“TO EVALUATE THE ANALGESIC EFFICACY OF INTRAPERITONEAL TRAMADOL VS. PLACEBO FOR POSTOPERATIVE PAIN RELIEF FOLLOWING LAPAROSCOPIC APPENDICECTOMY – A DOUBLE BLINDED ONE YEAR RANDOMIZED CONTROL TRIAL: SINGLE CENTRIC, HOSPITAL BASED STUDY”

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This is to certify that the dissertation entitled **"TO EVALUATE THE ANALGESIC EFFICACY OF INTRAPERITONEAL TRAMADOL VS. PLACEBO FOR POSTOPERATIVE PAIN RELIEF FOLLOWING LAPAROSCOPIC APPENDICECTOMY – A DOUBLE BLINDED ONE YEAR RANDOMIZED CONTROL TRIAL: SINGLE CENTRIC, HOSPITAL BASED STUDY"** is a bonafide research work done by **CANDIDATE REG. NO. BH0113012**.

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LIST OF ABBREVIATIONS USED

/min	-	Per minute
^0C	-	Degrees Celsius
^0F	-	Degrees fahrenheit
5HT	-	5 Hydroxytryptamine
$5HT_{3A}$	-	5 Hydroxytryptamine 3A
ASA	-	American Society of Anesthesiologists
AUC	-	Area under curve
BC	-	Before Christ
cms	-	Centimeters
CO_2	-	Carbon dioxide
DPQ	-	Dartmouth pain questionnaire
etc.	-	Etcetera
h	-	Hours
H_2O	-	Water
HCl	-	Hydrochloride
IV/i.v.	-	Intravenous
i.m.	-	Intramuscular
IVRA	-	Intravenous regional anaesthesia
kg	-	Kilograms
LA	-	Laparoscopic appendectomy
mg	-	Milligrams
min	-	Minute
ml	-	Milliliters
mL	-	Milliliters

mm Hg	-	Millimeters of Mercury
mm	-	Millimeters
MPQ	-	Mc Gill pain questionnaire
n	-	Total number
NMDA	-	N-methyl-D-aspartate receptor
NSAID	-	Nonsteroidal anti-inflammatory drugs
NY	-	New York
OA	-	Open appendectomy
p	-	Probability
PGI	-	Post Graduate Institute
PGIMER	-	Postgraduate Institute of Medical Education and Research
RIF	-	Right iliac fossa
SAGES	-	Society of American Gastrointestinal and Endoscopic Surgeons
SD	-	Standard deviation
SPET	-	Single positron emission tomography
TLC	-	Total leukocyte count
US	-	United States
USA	-	United States of America
VAS	-	Visual analogue score
VRS	-	Verbal rating scale
vs.	-	Versus
WBC	-	White blood cells
WDR	-	Wide dynamic range
WHYPQ	-	West Haven-Yale pain questionnaire

ABSTRACT

Background and Objectives

Early postoperative pain is common and predominant complaint which results in prolonged hospital stay. The present study explores effectiveness of intraperitoneal instillation of tramadol on postoperative pain relief and emergence of adverse effects following laparoscopic appendectomy.

Methodology

The present one year double blinded randomized controlled trial was done in the Department of General Surgery, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum from January 2014 to December 2014. A total of 60 patients undergoing elective laparoscopic appendectomy were enrolled. The selected patients were divided into two groups of 30 each as group A and B based on the drugs that is intraperitoneal tramadol 150 mg (diluted in 40 ml of normal saline) and 40 ml of intraperitoneal normal saline respectively.

Results

In group A, 53.33% of the patients were males compared and 46.67% in group B ($p=0.606$). The mean age in group A (26.13±9.96years) and group B (31.43±14.81years) were comparable ($p=0.110$). Both the groups were comparable in terms of demographic characteristics, clinical presentation and vitals ($p>0.050$) The mean VAS scores at beginning were significantly low in group A (1.53±0.94) compared to group B (2.93±1.17) and similar trend was noted at all the durations through the post operative period ($p<0.001$). Most of the patients in group A did not request for the post operative analgesia (56.67% vs

6.67%; p=0.011). In group A, significantly lower numbers of mean doses were administered (0.57±0.82 vs 2.20±0.92; p<0.001). The frequency of postoperative rescue analgesia significantly low in group A at 15 minutes, 30 minutes, 6 hours and 12 hours as compared to group B (p<0.050). Adverse events were noted in 23.33% of the patients with group A compared to 10% in group B (p=0.166). The mean hospital stay in group A was significantly low (p=0.017).

Conclusion and interpretation

Intraperitoneal instillation of tramadol offers effective postoperative visceral pain relief in laparoscopic appendectomy and incidence of adverse effects is well acceptable.

Keywords

Intraperitoneal instillation; Laparoscopic appendectomy; Post operative pain; Tramadol;

CONTENTS

LIST OF TABLES

LIST OF GRAPHS

LIST OF FIGURES

LIST OF PHOTOGRAPHS

INTRODUCTION

Acute appendicitis is inflammation of the vermiform appendix and remains the most common cause of the acute abdomen in young adults.[1] It is a common condition regarded as a surgical emergency though notoriously difficult to diagnose and associated with a variety of severe consequences.

The lifetime risk of developing appendicitis is approximately 7% and usually requires surgical treatment. The overall incidence of this condition is approximately 11 cases per 10,000 population per year. Acute appendicitis may occur at any age, although it is relatively rare at the extremes of age.[2] A male preponderance exists, with a male to female ratio of 1:1 to 3:1. The overall lifetime risk is 9% for males and 6% for females. A difference in diagnostic error rate ranges from 12% to 23% for men and 24%–42% for women.[3]

While the clinical diagnosis may be straightforward in some patients who present with classic signs and symptoms, atypical presentations may lead to diagnostic confusion and delay in treatment.[4] Abdominal pain is the primary presenting complaint of patients with acute appendicitis. The typical diagnostic sequence of colicky central abdominal pain followed by vomiting with migration of the pain to the right iliac fossa is present in only 50% of patients, to be specific, the patient describes a periumbilical colicky pain, which increases in severity during the first 24 hour, becoming constant and sharp, and shifts to the right iliac fossa. The initial pain represents a referred symptom resulting from the visceral innervation of the midgut, and the localised pain is caused by involvement of the parietal peritoneum after progression of the inflammatory process. Loss of appetite is often a

predominant feature. Constipation and nausea with profuse vomiting may indicate development of generalized peritonitis after perforation but it is rarely a major feature in simple appendicitis.[5]

The diagnosis of appendicitis can be challenging even in the most experienced hands, and is mostly a clinical one. Accurate anamnesis and physical examination are important to prevent unnecessary surgery and avoid complications. The probability of appendicitis depends on age, clinical setting, and symptoms.[6,7]

The mainstay of treatment is an appendectomy, and, consequently, this is one of the most common operations performed on the acute abdomen.[8] Open appendectomy (OA) has withstood the test of time for more than a century since its introduction by McBurney.[9,10] Since its initial description by Semm in 1983, laparoscopic appendectomy (LA) has struggled to prove its superiority over the open technique.[9,11] It is suggested that laparoscopic removal of an inflamed appendix may have benefits over open surgery.[12,13] Patients undergoing LA experience a reduction in wound infections, require less intraoperative and postoperative pain medication, stay less time in hospital, have quickened return of normal bowel function, and improved cosmetic outcome, avoiding a large laparotomy scar.[14]

Early postoperative pain is the most prevalent and dominant complaint that requires strong analgesia including opiates after elective laparoscopic surgeries. For that reason, many efforts have been made to improve postoperative analgesia, but postoperative pain, however, does not completely disappear and several studies have shown that visceral pain is the major component. Nonetheless, pain may be moderate to even severe for some patients during the first 24 postoperative hours,

and has frequently been treated with nonsteroid anti-inflammatory drugs (NSAIDs) or opioid treatment.[15]

The exact etiology of pain after laparoscopic surgeries is still unclear, however, it appears to be multifactorial and the causes include, abdominal wall trauma by trochar entrances, diaphragmatic irritation secondary to CO2 insufflation and pneumoperitoneum, type and temperature of insufflated gas and intraabdominal pH, residual intraperitoneal gas, intraabdominal trauma, microruptures of the parietal peritoneum due to abdominal distension, chemical irritation of the peritoneum, etc. Therefore, multimodal analgesic techniques are necessary. In order to reduce postoperative pain after the laparoscopy, several methods such as rectus cover block, intraabdominal drain placement, intraabdominal instillation of local anesthetics, intraperitoneal infiltration of the local anesthetics or opioids, the use of intramuscular morphine injections, patient-controlled analgesia, and injection of local anesthetics into the port sites are suggested.[15]

The preemptive intravenous and intraperitoneal application of local anesthetics is known to improve the postoperative outcome in abdominal surgery.[16] However, there is lack of consensus regarding the drug, dose, concentration, site, and route of administration.

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.[17] 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.[18] 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.[17-19-21]

However, there is scanty data on the effect intraperitoneal instillation of tramadol alone for the management of immediate postoperative pain in patients undergoing laparoscopic appendicectomy. Further several studies have assessed the role of intraperitoneal instillation of tramadol for the management of immediate postoperative pain in other laparoscopic surgeries and yielded controversial results. The pain in laparoscopic surgery being multifactorial we chose tramadol as it has multiple mechanism of pain relief as described above. This tempted us to evaluate the role of intraperitoneal instillation of tramadol on postoperative pain relief and emergence of adverse effects following laparoscopic appendectomy.

OBJECTIVES

The objectives of the present study were:

Primary

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

Secondary

To evaluate incidence of adverse effect (nausea, vomiting, shoulder pain, itching and shivering) following laparoscopic appendectomy.

REVIEW OF LITERATURE

Historical note on appendicitis

The word vermiform derived from the Latin word "Vermiforma" means worm shape, hence called 'vermiform'. Anatomically, it is one of the mobile viscera of abdomen about 1cm longer in male than in female. The appendix was probably first noted as early as the Egyptian civilization (3000BC). Appendix was not found by Aristotle and Galen because they both dissected lower animals, which do not have appendices. Celsus, however, probably discovered the appendix because he was allowed by Caesar to dissect criminals. Leonardo da Vinci first depicted the appendix in anatomic drawings in 1492.[22]

The first description of the appendix was reported by the Italian anatomist Berengario da Carpi (1460–1530), professor at the University of Bologna, in his Commentaria (1521) where he described an empty small cavity (addentramentum) at the end of the cecum. In 1543 De Humani Corporis Fabrica, Andreas Vesalius (1514–1564) then insisted on the appendix as one of the three openings of the cecum together with the ileum and the colon. Gabriel Falloppius (1523–1562) seemed to be the first to compare the appendix to a worm (vermiformis) in 1561.[22]

A post-mortem section of appendicitis was initially described by the leading German surgeon of the 18th century, Lorenz Heister (1638-1758), in 1711. Nevertheless, Garrison comments that "while the pathologic appearances, clearly described in the autopsy, had already been noted by Heister (1711), yet these landmarks left no impression upon practice whatever."[22]

The first report on an operated case of appendicitis is described by Claudius Aymand (1681-1740) who operated on an 11-year-old boy with a right scrotal hernia and a fistula. He identified the appendix, perforated by a pin within the scrotum, ligated the appendix and then removed it.[23,24]

The first operation for acute appendicitis was instead performed by J. Mestivier in 1759.[23] Mestivier described the case of a 45-year-old patient admitted to St. Andrew Hospital in Bordeaux for a mass localized on the right side of the umbilical area. The mass was fluctuant and was opened. A pint of pus came out. The patient died shortly after and during the autopsy it was found that the abscess had started from a small pin covered with salts perforating the appendix. The description of symptoms, possibly attributed to the pain of appendicitis, is found in the work of the German physician J.P. Frank, who writes of this picture as peritonitis muscularis in 1792.[23]

The first case in which perforation of appendix was recognized as the cause of death was reported in 18126 by John Parkinson (1755-1824), son of the more famous James renowned for describing Parkinson's disease. The case presented by John Parkinson was also the first case of appendicitis published in English. In 1813, Wegeler described in detail the case of an 18-year-old patient admitted for mild abdominal spasms for 3 days, followed by an acute and localized pain in the right lower quadrant, increasing at minimal palpation. The abdomen was tender, patient had constipation that was preceded by mild diarrhea, nausea and vomiting. The next day the extremities became cold and the patient died. On autopsy, there was a generalized peritonitis and the cecum was gangrenous. Wegeler commented that "this alteration seemed to start from the appendix that was red, enlarged and filled

with stones." In 1824 two more cases of appendix perforation with fatal peritonitis were reported in a classic paper by the French physician Louyer-Villemay. Only a few years later, in 1827, the French Francois Melier (1798-1866) was the first to describe what today is a chronic appendicitis and suggested a surgical approach.[23]

The first successful operation addressing an intestinal perforation due to an abscess of the appendix, was reported by the English surgeon Henry Hancock (1809-1880) at the Charing Cross Hospital in London.[23,25] This case was then followed in 1867 by the first in the US[23,26] authored by Willard Parker (1800-1884) from Francistown, NY. Parker advocated the opening of appendicular abscesses at an early stage. Other cases of successful operation of appendectomy with survival of the patients are from Richard John Hall in 1886[12] and Frank Woodbury in 1887. The latter wrote of a successful case operated by the surgeon Thomas George Morton (1835-1903). "The vermiform appendix was greatly swollen and exhibited a perforating ulcer extending three-fourths around its circumference and very near to the point of origin. A silk ligature was applied close to the caecum and at the terminal part of the appendix, and the intervening portion, comprising almost the whole organ was removed together with a large part of the omentum, which projected into the abscess cavity. The walls were then scraped with a curette and douched with simple warm water".[23]

Interestingly, the term "appendicitis" was introduced only in 1886 by Reginald Heber Fitz (1843-1913) in Boston and replaced the more generic "typhlitis" and "perityphilitis." He gave conclusive demonstrations of the pathology of perforating inflammation of the vermiform appendix in a series of 25 cases.[27] The most common sign of acute appendicitis, the "McBurney's point," was named after

and described by the New York surgeon Charles McBurney (1845-1913) in 1889.[28] The description of the site of pain in his famous article was "The seat of greatest pain, determined by the pressure of one finger, has been very exactly between an inch and a half and two inches from the anterior spinous process of the ileum on a straight line drawn from the process to the umbilicus".[23]

After 1890, the modern history of appendectomy was started with many surgeons who refined the operation proposing different approaches. The beginning of the 20th century corresponds also to the dawn of modern pathology, including accurate histological diagnosis of appendicitis, such as illustrated in 1908 by the renowned German pathologist Ludwig Aschoff.[23]

Epidemiology

The lifetime rate of appendicectomy is 12% for men and 25% for women, with approximately seven percent of all people undergoing appendicectomy for acute appendicitis. Over a 10 year period from 1987 to 1997, the overall appendicectomy rate decreased parallel to a decrease in incidental appendicectomy.[29,30] Appendicitis is most frequently seen in patients in their second through fourth decades of life, with a mean age of 31.3 years and a median age of 22 years. There is a slight male to female predominance (Male:Female 1.2 to 1.3:1).[31]

The incidence of appendicitis seems to have risen greatly in the first half of this century, particularly in Europe, America and Australia, with up to 16% of the population undergoing appendicectomy. In the past 30 years the incidence has fallen dramatically in these countries, such that the individual lifetime risk of appendicectomy is 8.6% and 6.7% among males and females respectively.[29] The

number of operations annually in England and Wales declined from 113,000 in 1966 to 48,000 in 1990,[32] while in Sweden there has been an annual decrease of 17% in the numbers of appendicectomies performed between 1987 and 1996.[33]

The incidence of appendicitis in India is lower when compared to western countries. However, still it is the third commonest operation among males and second common in females. This decline in incidence may be attributed to dietary habits. Furthermore, it seems that, the incidence of acute appendicitis is lower in South India compared to North India.[34]

Acute appendicitis is relatively rare in infants, and becomes increasingly common in childhood and early adult life, reaching a peak incidence in the teens and early 20s. After middle age the risk of developing appendicitis in the future is quite small. The incidence of appendicitis is equal among males and females before puberty. In teenagers and young adults the male-female ratio increases to 3:2 at age 25; thereafter the greater incidence in males declines.[8]

Clinical Features

The clinical features are more pronounced and progressive in obstructive than nonobstructive acute appendicitis. Pain that starts from periumblical area/epigastrium shifts to right iliac fossa in due course of time. Coughing causes localized pain in RIF in acute appendicitis and is absent in renal disease. Once parietal peritoneum is involved it produces more intense, constant and localized somatic pain that shifts and has changed its character. This classical visceralsomatic sequence is seen in only 50% of patients of acute appendicitis as early signs and symptoms depend upon the location of the tip of the appendix that is highly

variable.[35-38] In early appendicitis, the patient is initially afebrile or has a low-grade fever. Appendicitis in elderly is difficult problem resulting in incorrect diagnosis as well as high rate of perforation.[39] High fever is associated with a perforated appendicitis.[40] The clinical symptom/signs are detailed below.

Symptoms of acute appendicitis[35]

Symptoms	Signs	Special signs / tests
Pain	Increased temperature	Rovsing's sign
Anorexia	RIF tenderness	Pointing sign
Nausea	RIF Guarding	Release sign (Rebound)
Fever	Tachycardia	Copes-psoas test
Constipation	Brown-furred tongue	Obturator test
Diarrhoea	Foul breath	
	Hyperaesthesia	(Sherren's triangle)

Differential Diagnosis

Although acute appendicitis is the most common acute abdomen requiring surgical intervention yet in the absence of definite supportive diagnostic investigation it requires to be differentially diagnosed from a variety of clinical conditions. Even the most experienced physicians and surgeons are not able to diagnose appendicitis 100% of the times.

