# "A RANDOMIZED PLACEBO CONTROLLED TRIAL TO ASSESS POST OPERATIVE ANALGESIA AFTER PERIPORTAL INFILTRATION OF 0.75% ROPIVACAINE IN LAPAROSCOPIC APPENDICECTOMY"

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This is to certify that the dissertation entitled **"A RANDOMIZED PLACEBO CONTROLLED TRIAL TO ASSESS POST OPERATIVE ANALGESIA AFTER PERIPORTAL INFILTRATION OF 0.75% ROPIVACAINE IN LAPAROSCOPIC APPENDICECTOMY"** is a bonafide research work done by **REG NO. BH0110005.**


Dr. V. M. UPPIN MS
Professor and Head,
Department of General Surgery,
J. N. Medical College,
Nehru Nagar, Belgaum – 10

Date:
Place: Belgaum

Dr. A.S.GODHI MS
Principal,
J. N. Medical College,
Nehru Nagar, Belgaum – 10

Date:
Place: Belgaum

# LIST OF ABBREVIATIONS USED

| | |
|---|---|
| ANOVA | : Analysis of variance |
| ASA | : American society of anaesthesiologists |
| B.P. | : Blood pressure |
| C.V.S. | : Cardiovascular system |
| CNS | : Central nervous system |
| $CO_2$ | : Carbon dioxide |
| COX | : Cyclooxygenase |
| DB | : Diastolic blood pressure |
| DC | : Differential count |
| DM | : Diabetes mellitus |
| ECG | : Electrocardiogram |
| ESR | : Erythrocyte sedimentation rate |
| EtCO2 | : End-tidal carbon dioxide |
| FRC | : Functional residual capacity |
| GIT | : Gastrointestinal system |
| Hb | : Haemoglobin |
| HR | : Heart rate |
| Hrs | : Hours |
| HTN | : Hypertension |
| I.P. NO. | : In patient number |
| IAP | : Intra abdominal pressure |
| IV | : Intravenous |
| IVPCA | : Intravenous patient controlled analgesia |
| IVRA | : Intravenous regional anaesthesia |

| | | |
|---|---|---|
| MAP | : | Mean arterial pressure |
| $N_2O$ | : | Nitrous oxide |
| Na | : | Sodium |
| NMDA | : | N-methyl-d-aspartic acid |
| NO | : | Nitric oxide |
| NSAID's | : | Non steroidal anti inflammatory drugs |
| P.R. | : | Pulse rate |
| PABA | : | P-amino- benzoic acid |
| PaCO2 | : | Partial pressure of arterial carbon dioxide |
| PACU | : | Post anesthesia care unit |
| PCEA | : | Patient controlled epidural analgesia |
| PR | : | Pulse rate |
| R.R. | : | Respiratory rate |
| R.S. | : | Respiratory system |
| RA | : | Rescue analgesia |
| SB | : | Systolic blood pressure |
| STP | : | Shoulder tip pain |
| TC | : | Total count |
| TENS | : | Transcutaneous electrical nerve stimulation |
| VAS | : | Visual analogue scale |
| WDR | : | Wide dynamic range neurons |
| Wt | : | Weight |

# ABSTRACT

**Background and objectives**

Although laparoscopic Appenicectomy is characterized by reduced postoperative pain, many patients still complain of moderate abdominal pain during the first 24 hours. The objective of this study was to compare effect of peri portal infiltration of 0.75% Ropivacaine versus saline for post-operative analgesia in laparoscopic Appendicectomy.

**Methodology**

60 adult patients admitted to department of surgery posted for elective laparoscopic Appendicectomy in KLES Dr. Prabhakar Kore Hospital & MRC, Belgaum between age group 18 to 80 years of ASA-1 and ASA-2. 60 patients undergoing laparoscopic Appendicectomy were prospectively randomized into 2 groups. **Group (A) – Study group:** Patients received 20 ml 0.75% Ropivacaine periportally around all the three port sites at the start of surgery. **Group (B) - Placebo group:** Patients received 20 ml normal saline periportally at the same location. The evaluation of postoperative pain was done at fixed time interval according VAS. Analgesic requirements were analyzed.

**Results**

Mean pain scores upto 12 hours after surgery were lower in group (A) compared to group (B). This difference was statistically significant ($p<0.05$). However, pain scores after 12 hours did not differ significantly between the two groups. The mean total NSAID's usage in group(A) was lower as compared to group (B) and was found to be statistically significant ($p<0.001$).

**Conclusion**

To conclude, Ropivacaine is effective in preventing pain over the first 12h after laparoscopic Appendicectomy when preemptively given at the start of surgery.

**Key words**

Laparoscopic Appendicectomy; Ropivacaine; Post operative pain relief;

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# INTRODUCTION

Surgical pain is due to inflammation from tissue trauma (that is, surgical incision, dissection, burns) or Direct nerve injury (that is nerve transaction, stretching or compression).The patient senses pain through the afferent pain pathway which can be altered by various pharmacological agents.[1]

Although postoperative pain remains incompletely controlled in some settings, increased understanding of its mechanisms and the development of several therapeutic approaches have substantially improved pain control in past years Use of specific analgesic techniques such as regional analgesia could improve patient outcomes.[2]

Adequacy of postoperative pain control is one of the most important factors in determining when a patient can be safely discharged from surgical facility and has a major influence on the patient's ability to resume their normal activities of daily living.[3] Control of acute postoperative pain and the timing, and duration (e.g., preemptive analgesia), is important in facilitating short and long-term patient convalescence.[4]

Traditionally received opiates with acetaminophen for the management of their postoperative pain. The use of narcotic pain medications can be costly, decrease rates of early postoperative ambulation, lengthen hospital stays, and alter a patient's neurological examination. The use of alternative pain medications may benefit patients by resolving many of these issues.[5]

Inadequate pain control, apart from being inhumane, may result in increased morbidity or mortality. Evidence suggests that surgery suppresses the immune system

and that this suppression is proportionate to the invasiveness of the surgery. Good analgesia can reduce this deleterious effect. Data available indicate that afferent neural blockade with local anesthetics is the most effective analgesic technique. Next in order of effectiveness are high-dose opioids, epidural opioids and clonidine, patient controlled opioid therapy, and nonsteroidal anti-inflammatory agents.[6]

From the non-conventional methods, the infiltration of long-acting local anaesthetics as an adjuvant for regional or local anaesthetic techniques, improve postoperative pain management, furthermore, when administrated before surgery, these simple techniques can also decrease anaesthetic and analgesic requirement during surgery as well as reduce the need for opioid containing analgesic postoperatively.[6]

Periportal infiltration and intraperitoneal instillation of local anaesthetic in combination with general anaesthesia has been investigated in several interventional studies during laparoscopic surgeries. Approximately half of these studies showed reduction in the postoperative pain significantly.

Inspite of several advantages of laparoscopic procedures over laparotomy it does not take away the disadvantage like the post-operative pain which results in an unpleasant experience for the patient and there by delay the discharge. Pain usually occurs on the first day following surgery and it may be a visceral or parietal or shoulder tip pain in certain laproscopic surgeries[7]

Ropivacaine has been claimed superior as very small fraction of Ropivacaine is excreted unchanged in the urine , (about 1%).When liver is functioning normally , dose adjustments based on renal functions does not seem necessary . Also, it has differential blocking effect on nerve fibres. There is good differentiation between

motor and sensory blockade. There is more of sensory block and motor block is slower in onset and less intense, less cardio toxic and neuro toxic as compared to bupivacaine.[8]

Ropivacaine is one such local anaesthetic which has a good safety profile, 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.

Pain on the day of surgery is typically a diffuse abdominal pain or pain at operated site. 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 or extensive dissection at operated site.

Decrease in postoperative pain after infiltration of local anaesthetics into the operative wound have been observed among patients who undergo herniorhaphy and gynecological procedures.[9,] Continuous postoperative infusion of local anaesthetic agent into the abdominal wounds has reduced both postoperative pain and narcotic requirements.[12,13]

Thus, Effective postoperative pain control is an essential component of the care of the surgical patient. Inadequate pain control, apart from being inhumane, may result in increased morbidity or mortality. Evidence suggests that surgery suppresses the immune system and that this suppression is proportionate to the invasiveness of the surgery. Good analgesia can reduce this deleterious effect.[6]

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.[10,12,13]

So far, intense studies have been done to date on Bupivacaine but there is a scarcity of literature on Ropivacaine. Hence, Present study was designed to evaluate the effect of port site skin instillation of 0.75% ropivacaine for pain relief following laparoscopic appendicectomy.

# OBJECTIVES

The objectives of the present study were;

1. Comparing the effect of skin infiltration of 0.75% ropivacaine versus saline for post-operative analgesia in laparoscopic appendicectomy.
2. To assess the need of rescue analgesics in post-operative period in both groups.

