac was better than Tramadol when side effects were considered.

Neri E et al (2013)[31] conducted a double-blind, randomized, controlled trial to assess the effectiveness of sublingual Ketorolac Vs Tramadol in reducing fracture related pain among children.131 children were enrolled. In the study and assigned into Ketorolac (0.5 mg/kg) and placebo, or to Tramadol (2 mg/kg) and placebo by sublingual administration. Results showed that pain scores for Ketorolac were lower than those for Tramadol , but were not significant at any time point moreover, no statistically significant differences was observed with respect to side effects between the two groups. It was concluded that both Ketorolac and Tramadol were equally effective via sublingual route in managing pain among children with fractures and dislocations.

Motov S et al (2017)[32] conducted a randomized, double-blind trial to assess the analgesic effect of 3 doses of Ketorolac (10, 15, and 30 mg) given intravenously in emergency department patients. A total of 240 patients were enrolled in the trial with 80 in each dose group randomly assigned. The results showed that, at 30 minutes a reduction in pain was observed between the groups but was not statistically significant. No serious adverse effects were observed in any of the groups except dizziness, nausea, and headache. It was concluded that Ketorolac has similar analgesic effect at different doses given intravenously with minimum adverse effects reported.

Maslin B et al (2017)[33] conducted a review to know regarding the safety of Ketorolac use for postoperative pain. The review included clinical trials, retrospective studies and meta-analysis on Ketorolac use on bone healing, kidney function and blood loss. The resulted reported that Ketorolac in normal doses is safe to use in bone healing. The drug proves to be safe among healthy individuals but raises questions on its use in kidney dysfunction patients as well as in heart and liver disease conditions. Moreover,

prospective randomized controlled trials and meta-analyses included in this review could not gather much evidence to establish a point on Ketorolac leading to prolonged bleeding.

Cozzi G et al (2018)[34] conducted a multicentre randomized controlled trial in among children to assess the pain score reductions when children with acute abdominal pain received medication sublingually.210 children were randomized to receive Ketorolac 0.5 mg/kg or Tramadol 2 mg/kg sublingually or a melt in the mouth powder of 20 mg/kg Paracetamol. Results showed that pain scores at two hours were not significantly different between Ketorolac and Tramadol Vs paracetamol. It was concluded that sublingual route of administering analgesia was a suitable option for pain relief in children with acute abdominal pain.

Degala S and Nehal A (2018)[35] conducted a randomized controlled study to know the best analgesic between Tramadol and Ketorolac following maxillofacial surgery. A total of 46 patients were included in the study and were equally divided into two groups. Group 1 received intravenous Tramadol 100 mg and Group 2 received intravenous Ketorolac 30 mg 8h and 16 h following surgery. It was observed that, intravenous Tramadol resulted in better pain control than intravenous Ketorolac at every postoperative hour with a significant difference. Thus, the study concluded that Tramadol is a better choice over Ketorolac with keeping into consideration of the side effects observed in both.

Tramadol Hydrochloride

Tramadol is prescribed widely around the world for pain relief. A German drug company created the drug that specializes in treating pain in 1962. The medication was tested for 15 years in Germany before being approved and brought to the foreign market in 1977 under the brand name Tramal. The drug was a big success for the company.[36]

Tramadol is neither a non-steroidal anti-inflammatory drug (NSAID) nor a true opioid.[16] Tramadol exerts a unique dual mechanism of action: It binds weakly to μ-opioid receptors and inhibits neither neuronal reuptake of nor epinephrine and 5-hydroxytryptamine (serotonin).[37]

Recently, an anti-inflammatory effect has been demonstrated. Tramadol inhibits different types of experimental inflammation in rats.[11] Acute administration of Tramadol significantly reduces edema and hyperalgesia induced by yeast injection in the paw and reduces the amount of inflammatory exudates, as well as the concentration of prostaglandin E2.[11,12]

Katz et al (1996)[38] used Tramadol for the treatment of osteoarthritis. Tramadol is a centrally acting analgesic that has been shown to be effective in various acute and chronic pain states. Unlike other centrally acting analgesics, it exerts a dual action by binding to the opioid receptor site in the central nervous system and by weakly inhibiting the reuptake of biogenic amines. Tramadol is rapidly and almost completely absorbed, with an onset of action within 1 hour of oral administration. The recommended dosage is 50mg to 100mg every 4 to 6 hours; however, regular administration is an alternative, particularly for chronic pain states such as

osteoarthritis, where the use of the recently developed sustained release formulation may present an important advantage. Published studies evaluating specifically the use of Tramadol in this disease support its effectiveness. Nausea, drowsiness, dizziness, constipation and sweating have been reported in association with Tramadol use. Nausea occurs early in the course of administration and may be reduced by slowly titrating elderly population affected by osteoarthritis because, unlike non-steroidal anti-inflammatory drugs, it does not aggravate congestive heart failure or hypertension, nor does it have the potential to cause peptic ulcer disease. Compared with narcotics, Tramadol does not induce constipation, significant respiratory depression or have significant abuse potential.

Robert B. et al (1996)[39] concluded that composition comprising Tramadol and a non-steroidal anti-inflammatory drug is pharmacologically useful in treating pain and tussive conditions. The compositions are also subjected to less opioid side-effects such as abuse liability, tolerance, constipation and respiratory depression. Furthermore, where the components of the compositions are within certain ratios the pharmacological effects of the compositions are super additive (synergistic).

Paola Sacerdote et al (1997)[40] evaluated the effects of the acute and chronic administration of Tramadol on nociceptive thresholds (by the hot-plate test) and on immune responses (by measuring Concanavalin A-induced splenocyte proliferation, IL-2 production and natural killer activity) in mouse. After acute subcutaneous administration, Tramadol induced antinociception starting from a dose of 20 mg/kg, whereas it significantly enhanced the activity of natural killers and IL-2 production at doses as low as 1 mg/kg and a dose of 10 mg/kg started the splenocyte proliferation.

After the chronic administration, the antinociceptive effect of the drug was present still, whereas the immune modifications disappeared. Their results suggested that Tramadol could be a good choice for the treatment of pain in patients where immuno suppression may be particularly contraindicated.

Mauro Bianchi et al (1999)[11] examined the ability of the analgesic drug Tramadol to affect the development of inflammation in rats. The acute administration of Tramadol significantly reduced the hyperalgesia and the edema induced by yeast injection in the paw. Moreover, in the subcutaneous carrageenan induced inflammation, Tramadol reduced the amount of the exudates, as well as the prostaglandin (PG) E_2 like bio- and immune-activity in the exudates; on the contrary, leukotriene (LT) B_4 concentrations in the exudates were not changed. However, Tramadol did not affect the ability of macrophages to migrate towards the chemo tactic peptide N-formyl-L-methionil-L-leucyl-L-phenylalanine (FMLP). Our results suggests that Tramadol is able to inhibit the development of different types of inflammation in rat without affecting immune mechanisms, and contribute to explain the efficacy of this drug in the treatment of inflammatory pain.

Carola Buccellati et al (2000)[12] showed that the analgesic drug Tramadol relieved pain in inflammatory conditions by inhibiting the development of experimental inflammation and reducing prostaglandin (PG) E_2 concentrations in the inflammatory exudates. In this study, they evaluated the putative activity of Tramadol to suppress prostaglandin endoperoxide synthase-1 (PGHS-1), and prostaglandin endoperoxide synthase-2 (PGHS-2) activities in human whole blood *in vitro*. Platelet Thromboxane (Tx)B_2 production and monocyte PGE_2 production in LPS- stimulated blood were

measured in samples incubated with different concentrations (300 mg/ml, 3 μ g/ml, 30 μ g/ml) of Tramadol or its enantiomers. The formation of arachidonic acid metabolites was inhibited neither by Tramadol nor the enantiomers. Their results indicated that the anti-inflammatory effect of Tramadol demonstrated in some models was not related to a direct inhibitory effect on the formation of prostanoids.

Schnitzer T. et al (2003)[41] conducted the study of the rationale, efficacy and safety for a novel analgesic combination: Tramadol and acetaminophen (paracetamol). They concluded that Tramadol /acetaminophen combination, a new preparation was effective in acute or chronic moderate-to-moderately severe pain. The complementary actions of the constituent analgesics are beneficial; having the rapid onset of acetaminophen and the sustained effect of Tramadol . The analgesic efficacy of this combination was comparable to that of positive controls and its adverse event profile was in line with that of its single components.

Bianchi M. et al (2003)[42] compared the effects of Tramadol and paracetamol on synovial fluid concentrations of substance P and interleukin-6 in patients with knee osteoarthritis. They observed that both drugs significantly reduced the intensity of joint pain. The synovial fluid concentrations of substance P were significantly reduced only by the treatment with Tramadol . In this group of patients, IL-6synovial fluid concentrations were slightly, but not significantly, decreased. Paracetamol did not significantly change the synovial fluid concentrations of substance P and IL-6. This study concluded that the activity of Tramadol may involve the modulation of inflammatory mediators.

Eulalia Planas et al (2003)[43] reported an antagonistic interaction between Tramadol and non-steroidal anti-inflammatory drugs (NSAIDs), on gastrointestinal transit in rats. Transit was evaluated with charcoal and results were expressed as % inhibition. Tramadol and morphine had ED_{50}s of 120.70±9.54 and 3.20±0.26 mg/kg, respectively, while metamizol (85 mg/kg), paracetamol (100 mg/kg) or ibuprofen (50 mg/kg) had no effect. Tramadol plus an NSAID in all combinations, resulted in a rightward, non-parallel shift of the curves, which showed (two-way analysis of variance, ANOVA) significant differences from Tramadol alone for the dose ($P<0.0001$), the drug ($P<0.0001$) and their interaction ($P<0.0001$), demonstrating antagonism. No interaction was present for morphine plus NSAIDs. The results demonstrate that NSAIDs antagonize the constipating effects of Tramadol in rats, a fact that could have clinical relevance when combinations of these drugs are used in pain management in humans.

Gerccek A et al (2004)[44] compared the analgesic and anti-inflammatory effects of subcutaneous bupivacaine, morphine and Tramadol in rats. 0.25 % bupivacaine in Group B, 20 mg/kg Tramadol in Group T, 1 mg/kg morphine in Group M and 0.9% NaCl in Group S in a volume of 200 micro l were injected into the right hind paw of the rats (n: 40) 15 minutes before injection of 50 micro l 5 % formalin. Sedation and pain behavior scores, number of flinches and licking-time were recorded. The degree of dermal edema, intraneural edema, vasodilation, erythrodiapedesis, infiltration of polymorph nuclear leukocyte/lymphocyte and mast cell counts were analyzed histopathologically. In Group T and B, circumferential changes were lower than in Group M and S. The pain behavior scores were significantly lower in Group T and B. The number of flinches in Group T was lower than Group B and S. The vasodilation was significant only in Group M. The dermal edema was limited to deep dermis only

in Group T. Pre-inflammational subcutaneous Tramadol infiltration can provide effective analgesia and may have anti-inflammatory effects.

Norman R. Rosenthal et al (2004)[45] evaluated the efficacy and safety of Tramadol /acetaminophen combination tablets for the treatment of pain associated with osteoarthritis flare in an elderly patient population. The findings of this study demonstrated that combination therapy using one or two tablets of Tramadol /acetaminophen every 4 to 6 hours as add-on treatment for painful osteoarthritis flare in elderly patients with inadequate pain control from nonselective or COX-2–selective NSAID therapy decreased pain intensity, increased pain relief, improved over all osteoarthritis symptoms and physical function and received a favourable overall assessment of treatment.

Yong-min Liu et al (2008)[46] evaluated the effects of Tramadol on the pro-inflammatory responses in a rat model of incisional pain by investigating its effects on nociceptive thresholds and serum interleukin-6 (IL-6) and IL-2 levels. Forty-two male Sprague-Dawley (SD) rats scheduled for plantar incision were randomly divided into 7 groups (n=6 in each group). Rats in Group 1 receiving general anesthesia with no incision were served as control; At 30 min before skin incision, Groups 2∼5 were given 5 ml normal saline or 1, 10, and 20 mg/kg Tramadol , respectively, intraperitoneally (i.p.); Group 6 received 10 mg/kg Tramadol after operation; Group 7 received 10 mg/kg Tramadol before incision, followed by 200 μg/kg naloxone after operation.

Electronic von Frey filament was used to measure mechanical allodynia to evaluate the nociceptive thresholds 1 h before incision, and 1 h and 2 h after operation. Serum IL-6 and IL-2 levels were measured 2hrs after the operation by enzyme-linked immuno

sorbent assay (ELISA). The mechanical thresholds decreased significantly and serum IL-6 level increased significantly after operation in Group 2 compared with control (P<0.01) and these changes were reversed respectively by Tramadol in a dose-dependent manner (P<0.05 and P<0.01, respectively). IL-2 level remained unchanged after operation in Group 2, but decreased in Group 3 (P<0.05), then gradually returned to the normal level in Groups 4 and 5. The intra peritoneally injected Tramadol (10 and 20 mg/kg) produced a potent and dose-dependent antinociceptive effect on the lesioned paw. The antinociceptive effects of Tramadol were partially antagonized by Naloxone (200 μg/kg), suggesting an additional non-opioid mechanism.

The results suggested that Tramadol could be a good choice for the treatment of pain under the conditions that immuno suppression may be particularly contraindicated.

Irfan Shah et al (2008)[47] compared analgesic efficacy of Tramadol Hydrochloride with diclofenac sodium in dento-alveolar surgery. They concluded that the analgesic efficacy of the two drugs was equal except on day one when Tramadol did better than diclofenac. Tramadol can be used safely for post-operative analgesia after dento-alveolar surgery especially in situations where NSAIDs are contraindicated.

Selma S.A. et al (2010)[48] studied the effects of postoperative analgesia on acute phase response in thoracic surgery. They determined the influence of non-opiate (Group I- Methamisolnatrium) and opiate (Group II- Tramadol) postoperative analgesia on thoracic surgical patients' acute phase response, based on acute phase response protein serum values (IL-6 and C-reactive protein) 24, 48 and 72 hours after surgery. This study suggested that CRP enhanced values in both groups were the result of the response to surgery. The enhanced IL-6 values in group I and maintained IL-6 values within

reference range in group II, are the result of continuous Tramadol chloride opiate analgesia, which turned out to be more efficient and safer.

Passakorn Sawaddiruk et al (2010)[49] compared the efficacy and effectiveness of ULTRACET^{TM} and Tramadol /Acetaminophen in acute postoperative pain after upper extremity surgery and concluded that ULTRACET^{TM} has more efficacy and fewer side effects when compared with Tramadol and acetaminophen in acute postoperative pain surgery.

P. Kirdemir et al (2011)[50] studied the anti-inflammatory activities of Lornoxicam, Tramadol and Ketamine in acute inflammation rat model and compared their effects on acute phase proteins (CRP, IL-1, IL-6 and TNF a). Lornoxicam, Tramadol and Ketamine groups had 15 and the control group 10 rats. Before the procedure, basic values of hind leg paw volume were measured. Two test tubes were filled with tap water lateral malleolus of the right hind paw was marked and submerged into test tube up to the signed level and displaced volume of water was measured. According their groups Lornoxicam 1.3mg×kg−1, Tramadol 10mg×kg−1, Ketamine 10mg×kg−1 and 0.5 ml SF were intra peritoneally administered. 15 min. later 0.1 ml carrageenan solution was injected into the sub plantar area and paw volumes were measured at 3rd and 6th hours. At 6th hour 0.5 ml blood sample was obtained for acute phase protein values.

According control groups rat paw volumes, Lornoxicam and Ketamine groups had statistically significant lower values at 6thhour (p: 0.004, 0.003). Compared with control group, all the groups had lower CRP, IL-1b, IL-6 and TNFa values but Lornoxicam and Ketamine group had statistically significant low IL-1b values (0.023–0.014). Although Lornoxicam and Ketamine had lower values all three agents had effective anti-

inflammatory activities and they can be a good choice for post-operative pain management.

A.M. Spagnoli et al (2011)[51] compared Tramadol /Paracetamol combination and paracetamol in hand and foot surgery and concluded that combination of Tramadol /paracetamol allows better control of the postoperative pain after hand and foot surgery.

