“TO EVALUATE THE ANALGESIC EFFICACY OF INTRAPERITONEAL INSTILLATION OF TRAMADOL VERSUS BUPIVACAINE FOR POST OPERATIVE PAIN RELIEF FOLLOWING LAPAROSCOPIC APPENDECTOMY, A DOUBLE BLIND RANDOMIZED CONTROL TRIAL, HOSPITAL BASED STUDY”

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LIST OF ABBREVIATIONS USED

^0C	-	Degree centigrade
ASA	-	American Society of Anaesthesiologists
AUC	-	Area under curve
BC	-	Before Christ
BP	-	Blood pressure
cms	-	Centimeters
CO_2	-	Carbon dioxide
DPQ	-	Dartmouth pain questionnaire
E. coli	-	*Escherachiae coli*
h	-	Hour
H_2O	-	Water
HCl	-	Hydrochloric acid
HR	-	Heart rate
i.e.	-	That is,
IV PCA	-	Patient-controlled analgesia IV
IVRA	-	Intravenous regional anaesthesia
JCAHO	-	Joint Commission on Accreditation of Healthcare Organizations
kg	-	Kilogram
LA	-	Laparoscopic appendectomy
mg	-	Milligram
min	-	Minute

mL	-	Milliliter
ml/kg/min	-	Milliliter per kilogram per minute
MPQ	-	Mc Gill pain questionnaire
NMDA	-	N-methyl-D-aspartate receptor
NSAIDs	-	Nonsteroid anti-inflammatory drugs
OA	-	Open appendectomy
p	-	Probability value
RIF	-	Right iliac fossa
RR	-	Respiratory rate
Rt.	-	Right
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 scale
VRS	-	Verbal Rating Scale
vs	-	Versus
WBC	-	White blood cell
WDR	-	Wide dynamic range
WHYPQ	-	West Haven-Yale pain questionnaire
yr	-	Year

ABSTRACT

Background and Objectives

Early postoperative pain is the most prevalent and dominant complaint after elective laparoscopic surgeries. This study was aimed to compare the effectiveness of intraperitoneal instillation of tramadol versus bupivacaine for postoperative pain relief after laparoscopic appendectomy especially visceral and shoulder tip pain and to evaluate adverse effect such as nausea, vomiting, shoulder pain and shivering following laparoscopic appendectomy.

Methodology

This one year double blinded randomized controlled trial was done in the Department of General Surgery, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belagavi from January 2015 to December 2015. A total of 60 patients posted for elective laparoscopic appendectomy were studied. Based on computer generated random numbers, these patients were divided into two groups of 30 each as group A (intraperitoneal instillation of tramadol 150 mg) and Group B (intraperitoneal instillation of 0.5% bupivacaine).

Results

In the present study, most of the patients were females that is 53.33% and 60% in Group A and Group B respectively ($p=0.602$). The mean age in group A and group B was comparable (37.03 ± 1.00 vs 37.13 ± 0.73 years; $p=0.660$) The Mean pain scores at 4, 8, 16 and 24 in group A were significantly low compared to group B ($p<0.050$). At 24 hours interval significantly higher number of patients in group B (90%) required rescue analgesia compared to group A

(46.67%) ($p<0.001$). The overall requirement of analgesia was significantly high in patients with Group B that is, 10% of the patients did not required while 36.67% required 75 mg, and 150 mg each, 10% required 225 mg and 6.67% required 300 mg compared to 53.33%, 20%, 23.33%, 3.33% and 0% in group A. ($p=0.007$) The requirement of mean analgesia was significantly high in group B, (125.00 ±77.12 mg) compared to group A (57.50 ± 70.14 mg) ($p<0.001$). Overall incidence of adverse effects was comparable in group A and group B (76.67% vs 920%; $p=0.166$). At 16 hours, incidence of vomiting was significantly high in group A (23.33%) compared to nil in group B while in group B shoulder tip pain was noted among 10% of the patients while it was not reported by any of the patient in group A ($p=0.003$).

Conclusion and interpretation

Intraperitoneal instillation of tramadol offers excellent pain relief. However, its safety profile is comparable to that of intraperitoneal instillation with of 0.5% bupivacaine.

Keywords

Acute appendicitis; Bupivacaine; Intraperitoneal instillation; Tramadol;

CONTENTS

LIST OF TABLES

LIST OF GRAPHS

LIST OF FIGURES

LIST OF PHOTOGRAPHS

INTRODUCTION

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

The lifetime risk of developing appendicitis is approximately 7%. 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]

The clinical diagnosis may be straightforward in few patients who present with classic signs and symptoms, atypical presentations may lead to diagnostic confusion.[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 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 physical examination is 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 CO_2 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 anaesthetics, intraperitoneal infiltration of the local anaesthetics or opioids, the use of intramuscular morphine injections, patient-controlled analgesia, and injection of local anaesthetics into the port sites are suggested.[15]

Pain on the day of surgery is typically a diffuse abdominal pain, a more so to the right upper quadrant and right shoulder tip. The cause of this pain is thought to be related to abdominal muscle distension during laparoscopic procedure, irritative effects of residual carbon dioxide in the abdominal cavity and prolonged elevation of diaphragm by pneumoperitoneum.

The preemptive intravenous and intraperitoneal application of local anaesthetics 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.

By evaluating the pathophysiology of pain it is shown that it can be prevented or reduced by blocking the nociceptors before their stimulation by use of local anaesthetics.[17] Bupivacaine is one such local anaesthetic which has a good safety profile, it is long acting and free of side effects like gastritis due to NSAID's or nausea and vomiting and fear of drug dependence as in opioids.

Also, 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.[18] 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.[19] Tramadol has central analgesic effects due to monoaminergic and μ-receptor agonistic activities. It also has local anaesthetic properties, and the risk of serious adverse effects is limited.[20,21]

Intraperitoneal instillation of local aneasthetic and opioid is an easy, cheap and non invasive method which provides good analgesia in the immediate post operative period after laparoscopic surgery. The intraperitoneal administration of bupivacaine or tramadol is simple to use and effective in reduction of pain and therefore recommended in patients undergoing laparoscopic surgeries. However, there is scanty data on the effect intraperitoneal instillation of tramadol and bupivacaine for the management of immediate postoperative pain in patients undergoing laparoscopic appendectomy. Further several studies have assessed the role of intraperitoneal instillation of tramadol and bupivacaine for the management of immediate postoperative pain in other laparoscopic surgeries and yielded controversial results. Also, in previous studies these two drugs have been compared with the placebo (normal saline) separately however the two drugs have not been

compared with each other. The intraperitoneal route of administration of local anaesthetic is simple and used as a routine following minimally invasive surgeries but it must not be limited by use of local anaesthetics. This prompts search for new drugs that have longer duration of action. It is hoped that this development may lead ultimately to improvements in convalescence and to a reduction in the risk of hospital readmission after minimally invasive surgery.

This prompted us to compare the effectiveness of intraperitoneal instillation of tramadol versus bupivacaine for postoperative pain relief after laparoscopic appendectomy especially visceral and shoulder tip pain and to evaluate adverse effect such as nausea, vomiting, shoulder pain and shivering following laparoscopic appendectomy.

OBJECTIVES

The objectives of this study were;

Primary

To study the effectiveness of intraperitoneal instillation of tramadol versus bupivacaine for postoperative pain relief after laparoscopic appendectomy especially visceral and shoulder tip pain.

Secondary

To evaluate adverse effect such as nausea, vomiting, shoulder pain and shivering following laparoscopic appendectomy.

REVIEW OF LITERATURE

Historical note on appendicitis

The word vermiform derived from the Latin word "Vermiforma" which means worm shape, hence called 'vermiform'. Anatomically, it is one of the mobile viscera of abdomen measuring 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 appendix was reported by an 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 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 an autopsy, had already been noted by Heister (1711), yet these landmarks left no impression upon practice whatsoever."[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 drained. 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 1812 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 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 about 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 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]

EMBRYOLOGY OF THE APPENDIX[29,30]

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.

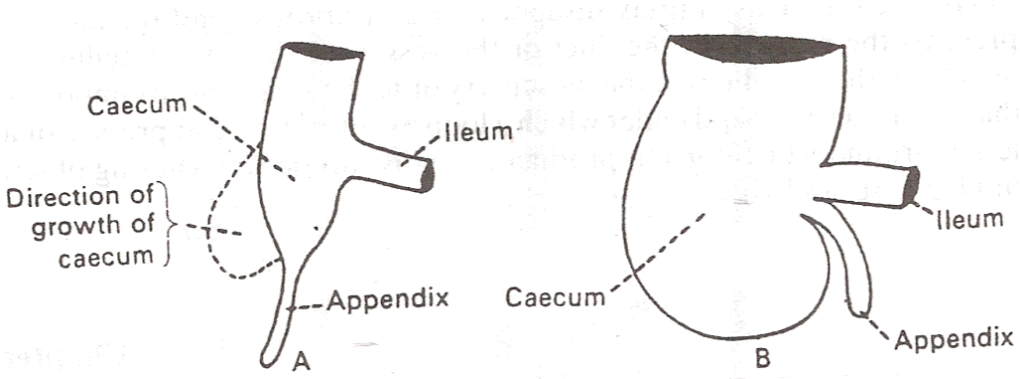


Figure 1. Development of the appendix[29]

Abnormalities in development

These are quite rare. These may occur in a form such as 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 a 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[29,30]

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 the anterior abdominal wall (Preileal 1%)

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

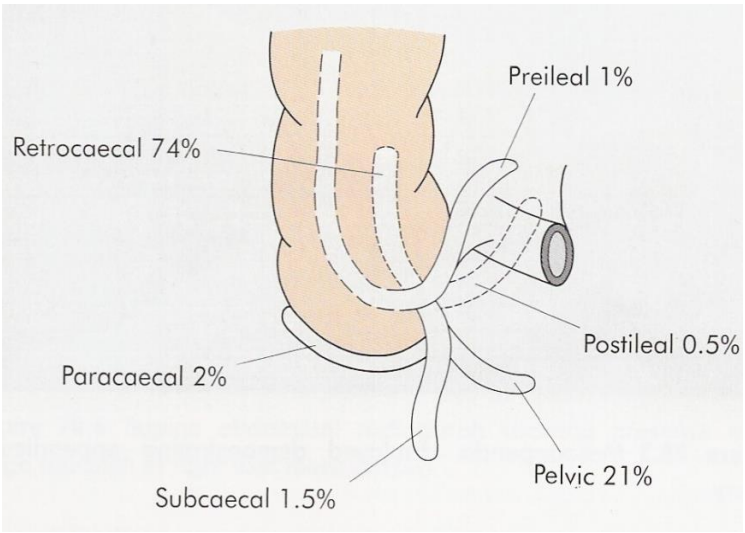


Figure 2. Various position of appendix[30]

The 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 in length, with an average of 9 cms in length. It is longer in children than in adults, which might get atrophied 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 sometimes 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.

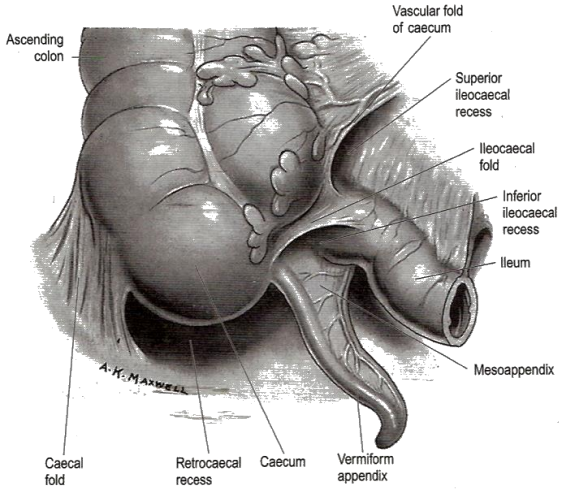


Figure 3. The peritoneal folds and recesses in caceal region[30]

Vascular supply and lymphatic drainage[29,30]

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.

