"COMPARISON OF LOW DOSE INTRAVENOUS KETAMINE INFUSION VERSUS PLACEBO FOR POSTOPERATIVE ANALGESIA FOLLOWING LAPAROSCOPIC APPENDICECTOMY UNDER GENERAL ANAESTHESIA: ONE YEAR HOSPITAL BASED DOUBLE BLIND RANDOMISED CLINICAL TRIAL"

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ENDORSEMENT

This is to certify that the dissertation entitled **"COMPARISON OF LOW DOSE INTRAVENOUS KETAMINE INFUSION VERSUS PLACEBO FOR POSTOPERATIVE ANALGESIA FOLLOWING LAPAROSCOPIC APPENDICECTOMY UNDER GENERAL ANAESTHESIA: ONE YEAR HOSPITAL BASED DOUBLE BLIND RANDOMISED CLINICAL TRIAL"** is a bonafide research work done by **(REG NO.BA0119011)** Department of Anaesthesiology, Jawaharlal Nehru Medical College, Nehru Nagar, Belagavi – 590 010.

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LIST OF ABBREVIATIONS USED

ASA	-	American society of Anaesthesiologists
CNS	-	Central nervous system
CO_2	-	Carbon dioxide
$O_{2\backslash}$	-	Oxygen
N_2O	-	Nitrous Oxide
CVS	-	Cardiovascular system
RS	-	Respiratory system
DBP	-	Diastolic blood pressure
ECG	-	Electrocardiogram
GIT	-	Gastrointestinal tract
Hb	-	Haemoglobin
HR	-	Heart rate
Inj.	-	Injection
IV	-	Intravenous
Kgs	-	Kilograms
L	-	Liters
Mg	-	Milligrams
Mins	-	Minutes
Ml	-	Milliliters
µg	-	Micrograms
MPG	-	Mallampati Grading
PR	-	Pulse rate
RBS	-	Random blood sugar

RR	-	Respiratory rate
SBP	-	Systolic blood pressure
SPO_2	-	Saturation percentage of oxygen
Sr	-	Serum
Temp	-	Temperature
TLC	-	Total Leucocyte count
VAS	-	Visual Analogue Scale
WDR	-	Wide Dynamic Range
DPQ	-	Dartmouth Pain Questionnairre
MPQ	-	McGill Pain Questionnairre
WHYPQ	-	West Haven – Yale Pain Questionnairre
QoR-40	-	Quality of recovery - 40
α	-	Alpha
β	-	Beta
NSAIDs	-	Non steroidal anti-inflammatory drugs
NMDA	-	N-Methyl-D-Aspartate

ABSTRACT

TITLE: "COMPARISON OF LOW DOSE INTRAVENOUS KETAMINE INFUSION VERSUS PLACEBO FOR POSTOPERATIVE ANALGESIA FOLLOWING LAPAROSCOPIC APPENDICECTOMY UNDER GENERAL ANAESTHESIA: ONE YEAR HOSPITAL BASED DOUBLE BLIND RANDOMISED CLINICAL TRIAL"

BACKGROUND:

In recent times laparoscopic appendicectomy is preferred more than open appendicectomy to decrease postoperative pain and length of hospital stay. However, the surgery is not always pain free. Several methods have been used to treat postoperative pain effectively following laparoscopic appendicectomy. Recent interest has been focused on the administration of N-methyl-D-aspartate receptor antagonists for the treatment of postoperative pain, of which Ketamine is an essential drug.

OBJECTIVE:

To evaluate the efficacy of low dose intravenous Ketamine infusion for acute postoperative pain management for laparoscopic appendicectomy.

METHODOLOGY:

The present study was conducted at KLE'S Dr. Prabhakar Kore Hospital and Medical Research Centre, Nehru Nagar, Belagavi 590010, on 90 adult patients undergoing elective laparoscopic appendicectomy under General Anaesthesia between January 2020 to March 2021. Patients were divided into 2 groups, Group A and Group B by computer generated randomisation table. After induction of general anaesthesia, patients in both the groups received one dose of intravenous Paracetamol at the dose of 15mg/Kg and laparoscopic appendicectomy was

done according to standard protocol. After extubation and shifting the patients to recovery, patients in group A were started with Ketamine infusion at the dose of 0.2mg/Kg/hour and continued for 24 hours. Group B patients were started with Normal Saline infusion at 3 ml/hour.

In the postoperative period patients were assessed for postoperative pain at 1,2,3,4,5,6,7,8,9,10,11,12,16,20 and 24 hours using VAS pain scale. If VAS>3 rescue analgesia in the form of Inj. Paracetamol 15mg/kilogram IV was given. Time of first rescue analgesia and the total analgesic consumed in the first 24 hours and side effects, if any, were noted.

RESULTS:

The two groups were comparable with respect to age, mean weight, ASA status and gender distribution. The mean VAS scores were significantly higher in group B when compared to group A from the 3rd hour onwards ($p<0.0001$). 9 patients in group A and all 45 in group B required rescue analgesia. This difference was statistically significant ($p<0.0001$). The time for requirement of first rescue analgesic was 7.11±6.19 hours in group A and that in Group B was 5.96±1.66 hours. Even though the time for first rescue analgesic is longer in group A, it was not statistically significant ($p = 0.2755$).

The total analgesic consumed is 1100 ± 396.86 mg in group A and in group B the total analgesic consumed was 1593±477.87 mg which was statistically significant ($p=0.0055$)

CONCLUSION:

Intravenous low dose Ketamine infusion at 0.2 mg/Kilogram/hour is effective for the management of acute postoperative pain following elective laparoscopic appendicectomy surgeries.

KEYWORDS: Low-dose intravenous Ketamine infusion, laparoscopic appendicectomy, postoperative pain.

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INTRODUCTION

In recent times laparoscopic appendicectomy is preferred more than open appendicectomy to decrease postoperative pain and length of hospital stay.[1] However, the surgery is not always pain free.[2,3,4] The cause for pain after laparoscopic surgery is uncertain, and it can be due to multiple factors including, trauma to abdominal wall by trochar insertion, irritation of diaphragm secondary to insufflation of carbon-di-oxide and creation of pneumoperitoneum, residual gas in the peritoneum, trauma to abdomen, microruptures of the parietal layer of peritoneum as a result of abdominal distension, chemical peritoneal irritation, etc.[2]

Pain in the postoperative period is one of the adverse encounters for a patient subjected to surgery. Meticulous care must always be taken to deal with postoperative pain prophylactically. If pain develops, then it is mandatory to treat it early and aggressively as it not only leads to increased morbidity and poor patient satisfaction, it can also lead to a condition of hyperalgesia called persistent postoperative pain (PPP). Studies done recently reveal that persistent postoperative pain has incidence of upto 40% out of which 18.3% patients range it to be in the moderate to severe grade.[5]

Several methods have been used to treat postoperative pain effectively following laparoscopic appendicectomy like opioids and NSAIDs given via parenteral or oral route, infiltration of opioids or local anesthetics intraperitoneally, patient-controlled analgesia, rectus sheath block, transverses abdominis plane block etc.[2, 6-9]

However, there has been a recent surge in the interest in the use of N-methyl-D-aspartate receptor antagonists to treat pain in the postoperative period, of which Ketamine is the main drug which is used either as a sole analgesic or as an adjuvant to other analgesics especially opioids.[10]

Ketamine was initially introduced as an anesthetic in 1960's.[11] Being a phencyclidine derivative, the drug exerts its pharmacological effects mainly by reversible non-competitive antagonism of N-Methyl-D-Aspartate receptors. It also acts on μ-opioid receptors, monoaminergic receptors, muscarinic receptors, gamma-aminobutyric receptors and many others.[22] The antagonistic effect of Ketamine on NMDA receptors present in the brain and spinal cord has analgesic action even at subanesthetic doses by alteration of central sensory modulating mechanism of pain[5] and it may also enhance the efficacy of treatment with opioids[12] and reduce the occurrence of chronic pain syndromes. Apart from the anesthetic use, it also plays a role to treat depression, complex regional pain syndrome, pain associated with cancer, addiction to alcohol and heroin.[5]

A large number of clinical trials testing the efficacy of Ketamine in treating postoperative pain have been published but due to the fear of adverse psychomimetic effects like hallucinations or nightmares, extensive use of the drug in clinical settings was limited. But a recent surge has occurred in using Ketamine infusions in emergency departments, in perioperative period for pain control, to treat refractory pain and pain in opioid tolerant patients.

Use of Ketamine as a standalone analgesic at subanesthetic dose, especially in acute postoperative pain has been sparsely evaluated in India and there is no established dosage regimen or suggested time for administration of ketamine infusion. Hence, we sought to assess the use and efficacy of intravenous low-dose ketamine infusion on duration of postoperative analgesia in patients subjected to laparoscopic appendicectomy under general anesthesia.

OBJECTIVES

Primary-

1. To evaluate the efficacy of low dose intravenous Ketamine infusion for treatment of acute postoperative pain after laparoscopic appendicectomy.

Secondary-

2. To study the side effects of drug, if any.
3. To compare the total analgesic required in the first 24 hours in both the study groups.

REVIEW OF LITERATURE

Appendicitis is one of the commonest emergency in the surgical field, requiring intervention by appendicectomy.[23]

Since the introduction of the procedure of open appendicectomy by McBurney in 1894, it has been the standard treatment of choice for more than one century. Then, the technique of laparoscopic appendicectomy was described by Kurt Semm in 1983, and gained popularity.[24] Though the laparoscopic technique has advantages like reduced pain, early mobility and return to normal activity, better cosmetic result and lesser chance of wound infections, it is not without disadvantages. It includes consumption of increased operating times, higher skill requirements with steep learning curve and higher costs borne by the hospital.[25]

In a study conducted by **Antonio Biondi et al**. comparison between the laparoscopic approach and the conventional open technique for appendicectomy was done. Retrospective data collected from 593 patients were analysed. This included 310 patients treated by open appendicectomy and 283 patients who were treated by laparoscopic technique. This study concluded that treatment by laparoscopic technique has many advantages and benefits clinically which includes shorter duration of hospital stay, early tolerance to food, faster return to work, lesser chance of wound infection and reduced requirement of postoperative analgesics, in comparison to open appendicectomy.[1]

Though pain occurring after laparoscopic procedure is significantly lesser in intensity and of shorter duration, patients do suffer from postoperative pain especially during the first 24 hours.

Several modalities have been used to treat pain in the postoperative period. It includes using intravenous opioids and nonsteroidal anti-inflammatory drugs, corticosteroids, local infiltration of the sites of incision, peritoneal infiltration of local anestheic solution, use of NMDA antagonists, alpha-2 adrenergic agonists, transversus abdominis plane block, rectus sheath block etc., [3]

A meta-analyses conducted by **Ye et al. in 2017,** identified randomized controlled trials which evaluated the analgesic effects of intravenous Ketamine compared with placebo in patients undergoing laparoscopic cholecystectomy. The outcomes evaluated were postoperative pain scores measured by visual analogue scale, use of opioids, presence of postoperative complications like vomiting, pruritis and ileus. The meta-analyses involved five trials with 212 patients who matched the inclusion criteria. Two out of the five studies used Ketamine with a starting bolus dose 0.3 mg/kilogram IV with subsequent continuous infusion 3µg/kilogram/min versus normal saline as the control group. IV opioids were used for rescue analgesia in both the studies. This metaanalyses concluded that intervention with Ketamine significantly reduced pain scores and consumption of opioids at 12, 24 and 48 hours in the postoperative period.[21]

In a study done by **Adriaenssens et al. in 1999**, the outcome of combining Ketamine and intravenous PCA with morphine was studied in subjects undergoing laparotomy. A total of thirty subjects were enrolled for the study and 15 were randomised to receive patient-controlled analgesia with saline and another 15 to receive PCA with Ketamine. After patient was shifted to recovery, analgesia was started when visual analogue score was more than 4. A bolus dose of intravenous Morphine 3 mg was administered to all patients with subsequent administration by PCA. An infusion of Ketamine at 2.5µg/kg/min or saline was started simultaneously. The outcomes were pain scores, consumption of morphine, and any side effects and they were evaluated up to 48

hours in the postoperative period. VAS scores were found to decrease considerably with time (P=0.0001) and were analogous in both groups (P=0.3083). Overall consumption of Morphine was found to be considerably reduced in the group administered with Ketamine (28 mg) when compared to the saline group (54 mg) (P= 0.0003). Nausea also was seen less frequently in the Ketamine group (P= 0.03). This study has concluded that low dose Ketamine infusion in addition to intravenous Morphine PCA can be used to treat pain after laparotomy surgeries successfully and use of such low doses avoids the psychomimetic effects of the drug. [12]

In a study conducted by **Urban M K et al. in 2008**, 26 patients undergoing posterior lumbar spinal fusions who were narcotic dependant in the preoperative period itself were evaluated. This study evaluated the use of ketamine as an adjunct in relieving postoperative pain in these patients. They were allotted into two groups. One was treated as control and the Ketamine group received 0.2mg/kg of the drug during induction followed by 2μg/kg/hour infusion for next 24 hours. After 15 minutes post extubation, both the groups were started with IV hydromorphone PCA. Pain measured by NRS, use of narcotics, sedation level, delirium and milestones of physical therapy upto discharge were analysed and Ketamine group had lesser pain scores (NRS 3.6 in ketamine group versus 5.5 in control group). Hydromorphone dose requirements were also less in Ketamine group when compared to control group but differences were insignificant.[18]

In another meta-analyses conducted by **Laskowski et al. in 2011,** randomized, double-blinded and placebo controlled studies published from the year 1966 to 2010 which used either intravenous bolus or infusion of ketamine in the perioperative period to treat postoperative pain were included. This analysis placed no limitation on the dose of ketamine or patients' age. There were a total of 70 trials that comprised 4,701 patients who matched the inclusion criteria, with 2652 receiving Ketamine and 2049 receiving placebo.