Differential diagnosis as per the age

Children	Adults	Adult females	Elderly
Gastroenteritis	Ureteric colic	Mittelschmerz	Diverticulitis
Mesentric adenitis	Perforated peptic ulcer	Salphingitis	Int. obstruction
Meckel's Diverticulitis	Pancreatitis	Pyelonephritis	Ca Colon
Intussusception	Rectus sheath haematoma	Torsion/ruptured Ovarian cyst	Torsion appendix epiploicae
Henoch-Schonlein purpura	Torsion testis	Ruptured ectopic gestation	Mesenteric infarction
Lobar Pneumonia	Regional enteritis	Endometriosis	Aortic aneurysm

Investigations

Although the diagnosis of acute appendicitis invariably is clinical yet it may be supported by exclusion after doing some investigations. No test yet devised that is 100% diagnostic. The only diagnostic procedure short of open exploration is diagnostic laparoscopy.[35]

White blood cell count

In 3/4th cases of acute appendicitis TLC is more than 12,000.[41] Tc- labeled WBC Scan has reported sensitivity of 98% and specificity of 95%. However, time constraint and availability is an issue.[35,42]

Urine examination

Though normal in many instances yet it may be showing pyuria/microscopic haematuria. If the surgeon is satisfied that appendicitis cannot be ruled out, operation under such circumstances is entirely justified; that may show inflammed appendix adhern to right ureter/bladder.[35]

Radiography

Finding as proposed by various authors on plain X-Ray abdomen as well as barium meal follow through are listed in table IV. It is pertinent to mention here that emergency barium enema is practiced in USA only and not in any other country.[35]

Plain X-ray abdomen and barium enema findings in acute appendicitis[35]

Plain X-ray findings	**Barium findings**
Fluid levels localized to caecum/terminal Ileum	Persistent non visualisation of appendix
Localised ileus with gas in caecum/ascending colon	Partially visualised appendix
Increased soft tissue density in right lower quadrant	Pressure defect on the caecum
Blurring of right flank stripe	Irritable caecum/ terminal ileum on screening
Faecolith in right iliac fossa	
Blurring of Rt. Psoas shadow	
Free intraperitoneal gas	
Deformity of the caecal gas shadow	

Ultrasonography of abdomen

More useful for differential diagnosis. With experience one may find acutely inflamed appendix as non-compressible, aperistaltic, tubular structure with a central dilated lumen surrounded by an inner echogenic mucosal layer and outer oedematous wall that shows few echoes.[35]

Management

Most of the history of appendicitis and appendectomy has been made during the past two centuries. Jacopo Berengario da Carpi gave the first description of this structure in 1522. Gabriele Fallopio, in 1561, appears to have been the first writer to compare the appendix to a worm. In 1579 Caspar Bauhin proposed the ingenious theory that the appendix served in intrauterine life as a receptacle for the faexes. Many of anatomists added more or less insignificant ideas concerning the structure of the appendix and entered upon useless controversy concerning the name, function, position of the appendix vermiformis. The first successful appendectomy was performed in 1735 by Claudius Amyand. Geillaume Dupuytren considered that acute inflammation of the right side of the abdomen arose from disease of the caecum and not the appendix. As surgeons were wary of opening the abdomen for examination, early stages of appendicitis remained unknown. John Parkinson was able to give a good description of fatal appendicitis in 1812. Surgeons began draining localised abscesses which had already formed. In 1880 Robert Lawson Tait made the first diagnosis of appendicitis and surgically removed the appendix.[43]

In 1886 Reginald Heber Fitz published a study on appendicitis and named the procedure an appendectomy. In 1889, Tait split open and drained an inflamed

appendix without removing it. Charles McBurney proposed his original muscle splitting operation in 1893 and this was modified by Robert Fulton Weir in 1900.[43]

Today we have a multiplicity of signs and symptoms, helping to diagnose appendicitis, and there are a lot of techniques for operation with little essential difference throughout. Kurt Semm performed the first laparoscopic appendectomy in 1981 which became a new gold standard in surgical treatment of acute and chronic appendicitis.[43]

The treatment of acute appendicitis is appendectomy. In the absence of appendicular mass, appendix should be removed at the earliest as the operative mortality is almost negligible but it may increase several fold if operation is delayed. The appendectomy may be either open or laparoscopic. Unlike Laparoscopic cholecystectomy, laparoscopic appendectomy has failed to establish itself as minimally invasive procedure of choice both in children and adults.[44-46]

Open Appendectomy

Conventional-appendectomy

Done by standard methods with the help of either of the available incisions (Grid Iron, Rutherdford-Morrison's, Rockey Davis, Lanz, Paramedian, Midline).[35]

Mini-appendectomy

This is done with the help of small transverse incision 2 to 2.5 cms starting from lateral border of rectus abdominis muscle and extended towards Mc Burney's point. Anterior sheath is cut in line of skin incision, rectus muscle retracted medial and blended posterior sheath/peritoneum cut in line of skin incision. Once

peritoneum is approached, with little manipulation appendix is delivered towards wound site and appendectomy completed as per standard protocol. Appendiceal stump is not buried and we do not close posterior peritoneum, retracted rectus muscle comes to its place once anterior sheath is closed. Skin is approximated with silk/clips/subcuticular prolene.[47,48]

Open appendectomy remains the most common approach due to less operative time and cost.[35]

Laparoscopic appendectomy

Since 1987, however, an increasing number of surgeons have come to prefer laparoscopic appendectomy. Laparoscopic appendectomy has now been improved and standardized.[49]

According to the 2010 Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) guideline, the indications for laparoscopic appendectomy are identical to those for open appendectomy. The 2010 SAGES guideline lists the following conditions as suitable for laparoscopic appendectomy:[50]

- Uncomplicated appendicitis
- Appendicitis in pediatric patients
- Suspected appendicitis in pregnant women

According to the SAGES guideline, laparoscopic appendectomy may be the preferred approach in the following cases:[50]

- Perforated appendicitis
- Appendicitis in elderly patients

- Appendicitis in obese patients

The SAGES guideline states that the laparoscopic approach should be preferred in women of childbearing age with presumed appendicitis.[50]

Laparoscopic appendectomy has some advantages, including decreased postoperative pain, better aesthetic result, a shorter time to return to usual activities, and lower incidence of wound infections or dehiscence. This procedure is cost-effective but may require more operative time and skill as compared with open appendectomy. Kouhia et al found that by 2008, operative time with laparoscopic appendectomy was only 10 minutes longer than with the open approach. In addition, patients who underwent open appendectomy returned to work later and had more complications.[51]

The reported results of laparoscopic and open-procedure appendectomies seem to overlap. In fact, the average rate of abdominal abscesses, negative appendectomies, and hospital stays are very similar, according to an overview of 17 retrospective studies.[52]

History of postoperative pain relief

H. David Reines, launched the discussion by defining pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage." Acute pain is a normal and predictable physiologic response to an adverse chemical, thermal, or mechanical stimulus; it is associated with surgery, trauma, or acute illness and is usually experienced for a limited and defined period of time.[53]

Knowledge of the history of pain management appears to begin with the case of a 5000-year-old cadaver that apparently experienced sciatic pain and had markings showing that treatment was attempted. "Pain has been part of our culture for a long time," said Dr. Reines. "It is a central metaphor of Judeo-Christian thought and sometimes believed to be a test of faith." [53]

A tincture of opium, or laudanum, was used as early as 1680 for the treatment of pain. "By the early 1800s," continued Dr. Reines, "pain was no longer considered to be something that people had to suffer. At that point, it was believed that a skilled surgeon could operate fast enough so that patients weren't in total agony." Morphine was isolated from heroin in 1803, but modern anesthesia use began around 1846 with the use of ether and chloroform. [53]

Pain treatment has evolved over the years. The first spinal anesthetic was performed just before the turn of the twentieth century, and cocaine was also used in the late 1800s for local anesthesia of the eye. A number of peripheral blocks were described and used by surgeons prior to World War II. "The use of intravenous (IV) drugs didn't arrive until the 1930s and were used a lot in World War II and thereafter," explained Dr. Reines. The use of morphine and cocaine was followed by meperidine and codeine and then fentanyl, oxycodone, and hydromorphone. In the 1950s and 1960s, most pain medication was given either subcutaneously or intramuscularly, and meperidine was used frequently. The use of patient-controlled IV (IV PCA) pain medication was proposed in 1979. In the 1980s, use of intrathecal opioids, epidurals, and continuous spinals began; by the 1990s, nonsteroidal anti-inflammatory drugs (NSAIDs) were being used for augmentation in a multimodal

approach, followed by preemptive pain management and the advent of new technologies such as a fentanyl patch. [53]

In 1999, the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) put forth new regulations in which they considered pain to be the fifth vital sign and mandated that all hospitals address patients' pain as part of their treatment programs. "Now we're in the 2000s," remarked Dr. Reines, "and there are new delivery systems available. There is more emphasis on preventing and relieving pain with medications that work faster and are easier to administer and on improved educational efforts for healthcare workers and patients." [53]

"In the practice guidelines for acute pain in the perioperative setting that were established about 10 years ago," continued Dr. Reines, "acute pain services and preoperative pain-directed history taking were believed to be necessary to collaborate with other healthcare professionals. To address this, we try to avoid opioid abstinence syndromes postoperatively and use patient-controlled analgesia (PCA) and epidural analgesia as needed. It was also recommended that multimodal techniques should be applied -- Ketorolac is still the only IV NSAID available in the US -- and epidural opioids with local anesthetics in combination with clonidine have been used. Finally, the early conversion to equidosed oral opioids has made a big difference in the way we treat our patients." [53]

Pain after laparoscopic surgeries

Laparoscopic approaches to surgery have increased dramatically over the past several years. However laparoscopic procedures are not pain free and pain

occurs after laparoscopy, but is usually less and shorter compared to the same conventional surgical procedure.[15]

Mechanism of pain in laparoscopy

Early postoperative pain is the most prevalent and dominant complaint that requires strong analgesia including opiates after elective laparoscopic surgeries. For that reason, many efforts have been made to improve postoperative analgesia, but postoperative pain, however, does not completely disappear and several studies have shown that visceral pain is the major component. Nonetheless, pain may be moderate or even severe for some patients during the first 24 postoperative hours, and has frequently been treated with nonsteroid anti-inflammatory drugs (NSAIDs) or opioid treatment.[15]

The exact etiology of pain after laparoscopic surgeries is still unclear, however, it appears to be multifactorial and the causes include, abdominal wall trauma by trochar entrances, diaphragmatic irritation secondary to CO2 insufflation and pneumoperitoneum, type and temperature of insufflated gas and intraabdominal pH, residual intraperitoneal gas, intraabdominal trauma, microruptures of the parietal peritoneum due to abdominal distension, chemical irritation of the peritoneum, etc.[15]

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.[54]

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.[55]

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.[56]

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.[57] 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.[58]

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.[56]

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.[59] 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 membranaes, an effect that was not seen with the use of humidified gas.[59]

Management of postoperative pain after laparoscopic surgeries

In order to decrease the postoperative pain after the laparoscopy, some methods such as rectus cover block, intraabdominal drain placement in order to throw out CO2 pneumoperitoneum, intraabdominal instillation of local anesthetics, intraperitoneal infiltration of the local anesthetics or opioids, the use of intramuscular morphine injections, patient-controlled analgesia, and injection of local anesthetics into the port sites are suggested.[15] The postoperative analgesic effect of intraperitoneal administration of local anesthesia after laparoscopic surgeries has proved to be effective and safe. However there is lack of consensus regarding the drug, dose, concentration, site, and route of administration and there is scanty data on the effect of the same procedure during laparoscopic appendicectomy.

Intraperitoneal administration of local anesthesia

In the studies, after the laparoscopic surgeries, the intraperitoneal local anesthetics are found to be very effective for the decrease in postoperative pain.[13] This non-invasive method has a minimum risk and it can be easily applied. Besides, there are studies showing that the application of intraperitoneal anesthetic administration is not useful for the prevention of postoperative pain.[60] Because laparoscopic surgery, a minimally invasive technique, is associated with reduced

surgical trauma, the use of local anesthetic infiltration for efficacious postoperative analgesia should allow widespread use of laparoscopic day-case surgery.[15]

Literature review

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

Altunkaya H. et al,[20] Golubovic et al,[61,62] Turan A.,[63] through their respective studies have demonstrated the intraperitoneal action of tramadol and have concluded that intraperitoneal administration of tramadol had some implications in reducing postoperative pain.

A study done by Hernandes–Pazon et al.[64] showed that intraperitoneal administration of local anaesthetic in combination with an opoid reduced the analgesic requirements during first 6 postoperative hours.

Golubovic et al.[62] in his study concluded that intraperitoneal administration of tramadol and or bupivacaine as effective method of management of postoperative pain after laproscopic cholecystectomy.

Another study by Akinsi et al.[65] concluded that iv tramadol provides superior postoperative pain relief as compared to intraperitoneal administration.

Studies done by Wilson et al[66] showed the limited benefits of NSAIDS for pain relief and also demonstrated the adverse effects related with use of NSAIDS.

Because of its both central and local action, the use of Tramadol HCl in this study arises with a thought that it may provide better postoperative pain relief as

compared to other drugs like bupivicaine and NSAIDS and hence provide a pain free experience to the patient which would be adored both by patient and doctors.

Most of the previous studies have shown local anaesthetic along with opiods can provide pain relief postoperatively when instilled intraperitoneally but only scant literature is available evaluating effectiveness of intraperitoneal administration of Tramadol alone for post laparoscopic surgery pain relief.

To best of our knowledge a thorough review of literature reveals no study which have assessed the analgesic efficacy of intraperitoneal instillation of tramadol during laparoscopic appendectomy. Thus, the present study is undertaken to assess the efficacy of intraperitoneal instillation of tramadol in alleviating the postoperative pain following laparoscopic appendectomy to further strengthen this hypothesis.

With the expanding role of ambulatory surgery and the need to facilitate an earlier discharge, improving postoperative pain has become an increasingly important issue. Keeping this in mind through this study has been planned.

This would also lead to early discharge from hospitals, early recovery, less respiratory complications and patients can get back to their routine activities, as pain postoperatively is a major discomfort for the patient and with this study we can help provide a comfortable and pain free postoperative period.

A study done by Goulbovic S et al[62] 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.[67] 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.[68] 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.[69] 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[70] 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.

A study[64] done in Munich showed that intraperitoneal administration of local anesthetic in combination with an opioid (morphine) reduced the analgesic requirements during the first 6 postop hours.

A study[63] in Edirne, Turkey demonstrated local effects of Intraperitoneal tramadol and bupivacaine in total abdominal hysterectomy.

Murthy BV et al.[71] studied the pharmacokinetics of a single bolus dose of tramadol 2 mg/kg injected either i.v. or into the caudal epidural space in 14 healthy children, aged 1-12 yr, undergoing elective limb, urogenital or thoracic surgery. After a single i.v. injection, the mean elimination half-life of tramadol was 6.4 (SD 2.7) h, with a volume of distribution of 3.1 (1.1) litre/kg and total plasma clearance of 6.1 (2.5) ml/kg/min. All of these pharmacokinetic variables were similar to those reported previously in adults. After caudal epidural administration, mean elimination half-life was 3.7 (0.9) h, volume of distribution was 2.0 (0.4) litre/kg and total clearance was 6.6 (1.9) ml/kg/min. The caudal/i.v. Quotient of the AUC was 0.83, which confirms that there is extensive systemic absorption of tramadol after caudal administration supporting the fact that Tramadol gets absorbed adequately from various fibrovascular surfaces in body.

BASIC SCIENCES

EMBRYOLOGY OF THE APPENDIX[72]

At an early embryonic stage it has the same caliber as the caecum and is in line with it. It is formed by excessive growth of the right wall of the caecum which pushes the appendix to the inner side. Congenital absence of the appendix is extremely rare.

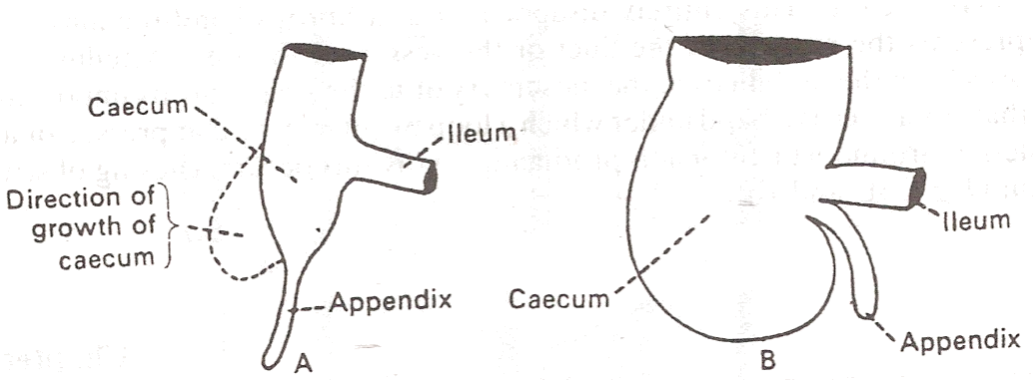


Figure 1. Development of the appendix

Abnormalities in development

These are quite rare. These may occur in form of agenesis, duplication diverticula and left sided appendix.

i) ***Agenesis*** – The vermiform appendix is absent at birth.

ii) ***Duplication*** – A few cases have been reported where there is double appendix

iii) ***Diverticula*** – It is very rarely seen in the appendix.

iv) ***Left sided appendix*** – In case of situs inversus, transposition of thoracic and abdominal viscera, in that case, appendix with caecum will be seen on the left side. In certain cases of non-rotation of the midgut, the ceacum and appendix may be seen as midline structure or on the left side.

ANATOMY OF VERMIFORM APPENDIX[73]

Position of appendix

The vermiform appendix is a narrow worm shaped tubular structure which springs from the posteromedial wall of the caecum. It may occupy one of the several following positions:

1) ***Retrocaecal appendix****:* behind the caecum and lower part of ascending colon (retroceacal 74%)

2) ***Pelvic appendix****:* may descend over the brim of the lesser pelvis (pelvic or descending 21%) in which case it lies in close relation to the right ureter in males and right uterine tube and ovary in females.

3) ***Subcaecal appendix****:* below the ceacum that is subcaecal 1.5%

4) ***Preileal****:* in front of terminal part ileum and may then be in contact with anterior abdominal wall (Preileal 1%)

5) ***Postileal****:* behind the terminal part of the ileum (Postileal 0.5%)

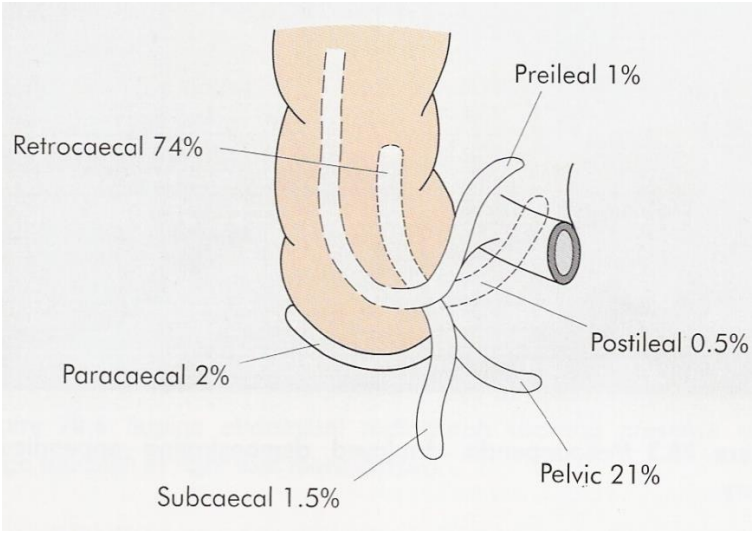


Figure 2. Various position of appendix

Commonest position is retrocaecal and the next common position is pelvic followed by subcaecal, preileal and postileal in descending order.

