"THE EFFECT OF PREEMPTIVE INTRAVENOUS PARACETAMOL ON POSTOPERATIVE ANALGESIC REQUIREMENTS IN PATIENTS UNDERGOING LAPAROSCOPIC SURGERIES UNDER GENERAL ANAESTHESIA"

REG NO. BA0110001

Dissertation

Submitted to the
KLE University, Belgaum, Karnataka

In Partial Fulfillment
of the requirements for the degree of

M. D.

in

ANAESTHESIOLOGY

DEPARTMENT OF ANAESTHESIOLOGY,
JAWAHARLAL NEHRU MEDICAL COLLEGE,
BELGAUM, KARNATAKA

APRIL - 2013

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ENDORSEMENT

This is to certify that the dissertation entitled **"THE EFFECT OF PREEMPTIVE INTRAVENOUS PARACETAMOL ON POSTOPERATIVE ANALGESIC REQUIREMENTS IN PATIENTS UNDERGOING LAPAROSCOPIC SURGERIES UNDER GENERAL ANAESTHESIA"** is a bonafide research work done by **CANDIDATE REG NO. BA0110001**.

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LIST OF ABBREVIATIONS USED

ASA	-	American Society of Anaesthesiologist
Cm	-	Centimeter
CNS	-	Central nervous system
COX	-	Cyclooxygenase
CYP1A2	-	Isoenzyme of cytochrome P450
CYP2D6	-	Isoenzyme of cytochrome P450
CYP2E1	-	Isoenzyme of cytochrome P450.
DC	-	Differential count
DF	-	Degree of freedom
ECG	-	Electrocardiogram
ETCO2	-	End-tidal corbon di-oxide.
ETT	-	Endotracheal tube.
g	-	gram
GSH	-	glutathione
h	-	hour
Hb	-	Haemoglobin
HR	-	Heart rate
5-HT3	-	5-hydroxytryptamine
I cells	-	Interneuron cells
I.P.	-	Inpatient number
IASP	-	International association for the study of pain
IM	-	Intramuscular
IV	-	Intravenous
Kg	-	Kilogram

MEAC	-	Minimum Effective Analgesic Concentration
MEC	-	Minimum effective Concentration
mg	-	Milli gram
Min	-	Minute
ml	-	Milli litre
mm	-	Milli meter
NaCL	-	Sodium chloride
NAPQI	-	N-acetyl P-benzo-quinone imine
ng	-	nanogram
NIBP	-	Non invasive blood pressure
NSAID's	-	Nonsteroidal anti inflammatory drugs
P	-	probability
PACU	-	Post anaesthetic care unit
PO	-	Per os
RBS	-	Random blood sugar
S.D.	-	Standard deviation
Sec	-	Second
SPO_2	-	peripheral oxygen saturation
TC	-	Total count
T cells	-	Transmitting neuron cells
VAS	-	Visual analog scale
µg	-	micro gram

ABSTRACT

Background and Objectives

To determine the effect of preemptive use of 1g of IV paracetamol on postoperative pain scores and analgesic requirements in patients undergoing laparoscopic surgeries under general anaesthesia.

Methods

Sixty two American Society of Anesthesiologists physical status I and II patients undergoing laparoscopic surgeries were randomly divided into 2 equal groups. In the group I, 1g of IV paracetamol and in group II 100 ml normal saline IV was administered 30 min before induction over 15 min. Postoperative visual analog pain scores and requirement of tramadol were assessed.

Results

In this study significant high mean pain scores were observed at 15 min and 30 min during post operative period in group II (2.61±0.56 and 3.84±1.55 respectively) compared to group I (2.06±0.63 and 2.35±1.17 respectively). (P value 0.0006 and 0.0001 respectively). There was no significant difference in mean pain scores at one, two and six hours in both groups, which was due to administration of the rescue analgesic drug. (p value > 0.05). The requirement for rescue tramadol analgesia was in 25.8% of patients in the group I compared to 64.5% of patients in group II. (P<0.05).

Conclusion and interpretation

To conclude, preemptive administration of 1g of IV paracetamol in patients undergoing laparoscopic surgeries provided good quality analgesia with decreased pain scores during the postoperative period, increased patient satisfaction and decreased postoperative tramadol consumption.

Key Words

Analgesia; Intravenous paracetamol; Laparoscopy; Postoperative pain.

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Chapter 1

Introduction

INTRODUCTION

Patient comfort is a great concern in 21st century. Minimal access surgical procedures produce less trauma with potential advantage of reduced postoperative pain, shorter hospital stays, more rapid return to normal activities and is cost effective than conventional open procedures.

The development of minimally invasive surgery has not only revolutionalized techniques of surgical procedures but this process has also influenced the practice of anaesthesiology.[1]

It is important that anaesthetic approaches are developed to ensure that these techniques are safe and associated with minimal postoperative complications and rapid recovery.

Laparoscopic operative techniques involve insufflation of carbon dioxide. Gases like helium, air can also be used. The operation table is tilted to 15 degree reverse tredelenburg for upper abdominal surgery like cholecystectomy. Techniques for pneumoperitoneum creation include insufflations after insertion of veress needle at infraumbilical region.[1]

Laparoscopic surgery is associated with a high incidence of minor morbidity. one early survey found that over 95% patients had some symptoms at 24 hrs, with neck and shoulder pain (80%), and abdominal pain (71%) being the most common, some patients also reported headaches, backache, sorethroat, nausea and weakness. Many of these symptoms were still present on the second postoperative day, and 31% of patients reported that they would have preferred

not to have been outpatients. Pain was the major cause accounting for 61% of these patients in laparoscopic surgeries. Although laparoscopic surgery results in substantially less severe and prolonged discomfort compared with the corresponding open procedure, postoperative pain is still considerable and needs to be treated effectively and safely to reduce post operative complications and hospital stay.[2]

Post operative pain is an acute pain which starts with surgical trauma. Despite advances in the knowledge, skill and sophisticated technology that characterizes most aspects of modern surgical treatment, many patients continue to experience considerable discomfort during post operative period. There appears to have been little improvement in this aspect of care of such patients over the past several decades.

Modern day anaesthesia is not just concerned with relieving pain during surgeries but also during post operative period. Evidence suggests that inadequate relief of postoperative pain may result in harmful physiologic and psychologic consequences that lead to significant morbidity and mortality which delays the recovery and return to daily living. It increases patient suffering, cost of treatment and prolongs hospital stay.

Various modalities have been tried for the management of post operative pain namely drugs like opioids, nonsteroidal anti-inflammatory drugs (NSAID's), paracetamol, local anaesthetics, ketamine and adjuvants. These drugs are commonly administered via oral, intramuscular (IM), intravenous (IV), intrathecal, epidural, rectal, and regional techniques.

NSAID's have long been used for preemptive, intraoperative and postoperative analgesia. NSAIDs exert anti inflammatory and analgesic effects through the inhibition of prostaglandin synthesis, by blocking the activity of cyclooxgenase (COX) but also inhibit platelet function, increase perioperative bleeding, gastrointestinal ulceration and have nephrotoxic effects in patients with and without preexisting renal insufficiency and also not desirable in lactating mothers.[3]

Opioid and nonopioid analgesics are widely used in the treatment of postoperative pain. Clinical use of opioids are restricted or they are used in low doses owing to their potential side effects such as nausea, vomiting, urinary retention, sedation, ileus, respiratory depression and abuse potential.

Acetaminophen or paracetamol is commonly used as a mild to moderate analgesic in the peri-operative setting and is especially more effective in laparoscopic surgeries, which are associated with less pain compared to open surgeries. As it has no COX1 or COX2 activity, it has no effect on platelet aggregation and devoid of side effects. Paracetamol IV preparation is good alternative with more advantages over IM and oral. IV administration of drugs are gaining more popularity because of its lesser invasiveness, lesser pain on administration, ease of administration, better patient acceptance, faster onset of action, more predictable bio-availability.

IV paracetamol recently introduced in India has a good safety profile and is used to provide effective analgesia for acute postoperative pain. The

preemptive use of IV paracetamol can gives rise to a subsiding pain pattern and decrease in analgesic requirements during the postoperative period.[4]

There is lack of data showing the effects of IV paracetamol as IV preparation of paracetamol was recently introduced. However, there is good evidence to show paracetamol as an effective and safe analgesic.[5]

A Cochrane systematic review[6] of oral paracetamol use in acute postoperative pain analysing 47 studies, including 4186 patients, found the number-needed-to-treat for at least 50% pain relief, over 4-6 hours was 3.8 (95% confidence intervals: 3.4-4.4). There was no significant difference in the frequency of reported adverse effects between paracetamol and placebo.

Hence, an attempt has been made to evaluate the effect of preemptive IV paracetamol on postoperative analgesic requirements in patients undergoing laparoscopic surgeries under general anaesthesia with placebo controlled trial.

Chapter 2

Objectives

OBJECTIVES

To determine the effect of preemptive use of 1g of IV paracetamol on postoperative pain scores and analgesic requirements in patients undergoing laparoscopic surgeries under general anaesthesia.

Chapter 3

Review of Literature

REVIEW OF LITERATURE

As knowledge of the epidemiology and pathophysiology of postoperative pain increases a new analgesic concept has been developed and applied for the prevention of pain whereby analgesic treatment is started prior to trauma and surgical intervention. Within this concept, referred to as preemptive analgesia, it is believed that through application of an analgesic medicine or technique, pain will either subside or be prevented prior to the painful stimulus. This affect is achieved by suppressing, either together or separately, central or peripheral sensitization. Preemptive analgesia gives rise to a subsiding pain pattern, a decrease in analgesic requirements, and a decline in morbidity, promoting wellness and shortening the length of hospital stays.[7,8]

Postoperative pain has to be treated in a fast and effective manner to avoid negative effects and complications. Pain management should be started prior to pain initiation. With a good analgesic treatment plan for the patient in place, the anxiety, morbidity, cost, and length of hospital stay in the postoperative period are decreased. Therefore, postoperative analgesia management is very important. As of yet, no optimal medicine or method for postoperative pain management has been found that is devoid of side effects. The aim of preemptive analgesia, which has been investigated in recent years, is to provide analgesia prior to a painful stimulus to prevent central sensitization caused by the painful stimulus and, consequently, to decrease the need for postoperative analgesia. The methods and agents for which preemptive analgesic effectiveness has been researched are

mostly NSAID's, opioids, ketamine, peripheral local anesthetics and epidural analgesia.

Local anesthetics, opioids, NSAIDs and acetaminophen group drugs can be delivered either alone or in combination for preemptive analgesia.

Paracetamol is a non-opioid agent, and it is believed that it primarily acts upon the central nervous system by way of central cyclooxygenase inhibition, and probably has an indirect influence on the serotoninergic system. Paracetamol has a good safety profile and easily passes through the blood brain barrier, which assures it as an effective analgesic.[9]

A study demonstrated that paracetamol rapidly passes the blood-brain barrier, reaches a high concentration in the cerebrospinal fluid and has an anti-nociceptive effect mediated by the central nervous system.[10]

This central effect has been regarded primarily as an indirect and reciprocal influence through cyclooxygenase enzyme inhibition, and probably through the serotoninergic system as well. Besides this central effect, it is accepted that paracetamol has a peripheral anti-inflammatory influence, although this effect is somewhat limited.[9]

The analgesic efficacy and tolerability of parenteral versus oral 1g paracetamol were compared in 323 patients immediately after a hallux valgus plasty performed with local anaesthesia. Patients were randomized into three groups: Group I received IV propacetamol 2g [= paracetamol 1g], Group II received oral paracetamol 1g, Group III served as the control group which

received saline as placebo for post operative pain scores in the immediate post operative period. The study[11] concluded that IV paracetamol has a faster analgesic effect at early time points, a higher effectiveness and a longer analgesic effect than an equivalent oral paracetamol dosage.

In another study,[12] 1g of IV paracetamol was administered 15 min before surgery in 40 ASA I and II patients undergoing laparoscopic cholecystectomy and randomly divided into 2 equal groups. In the first group, 1g IV paracetamol was given after intubation before start of the surgery in 15 minutes. In the control group 100 mL 0.9% NaCl was infused IV in 15 minutes. Postoperative pain was evaluated and recovery characteristics were evaluated, it was concluded that the preemptive use of 1g IV paracetamol offers effective analgesia and faster recovery.

The effect of 1g of IV acetaminophen, over a 24-h period at 6 h intervals was studied in patients after orthopedic surgery. In this study one hundred fifty-one patients (IV acetaminophen: 49; propacetamol: 50; placebo: 52) received at least one dose of study medication. The IV acetaminophen and propacetamol groups differed significantly from the placebo group regarding pain relief from 15 min to 6 h ($P < 0.05$) and median time to morphine rescue (IV acetaminophen: 3 h; propacetamol: 2.6 h; placebo: 0.8 h).[13]

In a study[9] conducted on 90 ASA I and II patients undergoing total abdominal hysterectomy, randomized into three groups: in Group I received 1g of IV paracetamol 30 minutes prior to induction, In Group II, 1g of IV paracetamol was given prior to skin closure. Group III served as the control group which

received saline as placebo. Postoperatively, all patients received morphine via patient-controlled analgesia. The study concluded that, in total abdominal hysterectomy, preemptive 1g of IV paracetamol provided good quality postoperative analgesia, with decreased consumption of morphine and minimal side effects.