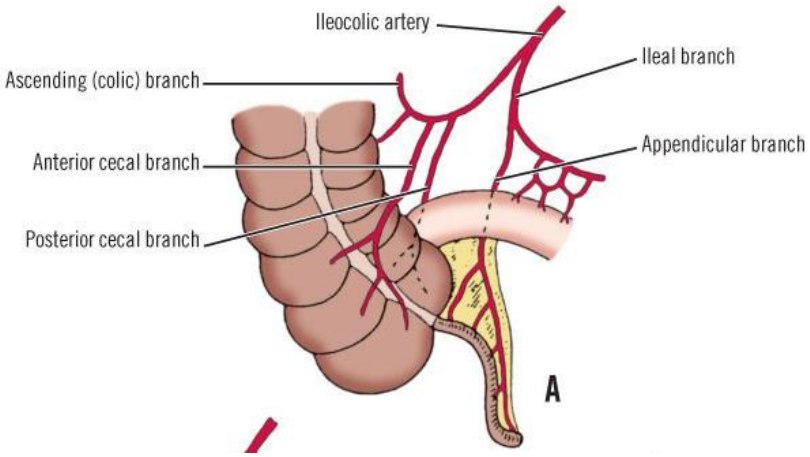


Figure 4. Blood supply of appendix

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[31]

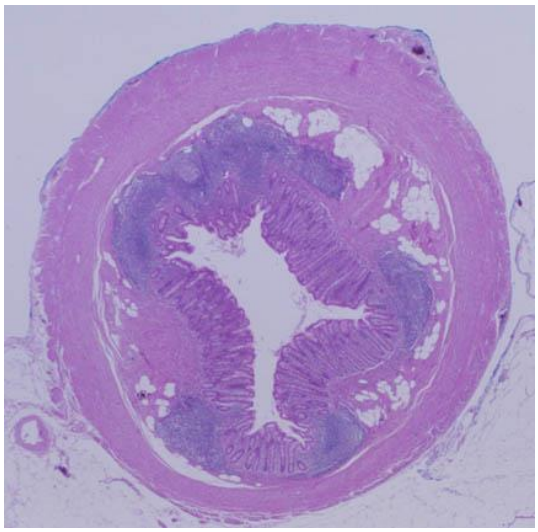


Figure 5. Normal histology of appendix

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. These are absent at the time of 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 a 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[30]

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[32]

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]

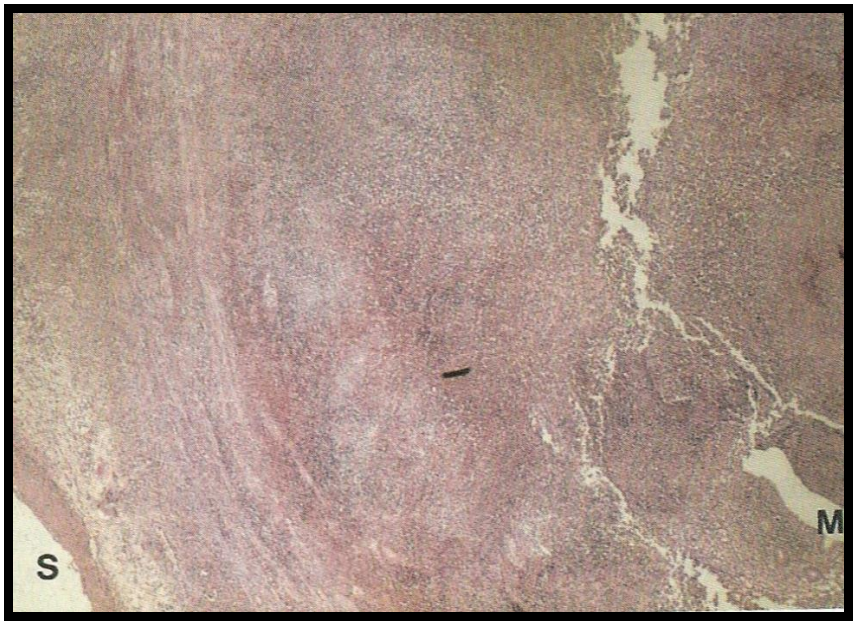


Figure 6. Histology of inflamed appendix

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 a 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 later 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 with 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.[32-34]

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 later 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.[35]

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, the most common is a fecolith. Fibrosis of the wall from previous attacks of acute appendicitis can be contributed by narrowing of the lumen with fecolith impaction and rarely appendicitis accompanies ileocaecal Crohn's disease.[35]

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 the 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.[35]

Bacteriology

Common organisms seen in patients with acute appendicitis.[32]

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

Epidemiology

The lifetime rate of appendectomy is 12% for men and 25% for women, with approximately seven percent of all people undergoing appendectomy for acute appendicitis. Over a 10 year period from 1987 to 1997, the overall appendectomy rate decreased parallel to a decrease in incidental appendectomy.[36,37] 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).[38]

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 appendectomy. In the past 30 years the incidence has fallen dramatically in these countries, such that the individual lifetime risk of

appendectomy is about 8.6% and 6.7% among males and females respectively.[36] The total number of operations annually in England and Wales declined from 113,000 in 1966 to 48,000 in 1990,[39] while in Sweden there has been an annual decrease of 17% in the numbers of appendectomies performed between 1987 and 1996.[40]

The incidence of appendicitis in India is lower when compared to western countries. However, it is still 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.[41]

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 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 case of a 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 visceral somatic sequence is seen in only about 50% of patients of acute appendicitis

as early signs and symptoms depending upon the location of the tip of the appendix that is highly variable.[42-45] 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.[46] High fever is often associated with a perforated appendix.[47] The clinical symptom/signs are detailed below.

Symptoms of acute appendicitis[42]

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	Intestinal 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 is devised that is 100% diagnostic. The only diagnostic procedure short of open exploration is diagnostic laparoscopy.[48]

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.[42,48]

Urine examination

Though normal in many instances yet it may be showing pyuria or 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 adhered to right ureter/bladder.[42]

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 only USA and not in any other country.[42]

Plain X-ray abdomen and barium enema findings in acute appendicitis[42]

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 effect 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 an 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.[42]

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 controversies concerning the name, function and 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 the 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.[49]

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.[49]

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 the new gold standard in surgical treatment of acute and chronic appendicitis.[4]

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.[50-52]

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).[42]

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.[53,54]

Open appendectomy remains the most common approach due to less operative time and cost.[42]

Laparoscopic appendectomy

Since 1987, however, an increasing number of surgeons have come to prefer laparoscopic appendectomy. Laparoscopic appendectomy has now been improved and standardized.[55]

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:[56]

- 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:[56]

- 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.[56]

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.[57]

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.[58]

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.[59]

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 the 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." [59]

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 anaesthesia use began around 1846 with the use of ether and chloroform. [59]

Pain treatment has evolved over the years. The first spinal anaesthetic 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. [59]

In 1999, the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) put forth the 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." [59]

"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." [59]

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.[60]

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 the internal organ or one of its covering. It is usually dull diffuse pain, which is frequently associated with the abnormal sympathetic or parasympathetic activity causing nausea, vomiting, sweating and changes in blood pressure or heart rate.[61]

Magnitude of the problem

Many factors influence the occurrence, intensity, quality and duration of postoperative pain like the site, nature and the 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.[61]

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).[62]

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 the C fibers. This protopathic pain is transmitted mainly by free nerve endings that sense mechanical or chemical tissue damage.[63-65]

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.[63-65]

Pain pathway

Pain is conducted along three neuron pathways; from the periphery to the cerebral cortex.[63-65]

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). [63-65]

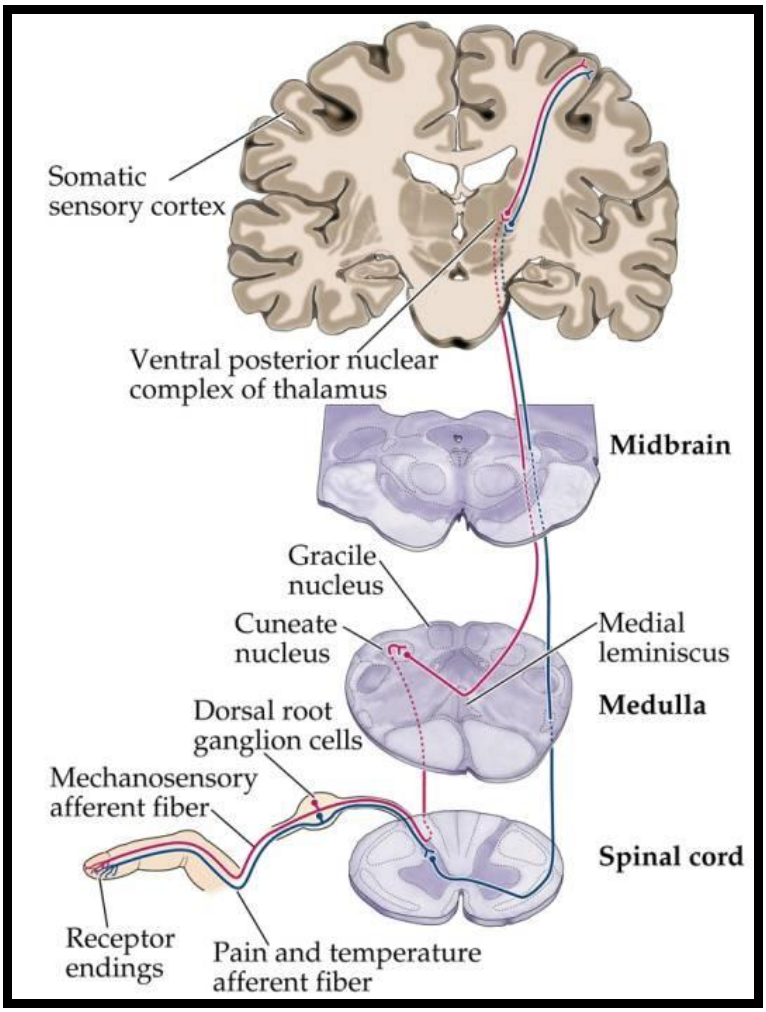


Figure 7. Pain pathway[63-65]

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". [64,65]

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. [64,65]

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, the nucleus raphe and the periaquiductal gray.[64,65]

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.[65-67]

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.[68]

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.[69]

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.[70]

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.[71]

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.[71]

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.[69]

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.[72]

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.[73]

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.[63]

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.[62]

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.[74]

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.[68]

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.[75]

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.[69]

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 the 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.[62]

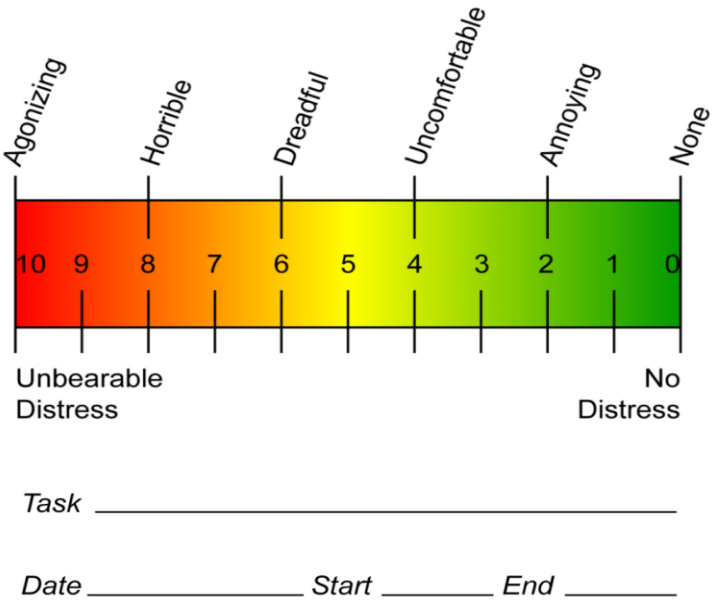


Figure 8. Visual analog scale

MANAGEMENT OF POSTOPERATIVE PAIN[62-65]

Prophylactic measures

The incidence, severity, and the 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. Intrapleural 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.[63]

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 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 CO_2 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 and 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.[76]

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.[77]

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 the postoperative pain, which may include the related C4 dermatome.[78]

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.[79] 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 the postoperative pain.[80]

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 warm gas was used, especially with respect to diaphragmatic and shoulder tip pain, with the lasting effect of three days.[78]

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.[81]

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 CO_2 pneumoperitoneum, intraabdominal instillation of local anaesthetics, intraperitoneal infiltration of the local anaesthetics 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 anaesthesia 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 appendectomy.