Primary outcome was total opioid consumption in the postoperative period. Secondary objectives were initial time of rescue analgesic administration, pain levels and any adverse effects. An increase in the duration to requirement of first analgesic dose and overall reduction in opioid consumption was observed in all studies in the Ketamine group with greatest efficacy observed in upper abdominal, thoracic and major orthopedic surgical subgroups. Though side effects like hallucinations and nightmares were seen in the Ketamine group, postoperative nausea and vomiting were observed less frequently. This study concluded that the analgesic effect of Ketamine was independent of the type of opioid administered intraoperatively, dose and timing of Ketamine given.[10]

In a study conducted by **Barreveld et al. in 2013**, 59 patients taking treatment with opioids for chronic pain undergoing non-oncologic surgery were studied. The study population were allotted into two groups. One group received hydromorphone PCA with continuous Ketamine intravenous infusion at 0.2mg/kilogram/hour and the other group received hydromorphone PCA with normal saline infusion. This study demonstrated that IV ketamine infusion in the postoperative period improved average pain scores in subjects being treated with moderate to large quantities of opioids for longstanding pain and subsequently got operated. Though this study demonstrated significant change in "average" pain intensity in the patients treated with Ketamine, no significant modification in "least" and "worst" pain intensity was observed. No adverse effects were demonstrated while infusing ketamine at a rate of 0.2 mg/kilogram/hr in the initial postoperative phase.[13]

In a randomized double-blinded placebo-controlled study conducted by **Garg et al. in 2014,** 66 patients who underwent elective spine surgery were evaluated. All patients received intraoperative analgesia with 0.1 mg/kg Morphine IV. Patients were allocated into three groups in the postoperative period and Group K received Ketamine bolus 0.25mg/kg followed by infusion 0.25mg/kg/hour. This group also received

Midazolam as 10µg/kg bolus, followed by 10µg/kg/hour infusion adjusted in the same syringe. Group D was administered bolus of Dexmedetomidine 0.5µg/kg over 10 minutes followed by infusion at 0.3µg/kg/hour. Group C received 0.9% saline infusion at the same volume of bolus and infusion. Pain scores assessed using Numerical Rating Scale at 0, 2, 6, 12, 18, 24 and 48 hours and when found to be >4, IV morphine 3mg was given. It was observed that the duration of pain-free period in Ketamine group was 860 minutes compared to 580 minutes in Dexmedetomidine group. Though few patients were found to have nausea, diplopia and dizziness in the Ketamine group, it was insignificant on comparison with the other two groups ($P>0.05$).[26]

Ali Hassan. M.R. et al. in 2016, conducted a study to analyse the effectiveness of two regimens of low doses of Ketamine infusion administered intraoperatively in reducing the opioid consumption during the first 24 hours. 50 patients scheduled for open gynaecological procedures were randomised into three groups randomly. Group A was administered normal saline infusion, group B received Ketamine at 0.25mg/kg/hour and group C was administered Ketamine infusion at 0.5mg/kg/hour in the intraoperative period. All three groups received intraoperative morphine at 0.1mg/kg. Outcomes were recorded at time 0, 10, 20, 30 minutes and 6, 12, 24 hours in the postoperative period. It was observed in this study that the total morphine consumption in the postoperative period during first 24 hours given via patient-controlled analgesia was reduced in group B and C. Group C also had significantly lower requirements of rescue analgesia and lesser VAS scores in the postoperative period. No adverse effects were observed in all three groups.[27]

In a study conducted by **Kator S et al. in 2016** a retrospective single-center analysis of health records of patients was done which included review of all patients with prescription of an IV ketamine infusion at doses less than 0.9mg/kilogram/hour from September 1, 2010 to August 31, 2013. A total of 396 patients were eligible for the final

analysis out of which 277 patients (69.9%) were given ketamine following a surgical procedure and the remaining 119 patients (30.1%) were administered Ketamine for medical treatment of pain. Ketamine was given for a mean duration of 35.69 hours with an initial median dose of 0.2mg/kilogram/hour. This study reported a reduction in pain scores from an average of 7.1+/- 2.63 SD before administering Ketamine to 6.42+/- 2.01 SD during the infusion. ($P<0.001$).[16]

In a review article published by **Schmid et al. in 1999,** the effectiveness of low dose Ketamine for management of acute postoperative pain was reviewed. Randomised double blinded prospective studies published between 1966 and 1998 December which reported pain scores were included. Routes of administration included intramuscular, subcutaneous, intravenous, intraspinal (which includes intrathecal, caudal, epidural) and via oral routes. This review includes 28 studies that fulfilled the aforementioned criteria and it concluded that Ketamine may play an essential role in the management of postoperative pain and to reduce side effects related to opioid administration. Also low dose Ketamine acts as an excellent adjuvant when used along with opioids, local anaesthetics and other analgesic agents.[14]

However, extensive literature search found very few studies determining the effect of intravenous Ketamine infusion on postoperative pain following laparoscopic appendicectomy. Hence this study was undertaken to determine the effect of postoperative intravenous Ketamine infusion on postoperative pain and analgesic requirement in the first 24 hours following laparoscopic appendicectomy.

BASIC SCIENCES

Pain:

Pain is defined by the International association for the study of pain as "an unpleasant sensory and emotional experience associated with actual tissue damage, or described in terms of such damage" [30]

The complex nature of pain perception includes a series of neurophysiologic processes, which is together called **nociception**. It has four distinct components which includes- Transduction, Transmission, Modulation and Perception. The nociceptive system is very complex and highly adaptable. The sensitivity of the components of this system can be altered by many of the physiologic and pathologic conditions. Many new medications have been developed to target and treat the causes by acting on the components of nociceptive system in both the peripheral nervous system and the central nervous system.[22]

Transduction is the process by which a thermal, chemical or mechanical noxious stimulus in the tissue is converted into an electrical impulse in the sensory nerve endings.

Transmission is the process by which the electrical impulses are conducted to the CNS with the major connections for these nerves located in the dorsal horn of the spinal cord and thalamus with projections to the cingulate, insular and somatosensory cortex.

Modulation is the neural process by which transmission of pain is altered. It is probable that both inhibitory and excitatory mechanisms modulate the pain impulse transmission in the PNS and CNS.

Perception of pain is mediated through the thalamus which acts as the central relay station for incoming pain signals and as the primary somatosensory cortex which serves to differentiate particular sensory experiences.

Pain, sometimes, may be perceived in the absence of the events of these four steps also.[22]

Neurophysiology of pain:

Nociceptors (pain receptors):

Nociceptors are a population of free nerve ending receptors present in the skin, muscles, joints, viscera, and vasculature. Nociceptors maybe either somatic that include those in skin and deep tissues like muscle, tendons, joints, or visceral nociceptors that include those in internal organs. They detect the noxious stimuli resulting from chemical, thermal or mechanical stimulus in the tissues. In normal tissues, nociceptors remain dormant until they reach a stimulus of sufficient intensity to overcome the threshold implying that they possess molecular and biophysical properties to selectively detect and respond to noxious stimulus.

Nociceptors can be divided into two major classes. The first class of receptors include myelinated, Aδ fibers of medium diameter size which mediate fast, well localized first pain. The second one includes unmyelinated C fibers of smaller diameter which carry poorly localized, slow second pain. Nociceptors not only serve to carry noxious stimuli in one direction from periphery to spinal cord but also act as a bidirectional signalling machine.[28, 31,33]

Electrophysiological studies recognized and further subdivided A-delta nociceptors into two, which include

Type I - they respond to both chemical and mechanical stimuli but have higher thresholds for heat, greater than 50^{o} C. They mediate first pain caused by pinprick and other intense mechanical stimuli.

Type II – these receptors have higher sensitivity to heat but higher threshold for mechanical stimuli, hence respond and mediate first pain to intense heat.

C fibers are polymodal and include receptors which are sensitive to both heat and mechanical stimuli. Silent nociceptors are a class of unmyelinated afferents responding only in the presence of inflammation.

Pain is clinically divided into acute and chronic pain.[28,31,32]

Acute pain:

Acute pain is caused by noxious stimulus due to injury, a disease process, or the abnormal function of muscle or viscera. It is due to nociception.

Acute pain is associated with a neuroendocrine stress response that is proportional to the intensity of pain. There are different forms of acute pain, commonest forms being post –traumatic, postoperative and obstetric. Other forms are those associated with acute medical illnesses like myocardial infarction, pancreatitis, renal calculi.

Acute pain is usually self- limited or usually resolves with treatment in a few days to weeks. When acute pain fails to resolve due to abnormal healing or inadequate treatment it becomes chronic. [34]

There are two types of acute pain: somatic and visceral.

Somatic pain:

Somatic pain is due to nociceptive input arising from skin, subcutaneous tissues, and mucous membranes. It is characterized by being localized and described as sharp, pricking, throbbing or burning sensation.[33] It is further classified into superficial and deep.

Superficial somatic pain is due to nociceptive input arising from skin, subcutaneous tissues, and mucous membranes. It is well localized and described as a sharp, pricking, throbbing, or burning sensation.

Deep somatic pain arises from muscles, tendons, joints, or bones. It usually has a dull, aching quality and is less well localized.[34]

Visceral pain:

Visceral pain is due to nociceptive input arising from internal organ or one of its covering. It is dull diffuse pain, which is frequently associated with abnormal sympathetic or parasympathetic activity causing nausea, vomiting, sweating and /or changes in blood pressure or heart rate.

Four subtypes are described: (1) true localized visceral pain, (2) localized parietal pain, (3) referred visceral pain, and (4) referred parietal pain.

Parietal pain is typically sharp and often described as a stabbing sensation that is either localized to the area around the organ or referred to a distant site. The phenomenon of visceral or parietal pain referred to cutaneous areas results from patterns of embryological development and migration of tissues, and the convergence of visceral and somatic afferent input into the central nervous system. Thus, pain associated with disease

processes involving the peritoneum or pleura over the central diaphragm is frequently referred to the neck and shoulder, whereas pain from disease processes affecting the parietal surfaces of the peripheral diaphragm is referred to the chest or upper abdominal wall.[34]

Chronic Pain:

Chronic pain is pain that persists beyond the usual course of an acute disease or after a reasonable time for healing to occur, this healing period can vary from 1 to 6 months. Chronic pain may be nociceptive, neuropathic, or mixed. It often has a psychological mechanisms or environmental component. Patients with chronic pain often have attenuated or absent neuroendocrine stress responses and have prominent sleep and mood disturbances.

Pain may also be classified according to pathophysiology as nociceptive or neuropathic pain, etiology as arthritis or cancer pain, or the affected area such as headache or low back pain. Such classifications are useful in the selection of treatment modalities and drug therapy. Nociceptive pain is caused by activation or sensitization of peripheral nociceptors, specialized receptors that transduce noxious stimuli. Neuropathic pain is the result of injury or acquired abnormalities of peripheral or central neural structures.

Many factors influence the occurrence, intensity, quality and duration of postoperative pain like the site, nature and duration of operation, type of incision (thoracic and upper abdominal operations are associated with the most severe pain), the preoperative psychological, physical and pharmacological preparation of the patient, added to this the anaesthetic management and the quality of postoperative care.[34]

Pain pathway:

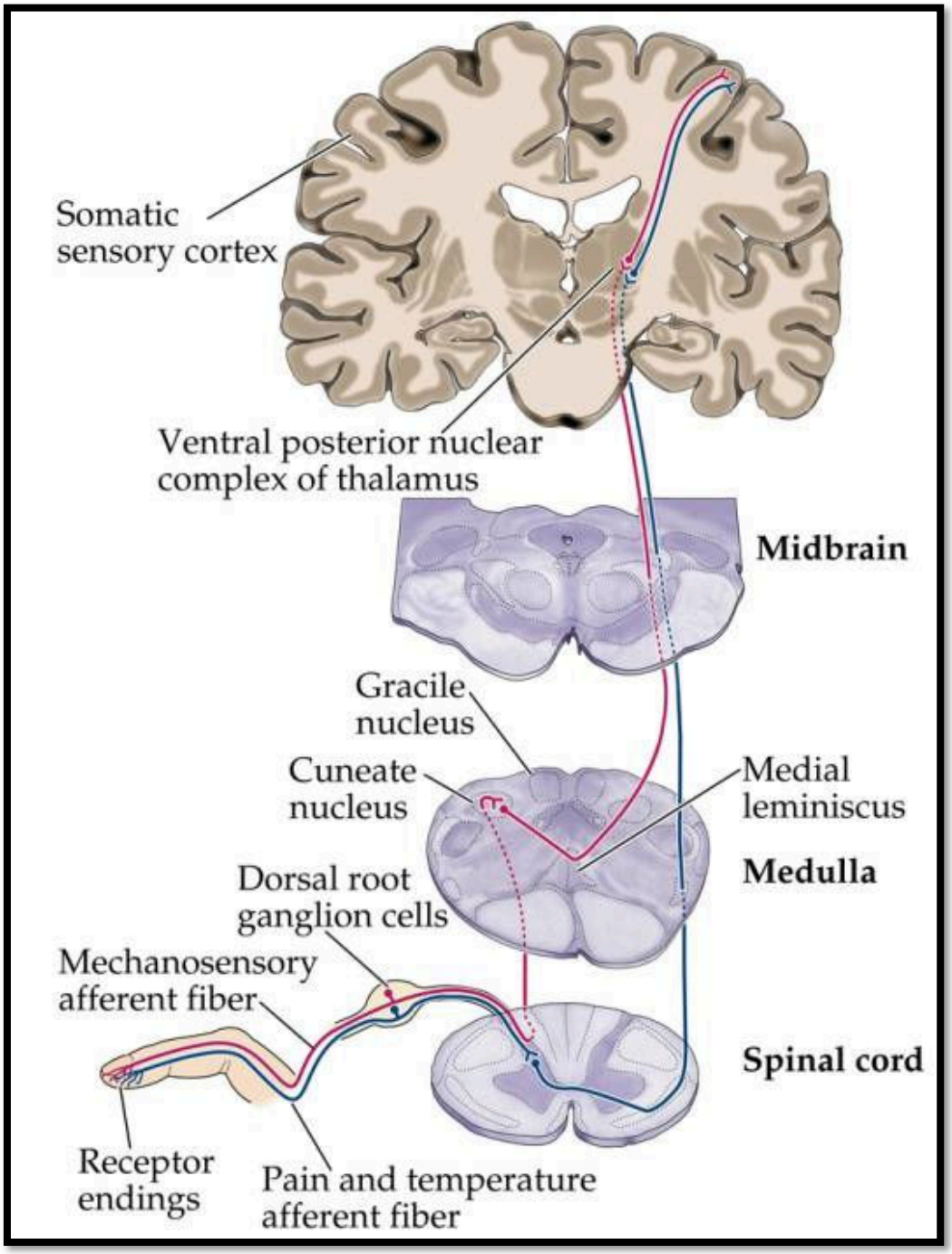


Figure 1: Pain Pathway

Pain is conducted along three neuron pathways; from the periphery to the cerebral cortex.[28,33]

First order neuron

Cells of these neurons are located in the dorsal root ganglia (for the body) and specific cranial nerve ganglia (for the head and neck) for example, Gasserian ganglion for trigeminal nerve. The Proximal end of their axons reach spinal cord via the dorsal sensory root of cervical, thoracic, lumbar, and sacral level (for the body) and through the cranial nerves (for head and neck).[28,33]

Second order neurons

Pain fibers may ascend or descend three spinal cord segments in the Lissauer's tract before synapsing with the second order neuron in the gray matter of the ipsilateral dorsal horn, this synapsing may be through interneurons. Second order neurons are either; nociceptive specific which serves only noxious stimuli and are normally silent or wide dynamic range (WDR) neurons that can receive also non-noxious afferent input. WDR neurons are more prevalent in the dorsal horn and are responsible for the increased intensity of firing in response to same stimulus "wind-up". [31,32]

Lamina II of the gray matter of the dorsal horn of the spinal cord, (also called the substantia gelatenosa) contains many interneurons and is believed to play a role in processing and modulating nociceptive input.[31,32]

Axons of most of the second order neurons cross the midline to the contra-lateral side of the spinal cord forming the lateral spinothalamic tract that send its fibers to the thalamus, the reticular formation, nucleus raphe and periaquiductal gray.[31,32]

Third order neurons

These are located in the thalamus and send their fibers to the somato-sensory area I and II in the cerebral cortex.[31,32,34]

Effects of postoperative pain:

Moderate to severe acute pain, regardless of its site, can affect nearly every organ function and may adversely influence postoperative morbidity and mortality.