The effect of 2g IV propacetamol administered 30 min before the end of surgery to demonstrate the effect on postoperative pain was studied in 42 ASA I and II, scheduled to undergo elective decompressive lumbar laminectomy with spinal fusion under general anaesthesia. The patients were randomly assigned by a closed envelope technique to receive an IV infusion every 6 h with either 2 g of propacetamol (propacetamol group n=21) or a placebo (placebo group n=21) during a period of 72 h. The patients received their first infusion 30 min before the end of the surgical procedure and concluded that the propacetamol provided satisfactory analgesia, and less side effects.[14]

The analgesic effect of IV paracetamol and IV morphine were compared in a study on postoperative pain control of patients undergoing knee arthroscopic surgery as day cases in 84 patients randomized into two groups, group I (paracetamol group) received 1 g of paracetamol IV infusion over 15 minutes whereas the morphine group received 0.1mg/kg as an IV bolus. These were given at the time of the intra-articular injection of 20 ml of 0.5% marcaine in all patients just before the reversal of general anaesthesia. It was Concluded that both IV paracetamol and IV morphine seems to have similar analgesic effect. However, side effects with IV paracetamol were much less.[15]

In a study[16] eighty children undergoing tonsillectomy were randomized to receive either acetaminophen 15 mg/kg IV (acetaminophen group) or meperidine 1 mg/kg IM (meperidine group), intraoperatively. The study concluded that Compared with IM meperidine, IV acetaminophen provided adequate analgesia, less sedation and earlier readiness for recovery room discharge.

In another study[17] the relative morphine consumption was assessed in a combined analgesic regimen after gynecologic surgery with IV doses of propacetamol 2g or ketorolac 30mg. Patients were assessed regarding total dose of morphine, pain intensity and global efficacy. They established that total morphine requirements were not significantly different between the propacetamol (10.6±4.8 mg) and ketorolac (10.2±4.4 mg) groups. The evolution of pain intensity also showed similar patterns in the two groups.

The effect of fentanyl and placebo with fentanyl and paracetamol was compared for analgesic efficacy, opioid sparing effects, and opioid-related side effects after laparoscopic cholecystectomy. In this study eighty patients undergoing laparoscopic cholecystectomy were randomized into two groups, who were given either an IV placebo or an IV injection of 1g paracetamol just before induction. Both groups received fentanyl during induction and IM diclofenac for pain relief every 8 hourly for 24 h after surgery. The postoperative pain relief was evaluated by a visual analog scale (VAS) and consumption of fentanyl as rescue analgesic in the postoperative period for 24 h after surgery was measured. The study[18] concluded that, IV paracetamol use is associated with a satisfactory analgesia and decreased opioid consumption.

The effect of paracetamol or valdecoxib with or without dexamethasone was studied on 160 patients undergoing laparoscopic cholecystectomy, randomized into four groups of 40 patients each. Groups 1 and 3 received parecoxib 40 mg IV during surgery and valdecoxib 40 mg × 1 per os (PO) for 7 post-operative days. Groups 2 and 4 received paracetamol 1 g × 4 IV during surgery and 1 g × 4 PO for 7 days. In addition, Groups 3 and 4 were given dexamethasone 10 mg IV intra-operatively. The patients were given oxycodone 0.05 mg/kg IV in phase 1 post-anaesthesia care unit (PACU 1) or 0.15 mg/kg PO in phase 2 post-anaesthesia care unit (PACU 2) as needed to keep visual analogue scale <3/10. It was concluded that paracetamol was as effective as parecoxib/valdecoxib for pain after laparoscopic cholecystectomy and dexamethasone decreased the need of oxycodone in phase 2 PACU. The effect of dexamethasone was similar in paracetamol and parecoxib/valdecoxib patients.[19]

The efficacy of IV paracetamol on early post-operative pain after laparoscopic cholecystectomy was studied in twenty-four patients randomized to receive paracetamol IV 1g (group 1) or 2g (group 2) at the end of surgery. All patients were provided 0.1 mg/kg of oxycodone IV 15 min. before the end of surgery. In the recovery room when the wound pain at rest was ≥3/10 and/or ≥5/10 during the wound compression, plasma sample was taken for the determination of oxycodone (minimum effective concentration, MEC), its metabolites and paracetamol. After that the patients were titrated with further doses of oxycodone IV to wound pain < 3/10 at rest and < 5/10 during wound compression, plasma sample was taken for the determination of minimum effective analgesic concentration (MEAC) of oxycodone. The total oxycodone

dose needed for pain relief was similar, about 0.3 mg/kg (range 0.2–0.5), in both groups (p = 0.80). At the onset of pain, P-oxycodone (MEC) was similar in both groups, 25 ng/ml (19–32) in group 1 and 24 ng/ml (16–34) in group 2. The pain relief (MEAC) was achieved in group 1 with P-oxycodone 70 ng/ml (30–131) and in group 2 with 62 ng/ml (36–100) (p = 0.48). In conclusion, there was no significant difference between the effect of paracetamol doses of 1 g and 2 g IV on the need of IV oxycodone.[20]

A study[21] aimed to compare the postoperative analgesic effects of preoperative IV paracetamol, diclofenac sodium and lornoxicam (NSAID's) on 60 patients with impacted third molar who underwent surgical removal were randomly allocated into three groups namely, group P (n=20), group D (n=20) and group L (n=20). Group P received preoperatively 1g paracetamol IV, group D 75 mg diclofenac sodium IM and group L 8 mg lornoxicam IV. Postoperative pain intensity, additional consumption of analgesics postoperatively and postoperative complications were compared among groups. The groups were comparable for pain scores ($p > 0.05$). Maximum pain scores were recorded in postoperative 4th hour in all groups (group L 22, 14-44 mm; group P 24, 13-43 mm; group D 14, 10-24 mm, $p = 0.117$). Patients experienced high satisfaction scores which were comparable among groups (group L 85, 75-100 mm; group P 87, 70-95 mm; group D 84, 77-98 mm, $p = 0.457$). Preoperative IM diclofenac, IV paracetamol and lornoxicam effectively decreased the pain scores. The patients were satisfied with the three postoperative pain management regimens.

The efficacy of IV paracetamol and IV lornoxicam on postoperative analgesia and the reduction in tramadol consumption was studied in 60 patients

undergoing thyroidectomy randomized into three groups: Group L received 8 mg of IV lornoxicam, Group P received 1g IV paracetamol and Group C received 100 ml of IV saline solution. Results showed that, the time to first analgesic requirement was approximately 127.5 min in Group L, 162.3 in Group P and 35.5 min in Group C, and the time was found to be significantly prolonged in Group L and Group P. Pain scores were significantly lower in Group P and Group L at 15 min, and 1, 8, 12, and 18 hours. Twenty-four hour analgesic consumption was significantly lower in Group P and Group L compared to Group C. Supplemental analgesics requirement was as follows: 100% in Group C, 50% in Group L and 55% in Group P. The degree of satisfaction with postoperative pain management was excellent in 90% in Groups L and P, versus in only 30% in Group C. Study concluded that, administration of IV lornoxicam and IV paracetamol following thyroid surgery decreased the postoperative pain scores and opioid requirement, as well as the incidence of nausea and vomiting, while also prolonging the time to the first analgesic supplement.[22]

Hence, with preemptive analgesic effect of IV paracetamol on mild to moderate pain and its high safety profile known in the literature, this study was aimed to determine the efficacy of preemptive use of IV paracetamol on post operative analgesia in patients undergoing laparoscopic surgeries.

Chapter 3

Basic Sciences

BASIC SCIENCES

PAIN

Historical review[23,24]

Man has been afflicted with the EVIL (pain) since his beginning, for as the records of every race are examined, one finds testimonials to the omnipresence of pain. Prayers, exorcisms and incantations bearing testimony to the prevalence of pain are found on Babylonian clay tablets, in Papyri written in the days of pyramid builders, in Persian leather documents, in inscriptions from Mycenae, on parchment rolls from Troy, Such records continue down through the ages in every civilization and in every culture.

Pain has been one of the greatest factors to affect the course of human events, for scarcely any man has escaped its throes. The cause of painful disease, in pre historic time was linked with intrusion of magic fluids, evil spirits, or pain demons into the body. Treatment consists of extracting the intruding object or frightening away the pain demons.

The ancient Egyptians believed painful afflictions other than wounds were caused by religious influences of their gods or spirits of the dead. The routes of departure of the intruding demons could be vomit, urine or the sweat.

In ancient India the earliest concepts of pain and other medical knowledge were attributed to the god Indra, as recorded in the Vedas and Upanishads. Buddha, about 500 B.C., attributed the universality of pain in life to the frustration of desires: “Birth is attended with pain, decay is painful, and disease in

painful. Union with the unpleasant is painful; painful is separation from the pleasant and any craving that is unsatisfied, that too is painful." Charaka, the first of India's great teachers of medicine, stated that all joy and pain was experienced in the heart, which was considered the seat of consciousness.

The ancient Chinese thought, any imbalance of the two forces (YIN and YANG), results in obstruction (deficiency) or outpouring (excess) in the circulation of the CHI (the vital energy), causes or ends up in disease and pain. Acupuncture therapy, at one or more of the 365 specific points located along the meridians, corrects the imbalance and eliminates the disease and pain.

In Greece – Alcamaeon produced the idea that the brain and not the heart was the center for pain. Alcamaeon reintroduced the idea that the brain is the center for pain. Herophilus and Bristratus of Alexandria provided anatomic evidence that the nerves attached to the neuraxis are of two kinds, those for movement and those for feeling.

In the middle Ages the center of medicine shifted to Arabia. Avicenna in his "Cannon of Medicine" codified all available medical knowledge and described aetiology of 15 different types of pain. In 1804 Descartes in his book "L Homme (Man)" described the conduction of sensation including pain via delicate threads contained in the nerves which connected the tissue to the brain.

The new era of analgesia was initiated with Joseph Priestley's discovery of nitrous oxide. Modern approach to the scientific study of pain and its control began in the 19^{th} century. Charles Beu described that the functions of dorsal root are distinct from those of the ventral root. After 15 years Johannes Muller fully

expounded this idea. The modern era of systemic analgesia began in 1806 when morphine was isolated by Sertuner and it was frequently used intramuscularly for preoperative medication and postoperative analgesia.

Prior to 1846, attempts to provide comfort during operative procedures were minimally effective and the development of surgery was necessarily limited. W.T.G. Morton's public demonstration of ether in that year revolutionized medical care throughout the world. The evolution of anaesthesiology as a medical specialty has facilitated the success of modern, complex surgical procedures. Beyond the obundation of consciousness and creation of a quiescent surgical field, anesthesiology applies principles of physiology, pathophysiology and pharmacology to assess and reduce surgical risk, maintain homeostasis, attenuate the surgical stress response, and provide analgesia.

Regional analgesia for the management of intractable pain was also introduced in the last century. The 19th century was to produce still another great advance in conquer of pain by neurosurgical techniques. Surgeons started interruption of afferent pathways to control pain.

During the first 50 years of 20th century neuroanatomic, neurophysiologic and psychologic research on pain continued at progressively greater pace. Extensive knowledge became available on nervous system and its functions.

The founding of the International Association for the Study of Pain (IASP) in 1974 and publication of its journal PAIN since 1975 must be considered among the most important developments in the field of pain research and therapy.

ANATOMICAL AND PHYSIOLOGICAL ASPECTS OF PAIN PERCEPTION

Definition of pain[23,24]

Pain is an extraordinarily complex sensation which is difficult to define and equally difficult to measure in an accurate objective manner. It has been variously defined as:

An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damages (IASP, 1986).

Pain is a complex constellation of unpleasant sensory, perceptual, and emotional experiences with associated autonomic psychological and behavioral responses.

Pain can be represented as a VENN DIAGRAM

This shows that the sensation of pain differs among individual patients.

Emotional – varies according to patient's psychological composition.

Rational – varies with patient's previous experience, insight and motivation.

Physical – varies with type and site of surgery.

Postoperative pain is usually transitory, which shows progressive improvement over a relatively short time course.

All pain perception depends upon the transmission of impulses through pathways within the nervous system from the site of the stimulus to the higher centers of the brain; they may impinge upon our consciousness and be interpreted. The principal parts of the nervous system involved in this process are:

- Receptors in the skin and other organ.
- Peripheral nerves.
- Neuronal aggregates in the spinal cord and associated fiber tracts.
- The brainstem and thalamus.
- The limbic system.
- The cerebral cortex.
- Other parts of the brain indirectly involved.

PAIN THEORIES IN THE TWENTIETH CENTURY[23,24]

Peripheral Pattern Theory by Sinclair and Weddell in 1950's stated that all fiber endings (apart from those that innervate hair cells) are alike, so that the pattern of pain is produced by intense stimulation of nonspecific receptors.

Central Summation Theory by Livingston in 1943 suggested that the intense stimulation resulting from nerve and tissue damage activates fibers that project to intern uncial neuron pools in the spinal cord which in turn project to brain mechanisms that underline pain perception.

Strong proposed the **Fourth Theory of Pain** and believed that pain can be separated into two components: the perception of pain and the reaction to pain.

Sensory Interaction Theory In 1959 by Noordenbos who believes that large fibers inhibit and small fibers excite central transmission neurons, which project to a multisynaptic system that leads to the brain.

Gate Control Theory: The term "Gate Control" is now applied to the rapidly acting mechanisms which accept and control the passage of impulses from the afferent fiber input to cells which may then trigger the various effector systems and evoke sensation (Melzack and Wall 1965, Wall 1978).