Intraperitoneal administration of local anaesthesia

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 anaesthetic 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 anaesthetic infiltration for efficacious postoperative analgesia should allow widespread use of laparoscopic day-case surgery.[15]

TRAMADOL[63,82]

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.

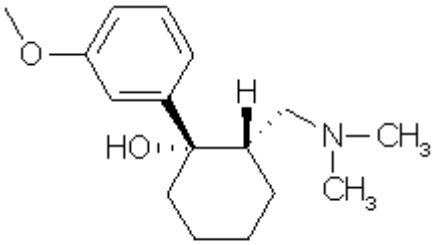


Figure 9. Chemical structure of Tramadol

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. Intravenous regional anaesthesia (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.

BUPIVACAINE

Source: A synthetic drug, was prepared by A. F. Ekenstam in 1957.

Chemistry: Molecular weight of the chloride salt is 325 and that of the basefonn is 288.

Melting point: 258°C

pH: Solutions containing epinephrine has a pH of about 3.5

pKa: 8.1

Chemical name: Bupivacaine is an anilide compound. Chemical name is - 1 -n-butyl-DL-piperidine- 2- carboxylic acid 2,6 dimethylanilide hydrochloride.

Molecular formula: $C_{18}N_2OH28HCl$.

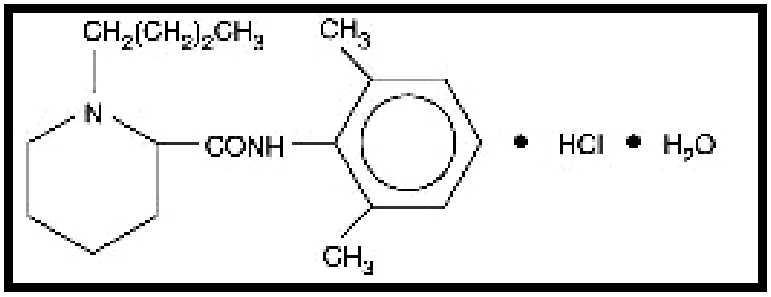


Fig. 10. Chemical structure :bupivacaine

Physiochemical properties

***Solubility*:** The base is sparingly soluble but the hydrochloride is readily soluble in water.

***Stability and sterilization*:** It is highly stable and can withstand repeated autoclaving.

Anaesthetic properties

Potency: Bupivacaine is approximately three to four times more potent than lidocaine and eight times more than procaine.

The **duration of action** for local anaesthesia is two to three times longer than that of mepivacaine or lidocaine and 20 to 25% longer than that of tetracaine.

Maximum safe dose*:* 3mgkg^{-1}.

Toxic effects of local anaesthetics

Local anaesthetic toxicity is a function of plasma free drug concentration and is influenced by the drug the dose and the injection site.

1. Central nervous system:

The early symptoms of toxicity are numbness of the tongue and circumoral region, tinnitus and are encountered most frequently in patients on intravenous antiarrhythmic therapy. Thus, central stimulation followed by depression, hysterical behavior, vertigo, tremor, convulsions, and respiratory failure may occur.[83]

2. Cardiovascular system

Local anaesthetics directly depress myocardial conduction and myocardial contractility in a dose-dependent manner, leading to hypotension, bradycardia, pallor, and sweating. This type of intoxication may be due to a rapid absorption of the drug.[84]

3. Respiratory depression

This may progress to apnea from medullary depression or respiratory muscle paralysis.[84]

4. Allergic phenomena

Allergy rarely takes the form of bronchospasm, urticaria or angioneurotic edema. It is well documented in association with the use of ester linked agents, including dermatitis in personnel handling procaine. Allergy to amide linked agents is extremely rare.[85]

5. Drug interactions

Non-depolarizing muscle relaxant blockade is potentiated by local anaesthetics. Pseudocholinesterase inhibitors can lead to decrease metabolism of

ester local anaesthetics. Cimetidine and propranolol decrease hepatic blood flow and lidocaine clearance. Opioids and adrenergic agonists potentiate the local anaesthetic pain relief.

Treatment of toxicity

Prevention of toxicity is important by avoidance of accidental intravascular injection and by avoidance of overdosing. Facilities for treatment must always be available before doing the block. The airway is maintained and oxygen administered using artificial ventilation if apnea occurs. Convulsions may be controlled with small increments doses of either diazepam (2.5 mg) or thiopentone (50 mg). Excessive doses should not be given to control convulsions, since cardiorespiratory depression may be exacerbated. If cardiovascular collapse occurs despite adequate oxygenation, it should be treated with an adrenergic drug with alpha and beta agonist properties, for example, ephedrine 3 to 5 mg increments. Bretylium should be considered for the treatment of ventricular arrhythmias produced by bupivacaine.

A study done in 2000 while comparing intraperitoneal 0.5% bupivacaine, 0.75% ropivacaine and saline instillation for postoperative pain relief found that local anaesthetics gave significantly good pain relief with ropivacaine being better than bupivacaine in both analgesia and opioid sparing effect.[86]

Many other studies during intraperitoneal instillation of 0.5% bupivacaine with or without adrenaline for postoperative pain relief in patients undergoing laparoscopic cholecystectomy, laparoscopic pelvic surgery and diagnostic laparoscopy. They concluded that locally instilled bupivacaine produces significant postoperative analgesia and the requirement of analgesics was reduced.[87-89]

In another study authors studied the effect of intraperitoneal local anaesthesia for postoperative pain relief for two different type of surgeries and showed that local anaesthetic was effective in reducing pain in laparoscopic fundoplication rather than laparoscopic hernia repair.[90]

Though all these studies proved that local instillation of bupivacaine is effective in postoperative pain relief, few earlier studies have different opinion. Studies conducted to assess postoperative analgesic effect of locally instilled bupivacaine in laparoscopic cholecystectomy patients reported that there is no significant postoperative pain relief in these patients.[90]

Literature review

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,[21] Golubovic et al,[91,92] Memis D et al.,[93] through their respective studies have demonstrated the intraperitoneal action of tramadol and have concluded that intraperitoneal administration of tramadol had some implications in reducing the postoperative pain.

A study done by Hernandes–Pazon et al.[94] showed that intraperitoneal administration of local anaesthetic in combination with an opoid reduced the analgesic requirements during first 6 postoperative hours.

Golubovic et al.[92] in his study concluded that intraperitoneal administration of tramadol and or bupivacaine as effective method of management of postoperative pain after laparoscopic cholecystectomy.

Another study by Akinsi et al.[95] concluded that IV tramadol provides superior postoperative pain relief as compared to intraperitoneal administration.

Studies done by Wilson et al[96] 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 the 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[92] in 2009 at clinic of Anaesthesiology 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 the 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.[97] 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.[98] 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.[99] 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[100] 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.

Murthy BV et al.[101] 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 IV 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 Area under curve (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.

Numerous advantages have been reported when comparing open versus minimally invasive abdominal surgical procedures (laparoscopy), including earlier return of bowel function, decreased postoperative pain, quicker recovery, and earlier hospital discharge. Although the magnitude of pain can be expected to be reduced when compared to open procedures, pain may still be a significant factor during the postoperative recovery period following laparoscopic surgery. Without effective treatment, this ongoing pain may delay recovery, mandate inpatient admission, and thereby increase the cost of such care. In addition to pain at the incisional and trocar insertion sites, there may also be shoulder and diffuse abdominal pain. Shoulder pain and diffuse abdominal pain may be due to peritoneal stretching and diaphragmatic irritation associated with the carbon dioxide insufflation.[62]

Although in most circumstances pain is treated with an approach which uses parenteral opioids and nonsteroidal anti-inflammatory agents combined with local infiltration of the incisional sites, other novel techniques have been reported. Given the problem of providing effective pain control, alternative agents such as pregabalin and ketamine have also been investigated. Despite their efficacy, all parenteral medications may be associated with adverse effects. Therefore, there has also been interest in the use of topical peritoneal medications including local anaesthetic agents.[62]

The local anaesthetic agent is aerosolized into the peritoneal cavity during the laparoscopic procedure. Targeting the peritoneum topically makes sense as it has

been shown that gas insufflation with increased intra-abdominal pressure results in peritoneal inflammation and neuronal rupture with a linear relationship between abdominal compliance during the procedure and the resultant severity of postoperative pain.[62]

However, to date, very few studies are available to know the analgesic efficacy of tramadol versus bupivacaine for post operative pain relief after laparoscopic appendectomy.

Hernandes-Palazon et al.[94] found that intraperitoneal administration of local anaesthetic (bupivacaine)in combination with an opioid (morphine) reduced the analgesic requirements during first 6 post operative hours, and that a combination is more effective for treatment of pain after laparoscopic cholecystectomy.

Thus this study is intended to show that intraperitoneal application of either tramadol or bupivacaine will reduce the pain along with other side effects such post operative nausea, vomiting, shoulder pain and shivering following laparoscopic appendectomy. It will also help in reducing post-operative non-steroid drug and opiate consumption. This study will show that intraperitoneal administration of tramadol or bupivacaine significantly reduces nausea and vomiting which will help realization of earlier recovery and discharge from the hospital.

Overall, this study will show that intraperitoneal analgesia with tramadol or bupivacaine is simple to use and effective in a reduction of pain and therefore recommended in patients undergoing laparoscopic appendectomy.

METHODOLOGY

The present study was done in the KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belagavi from January 2015 to December 2015.

Study design and duration

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

Study period

This study was done from January 2015 to December 2015.

Place

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

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

The sample size was calculated based on the following formula.

$$n=\frac{2(Z\alpha+Z\beta)^2S^2}{(x_1-x_2)^2}$$

$$=\frac{2(1.96+.84)^2>^2}{5^2}$$

=30 in each group

Selection criteria

Inclusion

- Patients aged 18 years and above.
- Patients of either sex.
- Patients with ASA grade I and II

Exclusion

- Unwilling patients.
- Those with history of anaphylaxis to opioids and local anaesthetics.
- Immunocompromised patients.
- 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, Belagavi.

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

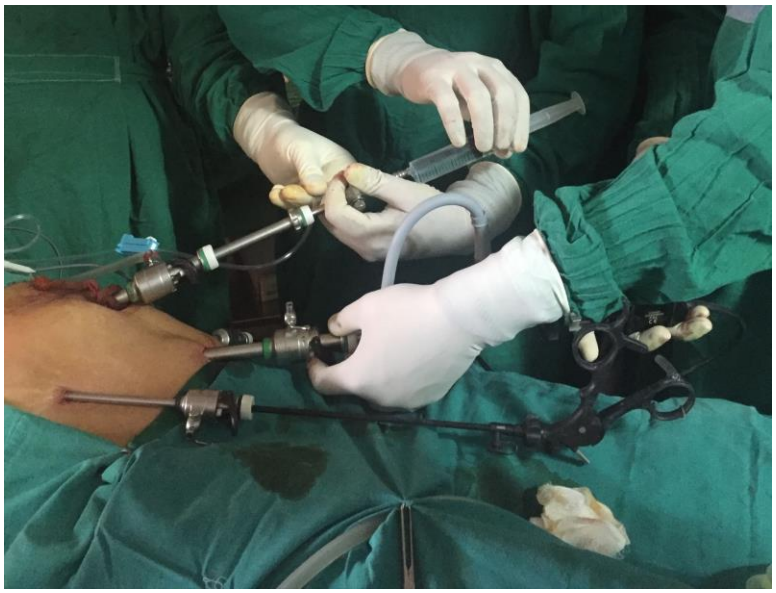
The demographic data such as age and sex, presenting complaints were noted. The patients were subjected to clinical examination and vitals were noted. The systemic examination was done and the clinical signs such as RIF tenderness, rebound tenderness and guarding were noted. There findings were recorded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

Randomization

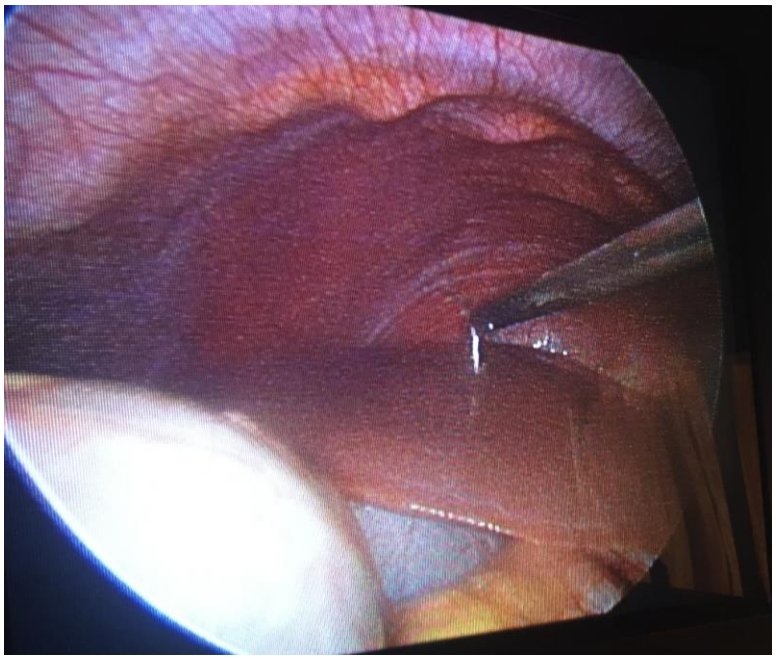
Patients were divided into two groups of 30 each as group A and B based on computer generated random numbers as below.