The three taenia coli of ascending colon and caecum converge on the base of appendix where they merge into its longitudinal muscular layer of appendix. The anterior taenia caecum is generally distinct and can be easily traced to the base of the appendix.

The appendix varies from 2 to 20 cms on length, with an average of 9 cms in length. It is longer in children than in adults, which might become atrophy and smaller after mid adult life .The lumen of appendix is small and communicates with the caecum by an orifice which is placed below and little behind the ileocaecal opening. The orifice is sometimes guarded by a semilunar valve formed by a fold of mucous membrane.

The luminal capacity of normal appendix is about 0.1ml i.e. there is no real lumen .Secretions as little as 0.5 ml Distal to the block increases the intraluminal pressure to about 60 cms of water.

Mesoappendix

The mesentery of the appendix is a triangular fold of peritoneum around the vermiform appendix. It is attached to the posterior surface of the lower end of the mesentery of the small intestine close to the ileocaecal junction. It usually reaches the tip of the appendix but some times fails to reach the distal third, in which case a vestigial low peritoneal ridge containing fat is present over the distal third. It encloses the blood vessels, nerves and lymph vessels of the vermiform appendix, and usually contains a lymph node.

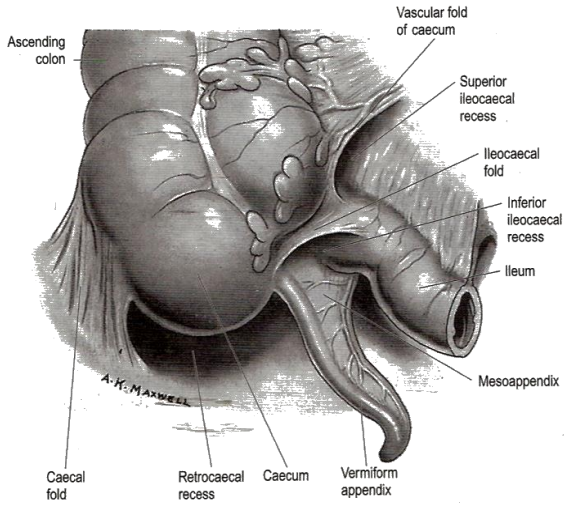


Figure 3. The peritoneal folds and recesses in caceal region

Vascular supply and lymphatic drainage

Appendicular artery

The main appendicular artery, a branch from the lower division of the ileocolic artery, runs behind the terminal ileum and enters the mesoappendix a short distance from the appendicular base. Here it gives off a recurrent branch, which anastomoses at the base of the appendix with a branch of the posterior caecal artery: the anastomosis is sometimes extensive. The main appendicular artery approaches the tip of the organ, at first near to, and then in the edge of, the mesoappendix. The terminal part of the artery lies on the wall of the appendix and may be thrombosed in appendicitis, which results in distal gangrene or necrosis. Accessory arteries are common, and many individuals possess two or more arteries of supply.

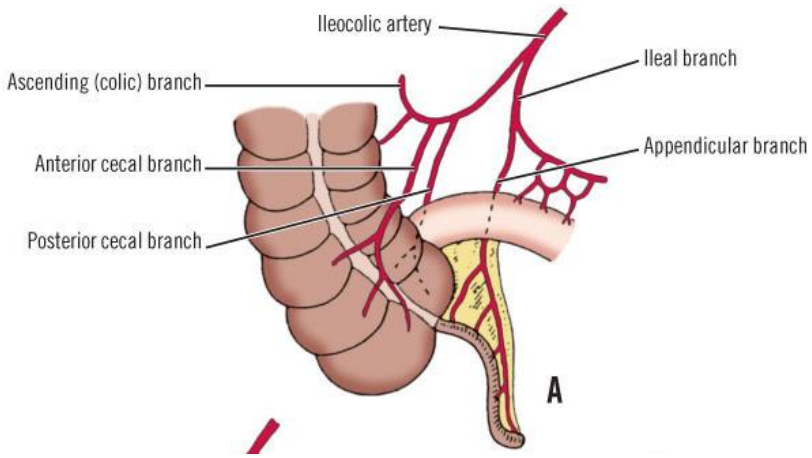


Figure 4. Blood supply of appendix

Appendicular veins

The appendix is drained via one or more appendicular veins into the posterior caecal or ileocolic vein and hence into the superior mesenteric vein.

Lymphatics

Lymphatic vessels in the appendix are numerous: there is abundant lymphoid tissue in its walls. From the body and apex of the appendix eight to 15 vessels

ascend in the mesoappendix, and are occasionally interrupted by one or more nodes. They unite to form three or four larger vessels which run into the lymphatic vessels draining the ascending colon, and end in the inferior and superior nodes of the ileocolic chain.

Innervation

The appendix and overlying visceral peritoneum are innervated by sympathetic and parasympathetic nerves from the superior mesenteric plexus. Visceral afferent fibres carrying sensation of distension and pressure mediate the symptoms of pain felt during the initial stages of appendicular inflammation. In keeping with other structures derived from the midgut, these sensations are poorly localized initially, and referred to the central (periumbilical) region of the abdomen. It is not until parietal tissues adjacent to the appendix become involved in any inflammatory process that somatic nociceptors are stimulated, and there is an associated change in the nature and localization of pain.

MICROSTRUCTURE OF THE APPENDIX[74]

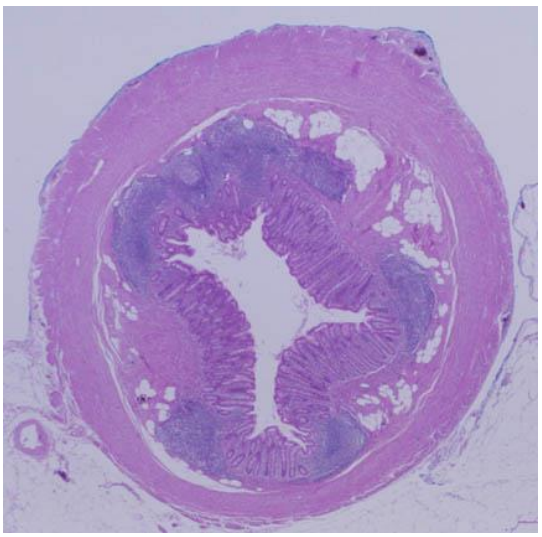


Figure 5. Normal histology of appendix

Histology

Vermiform appendix consists of the following coats:

Serosa

The serosa forms a complete covering, except along the mesenteric attachment. The longitudinal muscular fibres form a complete layer of uniform thickness, except over a few small areas where both muscular layers are deficient, leaving the serosa and submucosa in contact.

Muscularis Externa

The muscularis externa has outer longitudinal and inner circular layers of smooth muscle. The longitudinal fibres form a continuous layer but, with the exception of the uniform outer muscle layer of most of the appendix, macroscopically these are aggregated as longitudinal bands or taeniae coli. At the base of the appendix, the longitudinal muscle thickens to form rudimentary taeniae that are continuous with those of the caecum and colon. Between the taeniae coli the longitudinal layer is much thinner, less than half the circular layer in thickness.

Sub-Mucosa

The submucosa typically contains many large lymphoid aggregates that extend from the mucosa and obscure the muscularis mucosae layer, consequently this becomes discontinuous. These aggregates also cause the mucosa to bulge into the lumen of the appendix, so that it narrows irregularly. They are absent at birth but accumulate over the first 10 years of life to become a prominent feature. The submucosal lymphoid tissue frequently exhibits germinal centres within its follicles,

indicative of B-cell activation, as it is in secondary lymphoid tissue elsewhere. In adults, the normal layered structure of the appendix is lost and the lymphoid follicles atrophy and are replaced by collagenous tissue. In the elderly, the appendix may be filled with fibrous scar tissue.

Mucosa

The mucosa is covered by a columnar epithelium and M cells are present in the epithelium that overlies the mucosal lymphoid tissue. Glands (crypts) are fewer in number and thus less densely packed. They penetrate deep into the lymphoid tissue of the mucosal lamina propria.

SURFACE MARKING[73]

The surface marking commonly used for the base of the appendix is the junction of the lateral and middle thirds of the line joining the right anterior superior iliac spine to the umbilicus (Mc Burney's point).

PATHOLOGY[75]

Morphology

At earliest stages, only a scanty neutrophlic exudate may be found throughout the mucosa, submucosa and muscularis propria. Subserosal vessels are congested and often there is a modest perivascular neutrophilic infiltrate. The inflammatory reaction transforms the normal glistening serosa into a dull, granular, red membrane; this transformation signifies early acute appendicitis for the surgeon. At a later stage, a prominent neutrophilic exudate generates a fibrinopurulent reaction over the serosa.

The histologic criterion for the diagnosis of acute appendicitis is neutrophilic infiltration of the muscularis propria. Usually, neutrophils and ulcerations are also present within the mucosa. Since drainage of an exudate into the appendix from alimentary tract infection may also induce a mucosal neutrophils infiltrate, evidence of muscular wall inflammation is requisite for the diagnosis.[76-77]

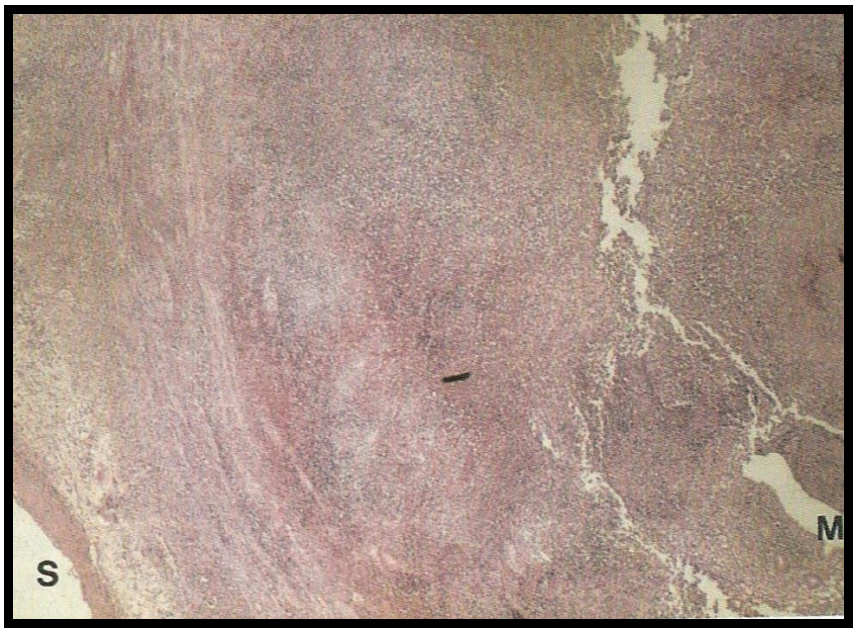


Figure 6. Histology of inflamed appendix

Etiopathogenesis

Obstruction of the lumen is the dominating factor in acute appendicitis. Fecoliths are usual cause of appendiceal obstruction. Less common is hypertrophied tissue, inspissated barium from previous X-rays, vegetable, fruit seed, worms (Entrobius vermicularis, Balantidum coli, Schistosoma haematobium).[35]

Faecoliths are found in 40% of cases of simple acute appendicitis, 65% of cases of gangrenous appendicitis without rupture, and nearly 90% of cases of gangrenous appendicitis with rupture.

There is a predictable sequence of events leading to eventual appendiceal rupture. The proximal obstruction of the appendiceal lumen produces a closed-loop obstruction, and continuing normal secretion by the appendiceal mucosa rapidly produces distension. The luminal capacity of the normal appendix is only 0. l milliliter (mL). Secretion of as little as 0.5 mL of fluid distal to an obstruction raises the intraluminal pressure to 60 cm of H_2O. Distension of the appendix stimulates nerve endings of visceral afferent stretch fibers, producing vague, dull, diffuse pain in the mid-abdomen or lower epigastrium. Peristalsis is also stimulated by the rather sudden distention, so that some cramping may be superimposed on the visceral pain early in the course of appendicitis. Distension continues from continued mucosal secretion and from rapid multiplication of the resident bacteria of the appendix. Distension of this magnitude usually causes reflex nausea and vomiting, and the diffuse visceral pain becomes more severe. As pressure in the organ increases, venous pressure is exceeded. Capillaries and venules are occluded, but arteriolar inflow continues, resulting in engorgement and vascular congestion. The inflammatory process soon involves the serosa of the appendix and in turn parietal peritoneum in the region, producing the characteristic shift in pain to the right lower quadrant.

The mucosa of the gastrointestinal tract, including the appendix, is susceptible to impairment of blood supply, thus its integrity is compromised early in the process, allowing bacterial invasion. As progressive distension encroaches upon first the venous return and subsequently the arteriolar inflow, the area with the poorest blood supply suffers most and ellipsoidal infarcts develop in the antimesenteric border. As distension, bacterial invasion, compromise of vascular

supply, and infarction progress, perforation occurs, usually through one of the infarcted areas on the antimesenteric border. Perforation generally occurs just beyond the point of obstruction rather than at the tip because of the effect of diameter on intraluminal tension.

This sequence is not inevitable, however, some episodes of acute appendicitis apparently subside spontaneously. Many patients who are found at operation to have acute appendicitis give a history of previous similar, but less severe, attacks of right lower quadrant pain. Pathologic examination of the appendix removed from these patients often reveals thickening and scarring, suggesting old, healed, acute inflammation.[75-77]

It is of great importance to recognize two types of Acute Appendicitis.

Non–obstructive acute appendicitis

The inflammation usually commences in the mucus membrane, less often in the lymph follicles and can terminate in one of the following ways: 1) Resolution, 2) Ulceration, 3) Suppuration, 4) Fibrosis, 5) Gangrene. Once infection reached the loose submucous tissues it progresses rapidly. The organ becomes turgid, dusky red, and haemorrhage occurs into the mucus membrane. The vascular supply of the distal part of the appendix is often in jeopardy because at this point the artery is intramural and liable to occlusion inflammation or thrombosis. This may lead to gangrene of the tip. Non –obstructive appendicitis may progress sufficiently slowly for protective barriers to form, and the resulting peritonitis is localized. In many instance the infection never progresses beyond the mucus lining (that is, Catarrhal inflammation).

Because the tip suffers most, after resolution of acute attack, fibrosis usually occurs there in and shrunken tip is a classical finding in recurrent appendicitis.[78]

Obstructive acute appendicitis

About two out of every three cases of acute appendicitis belong to this group. The obstruction can be in the lumen (fecolith, foreign body, or parasites); in the wall (adhesions and kinking). Of these, much the most common is a fecolith. Fibrosis of the wall from previous attacks of acute appendicitis can contribute by narrowing the lumen and promoting fecolith impaction and (rarely) appendicitis accompanies ileocaecal Crohn's disease.[78]

In obstructive appendicitis the products of inflammation become pent up so that the inflammation proceeds more rapidly and more certainly to gangrene or perforation. Often within twelve to eighteen hours the appendix distal to the obstruction become gangrenous. Close examination of gangrenous appendices directly after the removal shows conclusively that they usually belong to the obstructive group. Perforation occurs most often at the site of an impacted faecolith before protective adhesions have had time to form. The escaping purulent and gaseous contents are under high pressure and early widespread peritonitis is liable to ensue. Subphrenic and pelvic abscesses are the common later sequels if the patient survives that initial peritonitis.[78]

Bacteriology

Common organisms seen in patients with acute appendicitis.[75]

Aerobic and Facultative	Anaerobic
Gram-negative bacilli	Gram-negative baciili
E. coli	Bacteroides fragilis
Pseudomonas aeruginosa	Bacteroides species
Klebsiella species	Fusobacterium species
Gram-positive cocci	Gram-positive cocci
Streptococcus anginosus	Peptostreptococcus species
Streptococcus species	Gram-positive bacilli
Enterococcus species	Clostridium species

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.[79]

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.[80]

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 postoperative care.[80]

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).[81]

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.[82-84]

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.[82]

Nociceptors are either somatic that include those in skin and deep tissues (muscle, tendons, joints), or visceral nociceptors that include those in internal organs.[82-84]

Pain pathway

Pain is conducted along three neuron pathways; from the periphery to the cerebral cortex. [82-84]

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). [82-84]

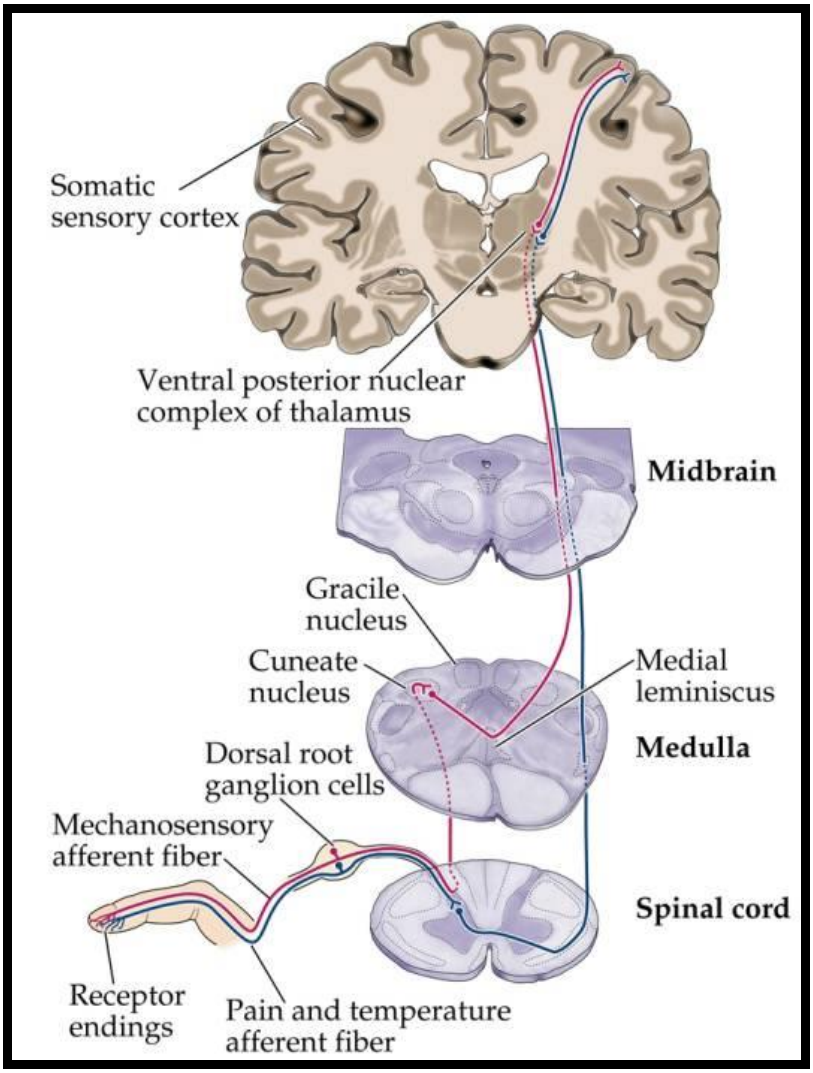


Figure 7. Pain pathway[82-84]

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". [83,84]

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. [83,84]

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.[83,84]

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.[84-86]

Effects of postoperative pain

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

Acute pain is typically associated with neuroendocrine stress response that is proportional to pain intensity, and it has been hypothesized that a reduction in surgical stress responses (endocrine, metabolic and inflammatory) will lead to a reduced incidence of postoperative organ dysfunction and thereby lead to an improved outcome. The latter suggests that effective postoperative pain management as a very important aspect of postoperative care.[87]

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.[88]

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.[89]

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.[90]

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.[90]

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.[87]

c. Gastrointestinal effects

Sympathetic hyperactivity induced by pain increases sphincter tone and decrease motility of intestine, causing ileus, pain also increases stress ulceration due to increase in gastric acid secretion.[91]

d. Endocrinal effects

The dominant neuroendocrine responses to pain involve hypothalamic-pituitary-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.[92]

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.[82]

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.[81]

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.[93]

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.[87]

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.[94]

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).