Acute pain is typically associated with neuroendocrine stress response that is proportional to pain intensity, and it has been hypothesized that a reduction in surgical stress responses (endocrine, metabolic and inflammatory) will lead to a reduced incidence of postoperative organ dysfunction and thereby lead to an improved outcome. The latter suggests that effective postoperative pain management as a very important aspect of postoperative care.[35]

a) Cardiovascular effects:

Cardiac morbidity is a major cause of perioperative death. The realization that, in high risk populations, perioperative myocardial ischemia is most likely to occur after surgery (from day one to day three postoperatively) has led to treatment strategies designed to prevent its development.[36]

Although a variety of factors may contribute to the development of postoperative myocardial ischemia, including hypothermia, anaemia, anxiety, and tracheal intubation / suctioning, responses to poorly controlled pain play a prominent role. In this regard, activation of sympathoadrenal, and neuroendocrine axis may have a major impact on myocardial oxygen supply and demand. Catecholamine-induced tachycardia, enhanced contractility, increased afterload and increased preload from hypervolemia caused by enhanced release of arginine vasopressin and aldosterone, are well characterized determinants of increased oxygen demand. Increased oxygen demand, with hypervolemia, may precipitate ischemia and acute cardiac failure, especially in patients with poorly compensated coronary artery or valvular heart disease.[37]

Myocardial oxygen supply may be diminished as a result of pulmonary dysfunction, in particular, atelectasis secondary to pain-induced hypoventilation and pulmonary edema resulting from stress-induced hypervolemia. Other causes of reduced oxygen supply include coronary artery constriction secondary to high circulatory levels of catecholamine and increased coronary

sympathetic tone, stress-induced increase in plasma viscosity and platelet-induced occlusion; and serotonin induced coronary vasospasm secondary to platelet aggregation.[38]

b) Pulmonary effects:

Pulmonary function may be dramatically altered by surgically induced pain. The classical pulmonary response to upper abdominal surgery, include an increase in respiratory rate with decreased tidal volume, vital capacity, forced expiratory volume and functional residual capacity. Those pathophysiologic alterations are characteristic of acute restrictive pulmonary disease and, as such, may be associated with clinically significant hypoxia and hypercarbia.[38]

Pain increases total body oxygen consumption and carbon dioxide production which necessitates an increase in the work of breathing. Patients with poor pain control (specially in upper abdominal and thoracic procedures) breath less deeply and have inadequate cough which leads to further reduction in the tidal volume and functional residual capacity, which in turn can cause atelectasis, intrapulmonary shunting and hypoxemia.[35]

c) Gastrointestinal effects:

Sympathetic hyperactivity induced by pain increases sphincter tone and decrease motility of intestine, causing ileus, pain also increases stress ulceration due to increase in gastric acid secretion.[39]

d) Endocrinal effects:

The dominant neuroendocrine responses to pain involve hypothalamic-pituitary-adrenocortical interactions. These interactions result in increased catecholamine and catabolic hormone release. This effects cause sodium and water retention, and increased levels of blood glucose, free fatty acids and lactate. The negative nitrogen balance and protein catabolism may impede patient's convalescence.[40]

e) Hematological effects:

The stress response causes decrease in the levels of natural anticoagulants, inhibition of fibrinolysis and increase in platelet reactivity which initiate a postoperative hypercoagulable state. This hypercoagulability causes a series of other events such as deep venous thrombosis and myocardial ischemia.[31]

f) Immunological effects:

The stress response potentiate postoperative immunosuppression; the extent of which correlates with the extent of surgery. Stress response has been reported to depress the reticulo-endothelial system which predispose to infection.[33]

g) Psychogenic effects:

Intense anxiety, fear, and the loss of control that accompany severe tissue injury may have profound impact on the hypothalamic-pituitary axis. Behavioral responses associated with poorly controlled pain include sleep deprivation and reduced morale.[41]

In many patients, uncontrolled postoperative pain can produce a series of long-term emotional disturbances, which could impair the patient's health, and cause undue fear and anxiety if subsequent surgery is required. Postoperative cognitive dysfunction occurs in up to 20% of patients after major non-cardiac surgery and may persist in about 10% of patients 3 months after surgery.[35]

h) Development of chronic pain:

Recently, it is accepted that neuropathic pain can develop after surgery, be persistent, and be the basis for ongoing suffering for the patient. The diagnosis of neuropathic pain can be obtained from the presenting features of burning, stinging or shooting pain, despite apparent tissue healing with a relative lack of response to doses of opioids used in the postoperative period.[42]

Lastly, optimizing treatment of acute postoperative pain can improve health-related quality of life, while poor postoperative pain control may interfere with patient's activities of daily living.

Measurement of pain:

Pain measurement is done by two methods;

1. Type I methods:

Those are objective methods, done by the physician as he assigns numbers about the patient condition. It includes the following:

Physiological indices

- Endocrinal (increase in serum cortisol and catecholamine).
- Cardiovascular (increase in blood pressure and heart rate)
- Respiratory (increase in respiratory rate and decrease in tidal volume)

Neuro-pharmacological

- Correlation with beta endorphin (decreased in acute painful conditions)
- Thermography (hypo-emission in chronic pain)

Neurological

- Nerve conduction velocity
- Evoked potentials
- Single positron emission tomography (SPET).

Behavioral

- Sighing, crying, shouting, trembling.

2. Type II methods:

It includes either:

Single dimension methods

- Category scale (verbal rating scale)
- Numerical rating scale
- Graphic rating scale

Multi-dimensional methods

- Mc Gill pain Questionnaire, MPQ
- Dartmouth pain Questionnaire, DPQ
- West Haven-Yale pain Questionnaire, WHYPQ.[36]

Measurement of pain in clinical practice depends largely on verbal dialogue between the patient and the doctor or nurse. A rating scale is mandatory in research projects and ideally when clinical data are being collected.

A number of individual differences between patients make comparisons of pain measurements more difficult. For example, the past experiences of the patients influence their present perception of pain. Also, demographic factors such as gender, age, and ethnic background influence the individual's perception of pain. Again, patients who are clinically depressed and anxious tend to report increased pain intensity.

Although pain is a subjective experience, great attention has been paid to the quantification of this experience. As pain is subjective experience, everyone has different perceptions of that experience. Differences are found in how individuals quantify pain. For example, some individuals would never say that their pain was a (10) on a scale from (0) to (10). On the other hand, other

individuals report their pain as a constant (10) despite looking calm and relaxed. Also, all numeric scales used to measure pain have floor and ceiling effects. If the patients describe their pain to be a (10), there is no way to report an increase in pain intensity.

Of the many methods of pain scoring VAS and VRS are the most commonly used in the single dimension method.

Visual analogue scale (VAS):

The visual analogue scale uses a straight line with extremities of pain intensity on either end. The line is typically 10 cm long with one end defined as "no pain" and the other end being excruciating unbearable pain". The line can be either vertical or horizontal. The patients are asked to place a mark on the line to describe the amount of pain that they are currently experiencing. The distance between the end labelled "no pain" and the mark placed by the patient is measured and rounded to the nearest centimeter. To assist in describing the intensity of pain, words can be placed along the scale (for example, mild, moderate, or severe). Such descriptors can help to orient the patient for the degree of pain; this particular variation of the VAS has been known as a graphic rating scale. Explanation to the patient is needed by the clinician when using the VAS. Occasionally, the patient may be confused about the line, perceiving it to represent time of degree of relief rather than degree of pain intensity.[33]

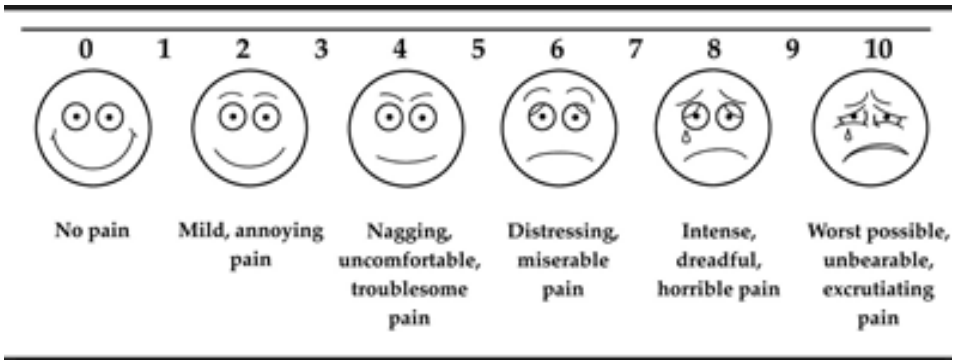


Figure 2: Visual Analogue Scale

MANAGEMENT OF POSTOPERATIVE PAIN

Prophylactic measures:

The incidence, severity, and duration of pain and suffering during the postoperative period can be decreased by proper preoperative and postoperative surgical and psychological care. Although the accepted definition of pain emphasizes the cognitive, emotional response to tissue damage, the role of psychological techniques in the relief of acute pain has been minimized. Psychoeducational care has beneficial effects on recovery, postoperative pain and psychological distress after surgery.

Psycho-educational care was classed as health-care information (information in preparation for surgery, timing of procedures, function and roles of health-care providers, self-care actions, and pain and discomfort information); skills teaching (coughing, breathing and bed exercises, relaxation, hypnosis); and psychosocial support (identifying and alleviating concerns, reassurance, problems solving, and encouraging questions).

Optimal surgical care also helps to decrease the severity of postoperative pain. Skillful and gentle handling of tissues while carrying out the operation and observance of other surgical principles assist to minimize trauma. Proper postoperative care help to decrease the magnitude of postoperative pain which involves continuing psychological support, proper care of wounds, early ambulation, and of course good nursing care.[28]

Active measures

Postoperative pain can be partially or completely relieved by one of the following methods:

1. *Systemic analgesics and adjuvant*

a) Opioids

b) Non-steroidal anti-inflammatory drugs

c) NMDA antagonists

d) Alpha-2 adrenergic agonists

e) Miscellaneous non-opioid compounds

2. Local infiltration and field block - Regional analgesia with local anaesthetics

a) Continuous segmental epidural block

b) Intrapleural instillation

c) Intraperitoneal instillation

d) Infiltration of the incision site

3. Regional analgesia with neuro-axial opioids and local anaesthetics

4. Regional analgesia with combined local anaesthetics and opioids

5. Electrical analgesia achieved with transcutaneous electrical stimulation or electro-acupuncture.[28]

Pain after laparoscopic surgeries:

Laparoscopic approaches to surgery have increased dramatically over the past several years. However laparoscopic procedures are not pain free and pain occurs after laparoscopy, but is usually less and shorter compared to the same conventional surgical procedure.[43]

Mechanism of pain in laparoscopic surgeries:

Early postoperative pain is the most prevalent and dominant complaint that requires strong analgesia including opiates after elective laparoscopic surgeries. For that reason, many efforts have been made to improve postoperative analgesia, but postoperative pain, however, does not completely disappear and several studies have shown that port site incision and visceral pain is the major component. Nonetheless, pain may be moderate or even severe for some patients during the first 24 postoperative hours, and has frequently been treated with nonsteroidal anti-inflammatory drugs (NSAIDs) or opioid treatment.[6,43]

The exact etiology of pain after laparoscopic surgeries is still unclear, however, it appears to be multifactorial and the causes include, abdominal wall trauma by trocar entrances, diaphragmatic irritation secondary to CO_2 insufflation and pneumoperitoneum, type and temperature of insufflated gas, residual intraperitoneal gas, intraabdominal trauma, microruptures of the parietal peritoneum due to abdominal distension, chemical irritation of the peritoneum, etc.[6]

Therefore, abdominal distention should be slow with adequate muscle relaxation to ensure suitable abdominal compliance. The prolonged presence of shoulder tip pain suggests irritation of the phrenic nerve that is caused by the persistence of gas in the abdomen (pneumoperitoneum). There is statistically significant correlation between the width of the gas bubble and pain score, and this pain can be reduced by the aspiration of the gas under the diaphragm.[2]

Factors associated with gaseous pneumoperitoneum:

1. ***Neuropraxia of the phrenic nerve***

It has been suggested that distention of the diaphragm during gas insufflations and the resultant phrenic nerve neuropraxia possibly contribute to postoperative pain, which may include the related C4 dermatome.[44]

2. ***The type of insufflated gas and intraabdominalpH***

The phrenic nerves may be damaged by the acid milieu created by the dissolution of CO_2. The intraperitoneal pH when CO_2 gas is insufflated has been measured to be 6.0, immediate postoperatively. On the first postoperative day, the pH rises to 6.4 to 6.7, and on the second postoperative day to 6.8 to 6.9. Thereafter it normalizes to above 7.0.[45]Similar values were found when argon gas was substituted.

3. ***Residual intraabdominal gas***

Several reports have indicated that residual intraabdominal gas after laparoscopy causes pain. Carbon dioxide dissolution, intraabdominal acidosis, and the consequent peritoneal irritation

occur for a longer period if the gas is not evacuated at the end of the laparoscopic procedure. Residual gas also may result in a loss of peritoneal surface tension and support to the abdominal viscera, thus contributing to postoperative pain.[46]

4. *Temperature of gas*

The effect of gas temperature on postoperative pain after gynaecologic laparoscopic procedures has been investigated in a prospective randomized study of standard insufflation gas (20^0 C) versus gas at body temperature. This study found that pain reduction was significantly greater for those patients in whom warmed gas was used, especially with respect to diaphragmatic and shoulder tip pain, with the lasting effect of three days.[44]

5. Humidity of gas

A prospective randomized controlled trail was conducted at the Queen Elizabeth Hospital, Adelaide, to investigate the outcome when humidified gas was insufflated during laparoscopic cholecystectomy instead of standard dry gas. This study demonstrated significantly reduced postoperative pain in patients who underwent humidified gas insufflation. The humidified insufflations showed a trend of less post operative analgesic consumption, along with shorter hospital stay and earlier return to work. The exact relation between dry gas and postoperative pain is not yet determined, but other animal studies have observed that dry gas insufflation is implicated in ultrastructural damage to exposed membranes, an effect that was not seen with the use of humidified gas.[47]

Management of post operative pain after laparoscopic surgeries:

In order to decrease the postoperative pain after the laparoscopy, some methods such as rectus sheath block, Transversus Abdominis plane block, intraabdominal drain placement in order to completely remove CO_2 pneumoperitoneum, intraperitoneal infiltration of the local anaesthetics or opioids, the use of systemic opioids, patient-controlled analgesia, and injection of local anaesthetics into the port sites are suggested.[6]

Of recent interest, is the use of N- methyl D- aspartate antagonists, especially Ketamine for the management of acute postoperative pain.

PHARMACOLOGY

Ketamine

HISTORY

Victor Maddox of Detroit synthesized phencyclidine and it was introduced into clinical use by Greifenstein and Johnstone in 1958. Ketamine was synthesized in 1962 by Stevens and was first used in humans in 1965 by Corssen and Domino.