Group A: Patients in this group received intraperitoneal instillation of tramadol 150 mg (diluted in 40 ml of distilled water).

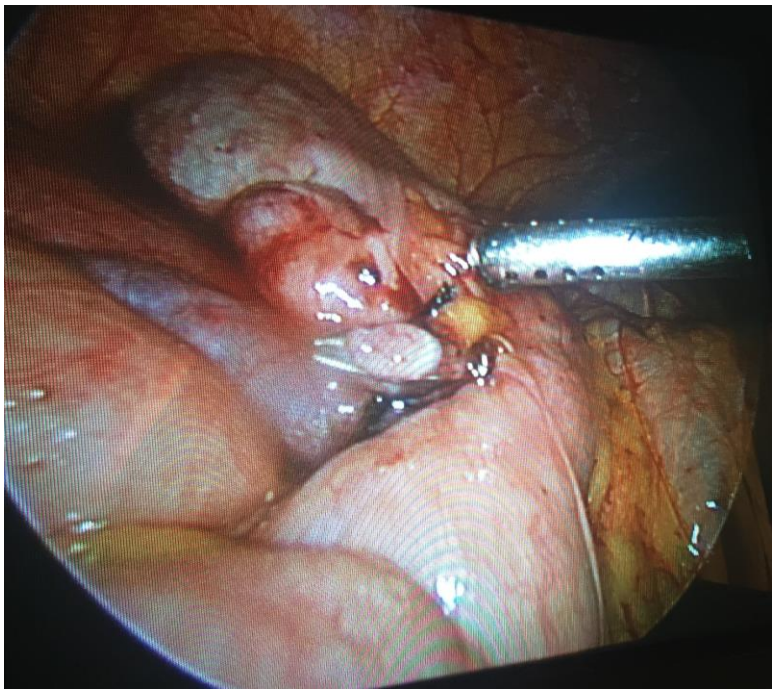
Group B: Patients in this group received intraperitoneal instillation of 0.5% bupivacaine (diluted in 40 ml of distilled water).



Photograph 1. Intraperitoneal instillation of drug



Photograph 2. Drug instillation in subdiaphragmatic fossa



Photograph 1. Drug instillation over the appendicular stump

Procedure

All the patients underwent laparoscopic appendectomy which was performed by experienced consultant surgeons. Anaesthetic procedure was standardized for all patients.The surgery was performed using similar instruments and suture materials under accepted general principles of surgery.

Intervention

Group A

Tramadol 150 mg diluted in 40 mL of normal saline, which was instilled intraperitoneally through laparoscopic port site under direct visualization.

Group B

Bupivacaine 0.5% diluted in 40 ml normal saline, which was instilled intraperitoneally through laparoscopic port site under direct visualization.

In both the groups 20mL of the study drugs was injected into the **sub diaphragmatic space**, and rest 20 ml in **right iliac fossa over the appendicular stump** 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.

Blinding

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

Postoperative care

Postoperatively patient was extubated and shifted to recovery room where observations will be made, recorded and analyzed by surgeon about study variables that is, pain, requirement of analgesia and complications and recorded by the surgeon, starting immediately after extubation.

Outcome variables

The primary end points were pain and the consumption of analgesia during the immediate post-operative period (first 2 hours) and subsequent 24 hours and requirement of anti emetics for post operative nausea and vomiting.

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.

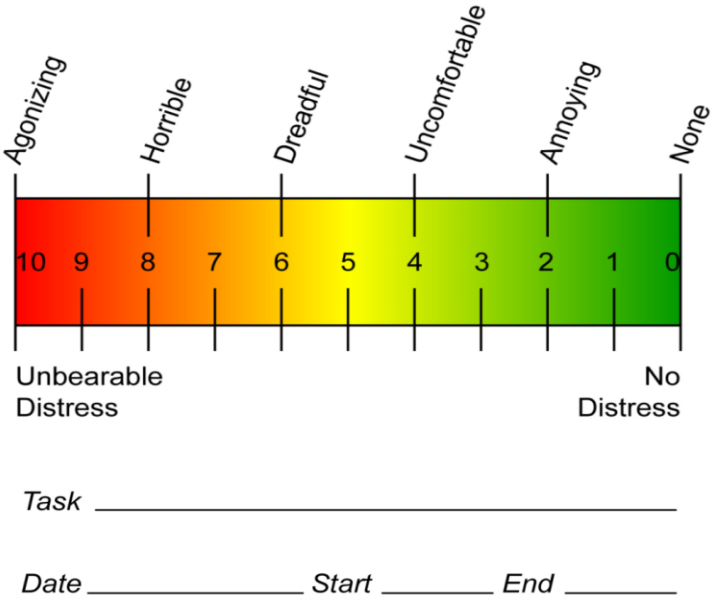


Figure 11.Visual analog scale

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.

Postoperative pain was monitored in terms of VAS scores by the surgeon at beginning 15, 30, 60 minutes and 4, 8, 16,and 24 hours.

Requirement of analgesia

Rescue analgesic requirement with 75 mg Diclofenac Sodium was noted by the surgeon at beginning 15, 30, 60 minutes and 4, 8, 16,and 24 hours..

Adverse effects

Incidence of nausea, vomiting, shoulder pain and itching were noted by the surgeon immediately postoperative, and at 4, 8, and 16 hours intervals.

Statistical analysis

The data was entered into the Microsoft Excel Spreadsheet (Annexure III). The data was analyzed using SPSS statistical software version 21.0. 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 and Mann-Whitney U test. A probability ('p' value) of less than or equal to 0.05 at 95% confidence interval was considered as statistically significant.

RESULTS

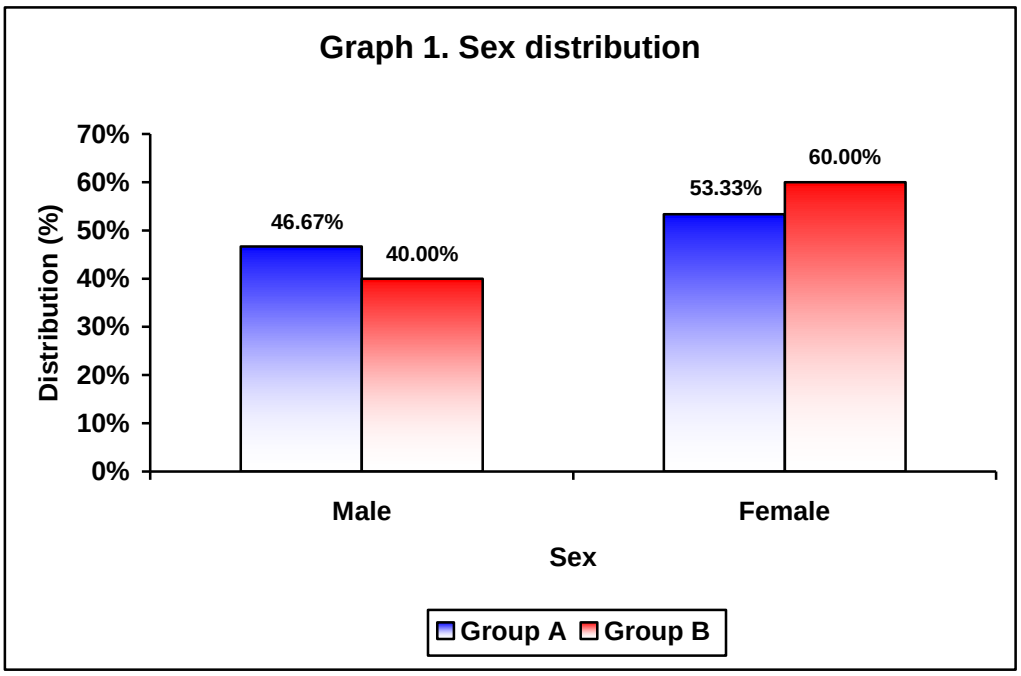
This one year double blinded randomized controlled trial was done in the Department of General Surgery, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belagavi from January 2015 to December 2015. A total of 60 patients posted for elective laparoscopic appendectomy were studied. Based on computer generated random numbers, these Patients were divided into two groups of 30 each as group A (Patients in this group received intraperitoneal instillation of tramadol 150 mg [diluted in 40 ml of distilled water]) and Group B (Patients in this group received intraperitoneal instillation of 0.5% bupivacaine [diluted in 40 ml of distilled water]).

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

Table 1. Sex distribution

Sex	Group A (n=30)		Group B (n=30)	
	Number	**Percentage**	**Number**	**Percentage**
Male	14	46.67	12	40.00
Female	16	53.33	18	60.00
Total	**30**	**100.00**	**30**	**100.00**

p = 0.602

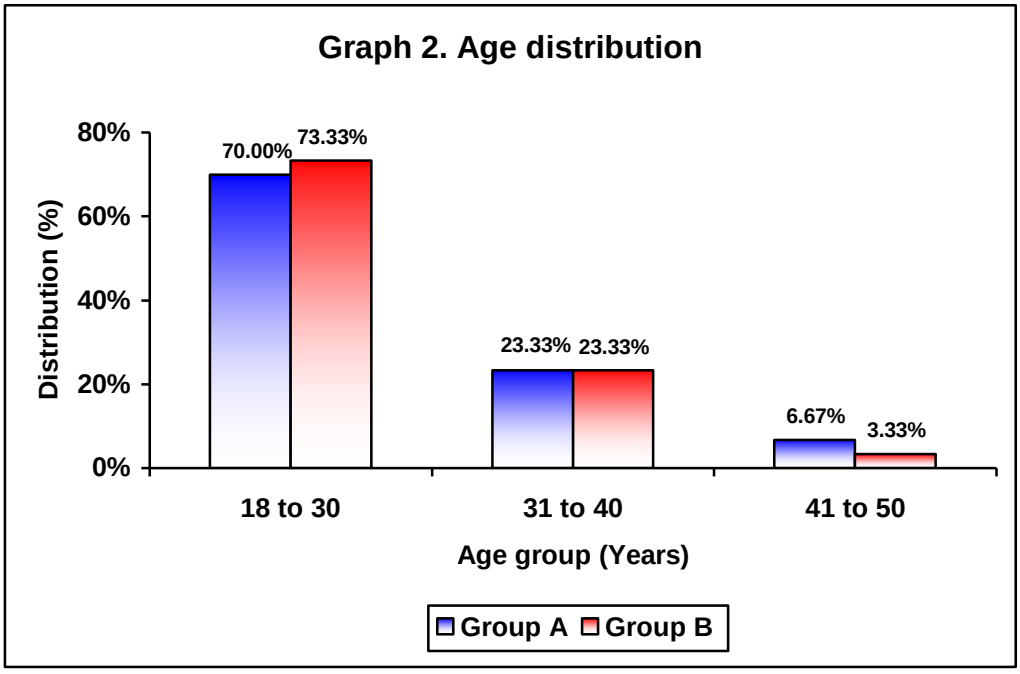


In the present study, 53.33% and 60% of the patients were females in Group A and Group B respectively. The male to female ratio in group A was 1:1.14 and in group B it was 1:1.5. However the sex distribution in both the groups was comparable (p=0.602).