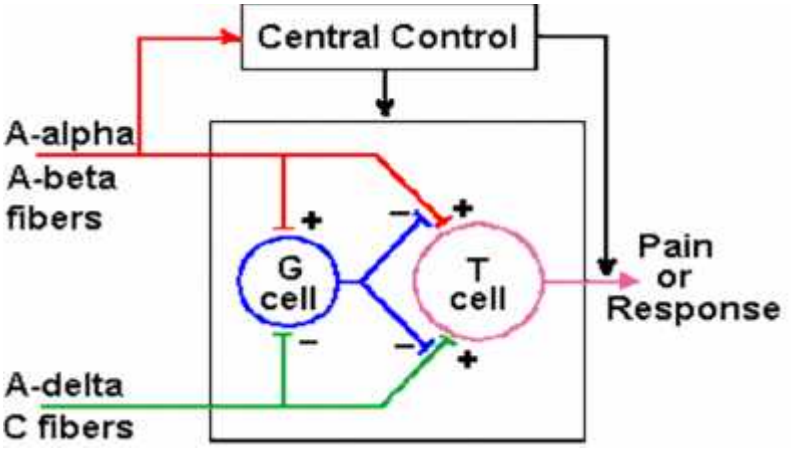


Fig 1. Gate control theory

Melzack and Wall (1965) observed in decerebrated and spinal cats, that peripheral stimulation of large myelinated fibers produced a negative dorsal root potential and that stimulation of C fibers caused a positive dorsal root potential. They postulated that these potentials, which were a reflection of presynaptic inhibition or excitation, modulated the activity of secondary transmitting neurons (T cells) in the dorsal horn, and that this modulation was mediated through an

inhibitory interneuron (I cell) placed the T cell in lamina V of the dorsal horn and the still unidentified inhibitory cells, in laminae II and III. The essence of this theory is the large diameter fibers excite the I cells, which is turn cause a presynaptic inhibition of T cells. Conversely the small pain afferent fibers inhibit the I cells leaving the T cells in an excitatory state.

Melzack and Wall emphasized that the transmission of pain impulses from the dorsal horn must also be under the control of a descending system of fibers from the brain stem, thalamus and limbic lobes. In their view, the descending control mechanism was sensitive to environmental factors and also utilized information from large primary afferents.

Pain receptors and peripheral afferent pathways[23,24]

The skin and subcutaneous tissues contain a variety of receptors of varying degree of complexity. These are the terminations of the unmyelinated and finely myelinated afferent nerves having their cell bodies in the posterior (dorsal) root ganglia of the spinal cord. The nerve ending which responds to painful stimulation are known as nociceptors. Some nociceptors respond mainly to mechanical injury whereas others, polymodal nociceptors are responsive to noxious heat and chemical irritation as well as mechanical injury. Receptors similar to those innervating the skin are found in muscle and visceral. Their response differs however and they will produce pain of a dull, vague nature following distension, stretch or traction and will not respond to burning, crush or incision. Central representation of somatic and visceral nociception may be

different thus accounting for some of the paradoxical difference between these two types of pain.

Afferent conduction[23,24]

The nerve fibers of which the nociceptors are the terminal portion are relatively small in cross section and comprise of finely myelinated delta fibers 1-5 micrometer in diameter with conduction rate at 5-45 m/sec. the unmyelinated C fiber diameter 0.4 – 1.1 micro meters conducting at 0.5 – 2.0 m/sec. other modalities of sensation are transmitted in the rapid myelinated A – beta fibers of 5-15 micrometer diameter with conduction at 30-100 m/sec. A-delta generated pain is well localized whereas C fiber pain is poorly localized.

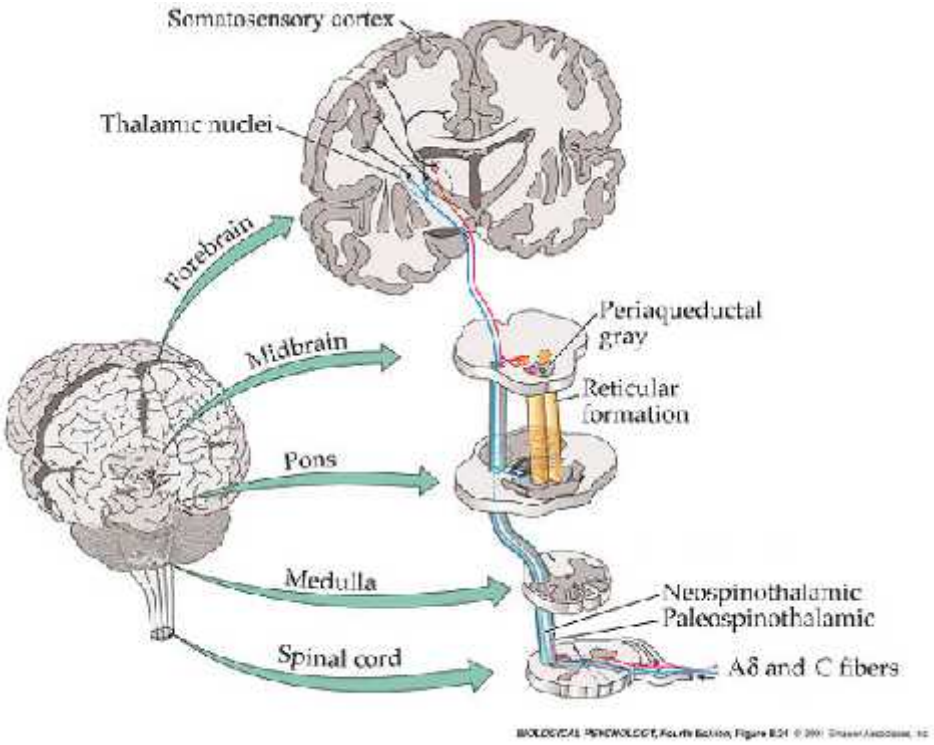


Figure 2. Pain Pathway[25]

Organization of pain pathways[23,24]

The cell bodies of the primary pain afferents (i.e. the first order neurons) are located in the dorsal root ganglia. Central extensions of the primary neurons project, via the dorsal root, to the dorsal horn of the spinal cord and in the case of cranial pain afferents, to the nucleus of the trigeminal nerve. These A-delta and C fibers occupy the lateral part of the root entry zone and within the spinal cord form a discrete bundle, the 'tract of lissauer' (Neospinothalamic tract). After traversing the lissauer's tract, they terminate in the dorsal horn of the spinal cord. In the dorsal horn, cell bodies are arranged in series of laminae some of which have classical names, but which are most simply given roman numerical by Rexed i.e. laminae I-IX.

The A-delta fibers terminate in lamina I, also known as the marginal cell layer of Waldeyer, whereas "C" fibers terminate in the lamina II also known as 'substantia gelationosa'. Many of the afferents ending in these marginal layers contain neuropeptides, including substance – p, cholecystokinin and somatostatin. There is increasing evidence that these peptides play an important role in the normal transmission of pain. Chemical destruction of fibers containing substance – P in animals produces analgesia. Most of the fibers terminate in the segment of their entry into the cord, but some extend rostrally and caudal tone or two adjacent segments ipsilaterally and some via the anterior commissure to the contralateral dorsal horn. Some pain fibers penetrate the dorsal gray matter and terminate in lamina V.

The secondary neurons connect with ventral and lateral horn cells in the same and adjacent spinal segments and subserve somatic and autonomic reflexes. In addition to this the secondary neurons decussate in the anterior spinal commissure to the opposite side and ascend in the anterolateral fasciculus (of which the lateral spinothalamic tract forms a major part) to the brain stem and thalamic structure.

The axon form each dermatome enters the spinal cord one to the three segments higher than the level of root entry. Crossing fibers are added to the inner side of the spinothalamic tract, so that the longest fibers from successively rostral segments occupy a progressively deeper position. Thus at the cervical level the fibers in the spinothalamic tract form without inwards are sacral lumbar, thoracic and cervical.

In addition to the lateral spinothalamic tract which is a fast conduction pathway that projects directly to the thalamus, the anterolateral fasiculus of the spinal cord contains a slowly conducting, medially placed system of fibers, which reaches the thalamus via one or more relays in the reticular core of the brain stem. This latter group of fibers if referred to as spinoreticulothalamic tract or paleospinothalamic tract. The conduction of diffuse, poorly localized pain arising from the deep structures (gut/periosteum) has been ascribed to this tract.

Thalamic terminus[23,24]

Most of the fibers of the lateral spinothalamic tract terminate in the nucleus ventralis posterolateralis. A lesser number of them terminate in the nucleus ventralis posteromedialis, the intralaminar nuclei and the venterobasal

complex, which also receive extensive projections from the brain stem reticular nuclei. Some afferent connections are also made with the hypothalamic nuclei.

Thalamo cortical projections[23,24]

The nuclei of the posterior thalamic complex send their projections to two main cortical areas, the post central cortex and the upper bank of the sylvian fissure.

Physiology and Psychology of pain[23,24]

Stimuli that produce pain vary for different tissues. An adequate stimulus for skin is one that produces tissue damage or injury viz, pricking, cutting crushing, burning and freezing. However these stimuli are inadequate when applied to stomach and intestines where the local effects of an engorged or inflamed mucosa, distension or spasm of smooth muscle and traction on the mesenteric attachment produces pain. In skeletal muscle, pain is produced by ischemia (intermittent claudication), necrosis, hemorrhage, injuries to connective tissue sheaths and injection of irritating solutions. Prolonged contraction of the skeletal muscle produces an aching type of pain. Ischemia is also the most important cause of pain in cardiac muscle. Joints are insensitive to pricking, cutting and cautery, but pain is produced by inflammation of the synovial membrane and by exposure to hypertonic saline. Arteries are a source of pain when pierced by a needle, or involved in an inflammatory process. Distension and excessive pulsation of meningeal arteries resulting in stretching of the dura, produces headache.

Perception of pain[23,24]

The threshold for the perceptions of pain i.e. the lower intensity of stimulus recognized as pain is approximately the same in all persons. However the emotional reaction and verbalization vary from individual with the personality and character of the individual. The threshold for pain is lowered by inflammation and raised by centrally acting analgesic drugs and lesions of the nervous system. Neurotic patients in general have the same pain threshold as normal subjects, but their reaction may be excessive or abnormal.

The conscious awareness of pain occurs only when the pain impulses reach the thalamocortical levels. The precise roles of the thalamus and cortical sensory areas in this mental process are not fully understood. However it is traditional teaching that the recognition of a noxious stimulus as such is the function of the thalamus, and that the parietal cortex is essential for the appreciation of the intensity, localization and other discriminating aspects of sensation. This seems to be an over simplification. Probably a close and harmonious relationship between the thalamus and cortex must exist in order for a sensory experience to be complete, that the cerebral cortex governs the patients reaction to pain cannot be doubted as frontal lobotomized subject react briefly, if at all to pain.

Methods of Pain Measurement[23,24]

One cannot determine for the individual patient how much nociception occurs in response to tissue damage for which we have to rely on the expression of the patient to accurately measure the subjective nature of pain.

Loser, of multidisciplinary pain centre, University of Washington put forward a multifaceted model as depicted in this figure. The core of the model is the immeasurable nociception resulting from tissue damage. The next layer is the human experience of emotional and sensory components integrated pain which is not available for direct inspection. Pain leads to suffering and suffering leads to painful behaviors which are available for observation in the form of:

a. Withdrawing
b. Grimacing
c. Crying
d. Asking for analgesics.

Thus if one relies on the patient's report of pain it is possible to measure pain intensity and the response to analgesic medications.

Introspective Method[23,24]

Patient or trained attender attempts to assess pain.

Behaviourise Method[23,24]

Some physical parameters which get altered in the presence of pain are objectively measured and correlated with the severity of pain e.g. like tachycardia, tachypnoea and increased blood pressure.

PAIN AS SELF-REPORT ON A SINGLE DIMENSION[23,24]

Verbal Descriptor Scales – Melzack and Torgerson introduced the following scale for pain intensity: "Mild, Discomforting, Distressing, Horrible, Excruciating."

Numeric Rating Scale – Here patients are asked to indicate how strong their pain is on a scale form 0 to 10 on which 0 represents "no pain at all" and 10 "the worst pain imaginable".

Visual Analog Scale (VAS) - Currently, the most commonly used method; first described by AITKEN is 1966. The subject makes a mark on a 10cms line – horizontal or vertical, one end of which is marked as "No pain" and the other as "The worst pain one can imagine". The position of the mark on the line measures how much pain the subject experiences.

Oral Analog Scale - First put forward by AUSTIN et. al. It is a simple and clinically relevant rating scheme. Absence of pain, presence of pain, and if the patient desired more analgesics are rated 0, 1 and 2 respectively. This rating is simple, yet addresses the essence of problem for the patient whether pain present and if it is, does the patient desire more pain relief with more analgesic medications.

PAIN AS SELF-REPORTS ON MULTIPLE DIMENSIONS[23,24]

McGill Pain Questionnaire – It scales pain in three dimensions: Sensory, Affective, and Evaluative.

West Haven-Yale Multidimensional Pain Inventory – This has been designed to be briefer and more classical in its psychometric approach.

Brief Pain Inventory – is a quick, multidimensional pain measurement that has demonstrated reliability and validity.

Memorial Pain Assessment Card – It scales pain, pain relief and mood on VAS and adds a set of adjectives reflecting pain intensity.

Pain Perception Profile is based on cross-modality matching.

ACUTE POSTOPERATIVE PAIN[23,24]

Postoperative pain is under treated for a number of reasons which include, lack of knowledge regarding the effective dose ranges and duration of action of opioids and unfounded fear of respiratory depression and addiction in hospitalized patients experiencing pain. The concept of postoperative pain management by anaesthesiologists is growing. These, along with the advent of newer opioids with higher safety levels and better techniques of administration, have brought about large improvements in the successful alleviation of postoperative pain.