# REVIEW OF LITERATURE

Laparoscopic surgery, also called minimally invasive surgery (MIS), bandaid surgery, or keyhole surgery, is a modern surgical technique in which operations in the abdomen are performed through small incisions(usually 0.5–1.5 cm) as opposed to the larger incisions needed in laparotomy. Keyhole surgery makes use of images displayed on TV monitors to magnify the surgical elements. Laparoscopic surgery includes operations within the abdominal or pelvic cavities, whereas keyhole surgery performed on the thoracic or chest cavity is called thoracoscopic surgery. Laparoscopic and thoracoscopic surgery belong to the broader field ofendoscopy.[15]

The majority of laparoscopic operations are performed as a short stay or even day care surgery.Although pain is less severe and of shorter duration than following open procedures,it can still be sufficiently intense to prevent early discharge.[16]

Pain tops the list of complaints following laparoscopic surgery, with up to 96% of patients complaining of post-operative pain. It is more intense immediately after surgery but decreases rapidly later.[16]

Laproscopic approach of minimally invasive surgery reduces pain and immobility in the postoperative period because of significantly reduced skin and muscle wounds. There is decreased duration of hospital stay and recovery is much faster as compared to open surgery. But one should remember that, there are disadvantages to laparoscopic surgeries. Surgical times may be longer, especially during the learning phase. Laparoscopic surgery can introduce new and serious complications especially anesthetic complications that do not exist or are rare with the traditional approach.[16]

The first recorded successful appendectomy was in 1735 when French surgeonClaudius Aymand[83] described the presence of a perforated appendix within the hernial sac of an 11-year-old boy who had undergone successful appendicectomy. The operation was performed on December 6, 1735, at St. George's Hospital in London. The organ was perforated by a pin the boy had apparently swallowed. The patient, Hanvil Andersen, made a spectacular recovery and was discharged a month later.[17]

There have been some cases of auto-appendectomies, i.e. operating on yourself. One was performed by Evan O'Neill Kane in 1921, but the operation was completed by his assistants. Another case is Leonid Rogozov who had to perform the operation on himself as he was the only surgeon on a remote Antarctic base.[82] In 1981, Semm, from the Universitats Frauenklinik, Kiel, Germany, performed the first laparoscopic appendectomy, published in the journal Endoscopy.

Let us now discuss in brief regarding standard procedure of appendicectomy.

Equipment's:

Before the procedure begins, all equipment must be present in the surgical arena and must be checked for proper working capacity. All methods of laparoscopic appendectomy require the standard laparoscopic equipment, including the following:

- Trocars
- Blunt graspers
- Electro cautery
- Laparoscope, 30º, 10 mm

Positioning

- Place the patient supine and tuck the left arm for initial peritoneal access.
- A single monitor is best positioned to the right of the patient, along the line of the right anterior superior iliac spine (ASIS).
- Upon abdominal insufflation and laparoscope insertion, steep Trendelenburg positioning allows proper placement of the last 2 trocars. After all of the trocars have been placed, placing the patient left side down aids gravity in relocating the small bowel away from the appendiceal/ ceacal field of vision.

Technique:

- Although not mandatory, a Foley catheter is helpful in decompressing the bladder, thereby maximizing the viewing field and improving working space.
- The patient is ready to be positioned as described above and prepared and draped in a sterile fashion.
- Make a 2-cm supra-umbilical curvilinear incision directly below the umbilicus.
- Perform meticulous dissection with use of electrocautery through the subcutaneous tissue, beyond the Scarpa fascia, down to the lineaalba, skeletonizing the fascia. Snowden-PencerHasson "S" retractors provide good visualization and angulation for incising the fascia in a longitudinal direction, for approximately 2 cm. Grasp the just incised fascial edges with 2 straight clamps, allowing both to be brought into the operating field.

- To provide anchoring for placement of the 12-mm Hasson trocar in the future steps, place an Ethicon Vicryl 0 UR stitch in the midline of both fascial edges.
- Continue blunt dissection with the S retractors to allow visualization of the peritoneum. Grasp the peritoneum with 2 straight clamps, side by side, in a horizontal manner. Use the fingertips to palpate the newly grasped peritoneum for any intra-abdominal contents.
- Use Metzenbaum scissors to cut 2-cm longitudinal incisions for entry into the peritoneal cavity. Then gently introduce the Hasson trocar through this defect and initiate $CO_2$ insufflation.
- Meticulously visualize the entire abdominal cavity.
- Place the patient into a steep Trendelenburg position for the placement of the next two 5-mm trocars.
- Place the first trocar to the left of the midline, 1 cm above the pubic ramus. Make a 1-cm horizontal incision. Be mindful of the demarcation of the dome of the bladder, making sure to stay cephalad, when the port enters the peritoneal cavity.
- Place the second 5-mm port 2 cm above and medial to the left ASIS. With the light of the scope, the vessels of the anterior abdominal wall can be highlighted to provide an appropriate roadmap in entering the abdominal cavity.
- Once all of the trocars have been placed and in order to obtain the best visualization of the proposed target, rotate the patient left side down while

maintaining the steep Trendelenburg position. This maneuver allows for the small bowel to retract away from the operating field via gravity.

- Place 2 atraumatic graspers through the 5-mm trocars, assisting the gravitational pull; grasping both the omentum and small bowel, place them toward the left upper quadrant. To visualize the appendix, follow the taenia coli down to its confluence at the base of the ceacum.

- Use the grasper to clutch the tip of the appendix through the suprapubic port, holding it up and out toward the left upper quadrant. This should provide good visualization of the mesoappendix and the appendiceal base.

- The next step is division of the mesoappendix. Once the entire mesoappendix has been coagulated and transected, the appendix should be well skeletonized.
- Remove the scope from the umbilical port and change to a 30º 5-mm scope for placement into the left ASIS port.
- Capitalizing on the angulation of the 30º scope, carefully check all sides of the clip. Make sure the clip is in the appropriate position with nothing inadvertently caught in its jaws.
- Through this entire process, the left hand remains on the tip of the appendix, maintaining the position of up and out toward the left upper quadrant.
- Close the clip and allow 15 seconds to transpire before firing at the base of the appendix; this permits the surface area to become consistent throughout the entirety of the appendix.
- Appendix can be removed out through the infra umbilical 10mm port with the help of grasper and reducer.

- Switch the scopes again (substitute 5 mm for the 10 mm) and place into the original Hassoninfraumbilical port. Again, visualize the appendiceal clip and the mesoappendix for any abnormalities.
- Irrigate and suction this area, as well as the pelvis if required.
- With the right hand, place the suction irrigator through the suprapubic port into the pelvis. With the left hand, using an atraumatic grasper with its jaws spread apart, hold away the pelvic contents through the ASIS port.
- Once irrigation and suction are completed, remove all instruments from the abdominal cavity.
- Under direct visualization, remove all ports beyond the fascia, helping to visualize any active hemorrhage. Cease abdominal insufflation and turn off the light source to the camera/scope. Release the Hasson trocar and remove it from the abdominal cavity.

For closure, place a Vicryl 0 UR stitch, in a figure-of-eight fashion, through the linea alba/fascia to close the infraumbilical port[17]

**Definition of pain**

Pain is a feeling triggered in the nervous system. Pain may be sharp or dull. It may come and go, or it may be constant. 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.[18]

Pain is clinically divided into, acute pain which is primarily due to nociception and chronic pain, which may also be due to nociception, but in which psychological

and behavioral factors often play a major role. Postoperative pain is one of the types of acute pain and can be further differentiated based on the origin and feature into somatic and visceral pain. Somatic pain is due to nociceptive input arising from skin, subcutaneous tissues, and mucous membranes. It is characterized by being well-localized and described as sharp, pricking, throbbing or burning sensation. Visceral pain on the other hand is due to nociceptive input arising from internal organ or one of its covering. It is usually dull diffuse pain which is frequently associated with abnormal sympathetic or parasympathetic activity causing nausea, vomiting, sweating and /or changes in blood pressure or heart rate.[19]

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

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

## 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).[20]

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

**Several types of this pain receptors are 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.

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

**Pain pathway**

Pain is conducted along three neuron pathways; from the periphery to the cerebral cortex.