Behavioral

- Sighing, crying, shouting, trembling.

2. Type II methods

It includes either:

Single dimension methods

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

Multi-dimensional methods

- Mc Gill pain Questionnaire, MPQ
- Dartmouth pain Questionnaire, DPQ
- West Haven-Yale pain Questionnaire, WHYPQ.[88]

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.[81]

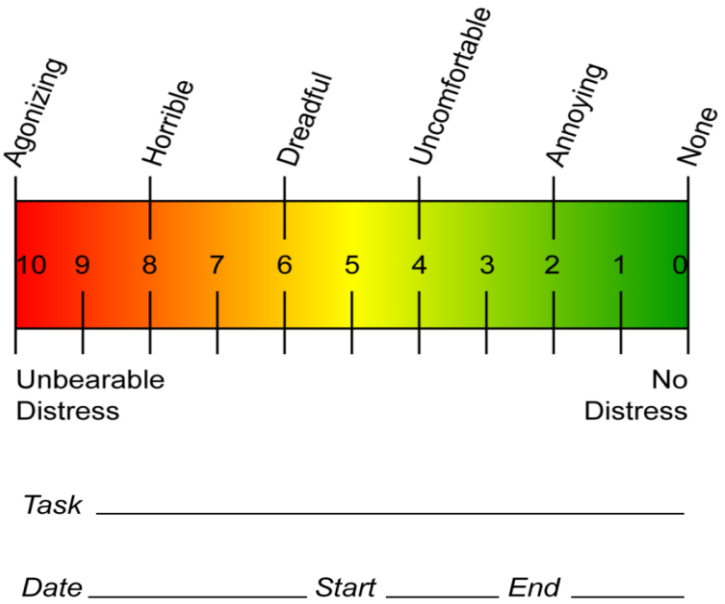


Figure 8. Visual analogue scale

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 while 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. Interapleural 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.[82]

TRAMADOL[82,95]

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

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

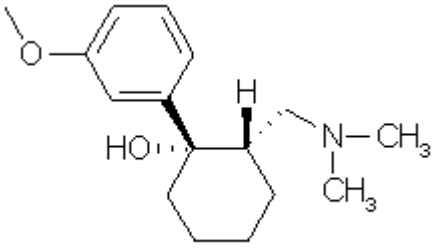


Figure 9. Chemical structure of Tramadol

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 anesthesia is as an opioid that has moderate affinity at mu receptors and weaker affinity for delta and kappa receptors. Tramadol has methyl group substitution on the phenolic moiety which explains its weak affinity for opioid receptors.

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

inhibition of neurotransmitter reuptake and that required for opioid receptor analgesia is the same.

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

Pharmacokinetics

Absorption

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

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

Distribution

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

Metabolism

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

The main metabolites are O–desmethyl tramadol and N-desmethyl tramadol. These main metabolites are again metabolized to secondary metabolites which are N-N-didesmethyl, N-N,O – tridesmethyl tramadol and N-O desmethyl tramadol 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 local anaesthesia 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 $5HT_{3A}$ 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 exacerbate 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.

METHODOLOGY

The present study was done in the KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum from January 2014 to December 2014.

Study design and duration

The one year study design was a double blinded randomized controlled trial.

Study period

This study was done from January 2014 to December 2014.

Place

The present study was carried out in the Department of General Surgery, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum a tertiary care teaching hospital attached to KLE University's Jawaharlal Nehru Medical College, Belgaum.

Source of Data

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

Sample size

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

Sampling procedure

Since no similar studies have been reported in the literature on effectiveness of intraperitoneal instillation of tramadol for postoperative laparoscopic appendectomy, applying thumb rule 60 cases undergoing elective laparoscopic appendectomy were included.

Selection criteria

Inclusion

- Patients aged 14 years and above.
- Patients of either sex.
- Patients with ASA grade I and II

Exclusion

- Uncooperative and unwilling patients.
- Those with history of anaphylaxis to opioids.
- Immunocompromised patients or severe hepatorenal impairment.
- ASA grade III, IV and V.
- Those needing conversion to open appendectomy.

Ethical clearance

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

Informed Consent

Patients fulfilling selection criteria were detailed about the nature of study and a written informed consent was obtained (Annexure I).

Method of collection of data

The demographic data such as age and sex, presenting complaints were noted. The patients were subjected to clinical examination and vitals were noted. The systemic examination was done and the clinical signs such as RIF tenderness, rebound tenderness and guarding were noted. There findings were recorded on a predesigned proforma (Annexure II).

Randomization

Patients were divided into two groups of 30 each as group A and B based on computer generated random numbers.

Surgical procedure

Patient placed supine under general anesthesia. The pneumoperitoneum was created by closed technique (Photograph-1). Trendelenburg with right side up was given during procedure for easy assess. The first 10 mm port was placed in the umbilicus for the 30-degree optical device of size 10 mm using permanent metallic trocar (Photograph-2). Two other ports were created at suprapubic (10 mm) and right iliac fossa (5mm) following trans-illumination of abdominal wall (Photograph-3). The surgeon was on the left side of the patient, with the first assistant on his right, and instrumentation table on lower right side of the patient while monitor was put on the upper right side of the patient. (Photograph-4)

The operation was performed with five permanent instruments: grasping forceps curved dissecting forceps, scissors, knot-pusher and specimen retriever. The surgical technique consisted of doing the following steps:

- The ileocecal appendix was held with grasping forceps introduced through right iliac fossa trocar; (Photograph-5)
- With the dissecting forceps in the suprapubic trocar, the appendix was separated from its mesoappendix using thermal coagulation and cutting going gradually to the base (Photograph-6A,B)
- Extracorporeal pre-tied two Roeder's knots (using 2-0 silk free tie) placed at the base of the appendix with optional one more distal, using knot pusher. (Photograph-7 A,B)
- Appendix was cut above/between two distal knots using scissors via suprapubic port, avoiding risk of extravasation of its content; (Photograph-8 A,B)
- Removal of the apprehended appendix done by pulling with specimen retrieving forceps immediately after section into the trocar (Photograph-9) and withdrawing the 10 mm trocar from the abdominal wall with the appendix inside and, afterward which was introduced again.
- The vicinity was cleaned with saline wash and suctioning if any spillage of content from cut ends was noticed.
- Abdominal cavity inspected thoroughly for any other gross pathology.
- Pneumoperitoneum was released and metallic ports were removed, further closing the incision sites using Vicryl 2-0 and Ethilone 3-0 as a standard in all patients.(Photograph-10)

- A single operating surgeon performed all the cases using similar technique.
- The general anesthesia protocol was remained same for all patients.

Intervention

Both Group A and Group B patients received intraperitoneal 40 mL of solution (drug / placebo) prepared by anesthetist under aseptic precautions, 20 mL of which was instilled into the sub diaphragmatic space (Photograph-11A) and remaining 20 mL was instilled in right iliac fossa over the appendicular stump and raw area (Photograph-11 B,C), under direct vision by the surgeon just before removal of trocars.

The instillation was done using metallic suction cannula keeping its knob at irrigation point and syringe nozzle attached to the inlet, while keeping suction outlet closed and secured ensuring no spillage or loss of drug. (Photograph-12 A,B)

Postoperative care

Postoperatively patients were shifted to recovery room, observations were made about outcome variable that is, pain, requirement of analgesia and complications and recorded by the surgeon, starting immediately after extubation.

Blinding

Both patients and surgeon / assistant were blinded and anesthetist loaded drug or normal saline according to random table chart and gave it to the surgeon for instillation.

Postoperative pain management

Pain was assessed using Visual Analogue Score (VAS) ranging from 0 to 10. Visual analogue scale was explained to the patient during pre operative visit considering zero as no pain and 10 as maximum pain point.

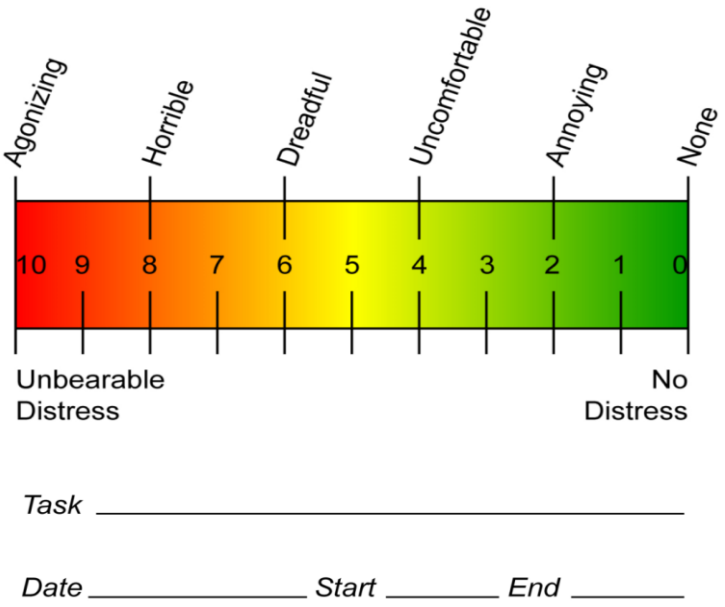


Figure 10. Visual analog scale

The VAS score ≤4 was regarded as satisfactory whereas patients reporting VAS score of >4 were administered for rescue analgesia with injection Diclofenac sodium 75 mg intramuscularly as a rescue analgesic.

Outcome variables

Pain

Postoperative pain was monitored in terms of VAS scores by the surgeon at 0 minute, 15 minutes, 30 minutes, 60 minutes, 6 hours, 12 hours and 24 hours.

Requirement of analgesia

Rescue analgesic requirement with 75 mg Diclofenac Sodium was noted immediately postoperative, 15 minutes, 30 minutes, 60 minutes, 6 hours, 12 hours and 24 hours.

Adverse effects

Incidence of following adverse effects was noted by the surgeon immediately postoperative, and at 4, 8, 16 and 24 hours intervals.

- Nausea
- Vomiting
- Shoulder pain
- Itching

Statistical analysis

The data was entered into the Microsoft Excel Spreadsheet (Annexure III). The data was analyzed using SPSS statistical software version 20.0. 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% confidence interval was considered as statistically significant.

RESULTS

This one year double blinded randomized controlled trial was done at KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum from January 2014 to December 2014.

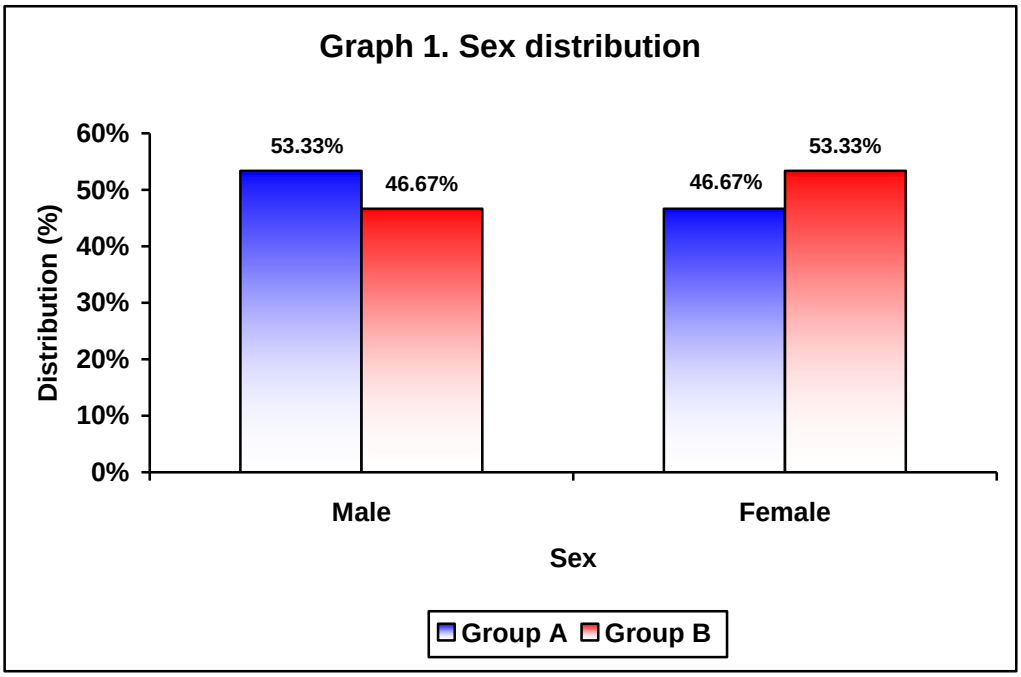
A total of 60 patients undergoing elective laparoscopic appendectomy were enrolled. These patients were divided into two groups of 30 each to as group A and B to receive either intraperitoneal tramadol 150 mg (diluted in 40 ml of normal saline) or 40 ml of intraperitoneal normal saline.

The data obtained was analysed and the final results were interpreted as below:-

Table 1. Sex distribution

Sex	Group A (n=30)		Group B (n=30)	
	No.	**%**	**No.**	**%**
Male	16	53.33	14	46.67
Female	14	46.67	16	53.33
Total	**30**	**100.00**	**30**	**100.00**

p = 0.606

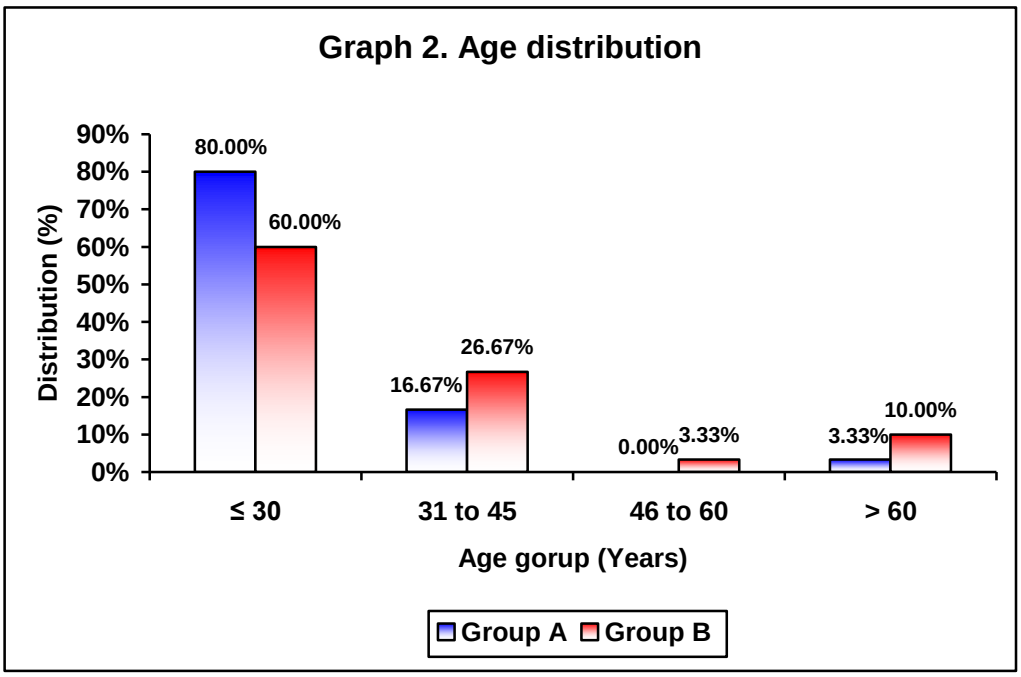


In the present study 53.33% of the patients in group A were males compared to 46.67% in group B. The male to female ratio in group A was 1.14:1 compared to 1:1.14 in group B. However the difference was statistically not significant (p=0.606).

Table 2. Age distribution

Age group (Years)	Group A (n=30)		Group B (n=30)	
	No.	**%**	**No.**	**%**
≤ 30	24	80.00	18	60.00
31 to 45	5	16.67	8	26.67
46 to 60	0	0.00	1	3.33
> 60	1	3.33	3	10.00
Total	**30**	**100.00**	**30**	**100.00**

p = 0.295



In this study most of the patients were aged ≤ 30 years that is, 80% in group A and 60% in group B but the difference was statistically not significant (p=0.295).

