“TO EVALUATE THE ANALGESIC EFFICACY OF INTRAPERITONEAL TRAMADOL VS PLACEBO FOR POST OPERATIVE PAIN RELIEF FOLLOWING LAPAROSCOPIC CHOLECYSTECTOMY, A DOUBLE BLIND RANDOMIZED CONTROL TRIAL, HOSPITAL BASED STUDY”

REG NO. BH0112009

Dissertation

Submitted to the
KLE University, Belgaum, Karnataka

In Partial Fulfillment
of the requirements for the degree of

MASTER OF SURGERY (M.S.)
in
GENERAL SURGERY

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

APRIL - 2015

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ENDORSEMENT

This is to certify that the dissertation entitled **"TO EVALUATE THE ANALGESIC EFFICACY OF INTRAPERITONEAL TRAMADOL VS PLACEBO FOR POST OPERATIVE PAIN RELIEF FOLLOWING LAPAROSCOPIC CHOLECYSTECTOMY, A DOUBLE BLIND RANDOMIZED CONTROL TRIAL, HOSPITAL BASED STUDY"** is a bonafide research work done by **CANDIDATE REGISTER NO. BH0112009**.

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LIST OF ABBREVIATIONS USED

^{0} C	-	Degree celcius
ACR	-	American College of Radiology
ALT	-	Alanine aminotransferase
ASA	-	American Society of Anaesthesiologists
AST	-	Aspartate aminotransferase
B.C.	-	Before Christ
BP	-	Blood pressure
CBC	-	Complete blood count
CBD	-	Common bile duct
cm	-	Centimeter
CNS	-	Central nervous system
CT	-	Computed tomography
CVS	-	Cardiovascular system
D.O.A.	-	Date of admission
D.O.D.	-	Date of discharge
D.O.S.	-	Date of surgery
DBP	-	Diastolic blood pressure
DLC	-	Direct leukocyte count
DPQ	-	Dartmouth pain Questionnaire
e.g.	-	For example
ERCP	-	Endoscopic retrograde cholangiopancreatography
ERCP	-	Endoscopic retrograde cholangiopancreatography
EUS	-	Endoscopic ultrasound
FBS	-	Fasting blood sugar

Hb	-	Haemoglobin
HBS	-	Hepatobiliary scintigraphy
hr	-	Hour
I.P.	-	In patient
IVRA	-	Intravenous regional anesthesia
Kgs	-	Kilograms
LC	-	Laparoscopic cholecystectomy
min	-	Minute
ml	-	Milliliter
mm	-	Millimeter
MPQ	-	Mc Gill pain Questionnaire
MRCP	-	Magnetic resonance cholangiopancreatography
MRI	-	Magnetic resonance imaging
n	-	Total number
NMDA	-	N-methyl-D-aspartate receptor
O.P.D	-	Out patient department
p	-	Probability
PGIMER	-	Post Graduate Institute of Medical Education and Research
SAGES	-	Society of American Gastrointestinal and Endoscopic Surgeons
SBP	-	Systolic blood pressure
SD	-	Standard deviation
SPET	-	Single positron emission tomography
Sr.	-	Serum
TLC	-	Total leukocyte count

UK	-	United Kingdom
USG	-	Ultrasound
VAS	-	Visual analogue scale
vs	-	Versus
WHYPQ	-	West Haven-Yale pain Questionnaire

ABSTRACT

Background and objectives

Postoperative pain remains one of the main cause of delay in resumption of activities after laparoscopic cholecystectomy. The study was undertaken to find the effectiveness of intraperitoneal instillation of tramadol for postoperative pain relief following laparoscopic cholecystectomy and adverse effects following laparoscopic cholecystectomy.

Methodology

This one year double blinded randomized controlled trial was done from January 2013 to December 2013 at KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum. A total of 60 patients undergoing elective cholecystectomy were enrolled. The patients were divided into two groups of 30 each as Group S (Normal Saline) and Group T (Tramadol).

Results

Most of the patients were males (66.67% each) in both the groups and male to female ratio was 2:1 ($p=1.000$). The mean age in group S was 42.20 ± 13.03 compared to 39.83 ± 11.66 years ($p=0.461$). Comorbid conditions and clinical presentation of the study population in group S and T were comparable ($p>0.050$). The mean duration of surgery was 96.37 ± 21.69 minutes in group S and in group T it was 96.83 ± 17.80 minutes ($p=0.928$). In patients with group T, the mean pain scores at all the intervals were significantly low ($p<0.050$) except at 24 hours ($p=0.210$). The requirement of analgesia was high in group S compared to group T immediate post op, 15 minutes, 50 minutes, 8 hours and 12

hours ($p<0.050$). The mean requirement of analgesia immediate post op, 15 minutes, 4 hours and 8 hours was low in group T compared to group S ($p<0.050$). Higher patients (30%) in group T did not require analgesia at all compared to group S ($p<0.001$). Higher incidence of adverse effects at 4 hours interval was 43% in group S compared to 40% in group T ($p>0.050$).

Conclusion and interpretation

Overall, intraperitoneal instillation of tramadol is beneficial in terms of postoperative pain relief following laparoscopic cholecystectomy.

Keywords

Laparoscopic cholecystectomy; Normal saline; Pain; Tramadol;

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INTRODUCTION

Gall stone disease is one of the most common condition encountered in general surgical practice in adult population.[1] The Gold standard treatment for symptomatic gallstone disease is laparoscopic cholecystectomy (LC) since 1990 and is one of the most common operation performed world wide. The advantages of LC include less postoperative pain, shorter hospital stays, a rapid return to work, less intra abdominal adhesions, a better cosmetic outcome and a significant decrease in perioperative septic complications. Also it can be performed safely as a day care procedure.[2]

Historically, contraindications to laparoscopic cholecystectomy have included obesity, pregnancy, acute cholecystitis and cardiovascular disease. With experience gained from laparoscopic surgery, laparoscopic cholecystectomy has been attempted successfully and has become the procedure of choice in each subgroup of patients.[3,4] A major benefit of laparoscopy in upper gastrointestinal surgery results from avoidance of an upper abdominal incision.

With the expanding role of ambulatory surgery and the need to facilitate an earlier hospital discharge, improving postoperative pain control has become an increasingly important issue.[5]

The international association for study of pain, defined pain as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, and causes the individual to react to remove the noxious stimulus”.

Also, pain is a complex summation of nociceptive input, emotion, state of arousal, thought process and social influences.[6]

In common with all other types of pain, acute postoperative pain is an extraordinarily complex sensation which may be described as an interpretation of these signals by higher centres involving memory experiences of painful situation, and an affective component which generally comprises anxiety and /or depression.[6]

Uncontrolled postoperative pain has an adverse sequel of delayed resumption of normal pulmonary function, restriction of mobility (thus contributing to thromboembolic complications), nausea and vomiting, increase in the systemic vascular resistance, cardiac work, and myocardial oxygen consumption through an increase in the catecholamine release induced by the stress response.[7]

Postoperative pain is the main cause of delay in resumption of normal daily activity after Laparoscopic cholecystectomy. Pain control is pertinent for optimal care in surgical patients. Despite better understanding of pain pathophysiology, pharmacology of analgesics and development of newer more effective analgesic techniques, many patients still continue to experience considerable discomfort.

Several mechanisms have been proposed for generation of pain following laparoscopy: ruptured blood vessels caused by rapid distension of the peritoneum; traumatic traction on the nerves; release of inflammatory molecules; trauma to the abdominal wall, and when the gallbladder is removed from the abdomen; pneumoperitoneum created by use of CO_2; maintenance of high abdominal pressure; irritation of the phrenic nerve; and application of cold CO_2.[8] This explains why no consensus can be reached regarding effective postoperative pain relief in patients

undergoing laparoscopic cholecystectomy, because pain is multifactorial.[9] The peritoneal origin of the pain suggests that analgesia delivered locally to the peritoneal cavity may be of benefit postoperatively[10]

It was proved that following laparoscopic cholecystectomy, the site of most severe pain was in the right upper quadrant and port wounds during first 24 hours.[11] The degree of pain after laparoscopic procedure is influenced by many factors including the volume of residual gas, the type of gas used for pneumoperitoneum, the pressure created by pneumoperitoneum, the temperature of the insufflated gas.[12]

Tramadol is a synthetic 4-phenyl-piperidine analogue of codeine. It has an affinity for μ-opioid receptors and inhibits the neuronal reuptake of serotonin and norepinephrine.[13] Tramadol has central analgesic effects due to monoaminergic and μ-receptor agonistic activities. It also has local anesthetic properties, and the risk of serious adverse effects is limited.[14-17] Local administration of tramadol has been found to be an effective analgesic when given intra-articularly or when added to local anesthetics for nerve blocks.[14]

The relation between the duration of preoperative symptoms and postoperative analgesic efficacy of intraperitoneal tramadol after laparoscopic cholecystectomy was studied. While tramadol provides better analgesia in patients with chronic pain or chronic inflammatory processes having had enough time to develop peripheral opioid and non-opioid receptors compared to acute pain conditions.[18]

However, there are limited numbers of studies assessing the analgesic efficacy of intraperitoneal instillation of tramadol during laparoscopic cholecystectomy. Also the available studies have reported varying results. Further adequacy of postoperative pain control is one of the most important factors in

determining when a patient can be safely discharged from surgical facility and has a major influence on the patient's ability to resume their normal activities of daily living.[19] Control of acute postoperative pain and the timing, is important in facilitating short and long-term patient convalescence. Hence, the present study was undertaken to assess the efficacy of intraperitoneal instillation of tramadol in alleviating postoperative pain following laparoscopic cholecystectomy.

OBJECTIVES

The objectives of the present study were;

- To study the effectiveness of intraperitoneal instillation of tramadol for postoperative laparoscopic cholecystectomy pain relief, especially visceral pain and shoulder pain.

- To improve pain relief after laparoscopic cholecystectomy.

- To improve incidence of adverse effect (nausea, vomiting, shoulder pain, itching and shivering) following laproscopic cholecystectomy.

REVIEW OF LITERATURE

Historical aspects

Archeological excavations demonstrating the presence of gall stones in young Egyptian women have confirmed that cholelithiasis has plagued mankind for over 2000 years.[20]

Gall stones were described before the modern era of cholecystectomy by Langen buch in the late 19th century. He widened the understanding of gall stone pathology and performed the first successful cholecystectomy. Numerous calculi were found in the gall bladder of the mummy of a priestess of Amenen of the 21st Egyptian dynasty [1500 B.C.]. Gallstones were first described by the Greek physician Alexander Trallianus who wrote about the calculi within the bile ducts[21] By the 16th century, both Vesailius and Fallopius described gallstones found in the gall bladder of the dissected human bodies.[22]

Laparoscopic cholecystectomy, which was introduced in 1987, is now the preferred method of cholecystectomy.[23]

First elective cholecystectomy was done by Bobbs in 1867, First successful cholecystectomy was done by Karl Langen Buch on July 15th 1882 in Berlin on a male patient suffering from biliary colic for years, First cholecystojejunostomy for CBD obstruction was done by Von Winiwarter in 1882, First successful choledochotomy by Courvoisier in 1882. First successful choledochojejunostomy by Sprengel in 1891,[22] First hepaticoduodenostomy by W. J. Mayo in 1905.[23]

In 1873 Maurice Schiff proposed the ingestion of bile salts as a treatment for gall stones. 50 years later the first report of successful oral gall stones dissolution was reported by New Bridge from the university of Minesuta.[24] First time accurate diagnosis of gall bladder disease was demonstrated by Graham and Cole by oral cholecystography, First PTC was done by Huard and Doxun in 1937.[22]

The endoscopic retrograde cholangiopancreatography was first performed by Mecune. In 1937, The concept of gall stones dissolution by administering bile salts was recognized by AG Rewbridge in 1937 and this was confirmed 20 years later by Johnston and Nakayama in 1957, Mirizzi introduced the operative cholangiography in 1937 in Argentina.[22]

Extra corporeal shock wave lithotripsy of gall stones was developed in the 1980 as a non invasive form of treatment in selected patients with symptomatic, uncomplicated cholelithiasis.[22]

The surgical techniques started to evolve in the late 1800, John Bobbs an Indiana surgeon and others attempted to perform cholecystolithotomy, removing the stone from the gall bladder and leaving the organ in situ, First percutaneous cholecystolithotomy was performed by Akiyama et al in 1985, Kerlan et al in 1985.[25]

Cope et al in 1990 removed the smaller calculi by wire baskets, fragmentation of larger calculi may be done with laser mediated intracorporal lithotripsy by Burhenne et al in 1975, Pinacus et al in 1989. Combined surgical and radiological intervention [mini cholecystotomy] was described by Burhenne et al in 1985.[25]

In 1985 first laparoscopically assisted cholecystectomy was performed by Muhe, Boblingen, Germany. In 1987, french surgeon in Lyon, Phillipe Mouret, performed the first video laparoscopic cholecystectomy.[25]

Cadiere and colleagues reported the first successful clinical implementation of telerobotics in 1998 when they accomplished a laparoscopic cholecystectomy using a prototype of the Da Vinci robotic surgical system.[25]

Laparoscopic anatomy

The advent and popularity of Laparoscopic cholecystectomy has led to a new look and insights into biliary anatomy especially of the Calot's triangle area and the term 'laparoscopic anatomy' has actually found a place even in anatomy texts. Although a detailed discussion of all the factors peculiar to laparoscopy that contribute to an increased incidence of injuries is beyond the scope of this review, the different anatomical 'laparoscopic view' of the area around the gallbladder especially the Calot's triangle does contribute to misidentification of structures. The method of retraction during the laparoscopic procedure tends to distort the Calot's triangle by actually flattening it rather than opening it out.[26] Also, the reluctance to (or difficulty in) performing a fundus first cholecystectomy during the laparoscopic procedure as opposed to the open procedure also contributes to the same lack of exposure of the Calot's triangle. Finally, the 'posterior' or 'reverse' dissection of the Calot's triangle, which is popular during a laparoscopic cholecystectomy, again gives a different view of the area and since the gallbladder is flipped over during this method may lead to further anatomical distortion.[27]

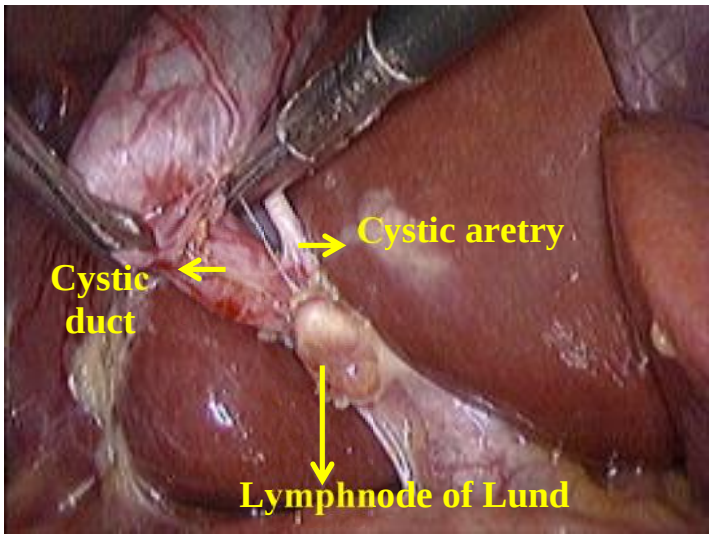


Illustration 1. Callot's triangle

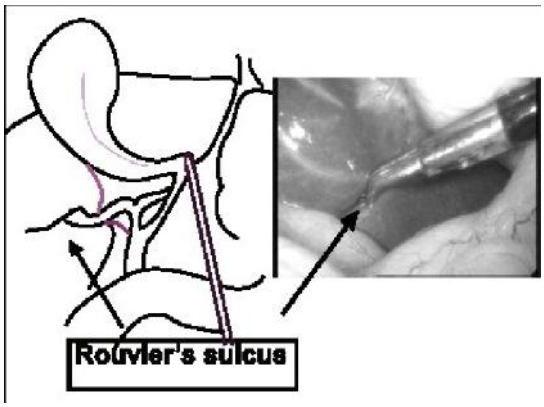


Illustration 2. Rouviere's sulcus[27]

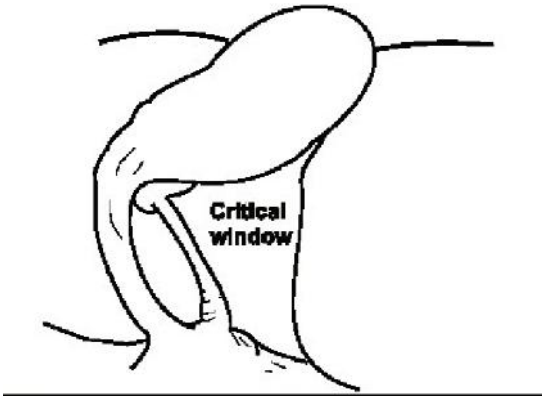


Illustration 3. The critical view or safety window[27]

The Rouviere's sulcus is a fissure on the liver between the right lobe and caudate process and is clearly seen during a LC during the posterior dissection in a majority of patients. It corresponds to the level of the porta hepatis where the right pedicle enters the liver. It has hence been recommended that all dissection be kept to a level above (or anterior) to this sulcus to avoid injury to the bile duct. Also, this being an 'extrabiliary' reference point it does not get affected by distortion due to pathology. Similarly, a clear delineation of the junction of the cystic duct with the gallbladder along with the demonstration of a space between the gallbladder and the liver clear of any other structure other than the cystic artery (safety window or critical view) is also recommended as an essential step to prevent bile duct injury.[27]

The epidemiology of gallstone disease in India

Although well documented by authors in India, the data has not received much attention in the West. In literature of Medicine and Gastroenterology published from the West, India is included along with countries with a low incidence of gallstones. The prevalence of gallstone disease varies in different parts of India.[28] Malhotra as early as in 1966 conducted an epidemiological study in Indian Railway employees and showed that North Indians had seven times higher prevalence of gallstones as compared to South Indian employees. In northern states including Kashmir where good epidemiological studies have been performed, a very high and increasing prevalence were reported.[29-33] Khuroo from Kashmir reported a prevalence of 6.12% (men 3.07% and women 9.6%) the prevalence increasing progressively to reach a peak in the sixth decade.[32] The prevalence rate is significantly higher in multiparous women.[32] There was no correlation with diet, obesity or socioeconomic status.[30]

A different picture arises from data available from south India. Jayanthi et al[34] reported that mixed and pigment stones were more common than cholesterol stones in Tamilnadu. They found no correlation with demographic features or social customs. An interesting observation that needs confirmation is an association with high consumption of tamarind. There is no scientific explanation for this observation. The overall prevalence of gallstones in Tamilnadu appears to be lower than in the North. However cholecystectomy once an extremely uncommon surgery in south India has become very frequent reflecting either a real increase in the prevalence of the disease, better diagnosis because of ease of detecting stones by abdominal ultrasound or the availability of Laparoscopic cholecystectomy.[28]

Clinical Manifestations of Gallstones

Four types of gallbladder diseases are recognised:

1. Asymptomatic gallstone disease.
2. Symptomatic gallstone disease
3. Pain abdomen from another etiology such as peptic ulcer, with asymptomatic gallstones
4. Cholecystitis with no gallstones

The decision to do surgery is based on a careful understanding of the above.

1. Asymptomatic Gallstones

Most do not develop symptoms even after follow up periods as long as 20 years. Approximately 20% of patients develop symptoms by 15 years. Asymptomatic gallstone disease (in many Western countries) does not need surgery

although there are exceptions. The role of prophylactic cholecystectomy in young patients from various parts of India is emphasized in many recent papers, but criticized in one.[35]

2. Symptomatic Gallstone Disease

a. Biliary colic

Frequently characterized as post prandial pain in the right upper abdomen. Contrary to popular belief it may not necessarily occur only after fatty foods.[28]

b. Acute Cholecystitis

Often patients will have history of biliary pain in acute cholecystitis; pain lasts for > 3 hours, associated with fever and right upper quadrant tenderness (Murphy's sign).[28]

c. Chronic Chlolecystitis

Patients will have episodic epigastric, right upper quadrant pain lasting for more than 30 minutes. Patients, may present with complications of gallstones-pancreatitis, choledocholithiasis and cholangitis.[28]

d. Choledocholithiasis

May be asymptomatic or present with biliary colic, acute cholangitis or pancreatitis.[28]

e. Acute Cholangitis

It is a medical emergency. Patients may present with Charcot's triad- right upper quadrant pain, fever and jaundice. With advances in clinical chemistry, imaging studies the diagnosis can be made before the classic triad develops.[28]

Diagnosis

Diagnostic tests[28]

- Abdominal Ultrasonography: Single most useful test to evaluate gallstones, CBD size and stones.
- Endoscopic Ultrasound (EUS): Excellent to evaluate CBD stone, size. Expensive. Not easily available.
- ERCP: As solely a diagnostic test it has lost its value. Can be used to do sphincterotomy, therapeutically
- HIDA, DIDA, Radioisotope Scans: Accurate identification of cystic duct obstruction. Diagnosis of acute cholecystitis.
- CT Scan Abdomen: Not ideal. Radiation. Not useful in pregnancy
- MRI/MRCP: MRCP does not require contrast. It can be safely used in 2nd/3rd trimester of pregnancy. Reduces the number of invasive ERCPs.