Table 2. Age distribution

Age group (Years)	Group A (n=30)		Group B (n=30)	
	Number	**Percentage**	**Number**	**Percentage**
18 to 30	21	70.00	22	73.33
31 to 40	7	23.33	7	23.33
41 to 50	2	6.67	1	3.33
Total	**30**	**100.00**	**30**	**100.00**

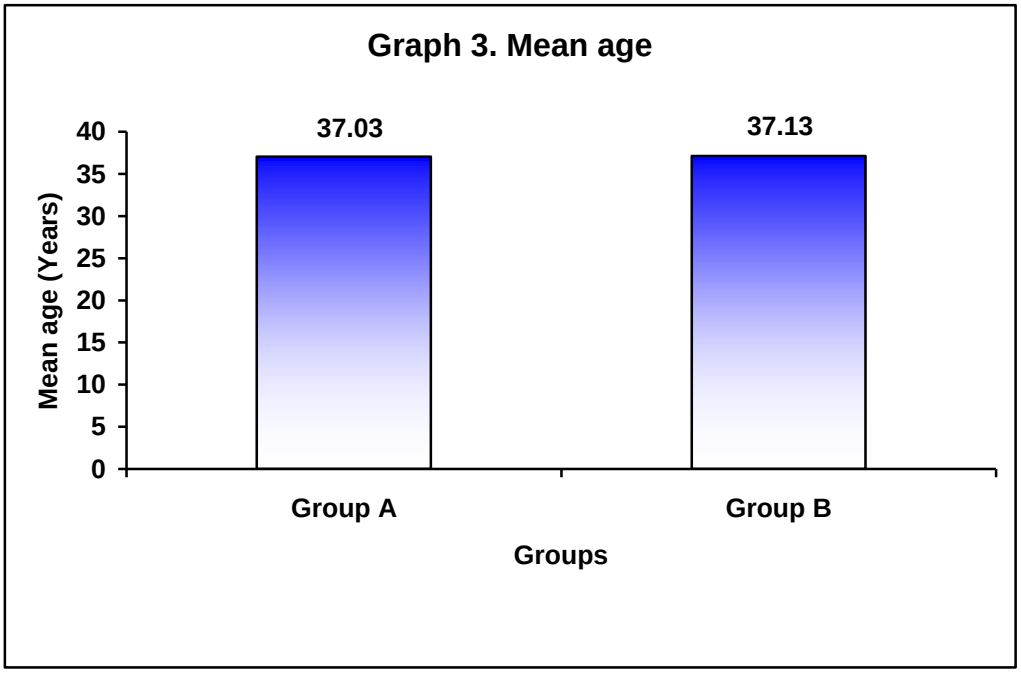
p = 1.000



In this study majority of the patients in group A (70%) and group B (73.33%) were aged between 18 to 30 years. However the age distribution in both the groups was almost equal statistically (p=1.000)

Table 3. Mean age

Variables	Group A (n=30)		Group B (n=30)		p value
	Mean	SD	Mean	SD	
Age (Years)	37.03	1.00	37.13	0.73	0.660

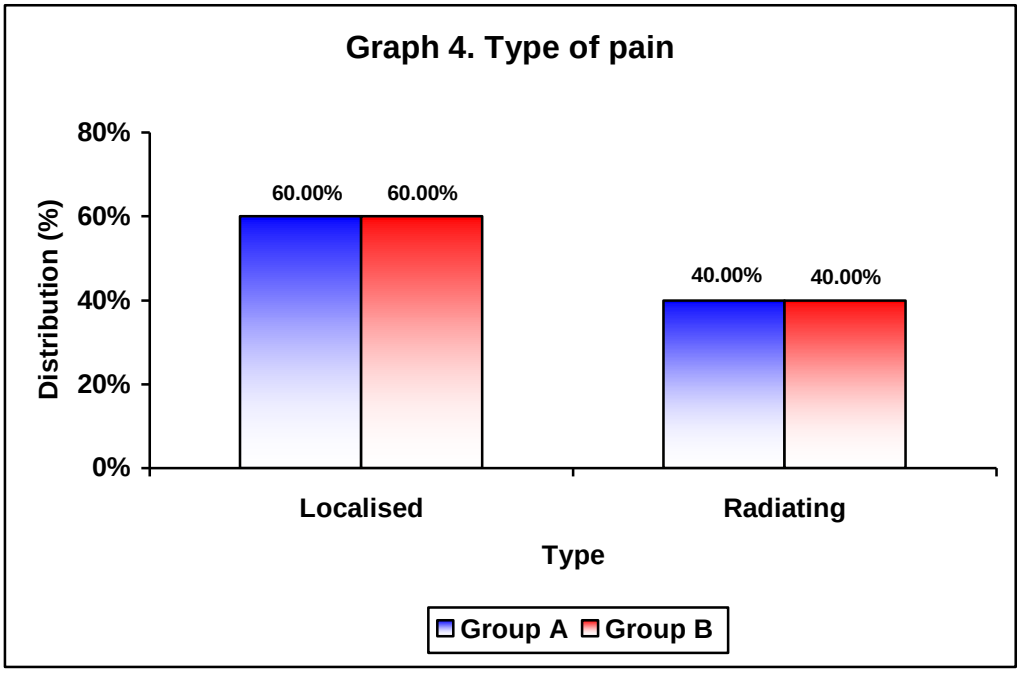


In the present study the mean age in group A and group B was also comparable (37.03 ± 1.00 vs 37.13 ± 0.73 years; p=0.660)

Table 4. Type of pain

Type	Group A (n=30)		Group B (n=30)	
	Number	**Percentage**	**Number**	**Percentage**
Localised	18	60.00	18	60.00
Radiating	12	40.00	12	40.00
Total	**30**	**100.00**	**30**	**100.00**

p = 1.000

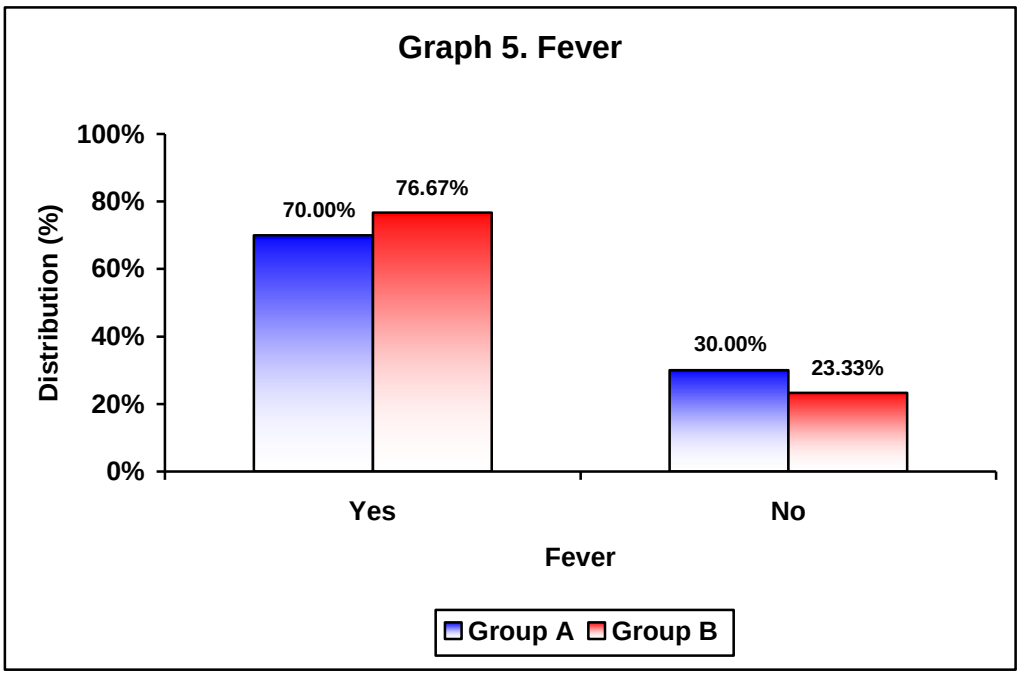


In this study most of the patients in group A and group B (60% each) reported localized pain (p=1.000).

Table 5. Fever

Fever	Group A (n=30)		Group B (n=30)	
	Number	**Percentage**	**Number**	**Percentage**
Yes	21	70.00	23	76.67
No	9	30.00	7	23.33
Total	**30**	**100.00**	**30**	**100.00**

p = 0.559



In the present study fever was reported by majority of the patients in group A (70%) and group B (76.67) (p=0.559).

Table 6. Comparison of fever

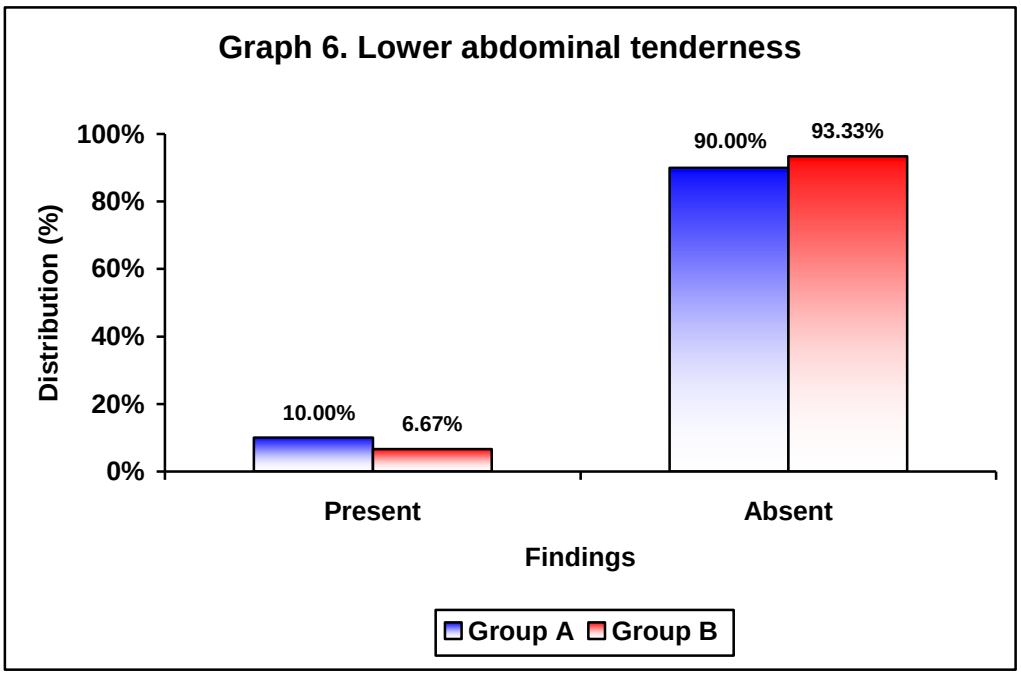
Variables	Findings	Group A (n=30)		Group B (n=30)		p value
		No	%	No	%	
Degree of fever	Mild	4	13.33	2	6.67	0.860
	Moderate	3	10.00	3	10.00	
	Severe	2	6.67	2	6.67	
	Absent	21	70.00	23	76.67	
	Total	**30**	**100.00**	**30**	**100.00**	
Type of fever	Continuous	5	16.67	4	13.33	0.842
	Intermittent	4	13.33	3	10.00	
	Absent	21	70.00	23	76.67	
	Total	**30**	**100.00**	**30**	**100.00**	

In this study most of the patients had mild fever in group A (13.33%) compared to 6.67% in group B. However this difference was statistically not significant (p=0.860). Further continuous fever was noted in 16.67% of the patients in group A compared to 13.33% in group B (p=0.842).