Table 3. Mean age

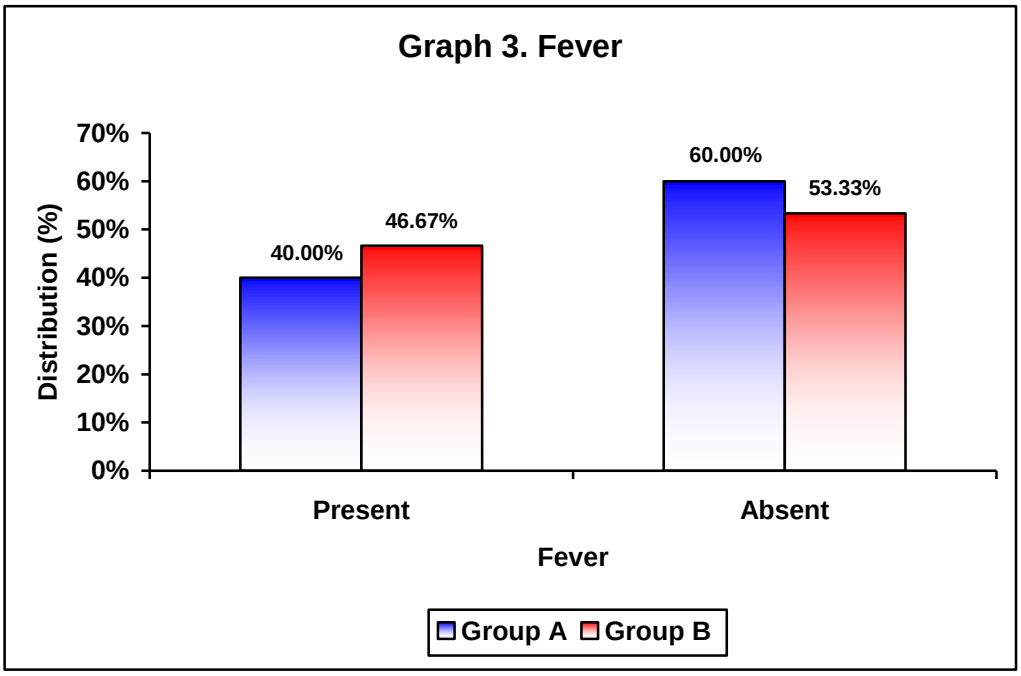
Variables	Group A (n=30)		Group B (n=30)		p value
	Mean	SD	Mean	SD	
Age (Years)	26.13	9.96	31.43	14.81	0.110

In the present study the mean age in group B was slightly high compared to group A but the difference was statistically not significant (p=0.110)

Table 4. Fever

Fever	Group A (n=30)		Group B (n=30)	
	No.	**%**	**No.**	**%**
Present	12	40.00	14	46.67
Absent	18	60.00	16	53.33
Total	**30**	**100.00**	**30**	**100.00**

p = 0.602

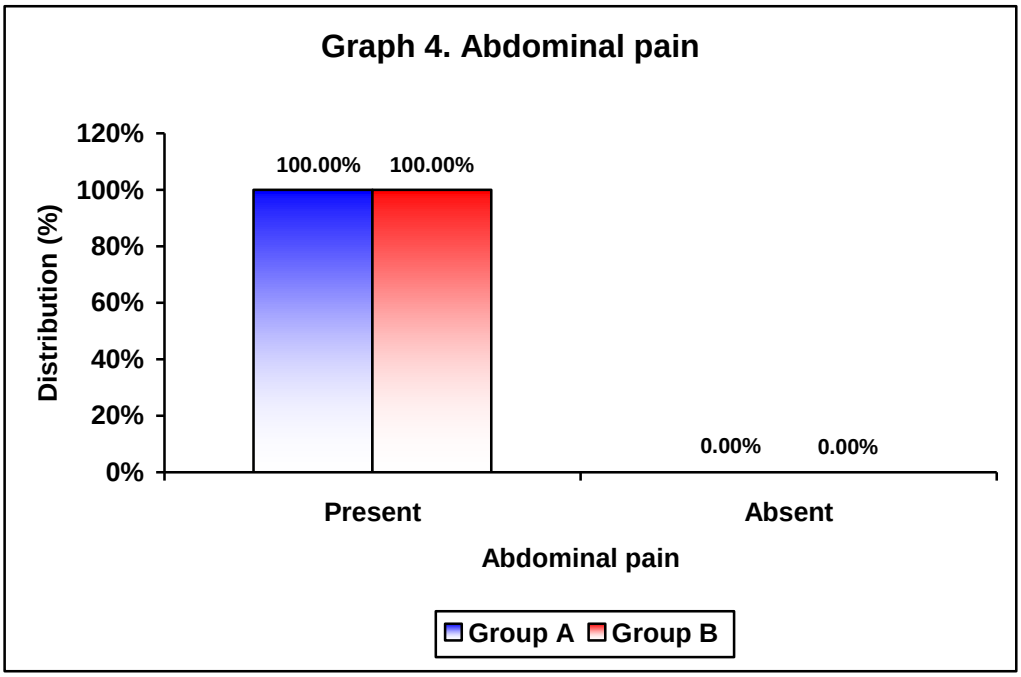


In this study 40% of the patients in group A presented with fever compared to 46.67% of the patients in group B (p=0.602).

Table 5. Abdominal pain

Abdominal pain	Group A (n=30)		Group B (n=30)	
	No.	**%**	**No.**	**%**
Present	30	100.00	30	100.00
Absent	0	0.00	0	0.00
Total	**30**	**100.00**	**30**	**100.00**

p = 1.000

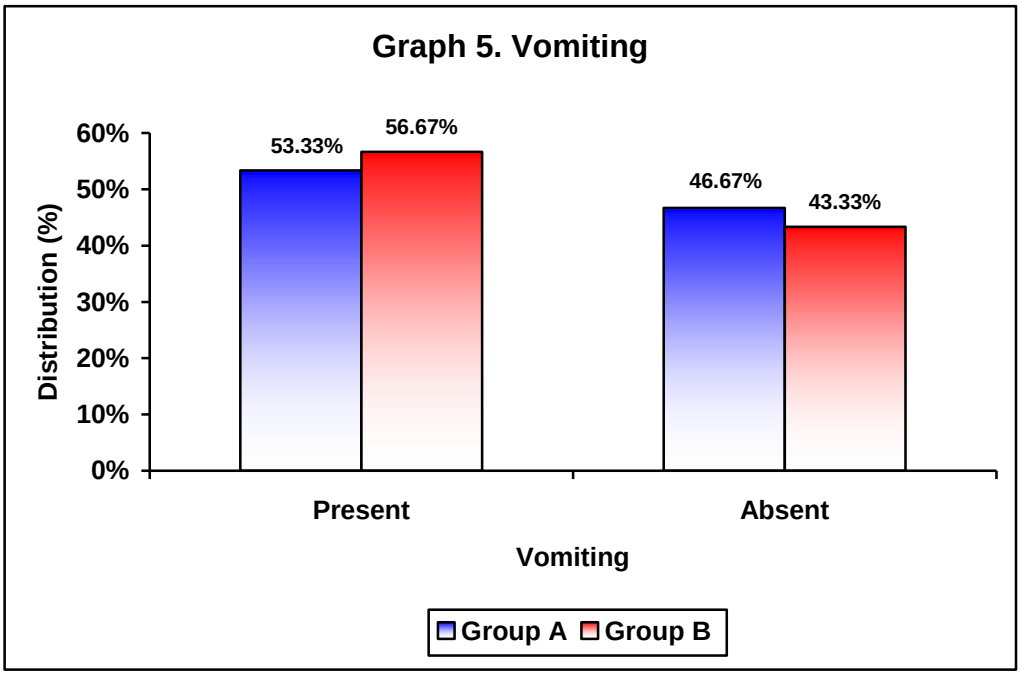


In the present study all the patients (100%) in group A and B presented with abdominal pain (p=1.000).

Table 6. Vomiting

Vomiting	Group A (n=30)		Group B (n=30)	
	No.	**%**	**No.**	**%**
Present	16	53.33	17	56.67
Absent	14	46.67	13	43.33
Total	**30**	**100.00**	**30**	**100.00**

p = 0.795

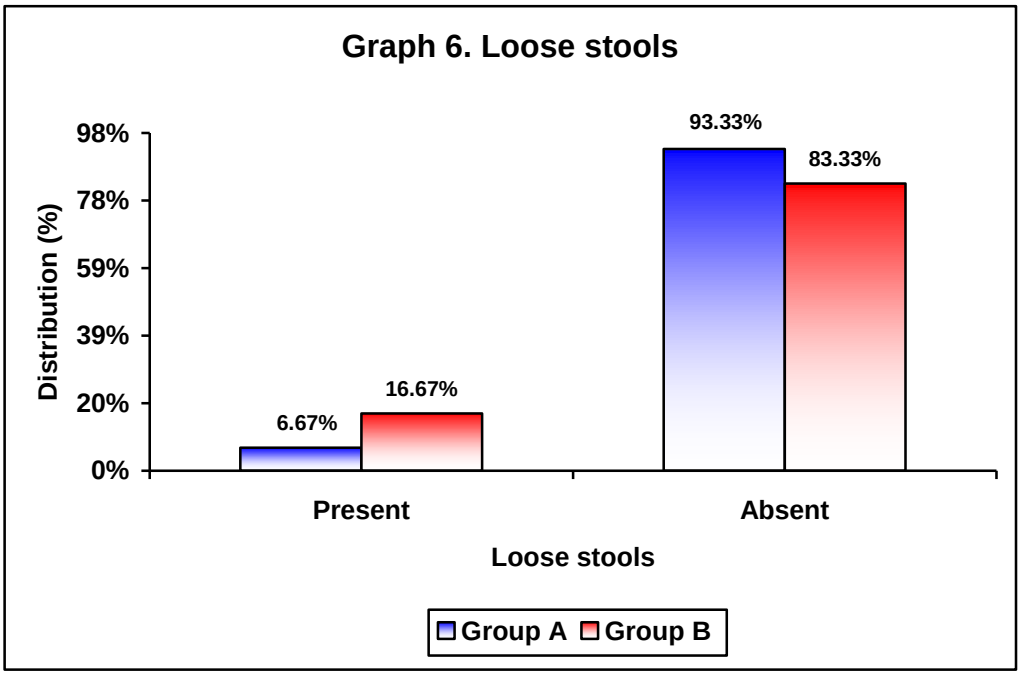


In this study 53.33% of the patients in group A reported vomiting compared to 56.67% in group B. However this difference was statistically not significant (p=0.795).

Table 7. Loose stools

Loose stools	Group A (n=30)		Group B (n=30)	
	No.	**%**	**No.**	**%**
Present	2	6.67	5	16.67
Absent	28	93.33	25	83.33
Total	**30**	**100.00**	**30**	**100.00**

p = 0.212

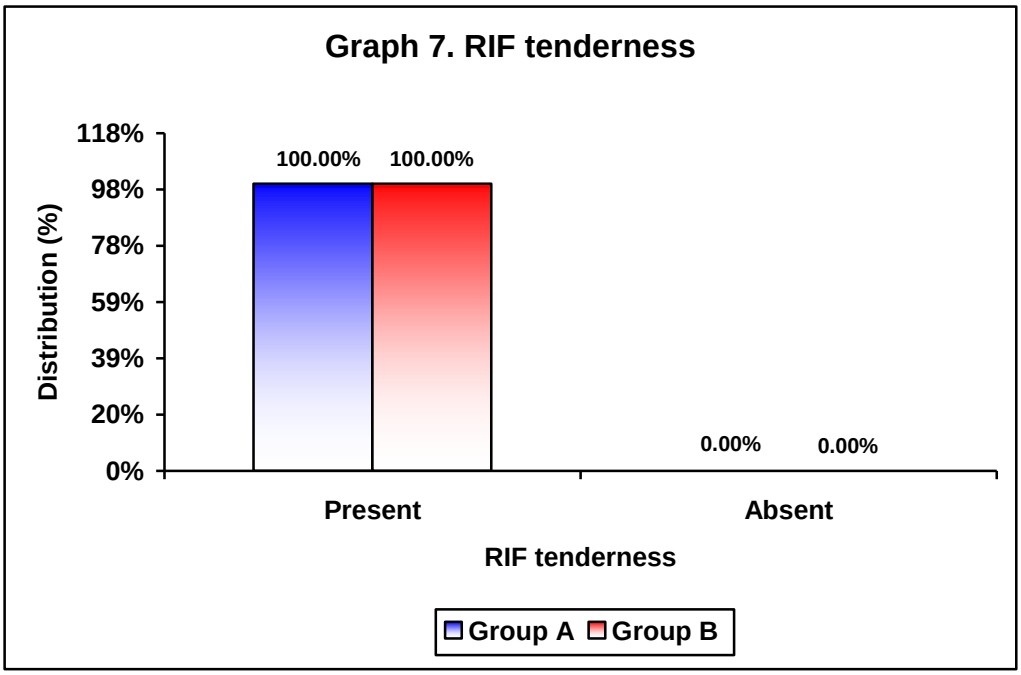


In the present study 6.67% of the patients in group A reported loose stools while in group B, loose stools was noted among 16.67% (p=0.212).

Table 8. RIF tenderness

RIF tenderness	Group A (n=30)		Group B (n=30)	
	No.	**%**	**No.**	**%**
Present	30	100.00	30	100.00
Absent	0	0.00	0	0.00
Total	**30**	**100.00**	**30**	**100.00**

p = 1.000

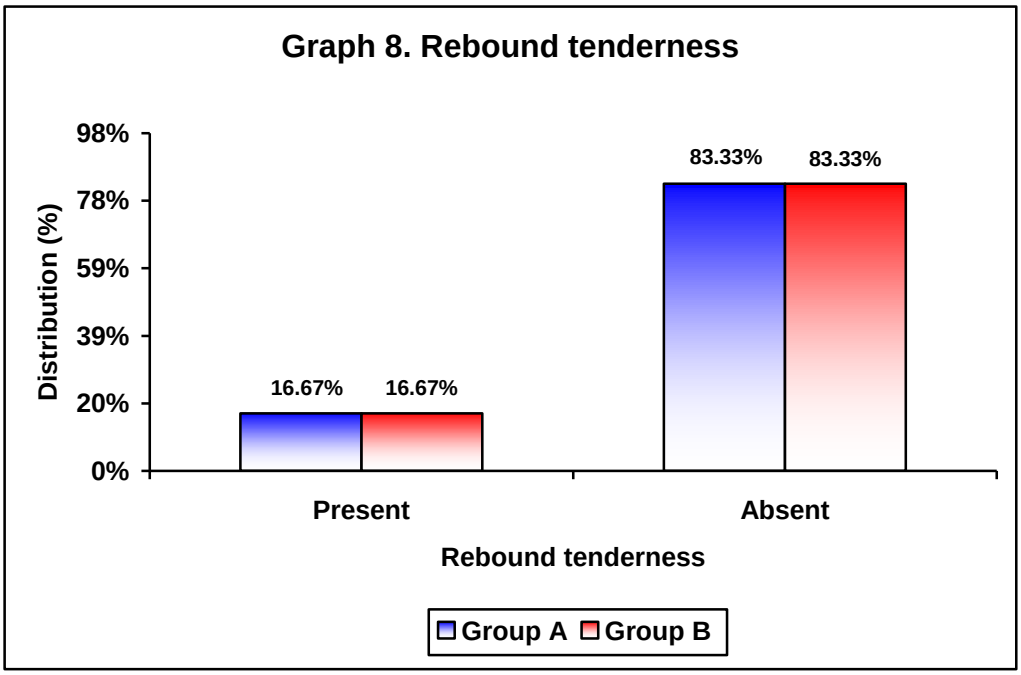


In this study RIF tenderness was noted among all the patients (100%) in group A and B (p=1.000).

Table 9. Rebound tenderness

Rebound tenderness	Group A (n=30)		Group B (n=30)	
	No.	**%**	**No.**	**%**
Present	5	16.67	5	16.67
Absent	25	83.33	25	83.33
Total	**30**	**100.00**	**30**	**100.00**

p = 1.000

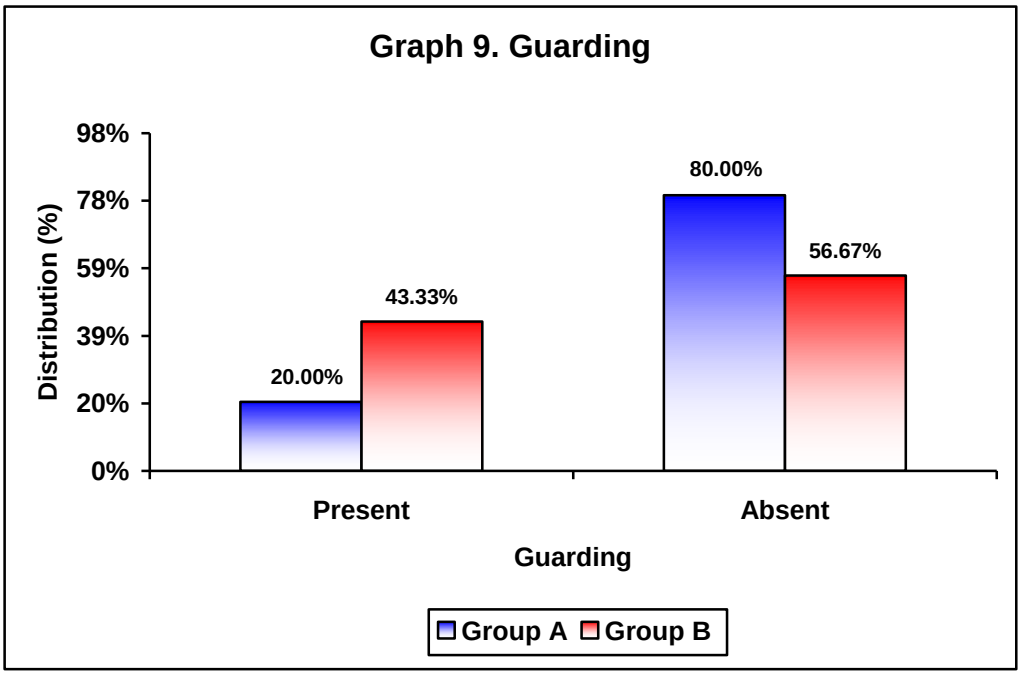


In the present study 16.67% of the patients each had rebound tenderness (p=1.000).

Table 10. Guarding

Guarding	Group A (n=30)		Group B (n=30)	
	No.	**%**	**No.**	**%**
Present	6	20.00	13	43.33
Absent	24	80.00	17	56.67
Total	**30**	**100.00**	**30**	**100.00**

p = 0.052

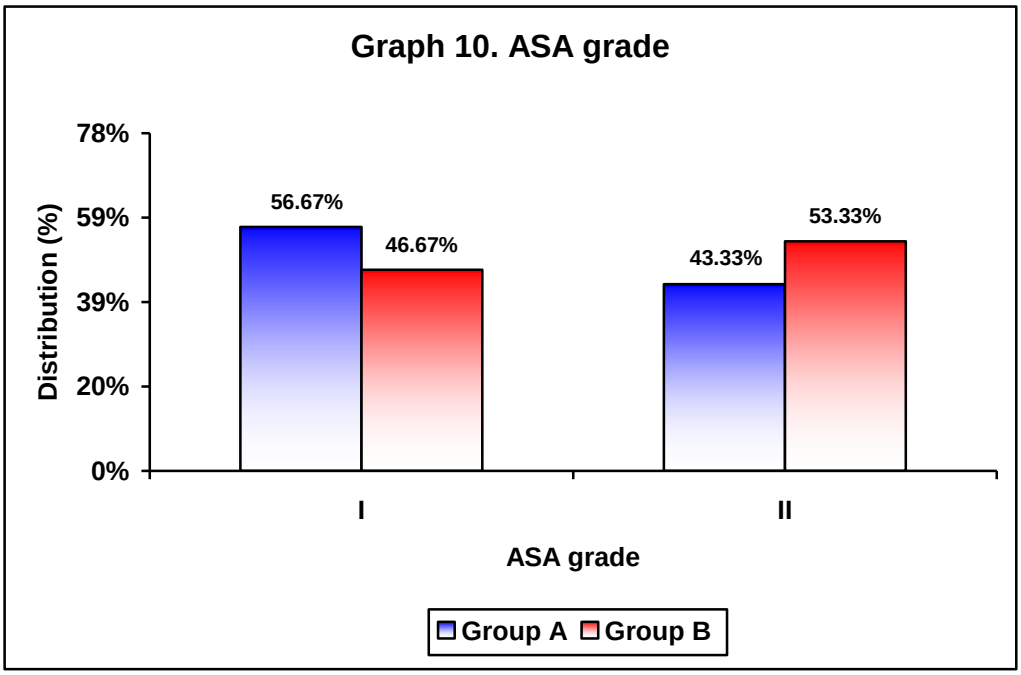


In this study 20% of the patients in group A had guarding compared to 43.33% of the patients in group B. However this difference was statistically not significant (p=0.052).