PHYSICOCHEMICAL CHARACTERISTICS

Ketamine is 2-0-chlorophenyl 2-methyl amino cyclohexanone hydrochloride. The molecular weight of 238 kd. It is partially water soluble and forms a white crystalline salt with a pKa of 7.5. It is prepared in a slightly acidic pH of 3.5-5.5 and is available in 1%, 5% and 10% solutions containing the preservative benzathonium chloride. Ketamine has a chiral center at the carbon-2 atom of its cyclohexanone ring and therefore it exists as the optical stereoisomers S(+) and R(−)ketamine. Ketamine was previously only available as a racemic mixture but now comes in its two stereoisomer varieties. S(+)ketamine binds NMDA receptors with affinity that is four times greater than that of R(−)ketamine. While the duration of S(+)ketamine is shorter than that of R(−)ketamine, S(+)ketamine has been shown to have an analgesic potency twice as great as the racemic mixture and four times as great as R(−)ketamine.[28]

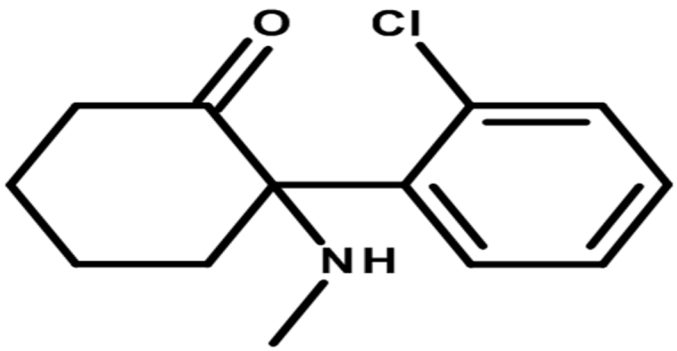


Figure 3: Chemical structure of Ketamine

PHARMACOKINETICS

The extreme lipid solubility of ketamine ensures its rapid transfer across the Blood - brain barrier. Peak plasma concentration occurs within 1 minute after IV administration and 5 minutes after IM injection. Not significantly bound to plasma proteins.

Distribution half life – 11 to 16 minutes.

Elimination half life – 2 to 3 hours.

Large volume of distribution – 3 L / kg.

Total body clearance – 1.4 L / min.

Alterations in hepatic blood flow influences ketamine clearance rate.

Metabolism is by the hepatic microsomal enzymes cytochrome P – 450. Major pathway is N-demethylation to form nor – ketamine (20-30% activity) which is then hydroxylated to form hydroxy norketamine. These products are conjugated to water soluble glucuronide derivatives and are excreted in the urine. Chronic administration of ketamine can stimulate the enzymes responsible for its metabolism (enzyme induction) and explain the observation of tolerance and dependance.[22]

MECHANISM OF ACTION [22]

Ketamine interacts with the following receptors.

A) N-methyl D- Aspartate receptor antagonism:

Non-competitive antagonist of the NMDA – receptor calcium pore. It also binds to the phencyclidine binding receptor site causing inhibition of the NMDA receptor activity (S(+) isomer more affinity)

B) Opioid receptors:

Ketamine may be an antagonist at mu receptors and an agonist at kappa receptors.

C) Mono aminergic receptors:

Antinociceptive actions may involve descending inhibitory monoaminergic pain pathways.

D) Muscarinic receptors:

Ketamine produces an antagonistic effect at these receptors. Anticholinergic symptoms are common.

E) Voltage sensitive calcium channels

PHARMACODYNAMICS [22,28]

Effect on the Central nervous system:

a) **Dissociative anaesthesia:** A cataleptic state, with profound analgesia, the eyes remain open with a slow nystagmic gaze. Noncommunicative, though wakefulness appears to be present. Corneal, cough and swallowing reflexes are present but not protective. Varying degrees of hypertonus and purposeless movements can occur. The patient is amnesic. In the thalamo neocortical projection systems, ketamine produces a functional disorganization of pathways and dissociation between the thalamocortical and limbic system. Plasma levels for anaesthesia

are 0.6 to 2 mcg / ml in adults and 0.8 to 4 mcg / ml in children. Duration of action is 10 to 15 minutes and full orientation occurs in 15 to 30 minutes.

b) Ketamine produces an increase in the cerebral blood flow and cerebral metabolic oxygen requirement. With increase in cerebral blood flow and generalized increase in the sympathetic nervous system response, there is an increase in the intra cranial pressure. Cerebrovascular response to carbon-di-oxide appears to be preserved with ketamine. Prior administration of thiopental, diazepam or midazolam can blunt the ketamine induced increase in cerebral blood flow and cerebral metabolic oxygen requirement.

c) Due to its excitatory central nervous system effects, the drug produces theta – wave activity as well as petitmal seizure like activity in hippocampus. Theta activity signals analgesic activity. Onset of delta activity coincides with the loss of consciousness. Ketamine does not alter the seizure threshold in epileptic patients but it can produce a myoclonic and seizure like activity without cortical epileptic activity.

d) **Emergence reaction**: Vivid dreaming, extracorporeal experiences (sense of floating) and illusions, may progress to delirium associated with excitement, confusion, euphoria and fear. This occurs in the first hour of emergence and usually abates within 1 to several hours. Emergence delirium occurs secondary to ketamine induced depression of the inferior colliculus and medial geniculate nucleus leading to misinterpretation of auditory and visual stimuli. The loss of skin and musculoskeletal sensation results in decreased ability to perceive gravity producing a sensation of bodily detachment (floating in space). Incidence 10 to 30 %. Prevention – benzodiazepines especially midazolam is more effective; can be given 5 minutes before induction. Inclusion of thiopental or inhalation can decrease the incidence. Premedication with atropine or droperidol may increase the incidence of emergence delirium.

Effect on the Respiratory system:

Ventilatory response to carbon-di-oxide is maintained; transient decrease in minute ventilation (1-3 min) can occur after a bolus dose; apnoea can occur after rapid IV or along

with an opioid. Respiratory depression can occur with the use of sedative and anaesthetic drugs. In children, it can cause respiratory depression. Bronchodilator activity is used to treat bronchospasm and status asthmaticus. Mechanisms include increased circulatory catecholamine concentrations, inhibition of catecholamine uptake, voltage sensitive calcium channel block and inhibition of post synaptic nicotinic or muscarinic receptors.

Effect on the Cardio vascular system:

Sympathetic and pulmonary arterial blood pressure, heart rate, cardiac output and myocardial oxygen requirements are increased after IV ketamine. Ketamine has a direct myocardial depressant effect (negative ionotropic) getting unmasked when the compensatory sympathetic nervous system activity is exhausted or following depletion of endogenous catecholamine stores. Enhances the dysrhythmogenicity of epinephrine. Mechanisms causing stimulation of sympathetic nervous system include: direct central nervous system stimulation and increased outflow, depression of baroreceptor reflex via N-methyl D-aspartate receptor, inhibition of norepinephrine uptake into post ganglionic sympathetic nerve endings and associated increase of plasma catecholamines. Methods used to block ketamine induced sympathetic stimulation are use of alpha and beta adrenergic antagonist, vasodilators, clonidine, prior administration of benzodiazepines, inhalational anaesthetics, barbiturates, and droperidol.

USES[22,28]

I. INDUCTION AND MAINTENANCE:

IM induction in children and mentally retarded patients, for burn dressing changes, wound debridements and skin grafting procedures. Induction agent of choice in patients with reactive airway disease or bronchospasm or asthma. Its use as cardiac stimulant is advantageous in trauma victims with acute hypovolemia provided there is sufficient sympathetic reserve. Patients with septic shock also benefit from ketamine. Ketamine anaesthesia is used for

cardiac tamponade, constrictive Pericarditis & congenital heart disease with right to left shunt. In patients with malignant hyperthermia and anterior mediastinal mass, ketamine use maintains spontaneous ventilation (inhalation contraindicated). Diazepam 0.5mg /kg IV and ketamine 0.5 mg /kg IV followed by a continuous infusion of ketamine 15 to 30 μg/kg /mint can be used in patients with coronary artery disease. Low dose ketamine can be used as an analgesic following thoracic surgery.

Induction: 0.5 – 2 mg /kg IV 4 - 6 mg/ kg IM

Maintenance: 0.5 – 1 mg /kg IV 30 – 90 μg/kg /min IV

II. SEDATION:

Ketamine sedation is used for paediatric procedures like cardiac catheterization, radiation therapy, dressing changes and dental work.

0.2 - 0.8 mg/kg IV

2 - 4 mg/kg IM Ketamine

0.5mg/kg IV combined with diazepam 0.15mg/kg IV is better accepted for supplementation of regional anaesthesia.

III. **NEURAXIAL ANALGESIA:**

Extra dural (30mg) and intrathecal (5mg) administration produces variable and brief analgesia.

Adverse Effects [22,28]

Increased Blood Pressure, tachycardia, tonic & clonic muscle movements, tremors and vocalization, emergence reaction, visual hallucination, vivid dreams or illusions. Less frequently bradycardia, hypotension, respiratory depression, apnoea, vomiting, cardiac arrhythmias, laryngospasms and airway obstructions occur. Rarely double vision, loss of appetite, nystagmus, skin rash (red skin) etc are noted.

MATERIALS AND METHODS

The present study was conducted at KLE'S Dr. Prabhakar Kore Hospital and Medical Research Centre, Nehru Nagar, Belagavi 590010, on patients undergoing laparoscopic appendicectomy under General Anaesthesia between January 2020 to March 2021.

Study design: A double blind randomized controlled trial.

Study Period: January 2020 to March 2021.

Sample size: A total sample size of 90 cases.

Sample size calculation

The minimum sample size formula based on mean and standard deviation is

$$n = \frac{(z_\alpha + z_\beta)^2 (s_1^2 + s_2^2)}{(\bar{X}_1 - \bar{X}_2)^2}$$

where, zα is linked with the level of significance,

zβ is linked with the power of the test.

For 5% level of the significance, zα =1.96 and zβ =0.84 for 80% power of the test.

$\bar{X}_1$ is the mean of the first group (2.6),

$\bar{X}_2$ is the mean of the second group (2.8),

s_1 is the standard deviation of the first group (2.7),

s_2 is the standard deviation of the second group (1.7).

With these values the sample size calculated was 90.

There were two groups having 45 cases in each group.

Selection criteria:

Inclusion criteria:

- Patients undergoing laparoscopic appendicectomy under GA.
- Age: 18 to 60 years group
- ASA Grade I and Grade II patients

Exclusion criteria:

- Age below 18yrs and above 60yrs.
- ASA Grade III and IV
- Patients with history of allergy to the study drug.
- Patients with psychiatric disorder.

Methodology:

After procurement of the approval of ethical committee and written informed consent, a total of 90 patients undergoing laparoscopic appendicectomy were included in the study.

After having met inclusion and exclusion criteria and having obtained informed consent, patients were randomized based on computer generated randomization table into one of the two groups.

Group A - Patients received Ketamine intravenous infusion at 0.2 mg/Kilogram/hour.

Group B - Patients received Normal Saline infusion at 3ml/hour.

A thorough pre-anaesthetic evaluation was done. Routine investigations such as Complete blood count, Random Blood Sugar, Urine routine examination, Chest Xray were done for all patients. Electrocardiography was done in patients above 40yrs of age. Patient was advised overnight fasting.

On the previous day, Visual Analogue Score was shown to the patient and explained its use for the postoperative pain assessment.

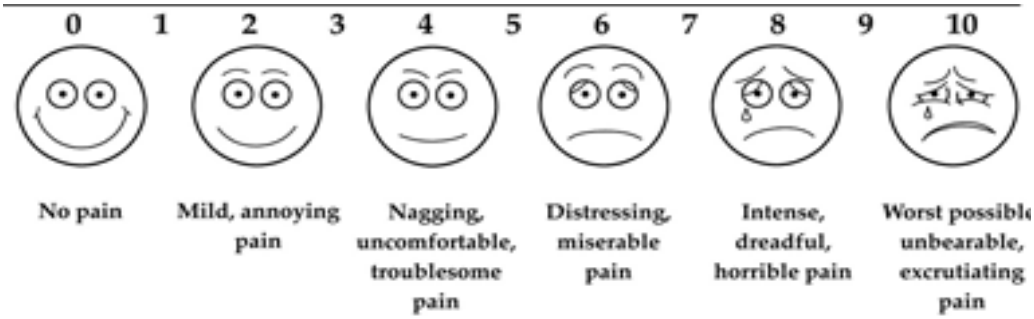
On the day of surgery, intravenous access was secured using 18G or 20G IV cannula and intravenous fluids started. In the operation theatre patients were monitored by pulse oximetry, noninvasive blood pressure measurement and electrocardiography. Following preoxygenation for three minutes, patient was premedicated with Inj. Glycopyrrolate 0.005mg/kg IV, Inj. Midazolam 0.05mg/kg IV and Inj.Fentanyl 2µg/kg IV. Induction of anaesthesia was done with Inj. Thiopentone sodium 5mg/kg IV, sufficient to obtund the eye-lash reflex, followed by Inj. Scoline 2mg/Kg IV to facilitate orotracheal intubation. After confirming bilateral equal air entry, endotracheal tube was secured with tapes at appropriate length and mechanically ventilated. General anaesthesia was maintained with O_2:N_2O in the ratio of 50:50 and 0.4% isoflurane with Inj. Vecuronium loading dose of 0.1mg/kg and intermittent top ups of $1/4^{th}$ of loading dose.

After instituting general anaesthesia, patients in both the groups received one dose of intravenous Paracetamol at the dose of 15mg/Kg.

At the end of procedure, patient was extubated after thorough suctioning and adequate reversal with Inj. Glycopyrrolate IV(0.01mg/kg) and Inj. Neostigmine IV(0.05mg/kg).

Patient was shifted to recovery and patients in group A were started with Ketamine infusion at the dose of 0.2mg/Kilogram/hour and continued for 24 hours. Group B patients were started with Normal Saline infusion at 3 ml/hour. VAS pain scores were assessed for postoperative pain, at hourly intervals for the first 1-12hrs, 4^{th} hourly for the next 12 hours postoperatively. Patients with VAS 3 or more was given rescue analgesia in the form of Paracetamol 15mg/kg IV. Total amount of analgesic consumed in 24 hours also was noted in both the groups. The infusion was made by an anaesthesiologist not engaged in the study. And the anaesthesiologist noting the study parameters was blinded to the infusion started.

VAS Pain scale:



Statistical Analysis

The data entry was made into the Microsoft Excel Spreadsheet. The obtained data was analysed using SPSS statistical software version 20.0. Student's unpaired 't' test was used to compare quantitative variables in both groups and the qualitative variables was compared using student's paired 't' test for each group independently and represented as mean and standard deviation. The categorical data are compared using Chi square test and expressed in terms of rates, ratios and percentages. Non- parametric data for discrete variables was analysed by using Mann Whitney Test and represented by median. A probability ('p' value) of less than or equal to 0.05 at 95% confidence interval was considered as statistically significant.