Yong-Jin Im et al (2015)[52] studied the pharmacokinetics of a sustained-release formulation of a Tramadol /acetaminophen combination in healthy subjects. They concluded that the sustained release combination Tramadol /acetaminophen tablet exhibited similar exposure and absorption rates compared with those of the immediate release formulation of Tramadol, O-desmethyl Tramadol and acetaminophen. The sustained release formulation may be more convenient for patients and has the potential to enhance compliance and pain control.

Takeshi Mochizuki et al (2016)[53] conducted a prospective, randomized, open-label clinical trial of Tramadol Hydrochloride/acetaminophen combination versus non-steroidal anti-inflammatory drug for the treatment of preoperative pain after total knee arthroplasty. They concluded that efficacy for perioperative pain management after total knee arthroplasty of Tramadol Hydrochloride/acetaminophen combination was superior to that of NSAID. Tramadol Hydrochloride/acetaminophen combination was also effective in improving the progress of rehabilitation.

Rudolf Martin Duehmke et al (2017)[54]did a review to assess the analgesic efficacy of Tramadol compared with placebo or other active interventions for chronic neuropathic pain in adults, and the adverse events associated with its use in clinical trials. They

searched CENTRAL, MEDLINE, and EMBASE for randomized controlled trials from inception to January 2017.They also searched the reference lists of retrieved studies and reviews, and online clinical trial registries. We included randomized, double-blind trials of two weeks' duration or longer, comparing Tramadol (any route of administration) with placebo or another active treatment for neuropathic pain, with subjective pain assessment by the participant. They concluded that there is only modest information about the use of Tramadol in neuropathic pain, coming from small, largely inadequate studies with potential risk of bias. That bias would normally increase the apparent benefits of Tramadol . The evidence of benefit from Tramadol was of low or very low quality, meaning that it does not provide a reliable indication of the likely effect, and the likelihood is very high that the effect will be substantially different from the estimate in this systematic review.

Surya Prakash Yarramalle et al (2018)[55] did study to evaluate the analgesic efficacy of Tramadol infusion versus Tramadol plus Ondansetron infusion in Medical Intensive Care Unit (ICU) patients. In the study 50 patients who experience pain other than postoperative pain were enrolled and randomized into two groups. Both the groups initially received 50 mg of Tramadol intravenously over 10 min followed by Group T+O received 10 mg/h Tramadol + 0.4 mg/h Ondansetron as an infusion. Group T received 10 mg/h Tramadol as infusion. Hemodynamic parameters along with pain assessment using Verbal Rating Scale (VRS) were analyzed at 0, 3, 6, 12, and 24 h. Rescue analgesia was administered if VRS >4. Side effects were noted by condition scoring criteria (CSC) scale. In the study Rescue analgesia was administered at 3 h, for three patients in T+O Group and 1 patient in T Group, but this is not statistically significant ($P = 0.153$). No rescue analgesia was required in both the groups at any other

point of time. There was fall in heart rate, systolic and diastolic blood pressures, respiratory rate at 0, 3, 6, 12, and 24 h in both the groups but not statistically significant. Grade 1 sedation of CSC scale was observed in two patients of Group T+O and one patient in Group T but not statistically significant ($P = 0.153$). No nausea and vomiting were seen. Finally they concluded that co-administration of Tramadol and Ondansetron can be practiced in medical ICU patients without any higher requirement in dosage of Tramadol .[55]

Third molar surgery

Third molar surgery has remained the mainstay of most Oral and Maxillofacial Surgery practices. Surgical removal of an impacted third molar (wisdom tooth) often involves pain, swelling and dysfunction during the postoperative period. The factors that contribute to determining this situation are many and complex, but they originate with the inflammatory process initiated by surgical trauma.[10]

Post-surgical squeal affect the daily life of the patient. **Gary D. Slade et al** studied the impact of third molar symptoms, pain, and swelling on oral health–related quality of life. Data from 480 patients with 4 third molars scheduled for removal were used in analysis. Questionnaires administered pre-surgery assessed patient's medical and dental history, their reasons for seeking third molar removal and socio-demographic characteristics. Adverse impacts on oral health-related quality of life were measured using the 14 item Oral Health Impact Profile (OHIP) questionnaire. The primary outcome variable was the percentage of people reporting 1 or more of the 12 non-specific OHIP items "fairly often" or "very often" during the 3 month before enrolment.

Their study showed that adverse impact on quality of life occurred for 1 in 8 patients seeking third molar surgery, and the probability increased 3-fold for patients who had experienced pain/swelling compared with those who were asymptomatic. [56]

NSAIDs and corticosteroids are the commonly prescribed anti-inflammatory agents for the control of inflammation after third molar surgery. Several authors have contributed data on the use of NSAIDS and corticosteroids after third molar extraction. The strength of the evidence provided by study depends on the success of its design in minimizing bias and maximizing attribution. Several studies have been conducted to evaluate the efficacy of various combinations of NSAIDS and corticosteroids in reducing the postsurgical sequelae experienced after oral surgical procedures, particularly after the removal of impacted third molar teeth. Recently, anti-inflammatory effect of Tramadol has been demonstrated. Many authors have contributed data on the use of combination of NSAIDS and Tramadol after third molar extraction.[11, 57, 58, 59]

There are no studies on the use of combination of Ketorolac and Tramadol in third molar surgery. This study is designed to evaluate and compare the analgesic and anti-inflammatory effect of Tramadol and Tramadol and Ketorolac Tromethamine in combination in mandibular third molar surgery.

Ketorolac in third molar surgery

Ong K S et al (2006)[60] conducted a study to compare the analgesic efficacy of a single-dose of Preoperative intravenous Tramadol versus Ketorolac in preventing pain after third molar Surgery. 64 patients undergoing elective third molar surgery were randomly assigned into two groups (32 in each group): Group I received Tramadol 50 mg, and Group 2 preoperatively received Ketorolac 30 mg intravenously.

After injecting the study drugs, a standard intravenous sedation technique was administered and the impacted third molars were removed under local anesthesia.Four primary end-points were used to assess difference in postoperative pain. Pain intensity measured by a 100-mm visual analogue scale hourly for 12 hour and concluded that Preoperative intravenous Ketorolac 30 mg is more effective than Tramadol 50 mg in the prevention of postoperative dental pain.

MM Shaik et al (2010)[61] conducted a comparative study to assess the efficacy, duration of action, onset of action, side effects of Tramadol and Ketorolac after the third molar tooth extraction surgery. 150 patients selected based on eligibility criteria were divided into Group A and B. Group A received 50 mg of Tramadol orally while Group B received 10 mg of Ketorolac orally. Result showed that the analgesic effect in Group A initiated within 1hour and at the end of 24 hours and pain intensity recorded was 2.12. In Group B, analgesic effect started within 30 minutes and at the end of 24 hours, the pain intensity reported was 2.98. Effects with Tramadol were sedation, dizziness and muscle relaxation along with sweating. In Ketorolac group, side effects observed were bleeding at the site of tooth extraction and epigastric pain. The analgesic effect of Tramadol lasted for 6 hours and that of Ketorolac for 5 hour. It was concluded that

Tramadol is a good analgesic for the relief of post-extraction pain and is more effective than Ketorolac for prolonged pain relief.

Isiordia-Espinoza MA et al (2011)[62] conducted a double-blind, randomized, placebo-controlled clinical trial to compare oral Ketorolac plus submucous local placebo with oral Ketorolac plus submucous local Tramadol post third molar impaction surgery for pan intensity. 30 patients were randomly divided into Group A and Group B. Group A received oral Ketorolac 10 mg, 30 minutes before surgery plus submucous local placebo and Group B received oral Ketorolac 10 mg, 30 minutes before surgery plus submucous local Tramadol. Results showed that pain intensity, number of patients requiring analgesic rescue medication, number of patients in each group not requiring analgesic rescue medication and total analgesic consumption showed statistical significance difference between the two treatment groups. It was concluded that oral Ketorolac plus submucous local Tramadol can be used as an alternative to Ketorolac alone for acute pain control after third molar disimpaction surgery.

Mishra H et al (2012)[63] Conducted a study to compare the analgesic efficacy and safety of single dose oral Ketorolac and Tramadol administered pre and postoperatively for dental extraction pain. To compare the analgesic efficacy and safety of single-dose oral Ketorolac and Tramadol administered pre and postoperatively for dental extraction pain hour before or half an hour after the procedure). Placebo was glucose powder filled in empty capsule. Pain assessment was done using a modified Verbal Rating Scale at 30 min, 2, 4, and 6 h after the procedure. Record of rescue analgesic (Ibuprofen 400 mg) during the 6 h study period, along with the time it was taken, was made. Record of any

adverse effects experienced, were also kept. Maximum pain scores for all of the six study groups, over the 6 h study period, were noted.

This study demonstrated that Tramadol and Ketorolac is equally effective in relieving pain in the first 6 h after molar extraction and therefore can be tried in patients who are intolerant to non steroidal anti-inflammatory drugs.

Trindade PA et al (2012)[64] conducted double-blinded, randomized, crossover trial on 47 volunteers to compare the clinical efficacy of sublingual Ketorolac and sublingual Piroxicam in managing pain, trismus and swelling after lower third molar extraction surgery. 47 patients first received Ketorolac sublingually followed by Piroxicam post washout period. Results reported that there was low pain intensity when treated with any of the drug. The mouth opening was also same in both the drugs. It was concluded that pain, trismus, and swelling after lower third molar extraction, were successfully controlled by sublingual Ketorolac or sublingual Piroxicam no significant differences were observed between the drugs.

Gopalraju P et al (2013)[65] conducted a comparative, prospective, randomized, controlled study to evaluate two different regimens of analgesics: a preoperative intravenous dose of either Tramadol or Ketorolac has given 10 min before surgery to assess their impact on clinical recovery after third molar surgery. Forty patients requiring surgical extraction of impacted mandibular third molars similar in position were enrolled in the study. Patients were randomly divided into two groups. Patients in Group 1 and Group 2 were administered either Tramadol 50 mg or Ketorolac 30 mg, intravenously, 10 min before to surgery. Postoperative pain difference was assessed by four primary points: pain intensity as measured by visual analogue scale hourly for 12 h, median time to rescue analgesics, number of analgesics , and patient's overall 5-point

global assessment scale. Throughout the 12 h investigation period, patients treated with Ketorolac reported significantly lower pain intensity scores, significantly longer time to rescue analgesics (Acetaminophen 500 mg) and fewer intakes of postoperative analgesics. In Group 2, 40% of the patient had overall good assessment as compared to that of Group 1 where only 25% of patients had good overall assessment. This study showed that pre-emptive use of Ketorolac 30 mg intravenously can reduce the severity of the postoperative sequelae of asymptomatic impacted mandibular third molar surgery.

Chetan R et al (2015)[66] conducted a double-blind, randomized, controlled clinical trial for assessing the efficacy of drug in controlling pain intensity post-surgery of impacted third molar. 40 patients were recruited and randomly assigned into Group A and Group B. Group A and Group B received 50 mg Tramadol and 10 mg of Ketorolac orally respectively. The results revealed that the analgesic effect in Group A initiated within 1 hour and reached the maximum in 4 hours. Pain intensity was 1.8. In Group B, analgesic effect started within 1hour and achieved its maximum effect at 1 hour itself. The pain intensity noted was 2.5. The analgesic effect of 50 mg Tramadol lasted for 6 hours and that of Ketorolac lasted upto 5 hour. It was concluded that Tramadol is safe and more effective than Ketorolac in relieving pain` intensity with prolonged effect after surgical removal of impacted third molar.

Isiordia-Espinoza MA et al (2016)[67] conducted a parallel, double-blind, randomized, placebo-controlled clinical trial to evaluate the analgesic efficacy of oral Ketorolac versus intramuscular Tramadol after a mandibular third molar surgery. Two groups, Group A and Group B were formed which consisted randomly assigned patients with 15 in each group. Group A, oral Ketorolac plus intramuscular placebo and Group B

received oral placebo plus intramuscular Tramadol 30 minutes prior surgery. Results reported that patients taking oral Ketorolac had longer time of analgesic and less postoperative pain compared intramuscular Tramadol group. It was concluded that oral Ketorolac had superior analgesic effect than Tramadol when administered before a mandibular third molar surgery.

Deepthi M et al (2016)[68] conducted a study on a total of 50 patients with symmetrically impacted mandibular third molars and were divided into two groups, 30mg intramuscular injection of Ketorolac and 75 mg diclofenac sodium were administered in the respective groups. The visual analogue scale was used to assess post operative pain for three days and the patients were also evaluated for the number of rescue analgesia. The data was statistically evaluated with paired t- test. The maximum time taken for pain perception for Group A Ketorolac was 5.48 hrs and Group B Diclofenac sodium was 4.9 hrs and p=0.235 which was not significant. The mean number of tablets taken by the patients in the first three post operative days was 3.24 in Group A i.e., Ketorolac and 4.04 in Group B i.e., Diclofenac sodium. The values were compared using the paired t test.

The p value = 0.004, which was significant.

Passi D et al in (2018)[69] conducted an interventional study to evaluate the analgesic efficacy of oral Ketorolac and Tramadol after a mandibular third molar surgery. **50 healthy patients aged 20-60 years were present in each group (Group A and Group B).** Group A received 10 mg of Ketorolac thrice a day and Group B received 50 mg Tramadol twice a day. Pain intensity was also recorded at different time intervals. Results revealed that pain relief in Ketorolac group was acquired within half hour but

lasted for only 4-5 hours only while in in Tramadol it lasted for a longer duration i.e., 8-10 hrs. Complications like nausea/vomiting and drowsiness/sedation were observed more in Tramadol group on the other hand, upper gastric pain/acidity was seen with Ketorolac group. The study concluded that oral Ketorolac was good analgesic for acute pain with etiology of surgery.

Tramadol in third molar surgery

Eman A. et al (2006)[57] investigated the anti-inflammatory effects of Ibuprofen and Tramadol by measuring C-reactive protein concentrations after removal of an impacted mandibular third molar. According to American Society of Anesthesiologists Forty-five Class I patients were randomly categorized into 3 equal groups according to postoperative analgesic medication. First group received Tramadol (100 mg every 8 hours), the second group received Ibuprofen (400 mg every 8 hours), and the last group received half doses of Tramadol and Ibuprofen in combination (50 mg Tramadol every 8 hours and 200 mg Ibuprofen every 8 hours). Measurement of C-reactive protein was done before surgery to exclude the presence of any preexisting inflammatory condition that might interfere with the study. C-reactive protein was also measured immediately after surgery and 72 hours postoperatively. At 72 hours, C-reactive protein had increased over post-surgery baseline by 123% in the Tramadol group (P <.001), 84% in the Ibuprofen group(P <.001), and only 37% in the combined analgesic group (P = .078). These results suggest that Tramadol may produce supra-additive anti-inflammatory effectswith Ibuprofen after third molar extractions.

Pozos-Guillen A et al (2007)[70] conducted a prospective, randomized, controlled, double-blind pilot study, 3 groups of 20 patients each were included: Tramadol preoperative, 100 mg intramuscularly (IM) 1 hour before surgery (group A); Tramadol postoperative, 100 mg IM immediately after surgery (group B); and saline (group C). We evaluated intensity of pain and analgesic consumption as was requested. The analgesic efficacy measured as complete relief of pain at 24 hours was 86% in the preemptive Tramadol compared with 70% and 36% for postoperative Tramadol administration and control group. A significant reduction in the consumption of analgesics was seen in preoperative group as compared with the postoperative and control groups. Adverse events were minimal and similar in all groups. This study suggests the preemptive use of Tramadol as an alternative for the acute pain treatment after the removal of an impacted mandibular third molar carried out under local anesthesia.

Shah A et al (2008)[47] conducted a study to find a safe and effective analgesic alternative to non-steroidal anti-inflammatory drugs (NSAIDs) for patients undergoing dent alveolar surgery who could not tolerate NSAIDs. We have compared on a double blind, randomized basis the efficacy of Tramadol Hydrochloride with Diclofenac Sodium. Sixty patients undergoing third molar surgery were divided into two groups. One group was given Tramadol Hydrochloride 50 mg three times daily and the second group diclofenac sodium 50 mg three times daily for three days. Pain control was measured using a 0 to 10 numerical scale. The analgesic efficacy of the two drugs was equal except on day one when Tramadol did better than diclofenac. Tramadol can be used safely for postoperative analgesia after dent alveolar surgery especially in situations where NSAIDs are contraindicated.