Delays in making the diagnosis of acute cholecystitis result in a higher incidence of morbidity and mortality. This is especially true for intensive care unit (ICU) patients who develop acalculous cholecystitis. The diagnosis should be considered and investigated promptly in order to prevent poor outcomes.[22]

Differential diagnosis[36,37]

- Cholelithiasis
- Choledocholithiasis
- Biliary Colic
- Biliary Disease
- Cholangitis
- Gallbladder Mucocele
- Gallbladder Cancer
- Gallbladder Tumors
- Gastric Ulcers
- Gastritis, Acute
- Cholangiocarcinoma
- Appendicitis
- Acute Mesenteric Ischemia
- Abdominal Aortic Aneurysm

Approach

The workup for cholecystitis may include laboratory tests (though these are not always reliable), radiography, ultrasonography, computed tomography (CT), magnetic resonance imaging (MRI), hepatobiliary scintigraphy (HBS), and endoscopy.

Laboratory investigations[38]

Although laboratory criteria are not reliable in identifying all patients with cholecystitis, the following findings may be useful in arriving at the diagnosis:

- Leukocytosis with a left shift may be observed in cholecystitis.
- Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels are used to evaluate the presence of hepatitis and may be elevated in cholecystitis or with common bile duct obstruction.
- Bilirubin and alkaline phosphatase assays are used to evaluate evidence of common duct obstruction.
- Amylase/lipase assays are used to evaluate the presence of pancreatitis. Amylase may also be elevated mildly in cholecystitis.
- An elevated alkaline phosphatase level is observed in 25% of patients with cholecystitis.

Imaging

The 2010 American College of Radiology (ACR) Appropriateness Criteria offer the following imaging recommendations:[39]

- Sonography is the preferred initial imaging test for the diagnosis of cholelithiasis, acute cholecystitis, and scintigraphy is the preferred alternative.
- CT is a secondary imaging test that can identify extrabiliary disorders and complications of cholecystitis, such as gangrene, gas formation, and perforation.
- CT with intravenous contrast is useful in diagnosing cholecystitis in patients with nonspecific abdominal pain.

- MRI, often with intravenous gadolinium-based contrast medium, is also a possible secondary imaging modality useful in confirming a diagnosis of acute cholecystitis.
- MRI without contrast is useful to eliminate radiation exposure in pregnant women for whom sonograms have not indicated a clear diagnosis.

Radiography

Gallstones may be visualized on noncontrast radiography in 10-15% of cases. This finding only indicates cholelithiasis, with or without active cholecystitis.

Ultrasonography

Ultrasonography is 90-95% sensitive for cholecystitis and is 78-80% specific. It provides greater than 95% sensitivity and specificity for the diagnosis of gallstones more than 2 mm in diameter. Studies indicate that emergency clinicians require minimal training in order to use right upper quadrant ultrasonography in their practice.[40,41]

Ultrasonographic findings that are suggestive of acute cholecystitis include the following: pericholecystic fluid, gallbladder wall thickening greater than 4 mm, and sonographic Murphy sign. The presence of gallstones also helps to confirm the diagnosis.[42]

Ultrasonography is performed best following a fast of at least 8 hours because gallstones are visualized best in a distended bile-filled gallbladder.[43]

Computed tomography and magnetic resonance imaging

The sensitivity and specificity of CT scan and MRI for predicting acute cholecystitis have been reported to be greater than 95%.[44] Spiral CT scan and MRI (unlike endoscopic retrograde cholangiopancreatography [ERCP]) have the advantage of being noninvasive, but they have no therapeutic potential and are most appropriate in cases where stones are unlikely.

Findings suggestive of cholecystitis include wall thickening (>4 mm), pericholecystic fluid, subserosal edema (in the absence of ascites), intramural gas, and sloughed mucosa. CT scan and MRI are also useful for viewing surrounding structures if the diagnosis is uncertain.

Hepatobiliary scintigraphy[38]

HBS has been found to be up to 95% accurate in diagnosing acute cholecystitis. The reported sensitivities and specificities of biliary scintigraphy are in the range of 90-100% and 85-95%.

In a typical study, the gallbladder, common bile duct, and small bowel fill within 30-45 minutes. If the gallbladder is not visualized, intravenous morphine administration can improve the accuracy of HBS by increasing resistance to flow through the sphincter of Oddi, resulting in filling of the gallbladder if the cystic duct is patent. The addition of morphine also reduces the number of false-positive scan results observed in patients who are critically ill and immobilized with viscous bile.

Endoscopic retrograde cholangiopancreatography

ERCP may be useful for visualizing the anatomy in patients at high risk for gallstones if signs of common bile duct obstruction are present. A study performed by Sahai et al found that ERCP was preferred over endoscopic ultrasonography and intraoperative cholangiography for patients at high risk for common bile duct stones undergoing laparoscopic cholecystectomy.[45]

Disadvantages of ERCP include the need for a skilled operator, high cost, and complications such as pancreatitis, which occurs in 3-5% of cases.

Histologic findings

Edema and venous congestion are early acute changes. Acute cholecystitis is usually superimposed on a histologic picture of chronic cholecystitis. Specific findings include fibrosis, flattening of the mucosa, and chronic inflammatory cells. Mucosal herniations known as Rokitansky-Aschoff sinuses are related to increased hydrostatic pressure and are present in 56% of cases. Focal necrosis and an influx of neutrophils may also be present. Advanced cases may show gangrene or perforation.[46]

Treatment

Treatment of cholecystitis depends on the severity of the condition and the presence or absence of complications. Uncomplicated cases can often be treated on an outpatient basis; complicated cases may necessitate a surgical approach. Antibiotics may be given to manage infection.

Surgical Treatment

Surgical treatment, if required, typically involves cholecystectomy, preferably laparoscopic. Percutaneous drainage may be considered in patients at high surgical risk.[47]

Cholecystectomy

Laparoscopic cholecystectomy is the gold standard for the surgical treatment of cholecystitis. Studies have indicated that early laparoscopic cholecystectomy resulted in shorter total hospital stays with no significant difference in conversion rates or complications.[48] The ACR 2010 criteria state that laparoscopic cholecystectomy is the primary mode of treatment for cholecystitis.[39]

The Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) issued guidelines for the clinical application of laparoscopic biliary tract surgery in 2010. The guidelines include detailed recommendations for making the decision to operate, performing the procedure, and managing postoperative care, with the patient's safety always the primary consideration. Recommendations are as follows:[49]

- Preoperative antibiotics should be considered only to reduce the possibility of wound infection in high-risk patients, and then limited to one preoperative dose.

- Intraoperative cholangiography may improve injury recognition and decrease the risk of bile duct injury.

- If bile duct injury occurs, the patient should be referred to an experienced hepatobiliary specialist before any repair is undertaken, unless the primary surgeon has experience with biliary reconstruction.

Early operation within 72 hours of admission has both medical and socioeconomic benefits and is the preferred approach for patients treated by surgeons with adequate experience in laparoscopic cholecystectomy.[50] Immediate cholecystectomy or cholecystotomy is usually reserved for complicated cases in which the patient has gangrene or perforation.

One study suggests that when CT scanning is performed as long as 72 hours prior to surgery, it may better detect acute gangrenous cholecystitis. Acute gangrenous cholecystitis was significantly correlated with perfusion defect of the gallbladder wall, pericholecystic stranding, and no-gallstone condition, which can be better observed through CT scanning when compared with ultrasonography.[51]

For elective laparoscopic cholecystectomy, the rate of conversion from a laparoscopic procedure to an open surgical procedure is approximately 5%. The conversion rate for emergency cholecystectomy where perforation or gangrene is present may be as high as 30%.[48]

Although laparoscopic cholecystectomy performed in pregnant women is considered safest during the second trimester, it has been performed successfully during all trimesters.

Pain after laparoscopy

Pain occurs after laparoscopy, but is usually less and shorter than that caused by the same surgical procedure made possible by laparotomy. The reduction in pain has made the early discharge from the hospital possible, provided that the control of the residual pain is adequate and that the drugs or techniques used for analgesia are safe enough.[52]

Pain may occur in the upper abdomen, lower abdomen, back, or shoulders. The greatest incidence of pain is in the upper abdomen.

Pain after laparoscopy may be transient or it may persist for at least two days. After laparoscopic cholecystectomy, visceral pain was found to predominate in the first 24 hours, whereas shoulder pain, minor on the first day, increased and becomes significant on the following day.[53]

Pain

Pain is not just a sensory modality but an experience .The International Association for the Study of Pain defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage." This definition recognizes the interplay between the objective, physiologic sensory aspects of pain and its subjective, emotional and psychological components.[54]

Pain is clinically divided into, acute pain which is primarily due to nociception and chronic pain, which may also be due to nociception, but in which psychological and behavioral factors often play a major role. Postoperative pain is one of the types of acute pain and can be further differentiated based on the origin

and feature into somatic and visceral pain. Somatic pain is due to nociceptive input arising from skin, subcutaneous tissues, and mucous membranes. It is characterized by being well-localized and described as sharp, pricking, throbbing or burning sensation. Visceral pain on the other hand is due to nociceptive input arising from internal organ or one of its covering. It is usually 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.[55]

Magnitude of the problem

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 post operative care.[55]

NEURO-PHYSIOLOGY OF PAIN

Nociceptors

Sensation is often described as either protopathic (noxious) or epicritic (non-noxious). Epicritic sensation (light touch, pressure, proprioception, and temperature discrimination) is characterized by low-threshold receptors (specialized endorgans on the afferent neurons) and conducted by large myelinated nerve fibers while; protopathic sensation (pain) is sub served by high-threshold receptors (free nerve endings).[56]

Noxious sensations can often be broken down into two components: a fast, sharp, and well-localized sensation “first pain” which is conducted by Aδ fibers; and a duller, slower onset, and poorly localized sensation “second pain” which is conducted by C fibers. This protopathic pain is transmitted mainly by free nerve endings that sense mechanical or chemical tissue damage.[6,57,58]

Several types of this pain is recognized

1. Mechano-nociceptors, which respond to pinprick.
2. Silent nociceptors, which respond only on the presence of inflammation
3. Polygonal mechano-heat receptors which is more prevalent and respond to excessive pressure, extreme of temperature, and pain producing substances.[6]

Nociceptors are either somatic that include those in skin and deep tissues (muscle, tendons, joints), or visceral nociceptors that include those in internal organs.[6,57,58]

Pain pathway

Pain is conducted along three neuron pathways; from the periphery to the cerebral cortex.[6,57,58]

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).[6,57,58]

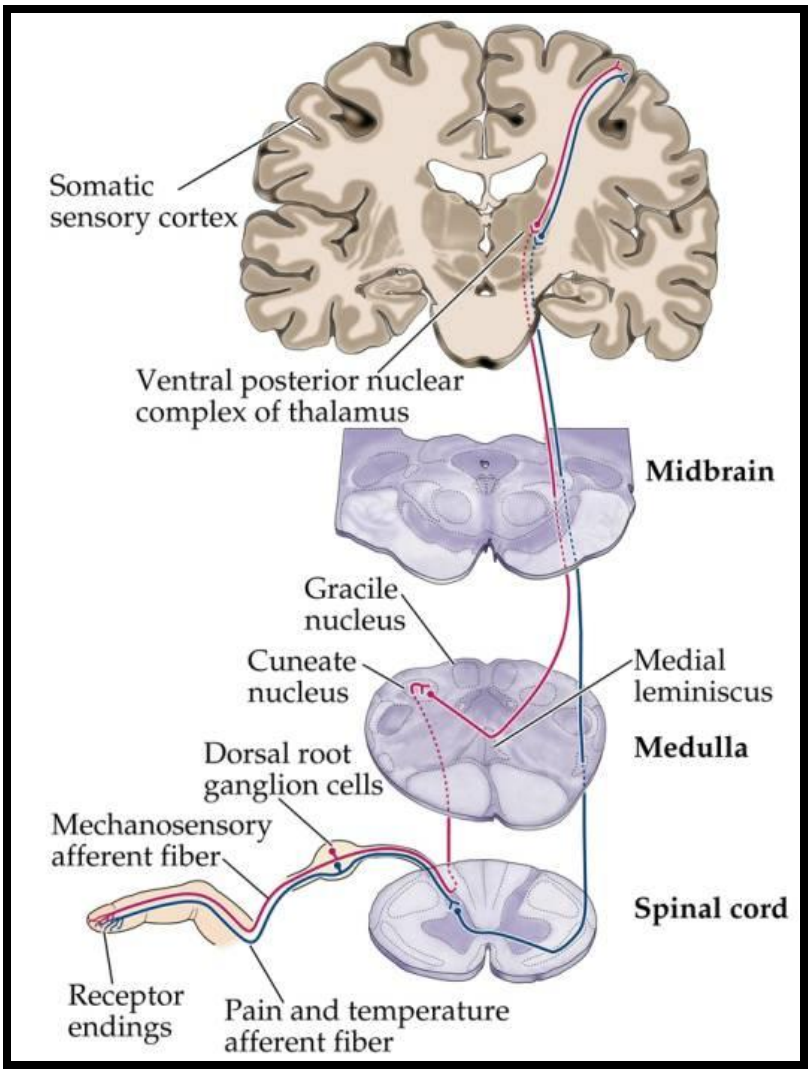


Illustration 4. Pain pathway[6, 57,58]

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".[57,58]

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.[57,58]

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.[57,58]

Third order neurons

Those are located in the thalamus and send their fibers to the somato-sensory area I and II in the cerebral cortex.[58-60]

Preemptive analgesia

Preemptive analgesia is defined as what is administered before surgical incision that prevents the development of central sensitization from incisional injury and inflammatory injuries (that is, intraoperative and postoperative periods). The combination of experimental data and positive clinical trials strongly suggests that preemptive analgesia is a clinically relevant phenomenon. Maximum benefit is observed when there is complete blockade of noxious stimuli.[61]

Mechanism of pain in laparoscopy

In addition to the trauma caused to the abdominal wall and the visceral organs by the endoscope and the surgical instruments, there are other mechanisms

responsible for pain after laparoscopy. Rapid distension of the peritoneum may be associated with tearing of blood vessels, traumatic traction of the nerves and release of inflammatory mediators. Peritoneal inflammation is probably also the origin of the upper abdominal pain after lower abdominal surgery or after diagnostic laparoscopy. This can persist for at least three days. Peritoneal biopsy performed two to three days after laparoscopy showed peritoneal inflammation and neuronal rupture, and there was a linear inverse relationship between abdominal compliance at the time of laparoscopy and severity of postoperative pain.[62]

Therefore, abdominal distention should be slow with adequate muscle relaxation to ensure suitable abdominal compliance. The prolonged presence of shoulder tip pain suggests excitation 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.[62]

a. 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.[63]

2. The type of insufflated gas and intraabdominal pH

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 at 6.0 immediately 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.[64] 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.[65]

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.[63]

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.[66] This

study demonstrated significantly reduced postoperative pain in patients who underwent humidified gas insufflation. The humidified insufflations showed a trend of less postoperative 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.[60]

b. Operational factors

1. Wound pain

The number and size of the incisions used vary between different procedures and also between different centers. Local anaesthesia administration to the wound created, is recommended by many authors, with significant pain reduction in both open[67] and laparoscopic procedures.[68] Not all studies have shown a significant difference, however for laparoscopic procedures, only small amounts of local anaesthesia will be required, minimal side effects are anticipated, and the use of local anaesthesia is recommended.[69]

2. Wound drainage

Wound drains after laparoscopic surgery usually is sited on the lateral aspect of the abdomen, traversing muscle layers. The umbilical incision is less commonly used due to a greater incidence of pain, infection, and potential incisional herniation at this site if the defect is not formally closed. It is recommended that the wound drainage be carefully individualized, rather than regarded as a routine consideration.

c. Socio-cultural and individual factors

The socio-cultural environment affects hospital stay and recovery time. This variable, encountered on almost a daily basis by most surgeons, was effectively demonstrated in a study comparing the course after laparoscopic cholecystectomy in French and American patients. Postoperative discomfort had resolved within two weeks in 73% of the French and in 93% of the Americans. A higher percentage of the Americans returned to work in a given period than did the French patients.[70]

It is accepted that despite the best practices, a multitude of factors including previous pain experiences and individual thresholds will influence individual postoperative pain perception and recovery time.

There is a substantial inter individual variation in the incidence and intensity of pain after laparoscopic cholecystectomy. The intensity of pain after laparoscopic cholecystectomy peaks within the first four to eight hours, has been reported to be unbearable upto the first postoperative morning in one third of the patients. It involves three different components with different intensity, time course and pathophysiological mechanisms. These pain components are incisional pain (parietal pain component); deep intraabdominal pain (visceral pain component) and shoulder tip pain (presumed referred visceral pain.) The intensity of visceral pain dominates in the immediate postoperative period.

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 is not only human but a very important aspect of postoperative care.[71]

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.[72]

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 axes 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.[73]

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.[74]

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.[74]

Pain increases total body oxygen consumption and carbon dioxide production which necessitated 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 this leads to further reduction in the tidal volume and functional residual capacity which in turn can cause atelectasis, intrapulmonary shunting and hypoxemia.[72]

c. Gastrointesinal 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.[75]

d. Endocrinal effects

The dominant neuroendocrine responses to pain involve hypothalamic-pitutary-adrenocortical interactions. Those interactions result in increased catecholamine and catabolic hormone release. This effects causes 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.[76]

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.[77]

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.[56]

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.[78]

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.[71]

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.[79]

Lastly, optimizing treatment of acute postoperative pain can improve health-related quality of life, while poor postoperative pain control may intervene 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).

Behavioural

- 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.[72]

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 most of the 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 labeled “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.[56]

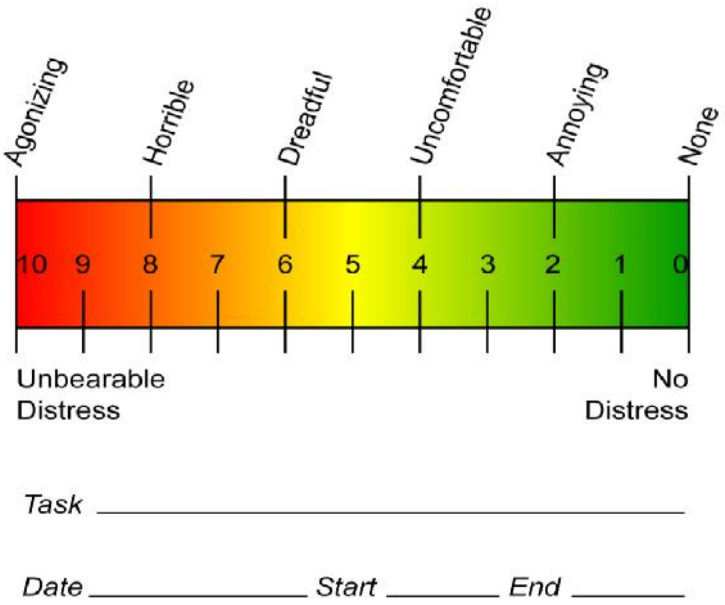


Illustration 5. Visual analogue scale

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.

Psychoeducational 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, carrying out the operation with dispatch 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.

ACTIVE MEASURES

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

1. Systemic analgesics and adjuvant

a. Narcotics

b. Non-steroidal anti-inflammatory drugs

c. Intravenous paracetamol

d. NMDA antagonists

e. Alpha-2 adrenergic agonists

f. Miscellaneous non-opioid compounds

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

a. Continuous segmental epidural block

b. Interpleural analgesia

c. Intraperitoneal analgesia

3. Regional analgesics with neuro-axial opioids

4. Regional analgesia with combined local anaesthetics and opioids

5. Electrical analgesia achieved with transcutaneous electrical stimulation or electroacupuncture.[6]

TRAMADOL[6,80]

First registered in Germany in 1973, first marketed in 1977 now coming off patent worldwide, Tramadol is a centrally acting analgesic that has low affinity for mu opioid receptors.