Factors that modify postoperative pain

a. The site, nature and duration of surgery.
b. The type and extent of the incision and other surgical trauma.
c. The physiologic and psychological make up of the patient.
d. Presence of complications related to surgery.

e. Preoperative psychological, physiologic and pharmacologic preparation of the patient.
f. The anesthetic management before, during and after surgery.
g. The quality of post operative care.

Adverse effect caused by post operative pain[23,24]

Physiologic

Include pulmonary, cardiovascular, gastrointestinal and urinary dysfunction, impairment of muscle metabolism and function and neuroendocrine and metabolic changes.

Respiratory

Surgery including that of the upper abdomen or thorax produces a number of pulmonary changes, including reduced Vital capacity and Forced expiratory volume. Upper abdominal incisions result in reflex mediated increase in tone of abdominal muscles during expiration and in a decrease of diaphragmatic function. The results are reduced pulmonary compliance, muscle splinting and inability to breathe deeply or cough forcefully leading to hypoxia, hypercarbia, retention of secretions, atelectasis, and pneumonia. Increased muscle tone increases oxygen consumption and lactic acid production.

Cardiovascular

Pain causes stimulation of sympathetic neurons and subsequent tachycardia, increased stroke volume, cardiac work and myocardial oxygen

consumption. The risk of myocardial ischaemia or infarction may be increased as is the risk of deep vein thrombosis when feat of aggravating pain results in reduced physical activity, venous stasis and platelet aggregations.

Gastrointestinal and urinary

Ileus, nausea, vomiting, hypomotility of the urethra and bladder and retention of urine can occur for a umber of reasons that include nociceptive impulses from viscera and somatic structure.

Neuroendocrine and metabolic

Suprasegemental reflex responses to pain, result in increased sympathetic tone, hypothalamic stimulation, increased catecholamine and catabolic hormone like cortisol, adrenocorticotrophic hormone, antidiuretic hormone, growth hormone, cyclic adenosine monophosphate, glucagon, aldosterone, renin, angiotensin 2 and decreased secretion of anabolic hormones insulin and testosterone. The effects of these changes include sodium and water retention and increased blood glucose, free fatty acids, ketone bodies, and lactate. Metabolism and oxygen consumption are increased and metabolic substrates are mobilized from storage depots. A catabolic state and negative nitrogen balance result, if the process continues.

Psychological

Postoperative pain is a major source of fear and anxiety for patient and if prolonged, leads to anger, resentment and lack of trust in the doctors and nurses who are perceived to be withholding pain relief. Pain leads to insomnia with

further delayed recovery. Some patients may even try self medication which could be hazardous.

The common methods for pain relief are:

1. **By increasing the pain threshold**

Pharmacologic:

a. Centrally acting analgesics
b. Peripherally acting analgesics

Non-pharmacologic:

a. Counseling
b. Hypnosis

2. **By modulating the pain pathways**

a. Transcutaneous electrical nerve stimulation
b. Acupuncture
c. Cryotherapy
d. Heat therapy

3. **By interrupting the nociceptive pathway**

a. Nerve blocks and Neurolysis
b. Surgical ablation – Cryoanalgesia

PARACETAMOL

History:

Julius Axelrod *(pictured)* and Bernard Brodie demonstrated that acetanilide and phenacetin are both metabolized to paracetamol, which is a better tolerated analgesic.[26]

Paracetamol was first marketed in the United States in 1953 by Sterling-Winthrop Co., which promoted it as preferable to aspirin since it was safe to take for children and people with ulcers.[27] In 1963, paracetamol was added to the British Pharmacopoeia, and has gained popularity since then as an analgesic agent with few side-effects and little interaction with other pharmaceutical agents.[28] Concerns about paracetamol's safety delayed its widespread acceptance until the 1970s, but in the 1980s paracetamol sales exceeded those of aspirin in many countries, including the United Kingdom. This was accompanied by the commercial demise of phenacetin, blamed as the cause of analgesic nephropathy and hematological toxicity.[29]

Structure and reactivity:

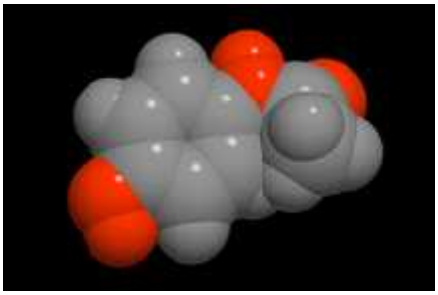
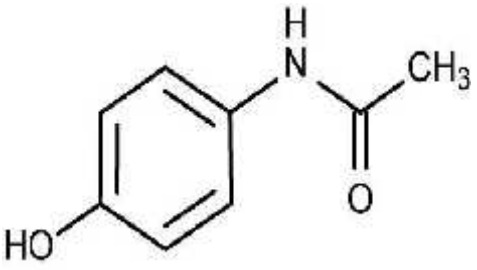


Figure 3. Paracetamol molecule polar surface area



***N*-(4-hydroxyphenyl) acetamide**

Paracetamol consists of a benzene ring core, substituted by one hydroxyl group and the nitrogen atom of an amide group in the *para* (1,4) pattern.[30,31] The amide group is acetamide (ethanamide). It is an extensively conjugated system, as the lone pair on the hydroxyl oxygen, the benzene pi cloud, the nitrogen lone pair, the p orbital on the carbonyl carbon, and the lone pair on the carbonyl oxygen are all conjugated. The presence of two activating groups also make the benzene ring highly reactive toward electrophilic aromatic substitution. As the substituents are *ortho, para*-directing and *para* with respect to each other, all positions on the ring are more or less equally activated. The conjugation also greatly reduces the basicity of the oxygens and the nitrogen, while making the hydroxyl acidic through delocalisation of charge developed on the phenoxide anion.

Synthesis:

In the laboratory, paracetamol is easily prepared by nitrating phenol with sodium nitrate, separating the desired *para*- nitrophenol from the *ortho*-byproduct, and reducing the nitro group with sodium borohydride. The resultant *4*-aminophenol is then acetylated with acetic anhydride. In this reaction, phenol is strongly activating, thus the reaction requires only mild conditions (cf. the nitration of benzene). The industrial process is analogous, but hydrogenation is used instead of the sodium borohydride reduction.

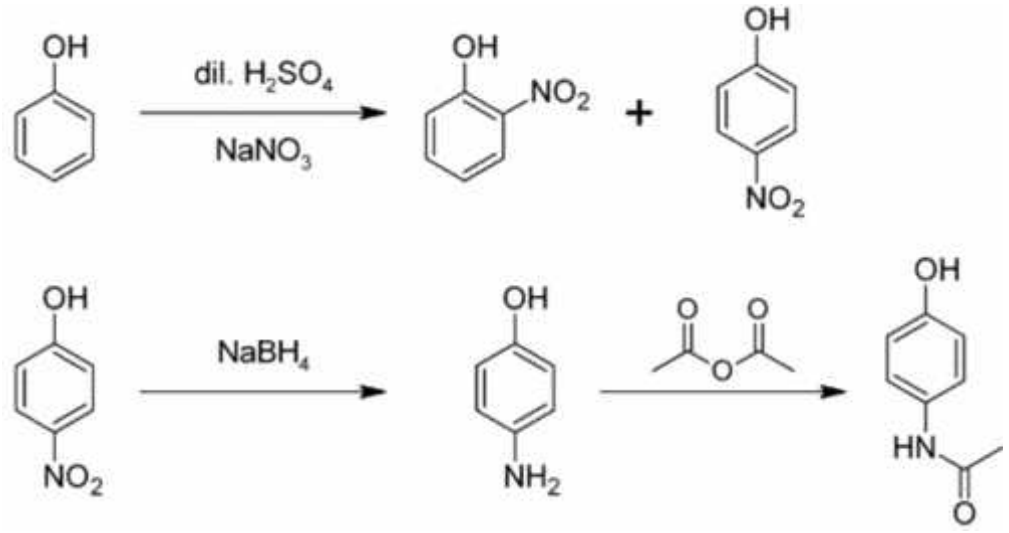


Figure 4. Synthesis of paracetamol

Classification

Paracetamol is part of the class of drugs known as "aniline analgesics"; it is the only such drug still in use today. It is not considered an NSAID because it does not exhibit significant anti-inflammatory activity (it is a weak COX inhibitor). This is despite the evidence that paracetamol and NSAIDs have some similar pharmacological activity.

Available Forms

Paracetamol is available in a tablet, capsule, liquid suspension, suppository, intravenous, and intramuscular form. The common adult dose is 500 mg to 1000 mg. The recommended maximum daily dose, for adults, is 4000 mg. In recommended doses, paracetamol is generally safe for children and infants, as well as for adults, although rare cases of acute liver injury have been linked to amounts lower than 2500 mg per day.

Pharmacokinetics

The time course of action is quick with iv paracetamol as it reaches peak plasma concentration as soon as infusion is complete (about 15 minutes). According to the product information, the analgesic effect starts within 5 minutes, peaks at 1 hour and lasts 4 to 6 hours. This is consistent with a plasma half-life of 2.7 hours - i.e. about two half-lifes. The antipyrexial activity lasts 6 hours.

This time course can be altered. If the speed of infusion is slowed down, then the onset and time to peak effect will be prolonged. If the patient is very heavy or large, the peak effect may be decreased (higher Volume of distribution and hence lower peak plasma levels). In liver failure, the metabolism may reduced, prolonging paracetamol action. In people taking enzyme-inducing agents or alcohol the metabolism of paracetamol may increase, hastening the decrease in paracetamol levels in plasma. Since the elimination is through the kidneys, patients in renal failure may take more time to clear paracetamol from the body. However, only less than 5% of given paracetamol is excreted unchanged, and its metabolites (also excreted through the kidneys) are inactive. Probenecid tends to increase plasma levels of paracetamol.[32] In the very young, metabolism and elimination take longer.

Metabolism

Main pathways of paracetamol metabolism. Pathways shown in blue and purple lead to non-toxic metabolites; the pathway in red leads to toxic NAPQI.

Paracetamol is metabolised primarily in the liver, into non-toxic products. Three metabolic pathways are notable:

- Glucuronidation is believed to account for 40% to two-thirds of the metabolism of paracetamol.[33]
- Sulfation (sulfate conjugation) may account for 20–40%.[34]
- N-hydroxylation and rearrangement, then GSH conjugation, accounts for less than 15%. The hepatic cytochrome P450 enzyme system metabolizes paracetamol, forming a minor yet significant alkylating metabolite known as NAPQI (*N*-acetyl-*p*-benzo-quinone imine) (also known as N-acetylimidoquinone). NAPQI is then irreversibly conjugated with the sulfhydryl groups of glutathione.[35]

All three pathways yield final products that are inactive, non-toxic, and eventually excreted by the kidneys. In the third pathway, however, the intermediate product NAPQI is toxic. NAPQI is primarily responsible for the toxic effects of paracetamol; this constitutes an example of toxication.

Production of NAPQI is due primarily to two isoenzymes of cytochrome P450: CYP2E1 and CYP1A2. The P450 gene is highly polymorphic, however, and individual differences in paracetamol toxicity are believed due to a third isoenzyme, CYP2D6. Genetic polymorphisms in CYP2D6 may contribute to significantly different rates of production of NAPQI. Furthermore, individuals can be classified as "extensive", "ultrarapid", and "poor" metabolizers (producers of NAPQI), depending on their levels of CYP2D6 expression. Although CYP2D6 metabolises paracetamol into NAPQI to a lesser extent than other P450 enzymes,

its activity may contribute to paracetamol toxicity in extensive and ultrarapid metabolisers, and when paracetamol is taken at very large doses. At usual doses, NAPQI is quickly detoxified by conjugation with glutathione.[43] Following overdose, and possibly also in extensive and ultrarapid metabolizers, this detoxification pathway becomes saturated, and, as a consequence, NAPQI accumulates causing liver and renal toxicity.