Table 11. ASA grade

ASA grade	Group A (n=30)		Group B (n=30)	
	No.	**%**	**No.**	**%**
I	17	56.67	14	46.67
II	13	43.33	16	53.33
Total	**30**	**100.00**	**30**	**100.00**

p = 0.438



In the present study 56.67% of the patients in group A had ASA I status compared to 46.67% in group B. However this difference was statistically not significant (p=0.438).

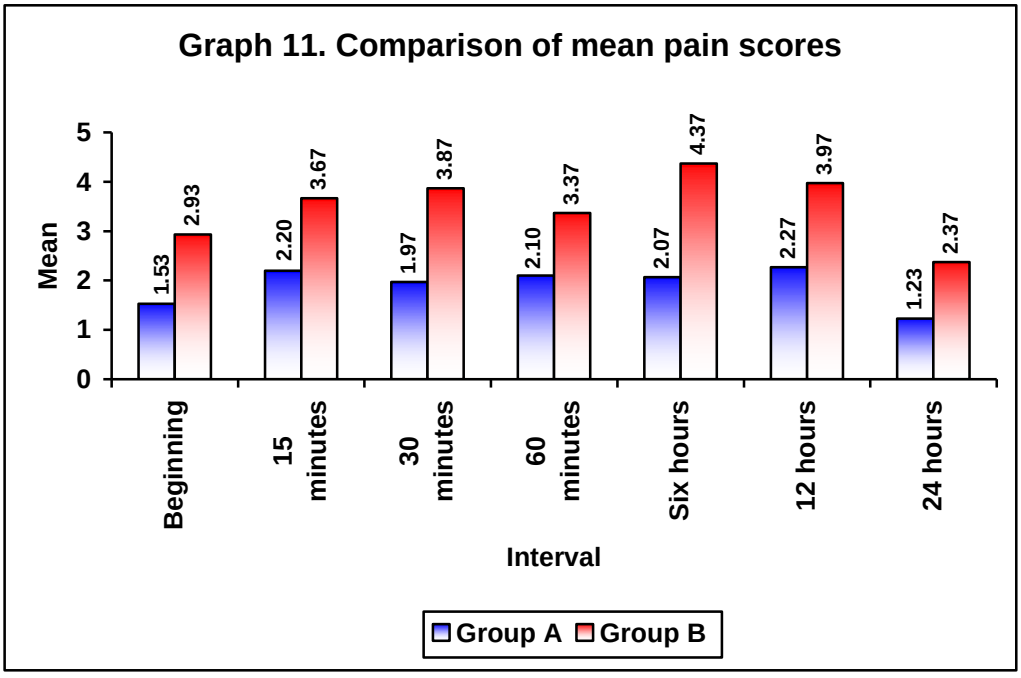
Table 12. Comparison of vitals

Parameters	Group A (n=30)		Group B (n=30)		p value
	Mean	**SD**	**Mean**	**SD**	
Pulse rate (/Minute)	96.27	7.50	96.53	7.10	0.888
Systolic BP (mm Hg)	120.60	8.00	124.27	10.75	0.140
Diastolic BP (mm Hg)	74.67	5.57	74.53	12.26	0.957
Temperature (^{0}F)	100.25	0.78	100.34	0.88	0.667
Respiratory rate (/Min)	16.77	2.82	17.07	2.12	0.643

Table 12 shows the comparison of mean pulse rate, systolic and diastolic blood pressure, temperature and respiratory rate. However the vitals status of the patients in group A and B did not vary significantly ($p>0.050$).

Table 13. Comparison of mean pain scores

Interval	Group A (n=30)		Group B (n=30)		p value
	Mean	SD	Mean	SD	
Beginning	1.53	0.94	2.93	1.17	**<0.001**
15 minutes	2.20	1.13	3.67	1.30	**<0.001**
30 minutes	1.97	1.27	3.87	2.03	**<0.001**
60 minutes	2.10	0.84	3.37	1.13	**<0.001**
Six hours	2.07	1.57	4.37	1.27	**<0.001**
12 hours	2.27	1.44	3.97	1.27	**<0.001**
24 hours	1.23	1.07	2.37	1.16	**<0.001**

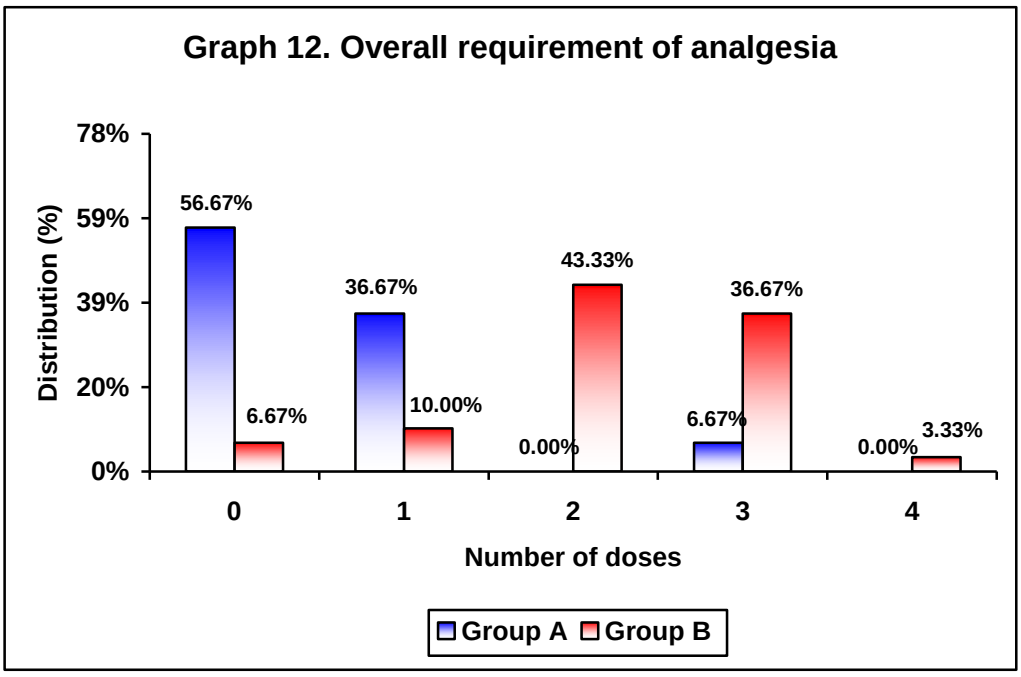


In the present study the mean VAS scores at beginning were significantly low in group A (1.53 ± 0.94) compared to group B (2.93 ± 1.17) and similar trend was noted at all the durations through the postoperative period ($p<0.001$)

Table 14. Overall requirement of analgesia

Number of doses	Group A (n=30)		Group B (n=30)	
	No.	%	No.	%
0	17	56.67	2	6.67
1	11	36.67	3	10.00
2	0	0.00	13	43.33
3	2	6.67	11	36.67
4	0	0.00	1	3.33
Total	**30**	**100.00**	**30**	**100.00**

p = 0.011



In the present study most of the patients in group A did not request for the postoperative analgesia (56.67%) compared to 6.67% in group B. This difference was statistically significant (p=0.011).

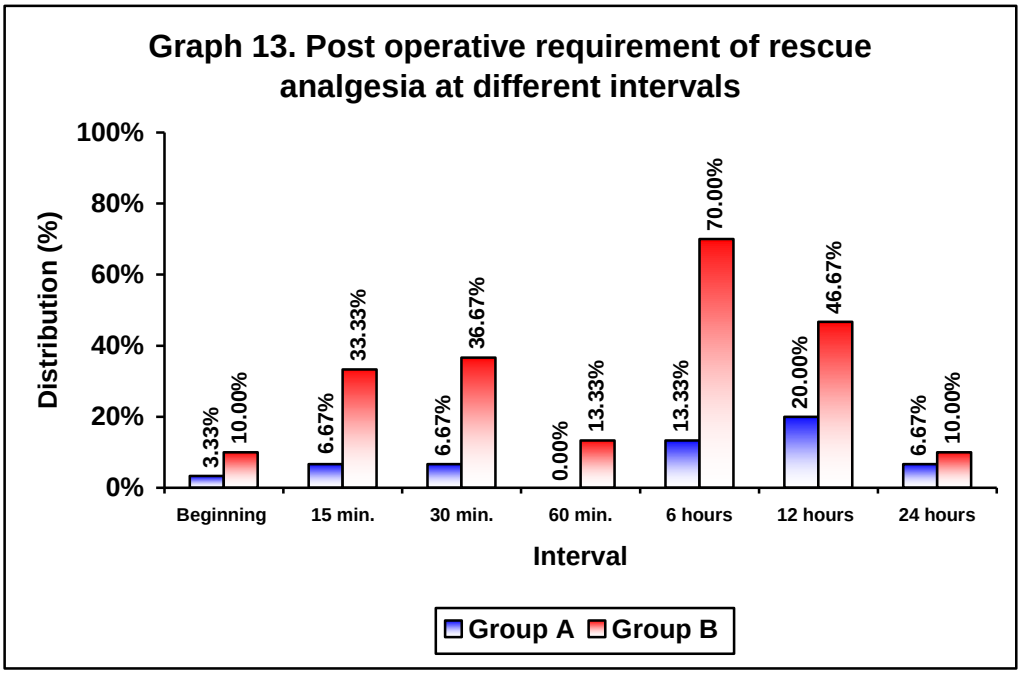
Table 15. Comparison of mean doses of rescue analgesia

Variables	Group A (n=30)		Group B (n=30)		p value
	Mean	**SD**	**Mean**	**SD**	
Number of doses	0.57	0.82	2.20	0.92	**<0.001**

In the present study among the patients with group A, significantly lower number of mean doses was administered (0.57 ± 0.82 vs. 2.20 ± 0.92; p<0.001) compared to group B.

Table 16. Postoperative requirement of rescue analgesia at different intervals

Interval	Requirement	Group A (n=30)		Group B (n=30)		p value
		No.	%	No.	%	
Beginning	Yes	1	3.33	3	10.00	0.306
	No	29	96.67	27	90.00	
	Total	**30**	**100.00**	**30**	**100.00**	
15 min.	Yes	2	6.67	10	33.33	**0.010**
	No	28	93.33	20	66.67	
	Total	**30**	**100.00**	**30**	**100.00**	
30 min.	Yes	2	6.67	11	36.67	**0.005**
	No	28	93.33	19	63.33	
	Total	**30**	**100.00**	**30**	**100.00**	
60 min.	Yes	0	0.00	4	13.33	0.056
	No	30	100.00	26	86.67	
	Total	**30**	**100.00**	**30**	**100.00**	
6 hours	Yes	4	13.33	21	70.00	**<0.001**
	No	26	86.67	9	30.00	
	Total	**30**	**100.00**	**30**	**100.00**	
12 hours	Yes	6	20.00	14	46.67	**0.028**
	No	24	80.00	16	53.33	
	Total	**30**	**100.00**	**30**	**100.00**	
24 hours	Yes	2	6.67	3	10.00	0.500
	No	28	93.33	27	90.00	
	Total	**30**	**100.00**	**30**	**100.00**	

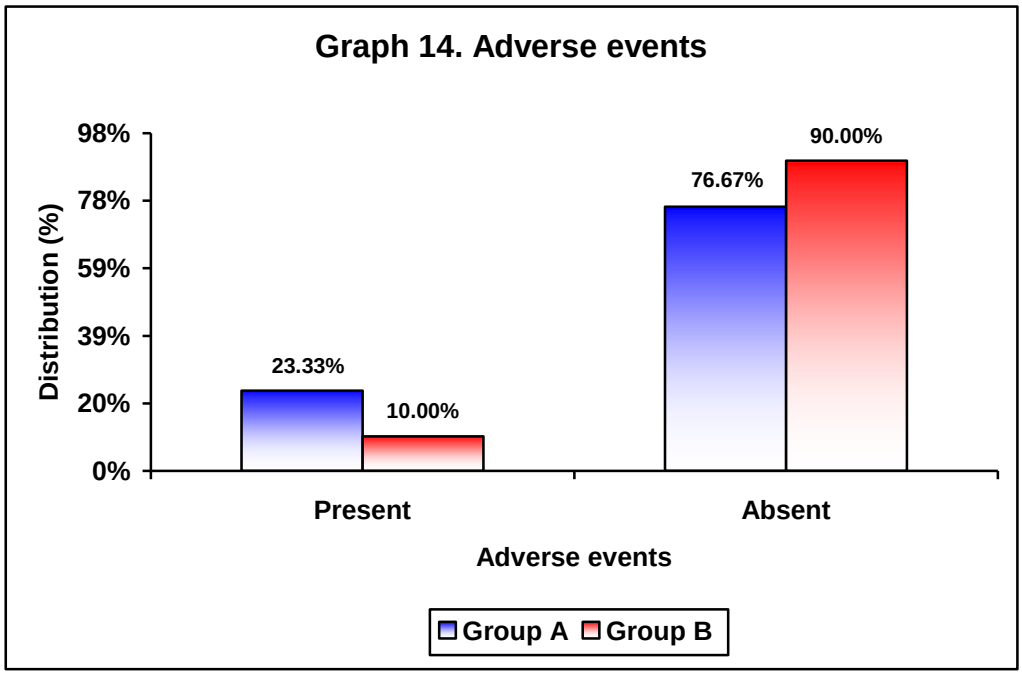


In the present study the frequency of postoperative rescue analgesia was comparable in group A (3.33%) compared to B (10%) at beginning (p=0.306). Further the frequency of requirement of rescue analgesia was significantly low in group A at 15 minutes (6.67% vs. 33.33%; p=0.010), 30 minutes (6.67% vs. 36.67%; p=0.005), 6 hours (13.33% vs. 70%; p<0.001) and 12 hours (20% vs. 46.67%; p=0.028) compared to group B. However, at 60 minutes and 24 hours the VAS scores were comparable in group A and B (p>0.050).

Table 17. Adverse events

Adverse events	Group A (n=30)		Group B (n=30)	
	No.	**%**	**No.**	**%**
Present	7	23.33	3	10.00
Absent	23	76.67	27	90.00
Total	**30**	**100.00**	**30**	**100.00**

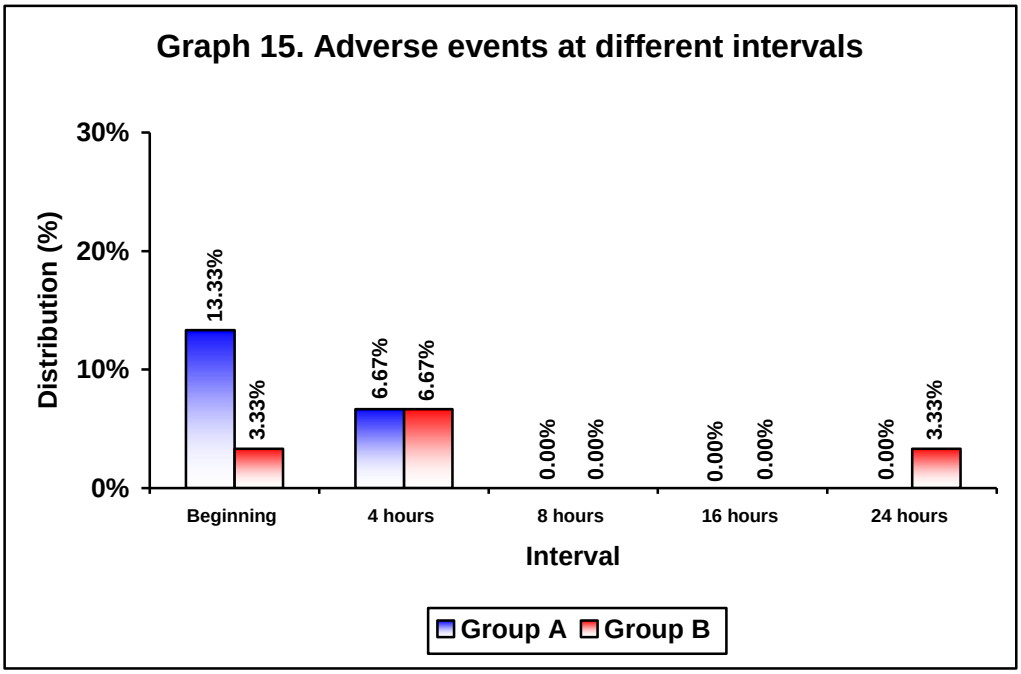
p = 0.166



In this study adverse events were noted in 23.33% of the patients with group A compared to 10% in group B. However this difference was statistically not significant (p=0.166)

Table 18. Adverse events at different intervals

Interval	Adverse events	Group A (n=30)		Group B (n=30)		p value
		No.	%	No.	%	
Beginning	Nausea	4	13.33	1	3.33	0.177
	Absent	26	86.67	29	96.67	
	Total	**30**	**100.00**	**30**	**100.00**	
4 hours	Nausea	2	6.67	2	6.67	0.694
	Absent	28	93.33	28	93.33	
	Total	**30**	**100.00**	**30**	**100.00**	
8 hours	Nausea	0	0.00	0	0.00	-
	Absent	30	100.00	30	100.00	
	Total	**30**	**100.00**	**30**	**100.00**	
16 hours	Nausea	0	0.00	0	0.00	-
	Absent	30	100.00	30	100.00	
	Total	**30**	**100.00**	**30**	**100.00**	
24 hours	Shoulder pain	0	0.00	1	3.33	
	Absent	30	100.00	29	96.67	0.500
	Total	**30**	**100.00**	**30**	**100.00**	



In the present study among the patients with group A, the frequency of nausea at beginning was 13.33% and at four hours it was noted in 6.67% of the patients. In group B, 3.33% and 6.67% of the patients had nausea at beginning and four hours. At 24 hours interval 3.33% of the patients in group B reported shoulder pain. However the frequency of adverse events was comparable in group A and B.

Table 19. Comparison of mean hospital stay

Variables	Group A (n=30)		Group B (n=30)		p value
	Mean	SD	Mean	SD	
Hospital stay (Days)	3.90	0.76	4.47	1.01	**0.017**

In the present study the mean hospital stay in group A was significantly low (3.90 ± 0.76 days) compared to group B (4.47 ± 1.01 days) (p=0.017).