Tramadol is synthetic analog of Codeine and is not currently classified as controlled substance, is only 5-10 times less potent than Morphine as an analgesic.

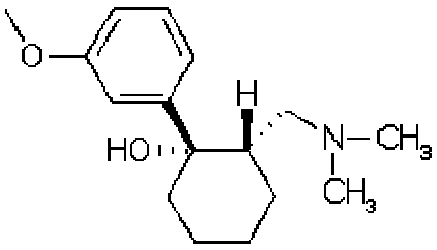


Illustration 6. Chemical structure of Tramadol

Chemistry:

Tran-(I)-2(Dimethylamino)methyl) - 1 - (3-methoxyphenyl) cyclohexonal hydrochloride. Tramadol is racemic mixture of two enantiomers which is more

effective than either enantiomer alone. The positive enantiomer binds to mu receptor and inhibits serotonin uptake. The negative enantiomer inhibits norepinephrine uptake at α_2 – adrenergic receptors.

Mechanism of Action:

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

Second mode is it inhibits pain via the drugs influence on the descending pain inhibitory systems, Tramadol influences these systems by preventing reuptake and enhancing the release of serotonin and norepinephrine. Both of these neurotransmitters inhibit the transmission of painful stimuli. Dose required for inhibition of neurotransmitter reuptake and that required for opioid receptor analgesia is the same.

Role of potassium channels in pain is setting the resting membrane potential and in controlling the excitability of neurons. The opening of nonspecific voltage dependent channels leads to hyperpolarization of cell membrane, which results in a decrease in cell excitability.

TRAMADOL provides analgesia by opoid and non-opoid mechanisms.

OPOID MECHANISM

By direct binding to μ-opioid receptors by parent compound and its metabolite.

NON OPOID MECHANISM (local action)

Increase in synaptic levels of 2 neurotransmitters ---> SEROTONIN and NOREPINEPHRINE.

The effect of the non-opioid component of tramadol is mediated through α-2-agonistic and serotoninergic activities, by inhibiting the re-uptake of norepinephrine and 5-hydroxytryptamine (SEROTONIN) and, possibly, by displacing stored 5-hydroxytryptamine from nerve endings

The monoaminergic activity of tramadol enhances the inhibitory activity of the descending pain pathways, resulting in a suppression of nociceptive transmission at the **spinal level**.

Tramadol exerts its sensory blocking action by a mechanism similar to that of Local anaesthetics in the form of blocking the voltage dependent sodium channels.

Pharmacokinetics

Absorption

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

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

Distribution

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

Metabolism

This is rapidly and extensively metabolized in liver. The principal metabolic pathway O-and N- demethylation involve cytochrome P-450 isoenzyme 2D6, 2B6, 3A4 respectively.

The main metabolites are M1 – O – desmethyl tramadol and (M2) N-desmethyl tramadol. These main metabolites are again metabolized to secondary metabolites which are N-N-didesmethyl (M3) N-N,O – tridesmethyl tramadol (M4) and N-O desmethyl tramadol (M5) all metabolites are conjugated with glucoronic acid and sulfate before excretion in urine. Only O-desmethyl tramadol is pharmacologicaly active, 10-30% of the drug is excreted unmetabolised in urine.

Elimination

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

Clinical uses

Used as an analgesic, analgesia begins with in 60 minutes of oral dosing and peak effect within 2-3 hours and duration of analgesia is 6 hours. Plasma concentration or pharmacological action is used as an adjuvant with LA in brachial plexus blockade. IVRA, epidural analgesia, postoperative shivering

Systemic effects

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

Cardiovascular System

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

Respiratory system

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

Gastrointestinal system

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

therefore sensitive to any rise of 5HT concentration resulting from inhibition of the 5HT transporter by Tramadol.

Central nervous system

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

Abuse and physical dependence

Have been reported although its abuse potential is unclear, should be avoided in patients with history of addiction. Tramadol should be avoided in patients taking monoamine oxidase inhibitors due to inhibitory effect of Tramadol on serotonin uptake.[6,80]

Literature review

Numerous advantages have been reported when comparing open versus minimally invasive abdominal surgical procedures (laparoscopy), including earlier return of bowel function, decreased postoperative pain, quicker recovery, and earlier hospital discharge. Although the magnitude of pain can be expected to be reduced when compared to open procedures, pain may still be a significant factor during the postoperative recovery period following laparoscopic surgery. Without effective treatment, this ongoing pain may delay recovery, mandate inpatient admission, and thereby increase the cost of such care. In addition to pain at the incisional and trocar insertion sites, there may also be shoulder and diffuse abdominal pain. Shoulder pain and diffuse abdominal pain may be due to peritoneal stretching and diaphragmatic irritation associated with carbon dioxide insufflation.[81]

Although in most circumstances pain is treated with an approach which uses parenteral opioids and nonsteroidal anti-inflammatory agents combined with local infiltration of the incisional sites, other novel techniques have been reported. Given the problem of providing effective pain control, alternative agents such as pregabalin and ketamine have also been investigated. Despite their efficacy, all parenteral medications may be associated with adverse effects. Therefore, there has also been interest in the use of topical peritoneal medications including local anesthetic agents.[81]

The local anesthetic agent is aerosolized into the peritoneal cavity during the laparoscopic procedure. Targeting the peritoneum topically makes sense as it has been shown that gas insufflation with increased intra-abdominal pressure results in peritoneal inflammation and neuronal rupture with a linear relationship between abdominal compliance during the procedure and the resultant severity of postoperative pain.[81]

A study done by Goulbovic S et al[82] in 2009 at clinic of Anesthesiology and Intensive Care, University Hospital Center, Rijeka, Croatia concluded that pain scores were significantly lower in group receiving the intra peritoneal bupivacaine with tramadol and bupivacaine compared to saline group. Intraperitoneal applications of these drugs reduced consumption of supplementary postoperative analgesic medication. Intraperitoneal administration of bupivacaine with tramadol and bupivacaine are simple to use and effective in a reduction of pain after laparoscopic cholecystectomy. No difference was noted between bupivacaine with tramadol and bupivacaine in postoperative visual analogue score and analgesic requirements.

A study done by Samar I. Jabbour-Koury et al.[83] in Aerican University of Beirut-MedicalCenter, Beirut, Lebanon in 2005, came to a conclusion that a multimodal approach to pain management following elective laparoscopic cholecystectomy is best achieved with a combination of 40 ml bupivacaine 0.25% intraperitoneal spray and 200 mg intravenous ketoprofen, achieving the least incidence of postoperative vomiting.

A study done in PGI Chandigarh by Neerja Bhradwaj et al.[84] in 2002 concluded that intraperitoneal instillation of 0.5% Bupivacaine reduced the pain in the initial postoperative period.

A study done by Gharaibeh KI et al.[85] in 2000 at department of General Surgery, Princess Basma Teaching Hospital, Faculty of Medicine, University of Science & Technology, Irbid, Jordan concluded that the raw area of the removed gallblader is at least partially responsible for shoulder pain after laparoscopic cholecystectomy. Local bupivacaine is effective in reducing such pain.

A study done by T. Chundrigar et al[86] in 1993 at Princess of Wales Hospital, Bridgend, Mid Glamorgan came to the conclusion that patients in the bupivacaine group had less pain in the early postoperative period and a lower incidence of pain in the right hypochondrium. Intraperitoneal bupivacaine is a simple and effective treatment for postoperative pain after laparoscopic cholecystectomy.

METHODOLOGY

This study was carried out at KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum from January 2013 to December 2013.

Study design

The study design was a double blinded randomized controlled trial.

Study period and duration

The present study was carried out for a period of one year from January 2013 to December 2013.

Place

This study was done under the Department of General Surgery of a tertiary care teaching hospital attached to KLE University's Jawaharlal Nehru Medical College, Belgaum.

Source of Data

Patients scheduled for elective laparoscopic cholecystectomy were included in the study.

Sample size

The study sample was comprised of 60 patients divided into two groups of 30 each.

Sampling procedure

Applying thumb rule, 60 cases of laparoscopic cholecystectomy were taken up for study. They were divided into two groups of 30 each using computer generated random numbers.

Selection criteria

Inclusion

- Patients aged 20 years and above.
- Patients of either sex.
- Patients with ASA grade I and II

Exclusion

- Uncooperative and unwilling patients.
- Patients with history of anaphylaxis to opioids.
- Patients with ASA grade III, IV and V.
- Immunocompromised patients
- Patients requiring conversion to open cholecystectomy.

Ethical clearance

The Ethical Clearance was obtained from the Institutional Ethics Committee, Jawaharlal Nehru Medical College, Belgaum prior to the commencement.

Informed Consent

Those patients who fulfilled selection criteria were briefed about the nature of study and a written informed consent was obtained (Annexure I) prior to the enrolment.

Method of collection of data

Patients satisfying selection criteria were interviewed and the demographic data such as age and sex, presenting complaints were noted. Further the patients were subjected to clinical and systemic examination and the findings were noted on a predesigned and pretested proforma (Annexure II).

Randomization

Patients were randomly assigned to one of the two groups using computer generated random numbers as below.

- Group T (n=30): Patients in this group received intraperitoneal tramadol 100 mg (diluted in 20 ml of distilled water).

- Group S (n=30): Patients in this group received 20 ml of intraperitoneal normal saline.

Procedure of laparoscopic cholecystectomy

Position

Classical supine position with the patient in 30^0 reverse trendelenburg tilt.

Nasogastric tube is used to ensure complete gastric deflation during the procedure, since a distended stomach and duodenal cap can obscure the operative field. The urinary bladder is emptied by a catheter prior to creation of pneumoperitoneum. If catheterization not done, it is important to percuss the suprapubic region to exclude a distended urinary bladder before inserting the Veress needle. The nasogastric tube is removed at the end of the operation.

Part preparation and draping done in the standard manner.

Access to peritoneal cavity

1. Closed peritoneal insufflation followed by insertion of the optical port
2. Open laparoscopy using the modified Hasson's cannula.

Closed pneumoperitoneum

This technique entails the initial creation of a carbon dioxide pneumoperitoneum using veress needle and electronic insufflators. Veress needle most often inserted at the subumbilical site where the optical port is introduced. To confirm the position of the Veress needle tip various tests are done, as follows:

1. Syringe aspiration test
2. Drop test
3. Negative pressure test
4. Early insufflation pressures.

Insufflation of the peritoneal cavity is then continued at an initial inflow rate of about 1 L/min. if this process proceeds smoothly without significant change in the cardiovascular changes, the insufflators can be switched to high flow to allow

complete filling of the peritoneal cavity to a pressure of approximately 10 to 15 mmHg. At this point the veress needle is withdrawn. During the insufflation all quadrants of the abdomen are percussed to confirm uniform distension.

A 10 m port is inserted at the subumbilical region, through which the camera (0 or 30^0) is introduced. Following this the abdomen is inspected.

1. To detect any injury to organs or vessels caused during insufflations and insertion of main trocar.
2. Exclusion of additional unsuspected intra abdominal pathology.
3. Assessment of the feasibility of laparoscopic cholecystectomy. After inspection, three more ports inserted under vision. 10mm left upper paramedian, placed 1cm lateral to linea alba and 3 cm below the left costal margin (to avoid the falciform ligament), 5 mm right upper midclavicular, 5 mm right lower axillary (Illustration 7).

The cystic pedicle is exposed by grasping the gallbladder fundus which is lifted in a lateral direction and rolled backwards to expose the subhepatic pouch. A second atraumatic grasper is applied to the neck which is lifted upwards and anteriorly. The cystic pedicle outlines the margins of the triangle of Calot and contains between its superior and inferior leaves the cystic duct (usually anteriorly), the cystic artery (above and behind the duct) and the cystic lymph node of Lund which is loosely applied to the neck of the gallbladder between the duct and artery. The prominent anterior free edge of the cystic pedicle is formed as the peritoneum folds over the cystic duct. The dissection of the pedicle is carried out using scissors, or atraumatic graspers and the superior leaf of the pedicle is divided. Once the cystic

duct and artery are well exposed, the cystic duct is clipped at the gallbladder end and cut followed by the cystic artery. The dissection is carried out between the loose fibrous layer which separates the gallbladder from the subjacent fascia covering the liver bed. Once separation of gallbladder is complete, the organ is held and extracted through the upper 10 mm port. Care is taken to avoid spillage of contents into the peritoneal cavity. After this final inspection is done to look for any oozing, heamostasis is achieved. All ports are removed under vision after decompressing the abdominal cavity to evacuate the carbon dioxide. Ports are closed using vicryl port closure for the rectus sheath and skin using ethilon. Sterile dressing applied.

Intervention

In both groups, 10mL of the study drug was injected into the sub diaphragmatic space, 5mL into the area of the gall bladder bed (Illustration 14 and 15) and 5mL was injected into the space between the liver and the kidney (Illustration 16) under direct vision by the surgeon just before removal of trocars. Postoperatively patients were extubated and shifted to recovery room where outcome variable including pain, requirement of analgesia and complications were observed and recorded by the surgeon.

Blinding

Both patients and surgeon were blinded and anaesthetist loaded drug or normal saline according to random table chart and gave it to the surgeon for infiltration.

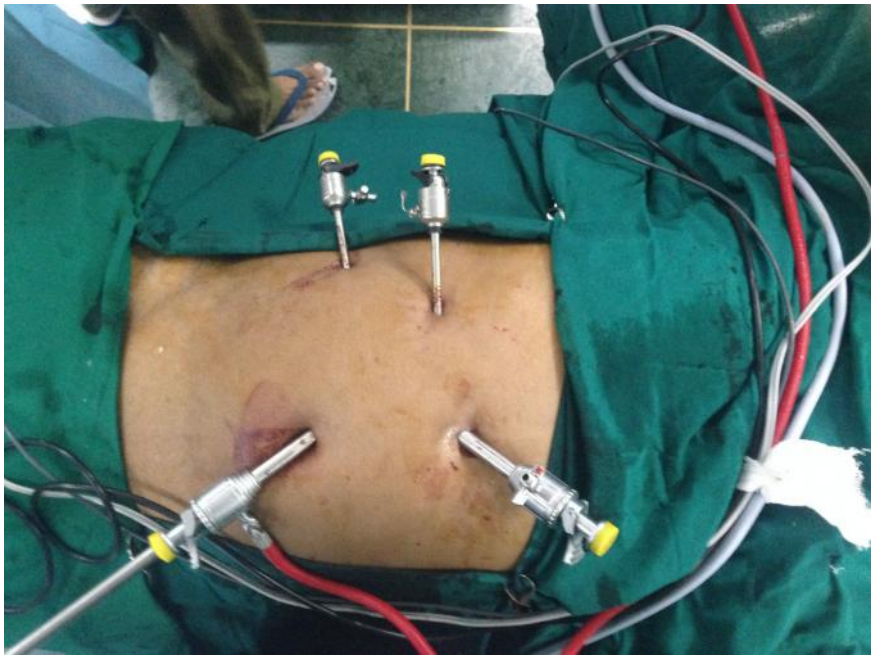


Illustration 7. Port placement

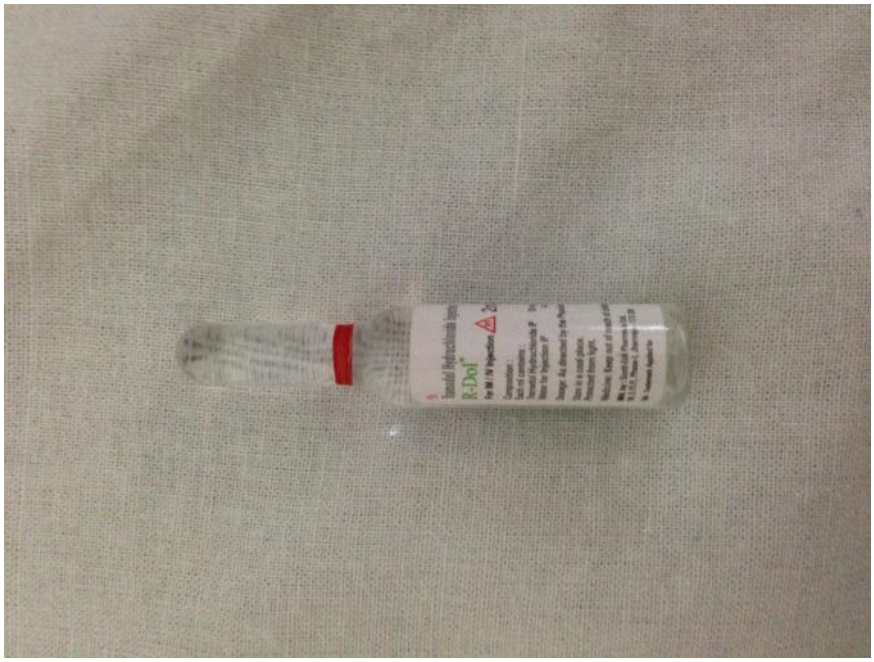


Illustration 8. Tramadol

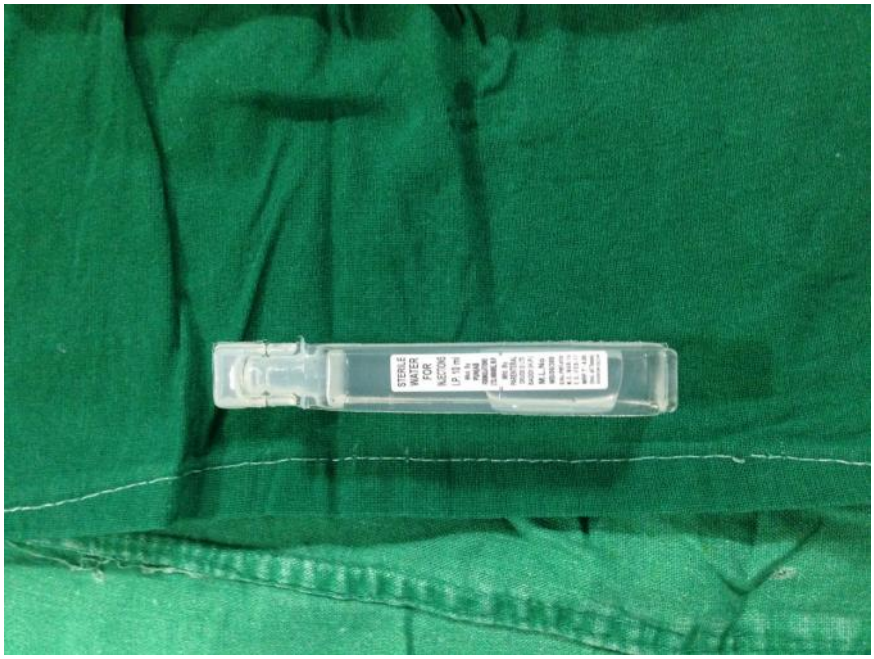


Illustration 9. Normal saline

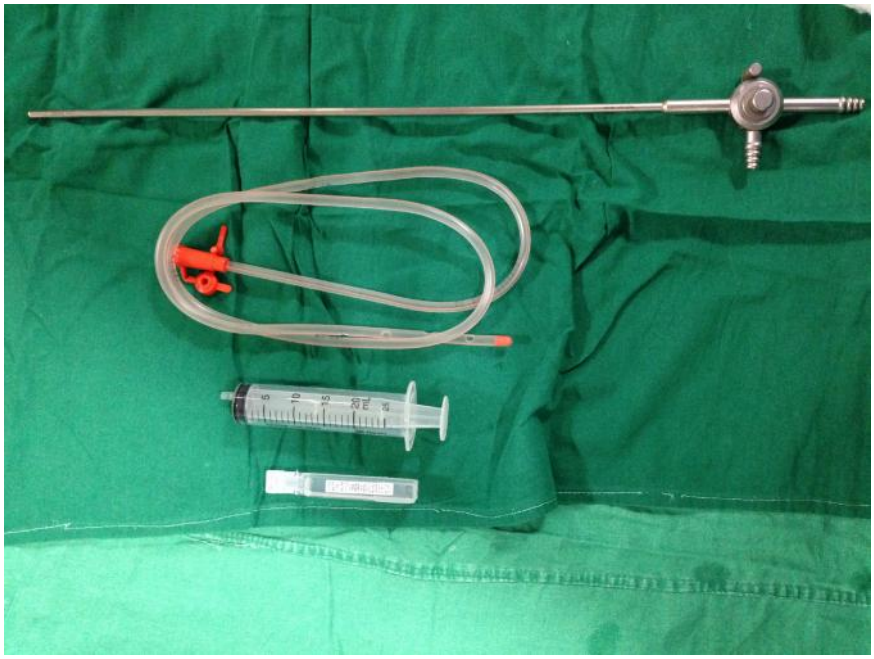


Illustration 10. Instruments used for instillation

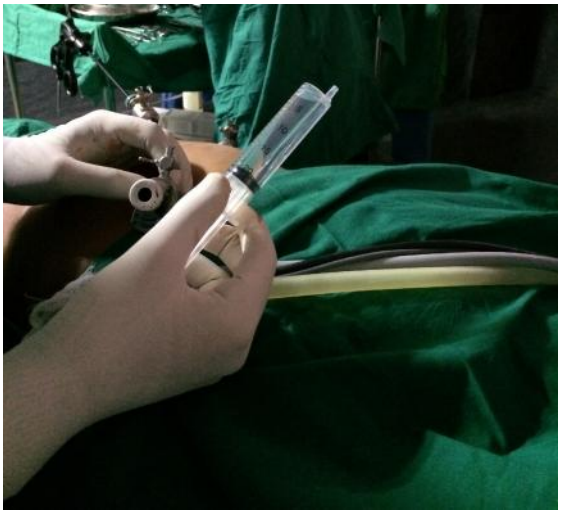


Illustration 11. Syringe loaded with 100 mg of tramadol and 20 ml distilled water