**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).

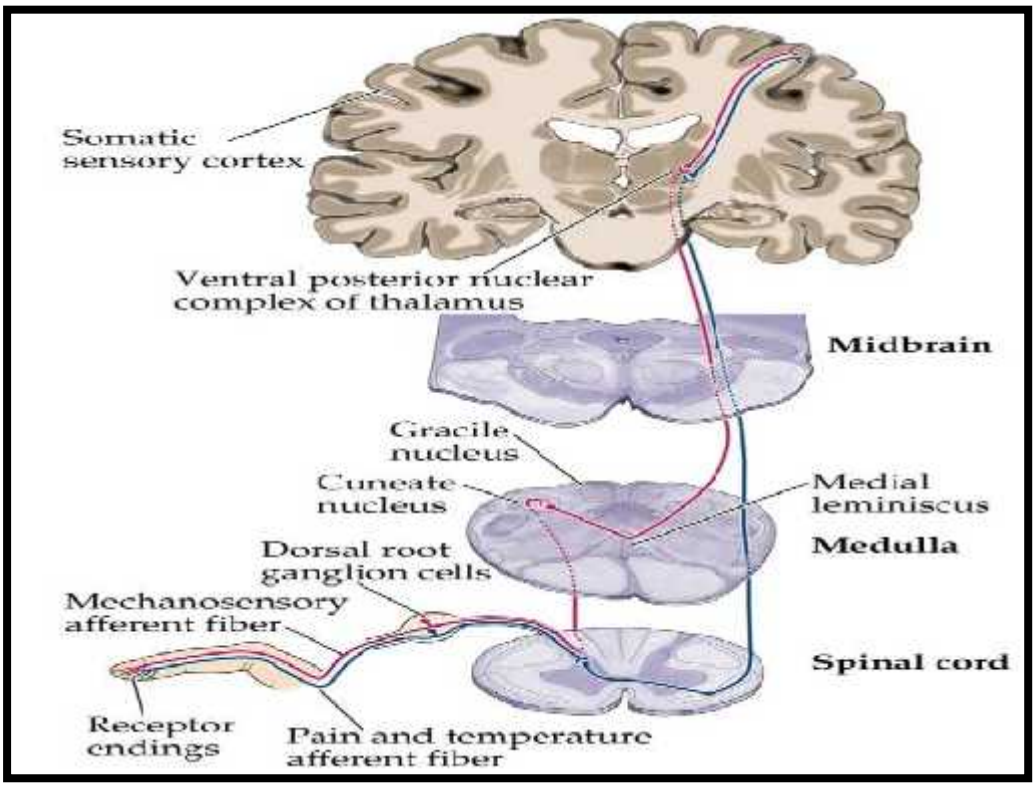



**Fig.1.Pain Pathway**

**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".

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

Axons of most of the second order neurons cross the midline to the contra-lateral side of the spinal cord forming the lateral spin thalamic tract that send its fibers to the thalamus, the reticular formation, nucleus raphe and periaqueductal gray.[21,22]

**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.[22,23,24]

**Pre-emptive analgesia**

In essence,pre-emptive analgesia is a theoretical construct where by the severity of pain that an individual experiences is reduced if some intervention can be applied before this noxious stimulus. It is an attempt to prevent or reduce the peripheral and central sensitization of nociceptors.Hence,Preemptive analgesia is

defined as what is administered before surgical incision that prevent the development of central sensitization from incisionalinjury and inflammatory injuries (that is, intraoperative and postoperative periods).The potential advantages being reduced opoid requirements,early return to normal activities and fewer adverse outcomes. The combination of experimental data and positive clinical trials strongly suggests that preemptive analgesia is a clinically relevant phenomenon. Maximum benefit is observed when there is complete blockade of noxious stimuli.[25]

**Post laparoscopy pain syndrome:**

The majority of laparoscopic operations are performed as short-stay or even day-care surgery. Although pain is less severe and of shorter duration than following open procedures, it can still be sufficiently intense to prevent early discharge. The pain after laparoscopic surgery has a spatial distribution and character that is so unique that it is often referred to as the "post-laparoscopic pain syndrome". Pain arises from the trocar insertion sites, the intra-abdominal trauma and also from the rapid distension of the peritoneum with traumatic traction on blood vessels and nerves, irritation of the phrenic nerve and release of inflammatory mediators. The pain presents as parietal pain in the insertion sites, visceral pain from the intra-abdominal wound and the irritated peritoneum, and pain referred to the shoulder tip, a characteristic feature, or to the back. Post-laparoscopic pain is most frequently located in the upper abdomen, independent of the intra-abdominal localization of the operation site.[7]Pain may occur in the upper abdomen, lower abdomen, back, or shoulders. The greatest incidence of pain is in the upper abdomen.

**Mechanism of pain in laparoscopy**

In addition to the trauma caused to the abdominal wall and the visceral organs by the endoscope and the surgical instruments, there are other mechanisms responsible for pain after laparoscopy. Rapid distension of the peritoneum may be associated with tearing of blood vessels, traumatic traction of the nerves and release of inflammatory mediators. Peritoneal inflammation is probably also the origin of the upper abdominal pain after lower abdominal surgery or after diagnostic laparoscopy. This can persist for at least three days. Peritoneal biopsy performed two to three days after laparoscopy showed peritoneal inflammation and neuronal rupture, and there was a linear inverse relationship between abdominal compliance at the time of laparoscopy and severity of postoperative pain.

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 (pneumo-peritoneum). 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.[26]

**a. Factors associated with gaseous pneumoperitoneum**

**1. Neuropraxia of the phrenic nerve**

It has been suggested that distention of the diaphragm during gas insufflations and the resultant phrenic nerve neuropraxia possibly contribute to postoperative pain, which may include the related C4 dermatome.[27]

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

The phrenic nerves may be damaged by the acid milieu created by the dissolution of $CO_2$. The intraperitoneal pH when $CO_2$ gas is insufflated has been measured at 6.0 immediately postoperatively. On the first postoperative day, 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.[28] Similar values were found when argon gas was substituted.

**3. Residual intraabdominal gas**

Several reports have indicated that residual intraabdominal gas after laparoscopy causes pain. Carbon dioxide dissolution, intraabdominal acidosis, and the consequent peritoneal irritation occur for a longer period if the gas is not evacuated at the end of the laparoscopic procedure. Residual gas also may result in a loss of peritoneal surface tension and support to the abdominal viscera, thus contributing to postoperative pain.[29]

**4. Temperature of gas**

The effect of gas temperature on postoperative pain after gynaecologic laparoscopic procedures has been investigated in a prospective randomized study of standard insufflation gas ($20^0$ C) versus gas at body temperature. This study found that pain reduction was significantly greater for those patients in whom warmed gas was used, especially with respect to diaphragmatic and shoulder tip pain, with the lasting effect of three days.[27]

**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.[30] This study demonstrated significantly reduced postoperative pain in patients who underwent humidified gas insufflation. The humidified insufflations showed a trend of less post-operative analgesic consumption, along with shorter hospital stay and earlier return to work. The exact relation between dry gas and postoperative pain is not yet determined, but other animal studies have observed that dry gas insufflation is implicated in ultrastructural damage to exposed membranaes, an effect that was not seen with the use of humidified gas.[30]

**b. Operational factors**

**1. Wound pain**

The number and size of the incisions used vary between different procedures and also between different centers. Local anesthesia administration to the wound created, is recommended by many authors, with significant pain reduction in both open[31] and laparoscopic procedures.[32] Not all studies have shown a significant difference, however for laparoscopic procedures, only small amounts of local anesthesia will be required, minimal side effects are anticipated, and the use of local anesthesia is recommended.[33]

**2. Wound drainage**

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

**c. Socio-cultural and individual factors**

The socio-cultural environment affects hospital stay and recovery time. This variable, encountered on almost a daily basis by most surgeons, was effectively demonstrated in a study comparing the course after laparoscopic cholecystectomy in French and American patients. Postoperation discomfort has resolved within two weeks in 73% of the French and in 93% of the Americans. A higher percentage of the Americans returned to work in a given period than did the French patients.[34]

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

There is a substantial inter individual variation in the incidence and intensity of pain after laparoscopic procedures. The intensity of pain after laparoscopic procedures peaks within the first four to eight hours has been reported to be unbearable up to the first postoperative morning in one third of the patients. It involves three different components with different intensity, time course and pathophysiological mechanisms. These pain components are incisional pain (parietal

pain component); deep intra-abdominal pain (visceral pain component) and shoulder tip pain (presumed referred visceral pain.)

**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 leads to an improved outcome. The latter suggests that effective postoperative pain management is not only human but a very important aspect of postoperative care.[35]

**a. Cardiovascular effects**

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

Although a variety of factors may contribute to the development of postoperative myocardial ischemia, including hypothermia, anemia, 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.[37]

Myocardial oxygen supply may be diminished as a result of pulmonary dysfunction, in particular, atelectasis secondary to pain-induced hypoventilation and pulmonary edema resulting from stress-induced hypervolemia. Other causes of reduced oxygen supply include coronary artery constriction secondary to high circulatory levels of catecholamine and increased coronary sympathetic tone, stress-induced increase in plasma viscosity and platelet-induced occlusion; and serotonin induced coronary vasospasm secondary to platelet aggregation.[38]

**b. Pulmonary effects**

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

Pain increases total body oxygen consumption and carbon dioxide production which 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.[35]

**c. Gastrointestinal effects**

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

**d. Endocrinal effects**

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

**e. Hematological effects**

The stress response causes decrease in the levels of natural anticoagulants, inhibition of fibrinolysis and increase in platelet reactivity which initiate a postoperative hyper-coagulable state. This hypercoagulability causes a series of other events such as deep venous thrombosis and myocardial ischemia.[4]

**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.[20]

**g. Psychogenic effects**

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

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

**h. Development of chronic pain**

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

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

**Measurement of pain**

Pain measurement is done by two methods;

**1. Type I methods**

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

**Physiological indices**

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

**Neuro-pharmacological**

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

**Neurological**

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

**Behavioural**

- Sighing, crying, shouting, trembling.