DISCUSSION

Acute appendicitis is a medical challenge even today and it still remains the most common gastrointestinal emergency in adults. With the emergence of laparoscopic appendectomy involving multiple smaller incisions, it resulted in improved postoperative care and healing time as compared to open techniques. Also, quick recovery and discharge from the hospital have popularized the technique.[4] Laparoscopic surgeries also results in less postoperative pain and/or reduced analgesic consumption as compared with open surgeries, which enables early resumption of routine activities by the patient.[96-98]

However, postoperative period in laparoscopic surgery also is not pain free.[96-98] Such patients experience pain especially in the upper and lower abdomen, back, and shoulder region. Pain intensity usually peaks during the first few postoperative hours and usually declines over the following 2 or 3 days. It is postulated that, the pain after laparoscopic surgeries results from the stretching of the parietal peritoneum, peritoneal inflammation, and phrenic nerve irritation caused by residual carbon dioxide in the peritoneal cavity.[99] Several studies have reported that, intraperitoneal instillation of local anesthetics or opioids helps in achieving postoperative analgesia and thereby decrease analgesic requirements via other routes of administration. However, there is lack of information regarding the type and the dose of local anaesthetic or opioid to be used for intraperitoneal use.[99]

A multimodal approach to achieve pain relief involving the use of non-steroidal anti-inflammatory drugs, opioids, and local anesthetic infiltration has been suggested as the optimal combination for laparoscopic surgery.[100] There are variety

of local anesthetic techniques available which have been investigated in order to find out their potential analgesic benefits in laparoscopic surgery. Likewise injecting local anesthetic into the peritoneum through the ports created, either before the start of surgery or prior to closure over the visceral peritoneum or into the surgical bed after the excision of the organ or under the diaphragm is reported to give quantifiable pain alleviation after laparoscopic surgery.[101]

Several other studies also have utilized this method of analgesia. Bupivacaine,[102] levobupivacaine,[103] lidocaine[104] and ropivacaine[105] have been used intraperitoneally in varying doses to achieve analgesia in various laparoscopic surgeries though the results are varying. Tramadol has central analgesic effects due to monoaminergic and μ-receptor agonistic activities while It also confers local anesthesia, and the risk of serious adverse effects limited.[17,19-21]

This dual mechanism of action of Tramadol prompted us to find the effect of intraperitoneal instillation of tramadol for the management of immediate postoperative pain in patients undergoing laparoscopic appendicectomy.

The present one year double blinded randomized controlled trial was done at in the Department of General Surgery, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum with a total of 60 patients undergoing elective laparoscopic appendectomy from January 2014 to December 2014. The selected patients were divided into two groups of 30 each as group A and B based on the drug to be instilled in peritoneal cavity that is Tramadol 150 mg (diluted in 40 ml of normal saline) and 40 ml of normal saline respectively. Both patient and the person

doing pain assessment (surgeon/assistant) were kept blinded to the nature of solution instilled to eliminate bias during evaluation of patient postoperatively.

In the present study the sex distribution was comparable in group A and group B as 53.33% in group A and 46.67% in group B were males. The male to female ratio in group A was 1.14:1 compared to 1:1.14 in group B (p=0.606). In this study the commonest age group was ≤ 30 years that is, 80% in group A and 60% in group B (p=0.295). The mean age in group A (26.13 ± 9.96 years) and group B (31.43 ± 14.81 years) were also comparable (p=0.110). These findings suggest that the demographic profile of the study population was comparable in both the groups.

In this study the clinical signs and symptoms including fever (p=0.602), abdominal pain (p=1.000), vomiting (p=0.795), loose stools (p=0.212), RIF tenderness (p=1.000), rebound tenderness (p=1.000) and guarding (p=0.052) were comparable in group A and B. With regard to anesthetic characteristics, ASA status was also comparable in group A and B (p=0.438). The clinical examination findings including mean pulse rate, systolic and diastolic blood pressure, temperature and respiratory rate do not vary significantly in patients with group A and B (p>0.050).

In the present study at beginning the mean VAS score in group A was 1.53 ± 0.94 which increased to 2.20 ± 1.13 at 15 minutes interval and remained stable in same range at 30 minutes (1.97 ± 1.27), 60 minutes (2.10 ± 0.84), 6 hours (2.07 ± 1.57), 12 hours (2.27 ± 1.44) and decreased to 1.23 ± 1.07. In group B, the mean VAS scores at beginning were 2.93 ± 1.17 which increased to 3.67 ± 1.30 at 15 minutes and peaked at 6 hours with mean VAS score of 4.37 ± 1.27 and reduced to 3.97 ± 1.27 at 12 hours. The lowest mean VAS score in group B were noted at 24

hours duration (2.37 ± 1.16). Further, during all the intervals the pain scores in group A remained significantly low compared to group B. These findings suggested that intraperitoneal instillation of 150 mg tramadol diluted in 40 ml of normal saline offers significant pain relief through out the postoperative period up to 24 hours with minimum variation compared to normal saline. The effective pain relief observed in group A was reflected by lower consumption of rescue analgesia.

In the present study among the patients in group A, more than half of the study population (56.67%) did not request for postoperative analgesia while 36.67% of the patients required one dose and only 6.67% of the patients requested for three doses of rescue analgesia. Whereas, in group B, maximum patients that is 43.33% required two doses, 36.67% required three doses, 10% required one dose and only 6.67% of the patients did not required rescue analgesia. In patients with group A, requirement of rescue analgesia was significantly low at 15 minutes (6.67% vs. 33.33%; p=0.010), 30 minutes (6.67% vs. 36.67%; p=0.005) 6 hours (13.33% vs. 70%; p<0.001) and 12 hours (20% vs. 46.67%; p=0.010) compared to group B. However, immediate postoperatively (3.33% vs. 10%; p=0.306), at 60 minutes (none vs. 13.33%; p=0.056) and 24 hours (6.67% vs. 10%; p=0.500) the requirement of rescue analgesia did vary significantly. Also the mean number doses in group A was significantly low compared to group B (0.57 ± 0.82 vs. 2.20 ± 0.92; p<0.001). The findings show that intraperitoneal instillation of 150 mg tramadol diluted in 40 ml of normal saline offers not only effective pain relief but also results in reduction of consumption in rescue analgesia. Hence avoiding discomfort and adverse effects related to repeated intramuscular / intravenous analgesic administration.

In the preset study the frequency of adverse events in group A was slightly high compared to group B but difference was statistically not significant (23.33% vs. 10%; p=0.166). Among the patients with group A, the frequency of nausea and shoulder pain was comparable at all the intervals (p>0.050). The occurrence of nausea has been observed in early postoperative period in both groups and might be a result of routine side effect of general anaesthesia. These findings suggest that, intraperitoneal instillation of 150 mg Tramadol diluted in 40 ml of normal saline is well tolerated and does not cause significant side effects. Furthermore, the mean hospital stay in group A was significantly low compared to group B (3.90 ± 0.76 vs. 4.47 ± 1.01 days; p=0.017). This may be probably due to the better pain relief and early resumption of routine activities by the patient.

Overall these findings suggest that, intraperitoneal instillation of 150 mg Tramadol diluted in 40 ml of normal saline is well tolerated, offers excellent pain relief, reduces the consumption of rescue analgesia and shortens duration of hospital stay. However we do not have adequate data to compare these findings due to scanty literature available. Nevertheless, these beneficial effects observed in the present study can be explained by several mechanisms.

Tramadol is a synthetic 4-phenyl-piperidine analogue of codeine. It has an affinity for μ-opioid receptors and inhibits the neuronal re uptake of serotonin and norepinephrine. It is a very weak μ-opioid receptor agonist and its analgesic action depends mainly upon generation of active metabolite (+)-O-desmethyl-tramadol (M1). It also has local anesthetic properties and local administration of tramadol has been found to be an effective analgesic.[20]

Studies have shown adequate absorption of Tramadol from various fibro vascular surfaces of body, achieving adequate blood levels.[71]

Tramadol provides analgesia by opioid and non-opioid mechanisms. Opioid mechanism involves direct binding to μ-opioid receptors by parent compound and its active metabolites, and non opioid mechanism **(**which is local action) involves Increase in synaptic levels of two neurotransmitters that is, serotonin and norepinephrine. The effect of the non-opioid component of tramadol is through α-2-agonistic and serotoninergic activities, by inhibiting the re-uptake of norepinephrine and 5-hydroxytryptamine (serotonin) and, most likely, 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 cord level. Tramadol also exerts its sensory blocking action just like a local anesthetic by blocking the voltage dependent sodium channels and this is the idea exploited behind instillation of tramadol at raw surface / appendicular stump and in sub-diaphragmatic space in this study.

Because of its both central and local action, the use of tramadol in this study arises with a thought that it may provide better postoperative pain relief as compared to other drugs having single mechanism of analgesia (example Bupivicaine and NSAIDS). Most of the previous studies have shown local anaesthetic along with opioids can provide pain relief postoperatively when instilled intraperitoneally but only scant literature is available on administration of tramadol alone intraperitoneally for postoperative pain relief .

Golubovic S et al[106] in 2007 found that intraperitoneal administration of tramadol had valuable implication in reducing VAS score / pain in patients undergoing laparoscopic cholecystectomy.

Another study by Golubonic S. et al[62] (2009) who used 50 ml of saline containing 100 mg of tramadol instilled in peritoneal cavity 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.

However, the findings of this study as well as the other studies were contradicted by Akinci et al in 2008[107] 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).

Another study done by Hernandes – Pazon et al.[64] showed that intraperitoneal administration of local anesthetic in combination with an opoid reduced the analgesic requirements during first 6 postoperative hours.

Golubovic et al.[62] in his study concluded that intraperitoneal administration of tramadol and/or bupivacaine is an effective method of management of postoperative pain after laparoscopic cholecystectomy.

Another study by Akinsi et al.[65] concluded that intra venous tramadol provides superior postoperative pain relief as compared to intraperitoneal administration.

Furthermore, the intraperitoneal local anesthetics are found to be very effective for the relieving postoperative pain.[108] This non-invasive method has a minimum risk and it can be easily applied. A similar study[68] in PGIMER, Chandigarh India on 40 ASA I and II patients of either sex, undergoing laparoscopic cholecystectomy under general anaesthesia in a double blind, randomized 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 trendlenburg 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.

The longer duration of sustained pain relief in this study in Group A, as compared to many other study results of Tramadol in literature, might be attributed to the higher dose of Tramadol used (150 mg).

With the expanding role of ambulatory surgery, the need to facilitate an earlier discharge, improving postoperative discomfort related to pain due to surgery and repeated intramuscular/intravenous analgesia has become an increasingly important issue. The present study showed that, single time intraperitoneal instillation of 150 mg tramadol diluted in 40 ml of normal saline offers excellent

pain relief and minimal discomfort and adverse effects/complications as compared to those with repeated intravenous/intramuscular analgesia, like thrombophlebitis, injection site pain, abscess formation etc. Hence reducing need for hospital stay just for analgesia postoperatively, while patient is fit to resume routine activities. However, large multicentric studies are required to confirm these findings.

CONCLUSION

Based on the findings of this study it is concluded that, intraperitoneal instillation of tramadol offers effective postoperative visceral pain relief in laparoscopic appendectomy while this effect on shoulder pain remains insignificant and needs further evaluation. Further, the incidence of adverse effects like nausea, vomiting, itching and shivering is well acceptable.

SUMMARY

Early postoperative pain is common and predominant complaint, which results in prolonged hospital stay. The present study explores effectiveness of intraperitoneal instillation of tramadol on postoperative pain relief and emergence of adverse effects following laparoscopic appendectomy.

The present one year double blinded randomized controlled trial was done in the Department of General Surgery, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum from January 2014 to December 2014. A total of 60 patients undergoing elective laparoscopic appendectomy were enrolled. The selected patients were divided into two groups of 30 each as group A and B based on the drugs that is intraperitoneal tramadol 150 mg (diluted in 40 ml of normal saline) or 40 ml of intraperitoneal normal saline respectively.

In group A, 53.33% of the patients were males compared and 46.67% in group B (p=0.606). The commonest age group was ≤30 years (80%) in group A as well as group B (60%) (p=0.295). The mean age in group A (26.13 ± 9.96 years) and group B (31.43 ± 14.81 years) were comparable (p=0.110). Both the groups were comparable in terms of demographic characteristics, clinical presentation and vitals (p>0.050) The mean VAS scores at beginning were significantly low in group A (1.53±0.94) compared to group B (2.93±1.17) and similar trend was noted at all the durations through the postoperative period (p<0.001). Most of the patients in group A did not request for the postoperative analgesia (56.67% vs. 6.67%; p=0.011). Among the patients with group A, significantly lower numbers of mean doses were administered (0.57±0.82 vs. 2.20 ± 0.92; p<0.001) compared to group B. The

frequency of postoperative rescue analgesia significantly low in group A at 15 minutes (6.67% vs. 33.33%; p=0.010), 30 minutes (6.67% vs. 36.67%; p=0.005), 6 hours (13.33% vs. 70%; p<0.001) and 12 hours (20% vs. 46.67%; p=0.028) as compared to group B. Adverse events were noted in 23.33% of the patients with group A compared to 10% in group B (p=0.166). The mean hospital stay in group A was significantly low (3.90 ± 0.76 days) compared to group B (4.47 ± 1.01 days) (p=0.017).

Intraperitoneal instillation of tramadol offers effective postoperative visceral pain relief in laparoscopic appendectomy. The incidence of adverse effects like nausea, vomiting, itching and shivering is well acceptable but its effectiveness for shoulder pain remains insignificant.

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ANNEXURE I – CONSENT FORM

Dear Mr./Mrs./Dr._____, you are kindly requested to enroll yourself in a research study tilted "TO EVALUATE THE ANALGESIC EFFICACY OF INTRAPERITONEAL TRAMADOL VS. PLACEBO FOR POSTOPERATIVE PAIN RELIEF FOLLOWING LAPAROSCOPIC APPENDECTOMY, A DOUBLE BLINDED ONE YEAR RANDOMIZED CONTROL TRIAL: SINGLE CENTRIC HOSPITAL BASED STUDY" being 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. **** *****, Asso. 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.

Your participation in study is voluntary. During the study you will be asked some questions and you are supposed to answer to the best of your knowledge. 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 POSTOPERATIVE PAIN RELIEF FOLLOWING LAPAROSCOPIC APPENDECTOMY, A DOUBLE BLINDED RANDOMIZED CONTROL TRIAL: SINGLE CENTRIC HOSPITAL BASED STUDY"

Purpose of the study

To study the effectiveness of intraperitoneal instillation of TRAMADOL vs. PLACEBO for postoperative laparoscopic appendectomy pain relief, especially visceral pain and shoulder pain.

To improve pain relief after laparoscopic appendectomy.

Procedures involved

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 150 mg (diluted in 40 ml of distilled water) or 40 ml of intraperitoneal normal saline.

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

In both groups, 20mL of the study drug will be injected into the sub diaphragmatic space rest 20 ml in right iliac fossa over the appendicular stump under direct vision by the surgeon just before removal of trocars from port sites.

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.
- Postoperative hospital course (monitoring of HR , BP , RR, temperature 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 appendectomy procedure and anaesthesia related risks in addition side effects related to tramadol is minimal and patient may experience postoperative shivering, nausea or vomiting.

Benefits of taking part in this research

- Prevention of postoperative pain.
- Lesser requirement of opioids and NSAIDS in postoperative period.
- Lesser incidence of postoperative nausea and vomiting.

Voluntary participation / withdrawal from the study:

Taking part in the study is voluntary. You may choose not to enroll yourself in this study and may choose to leave the study anytime in between.

Alternatives

Your decision regarding participation in study will not change present or future health care services offered to you at KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum. You would 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:

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

Authorization to publish result

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.

Questions/contact details

WHOM SHOULD I CONTACT IF I NEED SOME CLARIFICATION OR HELP AT ANYTIME DURING THE STUDY PERIOD?