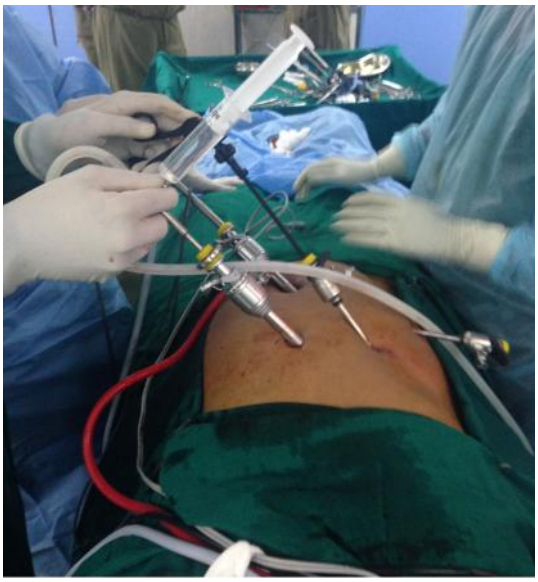


Illustration 12. Instillation of tramadol through irrigation suction cannula

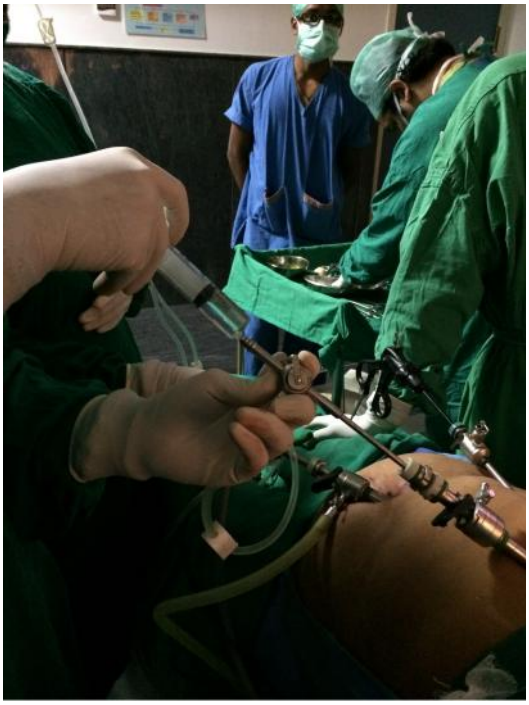


Illustration 13. Tramadol being instilled

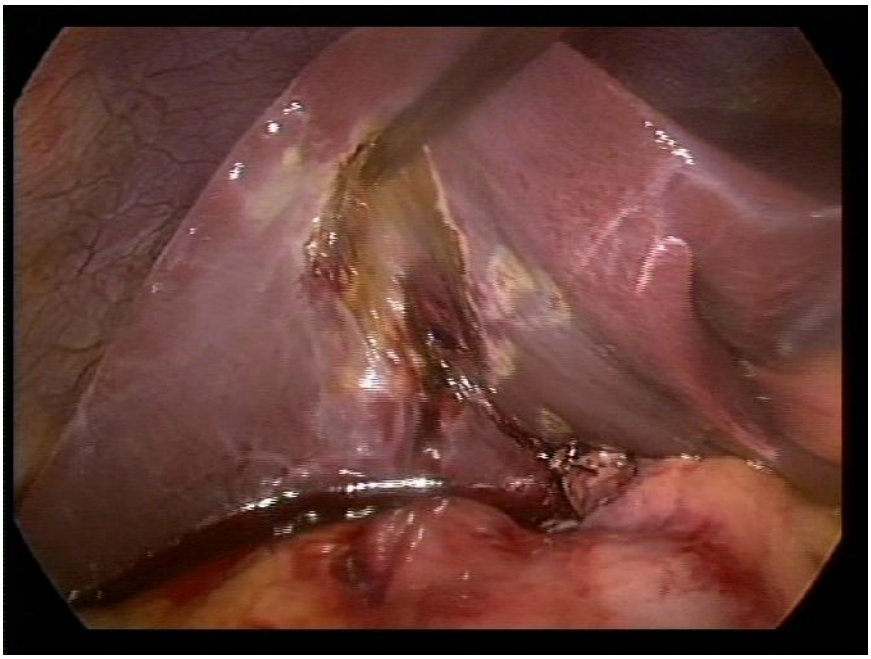


Illustration 14. Instillation of tramadol at gallbladder bed

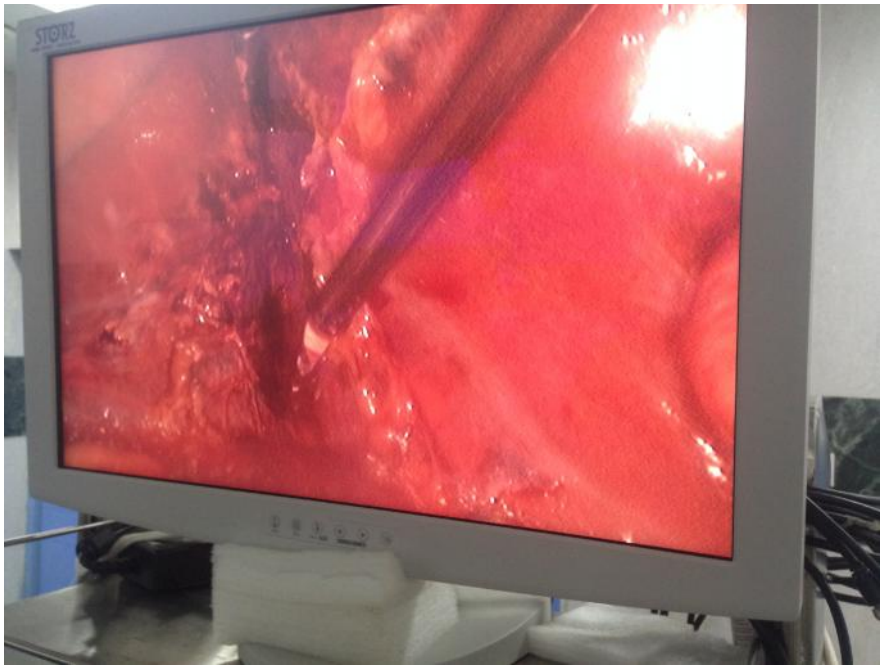


Illustration 15. Instillation of tramadol on liver bed

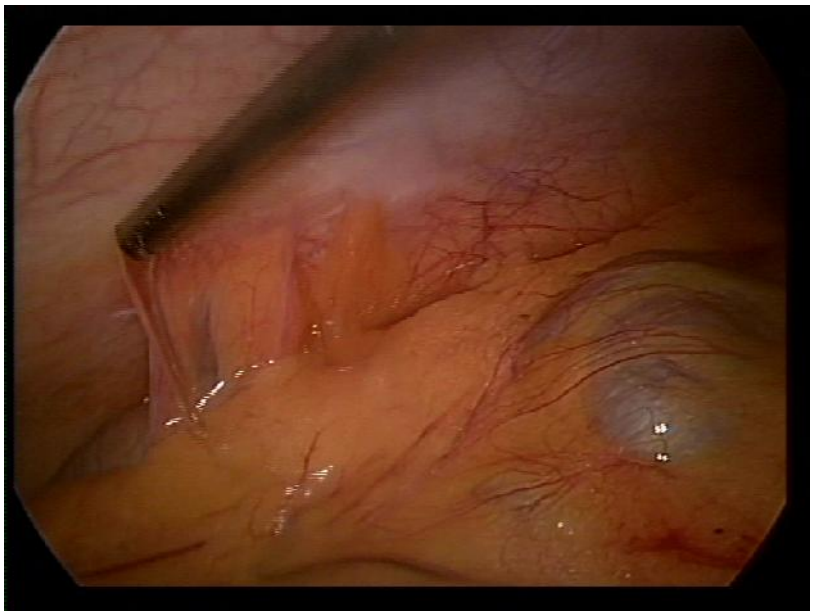


Illustration 16. Instillation of tramadol in Right morrisons

Outcome variables

Pain

Pain was assessed using Visual Analogue Score ranging from 0 to 10 considering 0 as no pain and 10 as maximum pain. Visual analogue scale of 0 to 10 was explained to patient during pre op visit, considering zero as no pain, 1 to 3 mild pain, 4 to 7 moderate pain and 7 to 10 severe pain. A score of below 4 out of ten was considered satisfactory. The assessment of pain was done immediate post op, 15 minutes, 30 minutes, 60 minutes, 4 hours, 8 hours, 12 hours, 16 hours and 24 hours. Patients with VAS greater than or equal to 4 were given inj. Diclofenac sodium 75mg im as a rescue analgesic.

Requirement of analgesia

Cumulative rescue analgesic requirement with 75 mg Diclofenac Sodium was noted immediately post op, 15 minutes, 30 minutes, 60 minutes, 4 hours, 8 hours, 12 hours and 24 hours.

Adverse effects

Incidence of adverse effect including nausea, vomiting, shoulder pain, itching were observed immediately post op, 4 hours, 8 hours, 12 hours, 16 hours and 24 hours.

Statistical analysis

The data obtained was coded and entered in Microsoft Excel Spreadsheet (Annexure III). The categorical data was expressed as rates, ratios and percentages

and comparison was done using Fishers exact test and chi-square test. Continuous data was expressed as mean ± standard deviation and the comparison was done using independent sample t test. A probability ('p' value) of less than or equal to 0.05 at 95% CI was considered as statistically significant.

RESULTS

The present one year double blinded randomized controlled trial was carried out at KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum from January 2013 to December 2013. A total of 60 patients posted for elective laparoscopic cholecystectomy under the Department of General Surgery were studied. The patients were divided into two groups of 30 each as below.

- Group T (n=30): Patients in this group received intraperitoneal tramadol 100 mg (diluted in 20 ml of distilled water).

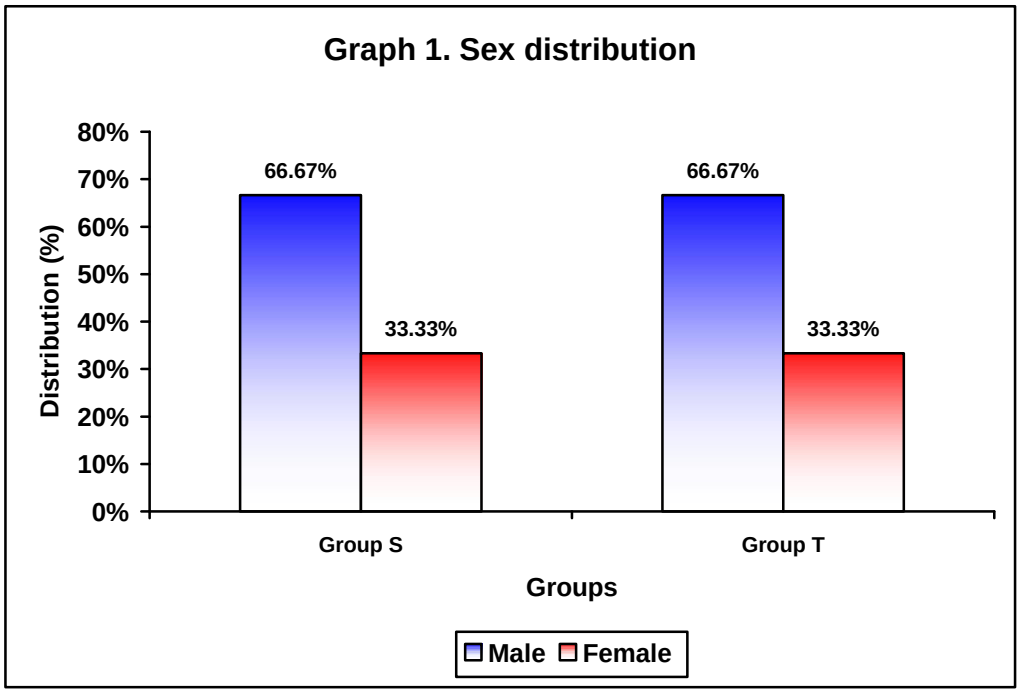
- Group S (n=30): Patients in this group received 20 ml of intraperitoneal normal saline.

The data obtained was tabulated and analysed. The final results and observations were tabulated as below.

Table 1. Sex distribution

Sex	Group S (n=30)		Group T (n=30)	
	Frequency	**Percentage**	**Frequency**	**Percentage**
Male	20	66.67	20	66.67
Female	10	33.33	10	33.33
Total	**30**	**100.00**	**30**	**100.00**

p = 1.000

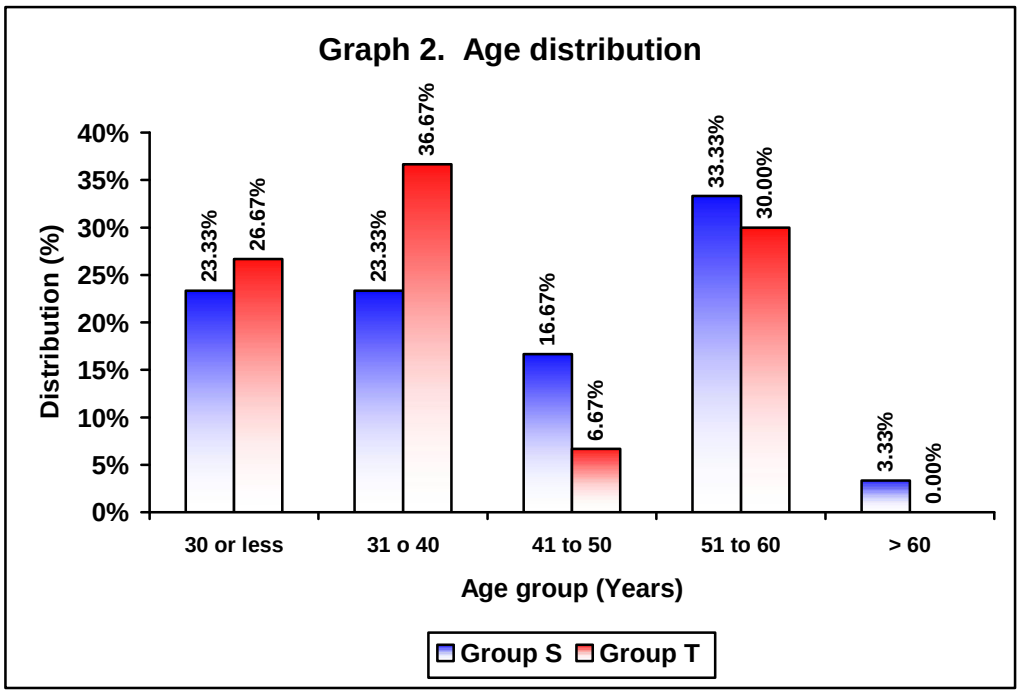


In the present study 66.67% of the patients each were males and 33.33% were females. The male to female ratio was 2:1 in group S and T. The sex distribution in group S and T was comparable (p=1.000).

Table 2. Age distribution

Age group (Years)	Group S (n=30)		Group T (n=30)	
	Frequency	**Percentage**	**Frequency**	**Percentage**
30 or less	7	23.33	8	26.67
31 to 40	7	23.33	11	36.67
41 to 50	5	16.67	2	6.67
51 to 60	10	33.33	9	30.00
> 60	1	3.33	0	0.00
Total	**30**	**100.00**	**30**	**100.00**

p = 0.510



In this study the commonest age group in patients with group S was 51 to 60 years (33%) compared to 31 to 40 in group T (36.67%). However the difference was statistically not significant (p=0.510).

Table 3. Comparison of mean age

Variables	Group S (n=30)		Group T (n=30)		p value
	Mean	SD	Mean	SD	
Age (Years)	42.20	13.03	39.83	11.66	0.461

In this study the mean age in group S was 42.20 ± 13.03 compared to 39.83 ± 11.66 years. However the difference was statistically not significant (p=0.461).

Table 4. Comparison of other comorbid conditions

Comorbid conditions	Findings	Group S (n=30)		Group T (n=30)		p value
		No.	%	No.	%	
Hypertension	Yes	5	16.67	4	13.33	1.000
	No	25	83.33	26	86.67	
	Total	**30**	**100.00**	**30**	**100.00**	
Diabetes mellitus	Yes	2	6.67	4	13.33	1.000
	No	25	83.33	26	86.67	
	Total	**27**	**90.00**	**30**	**100.00**	

In this study the comorbid conditions including hypertension and diabetes mellitus were comparable in both the groups (p=1.000).

Table 5. Comparison of clinical examination findings

Signs	Findings	Group S (n=30)		Group T (n=30)		p value
		No.	%	No.	%	
Tenderness	Yes	4	13.33	3	10.00	1.000
	No	26	86.67	27	90.00	
	Total	**30**	**100.00**	**30**	**100.00**	
Pain in Right hypochondrium	Yes	17	56.67	18	60.00	0.793
	No	13	43.33	12	40.00	
	Total	**30**	**100.00**	**30**	**100.00**	

In this study tenderness was noted in 13.33% and 10% of the patients in group S and T respectively. The right hypochondrium pain was present in 56.67% and 60% of the patients respectively. However these findings were comparable in group S and T (p>0.050).

Table 6. Comparison of mean duration of abdominal pain

Variables	Group S (n=30)		Group T (n=30)		p value
	Mean	SD	Mean	SD	
Duration (weeks)	7.18	4.48	6.60	3.65	0.587

In this study the mean duration of abdominal pain was comparable in group S and T (7.18 ± 4.48 vs 6.60 ± 3.65 weeks; p=0.587).