RESULTS

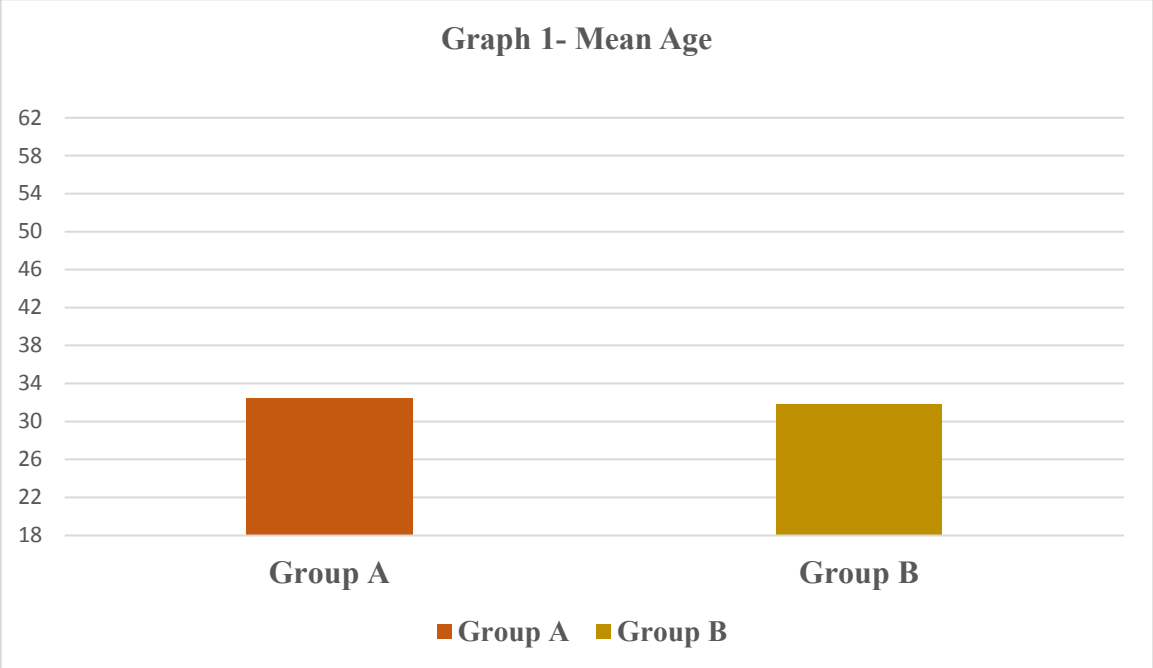
The present study was conducted to evaluate the efficacy of low dose intravenous Ketamine infusion in acute postoperative management in comparison with placebo in patients undergoing laparoscopic appendicectomy.

90 patients were enrolled for the study, keeping in mind the inclusion and the exclusion criteria. 45 patients in Group A receiving Ketamine infusion at 0.2 mg/kilogram/hour and 45 patients in Group B receiving normal saline infusion.

DEMOGRAPHIC DATA

Table 1: Mean Age

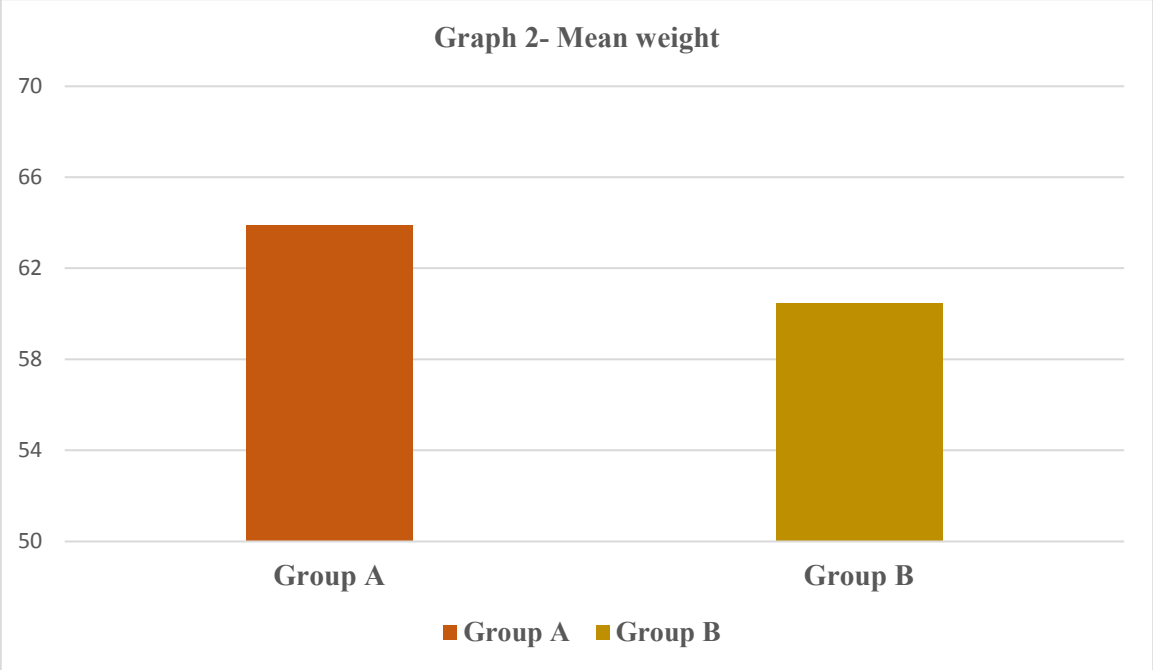
	Group 'A'		Group 'B'		p value
	Mean	Standard Deviation	Mean	Standard Deviation	
Age (years)	32.42	11.23	31.80	13.21	0.8103



In our analysis, there was no statistically significant difference in mean age between groups 'A' and 'B'. (32.42±11.23 years, 31.80±13.21 years respectively; p =0.8103). The p value was calculated using student's unpaired 't' test.

Table 2: Mean Weight

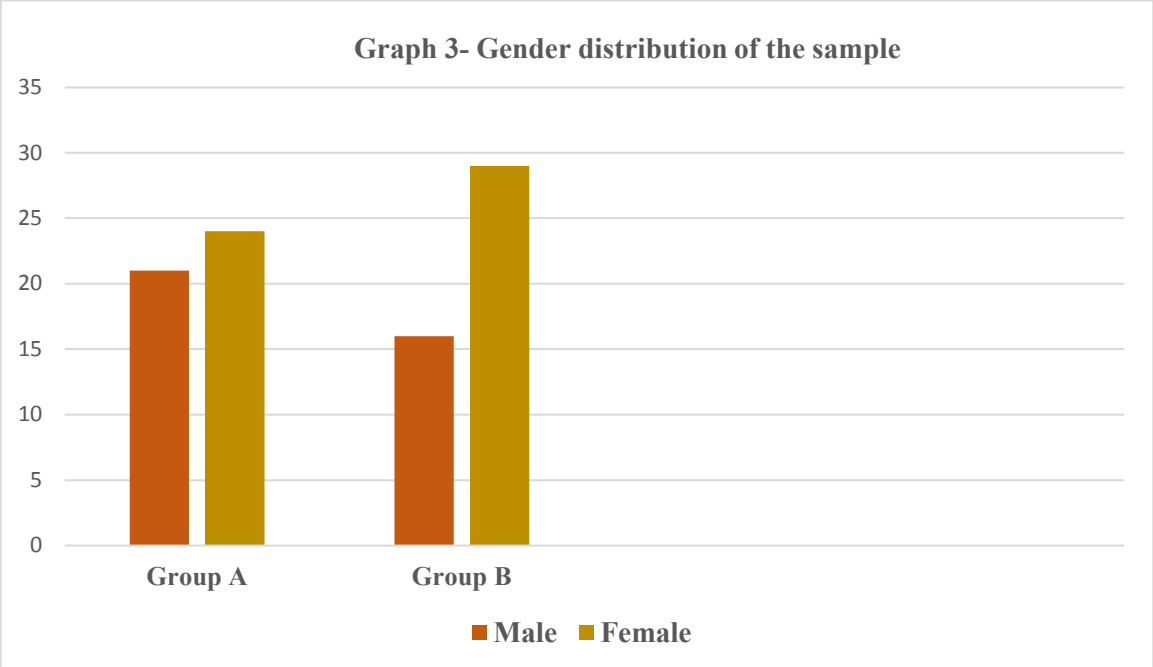
Group 'A'		Group 'B'		p value
Mean	S.D	Mean	S.D	
63.93	11.30	60.49	11.52	0.1557



In our analysis, there was no statistically significant difference in mean weight between groups 'A' and 'B'. (63.93±11.30 years, 60.49±11.52 years respectively; p =0.1557). The p value was calculated using student's unpaired 't' test.

Table 3: Gender distribution of the sample

	Group A		Group B		p value
	Number	Percent	Number	Percent	
Male	21	46.66	16	35.55	
Female	24	53.33	29	64.44	
Total	45	100	45	100	0.2841

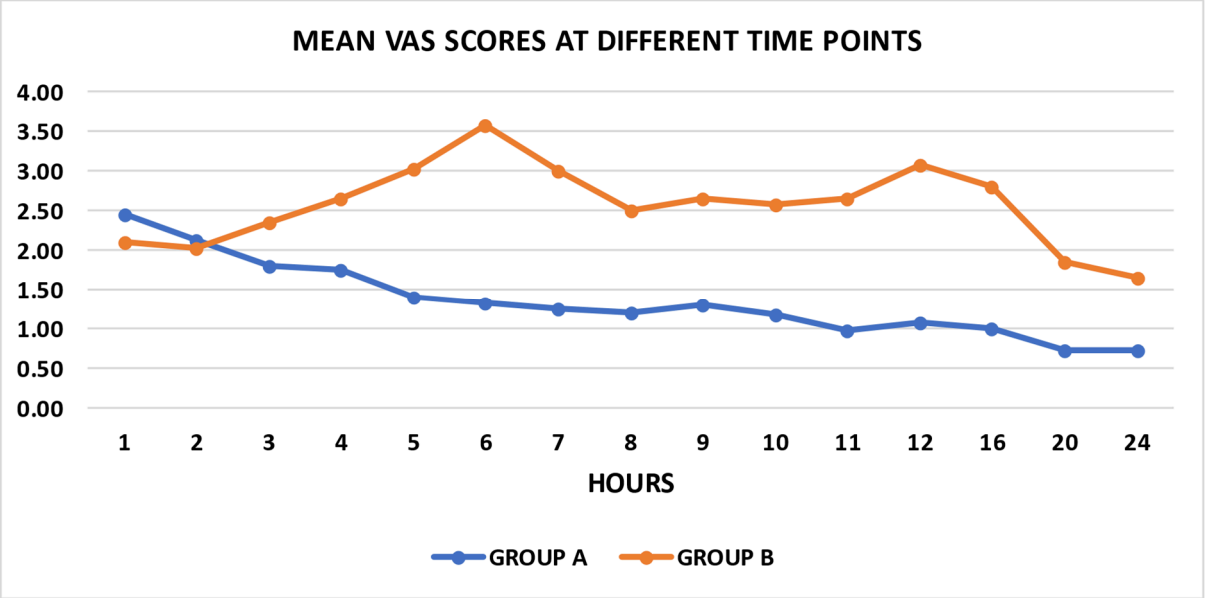


Of the total 45 patients in group A, 24 (53.33%) were female & 21 (46.66%) were male. Of the total 45 patients in group B, 29 (64.44%) were female & 16 (35.55%) were males. When compared the difference between the two groups was not found to be statistically significant (p =0.2841). Both the groups had similar demographic characteristics. The value of p was calculated using chi-square test.

Table 4: Comparison of mean VAS score

	Group A		Group B		
TIME	**MEAN**	**S.D.**	**MEAN**	**S.D.**	**p VALUE**
1st hour	2.44	0.99	2.11	0.65	0.0620
2nd hour	2.13	0.99	2.02	0.92	0.5822
3rd hour	1.80	0.99	2.36	1.25	0.0215
4th hour	1.76	1.07	2.64	1.11	0.0002
5th hour	1.40	0.96	3.02	1.24	<0.0001
6th hour	1.33	1.15	3.58	1.34	<0.0001
7th hour	1.24	0.98	3.00	1.24	<0.0001
8th hour	1.20	0.94	2.51	1.24	<0.0001
9th hour	1.31	1.10	2.64	1.23	<0.0001
10th hour	1.18	1.21	2.58	1.23	<0.0001
11th hour	0.98	0.89	2.64	1.13	<0.0001
12th hour	1.07	1.01	3.09	1.38	<0.0001
16th hour	1.00	1.33	2.80	1.50	<0.0001
20th hour	0.73	0.91	1.84	0.74	<0.0001
24th hour	0.73	0.96	1.67	0.64	<0.0001

Graph 4: Comparison of mean VAS score



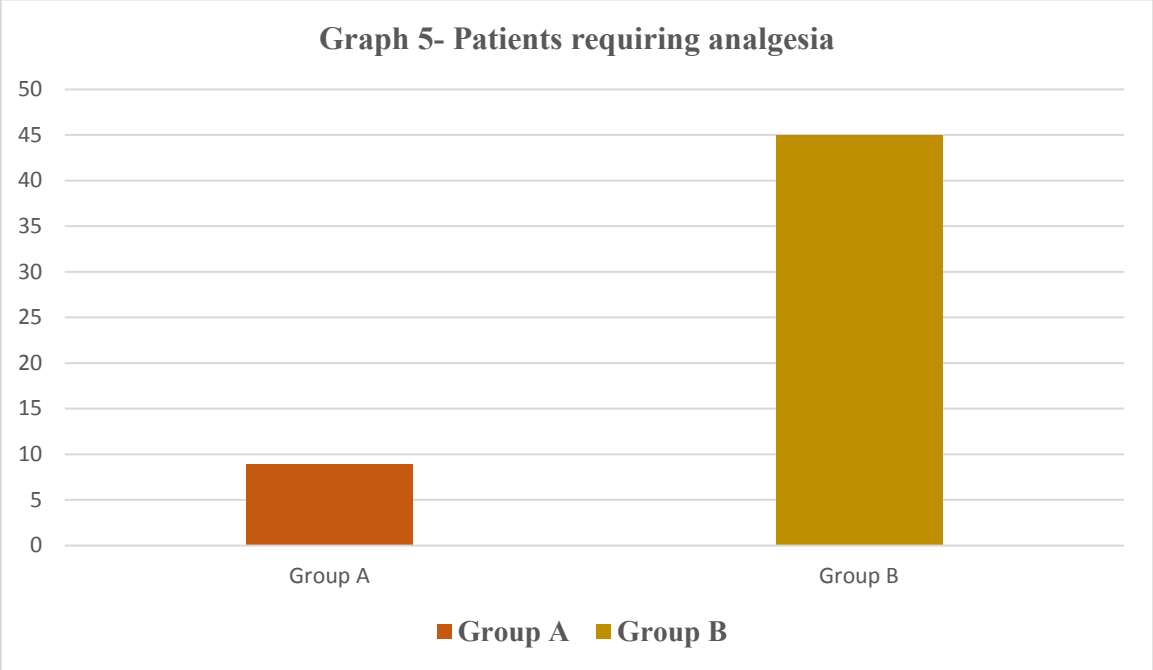
The p values for VAS score were calculated using student's unpaired t- test. In our study, we found that the mean VAS score at 1st hour post operatively was 2.44±0.99 in group A and 2.11±0.65 in group B and that the two groups were comparable (p=0.0620). The mean VAS score at 2nd hour post operatively was 2.13±0.99 in group A and 2.02±0.92 in group B and it was comparable between the two groups. (p=0.5822).