*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. ***** ******
Post Graduate Student
Dept. Of Gen. Surgery.
Jawaharlal Nehru Medical College
Nehru Nagar, KLE Hospital Road
Belgaum 590010
Mobile –***** *****

Dr. ****** *******
Asso. 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'/guardian name _____

Signature_____

Investigator – Dr. **** ***** Signature_____

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

Date___/___/____

Place _____

ANNEXURE II – PROFORMA

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 POSTOPERATIVE PAIN RELIEF FOLLOWING LAPAROSCOPIC APPENDECTOMY, A DOUBLE BLINDED ONE YEAR RANDOMIZED CONTROL TRIAL: SINGLE CENTRIC, HOSPITAL BASED STUDY" is as:

PATIENT DETAILS:

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

NAME: D.O.S:

SEX:

AGE:

ADDRESS:

Chief Complaints:

PAIN ABDOMEN: Yes / No

Duration

SITE OF PAIN: Umbilical region / right iliac fossa / left iliac fossa

TYPE OF PAIN: Radiating / localized

Throbbing / Pricking / Dull aching

INTENSITY: Mild / Moderate / Severe

ASSOCIATION WITH FOOD INTAKE: Yes / No

FEVER: Yes / No

Duration

Degree of fever Mild / Moderate / Severe

Type of fever Continuous / Intermittent / Spiking

HISTORY OF ANAPHYLAXIS TO OPOIDS YES / NO

GENERAL EXAMINATION:

Built and Nourishment:

Weight :

PULSE:

BP :

R/R :

TEMPERATURE:

PER ABDOMEN - TENDERNESS

Right iliac fossa

Left iliac fossa

Periumbilical

NORMAL ABNORMAL FINDINGS

CVS-

RESPIRATORY-

CNS-

INVESTIGATIONS:

CBC :

RBS:

Blood Urea:

Sr. Creatinine:

Bleeding time:

Clotting time:

Urine:

Routine

Microscopy

USG ABDOMEN:-

GROUP: GROUP A / GROUP B

OPERATION DETAILS: -

Date of Surgery:

Name of Surgery: LAPROSCOPIC APPENDECTOMY

Anaesthesia: GENERAL ANAESTHESIA

Duration of surgery:

ASSESSMENT OF POSTOPERATIVE PAIN - VISUAL ANALOGUE SCALE

0 – NO PAIN

1-3 – MILD PAIN

4-7 – MODERATE PAIN

8-10 – SEVERE PAIN

Postoperative pain scores and dose of analgesic given at

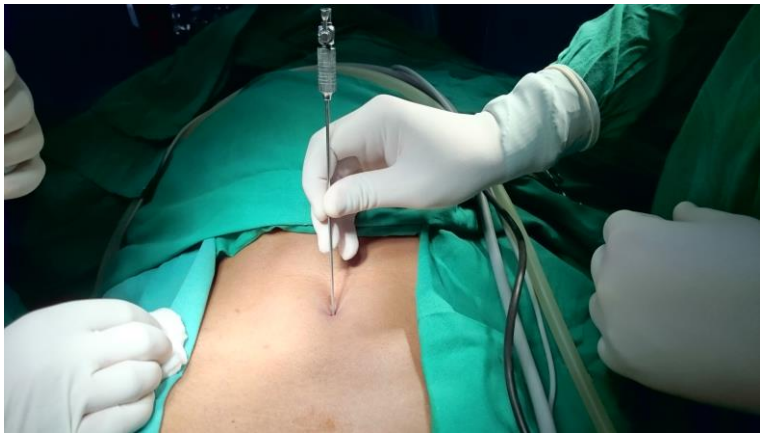
0 min 15 min 30 min 60 min 6hr 12hr 24hr

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

0 hr 4 hr 8 hr 16 hr 24 hr

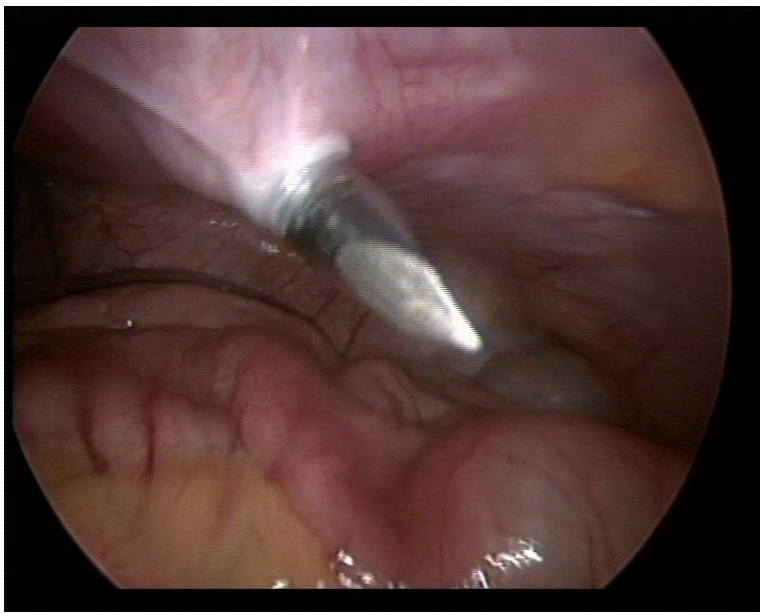
MEAN CUMULATIVE DOSE OF RESCUE ANALGESIC:

ANNEXURE III – PHOTOGRAPHS

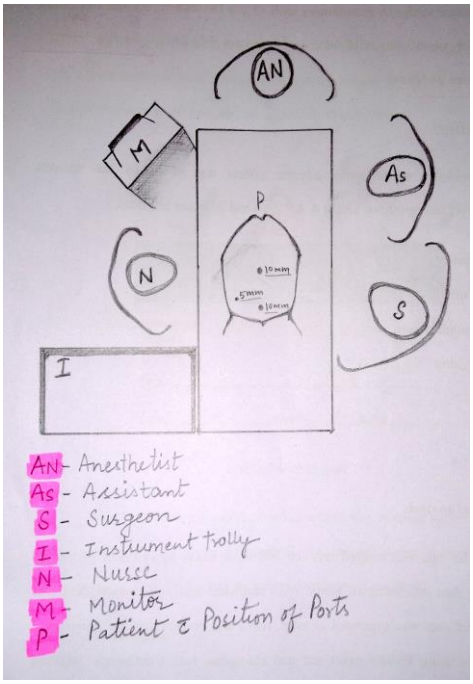


Photograph 1. Creating pneumoperitoneum using Veres needle

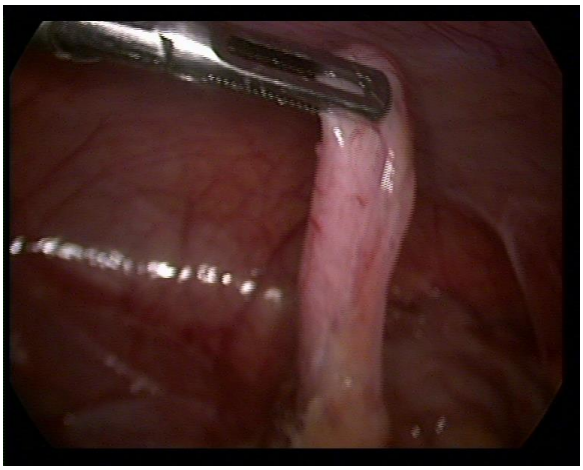
Photograph 2. 10 mm permanent metallic trocar



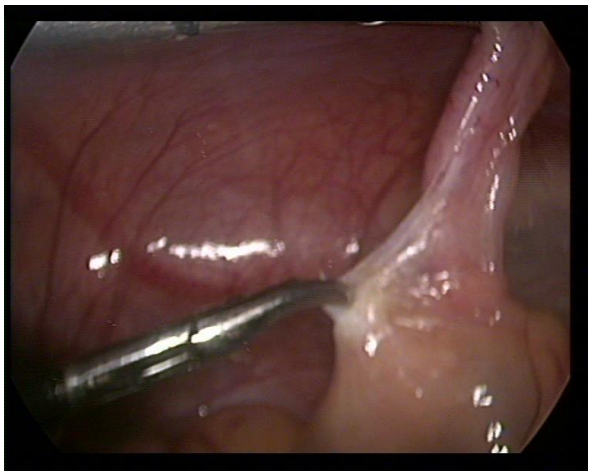
Photograph 3. Insertion of suprapubic port under vision



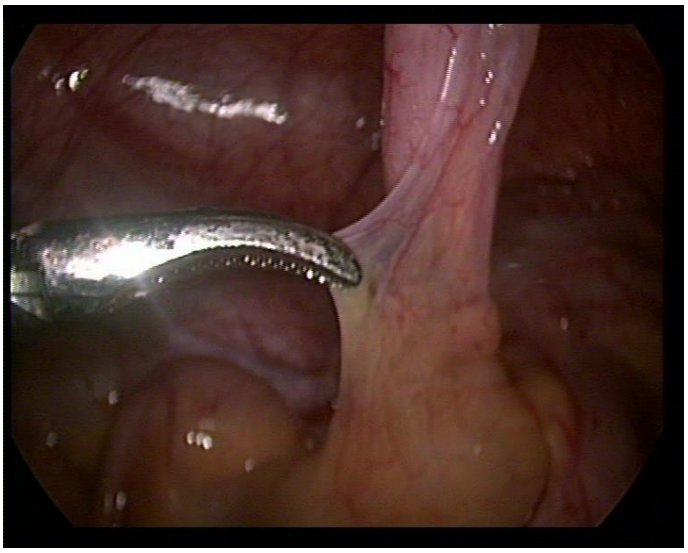
Photograph 4. Scheme of surgical set up



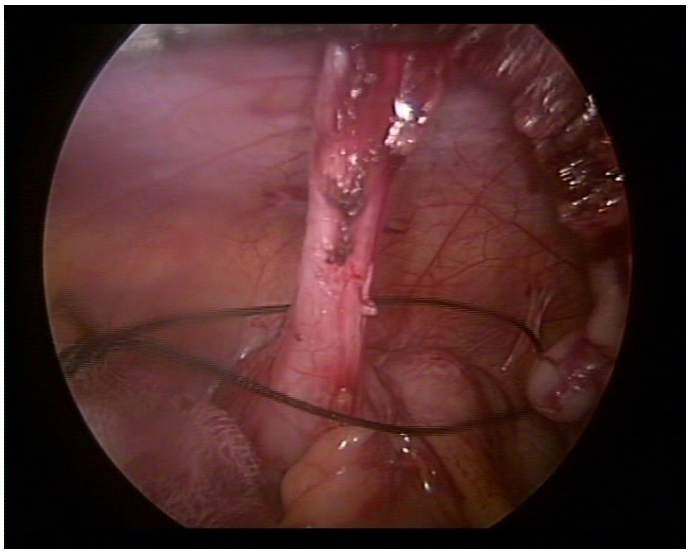
Photograph 5. Holding tip of appendix using grasping forceps



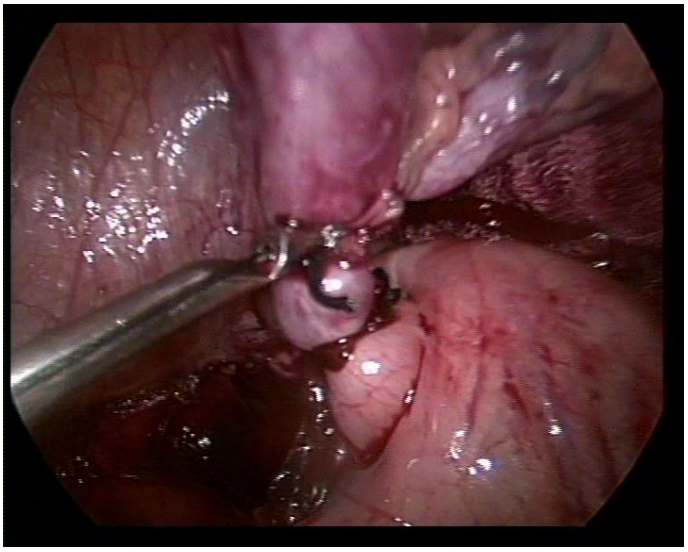
Photograph 6A. Dissection of mesoappendix using electro cauterization



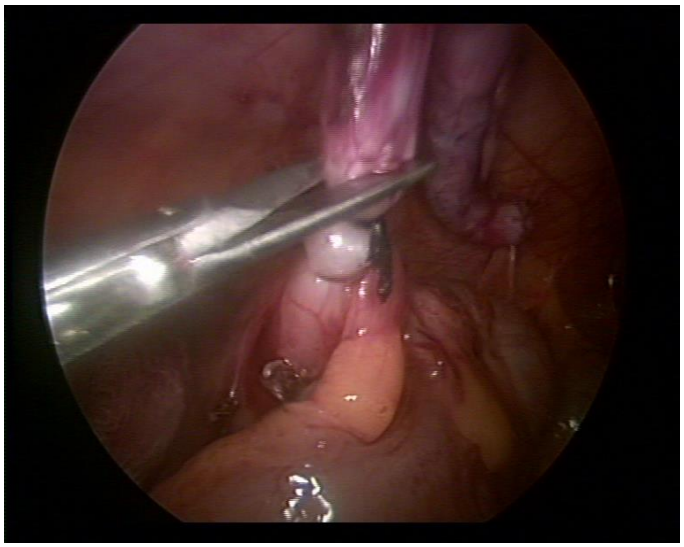
Photograph 6B. Dissection of mesoappendix using electro cauterization



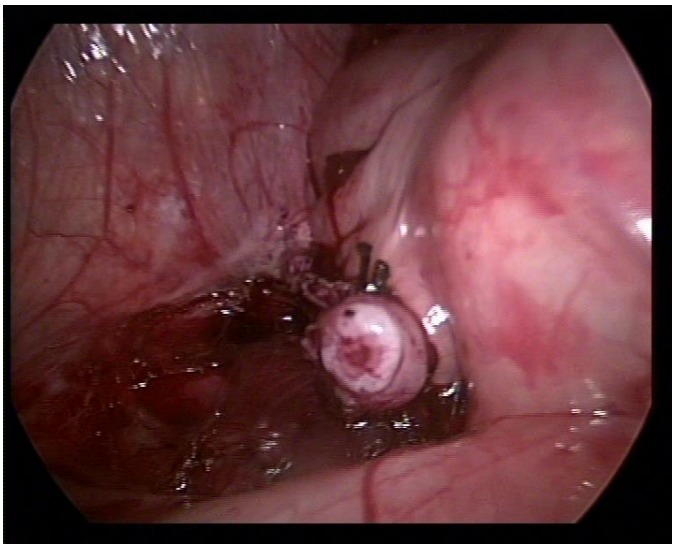
Photograph 7A. Putting Roeder's knot at base of appendix



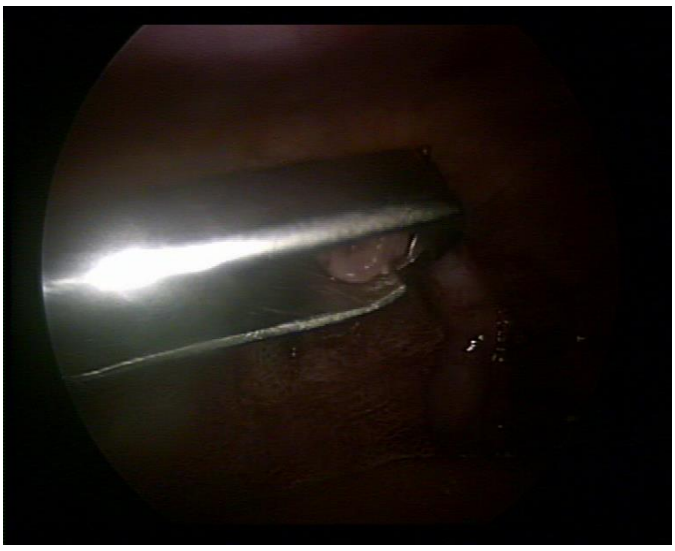
Photograph 7B. Placing Roeder's knot using knot pusher



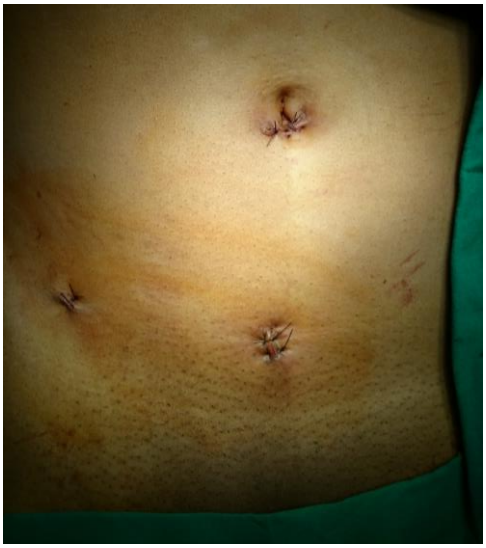
Photograph 8A. Cutting the appendix using the scissor



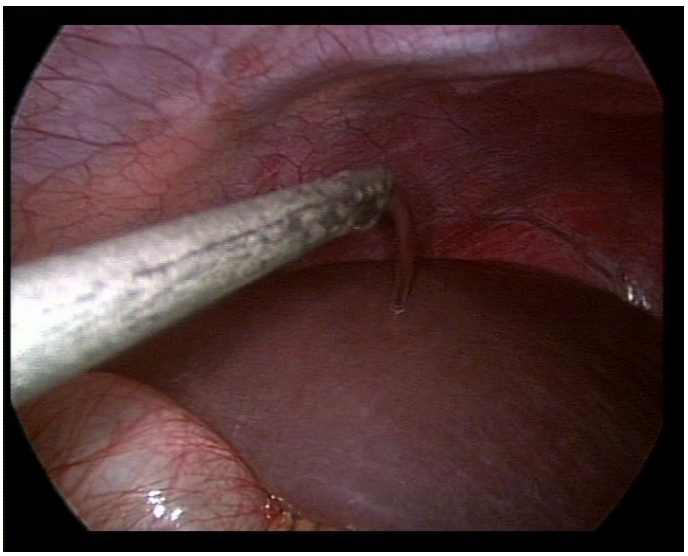
Photograph 8B. Appendix stumped with raw area



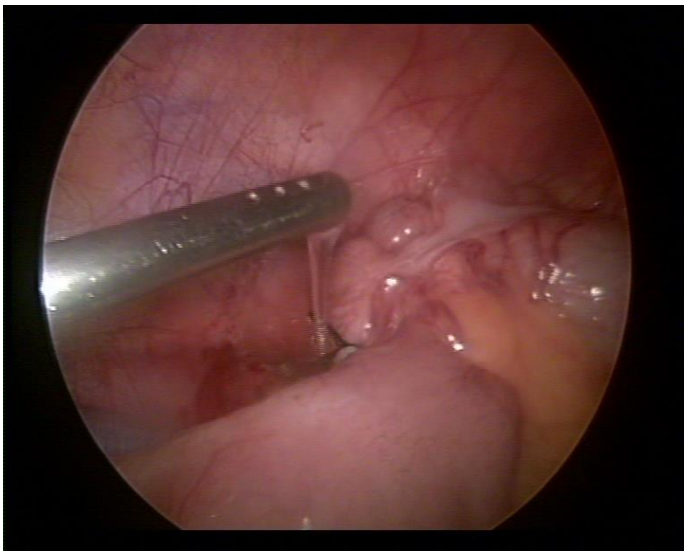
Photograph 9. Removing specimen using specimen retrieving forceps



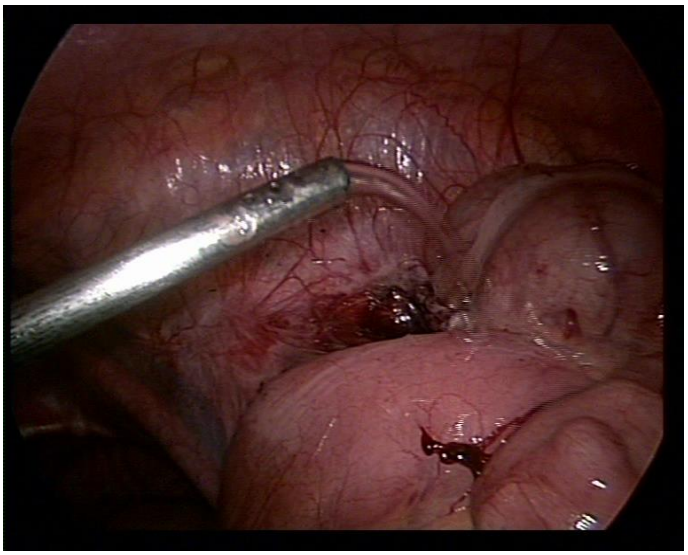
Photograph 10. Closed port sites



Photograph 11A. Instillation of solution in right sub-diaphragmatic space



Photograph 11B. Instillation of drug over the appendicular stump



Photograph 11C. Instillation of drug over raw area / appendicular stump

Photograph 12A. Metallic suction cannula adjusted for the instillation of drug

Photograph 12B. One ampule of Tramadol hydrochloride used in the study

ANNEXURE IV – KEY TO MASTER CHART

-	-	Absent
+	-	Present
^{0}F	-	Degree Fahrenheit
ASA	-	American Society of Anaesthesiologists
BP	-	Blood pressure
F	-	Female
M	-	Male
mg	-	Milligrams
mm Hg	-	Millimeters of mercury
N	-	Nausea
n	-	No
SP	-	Shoulder pain
VAS	-	Visual analog scale
y	-	Yes