**2. Type II methods**

It includes either:

**A) <u>Single dimension methods</u>**

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

**B) <u>Multi-dimensional methods</u>**

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

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

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

Although pain is a subjective experience, great attention has been paid to the quantification of this experience. As pain is subjective experience, everyone has different perceptions of that experience. Differences are found in how individuals quantify pain. For example, some individuals would never say that their pain was a

(10) on a scale from (0) to (10). On the other hand, other individuals report their pain as a constant (10) despite looking calm and relaxed. Also, all numeric scales used to measure pain have floor and ceiling effects. If the patients describe their pain to be a (10), there is no way to report an increase in pain intensity. Of 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.[20]

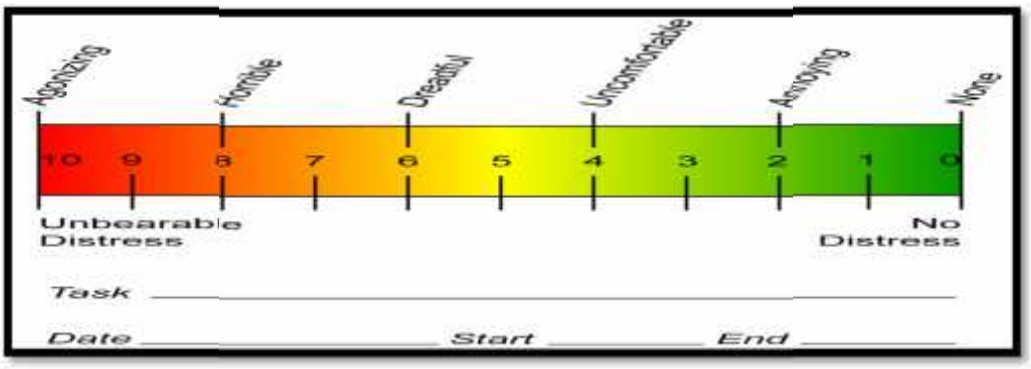



**Fig. 2. Visual analogue scale**

## MANAGEMENT OF POSTOPERATIVE PAIN

### Prophylactic measures

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

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

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

**ACTIVE MEASURES**

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

1. Systemic analgesics and adjuvant drugs.
2. Local infiltrations and field blocks.
3. Regional analgesia with local anaesthetics.
4. Regional analgesia with epidural or intrathecal opioids/ combined local anaesthetics and opioids
5. Non Pharmocological techniques: Electrical analgesia achieved with transcutaneous electrical stimulation or electroacupuncture.[4]

**1. Systemic analgesics and adjuvant**

**Drugs**

a) **Systemic opioids:**

Opioids act as agonists on central and peripheral opioid receptors. They may be administered by many different routes: oral, rectal, sublingual, transdermal, subcutaneous, intramuscular, intravenous, or neuroaxial. The intramuscular route is very often prescribed; however, it is an unpredictable delivery system because of wide swings in drug concentration. Therefore, it requires careful reassessment of the patient. Intravenous infusion administration results in a more constant blood level. , intravenous route provide good and rapid analgesia but produce marked respiratory depression and thus the patient must be observed for 15-20 minutes after first injection to assess pain relief and undesirable side effects.[43]

The drugs commonly used are morphine, meperidine, fentanyl, and hydromorphone. All of the narcotics, with the exception of remifentanil, have active metabolites that can result in an enhanced effect with impaired excretion or prolonged use. The metabolites of meperidine may cause seizures as they accumulate, and in the elderly patient, meperidine may cause psychosis or delerium as a result of its atropine-like effect on the central nervous system.[43]

Patient-controlled analgesia: used widely for the management of postoperative pain. The advantages of this modality are that the patient can obtain pain relief without waiting for a caregiver, no painful injections are required, and the patient retains a certain amount of control. The safety of this system depends on the proper functioning of the pump and its use by the patient alone, not someone else such as a well-meaning family member. The patient has to be conscious to activate the system. If a continuous infusion mode is used, a better level of analgesia may be provided, but the safety factor may be lost. In this mode, it would be prudent to carefully reassess the patient with a sedation score.[43]

Recent machines also provide a continuous infusion of analgesic which give the patient uninterrupted sleep but can lead to an increase in the total quantity of analgesic given.[44] Morphine is the least expensive and perhaps the most popular, but the development of side effects (pruritis, nausea, dysphoria) may require switching to an alternative.[45]Pumps also has got a “lock-out” system which provides an adequate time delay for the patient to achieve analgesia from each injected dose, and also guards against over dosage that can lead to respiratory depression

**1) <u>Oral opioids</u>:** can be very effective and can be used to rapidly wean a patient off parenteral therapy, thereby allowing earlier discharge from the hospital. Oxycodone as a controlled-release tablet can provide good pain control for up to 12 hours. This may be supplemented by oxycodone immediate-release concentrated solution or capsule for breakthrough pain. The use of oral opioid; immediate and sustained release preparations provides quick and effective analgesia and can be used to bridge the analgesic gap that is often apparent after patient-controlled analgesia has been stopped and the simple analgesics begins.[4]

Whatever the route of administration the cardinal rule is to give the patient sufficient amount of analgesic drug to provide effective sustained pain relief, with minimal side effects. Optimal doses of narcotics given to patients in pain depress the respiratory center slightly; they decrease the ventilation/perfusion abnormality and thus improve oxygenation of arterial blood, equally important the fact that pain relief permits patients to breath more deeply and to cough somewhat better when they are instructed by nursing and surgical staff.[43] Although opioid analgesics are effective in treating postoperative pain, concerns regarding their ability of increase nausea and vomiting and to produce respiratory depression have limited their use during laparoscopic procedures.

**<u>2) Transdermal opioids (Fentanyl patches)</u>:** provides excellent alternative, especially when oral route is not allowed. Transdermal route avoids hepatic first-pass metabolism and provide analgesia for two to three days, however its slow onset and the inability to rapidly change dosage in response to changing opioid requirement can limit its use.[4]

**3) Peripheral opioid analgesia:** Clinical studies have demonstrated that small doses of morphine applied peripherally to the site of tissue damage produce significant analgesia with minimal side-effects.[46]The majority of opioid-related side effects are associated with their central nervous system actions, so much; recent work has concentrated instead upon the presence and functions of opioid receptors on peripheral sensory nerves, endogenous opioid agonist production by inflammatory leukocytes, and work on the development of novel selectively peripherally acting opioid agonist. Inflammatory cells play a major role in peripheral opioid analgesia by migrating to and delivering opioid peptides to the receptors expressed by the sensory nerve terminal at the very site of tissue damage.

Having been attracted to injured and inflamed tissues, the extravasated inflammatory cells' production of opioids is governed by corticotrophin releasing hormone, interleukin-1B and catecholamines. Interestingly, effective central afferent nerve blockade modulates the recruitment of opioid producing inflammatory cells to damaged tissues. However studies demonstrated that the analgesic effect of peripherally applied opioids is only apparent in the presence of inflammation.

**Side effects:**

The goal of postoperative pain management is to relieve pain while keeping side effects to a minimum. After hundreds of years of advances, the mainstay of pain therapy is still the opioids. While they are very effective analgesics, opioids also carry with them many undesirable side effects: sedation, respiratory depression, nausea and vomiting, hypotension and bradycardia, pruritus, and inhibition of bowel function. The treatment of complications such as nausea and pruritus may include the

administration of antihistamines, which have an additive effect on sedation and respiratory depression.

Respiratory depression is the major life-threatening complication of opioids. The incidence of severe respiratory depression with patient-controlled analgesia pumps has been reported to be as high as 1 per 10,000 patients. These events are usually associated with an error in management.

No highly sensitive instrument is available to monitor respiratory depression in the extubated patient. The pulse oximeter may be used to monitor respiratory depression in the postanesthesia recovery unit or on the ward when continuous infusions of narcotics are being given, but pitfalls are associated with its use. The pulse oximeter is a poor measure of hypoventilation when the concentration of inspired oxygen is high. Since many postoperative patients receive added oxygen, the pulse oximeter detects respiratory depression very late. The additional oxygen maintains the oxygen saturation while the arterial carbon dioxide pressure may rise to >100 mm Hg.End-tidal carbon dioxide monitoring in the extubated patient is also not very accurate. It depends on adequate ventilation and air movement so that the carbon dioxide level in the nose or mouth reflects that in the alveoli. Depressed ventilation results in paradoxical breathing and little air movement; therefore, the end-tidal carbon dioxide concentration may be artificially low. Respiratory rate measurement also correlates poorly with respiratory depression.

The only noninvasive and readily available monitors of respiratory depression are the observation of paradoxical breathing and the level of consciousness or sedation of the patient. Therefore, respiratory pattern and sedation score should be documented in the charts of patients on opiates.Opioids stimulate circular smooth

muscles causing biliary colic, retention of urine and bronchial constriction which is also partly due to histamine release.[20]

Tolerance**:** When tolerance develops to a particular opioid, cross-tolerance to other opioids concomitantly develops.[48]

**b. Non-steroidal anti-inflammatory drugs**

Nonsteroidal anti-inflammatory drugs are used widely to treat pain and inflammation. They do not carry the same side effects of the opiates; therefore, although they are less potent than the narcotics, they can act as opiate-sparing agents.

The development of more potent and parenteral nonsteroidal anti-inflammatory analgesics such as ketorolac has led to an increase in their use. These drugs are particularly useful in managing the pain associated with minimally invasive surgery. However, associated side effects include peptic ulcer disease, gastrointestinal hemorrhage, renal dysfunction, altered liver function, and platelet dysfunction. These side effects limit the use of these agents in many patients during the perioperative period.