After 2 hours postoperatively, the VAS scores in Group B were at significantly higher levels when compared to Group A. At 3rd hour in the postoperative period, the mean VAS score was 1.80±0.99 in group A and 2.36±1.25 in group B and it was significant on statistical analysis (p=0.0215). At 4th hour post operatively the mean VAS score was 1.76±1.07 in group A and 2.64±1.11 in group B and it was highly significant (p=0.0002). Thereafter, the p value from 5th hour to 24th hour in the postoperative period between the two groups were highly significant (p= <0.0001).

The difference in mean VAS score between the two groups was statistically significant between the 4th- 24th hour of postoperative period.

Table 5: Total number of patients requiring rescue analgesia

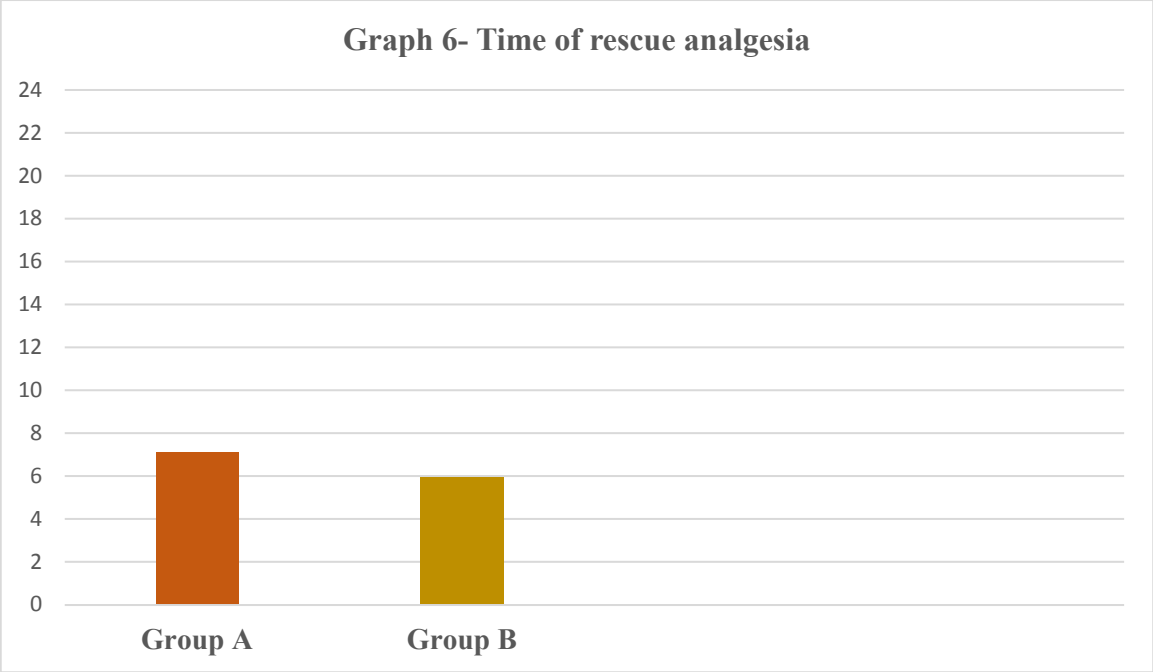
Rescue analgesia	Group A	Group B	p Value
Given	9	45	<0.0001
Not given	36	0	
Total	45	45	



In our study, 9 out of 45 patients in group A and all 45 patients in group B required rescue analgesia. The number of patients requiring rescue analgesia was higher in group B ($p<0.0001$) and was statistically highly significant. The p value was calculated using Chi-square test and it showed there is association between the groups and administration of analgesia.

Table 6: Time of rescue analgesia

	Group A		Group B		p value
Time in hours	MEAN	S.D	MEAN	S.D	0.2755
	7.11	6.19	5.96	1.66	



In Group A the mean time for rescue analgesic was 7.11±6.19 hours postoperatively and that in Group 2 was 5.96±1.66 hours. Though the time for initial analgesic request is prolonged in group 'A' the difference between the groups was not statistically significant (p = 0.2755).

Table 7: Total analgesic consumed in 24 hours

	Group A		Group B		p value
Total analgesic consumed	MEAN	S.D	MEAN	S.D	
(Paracetamol in mg)	1100	396.86	1593	477.87	0.0055

In group 'A' only 9 patients required analgesia and the mean dose of total analgesic consumed in the first 24 hours was 1100 ± 396.86 mg for these patients while in group 'B' all 45 of them required analgesic and the mean dose consumed was 1593±477.87 mg. This difference was statistically significant (p=0.0055)

DISCUSSION

Acute appendicitis is one of the most common emergencies in gastrointestinal surgery. When compared to open techniques, the surge of laparoscopic surgery results in decreased postoperative pain, quicker recovery and faster discharge from the hospital which benefits the patients in resuming their daily activities of life early.[1]

However, technique of laparoscopic surgery is not completely painless.[2-4] Pain in the postoperative period still remains a prevalent problem and may result in delayed discharge from the hospital. Pain intensity reaches a peak, usually, during the first few hours in the postoperative period and then gradually declines.[2]

The cause of pain after laparoscopic surgeries may result from factors like abdominal wall trauma due to incisions made for port insertion, irritation of phrenic nerve caused by pneumoperitoneum and residual carbon dioxide in the peritoneal cavity, intraabdominal trauma, microruptures of the parietal peritoneum as a result of abdominal distension, chemical peritoneal irritation, etc.[2]

Various techniques have been tried to achieve effective postoperative analgesia following laparoscopic surgery. These include administration of parenteral opioids, NSAID's, infiltration of port site with local anaesthetics, intraperitoneal instillation of local anaesthetics, techniques of regional anaesthesia like TAP block and rectus sheath block, complete evacuation of CO2 from abdominal cavity etc[2, 6-9]

Opioid analgesics are one among the commonly used drugs to treat pain post surgically, but they are accompanied by many side effects like respiratory depression, nausea, vomiting, sedation, tolerance etc which may prevent the rapid functional recovery.[28]

NSAIDs are associated with complications like gastric ulcers, gastrointestinal haemorrhages, anaphylaxis, decreased hemostasis, renal dysfunction, etc [22,28]

Infiltration of trocar site with local anaesthetics in patients following laparoscopic surgeries has been found to improve postoperative pain to only a limited extent.[29]

Peritoneal irrigation with local anaesthetics has not shown to have much advantageous effects in treatment of postoperative pain.[29]

Ketamine is a phencyclidine derivative which was first described in 1965 in literature and approved in 1970 by the FDA acting primarily on *N*-methyl-D-aspartate (NMDA) excitatory glutamate receptors which play a role in nociceptive transmission. Ketamine is a unique drug providing intense analgesia at subanaesthetic doses and evoking prompt induction of anaesthesia when administered intravenously at higher doses. The analgesic effects of ketamine are most likely due to its activity in the thalamic and limbic systems, which are responsible for the interpretation of painful signals.[22]

In recent times, ketamine has been brought into the limelight for its use at subanaesthetic doses in treating postoperative pain both as a solo medication and also as an adjunct to other analgesics, especially opioids.

In a study conducted by Al-Hassani et al in 2015, efficacy of preemptive Ketamine in patients undergoing appendicectomy was evaluated and the study concluded that Ketamine at the dose of 0.5 mg/kilogram given 10 minutes before surgical incision reduced pain intensity in the postoperative period upto 24 hours measured by VAS score. Hence, we conducted this study in patients undergoing appendicectomy believing that postoperative infusion would be efficacious in preventing pain.[19]

In an article published by Himmelseher in 2005, it was established that the efficacy of ketamine may not be evident when it is used in small doses like <0.15

mg/kilogram against the backdrop of multi-modal analgesia. In order to diminish sensitization of central and peripheral pain pathways, Ketamine must be supplied at least throughout the surgical procedure and for a period of time afterward, according to the dosing protocol. Studies were done to assess the effects of preemptive analgesic properties of Ketamine. However, inflammatory and nociceptive signals will be created throughout surgery and even afterwards. As a result, the author concluded that one single dose of short acting medication like ketamine, given before or after a surgical incision, will not offer enough pain relief that lasts long after surgery. Hence we used an infusion of Ketamine in our study.[20]

Ye et al in 2017 conducted a meta-analysis to assess the effectiveness of Ketamine for decreasing pain in patients undergoing laparoscopic cholecystectomy. Five studies were included out of which two studies administered Ketamine with a starting bolus dose of 0.3 mg/Kilogram IV with subsequent continuous infusion of 3μg/Kilogram/min. It concluded that intervention with Ketamine lead to considerable reduction of pain scores and consumption of narcotics upto 24 hours in the postoperative period in laparoscopic cholecystectomy. Hence, Ketamine infusion was found to be efficacious in treating pain following laparoscopic surgeries and we performed the study for laparoscopic surgeries.[21]

In a study published in 2013, Barreveld et al aimed to investigate the efficacy of a 0.2 mg/kilogram/hour ketamine infusion in combination with hydromorphone PCA in patients who were using opioids for longstanding pain and undergoing non-oncologic surgery. Although the ketamine group exhibited statistical significance in improving "average" pain scores, no considerable difference in patients' "least" and "worst" pain scores was observed. Using ketamine at a dose of 0.2 mg/kilogram/hour in the initial

postoperative phase had no negative side effects. As a result, we used Ketamine infusion at a rate of 0.2 mg/kilogram/hour in the postoperative period in our study.[13]

In a study by Urban M K et al. in 2008, 26 patients undergoing posterior lumbar spinal fusions who were narcotic dependant in the preoperative period itself were involved in the study to analyse the efficacy of Ketamine as an adjunct for treating postoperative pain. Ketamine at the dose of 0.2mg/kg during induction was given followed by 2μg/kg/hour infusion for next 24 hours along with IV hydromorphone PCA. Use of Ketamine led to lesser pain scores readings. So, we also used ketamine infusion for a period of 24 hours postoperatively. [18]

The present randomized clinical study was conducted on 90 ASA grade 1 and 2 patients aged between 18 to 60 years of either gender who were divided into 2 groups by computer generated randomization table.

Group A received ketamine infusion in the dose of 0.2 mg/kilogram/hour for 24 hours and Group B received normal saline infusion at 3ml/hour in patients undergoing laparoscopic appendicectomy under general anaesthesia at KLE'S Dr. Prabhakar Kore Hospital and Medical Research Centre and Charitable hospital, Nehru Nagar, Belagavi.. Pain scores were assessed using VAS scale at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 16, 20 and 24 hours in the postoperative period. When VAS score at any time was found to be greater than 3, rescue analgesia in the form of IV Paracetamol at the dose of 15 mg/kg was given.

In our study we found no statistically significant difference between group A and group B with regards to mean age (32.42 ± 11.23 and 31.80 ± 13.21 years respectively; p value = 0.8103) and mean weight (63.93 ± 11.30 and 60.49 ± 11.52 kgs respectively; p value = 0.1557).

Of the total 45 patients in group A, 24 (53.33%) were female & 21 (46.66%) were male. Of the total 45 patients in group B, 29 (64.44%) were female & 16 (35.55%) were males. When compared the difference between the two groups was not found to be statistically significant (p =0.2841).

In group A 84.44% patients were ASA grade I and 15.55% were ASA grade II. In group B 88.88% patients were ASA grade I while 11.11% were ASA grade II. The data was comparable in both groups (p =0.5351). Therefore, both the groups had similar demographic characteristics.

In the present study we found that the mean VAS score at 1st hour post operatively was 2.44 $\pm$ 0.99 in group A and 2.11 $\pm$ 0.65 in group B and was comparable in both the groups (p=0.0620). The mean VAS score at 2nd hour post operatively was 2.13 $\pm$ 0.99 in group A and 2.02 $\pm$ 0.92 in group B. Though group A recorded higher mean VAS score compared to group B it was statistically insignificant (p=0.5822). At 3rd hour post operatively the mean VAS score was 1.80$\pm$ 0.99 in group A and 2.36 $\pm$ 1.25 in group B. and the difference was found to be statistically significant (p=0.0215). At 4th hour post operatively the mean VAS score was 1.76 ± 1.07 in group A and increased to 2.64 $\pm$ 1.11 in group B and was statistically highly significant (p=0.0002). Further at 5th hour post operatively the mean VAS scores were reduced to 1.40 $\pm$ 0.96 in group A and increased to 3.02 $\pm$ 1.20 in group B and was highly significant (p<0.0001). The mean VAS score at 6th hour post operatively was 1.33 $\pm$ 1.15 in group A but further increased to 3.58 $\pm$ 1.34 in group B and was statistically highly significant (p<0.0001).

At 7th hour post operatively the mean VAS score was 1.24 $\pm$ 0.98 in group A and 3.00 $\pm$ 1.24 in group B and was highly significant (p<0.0001). At 8th hour post operatively the mean VAS score was 1.20 $\pm$ 0.94 in group A and 2.51 $\pm$ 1.24 in group B and was

statistically highly significant ($p<0.0001$). The mean VAS score at 9th hour post operatively was 1.31 $\pm$ 1.10 in group A and 2.64 $\pm$ 1.23 in group B and was highly significant ($p<0.0001$). At 10th hour post operatively the mean VAS score further decreased to 1.18 $\pm$ 1.21 in group A and 2.58 $\pm$ 1.23 in group B and was again statistically highly significant ($p<0.001$). The mean VAS score at 11th hour post operatively decreased to 0.98 $\pm$ 0.89 in group A and was 2.64 $\pm$ 1.13 in group B and was highly significant ($p<0.0001$). At 12th hour postoperatively the mean VAS was 1.07 ± 1.01 in group A and 3.09 ± 1.38 in group B and was highly significant ($p<0.0001$). The mean VAS score at 16th hour was 1.00 ± 1.33 in group A and 2.80 ± 1.50 in group B and was highly significant ($p<0.0001$).

The mean VAS score at 20th hour was 0.73 ± 0.91 in group A and 1.84 ± 0.74 in group B which was statistically highly significant ($p<0.0001$). The mean VAS score at 24th hour postoperatively was 0.73 ± 0.96 in group A and 1.67 ± 0.64 in group B. This was found to be statistically highly significant ($p<0.0001$).

The p value was found to be statistically highly significant from the 4th hour in the postoperative period on comparison of the mean VAS scores between both the groups. Hence, Ketamine was found to be highly effective for reducing postoperative pain following laparoscopic appendicectomy.

In group ‘A’ out of 45 patients only 9 required rescue analgesia and the total analgesic consumed in the first 24 hours was 1100 ± 396.86 mg while in group ‘B’ all 45 patients required rescue analgesia and the total analgesic consumed was 1593±477.87 mg ($p=0.0055$) showing that the required analgesic dose was much less when Ketamine infusion is administered which was statistically significant.

Also, in Group A the mean time for rescue analgesic was 7.11±6.19 hours postoperatively and that in Group 2 was 5.96±1.66 hours. Though the time taken to the need for requirement of initial analgesic dose was increased in group A, it was not statistically significant ($p = 0.2755$).

On comparison of mean VAS score within each group, group A recorded a gradual decrease in the values from 1st to 24th hour. This explains the cumulative effect of ketamine when administered for a prolonged duration.