Table 7. Comparison mean weight and vitals

Variables	Group S (n=30)		Group T (n=30)		p value
	Mean	SD	Mean	SD	
Weight (Kgs)	70.27	12.92	67.97	9.74	0.440
Pulse rate (/Minute)	82.20	7.07	78.27	9.46	0.074
Respiratory rate (/Minute)	20.40	1.77	20.53	1.66	0.764
SBP (mm Hg)	123.90	12.66	121.40	8.34	0.371
DBP (mm Hg)	76.93	6.90	77.40	5.26	0.769

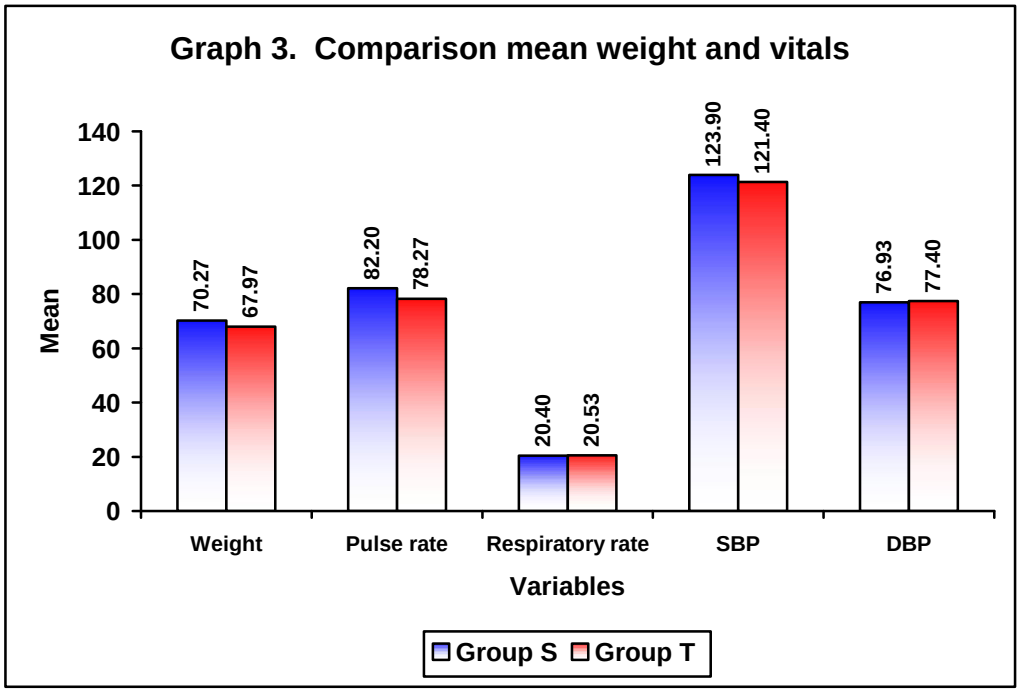


Table 7 and graph 3 shows comparison of mean weight and vitals. It was observed that the weight, pulse rate, respiratory rate, systolic and diastolic blood pressure were comparable in both the groups (p>0.050).

Table 8. Comparison of mean duration of surgery

Variables	Group S (n=30)		Group T (n=30)		p value
	Mean	SD	Mean	SD	
Duration (minutes)	96.37	21.69	96.83	17.80	0.928

In the present study mean duration of surgery was 96.37 ± 21.69 minutes in group S and in group T it was 96.83 ± 17.80 minutes. However the difference was statistically not significant (p=0.928).

Table 9. Comparison of postoperative mean VAS scores at different intervals

Intervals	Group S (n=30)		Group T (n=30)		p value
	Mean	SD	Mean	SD	
Immediate post op	3.13	1.01	0.20	0.41	<0.001
15 minutes	2.03	0.67	0.23	0.43	<0.001
30 minutes	1.47	0.68	0.33	0.48	<0.001
60 minutes	1.30	0.84	0.60	0.56	<0.001
4 hours	2.10	0.71	1.30	0.47	<0.001
8 hours	2.50	0.82	1.77	1.04	0.004
12 hours	2.37	0.93	1.87	0.78	0.027
24 hours	2.33	0.71	2.07	0.91	0.210

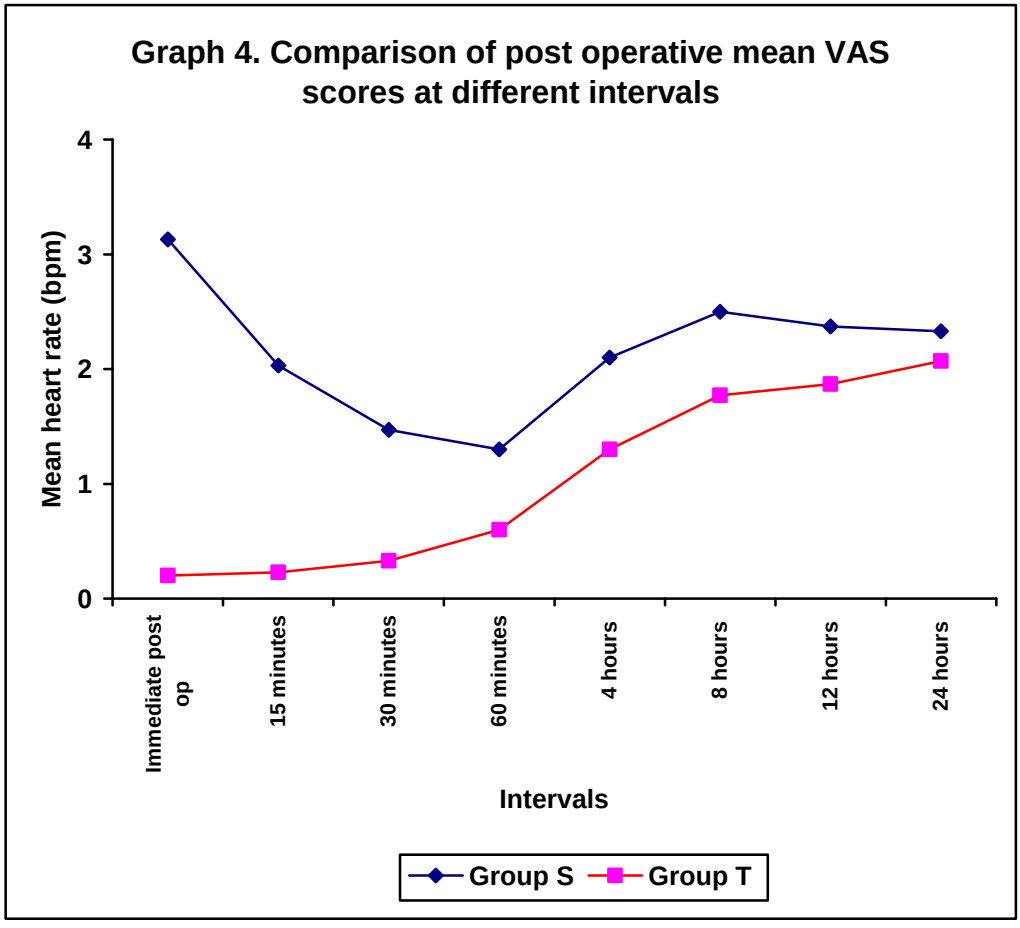
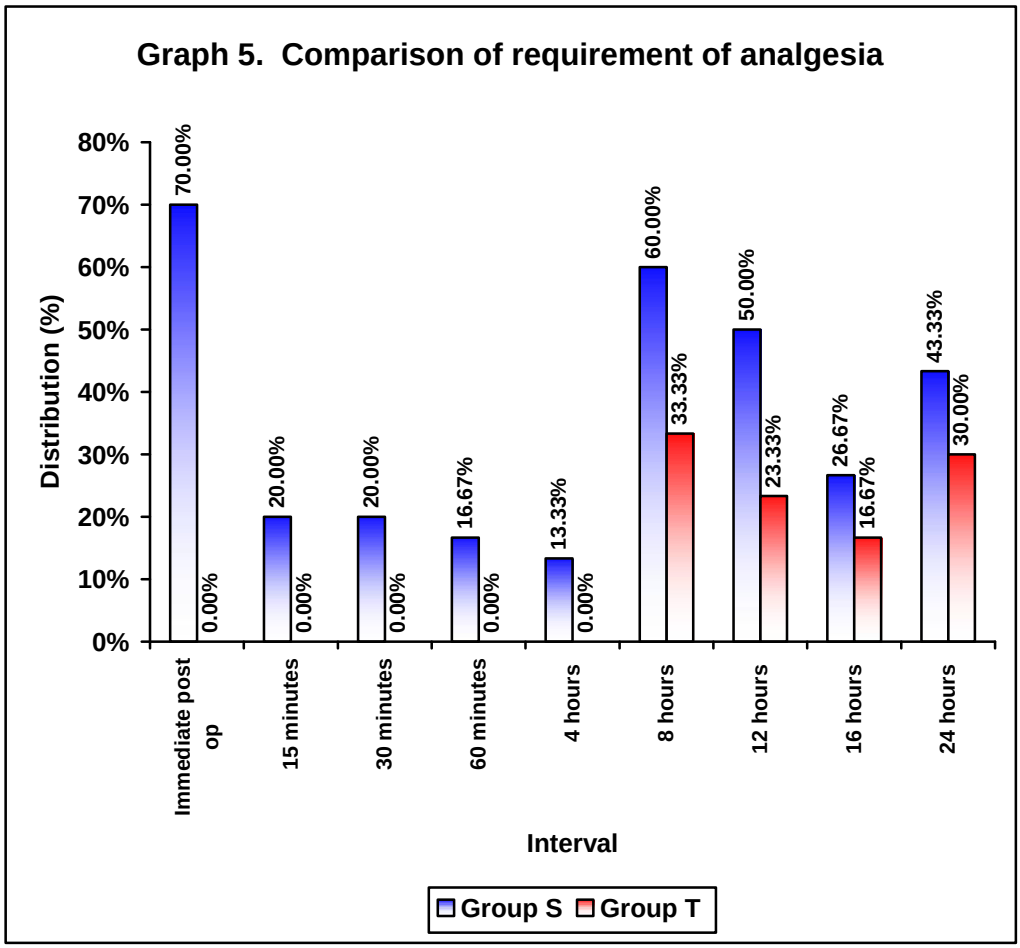


Table 9 and graph 4 shows the mean pain score at different intervals. It was observed that, in patients with group T, the mean pain scores at all the intervals were significantly low ($p<0.050$) except at 24 hours where the mean pain score in group T were low but the difference was statistically not significant ($p=0.210$).

Table 10. Comparison of requirement of analgesia

	Findings	Group S (n=30)		Group T (n=30)		p value
		No.	%	No.	%	
Immediate post operative	Yes	21	70.00	0	0.00	**< 0.001**
	No	9	30.00	30	100.00	
	Total	**30**	**100.00**	**30**	**100.00**	
15 minutes	Yes	6	20.00	0	0.00	**0.031**
	No	24	80.00	30	100.00	
	Total	**30**	**100.00**	**30**	**100.00**	
30 minutes	Yes	6	20.00	0	0.00	**0.031**
	No	24	80.00	30	100.00	
	Total	**30**	**100.00**	**30**	**100.00**	
60 minutes	Yes	5	16.67	0	0.00	**0.062**
	No	25	83.33	30	100.00	
	Total	**30**	**100.00**	**30**	**100.00**	
4 hours	Yes	4	13.33	0	0.00	**0.121**
	No	26	86.67	30	100.00	
	Total	**30**	**100.00**	**30**	**100.00**	
8 hours	Yes	18	60.00	10	33.33	**0.038**
	No	12	40.00	20	66.67	
	Total	**30**	**100.00**	**30**	**100.00**	
12 hours	Yes	15	50.00	7	23.33	**0.032**
	No	15	50.00	23	76.67	
	Total	**30**	**100.00**	**30**	**100.00**	
16 hours	Yes	8	26.67	5	16.67	**0.347**
	No	22	73.33	25	83.33	
	Total	**30**	**100.00**	**30**	**100.00**	
24 hours	Yes	13	43.33	9	30.00	**0.284**
	No	17	56.67	21	70.00	
	Total	**30**	**100.00**	**30**	**100.00**	



In the present study the requirement of analgesia was significantly high in group S as compared to group T at immediate post op, 15 minutes, 30 minutes, 8 hours and 12 hours ($p<0.050$). However, at 60 minutes, 4 hours, 16 hours and 24 hours duration the requirement of analgesia was low in group T compared to group S but the difference was statistically not significant ($p>0.050$).

Table 11. Comparison of postoperative mean requirement of analgesia at different intervals

Intervals	Group S (n=30)		Group T (n=30)		p value
	Mean	SD	Mean	SD	
Immediate post op	0.70	0.47	0.00	0.00	<0.001
15 minutes	0.20	0.41	0.00	0.00	0.012
30 minutes	0.07	0.25	0.00	0.00	0.161
60 minutes	0.07	0.25	0.00	0.00	0.161
4 hours	0.13	0.35	0.00	0.00	0.043
8 hours	0.60	0.50	0.33	0.48	0.039
12 hours	0.37	0.49	0.27	0.45	0.414
16 hours	0.27	0.45	0.17	0.38	0.356
24 hours	0.43	0.50	0.30	0.47	0.292

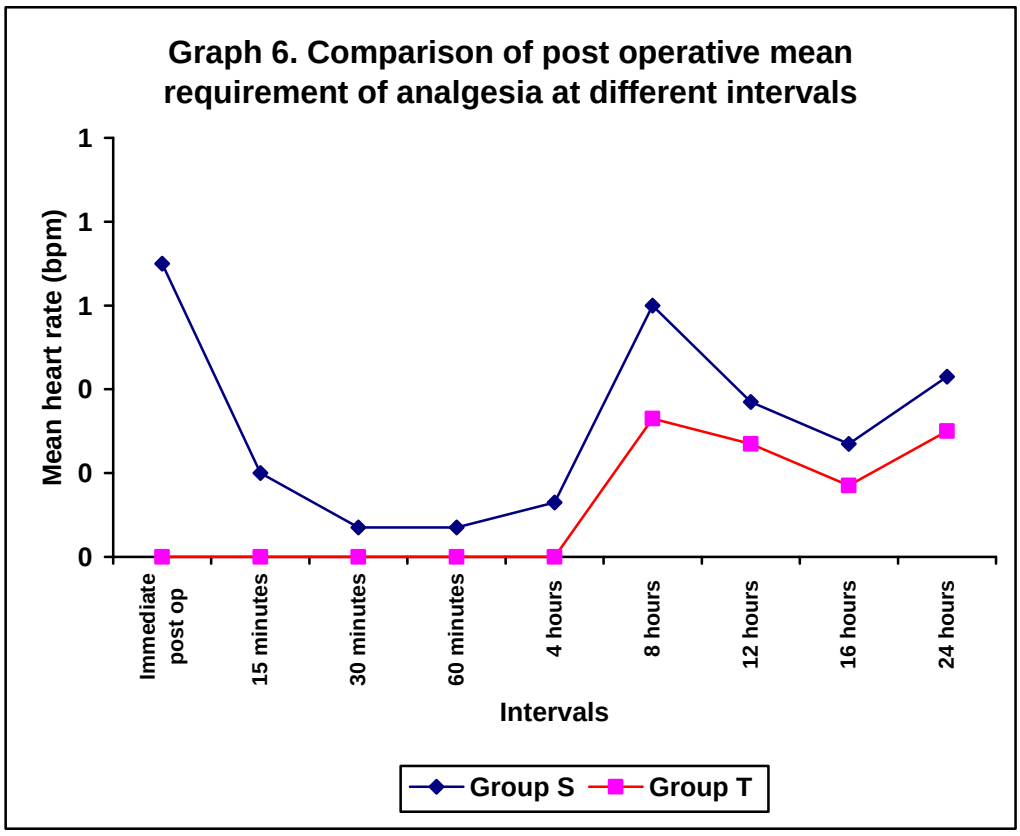
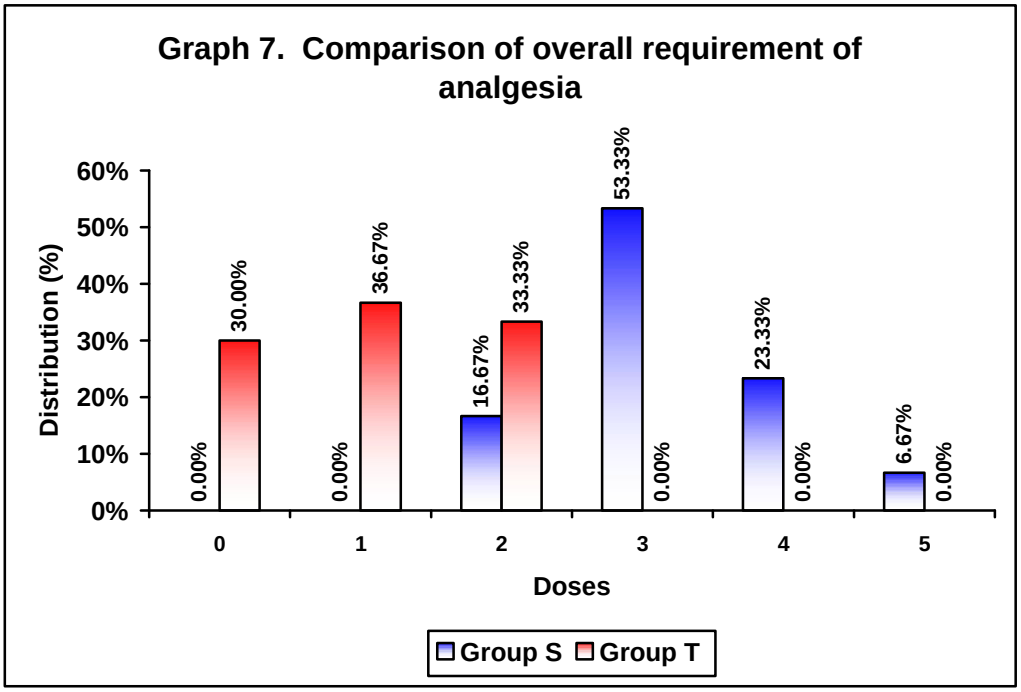


Table 11 and graph 6 shows comparison of mean requirement of analgesia at different intervals. It was observed that, the mean requirement of analgesia at immediate post op, 15 minutes, 4 hours and 8 hours was significantly low in group T compared to group S ($p<0.050$). Though the mean requirement in group T was less compared to group S at 30 minutes, 60 minutes, 12 hours, 16 hours and 24 hours the difference was statistically not significant ($p>0.050$).

Table 12. Comparison of overall requirement of analgesia

Doses	Group S (n=30)		Group T (n=30)	
	Frequency	Percentage	Frequency	Percentage
0	0	0.00	9	30.00
1	0	0.00	11	36.67
2	5	16.67	10	33.33
3	16	53.33	0	0.00
4	7	23.33	0	0.00
5	2	6.67	0	0.00
Total	**30**	**100.00**	**30**	**100.00**

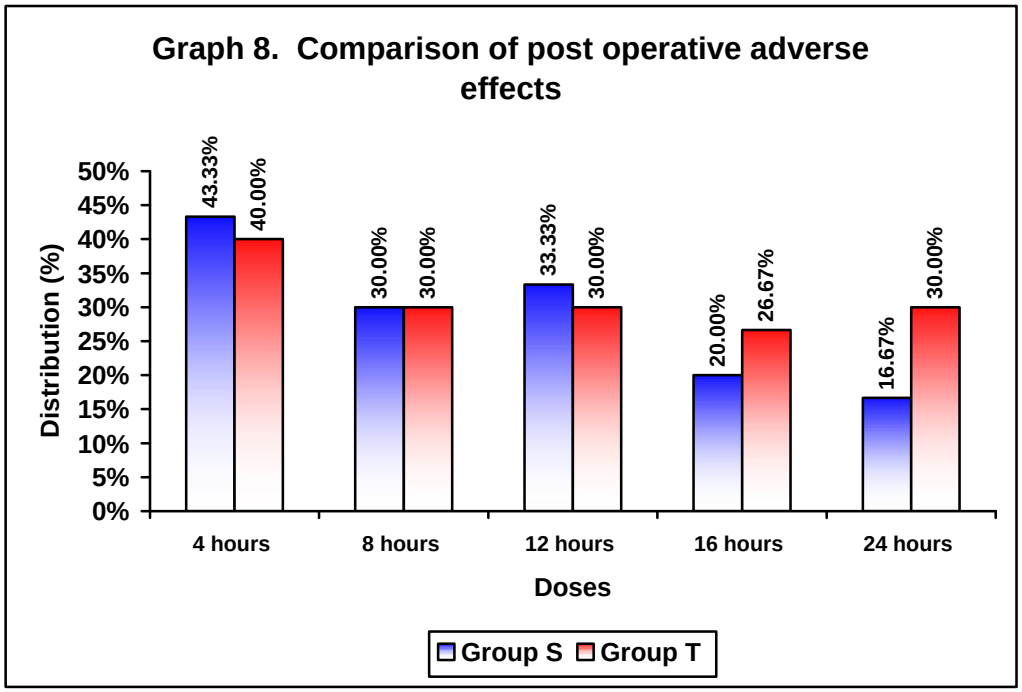
Chi-square test **p < 0.001**



In the present study significantly higher patients (30%) in group T did not require analgesia at all compared to S (p<0.001).