Hassan S S et al (2012)[71] conducted a study on twenty subjects selected randomly received butorphanol tartrate 1 mg intramuscular and 20 subjects received Tramadol Hydrochloride 50 mg intramuscular after the removal of mandibular third molars. Time of injection, amount of anesthetic injected, duration of surgery, adverse effects were recorded .The mean amount of LA administered in butorphanol group was 2.6450 ml and in Tramadol group was 2.640 ml respectively, the mean duration for surgery was 56.75 and 53.5 minutes for butorphanol and Tramadol groups respectively which was statistically not significant. Pain assessment was done with VAS which showed mean of 19.2 and 15.5 mm ($p = 0.001$) which was significant for butorphanol and Tramadol respectively after 12 hours. The mean time for rescue medication requirement was 5.9 hours (for Tramadol) and 8.4 hours (for butorphanol). Effective analgesic activity was seen by butorphanol 1 mg intramuscular then Tramadol 50 mg.

Jadson Alipio Santana de Sousa Santos et al (2012)[72] investigated the effect of preemptive analgesia with a combination of Tramadol and Dexamethasone or Tramadol + Diclofenac sodium in third molar surgery. They concluded that the combination of preemptive Tramadol and Dexamethasone was more effective in the control of postoperative swelling and trismus. Both protocols (Tramadol + Dexamethasone and Tramadol + Diclofenac sodium) demonstrated adequate analgesic efficacy, but Tramadol + Dexamethasone was more effective inreducing pain intensity.

Fabio A D et al (2012)[1] conducted a prospective, randomized, controlled, paired trial to perform a comparative analysis of the preemptive analgesic effect of Nimesulide and Tramadol chlorhydrate during third molar surgery. The study was carried out between March and November 2009, involving 94 operations in 47 male and female patients with bilateral impacted lower third molars in comparable positions. The sample was divided into two groups. Group A received an oral dose of 100 mg of Nimesulide 1 hr prior to surgery. Group B received an oral dose of 100 mg of Tramadol chlorhydrate 1 hr prior to surgery. The following aspects were evaluated in the postoperative period: adverse effects of the drugs; amount of rescue medication used (acetaminophen 750 mg); and pain 5, 6, 24, 36, 48, 60, 72 and 84 h after surgery using a visual analog pain scale. Peak pain occurred 5 h after surgery in both groups, with a mean pain score of 2.3 in Group A and 3.0 in Group B; this difference did not achieve statistical significance ($p > 0.141$). Based on the sample studied, Nimesulide and Tramadol chlorhydrate demonstrate similar preemptive analgesic effects when used in lower third molar surgeries.

Prathibha et al (2013)[73] did comparative study of intravenous Tramadol versus Ketorolac for preventing postoperative pain after third molar surgery. They evaluated two different regimens of analgesics: a preoperative intravenous dose of either Tramadol or Ketorolac given 10 min prior to surgery to assess their impact on clinical recovery after third molar surgery. They concluded that the use of pre-operative Ketorolac 30 mg IV offered an added advantage to the patients who undergone routine third molar extraction in terms of delay in onset of postoperative pain and increasing the painthreshold as compared with Tramadol 50 mg IV.

J. Perez-Urizar et al (2014)[22] compared compared the analgesic and anti-inflammatory efficacy, trismus control and tolerability of the combination of Lysine clonixinate and Tramadol (LCT) versus Tramadol (T) alone after surgical removal of impacted mandibular third molars. This study was a double-blind, randomized clinical trial, comprising two study groups of 20 patients each, who exhibited acute pain subsequent to surgical extraction of two mandibular third molars. Pain intensity was evaluated over a 96-h period using a visual analogue scale and a 5-point verbal rating scale. Secondary indicators of analgesic and anti-inflammatory effectiveness, trismus control and tolerability were determined. Patients administered LCT exhibited better therapeutic effects that those administered Tramadol .Fifty percent of patients in the LCT group rated this therapy as 'excellent analgesia' as compared to that of only 10% in the T group. The onset of the analgesic effect of LCT group was significantly rapid without any therapeutic failures. There were no significant differences among the groups with regard to anti-inflammatory effect or trismus. The results of this study suggested that the postsurgical analgesic efficacy of LCT in combination (LC 125 mg + T 25 mg) is superior to that obtained with T alone, administered at the dose of 50 mg, for up to 96 h after the extraction of both impacted mandibular third molars.

Ceccheti M M et al (2014)[74] conducted a study to assess analgesic and adjuvant anesthetic effects of sub mucosal Tramadol after third molar extraction. It was double-blind, split mouth, placebo-controlled, single-dose, crossover investigation, in which 52 patients underwent mandibular third molar extraction under local anesthesia. Surgical side was randomly assigned to sub mucosal 2 ml 100 mg Tramadol injection (group T) or normal saline solution (group P) immediately after surgery. Anesthetic blockade duration, time of intake and amount of rescue analgesic drug, and

postoperative pain intensity were recorded immediately after anesthesia cessation and 4, 8, 24, 48, and 72 hours after surgery. Data were submitted to analysis of variance and Wilcox on tests. Anesthetic blockade duration between groups was similar. Group T took significantly less rescue drug after 72 hours (P= .008). Time elapsed before first intake of rescue drug was more (P=.006), and pain intensity was significantly lower (P =.001) in T group.

Gonul O et al (2015)[75] conducted a study to evaluate the effectiveness of sub mucosal administration of Tramadol , for acute postoperative facial pain, following the extraction of impacted third molar teeth. This prospective, double-blind, randomized placebo controlled study included 60 ASA I-II patients undergoing impacted third molar surgery under local anaesthesia. Following the surgical procedure, patients were divided into two groups; group T (1 mg/kg Tramadol) and group S (2-mL saline). Treatments were applied submucosally after surgery. Pain after extraction was assessed By using a visual analogue scale (VAS) 0.5, 1, 2, 4, 6, 12, 24, and 48 h postoperatively. The time at which the first analgesic drug was taken, the total analgesic dose used, and any adverse tissue reactions were also noted . In group T, postoperative VAS scores were significantly lower as compared to that of in group S ($p < 0.05$). This study demonstrated that sub mucosal application of Tramadol postoperatively is an effective method for reducing acute post-operative facial pain after impacted third molar surgery.

Quadri A et al (2016)[76] conducted a study on one hundred patients for the removal of impacted mandibular third molars to compare the analgesic efficacy of Tramadol and Tapentadol in patients undergoing surgical extraction of impacted mandibular molars.

Patients were divided into two groups, i.e. group A and group B containing equal number of patients. Group A patients received 50mg Tramadol and group B patients received 50mg tapentadol orally immediately after surgery and 12 hours after surgery. VAS score of group A was 6.22±0.65 and group B was 5.92±0.97 at the end of 2 hours. VAS score of group A was 6.18±1.08 and group B was 5.76±1.25 at the end of 8 hours. VAS score of group A was 6.36±0.96 and group B was 6.46±1.2 at the end of 12 hours. VAS score of group A was 6.2±1.2 and group B was 6.2±1.47 at the end of 24 hours. VAS scores statistically were found to be in significant between two groups. All patients had moderate pain at the end of 2 hours, 92% of group A and 96% of group B patients had moderate pain at the end of 8 hours. Mild pain was noted in most patients around 24 hours according to the categorical pain scale.

Lars Erikson et al (2017)[77] conducted a study to evaluate the effectiveness and safety of pre-emptive single dose intravenous Tramadol 1mg/kg in combination with Midazolam in patients with dental fear and undergoing mandibular third molar. Pain was evaluated using VAS scale and safety was evaluated perioperative monitoring of saturation and blood pressure.

There was no difference in pain measured by VAS between the groups. It took quite longer time for first rescue pill in Tramadol vs. control group (157 vs. 110 min, $p = 0.049$). There was more commonly desaturation ($SpO_2 < 90\%$) found in Tramadol vs. placebo and control ($p < 0.01$). Increasing systolic blood pressure in the control group. There was decrease in diastolic blood pressure in Tramadol and placebo groups. In the Tramadol group, they saw more frequently mild side effects and concluded that

Tramadol gave no reduction in postoperative pain but an increased frequency of desaturation and side effects.

Punit S Dikhit et al in (2018)[78] conducted study to compare the preemptive analgesic effect of Diclofenac Sodium and Tramadol following surgical removal of mandibular third- molars. A double blind clinical study was conducted among 50 patients. Patients were divided into 2 groups. Group I and group II included 25 patients each who were given oral diclofenac sodium 50 mg and Tramadol 50mg tablets respectively, 1 hour before the procedure. All the operative procedures were done by a single operator. The 2 groups were compared and data was analyzed statistically. In diclofenac group the mean pain score at 2hr was 1.52, which increased at 4 hr and 6 hr with mean score of 2.6 & 3.44 respectively. The pain started reducing from 12hr after surgery, the mean score was 2.24 at 12 hr. In Tramadol group, mean pain score at 2 hr was 1.08, which was less compared to Diclofenac group. But pain score increased subsequently at 4 hr, 6 hr, 12 hr. The mean pain score was more in Tramadol group when compare to the Diclofenac group. They concluded that 50mg of oral Diclofenac sodium provides a better preemptive analgesia and also reduced post operative edema after surgical extraction of third molars when compare to the same dose of Tramadol . In terms of mouth opening there was no significant changes noted in both the groups.

MATERIALS AND METHOD

Materials and Method

An experimental study was designed to evaluate the clinical efficacy of sublingual Tramadol Hydrochloride alone versus a combination of sublingual Tramadol Hydrochloride and Ketorolac Tromethamine in the management of postoperative pain, swelling and trismus in third molar surgery.

Study design

Randomised, double blind, prospective and comparative in nature.

Study area

The study was conducted in the Department of Oral & Maxillofacial Surgery.

Study population

Patients requiring surgical removal of impacted mandibular third molar of mild to moderate difficulty level according to Pederson's index.

Sample size

The sample size calculation was done with the use of 'n master software 1.0 version'. The sample size calculation was based on proportions in which the groups were divided into 2. From the previous literature which gave two values for group A and group B. The power of the study was stated at 80% which could give statistically

significant result and the alpha error was set at 5%. The hypothesis was a two sided hypothesis which gave a sample size of 60 in each group.

Sampling technique

All selected patients according to inclusion criteria divided into two treatment groups, each group containing 60 patients using a computer generated random list.

Group A- Sublingual tablet Tramadol Hydrochloride 50 mg (i.e. **Tablet Contramal DT**)

Group B- Sublingual combination of Tramadol Hydrochloride 25 mg and Ketorolac Tromethamine10 mg (i.e. **Tablet Ketotram**)

Inclusion criteria

1. Patients requiring surgical removal of impacted mandibular third molar.

2. Patient with mild to moderate difficulty according to Pederson's index for impacted mandibular third molars.

3. Patients between 18-40 years of age (male and female) without any systemic condition.

Exclusion criteria

1. Patients with known allergy to Ketorolac, Tramadol, Amoxicillin, Clavulanic acid or Lignocaine Hydrochloride.
2. Patient suffering from epilepsy or any metabolic disorders.
3. Psychiatric disorders using Mono amine oxidase inhibitors like Isocarboxazid, Nialamide, Pheneizine etc.
4. History of GIT bleeding or ulceration.
5. Pregnant/lactating women.
6. Patients taking systemic steroids.
7. Patient not willing to volunteer for study.

Assessment of Parameters

The details recorded pre-operatively were facial baseline measurement (FM) and included inter-incisal distance (IID).

Pain

Pain was evaluated on Wong-Baker FACES Pain Rating Scale and values on 30min , 1hr, 2hr,4hr,6hr,12hr,24hr and 48hr post operatively and compared in the two study groups of patients.[79] **Fig.**

Swelling

The level of facial swelling was determined by a modification of the tape-measure method described by **Gabka and Matsumara**. Pre operatively and 1, 3, and 7 days

post operatively. Three measurements were made between five reference points: Mandibular angle (G), tragus (T), lateral canthus of the eye (L), outer corner of the mouth (A) and soft tissue pogonion (P) by using a measuring tape to follow the contour of the face The sum and mean of the 3 preoperative measurements was considered to be the baseline measurement for that side of the face. The difference between each postoperative measurement and the respective baseline value indicated the extent of facial swelling on that day.[80] **Fig. 2**

Trismus

Trismus was evaluated preoperatively and 1, 3, and 7 days postoperatively by measuring the distance between the mesial-incisal corners of the upper and lower right central incisors (inter incisal distance) at maximum opening of the jaws. The difference between the respective postoperative and preoperative measurements indicated the degree of trismus on that day. **Fig. 3**

Materials

1. Surgical instrument kit for removal of impacted mandibular third molar.**Fig.4**
2. Local anaesthetic solution consisting of 2% Lignocaine Hydrochloride with adrenaline 1: 2,00,000
3. Sublingual tablet Tramadol Hydrochloride 50 mg (Tablet Contramal DT, Abbott health care Pvt. Ltd) **Fig. 5**
4. Sublingual tablet Tramadol Hydrochloride 25 mg in combination with Ketorolac Tromethamine 10mg (Tablet Ketotram, Medley Pharmaceutical Ltd) **Fig. 6**
5. Tablet Amoxicillin 500 mg in combination with Clavulanic acid 125 mg (Tablet Augmentin^{TRN}, Glaxo SmithKline)
6. Tablet Ranitidine 150mg (Jb Chemicals and Pharmaceuticals Ltd.)
7. Vernier calliper
8. Measuring tape

Data Collection

Pre-Operative

1. Informed consent was taken from the patient before the surgical procedure.
2. After proper case history recording the surgical procedure was thoroughly explained to the patient.
3. Facial base line measurement and inter incisal distance were recorded according to the method mentioned above

Intra-Operative and Postoperative

1. Patients were prepared for surgery.
2. Local anaesthetic 2%Lignocaine with adrenaline 1:2,00,000 was administered.
3. Surgical removal of third molar was performed in a proper aseptic manner and with minimal trauma to the surrounding structures.
4. Access to the third molar was achieved from buccal aspect by raising a mucoperiosteal flap with Ward's I incision. Overlying bone was removed with round bur No: 8 and straight high speed hand piece under continuous irrigation with sterile saline solution. After thorough debridement and irrigation the flap was repositioned and sutured with 3-0 surgical silk suture. A single operator performed all the surgical procedures.
5. Sealed envelope containing either Tablet Contramal-DT or Tablet Ketotram were given to the patient and asked to consume the first dose immediately after completion of procedure and later to continue 8 hourly for 7 days.

6. Patients of both the groups received antibiotic, Tablet Amoxicillin 500 mg in combination with Clavulanic acid 125 mg (Tablet Augmentin^{TRN} 625mg, Glaxo SmithKline) 12 hourly for 5 days and antacid Tablet Ranitidine 150mg (Jb Chemicals and Pharmaceuticals Ltd.) 12 hourly for 7days.

7. Assessment of pain was done postoperatively at the interval of 30minutes and 1hour and 24 hr by the observer and later at the interval of 2hr, 4hr,6hr,12hr, and 48 hr was done by the patient himself using the **Wong-Baker Faces pain rating scale**.

8. Patient was recalled on 1st3rd and 7th post operative day for the assessment of parameters.

Statistical analysis

Data collected through the assessment form was entered into a computer using Microsoft Office Excel 2010. Statistics were performed using Statistical Package for Social Sciences (SPSS) version 21. The p-value was taken as significant when less than 0.05 (Confidence interval of 95% was taken) and power of the study at 80%.

Descriptive statistics on demographic details were obtained in numbers and percentages. Mean and standard deviations were obtained for pain, swelling and trismus at each time intervals. Man-Whitney test was performed to determine the statistical significant difference for pain between Tramadol and Tramadol plus Ketorolac group at each time intervals. Unpaired t test was performed to know the significant difference for swelling and trismus at each time intervals. Chi-square test was performed for the complications reported in each group.

Randomization

Numbers were assigned to patients visiting Department of oral and maxillofacial surgery and falling into inclusion criteria of the study and randomization was done through computer generated system as seen in **Table No.1**

Each group had 60 patients.

Group A (Tramadol Hydrochloride) – 60 Patients

Group B (Tramadol Hydrochloride plus Ketorolac Tromethamine) -60 Patients

Allocation concealment

The tablets delivered to the patients was covered in an opaque cover with the label hidden inside it regarding the drug delivered so that the type of tablet delivered to which group remained concealed from the patients as well as from the one distributing the tablets.