In group B, the mean VAS score was found to be less than 3 for the first 4 hours in the postoperative period. This maybe due to the residual analgesic effect of opioid administered during induction and one dose of IV paracetamol given after anaesthetic induction. The requirement of rescue analgesia in group B was more commonly during the 5th, 6th, 7th hours in the postoperative period, followed by 12th hour postoperatively indicated by the increase in mean VAS score to more than 3 during this period.

In a meta-analyses by Laskowski et al. in 2011, randomized, double-blinded clinical trials published from the year 1966 to 2010 which used either intravenous bolus or ketamine infusion to treat postoperative pain were included. A total of seventy studies including 4,701 patients with 2652 in Ketamine group and 2049 in placebo group were analysed. This research observed an increase in the time to requirement of rescue analgesic and overall reduction in opioid consumption when using Ketamine, with greatest efficacy observed in upper abdominal, thoracic and major orthopedic surgical subgroups. Though side effects like hallucinations and nightmares were seen in the Ketamine group, postoperative nausea and vomiting were observed less frequently. Similar results were observed in our study as well which was observed an overall reduction in the amount of rescue analgesic administered. However, no side effects were seen in our study.[10]

In a review article published by Radvansky BM et al in 2015, various side effects of the drug when used chronically has been enumerated. Common adverse effects of the drug listed were nausea, psychotomimetic effects like feelings of intoxication, increased confusion, lowered inhibition, disturbances in perception and headaches. Long-term use may lead to impairments in cognition, memory, and mood. Hepatotoxicity has been recorded with anaesthetic dosages and Ketamine infusions at low doses. In cases of chronic abuse, Ketamine induced uropathy has also been described.[5]

However, in our study we administered the infusion only for a period of 24 hours and also at a low dose of 0.2 mg/Kilogram/hour, hence, no adverse effects of the drug were observed.

Our study has certain limitations. In our study we have observed the VAS score for rest. However, the VAS score at movement have not been taken into account.

The future scope would be to study the effectiveness of IV low dose Ketamine infusion on other extensive laparoscopic surgeries like laparoscopic cholecystectomy for its analgesic action.

Our study demonstrates that low dose intravenous Ketamine infusion at the dose of 0.2 mg/Kilogram/hour is efficacious in treating acute postoperative pain following laparoscopic appendicectomy under general anaesthesia.

CONCLUSION

It is concluded from our study that use of low dose Ketamine intravenous infusion at 0.2 mg/Kilogram/hour is effective for the management of acute postoperative pain following elective laparoscopic appendicectomy surgeries. It is not associated with any adverse effects at this dose administered. Also, there was a reduction in the requirement of adjuvant analgesics when Ketamine was administered.

SUMMARY

The present study was conducted in the Department of Anaesthesiology, KLES Dr. Prabhakar Kore Hospital and MRC, Nehru Nagar, Belagavi after obtaining an approval from institutional ethics committee and written informed consent.

The study was conducted on 90 ASA grade I and II patients aged between 18 to 60 years belonging to either gender, undergoing elective laparoscopic appendicectomy under general anaesthesia. Thorough pre-anaesthetic evaluation was done. Computer generated randomization table was used to allocate the patients into 2 groups, Group A which received intravenous Ketamine infusion at 0.2 mg/Kilogram/hour and Group B which received normal saline infusion at 3 ml/hour. After induction of general anaesthesia, patients in both the groups received one dose of IV Paracetamol at 15mg/kilogram. Laparoscopic appendicectomy was done according to standard protocol.

After extubation, patients were shifted to recovery and patients in group A were started with Ketamine infusion at the dose of 0.2mg/Kilogram/hour and continued for 24 hours. Group B patients were started with Normal Saline infusion at 3 ml/hour. VAS pain scores were assessed for postoperative pain, at hourly intervals for the first 1-12 hours, 4^{th} hourly for the next 12 hours postoperatively. Patients with VAS 3 or more were given rescue analgesia in the form of Paracetamol 15mg/kilogram IV. Total amount of analgesic consumed in 24 hours also was noted in both the groups. Side effects, if any, were also noted.

The mean VAS scores were less than 3 at all time intervals in Group A while in group B the mean VAS score was at a comparatively higher level than group A at all time intervals and it was more than 3 during the 5^{th}, 6^{th}, 7^{th} and 12^{th} hour in the initial postoperative period. Nine patients in group A required rescue analgesia and all 45 patients required treatment with rescue analgesia in group B in the first 24 hours and the total analgesic consumed in the first 24 hours was 1100 ±

396.86 mg in group A and in group B the total analgesic consumed was 1593±477.87 mg which was statistically significant (p=0.0055). No side effects of the drug were noted in our study.

Thus, based on the results we conclude that use of low dose Ketamine intravenous infusion at 0.2 mg/Kilogram/hour is efficacious for the management of acute postoperative pain following elective laparoscopic appendicectomy surgeries with the reduction in the total requirement of rescue analgesic doses.

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Ethical Clearance

K.L.E. ACADEMY OF HIGHER EDUCATION AND RESEARCH
(Deemed – to- be- University)
Accredited 'A' Grade by NAAC (2nd Cycle) Placed in Category 'A' by MHRD (GoI)
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Ref: MDC/DOME/ **Date: 24/12/2019**

To,

BA0119011
PG student in Anaesthesiology,
J.N.Medical College,
BELAGAVI.

Sub: Institutional Ethical Clearance for the study.

With reference to the above, we wish to inform you that your proposed research project titled **"COMPARISON OF LOW DOSE INTRAVENOUS KETAMINE INFUSION VERSUS PLACEBO FOR POSTOPERATIVE ANALGESIA FOLLOWING LAPAROSCOPIC APPENDICECTOMY UNDER GENERAL ANAESTHESIA : ONE YEAR HOSPITAL BASED DOUBLE BLIND RAMNDOMISED CLINICAL TRIAL",** is ethical and justifiable.

The proposed research project has been cleared by the JNMC Institutional Ethics Committee on Human Subjects Research.

(Dr. Anita Dalal)
Member Secretary
JNMC Institutional Ethics Committee
on Human Subjects Research,
J.N.Medical College, Belagavi.

(Dr. Roopa M Bellad)
Chairman,
JNMC Institutional Ethics Committee
on Human Subjects Research,
J.N.Medical College, Belagavi.

ANNEXURE II- INFORMED CONSENT FOR PARTICIPATION IN RESEARCH STUDY

Mr./Miss./Mrs. _____ we are requesting you to enroll yourself in **"COMPARISON OF LOW DOSE INTRAVENOUS KETAMINE INFUSION VERSUS PLACEBO FOR POSTOPERATIVE ANALGESIA FOLLOWING LAPAROSCOPIC APPENDICECTOMY UNDER GENERAL ANAESTHESIA: ONE YEAR HOSPITAL BASED DOUBLE BLIND RANDOMISED CLINICAL TRIAL".** conducted by, Post Graduate in M.D. Anesthesiology J.N. Medical College, Belagavi under KLE university, Belagavi.

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.

Purpose of the study:

The purpose of research is to compare the effect of Ketamine on postoperative pain following laparoscopic appendicectomy surgery under general anaesthesia.

Procedure Involved:

If you agree to enroll in my study, I will ask you your present and past medical history. You will be clinically examined in detail and routine investigations like CBC, Urine routine examination, Chest X ray will be done accordingly. You will be allotted into one of the two groups randomly using computer generated software. One group will receive Ketamine and another group will receive placebo.

Benefits and Risks:

Ketamine provides better pain relief postoperatively. It is also a good bronchodilator. Although it is known to have psychomimetic effects they are not observed at the very low dose which is being used in the study.

Voluntary Participation/Withdrawal:

Taking part in the study is voluntary. You may choose not to enroll 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 your identity remaining 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 KLES' Hospital & MRC, Belagavi. There is no compensation or payment for such medical treatment by law.

Queries/ Contact details

In case you have any questions related to the study, in future or in case of study related injury or illness, you can contact Post Graduate student, Department of Anesthesiology, JNM College, KLES Hospital and MRC, Belagavi Dept.

If you have any queries about your rights as a study subject, Professor and head, Department of Pediatrics and Chairman, J.N. Medical College Institutional Ethical Committee for Human Subjects Research, J.N. Medical College, Belagavi.

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 form in my own 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: _____

Place : _____

Witness Name : _____ Signature: _____

Investigators Name: _____ Signature: _____

Date:

Place : _____

ANNEXURE III- PROFORMA

"COMPARISON OF LOW DOSE INTRAVENOUS KETAMINE INFUSION VERSUS PLACEBO FOR POSTOPERATIVE ANALGESIA FOLLOWING LAPAROSCOPIC APPENDICECTOMY UNDER GENERAL ANAESTHESIA: ONE YEAR HOSPITAL BASED DOUBLE BLIND RANDOMISED CLINICAL TRIAL "

Name & Address of the patient:

_____

Age of the Patient: _____ IP. No. _____

Weight of Patient: _____ Sex. _____

Height of patient: _____

Anaesthesiologist: _____ Surgeon: _____

PREANAESTHETIC EVALUATION:

Chief Complaints:

Past History:

- History of Diabetes Mellitus/Hypertension/Asthma/Tuberculosis
- Drug Therapy:
- Previous Anaesthetic procedure/Previous surgeries:
- History of renal disease, hepatic disease and neurological diseases.

General Physical Examination:

Weight: Temperature: Pallor: Height:

Cyanosis: Pedal edema: Clubbing:

Pulse : B.P: RR:

Airway Assessment:

Mouth Opening: Teeth:

Jaw Movements: MP Grading:

Investigations:

CBC: Urine Routine: Chest Xray:

RBS: ECG: (if patient is more than 40 years)

ASA Status: Grade 1 / 2

Diagnosis:

OBSERVATIONS:

Readings will be recorded in the following manner:

Time	VAS score	
	Group A	Group B
1st hour		
2nd hour		
3rd hour		
4th hour		
5th hour		
6th hour		
7th hour		
8th hour		
9th hour		
10th hour		
11th hour		
12th hour		
16th hour		
20th hour		
24th hour		

Total analgesic consumed	Group A	Group B

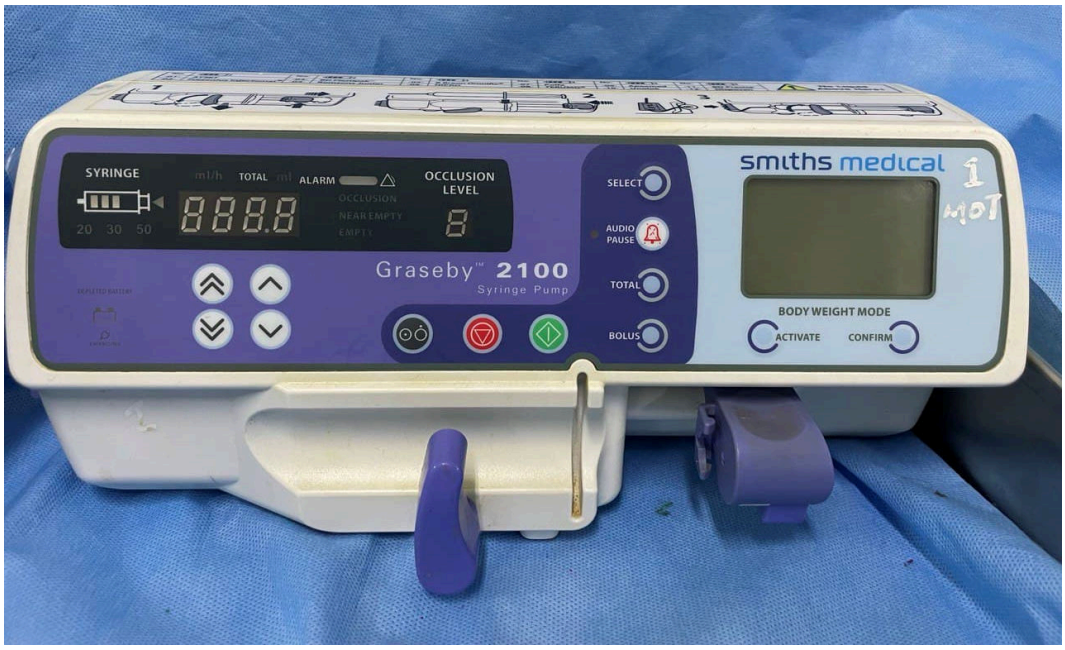
Time of administration of Paracetamol	Group A	Group B

Side Effects/ complications (if any) –

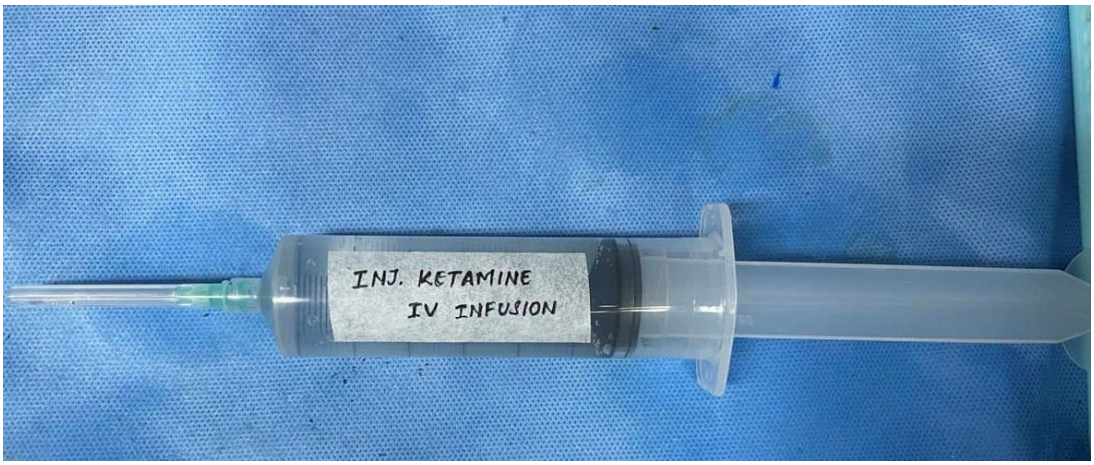
Signature of staff in charge:

ANNEXURE IV- PHOTOGRAPHS

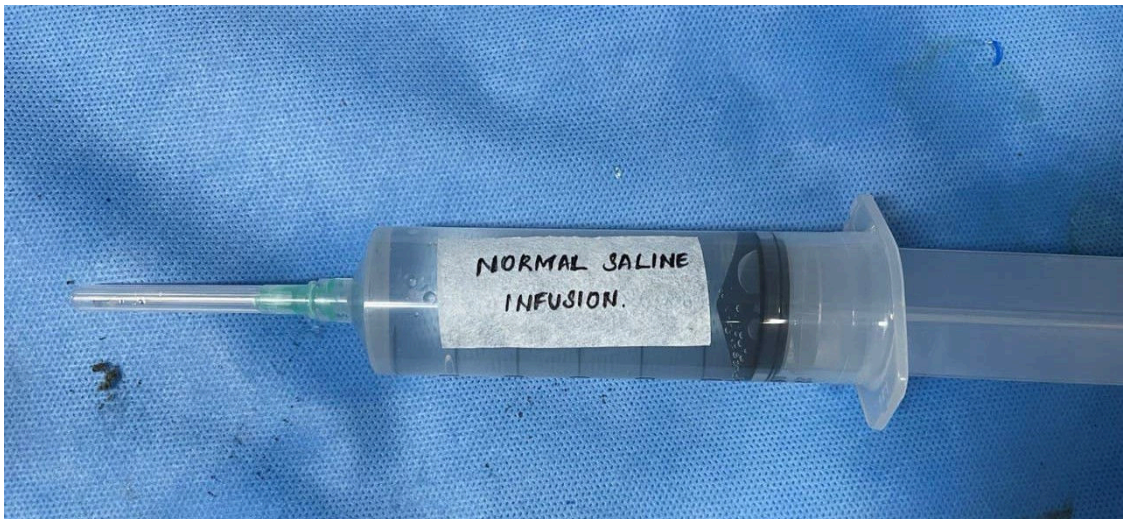
Photograph 1 – Ketamine



Photograph 2 – Infusion pump



Photograph 3- Ketamine infusion



Photograph 4- Normal saline infusion

ANNEXURE V – KEY TO MASTER CHART

ASA	-	American Society of Anaesthesiologist
bpm	-	Beats per minute
BPM	-	Breaths per minute
Kgs	-	Kilograms
VAS	-	Visual analogue scale
Hrs	-	Hours
Yrs	-	Years
mg	-	milligram
Group 1	-	Ketamine
Group 2	-	Normal saline