Table 13. Comparison of postoperative adverse effects

Interval	Adverse effects	Group S (n=30)		Group T (n=30)		p value
		No.	%	No.	%	
4 hours	Present	13	43.33	12	40.00	
	Absent	17	56.67	18	60.00	**0.793**
	Total	**30**	**100.00**	**30**	**100.00**	
8 hours	Present	9	30.00	9	30.00	
	Absent	21	70.00	21	70.00	**1.000**
	Total	**30**	**100.00**	**30**	**100.00**	
12 hours	Present	10	33.33	9	30.00	
	Absent	20	66.67	21	70.00	**0.781**
	Total	**30**	**100.00**	**30**	**100.00**	
16 hours	Present	6	20.00	8	26.67	
	Absent	24	80.00	22	73.33	**0.542**
	Total	**30**	**100.00**	**30**	**100.00**	
24 hours	Present	5	16.67	9	30.00	
	Absent	25	83.33	21	70.00	**0.222**
	Total	**30**	**100.00**	**30**	**100.00**	



In the present study higher incidence of adverse effects at 4 hours interval was 43% in group S compared to 40% in group T. However the incidence of adverse effects at all the intervals were comparable ($p>0.050$).

Table 14. Comparison of adverse effects at post operative

	Adverse effects	Group S (n=30)		Group T (n=30)	
		No.	**%**	**No.**	**%**
4 hours	Nausea	3	10.00	4	13.33
	Vomiting	1	3.33	1	3.33
	Sedation	9	30.00	9	30.00
	Total	**13**	**43.33**	**14**	**46.67**
8 hours	Nausea	5	16.67	5	16.67
	Sedation	4	13.33	4	13.33
	Shoulder pain	1	3.33	0	0.00
	Total	**10**	**33.33**	**9**	**30.00**
12 hours	Nausea	6	20.00	5	16.67
	Vomiting	2	6.67	1	3.33
	Shoulder pain	0	0.00	3	10.00
	Shivering	0	0.00	1	3.33
	Sedation	3	10.00	3	10.00
	Total	**11**	**36.67**	**13**	**43.33**
16 hours	Nausea	4	13.33	4	13.33
	Sedation	3	10.00	3	10.00
	Shoulder pain	2	6.67	1	3.33
	Vomiting	1	3.33	0	0.00
	Total	**10**	**33.33**	**8**	**26.67**
24 hours	Nausea	2	6.67	3	10.00
	Sedation	2	6.67	2	6.67
	Shoulder pain	2	6.67	4	13.33
	Shivering	1	3.33	0	0.00
	Vomiting	3	10.00	2	6.67
	Total	**10**	**33.33**	**11**	**36.67**

The incidence of adverse effects at different intervals is as shown in table 14.

DISCUSSION

Gallstone disease is a global health problem. The worldwide incidence is 10–20% of the whole adult population, making laparoscopic cholecystectomy one of the most frequently performed operations in the world.[2] Most patients are asymptomatic and gallstones are generally detected with ultrasonography during the evaluation of unrelated medical conditions.

Since the first Laparoscopic Cholecystectomy performed by Prof. Dr. Med Erich Mühe of Böblingen, Germany in 1985, the procedure has become widespread, significantly changing the surgical management of gallbladder disease. Over the past two decades, Laparoscopic cholecystectomy has become the gold standard for the surgical treatment of gallbladder disease. A shorter hospital stay (and thus, a more rapid return to normal activity and work), less postoperative pain, a faster recovery, better cosmesis, and lower cost are some of the advantages of Laparoscopic cholecystectomy over open surgery.[2]

However, postoperative pain remains one of the main cause of delay in resumption of activities after laparoscopic cholecystectomy. Despite better understanding of pain pathophysiology, pharmacology of analgesics and development of newer more effective analgesic techniques, many patients still continue to experience considerable discomfort. Laparotomy results mainly in parietal pain, laparoscopy has a visceral component, a somatic component and shoulder pain secondary to diaphragmatic irritation as a result of CO2 pneumoperitoneum.

To date, a number of methods have been tried to reduce postoperative pain after laparoscopic cholecystectomy such as use of non steroidal anti-inflammatory drugs,[87] use of local anesthetic intraperitoneally,[86] low pressure pneumoperitoneum,[88] use of humidified carbon dioxide,[89] time of instillation of drug intraperitoneally.[90]

Many authors have conducted studies on intraperitoneal administration of local anesthetics using bupivacaine, ropivacaine, buprenorphine during laparoscopic cholecystectomy for relief of postoperative pain. However scant studies were available to know analgesic efficacy of intraperitoneal tramadol for postoperative pain relief after laparoscopic cholecystectomy. The present study hypothesized that, analgesia delivered locally to the peritoneal cavity using tramadol may benefit the patients in peritoneal origin of the postoperative pain. Hence, the present study was planned to find the effectiveness of intraperitoneal instillation of tramadol for postoperative laparoscopic cholecystectomy in terms of pain relief, reduction in need for rescue analgesic after laparoscopic cholecystectomy, especially visceral pain and shoulder pain, incidence of adverse effect (nausea, vomiting, shoulder pain, itching and shivering) following laparoscopic cholecystectomy.

This one year double blinded randomized controlled trial was carried out on a total of 60 patients posted for elective cholecystectomy under the Department of General Surgery at KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum from January 2013 to December 2013. The patients were divided into two groups of 30 that is, group T (Patients received intraperitoneal tramadol 100 mg diluted in 20 mL of distilled water) and group S (Patients received 20 mL of intraperitoneal normal saline).

In the present slight male preponderance was observed with 66.67% of the patients each in both the groups and the male to female ratio was 2:1 in both the groups (p=1.000). In group S, 33% of the patients had age between 51 to 60 years and in group T 36.67% of the patients were aged from 31 to 40 years (p=0.510). The mean age in group S and group T was comparable (42.20 ± 13.03 vs 39.83 ± 11.66 years; p=0.461). These findings suggest that the demographic characteristics of the study population were comparable in both the groups.

Further, the history of comorbid conditions (hypertension and diabetes mellitus), presentation (tenderness and right hypochondrium), duration of abdominal pain, weight, vitals (pulse rate, respiratory rate, systolic and diastolic blood pressure) were comparable in group S and T (p>0.050). The mean duration of surgery among the patients with group S was noted as 96.37 ± 21.69 minutes and in group T it was 96.83 ± 17.80 minutes. However the difference was statistically not significant (p=0.928). These findings rule out the bias of the confounding variables in the outcome as the clinical presentation, examination and surgical characteristics were comparable in group S and T.

In the present study the mean pain scores in group T were found to be low immediate post op that is, 0.20 ± 0.41 and there was a gradual increase in score with respect to time interval with peak of 2.07 ± 0.91 at 24 hours. Whereas, in group S the mean pain scores immediate post op were at its peak that is, 3.13 ± 1.01 which decreased to 1.30 ± 0.84 at 60 minutes and further there was rise at 4 hours (2.10 ± 0.71) and 8 hours (2.50 ± 0.82) and marginally decreased at 12 hour (2.37 ± 0.93) and 24 hours (2.33 ± 0.0.71). But at any point of time the mean VAS remained significantly low (p<0.050) in patients with group T compared to group S except at

24 hours (p=0.210). These findings indicate that intraperitoneal instillation of tramadol results in significant lower pain among the patients undergoing laparoscopic cholecystectomy. These results were consistent with findings of Golubonic S. et al[82] (2009) who used 50 ml of saline containing 100 mg of tramadol instilled intraperitoneally in laparoscopic cholecystectomy and showed significant reduction in VAS in tramadol group as compared to control (saline) group at 30 minutes, 1 hour, 2 hour, 4 hour and 6 hours. Mean pain scores in control group were high as compared to tramadol group at all time intervals in first 24 hours. Another study by Golubovic S et al[91] in 2007 also found that intraperitoneal administration of tramadol had valuable implication in reducing VAS score / pain in patients undergoing laparoscopic cholecystectomy.

A similar study[84] in PGIMER, Chandigarh India on 40 ASA I and II patients of either sex, undergoing laparoscopic cholecystectomy under general anaesthesia in a double blind, randomised controlled manner divided the patients into two groups to receive 20 ml of normal saline intraperitoneally (group 1) or 20 ml of 0.5% bupivacaine with 1:200,000 adrenaline (group 2) instilled at the end of surgery in the trendlenberg position. Postoperatively the patients were assessed for pain scores at 1, 4, 8, 12 and 24 hours. The VAS was significantly higher in group 1 compared to group 2 at 1st, 4th and 8th postoperative hour ($P<0.001$; $p<0.05$). Authors concluded that intraperitoneal instillation of bupivacaine causes good pain relief after laparoscopic cholecystectomy.

Hernandes-Palazon et al[92] (2003) found that intraperitoneal administration of local anesthetic (bupivacaine) in combination with an opioid (morphine) reduced the

analgesic requirements during the first 6 postoperative hours, and that a combination is more effective for treatment of pain after laparoscopic cholecystectomy.

However, the findings of this study as well as the other studied was contradicted by Akinci et al in 2008[18] who showed that, pain scores in control group were less as compared to intraperitoneal tramadol group in first 24 hours postoperatively but, the findings were statistically not significant except at 15 minutes. These findings may be attributed to small sample size of study group in a study by Akinci et al[18] (n=20 in each group).

Peripheral antinocicepive effect of opioids occurred due to interaction of opioids with opioid receptor located on peripheral intact perineureium prevent entry of hydrophilic opioid molecule such as morphine, hydromorphine, oxydone, so block their access to the neural receptors while lipophilic opioids such as tramadol, buprenorphine, fentanyl can diffuse across the intact perineural barrier so results in better analgesia on intraperitoneal administration.

Tramadol is centrally acting synthetic opioid analgesic having affinity for μ-receptors and inhibit neural uptake of serotonin and norepinephrine. It also has local anesthetic property and its analgesic activity depends mainly upon generation of metabolite (+)-O-desmethyl-tramadol (M1).[13]

The present study showed significantly lower requirement of analgesia in patients with group T compared to group S ($p<0.050$). None of the patient required analgesia till 4 hour duration and further at 8 hours, 12 hours, 16 hours, and 24 hours 33.33%, 23.33%, 16.67% and 30% requested for analgesia. Whereas in group S, the requirement of analgesia was noted at every interval and minimum number of

patients requested for analgesia at 30 minutes and 60 minutes duration. However, the requirement of analgesia at every interval was low in group T compared to group S but it was statistically significant at post op immediately, 15 minutes, 30 minutes, 8 hours and 12 hours ($p<0.050$). Though, at 60 minutes, 4 hours, 16 hours and 24 hours interval, the requirement of analgesia was low in group T compared to group S, the difference was statistically not significant ($p>0.050$). Also, the number of doses required in group T were limited to a maximum of two doses that is, 30% did not request for post operative analgesia at all through out the monitoring and 36.67% required one dose and 33.33% requested for two doses. Whereas, in group S, few patients requested for even three (53.33%), four (23.33%) and five doses (6.67%) suggesting significantly higher requirement of analgesia in group S ($p<0.001$). These findings implicate the lower pain levels in patients with intraperitoneal instillation of tramadol undergoing laparoscopic cholecystectomy.

Mean cumulative requirement of rescue analgesic in 1st and 24 hour were significantly less in study group as compared to control group which is consistent with study done by Snjenaza et al[93] (2009). The findings of this study were consistent with a study done by Snjenaza et al[93] (2009) Who reported significantly less cumulative requirement of rescue analgesic in study group as compared to control group. Another study[84] from PGIMER, Chandigarh India also reported that, total number of patients requiring analgesics was higher for control group than study group ($p<0.050$).

In the present study higher incidence of adverse effects at 4 hours interval was 43% in group S compared to 40% in group T. At four hours interval, maximum patients complained of sedation (30%) in both the groups while at 8, 12, 16 hour and

24 hours maximum patients had nausea. However, the incidence of adverse effects at all the intervals was comparable in both the groups ($p>0.050$). A similar study[84] from PGIMER, Chandigarh India also reported no adverse effects in patients with study group compared to control group. Thus, tramadol when used at the same doses as in our study does not seem to carry the risks that are associated with potent opioids and thus can be safely given intraperitoneally.

The pain relief till 12 hours post operatively noted in the present study was statistically significant while though VAS scores were low at 24 hours interval in tramadol group but the difference was statistically not significant ($p=0.216$) The duration of pain relief observed in the present study was high compared to studies by Golubonic et S. al (2009)[82] who reported significant reduction in VAS in tramadol group as compared to control (saline) group till the duration of six hours and Hernandes-Palazon et al[93] (2003) also reported the same duration of pain relief with intraperitoneal administration of local anesthetic (bupivacaine) in combination with an opioid (morphine). However, a study[84] from PGIMER, Chandigarh using bupivacaine with 1:200,000 adrenaline showed significantly lower VAS scores at 1st, 4th and 8th postoperative hour ($p<0.05$). These findings implicate the beneficial effect of tramadol when instilled intraperitoneally as compared to local anaethetics such as bupivacaine and other drugs.

Overall the present study showed that, intraperitoneal instillation of tramadol results in good pain relief after laparoscopic cholecystectomy with no adverse effects and may be adopted in the routine practice.

CONCLUSION

Based on the findings of this it may be concluded that, intraperitoneal instillation of tramadol for postoperative laparoscopic cholecystectomy has beneficial effect in terms of postoperative pain relief following laparoscopic cholecystectomy and lower requirement of analgesia. However, the incidence of complications was comparable in both the groups.

SUMMARY

Gallstone disease is a global health problem and Laparoscopic cholecystectomy is the gold standard for the surgical treatment of gallbladder disease. However, postoperative pain remains one of the main cause of delay in resumption of activities after laparoscopic cholecystectomy. The present study was aimed to find the effectiveness of intraperitoneal instillation of tramadol for postoperative laparoscopic cholecystectomy in terms of pain relief, especially visceral pain and shoulder pain, incidence of adverse effect (nausea, vomiting, shoulder pain, itching and shivering) following laparoscopic cholecystectomy.

This one year double blinded randomized controlled trial was done under the Department of Surgery, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum from January 2013 to December 2013. A total of 60 patients posted for elective cholecystectomy were studied. The patients were divided into two groups of 30 each as Group T (Intraperitoneal tramadol) and Group S (Intraperitoneal normal saline).

In the present study 66.67% of the patients each were males and male to female ratio was 2:1 in group S and T (p=1.000). The commonest age group in patients with group S was 51 to 60 years (33%) compared to 31 to 40 in group T (36.67%) (p=0.510) and the mean age in group S was 42.20 ± 13.03 compared to 39.83 ± 11.66 years (p=0.461). Comorbid conditions including hypertension and diabetes mellitus were comparable in both the groups (p=1.000). Tenderness was noted in 13.33% and 10% of the patients in group S and T respectively. Right hypochondrium was present in 56.67% and 60% of the patients respectively

(p>0.050). The mean duration of abdominal pain was comparable in group S and T (7.18 ± 4.48 vs 6.60 ± 3.65 weeks; p=0.587). The mean duration of surgery was 96.37 ± 21.69 minutes in group S and in group T it was 96.83 ± 17.80 minutes (p=0.928). In patients with group T, the mean pain scores at all the intervals were significantly low (p<0.050) except at 24 hours (p=0.210). The requirement of analgesia was significantly high in group S compared to group T immediate post op, 15 minutes, 50 minutes, 8 hours and 12 hours (p<0.050). The mean requirement of analgesia immediate post op, 15 minutes, 4 hours and 8 hours was significantly low in group T compared to group S (p<0.050). Significantly higher patients (30%) in group T did not require analgesia at all compared to S (p<0.001). Higher incidence of adverse effects at 4 hours interval was 43% in group S compared to 40% in group T (p>0.050).

Overall, intraperitoneal instillation of tramadol for postoperative laparoscopic cholecystectomy is beneficial in terms of postoperative pain relief following laparoscopic cholecystectomy.

BIBLIOGRAPHY

1. Abbasi SA, Azami R, Haleem A, Tariq GR, Iqbal A, Almas D, et al. An audit of laparoscopic cholecystectomies performed at PNS Shifa. Pak Armed Forces Med J 2003;53:51–8.

2. Mehraj A, Naqvi MA, Feroz SH, ur Rasheed H. Laparoscopic cholecystectomy:an audit of 500 patients. J Ayub Med Coll Abbottabad 2011;23(4):88-90.

3. Yeh CN, Chen MF, Jan YY. Laparoscopic cholecystectomy in 226 cirrhotic patients. Experience of a single center in Taiwan. Surg Endosc 2002;16:1583–7.

4. Yeh CN, Chen MF, Jan YY. Laparoscopic cholecystectomy for 58 end stage renal disease patients. Surg Endosc 2005;19:915–8.

5. Paul FW. The changing role of non-opioid analgesic techniques in the management of postoperative pain. Anesth Analg 2005;101:5-22.

6. Miller RD. Miller's anaesthesia. 6th ed., Philadelphia: Elsevier, Churchill Livingstone; 2005.

7. Rawal N, Allvin R, Amilon A. Postoperative analgesia at home after ambulatory hand surgery: A controlled comparison of tramadol, metamizol and paracetamol. Anesth Analg 2001;92:347-51.

8. Inan A, Sen M, Dener C. Local anesthesia use for laparoscopic cholecystectomy. World J Surg 2004;28:741–4.

9. Wills VL, Hunt DR. Pain after laparoscopic cholecystectomy. Br J Surg 2000;87:273–84.

10. O'Hanlon D, Colber H, Ragheb J, McEntee J, Chambers F, Moriarty D. Intraperitoneal Pethidine versus Intramuscular Pethidine for the Relief of Pain after Laparoscopic Cholecystectomy. World J Surg 2000;26:1432-6.

11. Ure BM, Troidl H, Spangenberger W, Neugebauer E, Lefering R, Ullmann K, et al. Preincisional local anaesthesia with bupivacaine and pain after laparoscopic cholecystectomy:a double-blind randomized clinical trial. SurgEndosc 1993;7:482-8.

12. Aitola P, Airo I, Kaukinen S, Ylitalo P. Comparison of N2O and CO2 pneumoperitoneums during laparoscopic cholecystectomy with special reference to postoperative pain. Surg Laparosc Endosc 1998;8:140-4.

13. Grond S, Sablotzki A. Clinical pharmacology of tramadol. Clin Pharmacokinet 2004;43(13):879-923.

14. Dayer P, Desmeules J, Collart L. Pharmacology of tramadol. Drugs 1997;53 Suppl 2:18-24.

15. Robaux S, Blunt C, Viel E, Cuvillon P, Nouguier P, Dautel G, et al. Tramadol added to 1.5% mepivacaine for axillary brachial plexus block improves postoperative analgesia dose-dependently. Anesth Analg 2004;98:1172–7.

16. Altunkaya H, Ozer Y, Kargi E, Babuccu O. Comparison of local anesthetic effects of tramadol with prilocaine for minor surgical procedures. Br J Anaesth 2003;90:320–2.

17. Altunkaya H, Ozer Y, Kargi E, Ozkocak I, Hosnuter M, Demirel CB, et al. The postoperative analgesic effect of tramadol when used as subcutaneous local anesthetic. Anesth Analg 2004;99:1461–4.

18. Akinci SB, Saricaoglu F, Atay OA, Doral MN, Kanbak M. Analgesic effect of intra-articular tramadol compared with morphine after arthroscopic knee surgery. Arthroscopy 2005;21:1060–5.

19. Chung F, Ritchie E, Su J. Postoperative pain in ambulatory surgery. Anesth Analg 1997;85:808–16.

20. Karan JA, Rose GJ. Cholelethiasis and cholecystectomy. In:Zynnel MJ, Schwartz SI, ellis H eds. Manigots abdominal operation. 10th ed. New York: McGraw Hill Publishers; p. 1717-38.

21. Russell JC, Walsh SJ, Reed-Fourquet L, Mattie A, Lynch J. Symptomatic Cholelithiasis:A different disease in Men. Ann Surg 1998;227:195-200.

22. Blumgart LH. Gallstones and gallbladder. In: Blumgart LH, Fong Y eds Text book of Surgery of liver and biliary tract. Vol 1. London: Harcourt Publishers; 2002. p. 617-791.

23. Pickleman J, Ganzalez RP. The improving results of cholecystectomy. Arch Surg 1986;121:930-4.

24. Talamani MA, Gadacz TR. Gallstone dissolution Surg Clin North Am 1990;70 (6):1217-30.

25. Olsen DO. Laparoscopic Cholecystectomy In:MacJadyer BV eds. Laparascopic surgery of abdomen. New York:Springer Publication;2004.

26. Strasberg SM, Hertl M, Soper NJ. An analysis of the problem of biliary injury during laparoscopic cholecystectomy. J Am Coll Surg 1995;180: 101–25.