Blinding

To avoid bias in the study a double blinding was performed. The patients were not aware to which group they are belonging because the tablets were given in the same designed packets with same colour. Secondly, the person recording the parameters of pain, swelling trismus and complications at different intervals was kept unaware about the group he is examining.

1. The packets of Sublingual tablet Tramadol Hydrochloride 50 mg (i.e. **Tablet Contramal DT**) and combination of Tramadol Hydrochloride 25 mg and

Ketorolac Tromethamine10mg (i.e. **Tablet Ketotram**) was prepared by the operator and will be given to the patient after the completion of procedure.

2. The patient was brought in a different room and another observer unaware of the tablets given to the patient recorded the parameters.

3. The particular volunteer was unaware of the group they were included in.

Duration of study

The study was performed for a period of 18 months from January 2017 to July 2018.

Ethical clearance

The scientific and ethical clearance was obtained from the institutional review, Scientific and ethical committee.

Informed consent

A brief outline of the purpose of study along with the inclusion criteria was explained in the informed consent. The linguistics of the informed consent was as per the convenience of the patients. It was explained to the patients that their participation is voluntary, all the personal details are strictly confidential and their anonymity would be maintained. They were asked to raise their doubts or queries before signing the informed consent.

RESULTS

Results

The present study was undertaken to evaluate the analgesic and anti-inflammatory efficacy of Tramadol Hydrochloride and combination of Tramadol Hydrochloride and Ketorolac Tromethamine via sublingual route in patients undergoing mandibular third molar surgical extraction. The pain intensity post surgery was assessed using **Wong Baker Faces pain rating scale** at different time intervals in both the groups. Trismus was measured as the maximum distance between maxillary and mandibular central incisors on maximum mouth opening. Swelling was assessed by **Gabka and Matsumara** method.[80] The results obtained in the two groups for the above three parameters are as below:

Group A –

Tramadol Hydrochloride 50 mg i.e. (Tab. CONTRAMAL -DT)

A total of 60 patients were allocated in Group A from 18 years to 40 years of age.(Table no.2 & Graph no.1) shows the distribution of patients based on their age group in Group A. In group A , 8 patients belonged to age group 18-20 years, 3 into 21-23 years, 13 into 24-26 years, 10 into 27-29 years, 8 into 30-32 years, 6 into 33-35 years, 11 into 36-38 years and one into 39-41 years age group. The maximum patients were found from 24-26 years and the least were above 39 years of age. The mean age of patients in this group was 28.83±6.05. From 60 patients, 31 were males and 29 were females in Group A (Table no.3 & Graph no.2).

Group B-

Tramadol Hydrochloride 25mg + Ketorolac Tromethamine10mg i.e. (Tab. Ketotram)

A total of 60 patients were allocated in Group B from 18 years to 40 years of age. Table no.2 **& Graph no.1** shows the distribution of patients based on their age group in Group B. In group B, 6 patients belonged to age group 18-20 years, 11 into 21-23 years, 18 into 24-26 years, 11 into 27-29 years, 8 into 30-32 years, 3 into 33-35 years, 2 into 36-38 years and one into 39-41 years age group. Same as that of Group A, even in Group B the maximum patients were found from 24-26 years and the least were above 39 years of age. The mean age of patients in this group was 26.51±4.79. From 60 patients, 35 were males and 25 were females in Group B (Table no.3 & Graph no.2).

Pain

Group A

The table no.4 & graph no.3 represents the mean score of pain intensity of patients at different time intervals. 30 minutes after surgery the pain intensity was zero as the effect of anaesthesia has not let the patients feel pain. After 1 hour as the effect of local anaesthesia started weaning off the pain intensity started increasing. The mean score of pain intensity at 1 hour was 1.07±1.4. Following this pain decreased at 2 hours and 4 hours after which it again increased to 2.6±1.92 at 6 hours. Post 6 hours the pain intensity was seen decreasing steadily and reported to be 0.5±-.8 at 48 hours.

Group B

The table no. 5 & graph no.3 represents the mean score of pain intensity of patients at different time intervals. 30 minutes after surgery the pain intensity score was 0.10±0.4. After 1 hour as the effect of local anaesthesia started weaning off the pain intensity started increasing. The mean score of pain intensity at 1 hour was 1.00±1.3. Following this pain decreased at 2 and 4 hours after which it again increased to 1.83±0.76 at 6 hours. Post 6 hours the pain intensity was seen decreasing steadily same as that in Group A and reported to be 0.3±0.7 at 48 hours.

Between the groups

When statistical test was applied to know the difference between the two groups it was observed that a significant difference was present between Group A and Group B pain intensity only at 6 hours. For all other time intervals i.e. at 30 minutes, 1 hour, 2 hours, 4 hour, 12 hours, 24 hours and 48 hours no significant difference was found for pain intensity between Group A and Group B (Table no.6).

Swelling

Group A

Table no. 7 & graph no.4 shows the changes in swelling among patients receiving Tramadol Hydrochloride sublingually. It can be observed that the swelling increased post surgery on day 1 and then showed a decline in its values with the minimum swelling observed on day 7.

Group B

Table no. 8 & graph no.4 demonstrates the changes in swelling among patients receiving combination of Tramadol Hydrochloride and Ketorolac Tromethamine sublingually. It was observed that the swelling increased post surgery on day 1 and then showed a drop in its values with the minimum swelling observed on 7^{th} day.

Between the groups

When statistical tests were applied to know the difference in swelling between the groups it was observed that, no significant difference was present at baseline assuring that base line similarity was maintained between the groups. On day 1 a significant difference was observed in swelling between patients receiving Tramadol Hydrochloride and patients receiving combination of Tramadol Hydrochloride and Ketorolac Tromethamine with $p<0.05$. On day 3 as well a significant difference was observed in swelling between patients receiving Tramadol Hydrochloride and patients receiving combination of Tramadol Hydrochloride and Ketorolac Tromethamine with $p<0.05$ indicating that a combination of Tramadol Hydrochloride and Ketorolac Tromethamine is better in reducing swelling as compared to Tramadol Hydrochloride alone when given post mandibular third molar removal surgery. At the end on 7 day no significant difference was found between the groups signifying that at the end both drugs when given alone or in combination show a similar result of reducing swelling post surgery.(Table no.9)

Trismus

Group A

Table no. 10 & graph no.5 represents the changes in mouth opening before surgery, on day 1, on day 3 and on day 7. Mouth opening was maximum before surgery with a mean of 40.37±3.344 but reduced post surgically on day1 and then showed an increase on day 3 with mean of 33.40 ±4.056. The mouth opening came back to normal as it was before surgery within 7 days.

Group B

Table no.11 & graph no.5 represents the changes in mouth opening before surgery, on day 1, on day 3 and on day 7. Mouth opening was maximum before surgery with a mean of 39.48±2.487 but reduced post surgically on day1 and then showed an increase on day 3 with mean of 35.52 ±3.332. The moth opening came back to normal as it was before surgery within 7 days.

Between the groups

When statistical tests were applied to know the difference in mouth opening between the groups it was observed that, no significant difference was present at baseline. This indicated that the both groups were similar to each other before surgery. On day 1 a significant difference was observed in mouth opening between patients receiving Tramadol Hydrochloride and patients receiving combination of Tramadol Hydrochloride and Ketorolac Tromethamine with $p<0.05$. Similarly on day 3 a significant difference was observed in inter incisal distance between patients receiving Tramadol Hydrochloride and patients receiving combination of Tramadol

Hydrochloride and Ketorolac Tromethamine with $p<0.05$ indicating that a combination of Tramadol Hydrochloride and Ketorolac Tromethamine is better in the management of trismus compared to Tramadol Hydrochloride alone when given post surgically following surgical extraction of mandibular third molar. At the end on 7 day no significant difference was found between the groups signifying that at the end both drugs when given alone or in combination shows a similar result in the management of trismus following surgical extraction of mandibular third molar. Table No. 12

Complications

Table no.13 & Graph no.6 shows the number of patients who had complications due to the treatments given. It was observed that 20 patients in Group A suffered with complication while only 5 patients were found to have complications due to the study drug in Group B. Most common complications reported in patients of Group A were sedation, sweating, nausea, epigastric pain and bleeding at extraction site. Sedation was observed in 10 patients, sweating in 5 patients, nausea in 3 patients, epigastric pain in 3 patients and bleeding at the site in one patient. While in Group B, sweating, nausea and epigastric pain were the complications observed with sweating observed in one patient, nausea in one patients and epigastric pain in 3 patients.

When chi-square test was applied to know the difference in the presence of complication between the two groups, it was revealed that a statistical significant difference with $p<0.05$ was found between the groups with Tramadol Hydrochloride group showing more complications as compared to the group receiving combination of Tramadol Hydrochloride and Ketorolac Tromethamine sublingually. (Table no.14)

DISCUSSION

Discussion

Mandibular third molar impaction is the most common dental problem adhered by an individual from the age of 18 years. More than maxillary third molar, mandibular third molar is the one which is more prone to impaction with more predilections towards females. This is because the mandible is made up of dense and compact bone while that of maxilla is made up of spongy, porous bone thus allowing an easy escape of the third molar through the bone of maxilla. Around 48.19% of patients underwent surgical removal of third molar surgery according to **Ramamurthy A et al** in 2012.[81]Though the surgery is performed to overcome the difficulties faced by patients due to its impaction but still it has few of the short term effects on the patient undergoing surgery. The cons post surgical removal of mandibular third molar are, edema or swelling, pain, trismus, infection, prolonged bleeding from the operated site, alveolar osteitis, temporomandibular joint disorders, nerve disturbance and mandibular fracture.[82]Among all these; pain, swelling and trismus are the most common complications observed after surgical removal of mandibular third molar.

Though the surgery is carried under local anaesthetic nerve block to cease the pain sensation to the patients during surgery but soon as the effect of anaesthesia starts to wean off patients start feeling pain in varying intensities. This pain though temporary, still affects the quality of life of patients to a great extent and gives a miserable feeling. In order to minimize the intensity of pain many different groups of analgesics are present which are administered via different routes. Each route has its advantages and disadvantages. From the routes like, oral, intramuscular, and intravenous, sublingual route is the one which has been studied less and still has been found to be more effective

as compared to the other routes having fast onset from the available literature. Moreover, the combination of drugs may prove to be a better choice over a single drug effect, providing positive synergistic interaction and decrease in individual drug dose and possible side effects.[22]

Thus this study was undertaken in an attempt to compare the analgesic and anti-inflammatory efficacy of tablet Tramadol Hydrochloride and combination of tablet Tramadol Hydrochloride and Ketorolac Tromethamine when administered via sublingual route. Parameters which were compared between the two groups; pain, swelling, trismus and complications are discussed below.

In the present study all the patients were given same antibiotic tablet i.e. tablet Amoxicillin 500mg in combination with Clavulanic acid 125 mg. the only difference was in the analgesics administered between the groups. Group A received Tramadol Hydrochloride while Group B received combination of Tramadol Hydrochloride and Ketorolac Tromethamine.

According to the results obtained in the present study it was found that both, Tramadol Hydrochloride as well as combination of Tramadol Hydrochloride and Ketorolac Tromethamine proved to be effective in reducing pain post surgical removal of mandibular third molar. This suggests that the drugs very well carried out their analgesic work for which they were formed. It was found that after administering Tramadol Hydrochloride via sublingual route immediately after surgery, the pain intensity was very low with a mean of 0.00±0.0 after which it increased to 1.07±1.4. Following 1hour the pain intensity deceased to 0.47±0.9 than again started increasing. These peaks and falls in the intensity may be because, initially within 30 minutes,

though analgesic was taken but still its effect was not felt as the anaesthesia was still present. As the anaesthetic effect started to wean off, patients started experiencing pain and thus an increase at 1 hour is noted. But soon after this the drug showed its maximum potential leading to fall in the scores. Thus maximum action of the drug was observed 2 hours post surgery. A steady increase in the pain score was noted which reached maximum at 6 hours with a mean of 2.60±192 suggesting that after 2 hours the effect of drug was no more the same and showed a deprived action thus causing an increase in pain. As the drug was taken 8 hourly therefore post second dose of the drug, again a decrease in the score was found which further decreased after third dose.

Similarly in Group B wherein Tramadol Hydrochloride and Ketorolac Tromethamine combination was given, an increase in the score was observed in the initial hours after drug administration from 0.10 to 1.83 accounting for loss of anaesthetic effect post which it again decreased and again increased to maximum at 6hours. The pain intensity was minimum after third dose. These results are similar with the study conducted by **Shaik MM et al in 2010** wherein analgesic property of Tramadol was compared to Ketorolac when given orally.[61] Both the drugs proved to be effective in reducing pain intensity following third molar removal surgery. The variations observed were maximum pain at 30 mins following which it reduced every hourly and again started increasing achieving a peak at 6th hour. Following the second dose again a steady decrease was observed and attained the lowest value post forth dose. The maximum effect of Tramadol and Ketorolac was attained within 4 hours in the study reported by **Chethan R et al in 2015**.[66] while in the present study the maximum effect was attained within 2 hours. The reason for a quick effect in the present study may be due to the fact that the drug when given sublingually is readily absorbed, as it

shows its effect compared to the drug taken orally as in the study done by **Chethan R et al** . This theory is in support with **Perez Urizar J et al** which concluded that the onset of the drug is quick when given sublingually over other oral route.[22] Tramadol alone exhibited its maximum effects at the end of 1 hour as reported by **Passi D et al** which was similar to the results of the Tramadol group of our study.[69]

When comparison was done between the single drug group and the group with a combination drugs it was evaluated that the combination groups proved to be more effective in reducing pain as compared to a single drug group. The results of the present study are similar with **Isiordia-Espinoza MA et al** who conducted a study comparing the efficacy of Tramadol alone and Tramadol plus Ketorolac in relieving pain post third molar removal surgery. In their study it was observed that both the drugs were effective but Tramadol when administered alone maintained higher pain intensity values on Visual analog scale while those with the combination were seen with lower values. Moreover, just like in our study the significant difference was observed at 6 hours post surgery. Similarly in **Isiordia-Espinoza MA et al** the difference started to appear from 2 hours but the maximum difference in pain intensity between the two groups was at 6 hours.[62] **Lopez Munoz FJ et al** concluded that fourteen combinations of Tramadol and Ketorolac were found to have additive effect over pain and the combination therapy proved to be better over a single drug therapy.[24] In contrast was with the study reported by **Lepri A et al** in 2006 wherein, a randomized controlled trial was conducted to compare the efficacy of two groups in patients who underwent abdominal surgery, pain intensity was measured at different time intervals but at no point of time the two groups showed significant difference.[25]

When the groups in the present study were compared till the end of the assessment period it was found that both the drugs were equally effective after a period of time in relieving pain thus showing no significant difference between them. The results are in concordance with **Isiordia-Espinoza MA et al** wherein at the end of 12 hours post surgery, both Tramadol and Tramadol plus Ketorolac group showed intensity of pain on VAS. The duration of action was prolonged in Tramadol plus Ketorolac group as compared to the other group in the present study. [62] When Tramadol and Ketorolac were compared for the same parameter in **Chethan R et al** study, Tramadol showed a long lasting analgesic effect thus a combination of Ketorolac and Tramadol in our study would be an obvious reason for the prolonged action over Tramadol alone. Overall it was found that for controlling pain post surgery any of the drugs would go well but, in cases where a quick initiation of relief is required then a combination of Tramadol Hydrochloride and Ketorolac Tromethamine would be a great choice over only Tramadol Hydrochloride .[66]

The second most common complication following surgical removal of mandibular third molar is swelling or edema. Whenever a surgery is performed some amount of trauma is caused to the alveolar bone along with the tissues and blood vessels. This trauma causes increase in vascular permeability and thus leads to edema .[82] Apart from the trauma occurring during the surgery some other factors like the clinical skills of the surgeon performing surgery, classification of the tooth, presence of adverse habits in the patient like drinking alcohol or consuming tobacco, presence of systemic conditions especially diabetes do play a major role in swelling.[83] The more the tooth is embedded in the bony trabeculae, the larger is the swelling observed postoperatively. Class I cases of impacted third molars wherein third molar is embedded

into bone but has enough space mesially and distally for its removal are most commonly reported in clinics. Following this is Class II and Class III wherein molar is partially into the ramus on distal side or completely into the ramus respectively.[84] Based on the common findings of classification it has also been observed that maximum swelling is reported in Class II cases followed by Class I and Class III cases.[83] In the present study only those cases which were moderately difficult for surgical removal were included and were randomly allocated into the two intervention groups. Thus swelling as a reason for one class being more in a group as compared to other was not a possibility here because of similarity due to randomization. Moreover, other factors like contributing to swelling were also controlled as the sample was homogenous.