Table 7. Lower abdominal tenderness

Findings	Group A (n=30)		Group B (n=30)	
	Number	**Percentage**	**Number**	**Percentage**
Present	3	10.00	2	6.67
Absent	27	90.00	28	93.33
Total	**30**	**100.00**	**30**	**100.00**

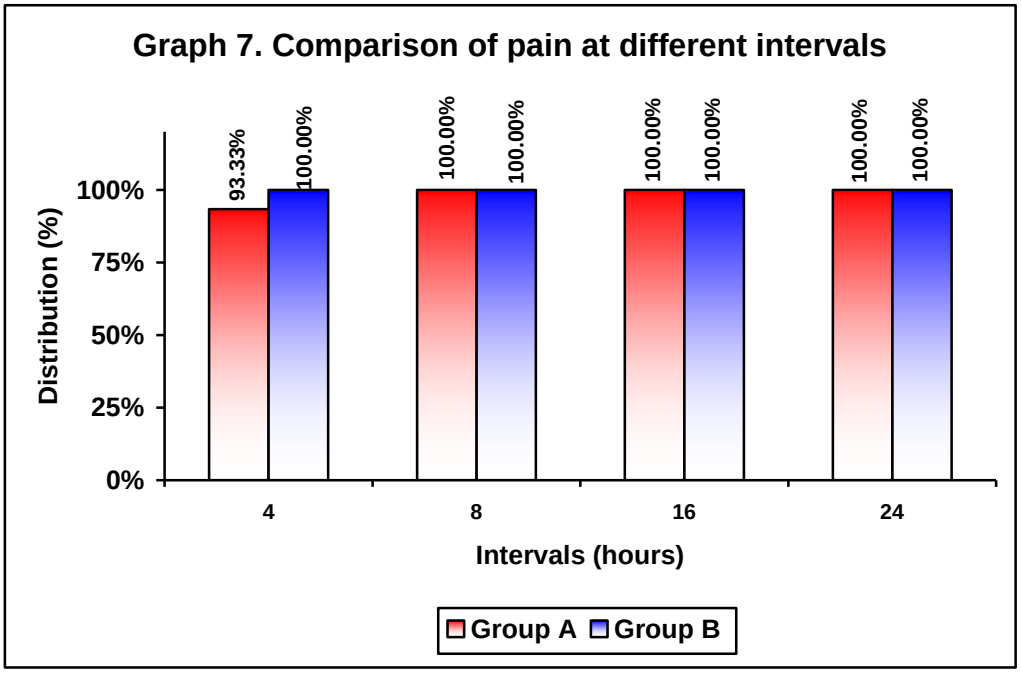
p = 0.640



In this study lower abdominal tenderness was present in 10% of the patients in group A compared to 6.67% in group B (p=0.640)

Table 8. Comparison of pain at different intervals

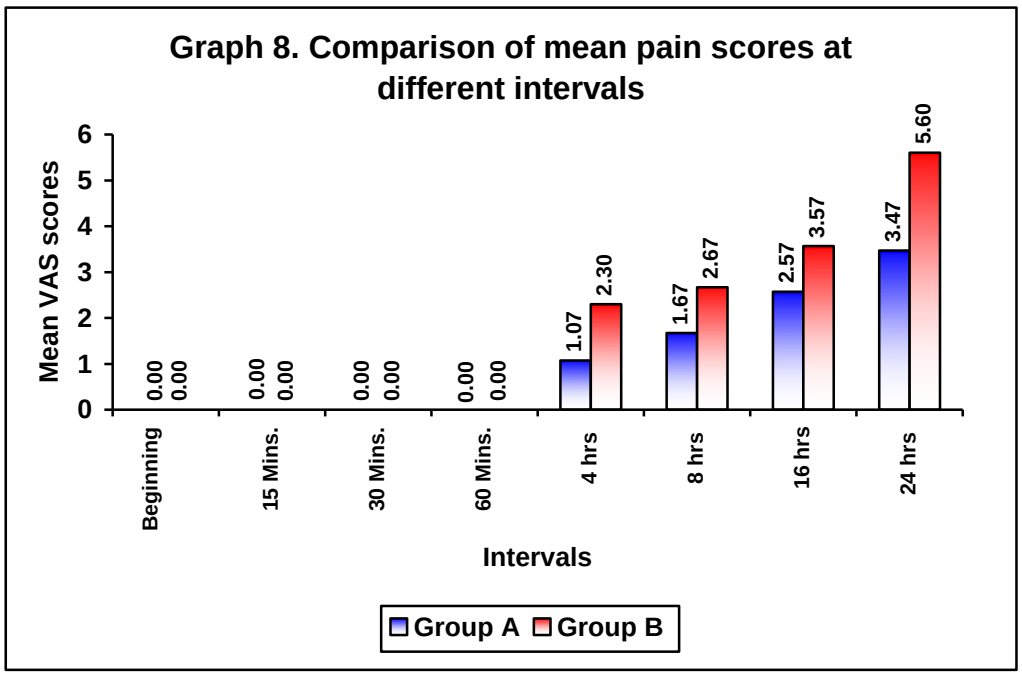
Intervals (hours)	Pain	Group A (n=30)		Group B (n=30)		p value
		No	%	No	%	
4	Present	28	93.33	30	100.00	0.492
	Absent	2	6.67	0	0.00	
	Total	**30**	**100.00**	**30**	**100.00**	
8	Present	30	100.00	30	100.00	-
	Absent	0	0.00	0	0.00	
	Total	**30**	**100.00**	**30**	**100.00**	
16	Present	30	100.00	30	100.00	-
	Absent	0	0.00	0	0.00	
	Total	**30**	**100.00**	**30**	**100.00**	
24	Present	30	100.00	30	100.00	-
	Absent	0	0.00	0	0.00	
	Total	**30**	**100.00**	**30**	**100.00**	



In the present study pain was reported by 93.33% of the patients in group A at 4 hours compared to 100% in group B (p=0.492). However, At 8, 16 and 24 hours interval all the patients in group A and B (100%) reported some degree of pain (p>0.05).

Table 9. Comparison of mean pain scores at different intervals

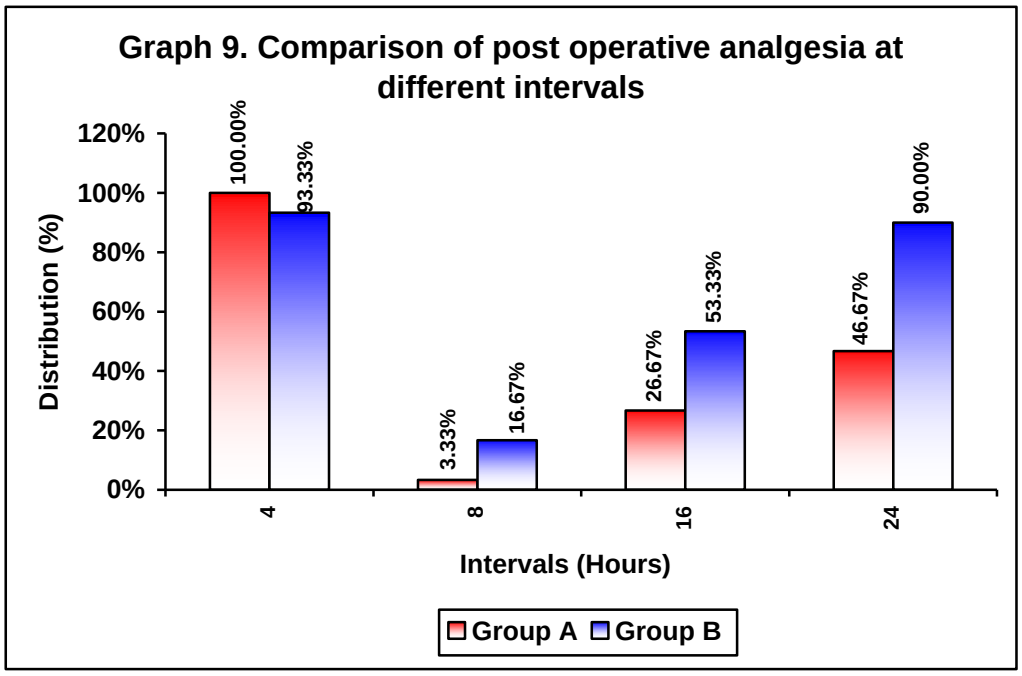
Intervals	Mean pain scores				p value
	Group A (n=30)		Group B (n=30)		
	Mean	SD	Mean	SD	
Beginning	0.00	0.00	0.00	0.00	-
15 minutes	0.00	0.00	0.00	0.00	-
30 minutes	0.00	0.00	0.00	0.00	-
60 minutes	0.00	0.00	0.00	0.00	-
4hrs	1.07	0.45	2.30	0.88	**<0.001**
8hrs	1.67	0.80	2.67	0.88	**<0.001**
16hrs	2.57	1.25	3.57	1.19	**0.002**
24 hrs	3.47	1.04	5.60	1.28	**<0.001**



In this study mean pain scores at 4, 8, 16 and 24 in group A were significantly low compared to group B ($p<0.050$).

Table 10. Comparison of post operative analgesia at different intervals

Intervals (hours)	Post operative analgesia	Group A (n=30)		Group B (n=30)		p value
		No	%	No	%	
4	Required	30	100.00	28	93.33	0.492
	Not required	0	0.00	2	6.67	
	Total	**30**	**100.00**	**30**	**100.00**	
8	Required	1	3.33	5	16.67	0.195
	Not required	29	96.67	25	83.33	
	Total	**30**	**100.00**	**30**	**100.00**	
16	Required	8	26.67	16	53.33	**0.035**
	Not required	22	73.33	14	46.67	
	Total	**30**	**100.00**	**30**	**100.00**	
24	Required	14	46.67	27	90.00	< **0.001**
	Not required	16	53.33	3	10.00	
	Total	**30**	**100.00**	**30**	**100.00**	

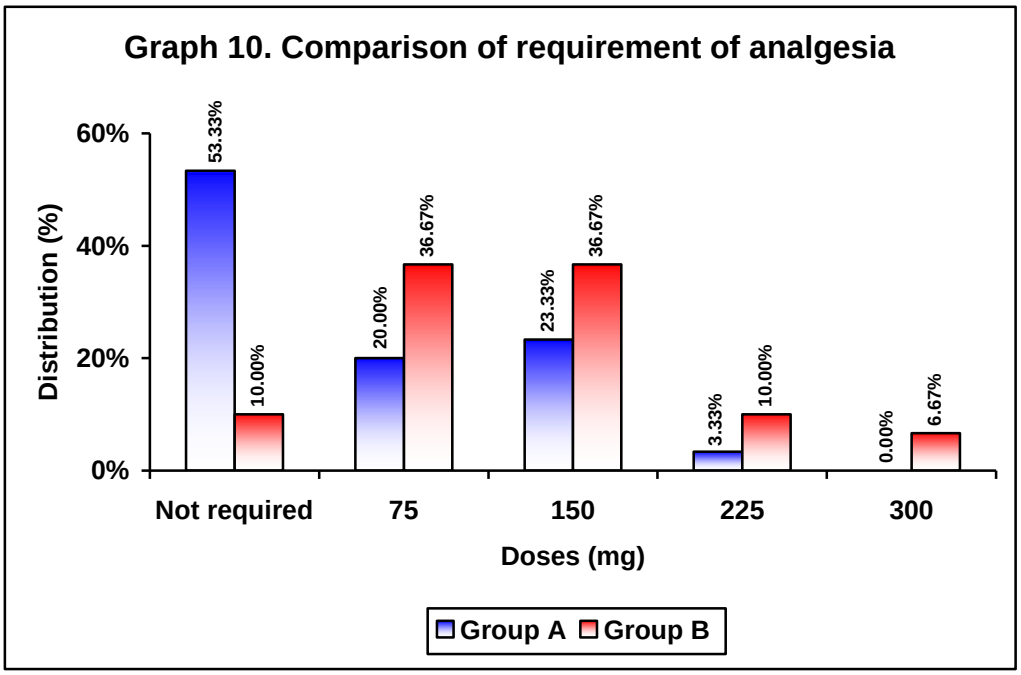


In this study at 16 hours interval significantly higher number of patients in group B (53.33%) required rescue analgesia compared to group A (26.67%) (p=0.035). Similarly at 24 hours interval significantly higher number of patients in group B (90%) required rescue analgesia compared to group A (46.67%) (p<0.001).