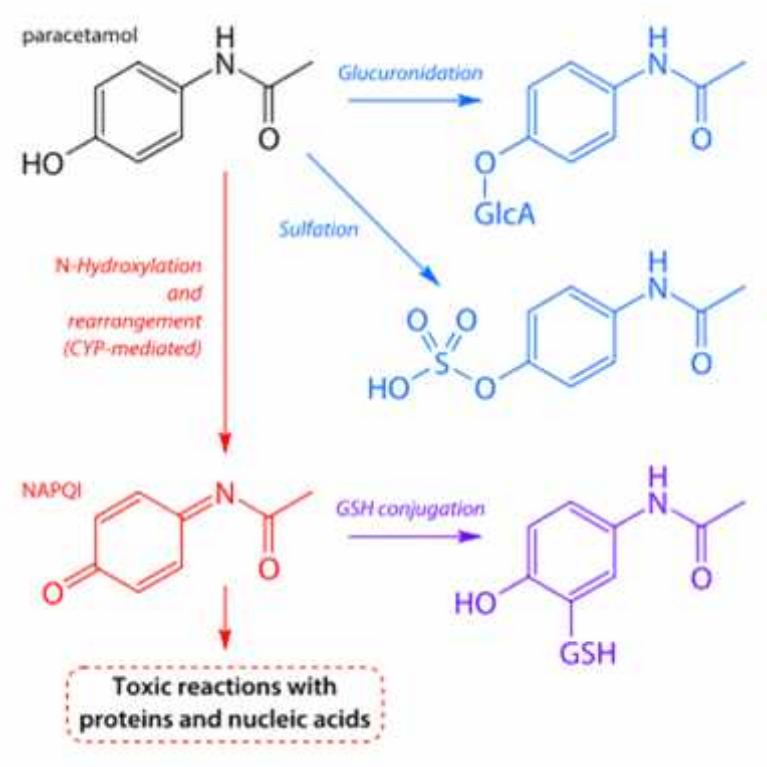


Figure 5. Metabolism of paracetamol

Mechanism of action:

To date, the mechanism of action of paracetamol is not completely understood. . It has always been thought to have a strong central action, supported by the fact that paracetamol is found in significant concentrations in the CSF after infusions in adults and in children.[35]

Prostaglandin synthesis relies on the action of cyclooxygenase (COX) enzymes on arachidonic acid. For this to occur, COX must be in an oxidised form. Paracetamol seems to reduce this oxidised form, rendering the enzyme less effective.[36]

Reduced amount of prostaglandins E2 in the CNS, thus lowering the hypothalamic set-point in the thermoregulatory centre, recent findings suggest that it is highly selective for COX-2, Because of its selectivity for COX-2 it does not significantly inhibit the production of the pro-clotting thromboxanes.. The other family of COX enzymes, COX 3, was thought to mediate analgesia in humans[37] but this theory has now lost favour, as COX 3 is not thought to be active in humans.[38]

Paracetamol is also thought to affect the endogenous cannabinoid system. Paracetamol is metabolised to AM404, also known as N-arachidonoylphenolamine.[39]

This compound prevents the reuptake of endogenous cannabinoids like anandamide from the synaptic cleft. Since blockade of cannabinoid type 1 receptors attenuate the action of paracetamol,[40] this theory is gaining credibility. AM404 is also a TPRV1 agonist, which is also activated by the analgesic drug capsaicin. Paracetamol may act along the same lines.

An articlein Nature Communications from researchers in London, UK and Lund, Sweden in November 2011 has found a hint to the analgesic mechanism of acetaminophen (paracetamol), being that the metabolites of acetaminophen e.g.

NAPQI, act on TRPA1-receptors in the spinal cord to suppress the signal transduction from the superficial layers of the dorsal horn, to alleviate pain.

COX, TPRV1 and cannabinoids in combination could be involved not only in pain, but also also thermoregulatory pathways.[39]

Another receptor for the action of paracetamol is the 5-HT3 receptor. A 5-HT3 antagonist was found to block the antinociceptive action of intrathecal paracetamol,[41] supporting this notion.

Dosage

Adults: Maximum of 1 gm IM/IV up to 4 times daily.

Children (<33 kg): 15 mg/kg IM / IV up to 4 times daily as required, or as prescribed. Minimum interval of 6 hours recommended in-between doses. Maximum dose is 60 mg /kg per day.

Uses:

Paracetamol is approved for reducing fever in people of all ages. Paracetamol has a well-established role in pediatric medicine as an effective analgesic and antipyretic.

Paracetamol is used for the relief of pains associated with many parts of the body. It has analgesic properties comparable to those of aspirin, while its anti-inflammatory effects are weaker. It is better tolerated than aspirin in patients in whom excessive gastric acid secretion or prolongation of bleeding time may be a concern.

Paracetamol can relieve pain in mild arthritis but has no effect on the underlying inflammation, redness, and swelling of the joint. It is as effective as the non-steroidal anti-inflammatory drug ibuprofen in relieving the pain of osteoarthritis of the knee.

Paracetamol has relatively little anti-inflammatory activity, unlike other common analgesics such as the NSAIDs, aspirin and ibuprofen.

Regarding comparative efficacy, studies show conflicting results when compared to NSAIDs. A randomized controlled trial of chronic pain from osteoarthritis in adults found similar benefit from paracetamol and ibuprofen.

Indications:

- Paracetamol is indicated for symptomatic relief of fever
- temporary reduction of mild to moderate aches and pain associated with cold, flu, headache, muscular aches, sprains, overexertion and osteoarthritis.
- In children, it can be useful for simple pain and discomfort.

Contraindications

- It is not advocated for those allergic to its ingredients.
- Not advocated in severe hepatocellular insufficiency and hepatic failure.
- Paracetamol Injection especially must be advocated with caution in those with a creatinine clearance <30 ml/minute, chronic alcoholism, chronic malnutrition (low reserves of glutathione stores) and dehydration.
- In pregnancy and lactation it should be given only if strictly required.

- There is inadequate safety data for intramuscular (IM) / IV paracetamol use in neonates, infants and children <6 months of age.

Adverse effects

- In recommended doses, the side effects of paracetamol are mild to non-existent.
- Skin rashes and other hypersensitivity reactions could occur and rare occasions it may cause hematological changes. Pain at injection site can occur with IM / IV.
- Prolonged daily use increases the risk of upper gastrointestinal complications such as stomach bleeding, and may cause kidney or liver damage.
- Hepatotoxicity, though extremely rare, can occur if therapeutic doses are exceeded. Hepatotoxicity is mediated by a reactive metabolic product (N-acetyl- p-benzoquinone-imine)[30] . A conservative estimate of a dose with the potential for hepatotoxicity in an adult is greater than 150 mg/kg body weight.
- A recent review of the tolerability of paracetamol[32] emphasized that although hepatotoxicity due to paracetamol over dosage is well recognized, standard recommended doses do not appear to have adverse effects in patients with liver disease. Hence, paracetamol is not contraindicated in patients with liver disease, provided that recommended doses are not exceeded.[42]
- Chronic users of paracetamol may have a higher risk of developing blood cancer.

Drug interactions

- Absorption of paracetamol is increased by concomitant metoclopramide. Probenecid can decrease it's clearance whilst cholestyramine diminishes absorption of paracetamol when coadministered.

TRAMADOL

First registered in Germany on 1973, first marketed in 1977 now coming off patent worldwide, Tramadol is a centrally acting analgesic that has low affinity for mu opioid receptors. Tramadol is synthetic analog of Codeine and is not currently classified as controlled substance, is only 5-10 times less potent than Morphine as an analgesic.

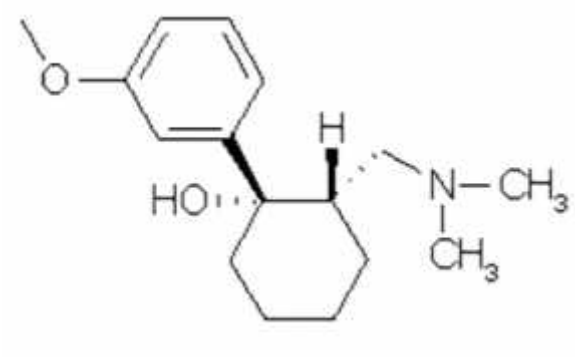


Figure 6. Chemical structure of Tramadol

Chemistry:

Tran-(I)-2(Dimethylamino)methyl) - 1 - (3-methoxyphenyl) cyclohexonal hydrochloride. Tramadol is racemic mixture of two enantiomers which is more effective than either enantiomer alone. The positive enantiomer binds to mu

receptor and inhibits serotonin uptake. The negative enantiomer inhibits norepinephrine uptake at α_2 – adrenergic receptors.

Mechanism of Action:

Tramadol follows two compartment model with one distribution phase and other elimination phase. First mode of anaesthesia is as an opioid that has moderate affinity at mu receptors and weaker affinity for delta and kappa receptors. Tramadol has methyl group substitution on the phenolic moiety which explains its weak affinity for opioid receptors.

Second mode is it inhibits pain via the drugs influence on the descending pain inhibitory systems, Tramadol influences these systems by preventing reuptake and enhancing the release of serotonin and norepinephrine. Both of these neurotransmitters inhibit the transmission of painful stimuli. Dose required for inhibition of neurotransmitter reuptake and that required for opioid receptor analgesia is the same. Role of potassium channels in pain is setting the resting membrane potential and in controlling the excitability of neurons. The opening of nonspecific voltage dependent channels leads to hyperpolarization of cell membrane, which results in a decrease in cell excitability.

Pharmacokinetics:

Absorption

May be administered orally, intramuscular or intravenous, is rapidly and almost completely absorbed but after oral administration only about 70% of drug is bioavailable due to first pass metabolism.

After multiple doses bioavailability increases to about 90% to 100%. This increased bioavailability is attributed to first pass liver metabolism.

Distribution

Highly lipid soluble, has good tissue affinity and ability to cross the blood brain barrier and placental barrier, T max is 1.8 ± 0.4 hours.

Metabolism

This is rapidly and extensively metabolized in liver. The principal metabolic pathway O-and N- demethylation involve cytochrome P-450 isoenzyme 2D6, 2B6, 3A4 respectively. The main metabolites are M1 – O – desmethyl tramadol and (M2) N-desmethyl tramadol. These main metabolites are again metabolized to secondary metabolites which are N-N-didesmethyl (M3) N-N,O – tridesmethyl tramadol (M4) and N-O desmethyl tramadol (M5) all metabolites are conjugated with glucoronic acid and sulfate before excretion in urine. Only O-desmethyl tramadol is pharmacologicaly active, 10-30% of the drug is excreted unmetabolised in urine.

Elimination

Tramadol has elimination half life of 5.2±0.9 hours and for its active metabolite O-desmethyl tramadol is 7.6±1.1 hours. During oral administration 90% of Tramadol is excreted by the kidneys and remaining 10% via faeces. Excretion is decreased in patients with renal compromise, however it does not decrease renal blood flow and is considered safe for kidneys.

Systemic effects

Tramadol does not cause the significant adverse effects common to opioids including respiratory depression, constipation or sedation.

Cardiovascular System

It does not have any negative haemodynamic effects and would be an alternative for patients with hypertension or other cardiac risk factors.

Respiratory system

Respiratory depression appears to be less than with equianalgesic doses of Morphine and is reversed by Naloxone.

Gastrointestinal system

Only minor delaying effects on the gastrointestinal transit time and causes less gastrointestinal irritation, so is useful analgesic as an alternative to nonsteroid anti-inflammatory drugs. Nausea and emesis are partly attributed to opioid receptors located in the chemoreceptor trigger zone in the area postrema.. The 5HT3A receptors are practically not effected, thus this receptor remains functional and therefore sensitive to any rise of 5HT concentration resulting from inhibition of the 5HT transporter by Tramadol.

Central nervous system

Tramadol can cause seizures and possibly excerbate seizures in patients with predisposing factors.

Clinical uses:

Used as an analgesic, analgesia begins with in 60 minutes of oral dosing and peak effect within 2-3 hours and duration of analgesia is 6 hours. Plasma concentration or pharmacological action is used as an adjuvant with local anaesthetic drugs in brachial plexus blockade, intravenous regional anaesthesia, epidural analgesia, postoperative shivering, adjuvant to general anaesthesia.

Abuse and physical dependence

Have been reported although its abuse potential is unclear, should be avoided in patients with history of addiction. Tramadol should be avoided in patients taking monoamine oxidase inhibitors due to inhibitory effect of Tramadol on serotonin uptake.[43,44]

Chapter 4

Methodology

METHODOLOGY

The present study was conducted in the Department of Anaesthesiology, KLES Dr. Prabhakar Kore charitable Hospital and Medical Research Centre, Belgaum during the period of January 2011 to December 2011.

Study design

A one year randomized placebo controlled trial.

Source of Data

Patients undergoing laparoscopic surgeries under general anaesthesia at KLES Dr. Prabhakar Kore Charitable Hospital and Medical Research Centre, Belgaum a teaching hospital attached to Jawaharlal Nehru Medical College, Belgaum.

Study Period

One year from January 2011 to December 2011.

Sample Size

A total of 62 patients divided into two groups using computer randomization.

Sampling procedure

Using results of previous studies, pilot study and based on the calculation in the following formula 31 patients were selected in each group.

$$\text{Sample Size (n)} = \frac{2 \times (Z\alpha + Z\beta)^2 (S1^2 + S2^2)}{(X_1 - X_2)^2}$$

$Z\alpha$ = 1.96 (α = 0.05)

$Z\beta$ = 0.84 (β=80%)

S_1 = 2

S_2 = 2

X_1 = 3.7

X_2 = 1.7

Selection criteria

Inclusion

- Patients undergoing laparscopic surgeries under general anaesthesia with duration of ninety minutes.
- ASA physical status I and II.
- Age between 18 to 60 years.
- Weight between 50 to 70 Kgs.

Exclusion

- History of allergic reactions to paracetamol.
- Chronic alcoholism, obesity, pregnancy, gastro oesophageal reflux.
- Patients having, hepatic, renal or neurological and bleeding disorders.
- History of usage of paracetamol, opioids, or NSAID's 48 hours before surgery.

Ethical clearance

Prior to the commencement, the study was approved by the Ethical and Research Committee, Jawaharlal Nehru Medical College, Belgaum.

Informed Consent

All the patients fulfilling selection criteria were explained about the nature of the study and intervention and a written informed consent was obtained from all the patients before enrollment (Annexure I).

Method of collection of data

After the enrollment, demographic data such as age and sex were recorded and patients were asked for the history. General physical examination, systemic examination was carried out. Routine investigations such as complete blood picture, Random Blood Sugar (RBS), Blood Urea, Serum Creatinine, Blood Grouping and Typing, Liver Function Tests, Chest X-ray, Electrocardiography (ECG) and Urine Examination were done and the data was recorded on a predesigned and pretested proforma (Annexure II).

Randomization

Patients were randomly allocated into two groups by computer generated randomization namely

- Group I (n=31) – Patients received 1g IV paracetamol over 15 minutes.
- Group II (n=31) – Patients received 100 ml IV normal saline over 15 minutes.