Nonsteroidal anti-inflammatory drugs act by inhibiting the enzyme cyclooxygenase (COX), which is responsible for the synthesis of prostaglandins. Prostaglandins are responsible for pain, fever, and vasodilatation in response to trauma. The major drawback of these medications is that they also block the beneficial effects of the prostaglandins: the decrease in the tissue inflammatory response to surgical trauma and the concomitant reduction in peripheral nociception and pain perception.[25]

NSAIDs have been used early in the setting of major surgery in combination with opioids, and the quality of analgesia from these combinations have been shown

to be better than that achieved by opioids alone. Moreover, it has consistently been shown that NSAIDs given soon after major surgery reduce opioid requirements by about onethird.[25]

NSAIDs can also have idiosyncratic side effects that are not prostaglandin-mediated. Such idiosyncratic reactions are rare but can be serious. These may include exacerbation of bronchospasm, bone marrow toxicity, dermatological reactions, hepatitis and CNS symptoms.

Cox – 2 inhibitors:

There are 2 isoforms of COX: COX-1 and COX-2. COX-1 is found in various tissues. The prostaglandin it produces protects gastric mucosa, limits acid secretion, enhances renal perfusion, and preserves platelet function. COX-2, instead, is induced by pain and inflammation. Therefore, COX-2 inhibitors can alleviate pain and inflammation without the deleterious side effects of the regular non-steroidal drugs, which block both enzymes .

These COX-2 inhibitors are now available for oral use. A parenteral preparation is under clinical trial for postoperative pain control and has been shown to be comparable to ketorolac in analgesia potency but without its deleterious side effects . This new group of analgesics may be safer and may eventually play a more extensive role in the management of acute postoperative pain.[25]

**c. Intravenous paracetamol**

Of the non-opioid analgesics, acetaminophen (also known as paracetamol) is perhaps the safest and most cost-effective non-opioid analgesic when it is administered in analgesic dosages. Although both parenteral and rectal acetaminophen

produces analgesic effects in the postoperative period, concurrent use with a NSAID is superior to acetaminophen alone. There is increasing evidence of a central antinociceptive effect, and potential mechanisms for this include inhibition of a central nervous system COX-2, inhibition of a putative central cyclooxygenase 'COX-3' that is selectively susceptible to paracetamol, and modulation of inhibitory descending serotinergic pathways. Paracetamol has also been shown to prevent prostaglandin production at the cellular transcriptional level, independent of cyclooxygenase activity. Paracetamol is therefore an effective postoperative analgesic, with potency slightly less than a standard dose of morphine or the NSAIDs. The introduction of an IV preparation and reports of the analgesic and anti-inflammatory properties and safety advantages of a nitric oxide (NO) releasing form may represent significant advances in the use of this drug.

**d. NMDA antagonists**

Ketamine is a unique IV anaesthetic with analgesiclike properties that has been used for induction and maintenance of anaesthesia, as well as an analgesic adjuvant during local anaesthesia. As a result of its well known side-effect profile, ketamine fell into disfavor in the late 1980s. However, adjunctive use of small doses of ketamine (0.1 to 0.2 $mgkg^{-1}$ IV) appear to be associated with an opioid-sparing effects and a less frequent incidence of adverse events and greater patient and physician acceptance. Several studies have described the use of small-dose ketamine in combination with local anaesthetics and/or opioid analgesics.[50]

Dextromethorphan, another NMDA receptor antagonist that inhibits wind-up and NMDA mediated nociceptive responses in dorsal horn neurons, has been alleged to enhance opioid, local anaesthetic and NSAID-induced analgesia. In patients

undergoinginguinal herniorrhaphy procedures, dextromethorphan (90 mg po) improved well-being and reduced analgesic consumption, pain intensity and sedation, as well as thermal-induced hyperalgesia.[51]

**e. Alpha-2 adrenergic agonists**

Clonidine also improved and prolonged central neur-axial and peripheral nerve blocks when administered as part of multimodal analgesic regimens. For example, epidural infusion of clonidine in combination with ropivacaine improved analgesia after major abdominal surgery in children. However, when used to treat postoperative pain, clonidine (0.3 mg IV) was apparently ineffective.

**f .Dexmedetomidineis**

A highly selective, centrally active alpha- 2-adrenergic agonist that provides both sedation and analgesia without significant ventilatory depression. Phase III studies in postoperative patients have shown that a continuous infusion of 0.2 to 0.7 μg/kg/hr easily maintains a patient at a Ramsay Sedation Score of 3 with a significant morphine-sparing effect and, most importantly, with no evidence of respiratory depression (21). The properties of this novel drug indicate it could be used intravenously even into the recovery period, with more safety than many presently available sedatives and analgesics. It may lend itself as a sole anesthetic agent for conscious sedation.[52]

**g. Remifentanilis**

A very potent m-opioid receptor agonist that is rapidly metabolized by circulating nonspecific esterases and rapidly cleared. It can provide very controllable analgesia depending on infusion rate. However, there are 2 potential dangers: it is a

very potent narcotic and will cause respiratory depression, and its rapid metabolism means that its analgesic effect will dissipate rapidly once the infusion is terminated.

**h. Miscellaneous non-opioid compounds**

Diverse arrays of non-opioid pharmacologic compounds used during the perioperative period, such as adenosine, droperidol, magnesium, neostigmine, and gabapentin, have been alleged to possess analgesic-sparing properties.

Gabapentin (a structural analog of gammaaminobutyric acid) is an anticonvulsant that has proven useful in the treatment of chronic neuropathic pain and may also be a useful adjuvant in the management of acute postoperative pain. For example, premedication with gabapentin (1.2 g po) reduced postoperative analgesic requirement significantly without increasing side effects.[53]

Magnesium, a divalent cation, is also alleged to possess antinociceptive effects. Bolus dose of magnesium (50 $mgkg^{-1}$ IV) at induction of anaesthesia also led to improved pain control and better patient satisfaction with less opioid medication after major orthopedic surgery. Of interest, intrathecal magnesium was reported to prolong fentanyl analgesia.[54]

Neostigmine, a cholinesterase inhibitor, has been reported to possess analgesic properties when doses of 10 to 200 μg were administered in the subarachnoid or epidural spaces. Although peripherally administered neostigmine failed to produce postoperative analgesia, epidurally administered neostigmine (1 μg/kg) produced more than 5 h of pain relief after knee surgery. The primary adverse effects associated with neuraxial neostigmine appear to be mild sedation and postoperative nausea and vomiting (15% to 30%).[55]

A new antiinflammatory drug, inositol triphosphate, reduced postoperative pain and the need for opioid analgesics after Laproscopic surgeries. However, additional well controlled clinical trials are needed with all of these novel adjunctive drugs.

**2. Local infiltration and field block**

Infiltration of the wounds with dilute solution of lignocaine or use of rectus block for abdominal incision has been found effective in partially relieving postoperative pain after laparoscopy. Nevertheless, preincisional local anaesthetic administration offers an obvious advantage over infiltration at the end of surgery because it can provide supplemental intraoperative analgesia as well as effective analgesia in the early postoperative period after emergence from anaesthesia.[5]

**Regional analgesia with local anaesthetics**

Regional anaesthesia is aimed at anesthetizing a larger part of the body such as a leg or arm.

Regional anaesthesia (or regional anesthesia) is anaesthesia affecting only a large part of the body, such as a limb or the lower half of the body. Regional anaesthetic techniques can be divided into central and peripheral techniques.

The **central techniques** include so called neuraxial blockade

1) Epidural anaesthesia

2) Spinal anaesthesia.

The **Peripheral techniques** can be further divided into plexus blocks such as

1) Brachial plexus blocks

2) Single nerve blocks.

Regional anaesthesia may be performed as a single shot or with a continuous catheter through which medication is given over a prolonged period, e.g. continuous peripheral nerve block. Regional anaesthesia can be provided by injecting local anaesthetics directly into the veins of an arm (provided the venous flow is impeded by a tourniquet.) This is called intravenous regional techniques (Bier block).

This differs from Local anaesthesia, which, in a strict sense, is anaesthesiaof a small part of the body such as a tooth or an area of skin, and

Epidural anaesthesia may be performed at any one of the four segments of the spine (cervical, thoracic, lumbar, and sacral). Sacral epidural anaesthesia is usually referred to as caudal anaesthesia. Thoracic epidural analgesia is technically more difficult and the possibility of injury to the spinal cord is greater.