Table 11. Comparison of requirement of analgesia

Analgesic doses (mg)	Group A (n=30)		Group B (n=30)	
	Number	Percentage	Number	Percentage
Not required	16	53.33	3	10.00
75	6	20.00	11	36.67
150	7	23.33	11	36.67
225	1	3.33	3	10.00
300	0	0.00	2	6.67
Total	**30**	**100.00**	**30**	**100.00**

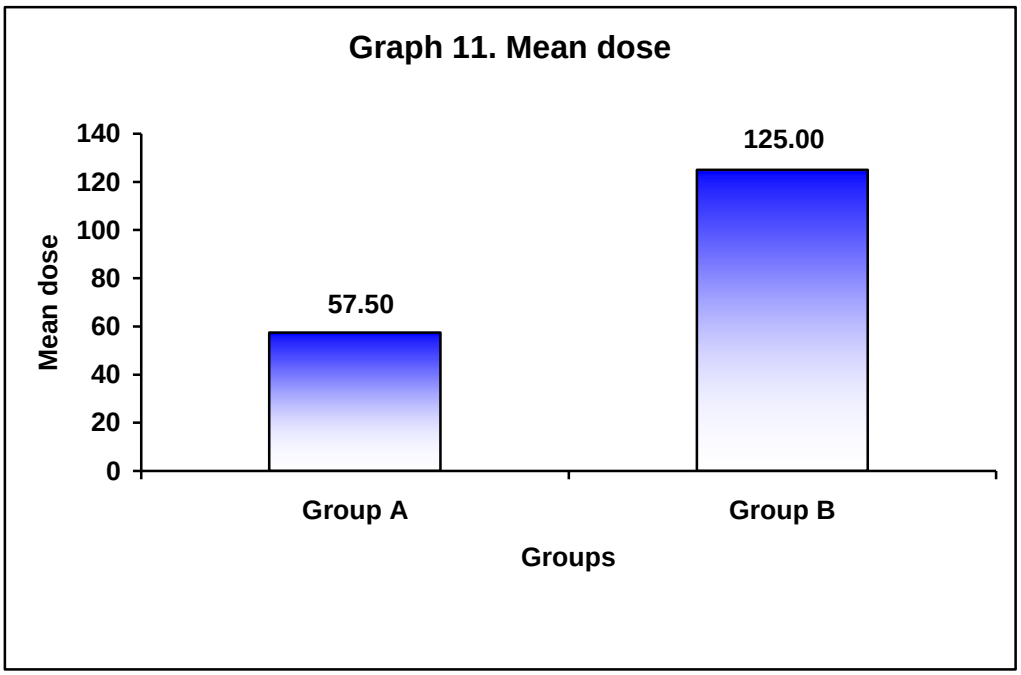
p = 0.007



In the present study the requirement of analgesic dose was significantly high in patients with Group B that is, 10% of the patients did not required analgesic dose while 36.67% required 75 mg, and 150 mg each, 10% required 225 mg and 6.67% required 300 mg compared to 53.33%, 20%, 23.33%, 3.33% and 0% group A. (p=0.007) respectively.

Table 12. Mean dose

Variables	Group A (n=30)		Group B (n=30)		p value
	Mean	**SD**	**Mean**	**SD**	
Mean dose	57.50	70.14	125.00	77.12	**<0.001**
median (Range)	70.14	0-225	77.12	0-300	**<0.001**



In this study requirement of mean analgesia was significantly high in group B, (125.00 ±77.12 mg) compared to group A (57.50 ± 70.14 mg) (p<0.001).

Table 13. Adverse events

Variables	Findings	Group A (n=30)		Group B (n=30)		p value
		No	**%**	**No**	**%**	
Adverse effect	Present	23	76.67	27	90.00	0.166
	Absent	7	23.33	3	10.00	
	Total	**30**	**100.00**	**30**	**100.00**	
at 16 hours	Shoulder tip pain	0	0.00	3	10.00	0.003
interval	Vomiting	7	23.33	0	0.00	
	Absent	23	76.67	27	90.00	
	Total	**30**	**100.00**	**30**	**100.00**	

In the present study overall incidence of adverse effects was comparable in group A and group B (76.67% vs 90%; p=0.166). At 16 hours, incidence of vomiting was significantly high in group A (23.33%) compared to nil in group B while in group B shoulder tip pain was noted among 10% of the patients while it was not reported by any of the patient in group A (p=0.003).

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.[102-104]

However, postoperative period in laparoscopic surgery also is not pain free.[102-104] 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.[105]

It is hypothesized that, intraperitoneal instillation of local anaesthetics or opioids helps in achieving postoperative analgesia and thereby decrease analgesic requirements via other routes of administration. However, data regarding the type and the dose of local anaesthetic or opioid to be used for intraperitoneal use is lacking.[105]

A multimodal approach to achieve pain relief involving the use of non-steroidal anti-inflammatory drugs, opioids, and local anaesthetic infiltration has been suggested as the optimal combination for laparoscopic surgery.[106] There are variety of local anaesthetic techniques available which have been investigated in order to find out their potential analgesic benefits in laparoscopic surgery. Likewise injecting local anaesthetic 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.[107]

Several other studies also have utilized this method of analgesia. Bupivacaine,[108] levobupivacaine,[109] lidocaine[110] and ropivacaine[111] 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 anaesthesia, and the risk of serious adverse effects limited.[17,20-21] 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 appendectomy.

Similarly, bupivacaine has a half-life of 2.5 to 3.5 hours and has been reported to provide pain control for an average of six hours.[112] The margin of safety of the bupivacaine needed for analgesia is wide. Thus, pain relief and patient comfort during the early postoperative period becomes increasingly important, as the need for analgesic may delay discharge. Several studies have described pain according to the presumed mechanism: visceral pain, which can theoretically be

blocked by intraperitoneal instillation, and parietal pain, which can be blocked by port site infiltration.[113-115]

This study was designed to evaluate the effectiveness of intraperitoneal instillation of tramadol versus bupivacaine for postoperative pain relief after laparoscopic appendectomy especially visceral and shoulder tip pain and to evaluate adverse effect such as nausea, vomiting, shoulder pain and shivering following laparoscopic appendectomy.

The present one year double blinded randomized controlled trial was performed in the Department of General Surgery, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belagavi. A total of 60 patients posted for elective laparoscopic appendectomy from January 2015 to December 2015 were studied. The patients were divided into two groups of 30 each as group A (Patients in this group received intraperitoneal instillation of tramadol 150 mg [diluted in 40 ml of distilled water]) and Group B (Patients in this group received intraperitoneal instillation of 0.5% bupivacaine [diluted in 40 ml of distilled water]) based on computer generated random number.

In the present study, frequency of appendicitis was slightly high in females as 53.33% and 60% of the patients were females in Group A and Group B respectively. The male to female ratio in group A was 1:1.14 and in group B it was 1:1.5 (p=0.602). However this difference observed was statistically not significant (p=0.602). Majority of the patients in group A (70%) and group B (73.33%) were young aged between 18 to 30 years and the age distribution pattern in both the groups was statistically almost equal (p=1.000). Also the mean age in group A

(37.03 ± 1.00)and group B was also almost equal (37.13 ± 0.73 years; p=0.660). These findings suggest that the demographic profile of the study population was comparable in both the groups ruling out the possible bias in the study results.

In this study the clinical signs and symptoms including fever (p=0.559), type of fever (0p=0.842) pain (p=1.000), lower abdominal tenderness (p=0.640), 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.

Overall these findings suggest that, demographic and clinical characteristics of the study population were comparable in group A and group B ruling out the possible bias in study results.

In the present study pain was not reported by any of the patient in group A as well as group B from beginning to 60 minutes, Pain was reported by 93.33% of the patients in group A at 4 hours compared to 100% in group B (p=0.492). But this difference was statistically not significant (p=0.492). However, at 8, 16 and 24 hours interval all the patients in group A and B (100%) reported some degree of pain (p>0.05). The mean pain scores were significantly low at 4 hours (1.07 ±0.45 vs 2.30 ± 0.88; p<0.001), 8 hours (1.67 ±0.80 vs 2.67 ± 0.88; p<0.001), 16 hours (2.57 ± 1.25 vs 3.57 ± 1.19; p=0.002) and 24 hours (3.47 ± 1.04 vs 5.60 ± 1.28; p<0.001) the mean pain scores in group A were significantly low compared to group B (p<0.050). Though, the mean pain scores in group A showed gradual increase from 4 hours to 24 hours mean pain scores in group A remained significantly low compared to group at all the intervals. These findings suggest that, intraperitoneal instillation of tramadol offers better pain control compared to intraperitoneal

instillation of 0.5% bupivacaine till 24 hours following laparoscopic appendectomy with gradual increase in intensity of pain but well within the tolerable limit.

In this study at 4 hours interval rescue analgesia was requested by all the patients in group A (100%) 93.33% of the patients in group B. However this difference was statistically not significant (p=0.492) At 8^{th} hour the requirement of rescue analgesia was comparable in group A and Group B (3.33% vs 16.67%;p=0.195) Also at 16 hours the requirement of rescue analgesia was comparable in group A and Group B (26.67% vs 53.33% ;p=0.035) similar trend was noted at 24 hours interval, that is significantly higher number of patients in group B (90%) required rescue analgesia compared to group A (46.67%). This difference was statistically significant (p<0.001). Furthermore, the requirement of analgesia dose was significantly high in patients with Group B that is, 6.67% of the patients in group B required cumulative analgesic dose as high as 300 mg while 10% of the patients required 225 mg and 36.67% required 150 mg and 75 mg each. While in group A, none of the required cumulative analgesic dose of 300 mg, 3.33% of the patients required 225 mg and 23.33% required 150 mg and 20% required 75 mg. This difference was statistically significant (p=0.007). Also, the requirement of mean analgesia was significantly high in group B, compared to group A (125.00 ±77.12 mgvs57.50 ± 70.14 mg; p<0.001). These findings hypothesize that, intraperitoneal instillation of tramadol significantly reduces consumption of rescue analgesia significantly compared to intraperitoneal instillation of 0.5% bupivacaine for the period of 24 hours following laparoscopic appendectomy.

In the present study incidence of adverse effects was high in both the groups that is, 76.67% of the patients in group A compared to 90% in group B. However

this difference was statistically not significant (p=0.166). However, at 16 hours interval, the incidence of vomiting was high in group A (23.33%) while in group B shoulder tip pain was noted among 10% of the patients. This difference was statistically significant (p=0.003). However, the complication of shivering was noted in any of the patients in either group. These findings showed that, the safety profile of intraperitoneal instillation of tramadol and 0.5% bupivacaine for the period of 24 hours following laparoscopic appendectomy is almost same. However, intraperitoneal instillation of tramadol results in vomiting at 16 hours following laparoscopic appendectomy and intraperitoneal instillation of 0.5% bupivacaine is associated with shoulder tip pain. However, the occurrence of vomiting has been observed in postoperative period in group A might be a result of routine side effect of general anaesthesia.

Overall, the findings of this study showed that intraperitoneal instillation of tramadol offers not only effective pain relief but also results in reduction of consumption in rescue analgesia compared to and intraperitoneal instillation of 0.5% bupivacaine. Hence avoiding discomfort and adverse effects related to repeated intramuscular / intravenous analgesic administration. Further, intraperitoneal instillation of Tramadol is well tolerated, offers excellent pain relief and reduces the consumption of rescue analgesia. However, we do not have adequate data to compare these findings due to scanty literature available on the comparison of intraperitoneal instillation of tramadol with intraperitoneal instillation of 0.5% bupivacaine. Nevertheless, the effects observed in this study may 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 anaesthetic properties and local administration of tramadol has been found to be an effective analgesic.[21]

Studies have shown adequate absorption of Tramadol from various fibro vascular surfaces of body, achieving adequate blood levels.[101] 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 anaesthetic 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 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[116] 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[92] (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[117] 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 Akinciet al[18] (n=20 in each group).