Procedure

After confirmation of nil by mouth status, baseline HR, NIBP, SpO2 readings were noted in pre-anaesthetic room. An IV line was secured with appropriate IV cannula and 500 ml crystalloids were started.

The study drugs were given intravenously as slow infusion 30 min before induction in pre-anaesthetic room. In group I, patients received 1g of IV paracetamol and in group II, patients received 100 ml IV normal saline over 15 min.

All the patients were pre-oxygenated with 100% oxygen by using Bain's circuit for three minutes. Anaesthesia was induced with injection thiopentone 5 mg/kg IV, injection fentanyl 2 µg/kg IV, injection vecuronium 0.1 mg/kg IV and trachea was intubated with appropriate size ETT.

Following intubation, maintenance of general anaesthesia was accomplished by providing isoflurane in 40/60 oxygen/nitrous oxide and, if required, 0.01 mg/kg vecuronium was administered. If the duration of surgery was more than 90 minutes, the cases were excluded from the study.

All the patients were monitored for HR, NIBP, SpO_2 and $ETCO_2$ throughout the procedure. Patients were extubated after reversal with glycopyrrolate (0.01 mg/kg) and neostigmine (0.05 mg/kg) and thorough suctioning.

Study variables

In the post anaesthesia care unit, postoperative pain score was measured by using VAS of ‘zero’ to ‘ten’ where ‘zero’ indicated no pain and ‘ten’ indicated worst imaginable pain. Postoperative pain was observed at the intervals of 15 minutes, 30 minutes, one hours, two hours and six hours. Injection tramadol 50 mg IV used as rescue analgesic, was given if the VAS score was more than three.[4]

Blinding

The pain score assessment was done by a trained nursing professional who was blinded to the study drugs administered.

Statistical analysis

Data obtained was coded and entered into Microsoft excel spreadsheet. The categorical data was expressed in terms of rates, ratios and percentage and continuous data was expressed as mean ± standard deviation (SD). The comparison between the two groups was done by student’s unpaired ‘t’ test and mann-whitney test. A probability value (p value) of less than or equal to 0.05 was considered as statistically significant.

Chapter 5

Results

RESULTS

The objective of the present study was to determine the effect of 1g of IV paracetamol compared to placebo in patients undergoing laparoscopic surgeries under general anaesthesia. The study was conducted in the Department of Anaesthesiology, KLES Dr. Prabhakar Kore Charitable Hospital and Medical Research Centre, Belgaum during the period of January 2011 to December 2011. A total of 62 ASA I and II aged between 18 to 60 years patients undergoing laparoscopic surgeries under general anaesthesia were randomly allocated into one of the two groups by computer generated randomization namely;

- Group I (n=31): Patients received 1 g IV paracetamol 30 min before induction over 15 minutes.

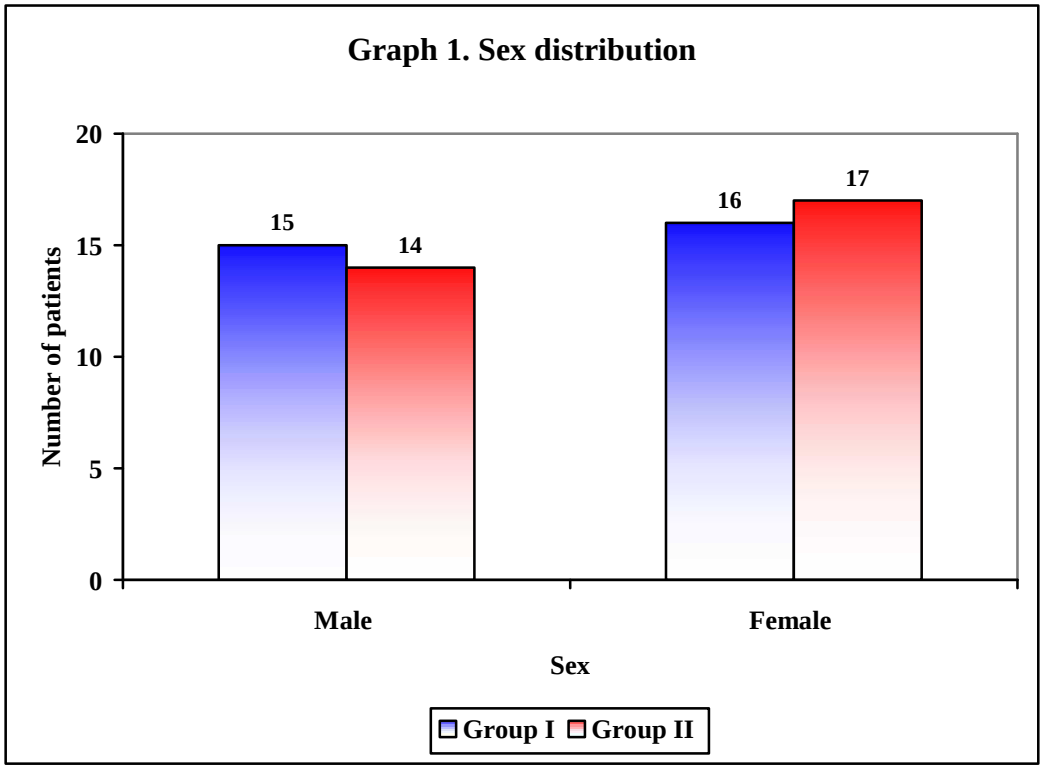
- Group II (n=31): Patients received 100 ml IV normal saline 30 min before induction over 15 minutes.

Data obtained was entered into Microsoft excel spread sheet and analysed as below.

Table 1. Sex Distribution

Sex	Group I (n=31)	Group II (n=31)
Male	15	14
Female	16	17
Total	**31**	**31**

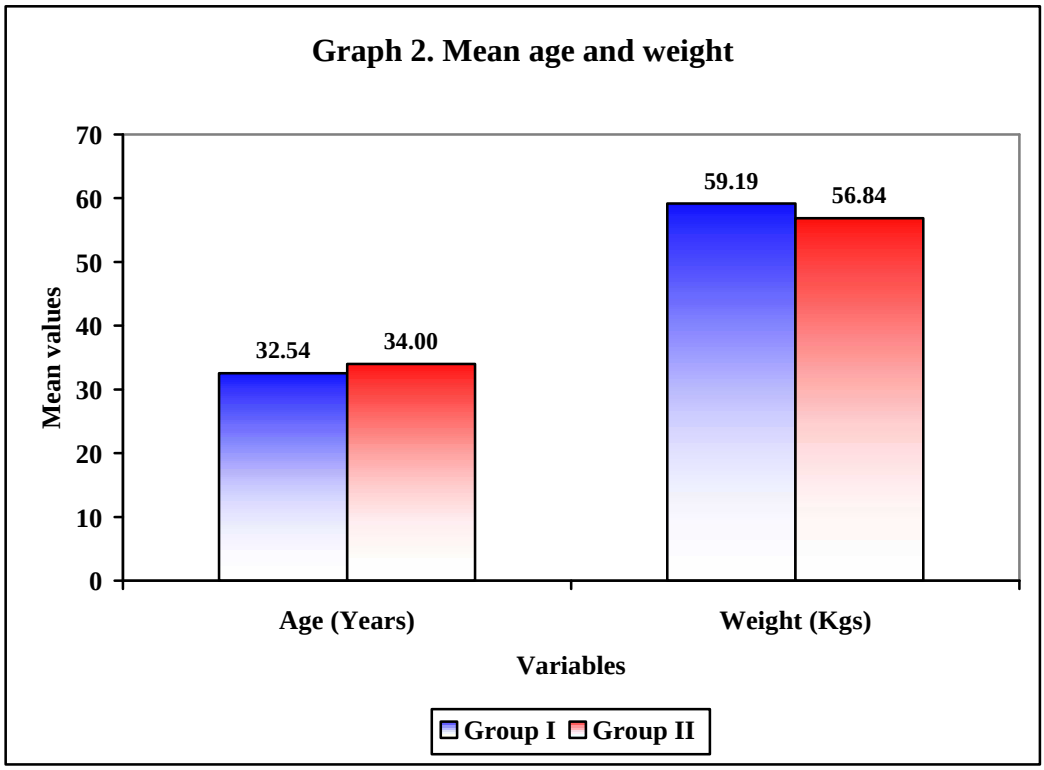
x^2=0.648E-01 **DF=1** **p=0.799**



The above table shows the number of male and female patients in the both the groups which was comparable and there was no statistical difference.

Table 2. Mean age and weight

Parameters	Group I (n=31)		Group II (n=31)		'p' value
	Mean	SD	Mean	SD	
Age (Years)	32.54	11.01	34.00	10.67	0.600
Weight (Kgs)	59.19	7.91	56.84	6.87	0.215

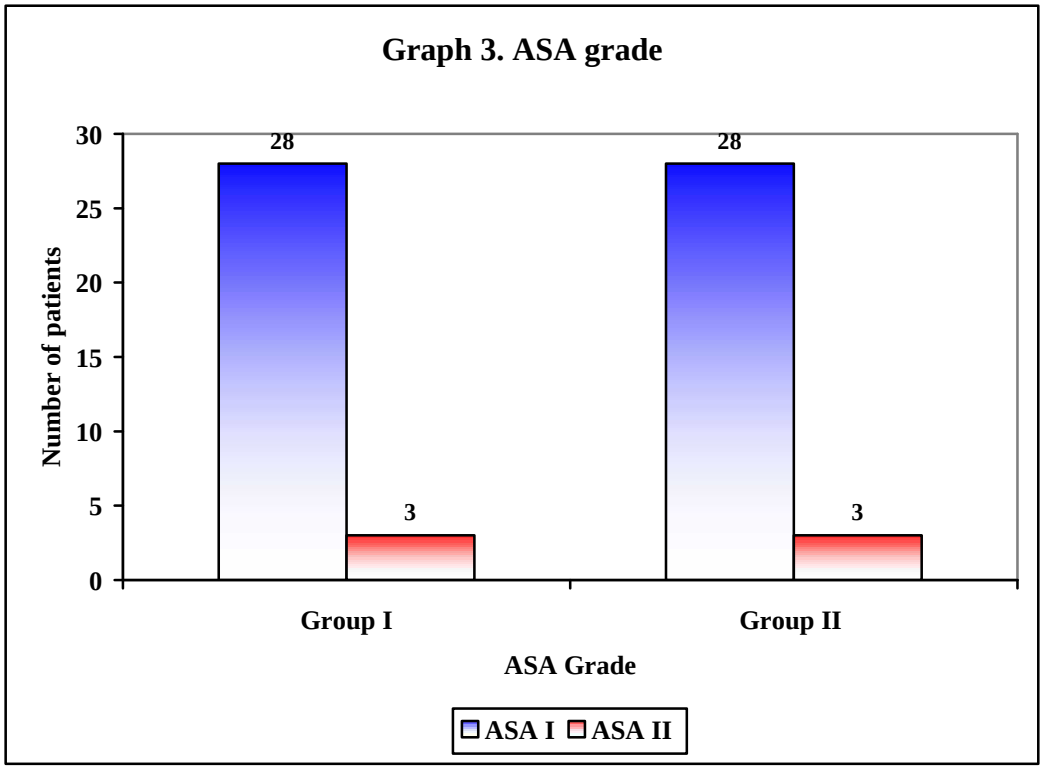


The above table shows the mean age and weight of the patients in group I and group II. There was no statistical difference between the two groups.

Table 3. ASA Grade

ASA grade	Group I (n=31)	Group II (n=31)
Grade I	28	28
Grade II	3	3
Total	**31**	**31**

x^2=0.000 **DF=1** **p=1.000**



As shown in the above table, number of ASA grade I and II patients in the both groups were comparable.

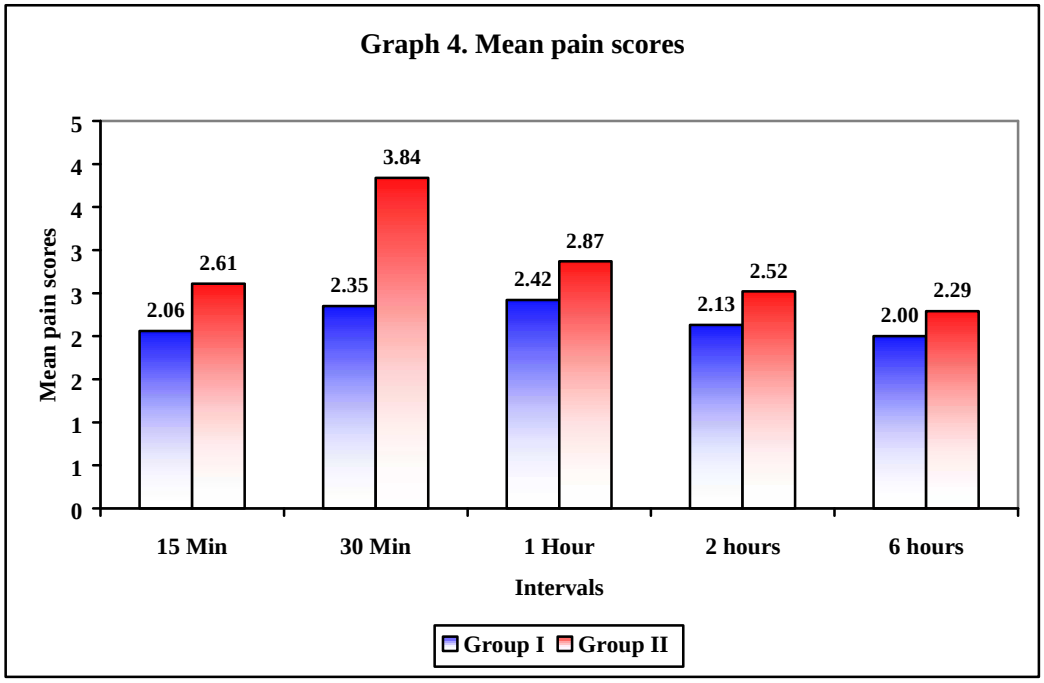
Table 4. Mean duration of surgery

	Group I (n=31)		**Group II (n=31)**		**'p' value**
	Mean	**SD**	**Mean**	**SD**	
Duration (Min)	74.35	13.34	71.61	14.34	0.438

The mean duration of surgery in group I was 74.35±13.34 whereas in group II was 71.61±14.34, which was statistically insignificant.