ANNEXURE VI –MASTER CHART

Serial number	Randomisation Number	In patient number	Age (Yrs)	Sex	ASA Grade	Baseline																						
						Weight(kgs)	HR (bpm)	SBP (mm Hg)	DBP (mm Hg)	Respiratory rate(BPM)	1st hour	2nd hour	3rd hour	4th hour	5th hour	6th hour	7th hour	8th hour	9th hour	10th hour	11th hour	12th hour	16th hour	20th hour	24th hour	Time for first rescue analgesia in hrs	Total analgesic consumed in 24 hrs in mg
1	1	996994	28	Female	1	45	80	100	60	12	2	2	2	2	2	2	2	2	2	2	2	6	2	2	16	900
2	1	996755	24	Female	1	43	80	110	70	14	2	1	1	2	1	1	1	1	1	1	1	1	1	1	NA	0
3	1	997431	28	Female	1	63	76	110	70	12	2	2	1	0	0	0	0	0	0	0	0	0	0	0	NA	0
4	1	997400	36	Male	1	73	94	120	90	13	2	1	1	1	0	0	0	0	0	0	1	1	0	0	NA	0
5	1	998361	22	Female	1	42	86	110	80	14	2	2	2	2	2	2	2	1	2	1	1	1	1	1	NA	0
6	1	998594	20	Male	1	42	76	120	70	14	2	2	2	2	2	2	2	2	2	5	2	2	2	2	10	900
7	1	1000774	50	Female	1	63	82	120	76	14	2	2	2	5	2	2	2	2	2	2	2	2	2	2	4	900
8	1	1001526	23	Male	1	63	86	110	80	14	2	2	1	1	2	1	1	2	2	1	1	1	1	1	NA	0
9	1	1002551	30	Male	1	82	96	130	90	16	2	2	2	2	2	1	1	2	2	2	2	2	1	1	NA	0
10	1	1002766	57	Female	1	72	70	130	80	14	2	2	2	2	1	1	1	1	1	1	1	1	1	1	NA	0
11	1	1006075	35	Female	1	68	104	130	90	14	2	2	1	1	1	0	0	0	0	0	0	0	0	0	NA	0
12	1	1005009	24	Male	1	72	92	110	70	14	2	2	2	2	1	1	1	1	2	0	2	2	1	1	0	NA	0
13	1	1006420	44	Male	2	71	82	130	100	12	2	1	2	2	1	1	1	1	1	1	1	1	1	1	0	NA	0
14	1	1005559	28	Female	1	59	84	110	80	12	2	2	2	1	1	1	2	2	1	1	1	1	1	1	1	NA	0
15	1	1013112	22	Male	1	58	84	140	80	14	2	2	1	1	1	1	2	1	2	2	2	2	1	2	2	NA	0
16	1	1015981	31	Male	1	72	80	140	90	14	2	2	1	2	2	2	2	1	1	1	1	1	1	1	1	NA	0
17	1	1017462	39	Female	2	62	82	160	100	14	2	2	5	2	2	1	1	1	1	1	1	1	1	1	1	3	900
18	1	1017928	50	Male	2	70	80	130	80	14	2	2	1	1	1	1	1	2	1	1	1	1	1	1	1	NA	0
19	1	1018533	18	Female	1	50	89	100	70	14	5	6	2	2	2	2	2	2	2	5	2	2	2	1	2	1	1800
20	1	1020515	45	Male	2	82	105	140	80	16	2	2	1	1	0	0	0	0	0	0	0	0	0	0	0	NA	0
21	1	1021296	25	Male	1	62	82	110	70	14	6	2	2	2	2	2	2	2	5	2	2	2	2	2	2	1	1800
22	1	102330	300	Female	1	58	104	130	80	14	2	2	2	2	2	6	2	2	2	2	2	2	2	1	2	6	900
23	1	1023940	25	Female	1	48	78	130	80	14	2	2	2	1	1	1	1	2	1	2	2	1	1	0	0	NA	0
24	1	1028488	34	Female	1	76	88	130	70	14	2	2	1	1	0	0	0	1	1	1	1	1	1	0	0	NA	0
25	1	1028613	22	Female	1	55	103	110	70	14	2	2	2	1	1	1	1	1	2	2	2	2	1	1	1	NA	0
26	1	1029834	27	Male	1	73	90	130	80	16	2	2	2	2	1	1	1	1	2	1	1	1	1	0	0	NA	0
27	1	1030346	26	Male	1	73	90	110	80	12	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	NA	0
28	1	1031136	21	Female	1	65	80	110	70	12	1	0	0	0	1	1	0	0	0	0	0	0	0	0	0	NA	0
29	1	1031285	53	Male	1	75	84	140	90	12	2	2	2	2	1	1	1	1	1	1	1	1	1	1	1	NA	0
30	1	1031778	32	Female	1	45	80	100	60	14	2	2	2	2	2	2	2	2	2	2	2	6	2	2	18	900
31	1	1032099	31	Male	1	72	94	130	80	12	2	2	1	1	1	1	1	1	1	1	1	1	0	0	0	NA	0
32	1	1032927	37	Female	1	63	80	110	70	14	2	2	2	2	1	1	1	1	1	1	1	0	0	0	0	NA	0
33	1	1033202	26	Male	1	69	60	120	90	12	0	0	0	1	1	1	1	2	1	1	0	0	0	0	0	NA	0
34	1	1033556	41	Male	2	82	86	140	80	14	2	2	2	3	2	2	2	1	1	0	0	0	0	0	0	NA	0
35	1	1033656	31	Male	2	75	90	140	90	12	2	2	2	2	1	2	1	1	2	1	1	0	0	0	0	NA	0
36	1	1033914	24	Female	1	67	92	130	90	14	2	2	2	5	2	2	2	2	1	1	2	1	1	1	1	4	900
37	1	1035039	22	Male	1	68	87	120	80	14	2	2	1	1	1	1	1	0	1	1	0	0	0	0	0	NA	0
38	1	1035551	31	Male	1	78	84	130	80	12	2	2	1	1	1	0	0	0	1	0	0	0	0	0	0	NA	0
39	1	1035308	21	Female	1	53	90	100	70	16	2	1	1	1	1	1	1	1	1	1	0	1	0	0	0	NA	0
40	1	1035899	62	Female	1	73	84	110	80	14	2	2	2	2	1	1	1	2	1	1	1	1	1	1	1	NA	0
41	1	1036239	32	Female	1	60	86	110	70	14	2	2	1	1	1	0	0	0	0	0	0	0	0	0	0	NA	0
42	1	1035875	52	Female	2	68	78	150	90	12	2	2	2	2	1	2	2	1	1	1	0	0	0	0	0	NA	0
43	1	1036165	51	Female	1	66	78	120	70	13	1	1	2	2	1	1	1	0	0	0	0	0	1	0	0	NA	0
44	1	1036777	30	Female	1	55	84	110	80	14	2	2	2	2	1	1	0	1	0	0	0	1	0	0	0	NA	0
45	1	1037350	19	Male	1	46	70	110	70	16	2	2	1	1	1	1	1	0	0	0	0	1	0	0	0	NA	0

Serial number	Randomisation Number	In patient number	Age (Yrs)	Sex	ASA Grade	Baseline																				Time for first rescu	Total analg esic consu
						Weight(kgs)	HR (bpm)	SBP (mm Hg)	DBP (mm Hg)	Respiratory rate(BPM)	1 st hour	2 nd hour	3 rd hour	4 th hour	5 th hour	6 th hour	7 th hour	8 th hour	9 th hour	10 th hour	11 th hour	12th hour	16th hour	20th hour	24th hour		
1	2	992949	23	Female	1	48	96	120	70	12	2	3	3	2	2	2	2	2	2	2	2	4	2	2	2	1800
2	2	993506	22	Female	1	50	78	110	80	14	2	2	2	2	2	4	2	2	2	2	2	5	2	2	6	1800
3	2	995458	42	Female	1	58	68	130	80	14	2	2	2	2	5	2	2	2	2	2	5	2	1	2	5	1800
4	2	997373	18	Female	1	45	86	100	70	16	2	2	3	3	3	3	3	5	3	2	2	2	2	2	8	900
5	2	996367	18	Female	1	43	90	110	70	14	2	2	2	2	2	6	2	2	2	2	2	5	2	1	6	1800
6	2	999374	22	Male	1	60	84	110	70	12	2	2	2	5	2	2	2	2	2	6	2	2	5	2	4	2400
7	2	999932	27	Male	1	75	80	120	80	14	2	2	2	2	2	5	2	2	2	2	2	5	2	2	6	1800
8	2	1002044	20	Female	1	53	76	110	80	14	2	2	2	2	2	2	5	2	2	2	2	3	5	2	7	1800
9	2	1002732	18	Female	1	48	96	110	80	16	1	1	0	0	0	5	0	0	5	1	2	2	1	5	6	2400
10	2	1022664	35	Female	1	65	86	130	80	14	2	2	2	2	2	5	2	2	2	2	5	2	2	1	6	1800
11	2	1024261	29	Female	1	54	80	130	80	14	2	2	5	2	2	2	2	2	6	2	2	2	2	2	3	1800
12	2	1025607	28	Female	1	62	86	110	74	14	2	2	2	2	2	2	5	2	2	1	1	2	2	1	7	900
13	2	1025953	44	Female	1	68	83	106	66	12	2	2	2	2	5	2	2	1	1	2	2	5	2	1	8	1800
14	2	1026500	42	Male	2	82	73	140	90	14	1	1	2	2	2	5	2	1	1	2	2	2	2	1	6	900
15	2	1029926	39	Male	1	82	90	110	70	14	2	6	2	2	2	2	2	5	2	2	2	2	2	2	2	1800
16	2	1033417	44	Male	2	76	84	130	80	14	2	2	1	1	2	2	5	2	2	2	2	2	5	2	1	7	1800
17	2	1034292	28	Female	1	53	86	130	80	14	2	2	2	2	2	5	2	2	2	2	2	5	2	2	2	6	1800
18	2	1034336	25	Female	1	46	68	100	70	14	2	1	1	2	2	5	2	2	2	1	1	1	1	1	1	6	900
19	2	1033971	25	Female	1	68	84	130	80	14	1	1	1	2	2	2	2	5	2	2	2	2	2	1	1	8	900
20	2	1036591	19	Male	1	53	78	130	80	14	2	2	5	2	2	2	2	1	2	5	2	2	1	1	1	3	1800
21	2	1037184	72	Male	1	65	63	160	90	14	2	1	1	2	5	2	2	1	1	1	1	5	2	2	1	5	1800
22	2	1037800	49	Female	2	68	80	110	70	15	2	2	1	1	1	1	2	5	2	2	2	2	2	2	2	8	900
23	2	1037802	68	Male	1	60	75	130	90	12	2	2	1	1	1	2	2	5	1	2	2	2	5	2	2	8	1800
24	2	1037949	20	Male	1	70	90	110	80	14	2	2	2	2	5	2	1	2	2	1	2	5	1	1	1	5	1800
25	2	1038596	20	Male	1	75	78	110	80	14	1	1	1	2	2	2	5	1	1	2	1	1	2	1	1	7	900
26	2	1039366	32	Female	1	60	83	110	70	12	2	2	2	1	1	2	2	2	5	2	2	2	1	2	1	9	900
27	2	1039545	19	Male	1	58	80	130	80	14	2	2	2	2	5	2	2	2	2	2	2	5	2	2	2	5	2400
28	2	1039407	28	Female	1	64	82	120	70	12	2	1	1	2	2	2	5	2	2	2	2	6	2	2	1	5	1800
29	2	1039696	52	Female	1	41	86	160	100	14	2	2	2	2	2	5	2	2	2	1	1	1	5	2	2	6	1800
30	2	1040060	18	Female	1	46	84	100	60	14	2	2	1	1	2	3	5	1	2	1	2	2	2	1	1	7	900
31	2	1040230	18	Male	1	57	91	120	80	14	2	2	1	1	2	2	5	2	2	2	2	2	5	2	2	7	1800
32	2	1040392	24	Female	1	43	78	110	60	13	2	1	2	2	2	5	2	2	2	2	2	6	2	2	2	6	1800
33	2	1039801	30	Female	1	53	79	130	90	12	2	2	2	2	2	5	2	1	2	2	2	2	2	2	2	6	900
34	2	1040706	34	Female	1	62	62	110	70	12	2	2	2	5	3	2	2	2	6	2	2	2	2	2	2	4	1800
35	2	1041862	32	Female	1	55	88	130	80	12	1	1	2	2	2	2	5	2	1	2	2	2	5	2	1	7	1800
36	2	1041934	35	Female	1	45	80	110	80	13	2	1	1	1	2	5	2	2	2	1	1	2	5	2	2	6	1800
37	2	1042081	20	Male	1	68	84	140	80	12	2	2	2	2	2	2	2	2	2	5	2	2	2	2	2	10	900
38	2	1043666	49	Female	2	71	58	140	80	16	2	2	2	2	5	2	2	2	2	5	2	2	2	2	2	5	1800
39	2	1046928	25	Female	1	68	96	140	90	14	2	2	2	2	2	5	2	2	2	2	2	2	2	1	1	6	900
40	2	1046220	43	Female	1	53	84	130	90	12	2	2	2	5	2	2	2	2	5	2	1	2	1	1	1	4	1800
41	2	1043185	41	Male	1	75	69	140	90	12	2	2	2	2	2	6	2	2	2	2	5	2	6	2	2	6	2400
42	2	1044158	51	Female	2	69	82	110	70	13	2	2	2	2	2	2	5	3	2	2	2	2	5	2	1	7	1800
43	2	1044269	18	Male	1	54	76	130	80	12	2	2	2	2	5	2	2	2	2	2	2	5	2	2	2	5	1800
44	2	1044736	30	Female	1	67	86	108	69	14	1	1	2	2	2	5	2	2	2	2	2	2	2	2	2	6	900
45	2	1046225	35	Male	1	86	75	120	76	12	2	1	2	2	2	5	2	2	2	5	2	2	2	2	2	6	1800