27. Nagral S. Anatomy relevant to cholecystectomy. J Minim Access Surg 2005;1(2):53–58.

28. Pichumoni CS. Increasing prevalence of gallstones: Diagnostic and therapeutic options. API India update. Available from: URL: www. apiindia.org/pdf/medicine_update.../ge_and_hepatology_05b.pdf Access Date:18.06.2014.

29. Sarin SK,Negi VS, Dewan R, Sasan S, Saraya A. High family prevalence of gallstones in the first degree relatives of gallstone patients. Hepatology 1995;22:138-41

30. Tandon, RK, Saraya A, Paul S, Kapur BM. Dietary habits of gallstone patients in Northern India. J Clin Gastroenterol 1996;22:23-7.

31. Sharma MP, Duphare HV, Nijhawan S, Dasarathy S. Gallstone disease in north India: Clinical and ultrasound profile in a referral hospital. J Clin Gastroenterol 1990;12:547-9.

32. Khuroo, M. S., Mahajan R, Zargar SA, Javid G, Munshi S. Prevalence of peptic ulcer in India:an endoscopic and epidemiological study in urban Kashmir. Gut 1989;30:930-4.

33. Kapoor VK, McMichael AJ. Gallbladder cancer: An Indian disease. Natl Med J India 2003;16:209-13.

34. Jayanthi V, Anand L, Ashok L, Srinivasan V. Dietary factors in pathogenesis of gallstone disease in southern India – A hospital based case-control study. Indian J Gastroenterol 2005;24:97-9

35. Kapoor VK. Cholecystectomy in patients with asymptomatic gallstones to prevent gall bladder cancer-the case against. Indian J Gastroenterol 2006;25:152-4

36. Oddsdottir M, Phaas TH, Hunter JG. Gallbladder and extrahepatic biliary system. In:Brucardi CF Eds. Schwartz's Principles of Surgery. 9th ed. USA:McGraw Hill Companies Inc;2009. p. 1135-66.

37. Chari RS, Shah SA. Biliary system In:Townsend CM Eds. Sabiston Textbook of Surgery. 18th ed. India:Elsevier Publication;2009. p. 1517-88.

38. Singer AJ, McCracken G, Henry MC, Thode HC Jr, Cabahug CJ. Correlation among clinical, laboratory, and hepatobiliary scanning findings in patients with suspected acute cholecystitis. Ann Emerg Med 1996;28(3):267-72.

39. Katz DS, Rosen MP, Blake MA, and Expert Panel on Gastrointestinal Imaging. ACR Appropriateness Criteria right upper quadrant pain. [online publication]. Reston (VA):American College of Radiology (ACR);2010:

40. Bingener J, Schwesinger WH, Chopra S, Richards ML, Sirinek KR. Does the correlation of acute cholecystitis on ultrasound and at surgery reflect a mirror image? Am J Surg 2004;188(6):703-7.

41. Rosen CL, Brown DF, Chang Y, Moore C, Averill NJ, Arkoff LJ, et al. Ultrasonography by emergency physicians in patients with suspected cholecystitis. Am J Emerg Med 2001;19(1):32-6.

42. Rubens DJ. Hepatobiliary imaging and its pitfalls. Radiol Clin North Am 2004;42(2):257-78.

43. Shah K, Wolfe RE. Hepatobiliary ultrasound. Emerg Med Clin North Am 2004;22(3):661-73 viii.

44. Kim YK, Kwak HS, Kim CS, Han YM, Jeong TO, Kim IH, et al. CT findings of mild forms or early manifestations of acute cholecystitis. Clin Imaging 2009;33(4):274-80.

45. Sahai AV, Mauldin PD, Marsi V, Hawes RH, Hoffman BJ. Bile duct stones and laparoscopic cholecystectomy:a decision analysis to assess the roles of intraoperative cholangiography, EUS, and ERCP. Gastrointest Endosc 1999;49(3 Pt 1):334-43.

46. Linder HH, Green RB. Embryology and surgical anatomy of the extra hepatic biliary tract. Surg Clin North Am 1964;44:1273.

47. Greenwald JA, McMullen HF, Coppa GF, Newman RM. Standardization of surgeon-controlled variables: impact on outcome in patients with acute cholecystitis. Ann Surg. 2000; 231(3):339-44.

48. Siddiqui T, MacDonald A, Chong PS, Jenkins JT. Early versus delayed laparoscopic cholecystectomy for acute cholecystitis:a meta-analysis of randomized clinical trials. Am J Surg 2008;195(1):40-7.

49. Overby DW, Apelgren KN, Richardson W, Fanelli R. SAGES guidelines for the clinical application of laparoscopic biliary tract surgery. Surg Endosc 2010;24(10):2368-86.

50. Binenbaum SJ, Teixeira JA, Forrester GJ, Harvey EJ, Afthinos J, Kim GJ, et al. Single-incision laparoscopic cholecystectomy using a flexible endoscope. Arch Surg 2009;144(8):734-8.

51. Wu CH, Chen CC, Wang CJ, Wong YC, Wang LJ, Huang CC, et al. Discrimination of gangrenous from uncomplicated acute cholecystitis: Accuracy of CT findings. Abdom Imaging 2011;36(2):174-8.

52. Joris J, Thiry E, Paris P, Weerts J, Lamy M. Pain after laparoscopic cholecystectomy:characteristics and effect of intraperitoneal bupivacaine. Anaesth Analg 1995;81:379-84.

53. Alexander JI. Pain after laparoscopy. British Journal of Anesthesia 1997;79:369.

54. Merskey H, Bogduk N. Classification of chronic pain - Descriptions of chronic pain syndromes and definitions of pain terms, 2nd ed. Seattle:IASP press;1994.

55. Macintyre PE, Ready LB. Acute Pain Management:A Practical Guide. 2nd ed., New York:Churchill Livingstone;2001.

56. Morgan GE, Mikhail MS, Murray MJ. Clinical Anesthesiology. 4th ed., USA:McGraw Hill;2006.

57. Carr DB, Goudas LC. Acute pain. Lancet 1999;353:2051-62.

58. Kelly DJ, Ahmad, Mahmoud, Brull, Sorin J. Preemptive analgesia:physiological pathways and pharmacological modalities. Can J Anesth 2001;48 (10):1000-10.

59. Hollmann MW, Durieux ME. Local anaesthetic and inflammatory response: Anesthesiology 2000;93:858.

60. Grubb BD. Peripheral and central mechanisms of pain. Br J Anaesth 1998;81:8.

61. Moiniche S, Kehlet H, Dahl JB. A qualitative and quantitative systematic review of preemptive analgesia for postoperative pain relief:the role of timing of analgesia. Anesthesiology 2002;96:725-41.

62. Alexander JI. Pain after laparoscopy. Br J Anesth 1997;79:369.

63. Korell M, Schmaus F. Pain intensity following laparoscopy. Surg Lapar Endos 1996;6:375-9.

64. Sharp JR, Pierson WP. Comparison of CO2 and N2O induced discomfort during peritoneoscopy under local anaesthesia. Gastroenterology 1982;82:453-6.

65. Alexander JI, Hull MGR. Abdominal pain after laproscopy:the value of a gas drain. Br J Obstet Gynaecol 1987;94:267-9.

66. Mounton WG, Bessel JR. A randomized controlled trial assessing the benefit of humidified insufflation gas during laparoscopic surgery. Surg Endos 1999;13:106-8.

67. Gibbs P, Purushottam A, Cushieri RJ Continuous wound perfusion with bupivacaine for postoperative pain. Br J Surg 1988;75:923-4.

68. Murrat SA, Baykan N.The effect and timing of local anaesthesia in laparoscopic cholecystectomy. Surg Lap Endos 1996;6:362-6.

69. Glaser F, Buhr HJ. General stress response to conventional and laparoscopic cholecystectomy. Ann Surg 1995;221:372-80.

70. Vitale GC, Collet D, Miller FB. Interruption of professional and home activity after laparoscopic cholecystectomy among French and American patients. Am J Surg 1991;161:396-8.

71. Kehlet H, Holte K. The effect of postoperative analgesia on surgical outcome. British Journal of Anaesthesia 2001;87:62-72.

72. Kehlet H. Acute pain control and accelerated postoperative surgical recovery. Surg Clin N Am 1999;79:431-45.

73. Warltier DC, Pagel PS, Kersten JR. Approaches to the prevention of perioperative myocardial ischemia. Anesthesiology 2000;92:253.

74. Ballanyne JC, Carr DB, DeFerranti S. The comparative effect of postoperative analgesic therapies on pulmonary outcome: Cumulative metaanalyses of randomized, controlled trials. Anesth Analg 1998;86:598.

75. Holte K, Kehlet H. Postoperative ileus- a preventable event. Br J Anesth 2000;87:1480-9.

76. Desborough JP. The stress response to trauma and surgery. Br J Anesth 2000;85:109.

77. White PF. The role of non-opioid analgesic techniques in the management of pain after ambulatory surgery. Anesth Analg 2002;94:577-85.

78. Eccleston C. Role of psychology in pain management. Br J Anesth 2001;87:144-52.

79. Macrae WA. Chronic pain after surgery. Br J Anesth 2001;87:88.

80. Hardman JG, Limbird LE. Goodman and Gilman's the pharmacological basis of therapeutics. 10th Ed. USA:McGraw Hill;2001.

81. Tobias JD. Pain management following laparoscopy: Can we do better?. Saudi J Anaesth 2013;7:3-4

82. Golubović S, Golubović V, Cindrić-Stancin M, Tokmadzić VS. Intraperitoneal analgesia for laparoscopic cholecystectomy:bupivacaine versus bupivacaine with tramadol. Coll Antropol 2009;33:299-302.

83. Jabbour-Khoury SI, Dabbous AS, Greges FJ, Azar MS, Ayoub CM, Khoury GS. Intraperitoneal and intravenous routesfor pain relief in laparoscopic cholecystectomy. JSLS 2005;9:316-29.

84. Bhardwaj N, Sharma V, Chari P. Intraperitoneal instillation of bupivacaine for postoperative pain relief after laparoscopic cholecystectomy. Indian J Anesth 2002;46(1):49-52

85. Gharaibeh KI, Al-Jaberi TM, Bupivacaine instillation into gallbladder bed after laparoscopic cholecystectomy: does in decrease shoulder pain ?, J Laparoendosc Adv Surg Tech A 2000;10(3):137-41

86. Chundrigar T, Hedges AR, Morris R, Stamatakis JD. Intraperitonel bupivacaine for effective pain relief after laparoscopic cholecystectomy. Ann R Coll Surg Engl 1993;75 (6):437-9.

87. Wilson YG, Rhodes M, Ahmed R, Daugherty M, Cawthorn SJ, Armstrong CP. Intramuscular diclofenac sodium for postoperative analgesia after laparoscopic cholecystectomy: A randomised, controlled trial. SurgLaparosc Endosc 1994;4:340–4.

88. Aitola P, Airo I, Kaukinen S, Ylitalo P. Comparison of N_2O and CO_2 pneumoperitoneums during laparoscopic cholecystectomy with special reference to postoperative pain. Surg Laparosc Endosc 1998;8:140-4.

89. Sajid MS, Mallick AS, Rimpel J, Bokari SA, Cheek E, Baig, M. Effect of Heated and Humidified Carbon Dioxide on Patients After Laparoscopic Procedures: A Meta-analysis. Surgical Laparoscopy, Endoscopy & Percutaneous Techniques 2008;18(6);539-46.

90. Barczynski M, Konturek A, Herman RM. Superiority of preemptive analgesia with intraperitoneal instillation of bupivacaine before rather than

after the creation of pneumoperitoneum for laparoscopic cholecystectomy:a randomized, double-blind, placebo-controlled study. Surg Endosc 2006;20:1088–93.

91. Golubovic S, Golubovic V, Cindric-Stancin, Soto-sek-tokmadzic V analgesic effect of intraperitoneal tramadol during laparoscopic cholecystectomy. Period Biol 2007;109:317–20.

92. Hernández-Palazón J, Tortosa JA, Nuño de la Rosa V, Giménez-Viudes J, Ramírez G, Robles R. Intraperitoneal application of bupivacaine plus morphine for pain relief after laparoscopic cholecystectomy. Eur J Anaesthesiol 2003; 20:891-6.

93. Golubović S, Golubović V, Cindrić-Stancin M, Tokmadzić VS. Intraperitoneal analgesia for laparoscopic cholecystectomy. Period Boil 2009;111:263–66.

ANNEXURE I – CONSENT FORM

Dear Mr/Mrs/Dr_____, you are kindly requested to participate in a research study tilted "TO EVALUATE THE ANALGESIC EFFICACY OF INTRAPERITONEAL TRAMADOL VS PLACEBO FOR POST OPERATIVE PAIN RELIEF FOLLOWING LAPROSCOPIC CHOLECYSTECTOMY, A DOUBLE BLINDED RANDOMIZED CONTROL TRIAL, HOSPITAL BASED STUD" conducted by Dr. **** *******, a post graduate student in M. S. General Surgery and study will be carried out under the direct supervision and guidance of Dr. ***** ******, Professor, Department of General Surgery, Jawaharlal Nehru Medical College, Belgaum.

You have been requested to participate in this as you fit into the laid out criteria for a study 'subject'/ participant.

During the study you will be asked some questions and you are supposed to answer to the best of your knowledge. Your participation in this research is voluntary. Your decision whether or not to participate in the study will not affect your treatment in any form during your hospital stay. If you decide to participate you are free to withdraw at any time.

TITLE OF THE STUDY

TO EVALUATE THE ANALGESIC EFFICACY OF INTRAPERITONEAL TRAMADOL VS PLACEBO FOR POST OPERATIVE PAIN RELIEF FOLLOWING LAPROSCOPIC CHOLECYSTECTOMY, A DOUBLE BLINDED RANDOMIZED CONTROL TRIAL, HOSPITAL BASED STUDY

OBJECTIVE/PURPOSE OF THE STUDY

Laparoscopic cholecystectomy has been the treatment of choice for gallbladder disease. Laparotomy results mainly in parietal pain, laparoscopy has a visceral component, a somatic component and shoulder pain secondary to diaphragmatic irritation as a result of CO2 pnemoperitoneum. In laparoscopic cholecystectomy, visceral pain predominates in first 24 hours but subsides soon after operation, whereas shoulder pain, less on the first day, increases and becomes significant on the following days.

To study the effectiveness of intraperitoneal instillation of TRAMADOL vs PLACEBO for postoperative laparoscopic cholecystectomy pain relief, especially visceral pain and shoulder pain. To improve pain relief after laparoscopic cholecystectomy you are being asked to participate in this research as you find all the criteria laid by the author of the study as 'subjects'.

The investigator/author of this study is Dr. ***** ******, a postgraduate student in Dept. of General Surgery, Jawaharlal Nehru Medical College and study will be carried out under the direct supervision and guidance of Dr. **** ******, Professor, Department of General Surgery, Jawaharlal Nehru Medical College, Belgaum. The study is self funded by the author the study.

PROCEDURES

IF you agree to enroll yourself in my study, you will be interviewed regarding your present, past and family history then you will be clinically examined in detail and investigated accordingly.

You will be randomly allocated either into study group or control group using computer generated numbers and you will receive intraperitoneal tramadol

100 mg (diluted in 20 ml of distilled water) or 20 ml of intraperitoneal normal saline.

Both patients and surgeon will be blinded and anaesthetist will load drug or normal saline according to random table chart and give it to the surgeon for infiltration.

In both groups, 10mL of the study drug will be injected into the sub diaphragmatic space, 5mL into the area of the gall bladder bed and 5mL will be injected into the space between the liver and the kidney under direct vsion by the surgeon just before removal of trocars. The surgeons will not known the treatment group until the end of the study. The parameter used for assessing postoperative pain will be:-

- Visual Analogue score ranging from zero to ten, considering zero as no pain and ten as maximum pain on first post op day.
- Cumulative rescue analgesic requirements in 1st and 24 hours.
- Rescue analgesic - 75 mg DICLOFENAC SODIUM
- Postoperative pain scores at 0 min, 15 min, 30 min, 60 min, 24 hr.
- Incidence of adverse effect (nausea, vomiting, shoulder pain, itching) at 0 hr , 4 hr , 8 hr , 16 hr , 24 hr

RISKS AND BENEFITS

There potential risks involved with the procedure is same as conventional laproscopic cholecystectomy procedure and anaesthesia related risks in addition side effects related to tramadol is minimal and patient may experience post op shivering, nausea or vomitting.

Benefits of taking part in this research

Prevention of post operative pain.

- Lesser requirement of opoids and NSAIDS in post operative period.
- Lesser incidence of post operative nausea and vomiting.

VOLUNTARY PARTICIPATION / WITHDRAWING / REMOVAL FROM THE STUDY

Taking part in the study is voluntary. You may choose not to enroll yourself in this study. Your decision will not change present or future health care services offered to you at KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum.

ALTERNATIVES

You would be simply be excluded from the study and all your details shall be kept confidential and you will get the routine line of management.

PRIVACY AND CONFIDENTIALITY

All data collected or disclosed by you during the course of participation of study, will be kept fully confidential. If however during the course it becomes necessary for the progress of the course to disclose the identity, it would be done so only after your informed & written consent.

The only people to know that you are a research subject are members of the research team. No information about you will be disclosed to other without your written permission except:

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

AUTHORIZATION TO PUBLISH RESULTS

The results of the study may be used to publish an article. When the results of research published or discussed, in a conference, no information will be displayed that would disclose your identity. Any information obtained in connection with this study and that can be identified with you will remain confidential.

FINANCIAL INCENTIVES FOR PARTICIPATION

No additional costs shall be incurred upon you for the purpose of this study. It is purely being done with the idea of research and all the cost of study will be borne by the investigator.

COMPENSATION

In the event that you become injured as a result of taking part in this study, treatment will be offered to you at KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum., or you will be given information about where to receive medical care in which case you/your insurance company will be responsible for the costs. However, no reimbursement, compensation or free medical care will be given. There is no compensation or payment for such medical treatment by law.

CONTACT DETAILS

You shall be free to contact the below mentioned name & addresses anytime during the study period for any clarification or help as you may desire for.

Dr. ** **********
M.B.B.S
(Post Graduate Student)
Department of Surgery
Jawaharlal Nehru Medical College
Nehru Nagar, KLE Hospital Road
Belgaum 590010
Mobile – ***** *****

Dr. *** **********
M S GEN. SURGERY
Professor
Department of Surgery
Jawaharlal Nehru Medical College
Nehru Nagar, KLE Hospital Road
Belgaum 590010
Mobile - **** ******

In case you need any further information regarding your rights as study participant you may contact:

Dr. ** *******
Chairman, College Ethical Dissertation
And Research Committee,
Jawaharlal Nehru Medical College
Nehru Nagar, KLE Hospital Road
Belgaum 590 010
Mobile - **** *****

CONSENT STATEMENT

I the undersigned Mr/Mrs/Dr_____ do hereby give consent for my participation in this research study after being explained in-depth about the important elements of this study in own my vernacular language.

I give this consent voluntarily in my sound mind knowing very well the risks involved and been given enough time to clear my doubts and other queries to participate as a 'subject' in this study. I do hereby also give consent for publication of this article in any media / journal and have no objections whatsoever.