Table 5. Mean pain scores

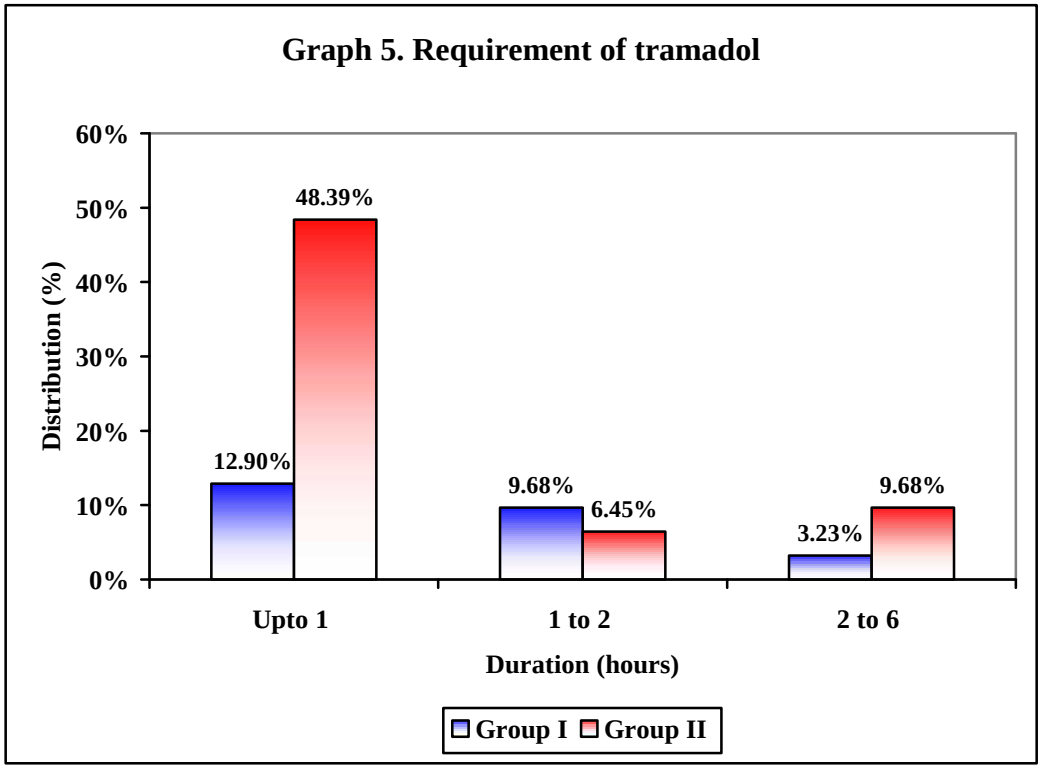
Intervals	Group I (n=31)		Group II (n=31)		p' value
	Mean	SD	Mean	SD	
15 minutes	2.06	0.63	2.61	0.56	0.0006
30 minutes	2.35	1.17	3.84	1.55	0.0001
1 hour	2.42	1.12	2.87	0.99	0.0989
2 hours	2.13	1.06	2.52	0.89	0.1219
6 hours	2.00	0.52	2.29	0.64	0.0549



The above table shows the mean pain scores in both the groups at 15 min, 30 min, one, two and six hours of the immediate post operative period. At 15 minutes and 30 minutes mean pain scores of group II were significantly more than those of group I ($p<0.05$). At one, two, six hours mean pain scores of the two groups were comparable and statistically not significant ($p<0.05$).

Table 6. Requirement of tramadol

Duration	Group I (n=31)		Group II (n=31)		'p' value
	Number	Percent	Number	Percent	
Upto 1 hour	4	12.90	15	48.39	0.0002
1 to 2 hours	3	9.68	2	6.45	0.6400
2 to 6 hours	1	3.23	3	9.68	0.3010
Total	**8**	**25.81**	**20**	**64.52**	0.0020



The table shows the requirement of analgesic drug in the immediate post operative period. The requirement of tramadol as a rescue analgesia in group II was significantly more than group I ($p<0.05$).

Chapter 6

Discussion

DISCUSSION

Management of post operative pain is one of the most important challenges which not only provide certain comfort for the patient, but facilitate early mobilization and length of hospital stay. The overall pain after laparoscopic surgeries is a conglomerate of three different components: incisional pain (somatic pain), visceral pain (deep intra-abdominal pain), and shoulder pain (referred to visceral pain). Besides showing individual variation in intensity and duration, the pain is often unpredictable.[18]

In the present study pain management was started prior to pain initiation on the basis of preemptive analgesia. The aim of preemptive analgesia, which has been investigated in recent years, is to provide analgesia prior to a painful stimulus to prevent central sensitization caused by the painful stimulus and, consequently, to decrease the need for postoperative analgesia.

Preemptive analgesia has been defined as treatment that: (1) starts before surgery; (2) prevents the establishment of central sensitization caused by incisional injury (covers only the period of surgery); and (3) prevents the establishment of central sensitization caused by incisional and inflammatory injuries (covers the period of surgery and the initial postoperative period).

Pain signals from damaged tissue are not transmitted to the central nervous system (CNS) through ‘hard-wired’ pathways. In contrast, nociceptive signals, once initiated, will launch a cascade of alterations in the somatosensory system, including an increase in the responsiveness of both peripheral and central

neurons. These alterations will increase the response to subsequent stimuli and thus amplify pain.[45]

Pre-emptive analgesia is a treatment that is initiated before and is operational during the surgical procedure in order to reduce the physiological consequences of nociceptive transmission provoked by the procedure. Owing to this 'protective' effect on the nociceptive pathways, pre-emptive analgesia has the potential to be more effective than a similar analgesic treatment initiated after surgery. Consequently, immediate postoperative pain may be reduced and the development of chronic pain may be prevented.[46]

Experimental evidence suggests that it may be possible, and indeed preferable, to prevent or 'pre-empt' the neurophysiological and biochemical consequences of a noxious input to the CNS rather than to begin treatment when these consequences are already established. Accordingly, prevention of postoperative pain may be more effective than treatment.[46]

In the present study, we used 1g IV paracetamol, as a preemptive analgesic in laparoscopic surgeries and assessed its effects on postoperative pain scores, and requirement of tramadol in the post operative period in 62 patients who underwent laparoscopic surgeries under general anaesthesia. These patients were randomly divided into two groups, I and II of 31 each. The patients in group I received 1g of IV paracetamol and patients in group II received 100 ml normal saline IV over 15 min, 30 min before induction of general anaesthesia.

In this study significant high mean pain scores were observed during post operative period at 15 min and 30 min in group II (2.61±0.56 and 3.84±1.55

respectively) compared to group I (2.06±0.63 and 2.35±1.17 respectively) (p value 0.0006 and 0.0001 respectively). There was no significant difference in mean pain scores at one, two and six hours in both groups, which was due to administration of the rescue analgesic drug. ($p>0.05$).

The requirement for rescue tramadol analgesia was in 25.8% of patients in the group I compared to 64.5% of patients in group II, which suggests that preemptive paracetamol group had less pain, high pain threshold or both. These results indicate that sufficient analgesic effectiveness was ensured in the postoperative period in Group I. Additionally, the low values of the pain scores in the group I may be explained by decreases in excitability in the central nervous system through blockade of nociceptive stimuli before damaging tissue architecture. We believe that since the preemptively delivered paracetamol prevents central sensitization, its analgesic effect continues longer than its effect period.

Paracetamol rapidly passes the blood-brain barrier, reaches a high concentration in the cerebrospinal fluid and has an anti-nociceptive effect mediated by the CNS.[47] This central effect has been regarded primarily as an indirect and reciprocal influence through cyclooxygenase enzyme inhibition, and probably through the serotoninergic system as well. Besides this central effect, it is accepted that paracetamol has a peripheral anti-inflammatory influence, although this effect is somewhat limited.[48]

It is also demonstrated that, the analgesic effect of IV paracetamol starts within 5 min, peaks at 1 hr and lasts 4 to 6 hrs.[10]

In a related study by Ziya Salihoglu, MD, Murat Yildirim, MD et al preemptive use of 1g IV paracetamol caused similar decrease in postoperative pain scores and requirement of rescue analgesia.[12] Similarly in another study Semih Arici, Alp Gurbet demonstrated significantly lower post operative pain scores and consumption of rescue analgesia in patients who received 1g IV preemptive paracetamol compared to patients who received normal saline.[9]

However, our study had a few limitations. we had given a single dose of 1g of IV paracetamol instead of tid or qid doses for all patients and lack of postoperative pain follow-up for prolonged duration. Divided dosing and prolonged follow-up could have improved the results of our study especially in patients who underwent extensive surgeries. It was not possible because most of the surgeries was performed on an ambulatory basis. Our study forms a sound basis for further studies. Comparative studies, which are made with higher number of patients, divided doses of paracetamol and prolonged post operative follow-up should be performed for defining the more beneficial effects of IV paracetamol.

Chapter 7

Conclusion

CONCLUSION

To conclude, preemptive administration of 1g of IV paracetamol in patients undergoing laparoscopic surgeries provided good quality analgesia with decreased pain scores during the postoperative period, increased patient satisfaction and decreased postoperative tramadol consumption. Hence 1g of IV paracetamol can be safely administered preemptively for postoperative analgesia for laparoscopic surgeries.

Chapter 8

Summary

SUMMARY

This study was carried out to assess the effect of 1g of preemptive IV paracetamol on post operative pain scores and requirement of tramadol in the post operative period in 62 ASA I and II patients who underwent laparoscopic surgeries under general anaesthesia. This study was conducted in the Department of Anaesthesiology, K.L.E.s Dr. Prabhakar Kore Charitable Hospital and Medical Research Centre, Belgaum during the period of January 2011 to December 2011. Patients were randomly divided into two groups, I and II of 31 each. Group I, received 1g IV paracetamol and group II, received 100 ml normal saline IV over 15 min, 30 min before induction of general anaesthesia.

In this study significant high mean pain scores were observed during post operative period at 15 min and 30 min in group II (2.61±0.56 and 3.84±1.55 respectively) compared to group I (2.06±0.63 and 2.35±1.17 respectively). (P value 0.0006 and 0.0001 respectively). There was no significant difference in mean pain scores at one, two and six hours in both groups, we beleive that it was due to administration of rescue analgesic drug ($p<0.05$). In post operative period, total requirement of tramadol as a rescue analgesia in group II (64.52%) was significantly more than group I (25.81%) ($p=0.002$).

Thus 1g of IV paracetamol administered preemptively decreases post operative pain scores and requirement of rescue analgesic in the immediate post operative period. Hence, 1g of IV paracetamol can be safely administered preemptively for postoperative analgesia for laparoscopic surgeries.

Chapter 9

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Annexures

Annexure I

ANNEXURE I – CONSENT FORM

Mr/Mrs/Miss. _____ we are requesting you to enroll yourself in study titled **",** conducted by Dr. **** ******, Post Graduate in M.D. Anaesthesiology under the guidance of Dr. ***** *****, Professor, Department of Anaesthesiology, J.N. Medical College, KLE university, Belgaum.

Respected Sir/Madam we request you to enroll yourself to participate in our study as you are eligible for participating in the study. During the study you will be asked some questions regarding your present complaint and you are supposed to answer to the best of your knowledge.

Your participation in research is voluntary. Your decision whether or not to participate in the study will not affect your relationship with J. N. Medical College. If you decide to participate you are free to withdraw at any time.

The purpose of research is to know **"The effect of preemptive intravenous paracetamol on postoperative analgesic requirements in patients undergoing laparoscopic surgeries under general anaesthesia" – A one year Randomized placebo controlled trial.**

Procedure Involved

If you agree to enroll yourself in my study, I will ask your present past and family history. Then you will be clinically examined in detail and routine investigations like Hb, TC, DC, Platelet Count, RBS, Blood Urea, Serum Creatinine, Blood Grouping, Chest X-ray, ECG, Urine Examination will be done. Half an hour prior to induction you will be received either 1g of (100ml) IV paracetamol or 100ml normal saline IV over 15 min. After that you will be received pre medication, IV induction agents and Muscle relaxation with

vecuronium. Then you will be intubated using appropriate size endotracheal tube and maintained with oxygen and volatile anesthetics. Then you'll be reversed with glycopyrrolate and neostigmine and thorough oral suctioning. Post-operative pain will be measured at 15 min, 30 min, one, two and six hours by using visual analogue scale (VAS) for pain and you'll receive inj. Tramadol 50mg IV as rescue anaelgesic if VAS score more than three.

Risks

There is no risk involved with use of intravenous Paracetamol. Rarely it causes allergic skin reactions, however, if there is a pre-existing liver insufficiency, paracetamol can be hepatotoxic in high doses.