In our study, when swelling between the two groups was compared before third molar surgery, no significant difference was observed among them indicating a baseline similarity. Post surgery when swelling was evaluated on 1st day in Tramadol group an increase in the size of the swelling was observed from 11.22mm to 13.73mm. Reason being the damage caused to the tissues due to surgery. When swelling was again measured on 3rd day very negligible reduction was observed from 13.73mm to 13.11mm. This shows that Tramadol was still not very effective by 3rd day and required longer period to show its actions. When the last reading on 7th day post surgery was obtained it was found that the swelling deceased from 13.11mm on 3rd day to 11.35mm on 7th day. The reading of 7th day was quite close to the baseline readings indicating that at least 7 days are required for Tramadol to bring back the inflammatory condition to normal after surgery. The fact was confirmed by the study reported by **Dikhit PS et al** wherein Tramadol was consumed orally and was compared with diclofenac sodium. In their study, the readings were acquired before surgery and on 5th day post surgery.

On 5th day it was noted that the mean difference in the swelling from baseline and 5th day was 0.05mm accounting to only 2.1% deviation in swelling from the pre surgical readings. No significant difference was found between baseline and 5th day in Tramadol group with respect to angle tragus score. The similar was noted for angle-canthus and angle-ala scores. For angle-canthus the difference between baseline and 5th day in swelling was 0.01mm accounting to 0.81% alteration while that in angle-ala scores was 0.12 mm. accounting to 1.68%differnce at two time intervals. No significant difference was observed between pre surgical readings and reading on 5th day indicating concluding that Tramadol is effective in reducing anti-inflammatory action but takes at least 5 days to show its effects.[85]Even the studies performed on rats by **Mauro Bianchi in 1999** suggested that Tramadol is effective in inhibiting the development of different inflammatory cells in the exudate without affecting the immune mechanisms of animals. [11]

In the group receiving combination of Tramadol Hydrochloride and Ketorolac Tromethaminein the present study it was observed that on 1st day an increase in swelling was noted which was because of the tissue damage and increased vascular permeability after third molar disimpaction surgery. A mean increase of 1.86 mm was observed from pre treatment reading to readings on 1st day. When follow up was done on 3rd day this group showed a large amount of reduction in swelling from that of 1st day. The swelling deceased from 13.08mm to 11.48mm. The results indicate that unlike Tramadol, this combination of Tramadol and Ketorolac was quick enough to show its anti-inflammatory actions. On 7th day very insignificant difference was noted in swelling from that of 3rd day representing that the maximum action of combination groups exhibits in 3 days or 72hours post which the drug may not prove to be that effective.

Paiva-Oliveira JG et al reported that, when corticosteroid was compared to an NSAID, the swelling subsided within 24 hours and by the end of 7th day no significant difference was observed in swelling from preoperative phase to the 7th day. The reason for early action of NSAID i.e., Ketorolac in their study may be because the patients undergoing third molar surgery had received the medication before intervention while in our study the drug regimen was started post surgery with the synergistic action of Tramadol and Ketorolac the swelling reduced within 3 days to a large extent.[86] similarly, in **Trindade PAK et al** study, when sublingual Ketorolac was compared with Piroxicam it was noted that, Ketorolac showed a better performance over Piroxicam. The mean increase in swelling post surgical removal of mandibular third molar on 2nd day in Ketorolac group was 3.2mm while that with other NSAIDs was almost 6mm. At the end of 7th day, no swelling was visible in Ketorolac group while negligible swelling was still present in Piroxicam concluding that Ketorolac when administered alone also proves to be superior that other NSAIDs. Thus, the combination intervention in our study would definitely bring positive changes by reducing swelling.[64]

When both the groups in the present study were compared, that is Tramadol and Ketorolac plus Tramadol groups respectively it was found that, a significant difference in swelling was present since day one with a mean difference of 0.65mm between the groups. By the end on 3rd day the difference between them increased to 1.6mm and again returned back to 0.15 mm which was not significant. Thus it can be inferred that though both the groups had difference in the initiation of action. However at the end both the groups gave similar results in reducing the swelling. Since there are no studies which compared Tramadol and similar combination like the present study for swelling in the literature so we have compared these findings with the studies using Tramadol

with other NSAIDs. **Pillai AK et al** reported that the combination of NSAID with Tramadol was less effective than NSAID with corticosteroid. But when results of individual groups were considered, the Tramadol with NSAID group too was effective on 3rd day for swelling reduction. And by 7th day no swelling was reported by the patients receiving this combination which is similar to the results of our study.[87] When **Dikhit P et al** compared Tramadol alone with diclofenac alone, the diclofenac group patients demonstrated better consequences on swelling than Tramadol alone. The percent change in ala-tragus scores denoting swelling pre to post readings in diclofenac group was 0.77% while that in Tramadol was almost 2.11%; for ala-canthus was 0.08% and 0.81 , for angle-ala was 1.12% and 1.68% in diclofenac and Tramadol group respectively. Therefore the synergistic action of the two drugs in our study would be the definite reason for Tramadol plus Ketorolac being superior over Tramadol alone. The results of the present study were also seen in accordance with **J Perez-Uruzar et al** which demonstrated that patients in Tramadol group exhibited a greater amount of swelling which accounted to 13.5% while that in combination group (Tramadol and other NSAIDs that is lysine clonixinate) exhibited only 6.1% swelling which gave a significant difference between the two therapies.[22]

The third most common complication which occurs after surgical removal of mandibular third molar surgery is trismus or limitation in maximum mouth opening when measured from incisal end of maxillary central incisors to the incisal end of mandibular central incisors. It is a sequel of inflammatory reactions similar to swelling which is caused by prolonged spasm of muscles of mastication of the jaw. Though even this complication is for a time being but still has a remarkable impact on the quality of life of the patient to a great extent. **Shulman DH et al** reports that the patient starts

experiencing limitation in mouth opening soon after surgery but it reaches its peak by 2nd day and later starts to resolve slowly.[88] Unlike pain, trismus severity has nothing to do with the difficulty of the case according to **Garcia Garcia A et al**.[89]A strong relation has been established in the literature between pain and trismus and it is believed that, when the patients tries to open his/her mouth post surgery it tremendously pains and that restricts the patients from further opening the mouth to the fullest. [90]

In the present study the mean mouth opening in Tramadol Hydrochloride group before surgery was 40.37mm. The trismus reached maximum within 24 hours and reached a mean of 26.73mm. The results were confronted by the author **Shulman DH et al** in his study. Post 1st day, the mouth opening started to increase and thus trismus decreased. It increased from a mean of 26.73mm on 1st day to 33.40mm on 3rd day. A sharp increase in mouth opening was continued till 7th day and reached a mean of 40.87mm. This indicates that Tramadol has a longer duration of action.[88]

Dikhit PS et al gave similar results in their study which compared Tramadol with diclofenac. Within 5 days the mouth opening reached normal with a difference of only 0.17mm from preoperative to post operative day the % change in mouth opening was reported to be 1.68%. **Hasan LS** demonstrated that, as limitation in mouth opening occurs because of pain during opening the mouth therefore Tramadol given before forceful mouth opening exercise helped patients in relieving pain and thus a gain in the mouth opening was accounted at every visit. A net gain of 17mm in inter-incisal distance was acquired on 3rd day after administering Tramadol.[91]

In the group receiving Tramadol plus Ketorolac in the present study similar king of results were found as that of Tramadol alone but with greater differences at different

time intervals. Before surgery the mean mouth opening in combination group was 39.48mm. On first day as reported by **Shulman DH et al** the mouth opening reduced to 29.65mm in our study. After this phase a steady increase in this value was observed. As described by **Trindade PAK et al** the mean score for mouth opening increased from 29.65mm on 1st day to 35.32mm on 3rd day which was clinically significant.[64] Following this the mouth opening kept on increasing and reached the preoperative values on 7th day with a mean of 40.47mm. When Ketorolac alone was studied for its use in reducing trismus it was found that, an increase in 30.6mm of mouth opening was observed on 2nd day post operatively. It further increased to 88.8mm giving a mean difference of 11.2 from 2nd to 7th day. By 7th day the mouth opening was same rather more than that of baseline. The reason maybe, the baseline mouth opening itself was less due to difficulty in mouth opening because of impacted third molar. Similar was observed in **Paiva-Olivera JG et al** study wherein the mouth opening drastically reduced on 1 day and reached maximum on 2nd day. Post 2nd day a negligible increase was found in inter-incisal distance with a mean increase of 1.74mm on 3rd day from that of 2nd day.[86] In our study the results were found contrasting for 3rd day which showed a greater amount of increase as compared to the previous day. The reason may be, our study used a combination of drugs which the other study used only Ketorolac. This proves that a combination drug is superior to single drug. The mouth opening returned to that of preoperative value by 7th day which was also recognised in the present study.

When both the groups were compared for trismus in the present study, the combination group proved to be more effective than the single drug group on day 1as it helped in reducing the immediate trismus occurring post surgery. The mean reduction in mouth opening on Tramadol group was 13.64mm while that in combination therapy

group was only 9.83mm. On 3rd day the mean increase in mouth opening in Tramadol was 6.67mm while that in combination was5.67mm. the reason here for a better result of Tramadol group over combination was, the trismus was controlled by 1st day itself in combination groups and thus the difference between 2st and 3rd day was not much. But still it won't deny the fact that the mean inter-incial opening remained on a higher side in combination group over Tramadol alone. By 7th day no significant difference was observed between both the groups. **J.Perez-Urizar et al** when compared Tramadol alone with a combination therapy it gave a similar result.[22]The trismus values were more in Tramadol group than that of combination group but at the end of 72 hours both the groups performed similar way showing no significant difference in their actions. In **Bangbose BO et al** study the combination group presented a lower score of trismus over a single drug therapy on 1st and 2nd day. The difference in this case too was not significant at the end of 7th day like the present study.[92]

When it comes to complications other than the discussed non-avoidable ones Tramadol drug reports a higher percentage in the literature. Other complications stated in the literature with the administration of Tramadol are nausea, vomiting, dizziness, sweating, constipation, headache, dry mouth and respiratory depression .[93] Moreover, reports are also available on the fact that Tramadol induces a drug dependent response in patients and the dose should be adjusted while administering the drug to those patients suffering from renal failure, allergic to the drug or are allergic to any other opioids .[93] In the present study the adverse effects observed with Tramadol were sedation, sweating, nausea, epigastric pain and bleeding at extraction site. Among these sedation was observed in maximum patients followed by sweating and nausea. The results were similar with the findings of **J. Perez-Urizar et al** study who reported that

20% of the patients receiving Tramadol suffered with the adverse effects of this drug. Nausea, dizziness and drowsiness were the events reported in their study.[22] While in our study the percentage with complications was a bit higher by 13.3%. Sedation was also reported to be highest in Tramadol group by **Lepri A et al** in 2006.[25] Alike results were presented by **Isiordia-Espinoza MA et al** with no complications in Tramadol receiving group.[62]

When it came to the combination of the drugs a less percentage was observed in the present study. Only 5% of the patients suffered from the adverse effects and the result statistically significant compared to Tramadol group alone. Contrast was observed in **Isiordia-Espinoza MA et al** study wherein none of the patients in the combination groups reported with any complications and thus no significant difference was observed I Tramadol alone and combination group.[62] While results were in accordance with **Lepri A et al** study in which sedation was found to be significantly more among Tramadol receivers over combination drug receivers.[25] The adverse reactions reported in Tramadol plus NSAID group was 15% while that in single drug group was 20%.[22] The difference was significant among the groups with nausea, drowsiness and dizziness present in both.

Moreover, literature states many different routes via which the drug is administered. Intravenous, intramuscular, oral and sublingual are the stated routes. Each route will have its advantages and disadvantages. Like for intravenous group, though the action may initiate quickly but the person needs to be skilled while administering the drug intravenously. Over that, even if the action is quick but the drug is directly administered into the systemic circulation increasing the risk to the patients

as well. Intramuscular and oral both prove to be beneficial routes in reducing the discussed complications after third molar impaction surgery. Oral drug may take a longer time as compared to intramuscular. But when intramuscular and sublingual routes are compared, sublingual proves to be superior among them.[22] The sublingual drugs escapes through first pass metabolism into liver and thus more amount of drug is available for acquiring the desired effect. It also does not pass into the gastrointestinal track unlike oral route and thus, prevents gastrointestinal disturbances to a large extent.[64] The sublingual area is highly vascular. Therefore when the drug is administered via this route it quickly enters into the venous blood through the small veins in sublingual area following which it reaches the internal jugular vein and starts its actions making it superior over oral and intramuscular routes.[13]

Overall, it can be seen that combination of Tramadol Hydrochloride and Ketorolac Tromethamineproves to be effective in reducing pain, minimizing swelling and increasing mouth opening post surgical removal of mandibular third molar over Tramadol Hydrochloride alone. Even the complications discussed are favouring the combination dose to be safer over single drug dose.

SUMMARY & CONCLUSION

Summary and Conclusion

Mandibular third molar impaction has become one of the most common dental problems among the people from 18 years onwards. The condition is more common in mandible than in maxilla due to the compact and dense nature of the bone. The only choice which remains in such cases is surgical removal of the tooth. Though the surgery is performed with an aim of providing relief to the patients it may lead to post surgical complication like pain, swelling and trismus. To alleviate this many pharmacologic agents are available in market. The present study was aimed in comparing analgesic and anti-inflammatory effect of Tramadol and Tramadol with Ketorolac Tromethamine in combination in mandibular third molar surgery.

A total of 120 patients requiring surgical removal of mandibular impacted third molar were selected and were randomized into Tramadol group or Tramadol plus Ketorolac group. Tramadol group received 50mg of tablet sublingually every 8 hours for 7 days while the combination groups received Tramadol of 25mg and Ketorolac of 10 mg 8 hourly for 7 days. The parameters like pain, swelling, trismus were assessed at different time intervals. Pain was assess before surgery, 30 minutes after surgery, 1hour, 2 hours, 4 hours, 6 hours, 12 hours, 24 hours and 48 hours post surgery. Swelling and trismus were assess before treatment, on 1st day, 3 rd day and 7 th day post surgery.

Results obtained were, a significant difference in pain was obtained only at 6 hours between the two groups. While for swelling and trismus, a significant difference was noted on 1st day and 3rd day. When it came to 7th day, both the drugs showed similar actions by bringing the facial symmetry and mouth opening back to normal. When

complications were assessed in both the groups it was found that 33.3% of the patients in Tramadol groups suffered with complications while only 5% in Tramadol plus Ketorolac group had complications due to the drugs. This difference was significant among the groups.

It was concluded that no significant difference was present between Tramadol Hydrochloride and combination of Tramadol Hydrochloride and Ketorolac Tromethamine in long term. The combination can be called as superior to single drug only in initial phases .but after a certain point of time both the drugs are equally effective. Moreover, combination shows a quick action as compared to Tramadol but the effects of Tramadol lasts for a longer duration. Further studies by age and gender matching can be conducted to know in detail about the differences between both the groups.

Conclusion

Within the confines of this study it can be concluded that there is no significant difference between Tramadol Hydrochloride and combination of Tramadol Hydrochloride and Ketorolac Tromethamine in long term. The combination proves to be effective in reducing pain, swelling and trismus in initial period but after a certain point of time both the drugs are equally effective. Along with this it cannot be over ruled that the combination shows a quick action as compared to Tramadol but the effects of Tramadol lasts for a longer duration. Moreover, though both the groups seem to be similar at the end, one should not forget to consider the adverse effects which are noted significantly more with Tramadol administration over combination drug.

Limitation of our study

The limitations of the study cannot be ruled out. The age and gender matching was not considered in the present study. Future studies are required with larger sample size for consolidating the result of this study.

Though there were certain limitations in the study, results were found to be promising.