Another study done by Hernandes–Pazon et al.[94] showed that intraperitoneal administration of local anaesthetic in combination with an opoid reduced the analgesic requirements during first 6 postoperative hours.

Golubovicet al.[92] 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.[95] concluded that intravenous tramadol provides superior postoperative pain relief as compared to intraperitoneal administration.

The efficacy of local anaesthetic instillation in pain control with intraperitoneal instillation of 0.5% bupivacaine has been demonstrated in numerous other studies in laparoscopic cholecystectomy. Some used bupivacaine 0.25% while others used 0.125% bupivacaine[83] and found a good post operative pain relief. A systemic review and meta-analysis for the effect of intraperitoneal local anaesthetic in laparoscopic cholecystectomy was done and 12 out of 24 studies reported a significant improvement in pain during early post operative period.[57] The results correlate well with the results claimed in our study.

Furthermore, the intraperitoneal local anaesthetics are found to be very effective for the relieving postoperative pain.[118] This non-invasive method has a minimum risk and it can be easily applied. A similar study[89] 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.

Similarly Bhardwaj et al,[89] conducted study in patients undergoing laparoscopic cholecystectomy. He instilled 20 ml 0.5% bupivacaine only at the end of surgery in the trendelburg position. Post operatively they assessed for vital signs (heart rate, blood pressure and respiratory rate), pain scores (VAS, VRS and shoulder pain) and analgesic consumption.[97] They found that it reduced post operative cholecystectomy pain and analgesic consumption.

These findings contradict results observed in the present study which can be explained by the different surgical settings involved, different dose regimen of bupivacaine and the different surgical settings, as the latter studies were mostly conducted in the patients undergoing laparoscopic cholecystectomy.

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, intraperitoneal instillation of tramadol offers excellent pain relief and minimal discomfort and has excellent safety profile compared to intraperitoneal instillation of 0.5% bupivacaine and those with repeated intravenous/intramuscular analgesia, like thrombophlebitis, injection site pain, abscess formation etc. and enables patient to be fit and resume routine activities early.

The limitations of this study were, small sample size, and study design that is single centre study involved only elective laparoscopic appendectomy. However, large multicentric studies involving patients from both elective and emergency laparoscopic appendectomy may confirm these findings.

CONCLUSION

Based on the findings of this study it may be concluded that, intraperitoneal instillation of tramadol offers excellent pain relief, and it is as safe as 0.5% bupivacaine.

SUMMARY

Early postoperative pain is the most prevalent and dominant complaint after elective laparoscopic surgeries. This study was aimed to compare the effectiveness of intraperitoneal instillation of tramadol versus bupivacaine for postoperative pain relief after laparoscopic appendectomy especially visceral and shoulder tip pain and to evaluate adverse effect such as nausea, vomiting, shoulder pain and shivering following laparoscopic appendectomy.

This one year double blinded randomized controlled trial was done in the Department of General Surgery, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belagavi from January 2015 to December 2015. A total of 60 patients posted for elective laparoscopic appendectomy were studied. Based on computer generated random numbers, these patients were divided into two groups of 30 each as group A (intraperitoneal instillation of tramadol 150 mg) and Group B (intraperitoneal instillation of 0.5% bupivacaine).

In the present study, most of the patients were females that is 53.33% and 60% in Group A and Group B respectively (p=0.602). Majority of the patients in group A (70%) and group B (73.33%) were aged between 18 to 30 years (p=1.000). The mean age in group A and group B was comparable (37.03 ± 1.00 vs 37.13 ± 0.73 years; p=0.660) Most of the patients in group A and group B (60% each) reported localized pain (p=1.000). Symptoms of fever were reported by majority of the patients in group A (70%) and group B (76.67) (p=0.559). Lower abdominal tenderness was present in 10% of the patients in group A compared to 6.67% in group B (p=0.640) Pain was reported by 93.33% of the patients in group A at 4

hours compared to all the patients (100%) in group B (p=0.492). However, At 8, 16 and 24 hours interval all the patients in group A and B (100%) reported some degree of pain (p>0.05). Mean pain scores at 4, 8, 16 and 24 hours the mean pain scores in group A were significantly low compared to group B (p<0.050). At 24 hours interval significantly higher number of patients in group B (90%) required rescue analgesia compared to group A (46.67%) (p<0.001). The overall requirement of analgesia was significantly high in patients with Group B that is, 10% of the patients did not required while 36.67% required 75 mg, and 150 mg each, 10% required 225 mg and 6.67% required 300 mg compared to 53.33%, 20%, 23.33%, 3.33% and 0% in group A. (p=0.007) The requirement of mean analgesia was significantly high in group B, (125.00 ±77.12 mg) compared to group A (57.50 ± 70.14 mg) (p<0.001). Overall incidence of adverse effects was comparable in group A and group B (76.67% vs 920%; p=0.166). At 16 hours , incidence of vomiting was significantly high in group A (23.33%) compared to nil in group B while in group B shoulder tip pain was noted among 10% of the patients while it was not reported by any of the patient in group A (p=0.003).

Intraperitoneal instillation of tramadol offers excellent pain relief. However, its safety profile is comparable to that of intraperitoneal instillation with of 0.5% bupivacaine.

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ANNEXURE I – CONSENT FORM

Dear Mr./Mrs./Dr._____, you are kindly requested to participate in a research study tilted "TO EVALUATE THE ANALGESIC EFFICACY OF INTRAPERITONEAL INSTILLATION OF TRAMADOL VERSUS BUPIVACAINE FOR POST OPERATIVE PAIN RELIEF FOLLOWING LAPAROSCOPIC APPENDECTOMY, A DOUBLE BLIND RANDOMIZED CONTROL TRIAL, HOSPITAL BASED STUDY" conducted by Dr. ***** ******, a post graduate student in M.S. General Surgery in Jawaharlal Nehru Medical College, Belagavi.

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

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

Title of the study

"TO EVALUATE THE ANALGESIC EFFICACY OF INTRAPERITONEAL INSTILLATION OF TRAMADOL VERSUS BUPIVACAINE FOR POST OPERATIVE PAIN RELIEF FOLLOWING LAPAROSCOPIC APPENDECTOMY, A DOUBLE BLIND RANDOMIZED CONTROL TRIAL, HOSPITAL BASED STUDY"

Objective/purpose of the study

Laparoscopic appendectomy has been the treatment of choice for acute or chronic appendicitis. Laparotomy results mainly in parietal pain, laparoscopy has a visceral component, a somatic component and shoulder pain secondary to diaphragmatic irritation as a result of CO_2 pnemoperitoneum. In laparoscopic appendecectomy, visceral pain predominates in first 24 hours but subsides soon after operation, whereas shoulder pain, less on the first day, increases and becomes significant on the following days.

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

To improve pain relief after laparoscopic appendectomy.

You are being asked to participate in this research as you find all the criteria laid by the author of the study as 'subjects'. The investigator/author of this study is Dr. ***** ******, a postgraduate student in Dept. of General Surgery, Jawaharlal Nehru Medical College.

The study is self funded by the author the study.

Procedures

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

You will be randomly allocated either into study group or control group using computer generated numbers and you will receive intraperitoneal tramadol 150 mcg (diluted in 40 ml of distilled water) or 0.5% of bupivacaine (diluted in 40 ml of distilled water). Both patients and surgeon will be blinded and anaesthetist will

bupivacaine or tramadol according to random table chart and give it to the surgeon for infiltration.

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

The surgeons will not know 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 6 and 24 hours.
- Rescue analgesic - 75 mg DICLOFENAC SODIUM
- Postoperative pain scores at 6,12,24 hours . Incidence of adverse effect (nausea, vomiting, shoulder pain, itching) at 6 , 12 , 24 hours.
- Postoperative hospital course (monitoring of HR , BP , RR, temperature at 6 , 12 , 24 hours)

Risks and benefits

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

Voluntary participation / withdrawing / removal from the study

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

Alternatives

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

Privacy and confidentiality

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

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

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

Authorization to publish results

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

Financial incentives for participation

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

Compensation

In the event that you become injured as a result of taking part in this study, treatment will be offered to you at KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belagavi., or you will be given information about where to receive

medical care in which case you/your insurance company will be responsible for the costs. However, no reimbursement, compensation or free medical care will be given. There is no compensation or payment for such medical treatment by law.

Contact details

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

Dr. ** ********
(Post Graduate Student)
Department of Surgery
Jawaharlal Nehru Medical College
Nehru Nagar, KLE Hospital Road
Belagavi - 590 010
Mobile No.: ***** *****

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_____

Investigators name_____

Signature_____

Witness' name_____

Signature_____ Date___/___/____

ANNEXURE II – PROFORMA

The proposed proforma / questionnaire to be used for data collection for the study tilted "TO EVALUATE THE ANALGESIC EFFICACY OF INTRAPERITONEAL INSTILLATION OF TRAMADOL VERSUS BUPIVACAINE FOR POST OPERATIVE PAIN RELIEF FOLLOWING LAPAROSCOPIC APPENDECTOMY, A DOUBLE BLIND RANDOMIZED CONTROL TRIAL, HOSPITAL BASED STUDY" is as:

Patient details

In Patient /Out Patient number:

Date of Admission :

Date of Surgery :

Name :

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 / local anaesthetic Yes / no

General examination

Built and nourishment:

Weight:

Pulse :

Bp :

R/r :

Temperature:

Per abdomen – tenderness:

Right iliac fossa:

Left iliac fossa:

Lower abdominal tenderness:

Generalised tenderness:

	Normal	abnormal findings
Cardiovascular	:	
Respiratory	:	

Central nervous system:

Investigations

Conplete blood count :

Random blood sugar :

Blood urea :

Serum Creatinine :

Bleeding time :

Clotting time :

Urine :

Routine :

Microscopy :

Usg abdomen / x ray abdomen erect

Group

Group a Group b

Operation details

Date of Surgery :

Name of Surgery

Laproscopic appendectomy

Anaesthesia

General anaesthesia :

Duration of Surgery :

Drug used for Instillation

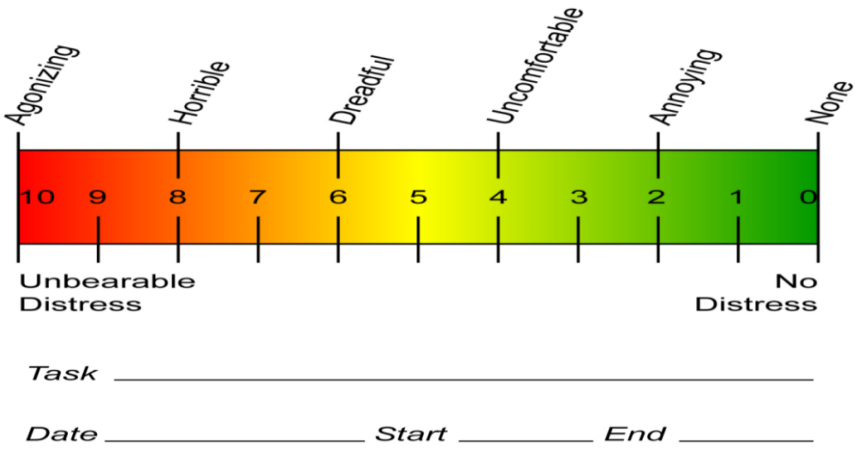
Tramadol and Bupivacaine :

Dosage of Drugs Used for Instillation

150 mg Tramadol (diluted in 40 ml distilled water) and .5% Bupivacaine (diluted in 40 ml distilled water)

Area of Instillation:

20 ml in sub diaphragmatic space and 20 ml in right iliac fossa over appendicular stump.



Assessment of post operative pain - visual analogue scale

0 – No pain

1-3 – Mild pain

4-7 – Moderate pain

8-10 – Severe pain

Postoperative pain scores and dose of analgesic given at

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

ANNEXURE III-KEY TO MASTER CHART

VAS	-	Visual analog scale
H/o	-	History of
Kgs	-	Kilograms
/Min	-	Per minute
BP	-	Blood pressure
mmHg	-	Millimeters mercury
^{0}C	-	Degree centigrade
hrs	-	hours
hr		hour
mg	-	milligram
F	-	Female
M	-	Male