**a.Epidural analgesia after surgery:**

Epidural analgesia has been demonstrated to have several benefits after surgery, including:

- Effective analgesia without the need for systemic opioids.[83]
- The incidence of postoperative respiratory problems and chest infections is reduced.[84]
- The incidence of postoperative myocardial infarction ("heart attack") is reduced. [85,86]

- The stress response to surgery is reduced.[84,86]
- Motility of the intestines is improved by blockade of the sympathetic nervous system.[84,87]
- Use of epidural analgesia during surgery reduces blood transfusionrequirements.[84]

Despite these benefits, no survival benefit has been proven for high-risk individuals.[85]

**b. Interpleural analgesia**

Interpleural regional analgesia consists of the installation of local anaesthetic in the space between the parietal and visceral pleura through a catheter. The technique is becoming increasingly popular in the treatment of postoperative pain after surgery involving thoracic dermatomes, for example cholecystectomy, splenectomy, nephrectomy, breast surgery, and chest wall operations.[20]

Analgesia after interpleural injection of local anaesthetics seems to be due to the diffusion of the drug through the parietal pleura into the subpleural and then the paravertebral space, where the intercostals nerves are only covered by the parietal pleura, i.e. the effect is via multiple intercostals nerve blockade.[56]

Addition of adrenaline can prolong the duration of analgesia and decrease the absorption of the drug into the systemic circulation which may cause systemic toxicity.[4]

**c. Intraperitoneal analgesia**

The role of intraperitoneal local analgesic instillation is“preemptive analgesia” which refers that previously administeredmedications modulate the arousal of nociception action in

the post-operative period sparing pain-after analgesics. Thepreemptive analgesia prevents the formation of central sensitization to painful stimuli by decreasing response from pain sensation.As a preemptive method current studiesand meta-analysis demonstrates the local anesthesia instillation into the peritoneal space as a safe and effective methodin diminishing early post-operative pain. In various studies,ropivacaine showed less cardiotoxicity and central nervoussystem side effects compared to bupivacaine in same plasmaconcentration even in large dose (300 mg) of intra-peritoneal instillation.[58]

Although studies vary with timing of instillation and type of medications and yet no credible guideline has been established for the maximal effect, the attractive fact that feasible laparoscopic ropivacaine instillation encompasses significant reduction in postoperative pain and decrement of analgesics without toxicity. In this current study instillation of 2 mg/kg of ropivacaine into the subhepaticspace before operation showed significant pain and analgesic reduction on the basis of patients' oriented pain investigation of computerized PCA and VAS score[58]

Intraperitoneal instillation of local anesthetics is another simple, yet effective, technique for providing pain relief during the early postoperative period after laparoscopic procedures. It was found that the response to intra-peritoneal local anesthetics is mediated by local peritoneal effects rather than by systemic absorption. Addition of adrenaline to intra-peritoneal local anesthetic led to a lower peak serum concentration of drug and a delayed time to reach peak serum concentrations when compared to the plain solutions.[57]

Local anaestheticinstillation (Ropivacaine) at the end of laparoscopy prevents postoperative pain and dramatically decrease the need for morphine. This technique

improves patient comfort, shortens the stay in the postoperative care unit and decrease nursing care in the ward.

**3. Regional analgesics with neuro-axial opioids**

Several mechanisms have been proposed to explain movement of opioids between the epidural space and spinal cord including: diffusion through the spinal meninges, preferential diffusion through the spinal nerve root cuff and uptake by radicular arteries traversing the epidural space with subsequent distribution to the spinal cord.

For epidural injection, a dose of 2 to 5 mg of morphine produces analgesia in 15 to 30 minutes and lasts 6 to 24 hours. Epidural injection of 20 to 100 mg of meperidine produces analgesia in 5 to 10 and lasts six to eight hours. Fentanyl, like meperidine, is lipophilic drug that rapidly traverses the dura and penetrates the spinal cord to produce analgesia in 5 to 10 minutes, but lasts four to six hours only. To offset this drawback, the initial bolus can be followed by continuous infusion with an accurately calibrated infusion pump. Sophisticated infusion pumps permit precise titration of opioids; consequently they are used with greater frequency for epidural and subarachnoid administration of these agents.[4]

For subarachnoid injection, the dose of narcotics should be limited to 0.5 to 1 mg morphine, 10 to 30 mg meperidine, or an equi-analgesic dose of some other narcotic diluted to 1 ml in saline. With morphine analgesia develops in 15 to 30 minutes and last 8 to 24 hours while with meperidine analgesia occurs more rapidly and lasts 15 to 24 hours.[4]

Clonidine (selective 2-adrenergic agonists) has shown to have longer lasting analgesia when coadministered with epidural opioids in a dose of 3 to 5 µg $kg^{-1}$. However, it can cause hypotension by central vasomotor effect. Adrenaline also prolongs the analgesia of epidural opioids, possibly due to reduction of vascular uptake.

**4. Regional analgesia with combined local anesthetics and opioids**

This approach combines the advantages of local anesthetics (more rapid analgesia and more effective blockade) and the advantage of opioids (prolonged analgesia).[5]

**Complications of regional anesthesia:**

Unlike a minor local anesthetic infiltration to allow a wound to be sutured, or a skin lesion to be excised, regional anesthesia may involve large doses of local anesthetic, or administration of the local anesthetic very close to, or directly into the central nervous system. Therefore there is a risk of complications from local anesthetic toxicity (such as seizures and cardiac arrest) and for a syndrome similar to spinal shock.

Most regional anesthetic techniques, even in expert hands, have a failure rate of 1–10%. Therefore, general anesthesia may become necessary even when a procedure was initially planned to be conducted under a regional technique.

For these reasons, regional anesthesia is only ever conducted in an environment that is fully equipped and staffed to provide safe general anesthesia should this be needed.

**5. Non-pharmacologic techniques**:

Opioid and non-opioid analgesics all come with potential side effects. Therefore, alternative therapies have been explored with varying success. Electrical stimulation of peripheral nerves may influence pain inhibitory pathways, inhibit substance-P release, and perhaps cause the release of endogenous opiate substances. The efficacy of these modalities in reducing the requirement for conventional pain medications is still controversial.[6]

Other non-pharmacologic approaches that have been used as analgesic adjuvant in the perioperative period include cryo-analgesia, ultrasound, and laser stimulation, as well as hypnotherapy.[6]

**Electrical analgesia**

Another form of postoperative pain control is the use of transcutaneous electrical nerve stimulation (TENS) near the incision site. TENS is often effective in relieving postoperative pain and reducing narcotic requirement. TENS appears to be most effective relieving pain caused by trauma to muscles, bone, and peripheral nerves. TENS also reduce the intensity of exercise-induced pain and facilitated ambulation after abdominal surgery. Patients with fully localized visceral pain and those who are anxious or depressed are less likely to benefit from TENS.[59] Studies suggest that the location, intensity, timing, and frequency of electrical stimulation are all important variables influencing the efficacy of electro-analgesic therapies. Of interest, simple mechanical intradermal needles placed in the paravertebral region before abdominal surgery reduced postoperative pain and the opioid analgesic requirement as well as postoperative nausea and vomiting.[60]

Also transcutaneous acupoint electrical stimulation reduced postoperative nausea, but not vomiting, in outpatients undergoing laparoscopic cholecystectomy.60

**LOCAL ANAESTHETICS PHARMACOLOGY**:

General properties of local anesthetics:

Local anesthetics interrupt neural conduction by inhibiting the influx of sodium ions.

a) Greater lipid solubility enhances diffusion through nerve sheaths, as well as the neural membranes of individual axons comprising a nerve trunk. This property correlates with potency because a greater portion of an administered dose can enter neurons. Because bupivacaine is more lipid soluble than lidocaine, it is more potent and is prepared as a 0.5% concentration (5 mg/mL) rather than a 2%concentration (20 mg/mL).89

b) Like other drugs, local anesthetic vary in their tendency to bind with plasma proteins.This propertyof protein binding correlates with their affinity for protein within sodium channels and predicts the duration they will sustain neural blockade. Bupivacaine has the greatest percent protein binding and is the longest acting of local anesthetics available in dental cartridges.[89]

c) The terminal amine may exist in a tertiary form (3 bonds) that is lipid soluble or as a quaternary form (4 bonds) that is positively charged and renders the molecule water soluble. As explained above, the aromatic ring determines the actual degree of lipid solubility, but the terminal amine acts as an ‘‘on-off switch’’ allowing the local anesthetic to exist in either lipid-soluble or water-soluble conformations. The tertiary and quaternary forms each play a pivotal role in the sequence of events leading to conduction block. For the local anesthetic base to be stable in solution, it is

formulated as a hydrochloride salt. As such, the molecules exist in a quaternary, water-soluble state at the time of injection. However, this form will not penetrate the neuron. The time for onset of local anesthesia is therefore predicated on the proportion of molecules that convert to the tertiary, lipid-soluble structure when exposed to physiologic pH (7.4). The ionization constant (pKa) for the anesthetic predicts the proportion of molecules that exists in each of these states.

d), the acidic environment associated with inflamed tissues favors the quaternary, water-soluble configuration even further. Presumably, this accounts for difficulty when attempting to anesthetize inflamed or infected tissues; fewer molecules exist as tertiary lipid-soluble forms that can penetrate nerves. In these situations, bupivacaine (pKa 8.1) would be least effective and mepivacaine (pKa 7.6) would be most likely to provide effective anesthesia

The myelinated nerves are protected by the myelin sheath which acts as an insulator. There is a resting potential of -70 mV on the outside of the membrane, which rises to about -55 mV, the firing threshold, before it jumps up to +20 mV to form an action potential which constitutes a change of about 90 mV. This is associated with movement s of sodium ions inwards and potassium ions outwards. The membrane becomes depolarized. During recovery, the ions reverse the direction of their movements across the cell membrane. Local anesthetics prevent the depolarization of the nerve membrane and so prevent conduction of impulses.[61]