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TABLES

Tables

Table No. 1 : Randomization

Subject	Group Assigned	Subject	Group Assigned	Subject	Group Assigned	Subject	Group Assigned
1	T group	**31**	T + K group	**61**	T group	**91**	T + K group
2	T group	**32**	T group	**62**	T group	**92**	T + K group
3	T + K group	**33**	T + K group	**63**	T + K group	**93**	T + K group
4	T + K group	**34**	T + K group	**64**	T + K group	**94**	T + K group
5	T group	**35**	T group	**65**	T group	**95**	T + K group
6	T group	**36**	T + K group	**66**	T group	**96**	T + K group
7	T group	**37**	T group	**67**	T group	**97**	T + K group
8	T group	**38**	T group	**68**	T group	**98**	T group
9	T + K group	**39**	T group	**69**	T + K group	**99**	T + K group
10	T + K group	**40**	T + K group	**70**	T + K group	**100**	T + K group
11	T + K group	**41**	T + K group	**71**	T + K group	**101**	T + K group
12	T + K group	**42**	T group	**72**	T + K group	**102**	T group
13	T group	**43**	T + K group	**73**	T group	**103**	T group
14	T group	**44**	T group	**74**	T group	**104**	T group
15	T group	**45**	T + K group	**75**	T + K group	**105**	T group
16	T group	**46**	T group	**76**	T + K group	**106**	T + K group
17	T group	**47**	T + K group	**77**	T + K group	**107**	T group
18	T group	**48**	T + K group	**78**	T group	**108**	T group
19	T group	**49**	T group	**79**	T + K group	**109**	T group
20	T group	**50**	T group	**80**	T + K group	**110**	T + K group
21	T + K group	**51**	T + K group	**81**	T + K group	**111**	T + K group
22	T + K group	**52**	T + K group	**82**	T group	**112**	T group
23	T group	**53**	T group	**83**	T group	**113**	T group
24	T group	**54**	T + K group	**84**	T + K group	**114**	T + K group
25	T group	**55**	T group	**85**	T + K group	**115**	T group
26	T group	**56**	T group	**86**	T + K group	**116**	T + K group
27	T group	**57**	T group	**87**	T group	**117**	T + K group
28	T group	**58**	T + K group	**88**	T group	**118**	T + K group
29	T + K group	**59**	T + K group	**89**	T group	**119**	T + K group
30	T + K group	**60**	T + K group	**90**	T group	**120**	T + K group

Table No. 2: Distribution of patient based on age groups in Group A and B

Age Group	Group A	Group B
18-20	8	6
21-23	3	11
24-26	13	18
27-29	10	11
30-32	8	8
33-35	6	3
36-38	11	2
39-41	1	1
Total	60	60
Mean±SD	28.83±6.05	26.51±4.79

Table No. 3: Distribution of patient based on gender in Group A and B

Gender	Group A	Group B
Males	31	35
Females	29	25
Total	60	60

Table No.4: Distribution of pain intensity in Group A at different time intervals

Time interval	N	Mean	Std. Deviation
Pain30min	60	.00	.000
Pain1hr	60	1.07	1.448
Pain2hr	60	.47	.929
Pain4hr	60	.73	1.274
Pain6hr	60	2.60	1.92
Pain12hr	60	.63	1.134
Pain24hr	60	.90	1.537
Pain48hr	60	.50	.873

Table No.5: Distribution of pain intensity in Group B at different time intervals

Time interval	N	Mean	Std. Deviation
Pain30min	60	.10	.440
Pain1hr	60	1.00	1.302
Pain2hr	60	.43	.831
Pain4hr	60	.97	1.248
Pain6hr	60	1.83	0.76
Pain12hr	60	.77	1.110
Pain24hr	60	.58	1.289
Pain48hr	60	.30	.720

Table No.6: Difference between the pain intensity at different time intervals between the groups

Time Intervals	Groups	N	Mean	p value
Pain30min	Tab. Tramadol	60	0.0	0.081
	Tramadol+Ketorolac	60	0.10	
	Total	120		
Pain1hr	Tab. Tramadol	60	1.07	0.928
	Tramadol+Ketorolac	60	1.00	
	Total	120		
Pain2hr	Tab. Tramadol	60	0.47	0.962
	Tramadol+Ketorolac	60	0.43	
	Total	120		
Pain4hr	Tab. Tramadol	60	0.73	0.198
	Tramadol+Ketorolac	60	0.97	
	Total	120		
Pain6hr	Tab. Tramadol	60	2.6	**0.006***
	Tramadol+Ketorolac	60	1.83	
	Total	120		
Pain12hr	Tab. Tramadol	60	0.63	0.381
	Tramadol+Ketorolac	60	0.77	
	Total	120		
Pain24hr	Tab. Tramadol	60	0.90	0.163
	Tramadol+Ketorolac	60	0.58	
	Total	120		
Pain48hr	Tab. Tramadol	60	0.50	0.173
	Tramadol+Ketorolac	60	0.30	
	Total	120		

*significant with $p<0.05$

Table No.7: Descriptive data regarding swelling in Group at different Time intervals

Time interval	N	Mean	Std. Deviation
Pre surgical	60	11.2265	0.11196
Day 1	60	13.7350	1.11975
Day 3	60	13.1183	1.11636
Day 7	60	11.3550	0.94894

Table No. 8: Descriptive data regarding swelling in Group B at different time intervals

Time interval	N	Mean	Std. Deviation
Pre surgical	60	11.2233	.86659
Day 1	60	13.0833	1.00645
Day 3	60	11.4817	1.05549
Day 7	60	11.2050	0.86679

Table No.9: Difference between swellings at different time intervals between the groups.

Time Intervals	Groups	N	Mean	t test	p value
Baseline	Tab. Tramadol	60	11.2265	0.20	0.98
	Tramadol+Ketorolac	60	11.2233		
	Total	120			
On day 1	Tab. Tramadol	60	13.7350	3.353	**0.001***
	Tramadol+Ketorolac	60	13.0833		
	Total	120			
On day 3	Tab. Tramadol	60	13.1183	8.252	**0.000***
	Tramadol+Ketorolac	60	11.4817		
	Total	120			
On day 7	Tab. Tramadol	60	11.3550	0.904	0.368
	Tramadol+Ketorolac	60	11.2050		
	Total	120			

*significant with $p<0.05$

Table No.10: Descriptive data regarding trismus in Group A at different time intervals

Time interval	N	Mean	Std. Deviation
Pre surgical	60	40.37	3.344
Day 1	60	26.73	4.016
Day 3	60	33.40	4.056
Day 7	60	40.87	3.270

Table No.11: Descriptive data regarding trismus in Group B at different time intervals

Time interval	N	Mean	Std. Deviation
Pre surgical	60	39.48	2.487
Day 1	60	29.65	3.384
Day 3	60	35.52	3.332
Day 7	60	40.47	2.740

Table No.12: Difference in trismus at different time intervals between the groups

Time Intervals	Groups	N	Mean	t test	p value
Baseline	Tab. Tramadol	60	40.37	1.642	0.103
	Tramadol+Ketorolac	60	39.48		
	Total	120			
On day 1	Tab. Tramadol	60	26.73	4.302	**0.000***
	Tramadol+Ketorolac	60	29.65		
	Total	120			
On day 3	Tab. Tramadol	60	33.40	2.829	**0.005***
	Tramadol+Ketorolac	60	35.52		
	Total	120			
On day 7	Tab. Tramadol	60	40.87	0.729	0.469
	Tramadol+Ketorolac	60	40.47		
	Total	120			

*significant with $p<0.05$

Table No.13: Occurrence of complications between the two groups after receiving the treatment

Groups	Complications present	Complications absent
Group A	20	40
Group B	5	55

Table no. 14- Comparison of occurrence of complications between the two groups after receiving the treatment

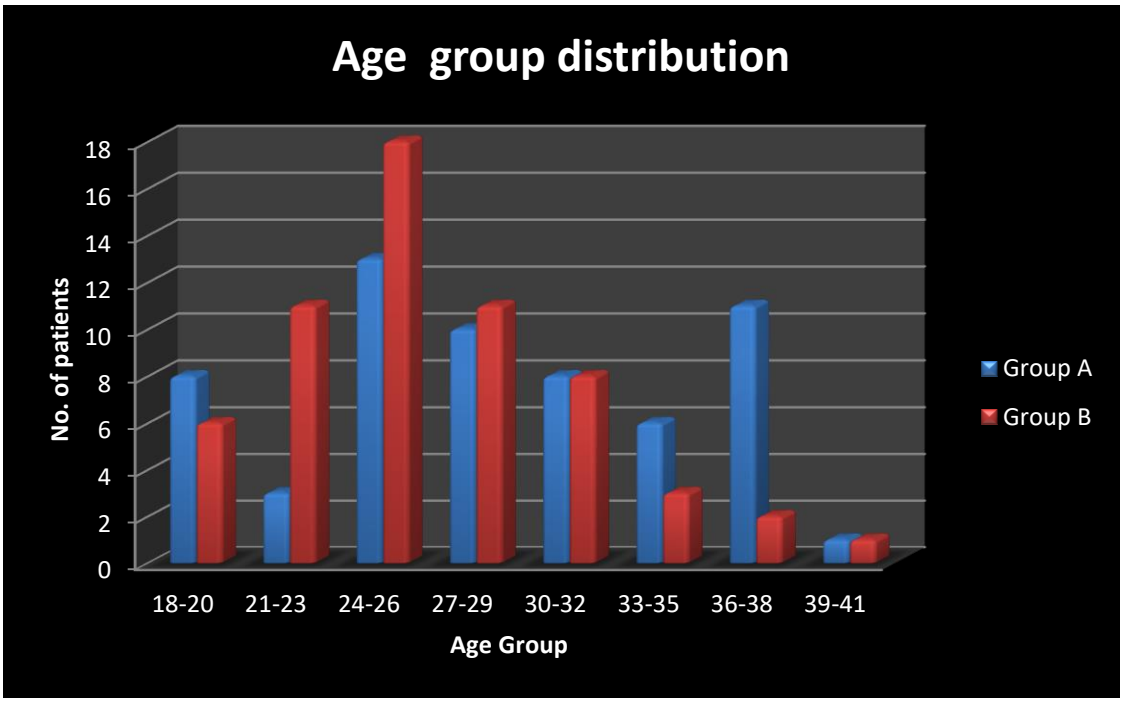
Groups	Complications	
	Absent	**Present**
Tramadol	40	20
Tramadol+Ketorolac	55	5
Chi-square value	11.368	
p value	**0.001***	

*significance at $p<0.05$

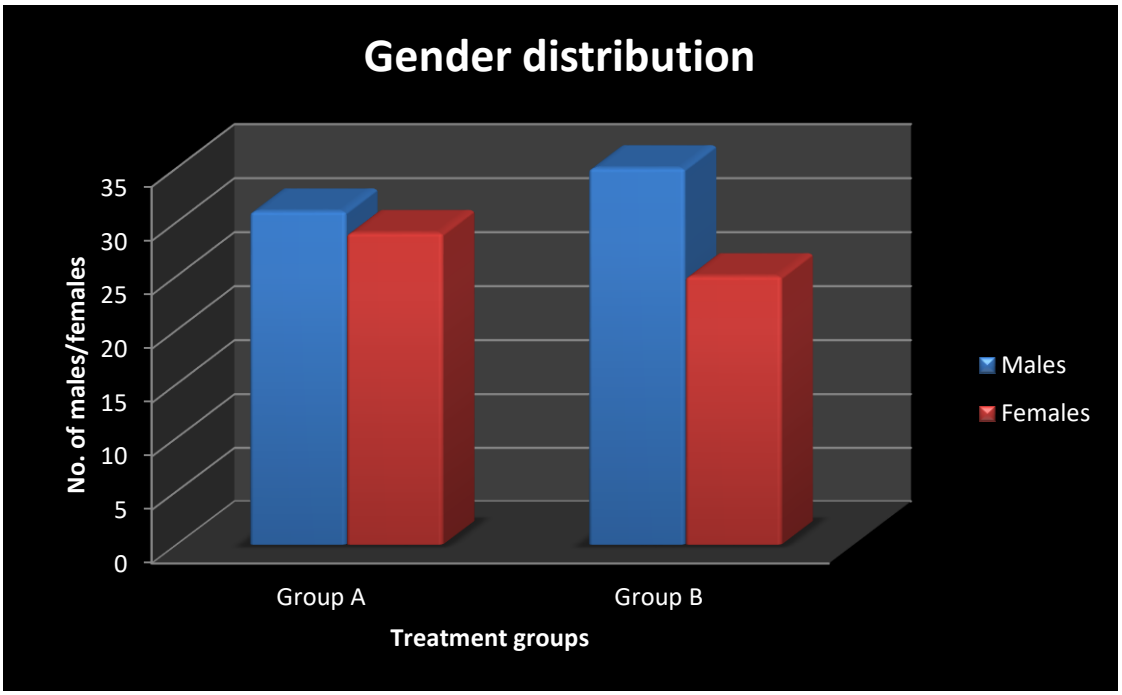
GRAPHS

Graphs

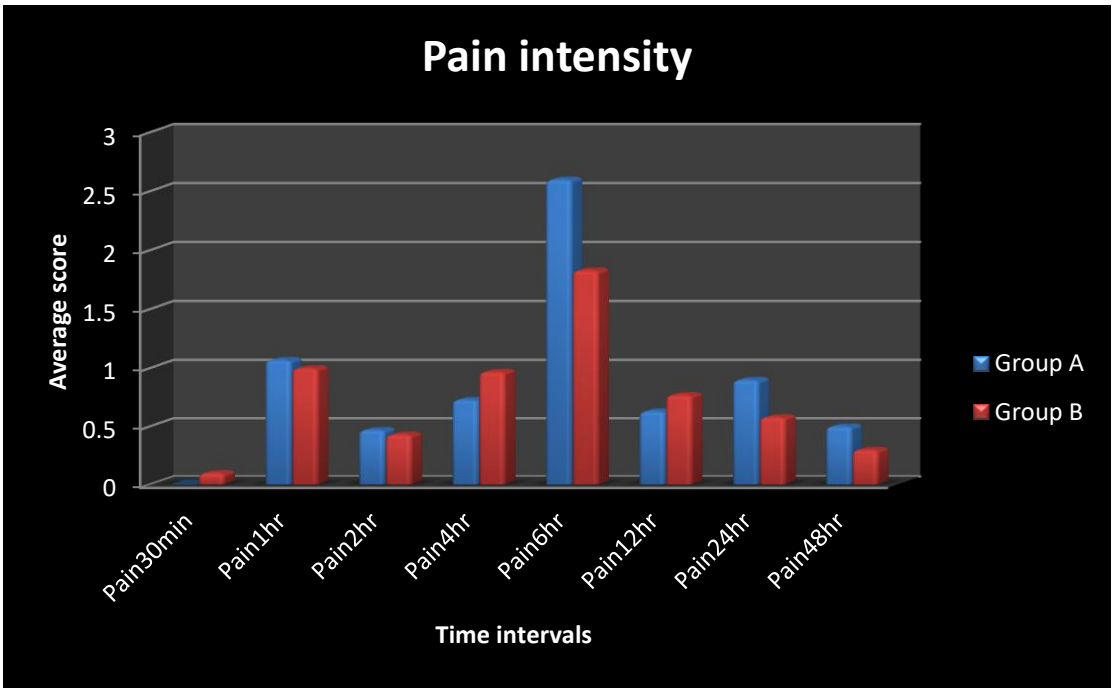
Graph No.1: Bar diagram representing age distribution in group A and B