Benefits

It is an effective and safe anaelgesic for control of acute post-operative pain.

Voluntary Participation/Withdrawal

Taking part in the study is voluntary. You may choose not to enroll yourself in this study. Your decision will not change present or future health care services offered to you at K.L.E. hospital.

Alternatives

Even if you decline the participation in the study, you will get the routine line of management.

Privacy and Confidentiality

The only people to know that you are a research subject are members of the research team. No information about you or information provided by you

during the research will be disclosed to other without your written permission except:

1. In emergency to protect your rights and welfare.
2. If required by law.

Authorization to Publish Results

When the results of the research are published or discussed, in a conference, no information will be displayed that would disclose your identity. Any information that is obtained in connection with this study and that can be identified with you will remain confidential.

Financial Incentives for participation

No financial incentives are being offered to enrolled patients. It is purely being done with the idea of research and all the cost of the study will be borne by the investigator.

Compensation

In the event of injury related to the study, treatment will be made available through KLE Hospital & MRC, Belgaum. There is no compensation or payment for such medical treatment by law. If you are injured you may contact Dr. ***** ******, at Department of Anaesthesiology, KLE Hospital& MRC or by Ph. No: **** *****.

Questions

In case you have any questions related to the study, in future or in case of study related injury or illness, you can contact Dr. ***** *****, Department of Anaesthesiology, KLE Hospital and MRC, Ph No. **** ****** or phone number ***** ***** or Dr. ****** ****** Professor, Dept Of Anaesthesiology, KLE

Hospital and MRC, Belgaum Ph: ****** ******.

If you have any queries about your rights as a study subject, you may call Dr. **** *****, Principal and Chairman, J.N. Medical College Institutional Ethical Committee for Human Subjects Research, Ph. ****** ****** at J.N. Medical College, Belgaum.

Consent for participation in research trial

I, _____ voluntarily agree for the participation as a subject of study. By signing this consent form I am not giving up any of my legal rights, I may withdraw from the study anytime. I am signing the consent form after having read or been read for me in vernacular language, including the risks and the benefits and having all my questions answered.

Subject Name : _____

Signature or the Left Thumb Print of Subject : _____

Date :

Witness Name : _____ *Signature:* _____

Date :

Investigators Name: _____ Signature:_____

Date :

Place : _____

Annexures

Annexure II

ANNEXURE II – PROFORMA

"The effect of preemptive intravenous paracetamol on postoperative analgesic requirements in patients undergoing laparoscopic surgeries under generalanaesthesia" – A one year Randomized placebo controlled trial.

Name&Address of the patient : _____

_____

Age & sex of the Patient:_____ IP. No._____

Weight of Patient:_____ ***ASA grade:***

Anaesthesiologist : _____ ***Surgeon : _____***

PREANAESTHETIC EVALUATION :

Chief Complaints :

Past History :

1. History of Hypertension, Diabetes Mellitus, gastroesophageal reflux, Addiction.
2. History of usage of paracetamol, opioids, or NSAIDs 48 hs before surgery.
3. History of renal disease, hepatic disease and neurological diseases.
4. History of allergy to analgesic drugs such as paracetamol and tramadol.

Family History

General Physical Examination :

Weight :	Height:	Temperature :
Pallor :	Cyanosis :	Pedal Edema :
Clubbing :	Pulse :	B.P :

RR: M.P Grading Thyro mental distance

Mouth opening TMJ examination

SYSTEMIC EXAMINATION :

Respiratory System : Cardiovascular System :

Central Nervous system: Per Abdomen :

Spine assessment:

INVESTIGATIONS :

Diagnosis :

Proposed Surgery :

Duration of surgery:

Inclusion Criteria :

1. Patients undergoing laparscopic surgeries under general anaesthesia with duration of ninety minutes.
2. ASA physical status I and II.
3. Age between 18 to 60 yrs.
4. Weight between 50 to 70kgs.

Exclusion Criteria

1. History of allergic reactions to paracetamol.
2. Chonic alcoholism, obesity, pregnancy, gastro oesophageal reflux.
3. Patients having, hepatic, renal or neurological and bleeding disorders.

4. History of usage of paracetamol, opioids, or NSAIDS 48 hs before surgery.

Methodology

After obtaining the approval of ethical committee and written informed consent, a total of 62 ASA I and II patients undergoing laparoscopic surgeries with duration of 90 minutes under general anaesthesia will be included in this study.

Patients randomly divided into two groups of 31 each by using computer randomization table. In group I, 1g IV paracetamol and in group II, 100ml IV normal saline will be administered 30 min before induction over 15 min. In operating room, patients will be attached to pulse oxymeter, electrocardiogram, and noninvasive blood pressure moniter.

All patients will be pre-oxygenated with 100% oxygen by using Bain's circuit for thee min. Anaesthesia will be induced with Inj. Thiopentone 5mg\kg IV, Inj. Fentanyl 2 micro\kg IV, Inj.vecuronium 0.1 mg/kg IV will be administered and trachea will be intubated with appropriate size ETT. Following intubation, maintenance of general anaesthesia will be accomplished by providing isoflurane in 40/60 oxygen/nitrous oxide and, if required, 0.01mg/kg vecuronium will be given.

All patients will be monitored and Patients will be extubated after reversal with glycopyrrolate (0.01mg/kg) and neostigmine (0.05mg/kg) and thorough suctioning.

In the post anaesthesia care unit, postoperative pain will be measured by using visual analog scale (VAS:0-10; 0:no pain, 10: worst imaginable pain), by trained nursing professional who does not know which patient received

paracetamol. Postoperative pain will be observed at 15min, 30min, 1h, 2h and 6hs. Inj.Tramadol 50mg IV will be given as a rescue analgesic if the VAS score is more than thee.

Assessment of postoperative pain using VAS (visual analog scale):

	Group I	**Group II**
VAS at 15 min		
VAS at 30 min		
VAS at 1 h		
VAS at 2 h		
VAS at 6 h		

Assessment of postoperative tramadol consumption

	Group I	**Group II**
0 – 1h		
1 – 2h		
2 – 6h		
Total tramadol consumption		

Annexures

Annexure IV

ANNEXURE IV – MASTER CHART – GROUP I

Serial Number	In Patient Number	Sex	Age (Years)	Weight (Kgs)	Diagnosis	ASA Grade	Surgery	Duration of surgery (min)	Post operative pain (VAS) - Intervals					Tramadol Consumption (mg)			
									15 Min	30 Min	1 Hour	2 Hours	6 Hours	Upto 1 Hour	1 to 2 hours	2 to 6 hours	Total
1	407112	F	50	55	CL	I	LC	80	3	6	2	2	2	50	-	-	50
2	406987	F	20	52	A	I	LA	70	2	1	2	2	1	-	-	-	-
3	407070	F	20	58	A	II	LA	65	1	3	2	1	2	-	-	-	-
4	400796	F	20	60	CL	I	LC	80	2	1	2	2	1	-	-	-	-
5	411873	M	20	68	CC	I	LC	90	2	4	2	2	2	50	-	-	50
6	412014	M	21	62	PA	I	DL	60	2	2	3	1	2	-	-	-	-
7	412518	M	22	66	A	I	LA	70	2	3	5	2	2	-	50	-	50
8	414576	F	22	50	PI	I	DL	60	2	1	1	1	2	-	-	-	-
9	416844	M	24	64	A	I	LA	60	1	1	2	3	2	-	-	-	-
10	416286	M	24	70	PA	I	DL	90	3	2	1	2	2	-	-	-	-
11	417144	F	25	54	L3 P3	I	LS	60	2	2	2	1	3	-	-	-	-
12	417145	F	26	56	L2 P2	I	LS	45	2	2	3	2	2	-	-	-	-
13	419250	M	26	62	A	II	LA	90	2	3	2	6	2	-	-	50	50
14	424404	M	26	66	CL	I	LC	90	1	2	2	3	3	-	-	-	-
15	426108	F	27	46	SI	I	DL	70	3	2	2	1	2	-	-	-	-
16	427073	M	27	72	CL	I	LC	90	2	2	1	1	2	-	-	-	-
17	428503	M	29	68	A	I	LA	90	3	2	5	3	2	-	50	-	50
18	431305	M	30	58	A	I	LA	65	2	2	2	2	2	-	-	-	-
19	432145	M	32	60	A	I	LA	75	3	2	2	2	2	-	-	-	-
20	432354	F	35	48	A	II	LA	80	1	2	2	2	3	-	-	-	-
21	433745	F	36	52	A	I	LA	90	2	2	3	3	2	-	-	-	-
22	433750	M	37	64	A	I	LA	90	3	2	6	3	2	-	50	-	50
23	435452	F	37	50	PI	I	DL	50	2	2	2	1	2	-	-	-	-
24	435456	F	40	52	SI	I	DL	70	2	2	2	2	3	-	-	-	-
25	435806	F	40	50	PI	I	DL	60	2	2	3	1	1	-	-	-	-
26	436042	M	42	62	A	I	LA	90	3	5	2	3	2	50	-	-	50
27	437834	F	43	48	PI	I	DL	60	1	2	2	3	2	-	-	-	-
28	441764	F	46	54	DUB	I	DL	80	2	5	2	2	2	50	-	-	50
29	441880	F	52	64	CC	I	LC	75	2	2	3	1	2	-	-	-	-
30	443020	M	54	74	CC	I	LC	80	2	2	2	3	2	-	-	-	-
31	443218	M	56	70	PA	I	DL	80	2	2	3	3	1	-	-	-	-

ANNEXURE IV – MASTER CHART – GROUP II

Serial Number	In Patient Number	Sex	Age (Years)	Weight (Kgs)	Diagnosis	ASA Grade	Surgery	Duration of surgery (min)	Post operative pain (VAS) - Intervals					Tramadol Consumption (mg)			
									15 Min	30 Min	1 Hour	2 Hours	6 Hours	Upto 1 Hour	1 to 2 hours	2 to 6 hours	Total
1	402875	F	27	55	SI	I	DL	75	3	6	4	3	2	50	-	-	50
2	407700	F	40	48	PI	II	DL	65	2	4	3	2	3	50	-	-	50
3	407933	F	28	57	P3 L3	I	LS	45	3	5	2	2	3	50	-	-	50
4	408045	F	45	52	CL	I	LC	90	4	5	3	2	2	50	-	-	50
5	409526	F	24	53	EM	I	DL	60	2	4	2	3	2	-	-	-	-
6	412217	F	30	49	PI	I	DL	40	3	2	2	3	2	-	-	-	-
7	413176	F	34	53	OC	I	LO	60	3	5	2	2	3	50	-	-	50
8	412734	F	32	58	PI	I	DL	60	2	6	3	2	3	50	-	-	50
9	414101	F	27	52	PI	I	DL	60	3	2	3	5	3	-	-	50	50
10	416235	F	37	48	SI	II	DL	70	2	3	2	2	2	-	-	-	-
11	414508	M	30	66	A	I	LA	70	3	5	2	3	3	50	-	-	50
12	418073	M	30	70	A	I	LA	90	2	3	5	2	3	-	50	-	50
13	426106	F	37	56	OC	I	LO	60	2	3	3	2	3	-	-	-	-
14	426796	M	35	54	CL	I	LC	90	3	6	4	2	3	50	-	-	50
15	427490	M	26	63	A	I	LA	60	2	3	3	2	2	-	-	-	-
16	427532	M	60	54	CC	I	LC	90	3	3	6	3	2	-	50	-	50
17	427827	F	40	50	A	I	LA	60	2	3	2	5	3	-	-	50	50
18	428253	M	58	62	CC	I	LC	90	3	2	2	3	2	-	-	-	-
19	428758	M	26	66	A	I	LA	85	3	2	1	2	3	-	-	-	-
20	428986	M	26	64	A	II	LA	90	2	1	3	2	3	-	-	-	-
21	432009	F	26	56	PI	I	DL	75	3	5	3	2	1	50	-	-	50
22	430801	M	35	70	PA	I	DL	70	3	6	3	2	2	50	-	-	50
23	432327	M	18	64	A	I	LA	90	3	2	3	4	2	-	-	50	50
24	432349	F	60	48	CL	I	LC	80	3	5	2	3	2	50	-	-	50
25	433012	F	26	54	PI	I	DL	75	2	3	3	2	2	-	-	-	-
26	433004	M	27	64	A	I	LA	80	3	5	2	2	1	50	-	-	50
27	436732	M	45	66	A	I	LA	90	2	6	4	2	2	50	-	-	50
28	445271	F	28	52	PI	I	DL	60	3	2	3	3	2	-	-	-	-
29	445272	F	21	46	PI	I	DL	60	2	5	3	2	1	50	-	-	50
30	445486	M	36	58	A	I	LA	60	3	2	3	1	2	-	-	-	-
31	444562	M	40	54	CL	I	LC	70	2	5	3	3	2	50	-	-	50

ANNEXURE IV – KEY TO MASTER CHART

A	-	Appendicitis
ASA	-	American Society of Anaesthesiologists
CC	-	Chronic cholicystitis
CL	-	Cholilithiasis
DL	-	Diagnostic laparoscopy
DH	-	Diagnostic histerolaparoscopy
F	-	Female
L	-	Living
LA	-	Laparoscopic appendectomy
LC	-	Laparoscopic cholecystectomy
LO	-	Laparoscopic ovariotomy
LS	-	Laparoscopic ovariotomy sterilization
M	-	Male
mg	-	Milligram
Min	-	Minutes
P	-	Parity
PA	-	Pain abdomen
PI	-	Primary infertility
SI	-	Secondary infertility
VAS	-	Visual analog scale