**Characteristics and Clinical Correlates:**[89]

| Characteristic | correlate | Explanation |
|---|---|---|
| **Lipid solubility** | **Potency** | **Greater lipid solubility enhances diffusion through neural coverings and cell membrane, allowing a lower milligram dosage.** |
| **Dissociation constant** | **Time of onset** | **Determines the portion of an administered dose that exists in the lipid-soluble, tertiary molecular state at a given pH. Agents having a lower pKa have a greater proportion in the tertiary, diffusible state, and this hastens onset.** |
| **Chemical linkage** | **Metabolism** | **Esters are principally hydrolyzed in plasma by cholinesterase's;amides are primarily biotransformed with in the liver** |
| **Protein binding** | **Duration** | **Affinity for plasma proteins also corresponds to affinity for protein at the receptor site within sodium channels, prolonging the presence of anesthetic at the site of action** |

**PHARMACOKINETICS OF LOCAL ANAESTHETICS**

**1. Absorption**

Factors that affect the absorption of local anesthetic are:

a) **Site of injection:** Highly vascular tissues show increase in the systemic absorption of local anesthetic and thus increase toxicity (I.V> tracheal>epidural >subcutaneous).

b) **Presence of vasoconstrictors:** Vasoconstrictors decrease the systemic absorption and thus decrease the toxicity; this is only effective in short acting local anesthetic for example, lignocaine.

c) **Type of local anesthetic:** Local anesthetics with high tissue binding are more slowly absorbed e.g. etidocaine.[20]

**2. Distribution**

Distribution of local anesthetics is affected by:

a) **Tissue perfusion:**Highly perfused organs (brain, liver) show higher uptake than poorly perfused organs (muscles and fat).

b) **Plasma protein binding:**the higher the protein binding the longer the time of retain of local anesthetic in the blood.

**3. Metabolism**

The metabolism and excretion local anesthetics differ depending upon their structure. Ester local anesthetics are predominantly metabolized by pseudo cholinesterase. Also one of the metabolites of ester local anesthetics is P-amino-benzoic acid (PABA) which is highly allergenic. Patients with genetically abnormal pseudo cholinesterase are at increased risk of toxic side effects.

Amide local anesthetics are metabolized by microsomal enzymes in the liver. Decrease in hepatic function or liver blood flow will reduce the metabolic rate and predispose patients to systemic toxicity. And allergic manifestations are less common.[20]

**4. Protein binding**

Local anesthetics are bound to plasma proteins to varying degrees. It is assumed sometimes that drugs with the greatest degrees of protein binding are less toxic because only a small fraction of the total amount in plasma is free to diffuse into the tissues and produce toxic effects. Furthermore, even if a drug is bound to protein, it is still available to diffuse into the tissues down a concentration gradient, as the bound portion is in equilibrium with that in solution in plasma.[4]

**Ropivacaine pharmacology and review:**

**INTRODUCTION:**

Ropivacaine is unique long acting local anesthetic which differs both qualitatively and quantitatively from previously used local anesthetics. Ropivacaine exhibits linear kinetics.

It has lower systemic toxicity than bupivacaine and levobupivacaine. Its wider safety margin allows the use of higher concentrations (up to 10mg/ml) and doses (upto 300mg) compared with Bupivacaine (where the maximum dose recommended is up to 200mg)

Profile of anesthesia with ropivacaine includes short onset time, profound sensory and motor block and motor/sensory separation upon cessation of effect which allows patients to benefit from early mobilization.

It is less potent than bupivacaine and has shorter duration of action. It provides effective analgesia after surgery. It is given by continuous peripheral infusion or infiltration with virtually no motor block, to provide reliable post-operative pain relief

and a reduced need for additional analgesia. The motor/sensory separation, which is a characteristic of ropivcaine has advantages for early mobility post operatively.

Historically, Bupivacaine is used as it had a long duration of action, but subsequently it was found that "propyl derivatives" of pipecoloxylidides were less toxic than 'butyl derivatives' (bupivacaine).Thus Ropivacaine was developed after bupivacaine was noted to be associated with significant number of cardiac arrests.[90]Despite being in the market for close to three decades internationally, it was only introduced in to Indian market very recently.

It is the first local anesthetic to be presented as an almost pure S-enantiomer (>99% pure)[91]It is used as local anesthetic including infiltration, nerve block , epidural and of late for intrathecal anesthesia in adults and children over 12 yrs of age . It is also used for peripheral nerve blocks and caudal epidural anesthesia in children 1 to 12 yrs of age for surgical pain relief.

**CHEMICAL STRUCTURE:**

Ropivacaine is an amino amide class of local anesthetic chemically described as S-(-)-1-propyl-$2^1$, $6^1$-pipecoloxylidide hydrochloride monohydrate. The International Union of Pure and Applied Chemistry name is (S)-N-(2, 6-dimethylphenyl)-1-propylpiperidine-2-carboxamide. The drug substance is a white crystalline powder, with a molecular formula of Ropivacaine is $\mathbf{C_{17}H_{26}N_2O}$ and molecular weight is 274.4 g/mol.The chemical structure is given in the following figure.[92]

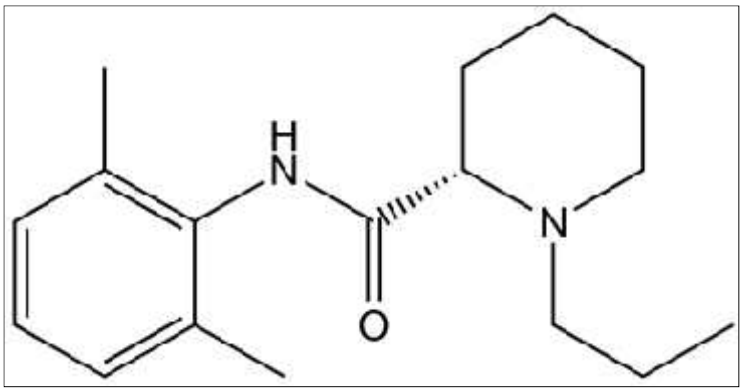



**Fig:3 Chemical structure : Ropivacaine**

**Physical properties:**

Enantiomers exist in two different spatial configurations, like right- and left-handed gloves, and are present in equal amounts in a racemic solution. They are optically active and can be differentiated by their effects on the rotation of the plane of a polarised light into dextrorotatory [clockwise rotation (R+)] or levorotatory [counterclockwise rotation (S-)] stereoisomers. The physicochemical properties of the two enantiomeric molecules are identical, but the two enantiomers can have substantially different behaviours in their affinity for either the site of action or the sites involved in the generation of side effects. R(+) and S(-) enantiomers of local anaesthetics have been demonstrated to have different affinity for different ion channels of sodium, potassium, and calcium; this results in a significant reduction in central nervous system (CNS) and cardiac toxicity (cardiotoxicity) of the S(-)enantiomer as compared with the R(+)enantiomer.[93]

The technological advancements have made it possible to develop Ropivacaine as an optically pure S (-) enantiomeric from the parent chiral molecule propivacaine. It belongs to the group of local anaesthetics, the pipecoloxylidides and has a propyl group on the piperidine nitrogen atom compared to bupivacaine, which has a butyl group.[94]

**MECHANISM OF ACTION:**

**R**opivacaine reversibly interferes with the entry of sodium in nerve cell membranes, leading to decreased permeability to sodium and thus

a. Block generation and conductance of nerve impulses.

b. Slows propagation of nerve impulses

c. Reduce the rate of rise of action potential.

This action is potentiated by dose-dependent inhibition of potassium channels[95].Ropivacaine is less lipophilic than bupivacaine and is less likely to penetrate large myelinated motor fibres; therefore, it has selective action on the pain-transmitting A β and C nerves rather than Aβ fibres, which are involved in motor function.[92]

The order of loss of nerve function is:

1. Pain
2. Temperature
3. Touch
4. Proprioception
5. Skeletal muscle tone

**PHARMACOKINETICS:**

**Absorption:**

The plasma concentration of ropivacaine depends on the total dose administered and the route of administration, as well as the haemodynamic and circulatory condition of the patient and vascularity of the administration site.[96]

When ropivacaine was administered intravenously in subjects, its pharmacokinetics were linear and dose proportional up to 80 mg.[96] The absorption of ropivacaine 150 mg from the epidural space is complete and biphasic. The mean half-life of the initial phase is approximately 14 minutes, followed by a slower phase with a mean absorption $t_{1/2}$ of approximately 4.2 hours.

**Distribution:**

Ropivacaine is bound to plasma proteins to an extent of 94%, mainly to α1-acid glycoprotein. The total plasma concentration increase during continuous epidural infusion of ropivacaine[96,97] is caused by an increase in the degree of protein binding and subsequent decrease in clearance of ropivacaine.[97]

Ropivacaine rapidly crosses the placenta during epidural administration for caesarean section, resulting in near complete equilibrium of the free fraction of ropivacaine in the maternal and foetal circulation.[98] However, the total plasma concentration of ropivacaine was lower in the foetal circulation than in the maternal circulation, reflecting the binding of ropivacaine to α1-acid glycoprotein, which is more concentrated in maternal than in foetal plasma.

**Metabolism:**

Ropivacaine is metabolised extensively in the liver, predominantly by aromatic hydroxylation to 3'-hydroxy-ropivacaine by cytochrome P450 (CYP) 1A2 and N-dealkylation to 2',6'-pipecoloxylidide by CYP3A4.[99,100]

**Excretion:**

The kidney is the main excretory organ for ropivacaine, accounting for 86% of the excretion of the drug in urine after a single intravenous dose administration. It has a mean ± SD terminal half-life of 1.8 ± 0.7 h and 4.2 ± 1.0 h after intravenous and epidural administration, respectively.