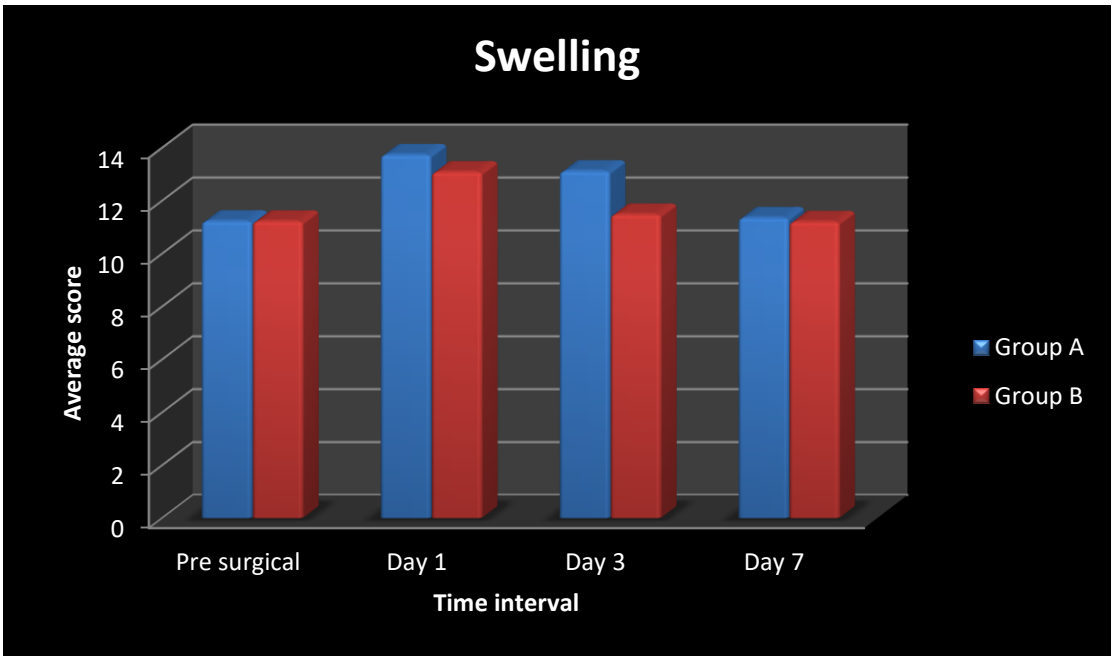
Graph No.2: Bar diagram representing gender distribution in group A and B



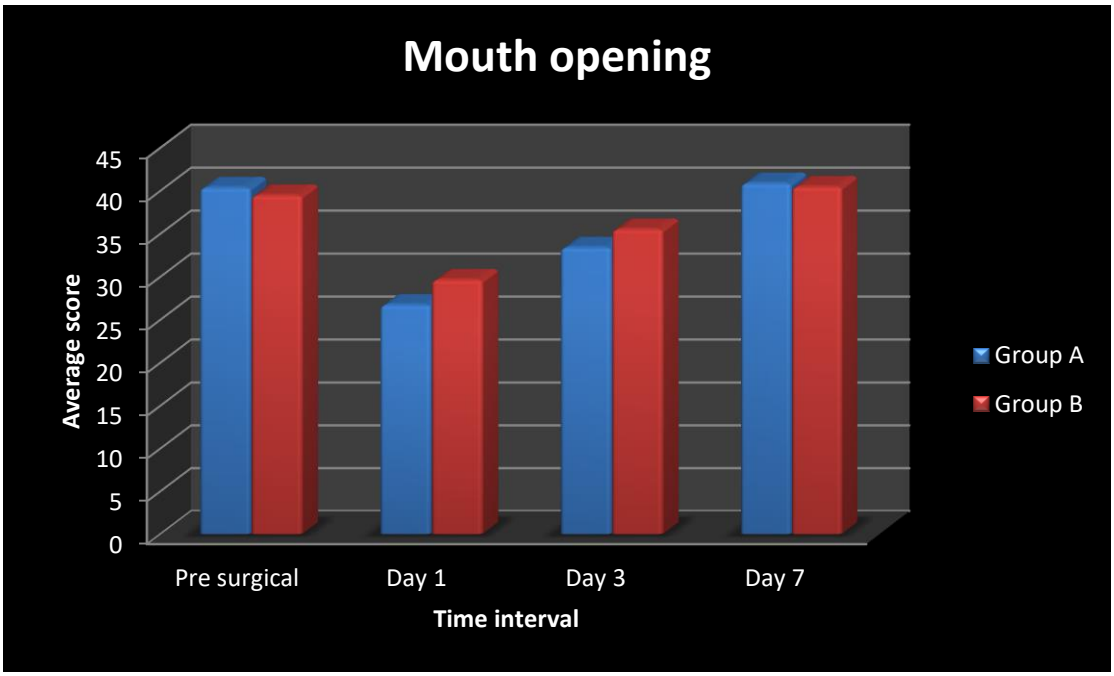
Graph No.3- Bar diagram representing pain intensity in group A and B at different time intervals



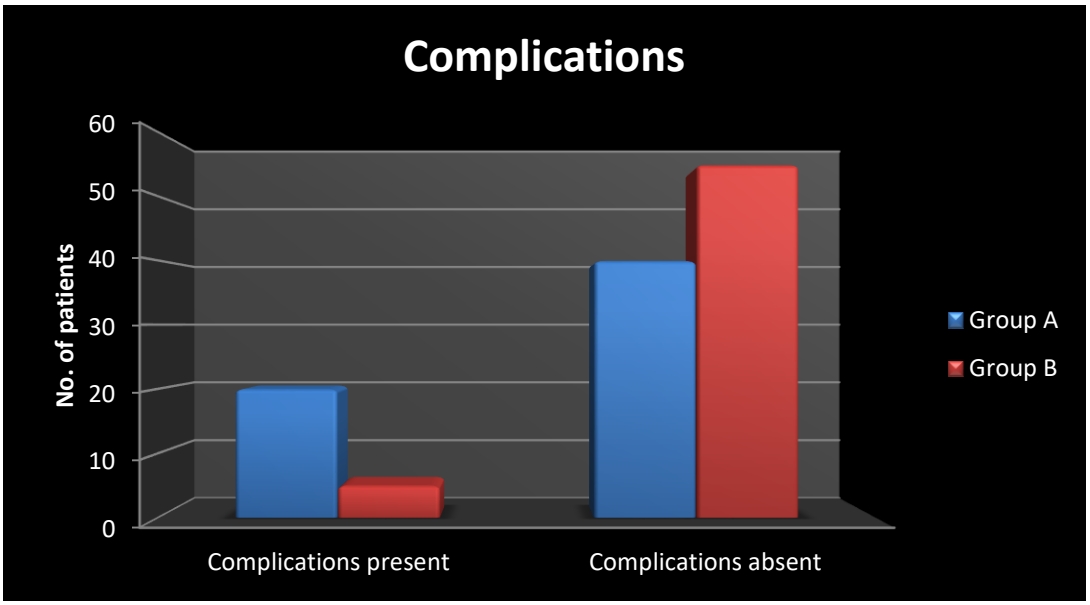
Graph No.4- Bar diagram representing swelling in group A and B at different time intervals



Graph No. 5- Bar diagram representing mouth opening of group A and B at different time intervals



Graph No.6-Bar diagram representing complications observed in the two Groups



FIGURES

Figures

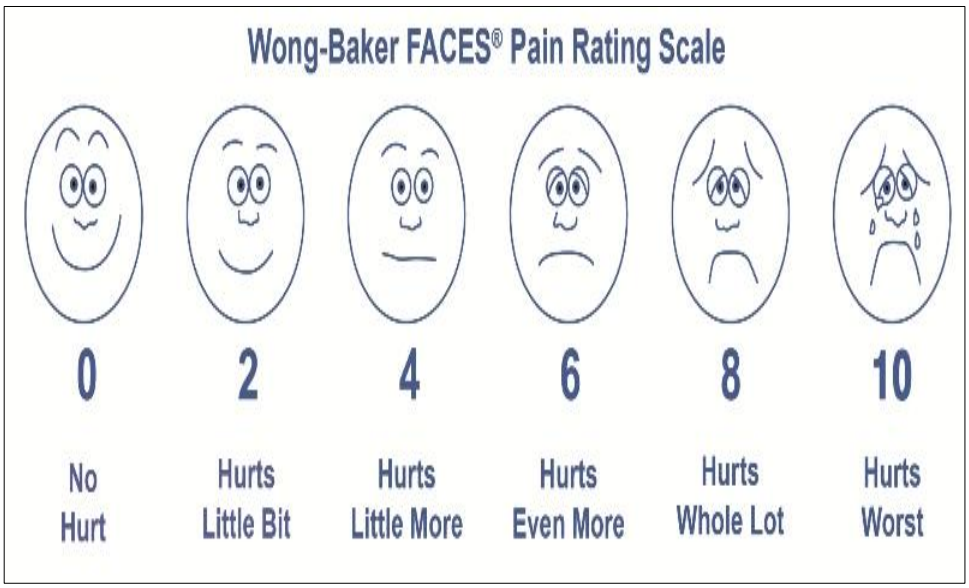


Fig.1 Wong-Baker FACES Pain Rating Scale

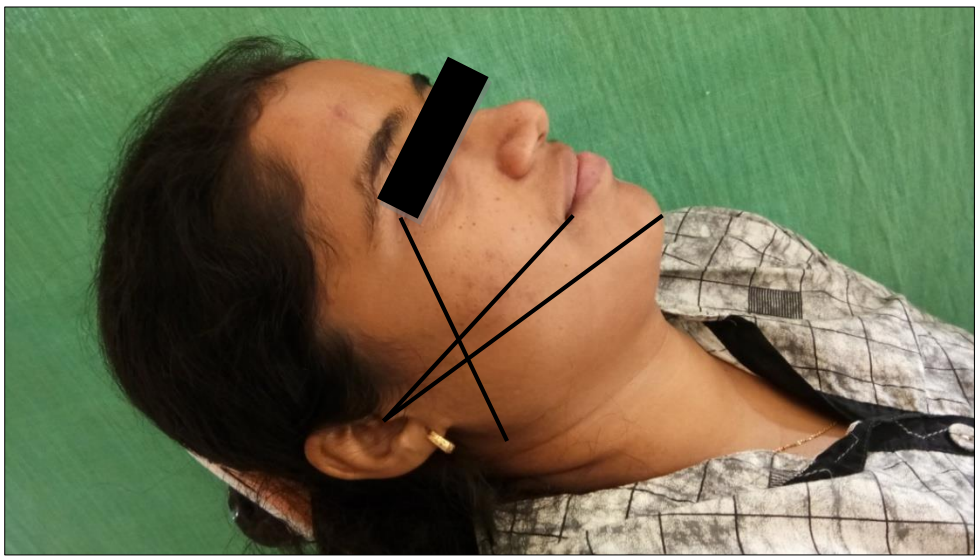


Fig .2 Assessment of swelling

Fig.3 Assessment of Trismus

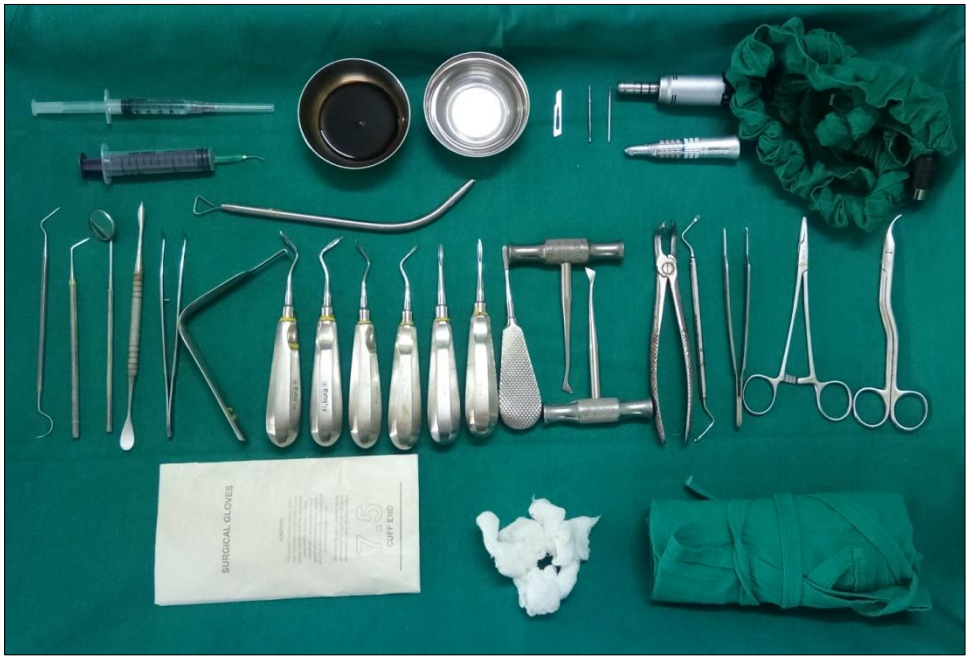


Fig.4 Surgical instrument Kit

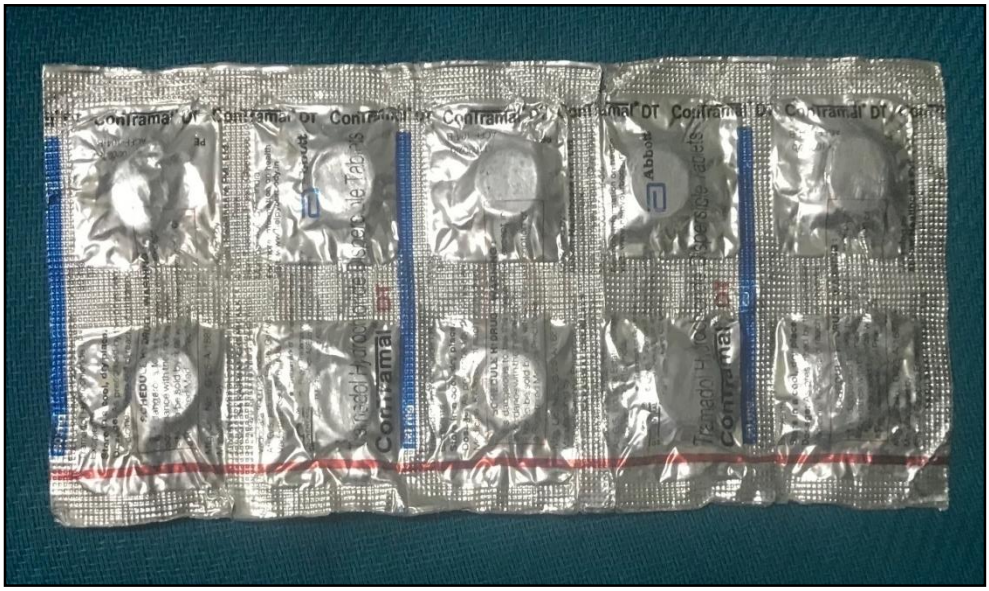


Fig.5 Tablet Contramal - DT

Fig.6. Tablet Ketotram

ANNEXURE

Annexure

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 -

- Orthodontic
- Periodontitis
- Carious
- Others

Past Medical History -

Past Dental History -

Drug Allergy History -

Family History -

Personal history :

- Diet
- Oral habits
- Sleep
- Oral hygiene

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

DEPARTMENT OF ORAL & MAXILLOFACIAL SURGERY
INFORMED CONSENT FORM
(Confidential)

"TO COMPARE ANALGESIC AND ANTI-INFLAMMATORY EFFICACY OF SUBLINGUAL TABLET TRAMADOL VERSUS SUBLINGUAL TRAMADOL PLUS KETOROLAC AFTER THE SURGICAL EXTRACTION OF IMPACTED MANDIBULAR THIRD MOLARS:A RANDOMIZED, DOUBLE BLIND PROSPECTIVE STUDY"

I _____ 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 doctors have informed me about this research project suitably and sufficiently to my satisfaction. I agree to the treatment modality to be given to me and I am aware of the effects and complications of the said drugs. I agree to allow my photographs to be drawn as required. I agree to take part in this project and will not mix and 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 cooperate 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	Signature	Date	Time
3.				
	Investigator's name	Signature	Date	Time

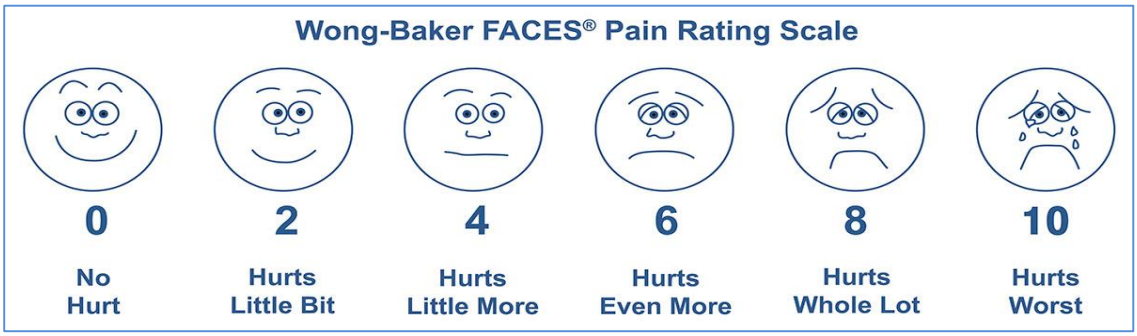
ANNEXURE – III

ASSESSMENT FORM

Pain:

Pain score on **Wong–Baker FACES pain rating scale (For pain)**

	0	2	4	6	8	10
30 mins						
1 hours						
2 hours						
4 hours						
6 hour						
12 hours						
24 hours						
48 hours						



Swelling:

Pre Operative	1st post Operative Day	3rd post Operative Day	7th post Operative day

Trismus:

Pre Operative	1st post Operative Day	3rd post Operative Day	7th post Operative day

Master Sheet

Subject	Group Assigned	Age	Gender	PAIN								SWELLING				TRISMUS				COMPLICATIONS
				30min	1hr	2hr	4hr	6hr	12hr	24hr	48hr	Pre	1st	3rd	7th	Pre	1st	3rd	7th	
1	Group A	26	M	0	0	0	0	2	0	0	0	11.9	14.6	14	12.2	38	22	28	37	
2	Group A	18	F	0	2	0	0	0	2	2	0	11.6	13.8	13	11.6	42	26	32	42	Sedation
3	Group B	23	M	0	2	0	0	2	0	0	0	10.8	12	11.9	10.8	41	28	36	41	
4	Group B	32	M	0	0	0	0	2	2	0	2	10.4	12.8	11.6	10.4	40	30	35	40	
5	Group A	23	M	0	0	0	2	2	0	0	0	10.3	15	13.8	11.5	44	30	36	43	
6	Group A	29	M	0	2	0	0	0	0	2	2	11.4	13	12.2	11.4	46	30	38	45	Sweating
7	Group A	29	F	0	0	4	0	2	0	0	0	11.6	14	13.5	11.6	48	31	40	48	
8	Group A	25	F	0	2	0	2	2	4	0	0	11.6	13.5	13	11.7	37	22	29	37	
9	Group B	25	M	0	2	2	0	2	2	2	2	10.6	12.9	12.5	10.6	32	21	27	32	
10	Group B	32	M	0	0	0	0	4	0	0	0	11.2	11.9	11.5	11.2	35	24	30	35	
11	Group B	28	F	0	4	0	2	2	0	0	0	11.8	13	12.6	11.8	38	30	38	42	
12	Group B	29	M	0	0	0	0	2	0	0	2	12	14.2	13.3	12	42	32	37	41	Sweating
13	Group A	32	M	0	0	0	0	4	0	4	0	11.3	12.8	11.4	11.2	39	23	30	39	
14	Group A	25	F	0	0	2	2	2	0	0	0	12.2	15.9	13.1	12.2	49	32	40	48	
15	Group A	33	M	0	2	0	0	0	2	0	0	11.5	12	11.8	11.5	46	30	38	46	
16	Group A	26	M	0	0	0	4	8	2	0	0	10.5	12.5	13.2	10.7	42	27	33	40	
17	Group A	23	F	0	2	0	0	2	0	2	0	11.7	14.6	14	11.8	41	27	34	41	
18	Group A	36	M	0	0	0	6	0	0	2	0	10.2	10.9	10.2	10.2	42	26	35	42	
19	Group A	27	M	0	2	0	0	2	0	2	0	11	13.8	12.2	11.3	43	27	32	42	
20	Group A	24	F	0	2	0	2	2	0	2	0	10.2	12.8	11.8	10.2	38	23	29	38	
21	Group B	21	M	2	2	0	2	4	0	0	0	11.5	13.5	12.6	11.5	40	30	35	40	
22	Group B	23	M	0	2	0	2	2	0	0	2	10.2	13	11.9	10.1	40	31	39	44	
23	Group A	18	M	0	0	0	0	2	0	0	0	11.5	13.4	13	11.5	42	26	33	42	Sedation
24	Group A	19	M	0	2	0	0	0	2	6	2	10.2	13.2	13.4	10.4	40	25	33	40	
25	Group A	19	F	0	0	2	2	0	0	6	2	12	14.5	13.4	12	39	23	28	39	
26	Group A	29	M	0	0	0	0	2	0	6	2	11.9	13.8	13.8	11.9	45	40	43	44	
27	Group A	38	F	0	4	0	0	0	4	0	0	11.2	13.6	13.2	11.2	40	32	38	48	
28	Group A	19	F	0	0	0	4	8	2	2	0	10.9	13.2	12.9	10.9	40	28	32	40	Sedation
29	Group B	32	M	0	0	0	2	4	2	0	0	9.8	12	11	9.8	39	29	35	38	
30	Group B	26	M	0	2	2	0	0	0	2	0	12.9	14.1	13.9	12.9	41	30	37	40	
31	Group B	28	M	0	4	0	2	2	0	0	0	11.6	13.8	13	11.5	40	28	35	40	
32	Group A	32	M	0	0	2	0	2	0	0	2	10.2	14	13.8	10.2	39	23	28	38	
33	Group B	38	F	0	2	0	2	2	0	0	2	10.2	13	11.9	10.2	40	30	40	44	
34	Group B	28	M	0	2	0	0	2	4	0	0	12	15	13.8	12	42	30	37	41	
35	Group A	36	M	0	2	0	0	2	0	2	0	11.5	14.5	13.6	11.8	38	19	29	38	
36	Group B	24	M	0	2	0	0	2	0	0	0	11.6	13	12.5	11.6	40	34	40	46	
37	Group A	26	F	0	0	2	0	0	2	2	2	10.6	13	12.8	10.6	42	30	36	42	Epigastric pain
38	Group A	17	M	0	6	0	2	2	0	0	0	11	14	16.2	14.4	40	26	30	40	
39	Group A	36	F	0	0	2	0	2	4	0	2	9.8	11.3	11	9.8	41	28	32	40	Sedation
40	Group B	25	F	0	0	2	2	2	2	2	0	12.2	14.5	12	12.2	38	28	33	37	Nausea
41	Group B	20	F	0	2	2	4	2	0	0	0	10.4	12	11.9	10.4	39	24	30	39	

Subject	Group Assigned	Age	Gender	PAIN								SWELLING				TRISMUS				COMPLICATIONS
				30min	1hr	2hr	4hr	6hr	12hr	24hr	48hr	Pre	1st	3rd	7th	Pre	1st	3rd	7th	
42	Group A	25	F	0	2	0	0	2	0	2	0	12	13.9	12.9	12	43	29	32	43	
43	Group B	27	F	2	0	0	0	2	0	0	0	11	13.8	11.8	11	38	27	33	37	
44	Group A	25	F	0	0	0	0	2	0	2	2	10.2	12.8	12	10.3	45	38	42	44	
45	Group B	20	M	0	0	0	2	2	0	0	0	8.9	10.8	11	8.9	38	32	35	40	
46	Group A	26	M	0	2	0	0	0	2	0	0	11	12.8	12.2	11	40	30	36	40	
47	Group B	32	F	0	0	0	2	4	0	0	0	9.8	12	11.1	9.8	40	32	38	40	
48	Group B	25	M	0	0	0	0	2	2	0	0	12	14	12	12	42	34	39	42	
49	Group A	29	F	0	0	0	2	4	0	0	0	11.5	14.2	13.8	11.5	37	22	28	37	Sedation
50	Group A	40	M	0	0	0	0	2	0	0	2	11.9	14.3	13.9	11.9	42	29	36	45	
51	Group B	47	M	0	4	0	2	0	2	2	0	11.5	13	11.3	11.5	40	38	40	40	
52	Group B	26	F	0	2	0	2	4	0	2	0	12.8	14	12.8	12.7	37	27	32	37	
53	Group A	35	M	0	2	0	0	0	0	0	0	11.4	14.5	13.9	11.5	42	26	33	42	Bleeding at extraction site
54	Group B	27	M	0	2	0	2	2	4	0	0	11.8	13	11.9	11.7	38	28	33	37	
55	Group A	29	M	0	4	2	0	0	2	0	0	13	15.5	15	13	39	23	30	38	
56	Group A	33	F	0	2	0	0	0	2	0	0	12.6	15	14.5	12.6	38	32	39	42	
57	Group A	32	M	0	0	0	2	2	0	0	0	9.9	12.5	11.6	9.9	43	29	36	43	
58	Group B	19	M	0	2	0	2	2	0	2	0	11.6	14.6	11.9	11.5	42	31	37	41	
59	Group B	30	F	0	0	0	0	4	0	0	0	12	14.5	12.5	12	39	28	34	38	
60	Group B	26	M	0	2	0	2	2	2	0	0	11.8	13	11.8	11.8	40	30	35	40	
61	Group A	32	F	0	0	0	0	0	0	0	0	11.8	13.9	12.8	11.8	32	26	40	46	Nausea
62	Group A	32	M	0	0	0	2	2	0	0	0	12	15.5	14.2	12	39	27	32	38	
63	Group B	23	F	0	4	0	0	2	0	0	0	9.9	11.8	11.9	9.9	39	32	38	42	
64	Group B	24	F	0	0	0	0	2	2	0	0	12.6	14	12.9	12.6	38	32	38	40	
65	Group A	36	M	0	2	0	0	0	2	0	2	11.6	15.2	14.8	11.6	42	25	33	41	
66	Group A	25	M	0	0	2	0	2	0	0	0	11.8	13.8	13	11.8	38	23	28	35	Epigastric pain
67	Group A	35	F	0	2	0	0	0	0	0	2	12.8	15	14.8	12.8	36	31	38	38	
68	Group A	36	M	0	0	0	2	2	0	0	2	11.5	13.9	13	11.6	32	26	40	46	
69	Group B	26	F	0	0	0	2	2	0	2	0	13	14.8	13.8	13	39	27	33	38	Epigastric pain
70	Group B	33	M	0	0	0	0	2	0	0	2	11.4	14	11.4	11.4	45	24	40	44	
71	Group B	23	M	0	0	0	0	8	2	6	0	11.9	13.8	11	11.8	37	28	31	37	
72	Group B	24	F	0	0	0	0	2	0	0	0	11.5	13.8	12.2	11.4	40	28	40	40	
73	Group A	36	F	0	2	0	0	2	0	0	0	12	15	14	12	38	27	32	38	Nausea
74	Group A	30	F	0	0	0	2	6	0	0	0	9.8	12.5	12.3	9.9	42	25	33	42	Sedation, Sweating, Nausea
75	Group B	38	M	0	0	0	0	2	0	0	0	11	12	11	11	38	30	32	38	
76	Group B	32	M	0	2	0	0	2	0	0	0	10.2	11.9	11	10.1	43	41	38	42	
77	Group B	25	M	0	0	0	0	2	0	2	0	12	13	11.5	12	41	33	37	41	
78	Group A	38	F	0	0	0	0	0	2	0	0	8.9	11.7	11.9	8.9	40	26	33	40	
79	Group B	32	F	0	0	0	0	0	0	0	0	9.8	10.9	9	9.7	40	29	35	40	
80	Group B	35	F	0	2	0	2	2	0	0	0	11	13.2	10.5	11	32	26	30	32	
81	Group B	25	F	2	2	0	0	2	2	0	0	10.6	12.1	10.6	10.6	38	28	33	38	
82	Group A	32	F	0	4	0	0	4	0	2	0	11	14.2	12.8	11	38	21	30	38	
83	Group A	28	F	0	0	2	2	2	0	0	0	10.4	12.5	11.9	10.5	39	22	29	39	Sweating
84	Group B	24	M	0	0	2	0	4	0	0	0	11.5	14.1	11.1	11.4	39	28	32	39	
85	Group B	23	F	0	2	2	2	6	2		0	10.2	13.2	9.8	10.3	40	30	35	40	
86	Group B	27	M	0	4	0	0	0	0	0	0	10.9	12.7	10	10.9	38	28	34	40	

Subject	Group Assigned	Age	Gender	PAIN								SWELLING				TRISMUS				COMPLICATIONS
				30min	1hr	2hr	4hr	6hr	12hr	24hr	48hr	Pre	1st	3rd	7th	Pre	1st	3rd	7th	
87	Group A	35	M	0	0	0	0	0	0	0	0	12.2	15.3	14.4	12.3	38	28	32	38	
88	Group A	37	M	0	0	0	2	2	0	2	0	11.6	13.9	13.9	11.6	40	29	35	45	
89	Group A	36	F	0	0	0	0	4	0	2	0	12	16	14.8	12.4	42	27	35	42	Sedation
90	Group A	28	M	0	2	0	2	2	0	2	0	10.2	13.6	12.3	10.2	40	29	38	42	
91	Group B	27	M	0	0	2	2	4	0	2	0	11.2	12.3	10.8	11.1	40	33	40	45	
92	Group B	21	F	0	0	0	0	6	0	0	0	11.9	12.9	11	11.8	39	28	33	39	
93	Group B	23	F	0	0	0	2	4	2	0	0	12	13.8	11.8	12	40	29	35	40	
94	Group B	29	M	0	0	0	0	2	0	0	0	10.2	13	9.8	10.1	39	32	37	41	
95	Group B	27	F	0	0	0	2	2	0	2	0	11.5	12.5	11.9	11.5	38	35	33	37	
96	Group B	19	M	0	0	0	0	0	2	0	0	10.2	12	9.6	10.2	37	25	28	32	
97	Group B	30	M	0	0	0	0	2	2	0	2	11	13	10.8	11	42	30	37	41	
98	Group A	20	F	0	0	2	0	4	0	0	2	11.6	14.2	14	11.6	40	24	30	40	
99	Group B	24	M	0	0	0	4	8	2	0	0	10.2	11.2	9.5	10.2	41	28	36	40	
100	Group B	25	M	0	0	0	0	4	0	0	0	11.7	13.9	11	11.7	40	32	40	42	
101	Group B	23	F	0	0	0	0	0	2	0	0	10.5	12	10.9	10.5	46	33	41	46	
102	Group A	19	M	0	0	0	0	2	0	0	2	12.9	14.9	14.1	12.9	41	32	39	41	
103	Group A	23	F	0	2	0	0	4	0	2	0	9.8	12.2	11.8	10	39	23	30	39	Epigastric pain
104	Group A	25	F	0	0	0	0	4	2	0	2	10.2	13.6	13	10.3	44	28	35	44	Epigastric pain
105	Group A	24	M	0	4	2	0	4	0	0	0	11.5	14	11.5	11.5	40	24	30	40	
106	Group B	23	F	0	0	2	0	2	0	0	0	11.5	12	10.9	11.4	39	30	35	39	Epigastric pain
107	Group A	29	F	0	2	0	2	2	0	0	0	12	14.9	13.9	12.2	42	28	33	40	
108	Group A	27	F	0	0	0	0	0	2	0	0	11.8	13.8	13.2	11.9	42	29	34	39	
109	Group A	29	F	0	0	0	0	2	0	0	0	11.2	11.9	11.3	11.2	35	21	28	35	Sedation
110	Group B	26	F	0	0	0	4	2	0	0	0	12.2	14.9	11.6	12.3	39	27	33	39	
111	Group B	25	F	0	2	0	0	0	0	6	2	11.2	11.9	10.8	11.3	37	24	31	37	
112	Group A	31	F	0	4	2	0	0	0	0	0	10.6	13.2	13.6	10.6	32	19	26	32	
113	Group A	35	M	0	0	0	0	4	0	0	0	10.4	13.4	12.9	10.4	40	24	30	40	
114	Group B	20	M	0	2	0	0	6	0	0	0	11.6	13	10.9	11.6	40	32	34	40	
115	Group A	38	M	0	0	2	0	2	0	0	0	10.8	12.8	12.8	10.8	41	26	33	41	
116	Group B	26	F	0	0	2	2	2	2	0	0	11.6	13.9	11	11.6	46	34	40	36	
117	Group B	22	M	0	2	2	0	2	0	2	2	11.3	13	10.8	11.3	40	31	38	43	Epigastric pain
118	Group B	29	M	0	0	2	4	2	2	0	0	10.3	14	9.8	10.3	42	30	38	41	
119	Group B	19	F	0	0	2	0	4	0	0	0	11.5	13	11	11.5	38	27	32	37	
120	Group B	33	M	0	0	2	0	2	2	0	0	11.9	14	11.3	11.9	38	29	32	38	