Signature or left thumb print of participant or legally authorized representative

Participant' name _____

Signature_____

Witness' name _____

Signature_____

Investigators name – Dr. ***** ****** Signature_____

GUIDE - Dr. ***** ***** Signature_____

Date ___/___/____

Place _____

ANNEXURE II

PROFORMA / QUESTIONNAIRE TO BE USED FOR DATA COLLECION

The proposed proforma / questionnaire to be used for data collection for the study tilted **"TO EVALUATE THE ANALGESIC EFFICACY OF INTRAPERITONEAL TRAMADOL VS PLACEBO FOR POST OPERATIVE PAIN RELIEF FOLLOWING LAPROSCOPIC CHOLECYSTECTOMY, A DOUBLE BLINDED RANDOMIZED CONTROL TRIAL, HOSPITAL BASED STUDY"** is as:

PATIENT DETAILS:

I.P/ O.P.D NO.: D.O.A:

NAME : D.O.S:

SEX : D.O.D:

AGE:

OCCUPATION:

ADDRESS :

Chief Complaints: YES / NO Duration

PAIN ABDOMEN:

SITE OF PAIN -

RIGHT HYPOCHONDRIUM

TYPE OF PAIN: RADIATING / THROBBING / PRICKING TYPE / DULL ACHING TYPE

INTENSITY:

MILD	MODERATE	SEVERE

FEVER: YES / NO

DURATION -

DEGREE OF FEVER--

MILD	MODERATE	SEVERE

TYPE OF FEVER----

CONTINUOUS	INTERMITTENT	SPIKING

HISTORY OF ANAPHYLAXIS TO OPOIDS YES / NO

Past History:

GENERAL EXAMINATION:

BUILT AND NOURISHMENT:

WEIGHT:

PULSE:

BP :

R/R :

TEMPERATURE:

PALLOR:

ICTERUS:

CYANOSIS:

CLUBBING

LYMPHADENOPATHY

EDEMA

SYSTEMIC EXAMINATION:

PER ABDOMEN

TENDERNESS YES/NO

- RIGHT HYPOCHONDRIUM
- EPIGASTRIUM
- BOWEL SOUNDS NORMAL ABNORMAL

FINDINGS:

RESPIRATORY-

CVS-

CNS-

INVESTIGATIONS:

CBC:

Hb- ( ) TLC- ( ) DLC- (N- , L- , M- ,E-)

FBS : ( )

Blood Urea ( )

Sr. Creatinine ( )

Urine :

Routine

Microscopy

USG ABDOMEN:-

GROUP : GROUP A / GROUP B

OPERATION DETAILS: -

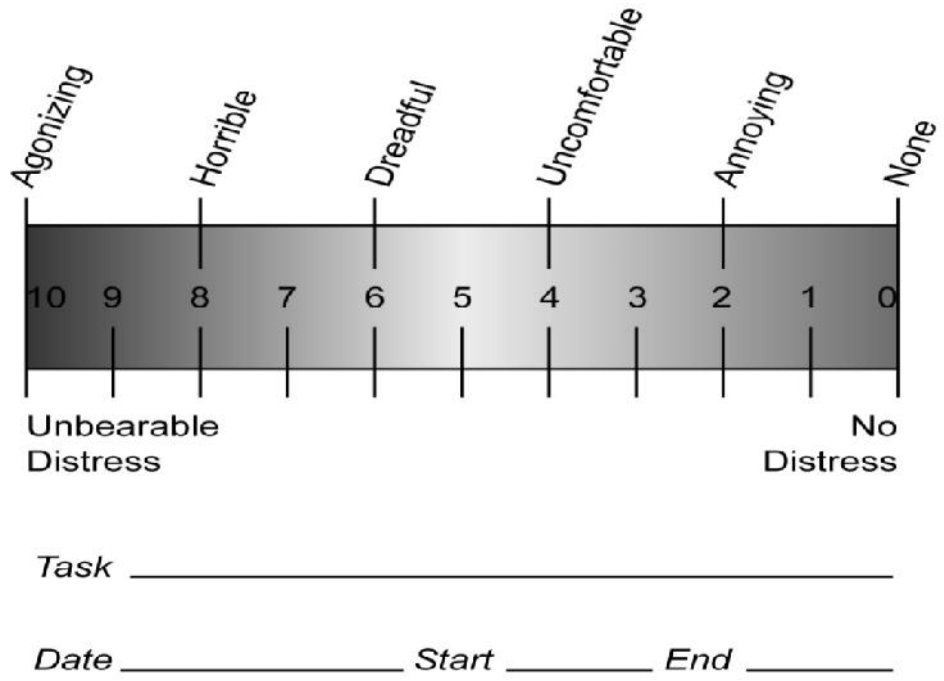
DATE OF SURGERY:

NAME OF SURGERY: LAPROSCOPIC CHOLECYSTECTOMY

ANAESTHESIA: GENERAL ANAESTHESIA

DURATION OF SURGERY:

ASSESSMENT OF POST OPERATIVE PAIN



VISUAL ANALOGUE SCALE

0– NO PAIN; 1-3 – MILD PAIN; 4-7 – MODERATE PAIN; 8-10 – SEVERE PAIN

Postoperative pain scores at

0 min	15 min	30 min	60 min	4 hr	8hr	16hr	24 hr

Incidence of adverse effect (nausea, vomiting, shoulder pain, itching,shivering) at

0 min	4 hr	8hr	16hr	24 hr

ANNEXURE III – KEY TO MASTER CHART

F	-	Female
Kgs	-	Kilograms
M	-	Male
mm Hg	-	Millimeter of mercury
N	-	Nausea
n	-	No
post op	-	Post operative
se	-	Sedation
sp	-	Shoulder pain
T	-	Tramadol
v	-	Vomiting
VAS	-	Visual analog scale
y	-	Yes

ANNEXURE III - MASTER CHART GROUP T

Serial number	IP Number	Group	Sex	Age (Years)	History		Duration of pain abdomen	Examination					Per abdomen			Duration of surgery (minutes)	Post operative assessment for analgesia and efficacy																			
											BP						Pain (VAS Scores at different intervals)								Requirement of analgesia (intervals)								Adverse effects			
					Hypertension	Diabetes		Weight (Kgs)	Pulse rate (/Minute)	Respiratory rate (/Minute)	Systolic (mm Hg)	Diastolic (mm Hg)	Tenderness	Right hypochondrium	Bowel sounds		Immediate post op	15 minutes	30 minutes	60 minutes	4 hour	8 hours	12 hours	24 hours	Immediate post op	15 minutes	30 minutes	60 minutes	4 hour	8 hours	12 hours	16 hours	24 hours	4 hour	8 hours	12 hours	16 hours
1	534732	T	F	52	n	n	3	60	64	20	120	80	n	y	y	110	1	1	1	1	1	2	3	4	0	0	0	0	0	0	1	0	1	se	se	-	-
2	532761	T	F	34	n	n	5	84	66	20	110	70	n	y	y	100	0	0	0	1	2	4	2	3	0	0	0	0	0	1	0	0	0	-	N	sp,N,v	-
3	528716	T	F	40	n	n	4	78	92	22	130	80	n	y	y	96	0	0	0	0	1	1	2	3	0	0	0	0	0	0	0	0	1	-	se	se	se
4	508875	T	M	25	n	n	6	70	84	22	120	80	n	n	y	100	0	0	1	1	1	1	3	2	0	0	0	0	0	0	0	1	0	-	-	-	-
5	534908	T	M	22	n	n	12	58	78	22	120	86	n	y	y	120	0	0	0	0	2	3	2	2	0	0	0	0	0	1	0	1	0	se	-	sp	sp
6	520080	T	M	52	y	n	10	70	78	20	110	70	n	n	y	110	0	0	0	0	1	1	2	1	0	0	0	0	0	0	0	0	0	-	N	N	N
7	520111	T	M	32	n	n	4	68	86	22	126	76	n	n	y	80	0	0	0	0	1	1	2	3	0	0	0	0	0	0	1	0	1	-	-	-	-
8	510080	T	M	50	n	y	5	70	70	22	110	70	n	n	y	65	1	1	1	1	2	1	2	2	0	0	0	0	0	1	0	0	0	-	-	-	-
9	536481	T	F	38	n	n	9	56	64	22	130	80	n	y	y	110	0	0	0	0	1	2	3	2	0	0	0	0	0	0	1	0	0	se	-	-	-
10	537348	T	M	34	y	y	6	65	82	18	130	86	n	y	y	120	0	0	0	1	1	1	3	2	0	0	0	0	0	0	1	0	0	N	N	-	-
11	543487	T	F	27	n	n	3	68	88	22	116	70	n	y	y	90	0	0	0	0	1	1	1	1	0	0	0	0	0	0	0	0	0	se	-	-	-
12	516229	T	M	53	n	n	0.1	60	66	20	120	80	n	y	y	80	1	1	1	1	2	4	2	3	0	0	0	0	0	1	0	0	0	-	-	-	-
13	533518	T	F	55	n	n	4	75	66	18	120	70	n	y	y	110	0	0	0	1	1	1	2	3	0	0	0	0	0	0	0	0	1	-	-	-	-
14	534908	T	F	60	n	n	6	60	86	22	146	80	n	y	y	100	0	0	0	0	1	3	1	1	0	0	0	0	0	1	0	1	0	se,N	N	N	-
15	539684	T	M	19	y	n	7	65	74	22	130	80	n	y	y	95	0	1	1	1	1	2	3	3	0	0	0	0	0	0	1	0	1	-	-	-	-
16	539544	T	F	30	y	n	10	72	82	20	120	80	n	n	y	60	0	0	0	0	1	1	1	1	0	0	0	0	0	1	0	0	0	-	-	-	N
17	540139	T	F	35	n	n	14	76	82	22	124	80	n	n	y	100	0	0	0	0	1	1	3	1	0	0	0	0	0	0	1	1	0	-	-	-	-
18	542336	T	F	28	n	y	6	90	76	22	116	70	n	n	y	110	1	1	1	1	2	3	1	1	0	0	0	0	0	1	0	0	0	se,N	se	se	se
19	554883	T	F	52	n	n	8	85	76	18	110	70	n	n	y	120	0	0	1	1	1	2	1	3	0	0	0	0	0	1	0	0	1	-	-	-	-
20	550632	T	F	56	n	n	5	60	76	22	120	70	n	n	y	86	0	0	0	0	1	1	1	3	0	0	0	0	0	0	0	0	0	N	N	N	N
21	552121	T	M	30	n	y	6	65	76	22	130	80	n	y	y	100	0	0	0	0	2	1	2	1	0	0	0	0	0	0	0	0	0	-	-	-	-
22	552345	T	M	49	n	n	4	75	86	18	130	84	n	y	y	90	1	1	1	1	1	1	3	3	0	0	0	0	0	0	1	0	1	-	-	-	-
23	546074	T	F	40	n	n	6	52	86	22	120	80	y	y	y	95	0	0	0	1	2	4	1	3	0	0	0	0	0	1	0	0	1	se	-	-	-
24	550573	T	F	28	n	n	4	58	62	18	110	80	n	y	y	120	0	0	0	1	1	2	1	1	0	0	0	0	0	0	0	0	0	v	-	-	-

ANNEXURE III - MASTER CHART GROUP T

Serial number	IP Number	Group	Sex	Age (Years)	History		Duration of pain abdomen	Examination					Per abdomen			Duration of surgery (minutes)	Post operative assessment for analgesia and efficacy																			
											BP						Pain (VAS Scores at different intervals)								Requirement of analgesia (intervals)								Adverse effects			
					Hypertension	Diabetes		Weight (Kgs)	Pulse rate (/Minute)	Respiratory rate (/Minute)	Systolic (mm Hg)	Diastolic (mm Hg)	Tenderness	Right hypochondrium	Bowel sounds		Immediate post op	15 minutes	30 minutes	60 minutes	4 hour	8 hours	12 hours	24 hours	Immediate post op	15 minutes	30 minutes	60 minutes	4 hour	8 hours	12 hours	16 hours	24 hours	4 hour	8 hours	12 hours	16 hours
25	550676	T	F	53	n	n	11	75	76	20	124	80	y	y	y	96	0	0	0	0	1	1	1	2	0	0	0	0	0	0	0	0	0	se	-	-	-
26	545794	T	F	55	n	n	12	67	92	18	120	80	n	y	y	110	0	0	0	1	2	3	1	2	0	0	0	0	0	1	0	0	0	-	-	-	-
27	513253	T	F	33	n	n	16	82	92	20	130	80	n	y	y	120	0	0	0	0	1	1	1	1	0	0	0	0	0	0	0	0	0	-	se	se	se
28	516481	T	F	37	n	n	4	62	76	18	120	80	n	n	y	80	1	1	1	2	2	1	2	1	0	0	0	0	0	0	1	0	1	se	-	sp,N,sh	N
29	519684	T	F	40	n	n	3	55	70	20	110	70	y	n	y	72	0	0	0	1	1	2	2	2	0	0	0	0	0	0	0	1	0	-	-	-	-
30	530163	T	F	36	n	n	5	58	96	22	120	80	n	n	y	60	0	0	1	1	1	1	2	2	0	0	0	0	0	0	0	0	0	-	-	-	-

ANNEXURE III - MASTER CHART GROUP T

24 hours
-
sp
se
-
sp
N
-
-
-
-
-
-
-
-
-
N
-
se
sp
v
-
-
-
-

ANNEXURE III - MASTER CHART GROUP T

24 hours
-
-
-
sp,N,v
-
-

ANNEXURE III - MASTER CHART GROUP S

Serial number	IP Number	Group	Sex	Age (Years)	History		Duration of pain abdomen	Examination					Per abdomen			Duration of surgery (minutes)	Post operative assessment for analgesia and efficacy																			
											(mm Hg)						Pain (VAS Scores at different intervals)								Requirement of analgesia (intervals)								Adverse effects			
					Hypertension	Diabetes		Weight (Kgs)	Pulse rate (/Minute)	Respiratory rate (/Minute)	Systolic	Diastolic	Tenderness	Right hypochondrium	Bowel sounds		Immediate post op	15 minutes	30 minutes	60 minutes	4 hour	8 hours	12 hours	24 hours	Immediate post op	15 minutes	30 minutes	60 minutes	4 hour	8 hours	12 hours	16 hours	24 hours	4 hour	8 hours	12 hours	16 hours
1	529520	S	F	26	n	n	0.1	55	86	18	130	80	n	y	y	100	3	1	1	1	2	3	3	3	1	0	0	0	0	1	1	0	1	se	se,sp	N,v	-
2	521188	S	M	22	n	n	5	88	82	20	140	78	n	y	y	110	2	3	1	1	2	4	2	3	0	1	0	0	0	1	0	0	1	-	-	-	-
3	542336	S	F	34	n	n	10	65	80	18	116	70	n	y	y	120	3	1	1	1	2	3	2	3	1	0	0	0	0	1	0	0	1	-	se	se	se
4	530993	S	F	35	n	n	14	65	92	20	100	70	n	y	y	100	2	2	2	3	4	1	3	2	0	0	0	1	1	0	1	0	0	-	-	-	-
5	566815	S	M	61	n	y	7	72	72	22	122	80	n	y	y	120	3	2	1	1	1	1	3	2	1	0	0	0	0	0	1	0	0	se	N	N	-
6	515482	S	F	42	n	y	5	63	82	22	130	90	n	y	y	60	3	2	1	1	2	2	3	2	1	0	0	0	0	0	1	0	0	-	-	-	-
7	522949	S	M	19	y	n	9	78	90	22	110	70	n	y	y	70	3	1	1	1	3	2	3	1	1	0	0	0	0	1	0	0	1	-	-	-	-
8	549297	S	M	23	n	n	0.1	75	92	22	124	80	n	y	y	120	4	2	1	1	2	2	3	3	1	0	0	0	0	0	1	0	1	N	N	N	-
9	540319	S	F	52	y	n	0.1	62	96	20	140	70	y	n	y	110	2	2	3	1	2	3	1	2	1	0	0	0	0	1	0	0	0	-	-	-	-
10	521188	S	F	51	n	n	5	60	90	20	116	80	n	n	y	120	3	1	1	2	2	2	3	3	1	0	0	0	0	0	1	0	1	-	-	-	-
11	548209	S	F	55	n	n	7	80	72	22	130	80	y	n	y	110	2	3	1	1	2	3	2	3	0	1	0	0	0	1	0	0	1	se	-	-	-
12	534908	S	F	28	n	n	12	57	82	20	110	74	n	n	y	120	5	2	2	1	2	3	3	2	1	0	0	0	0	1	1	0	0	-	-	N	sp,N,v
13	516481	S	M	20	n	n	20	68	72	20	134	70	n	n	y	110	2	3	1	1	2	3	1	3	0	1	0	0	0	1	0	0	1	-	-	-	-
14	547715	S	F	60	n	n	8	87	78	20	136	70	n	y	y	80	4	2	2	2	2	3	1	4	1	0	0	0	0	1	0	0	1	se	-	-	-
15	558682	S	F	39	n	n	9	71	76	20	114	70	n	n	y	110	5	3	2	2	3	1	2	2	1	0	0	0	1	0	0	1	0	N	N	N	N
16	518301	S	M	38	n	n	13	82	69	18	136	78	n	n	y	120	2	2	2	5	4	1	2	2	0	1	0	1	1	0	0	1	0	-	-	-	-
17	562685	S	F	35	n	n	6	64	89	18	130	90	y	y	y	60	4	2	1	1	2	3	1	2	1	0	0	0	0	1	0	1	0	se	se	se	se
18	547393	S	M	43	n	n	8	78	80	18	110	78	n	n	y	96	5	3	2	1	2	2	2	2	1	0	0	0	0	0	1	0	-	-	-	-
19	545983	S	F	30	y	n	3	76	80	20	120	64	n	y	y	100	4	2	2	1	2	3	2	2	1	0	0	0	0	1	0	0	0	-	-	-	-
20	546074	S	F	56	n	n	6	49	82	20	134	80	n	y	y	80	2	2	3	1	1	2	4	2	0	0	1	0	0	0	1	0	0	N	N	v	-
21	525420	S	F	35	n	n	0.1	53	80	22	120	77	y	y	y	110	4	2	1	1	2	3	1	2	1	0	0	0	0	1	0	1	0	-	-	-	-
22	540139	S	F	56	y	y	7	68	68	26	94	92	n	n	y	120	3	1	1	1	3	3	1	3	1	0	0	0	1	1	0	0	1	-	-	-	N
23	549309	S	F	47	n	n	9	56	80	20	136	86	n	n	y	50	4	2	1	1	2	2	2	1	1	0	0	0	0	0	0	1	0	se	-	-	-
24	563921	S	M	56	y	n	10	78	88	18	120	68	n	n	y	75	4	2	1	1	2	3	3	2	1	0	0	0	0	1	1	0	0	se	-	-	-

ANNEXURE III - MASTER CHART GROUP S

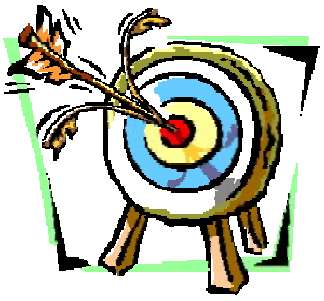
Serial number	IP Number	Group	Sex	Age (Years)	History		Duration of pain abdomen	Examination					Per abdomen			Duration of surgery (minutes)	Post operative assessment for analgesia and efficacy																			
											(mm Hg)						Pain (VAS Scores at different intervals)								Requirement of analgesia (intervals)								Adverse effects			
					Hypertension	Diabetes		Weight (Kgs)	Pulse rate (/Minute)	Respiratory rate (/Minute)	Systolic	Diastolic	Tenderness	Right hypochondrium	Bowel sounds		Immediate post op	15 minutes	30 minutes	60 minutes	4 hour	8 hours	12 hours	24 hours	Immediate post op	15 minutes	30 minutes	60 minutes	4 hour	8 hours	12 hours	16 hours	24 hours	4 hour	8 hours	12 hours	16 hours
25	519353	S	M	55	n	y	4	80	86	22	140	76	n	n	y	80	4	2	1	1	1	2	4	3	1	0	0	0	0	0	1	0	1	v	N	N	-
26	510438	S	F	50	n	n	5	67	80	22	146	70	n	y	y	100	3	1	1	1	2	3	1	3	1	0	0	0	0	1	0	0	1	se	-	-	-
27	544571	S	F	38	n	n	6	56	86	20	110	80	n	y	y	90	2	2	3	1	1	3	3	2	0	0	1	0	0	1	1	0	0	-	-	-	-
28	540008	S	F	52	n	n	10	112	82	22	119	80	n	y	y	80	2	3	1	1	2	3	2	1	0	1	0	0	0	1	0	1	0	-	se	se	se,sp,N
29	526214	S	F	50	n	n	12	68	88	20	130	80	n	n	y	110	2	3	2	1	2	2	2	3	0	1	0	0	0	0	0	0	1	se	-	-	-
30	522949	S	M	58	n	y	5	75	86	20	120	77	n	y	y	60	3	2	1	1	2	4	2	2	1	0	0	0	0	1	0	1	0	-	-	-	-

ANNEXURE III - MASTER CHART GROUP S

24 hours
-
-
se,sp
-
-
N,v,sh
-
-
-
-
-
-
-
-
v
-
se,sp
-
-
-
-
N,v
-
-

ANNEXURE III - MASTER CHART GROUP S

Introduction



Objectives

Review of Literature

Methodology

Results

Discussion

Conclusion

Summary

Bibliography

Annexure-I

Annexure-II

Annexure-III