**Relative potency:**

A strict correlation exists between the lipid solubility of the local anaesthetic and its potency and toxicity. According to minimum local anaesthetic concentration (MLAC) studies, which are based on effective analgesia in 50% of patients) ropivacaine has similar potency to bupivacaine at higher doses (eg, doses required for peripheral nerve blocks for surgical anaesthesia), ropivacaine is less potent than bupivacaine and levobupivacaine at lower doses, such as those used for epidural or intrathecal analgesia. Providing anaesthesia or analgesia for the majority of patients is more clinically relevant than the MLAC and, at higher doses used in clinical practice, this potency difference is not always evident.

**Tolerability:**

Reactions to ropivacaine are characteristic of those associated with other amide-type local anaesthetics.

In adults at least, Ropivacaine is generally well tolerated regardless of the route of administration[96]. In a pooled analysis of data from controlled clinical trials adverse events that occurred in ≥5% of patients who received ropivacaine 0.125-1% via various routes of administration for surgery, labour, Caesarean section, postoperative pain management, peripheral nerve block or local infiltration (n=1,661)

were hypotension (32%), nausea (17%), vomiting (7%), bradycardia (6%), and headache (5%)[96]. These events are a consequence of nerve block and occurred with similar incidence in patients (n=1433) who received bupivacaine 0.25–0.75% for same indications (29%, 14%, 6%, 5%, and 5%, respectively)[96].

Epidural administration of ropivacaine for surgery generally produced dose-dependent adverse events similar to those observed with equal doses of bupivacaine[96].

The incidence of ropivacaine-induced cardiovascular symptoms may be age-related;[101] patients aged ≥61 years who received epidural ropivacaine 1% had a significantly higher incidence of bradycardia ([58%] vs [15%] patients aged 41-60 years; P=0.005) and hypotension ([74%] vs [20%] patients aged 18-40 years; P=0.002).[101] The cardiovascular events are also related to toxicity due to sudden IV injection or massive absorption from peripheral nerve blocks.

**ADVERSE EFFECTS:**

Excessive plasma levels are due to over dosage, unintentional intravascular injection or slow metabolic degradation. The mean doses at which CNS symptoms of toxicity begin to occur in human beings are 4.3 and 0.6micro grams/ml of the total and free plasma concentrations respectively. When prolonged blocks are used the risks of reaching a toxic plasma concentration or inducing local neural injury are increased. Various possible side effects are:

a.Injection site pain

b.Cardiovascular system toxicity : Vasovagal reaction , syncope , postural hypotension , non specific ECG abnormalities.

c.Gastrointestinal system toxicity:Fecal incontinence , tenesmus , nausea , vomiting

d. Central nervous system toxicity: Tremor, Horner's syndrome, Dyskinesia, Neuropathy, vertigo, convulsion and coma. Because of depressant effect of Ropivacaine on medulla, excitatory stage of CNS might not occur.

**MANAGEMENT OF COMPLICATIONS**:

Discontinuation of Ropivacaine should be done at the first sign of toxicity. As no specific antidote is available, symptomatic and supportive management should be done promptly. Any change in mentation need oxygen administration. Secure airway and provide assisted ventilation if any signs of respiratory depression are observed..Convulsions can be treated with Barbiturates, specific anticonvulsants or neuro muscular blockers. In case of cardiac arrest, prolonged resuscitative efforts might be required.

**CARDIOTOXICITY AND CNS TOXICITY IN COMPARISON TO BUPIVACAINE:**

The incidence of cardiotoxicity and central nervous system (CNS) toxicity as a result of inadvertent intravascular injection of ropivacaine appears to be low[102]. According to a pooled analysis of data from ≈3000 patients in 60 clinical studies, the incidence of probable accidental IV injection of ropivacaine was ≈0.2% (six patients) and only one patient experienced convulsions; no patient showed symptoms of cardiotoxicity.[102]

The convulsive local anaesthetic doses of bupivacaine and ropivacaine were studied in different animal models; bupivacaine has a 1.5- to 2.5-fold lower convulsive threshold when compared to ropivacaine. On the basis of animal and

volunteer studies, it can be concluded that ropivacaine seems to be less neurotoxic and cardiotoxic than bupivacaine.

**DRUG INTERACTIONS:**

Ropivacaine should be used with caution in patients receiving other local anaesthetics or agents structurally related to amide-type local anaesthetics, since the toxic effects of these drugs are additive.

Cytochrome P4501A2 metabolises ropivacaine to 3-hydroxy ropivacaine, the major metabolite. Thus, strong inhibitors of cytochrome P4501A2, such as fluvoxamine, given concomitantly during administration of ropivacaine, can interact with ropivacaine and thus lead to increased ropivacaine plasma levels. Caution should be exercised when co-administering CYP1A2 inhibitors. Possible interactions with drugs known to be metabolised by CYP1A2 via competitive inhibition such as theophylline and imipramine may also occur.[103]

# METHODOLOGY

The present study was conducted in the Department of General Surgery, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum over a period from January 2011 to December 2011 on 60 patients with posted for elective laparoscopic Appendicectomy

**Study design**

The study design was one year randomized clinical trial.

**Study period and duration**

The present one year study was conducted during the period of January 2011 to December 2011.

**Source of data**

Patients admitted in Department of Surgery, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum posted for elective laparoscopic appendicectomy in between age group 18 to 80 years.

**Method of collection of data**

**Sample size**

Present study was conducted on 60 adult patients of either sex between age group 18 to 80 years of ASA-1 and ASA-2 undergoing elective laparoscopic Appendicectomy.

**Sampling procedure**

The sample size was calculated based on the formula mentioned below.

$N= 2 (Z\alpha + Z\beta)^2 pq / d^2$

Where $P = p1 + p2 / 2$

**Randomization**

A total of 60 patients divided into two groups of 30 patients each randomly by computer generated randomization sheet.

**Selection criteria**

***Inclusion criteria***

- Adult patients with age between 18 to 80 years of both sexes.
- Patients undergoing elective laparoscopic appendicectomy with ASA-1 and ASA-2 grade under general anaesthesia

***Exclusion criteria***

- Patient's refusal.
- ASA grade III and IV.
- History of previous abdominal surgery.
- Patients with
    - Allergy to protocol drug.
    - Conversion to open appendicectomy is done for any reason.
    - Drain is placed.
- Patient suffering from chronic pain disease other than appendicitis

- Any patient who has received opioids or tranquilizers treatment for more than one week before appendicectomy

The study was approved by the Ethical and Research Committee of Ethics Committee, Jawaharlal Nehru Medical College, Belgaum. Patients admitted in the wards of Department of General Surgery at KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum undergoing elective laparoscopic appendicectomy were evaluated based on selection criteria. The selected patients were briefed about the nature of the study and a written informed consent was obtained (Annexure–I). Demographic data like gender and age were collected along with relevant history and recorded on predesigned and pretested proforma (Annexure-II).

Enrolled patients were explained about the use of visual analogue scale employed in this study. Further the patients were divided into two groups of 30 patients each randomly using computer randomization table.

**Group A (Study group):** Patients received 20 ml 0.75% of ropivacaine at peri portal sites at the start of surgery before insertion of laparoscope ports.

**Group B (Placebo group):** Patients received 20 ml normal saline at peri portal sites at the same location.

All patients received alprazolam 0.5 mg orally and ranitidine 150 mg orally night before surgery. All patients underwent similar general anaesthetic procedure.

All patients were premedicated with Inj Fentanyl 2micro grn/kg , Inj midazolam 0.04mg/kg.

General anaesthesia was induced using 5 $mgkg^{-1}$ thiopentone, 1$ugkg^{-1}$ fentanyl, and the trachea was intubated after succcinylcholine 2 $mgkg^{-1}$ was taken effect. General anaesthesia was maintained by controlled mechanical ventilation with 0.5mac halothane and oxygen/nitrous oxide mixture (50%/50%). The mechanical ventilation was set to maintain the $PaCo_2$ between 32 and 40 mm Hg depending on the different stages of laparoscopy. Muscle relaxation was maintained with vecuronium 0.08 $mgkg^{-1}$ initially and repeated every 20 minutes thereafter. The neuromuscular blockade was antagonized systematically with neostigmine 0.05 $mgkg^{-1}$ and glycopyrrolate 0.01 $mgkg^{-1}$. Monitoring consisted of electrocardiography, pulse oximetry, end-tidal capnography, and non invasive blood pressure.

The laparoscopic procedure was done in standard fashion. The peritoneal cavity was insufflated using a $CO_2$ pneumoflater at an intraperitoneal pressure of 12 mm Hg.

After the induction of anaesthesia patients were randomly assigned to one of two groups in a double-blinded manner.

Patients in group a received 20 ml of peri portal infiltration of 0.75% Ropivacaine at port sites before the start of surgery before the placement of ports. Patients in group B received 20 ml of normal saline at port sites before the start of surgery. The surgeon was blinded for the nature of the solution used.

Before Supra umbilical incision was taken, 2ml of Drug or Normal saline was infiltrated intracutaneously in that region. After skin incision, the Fascia, muscle, preperitoneal space and parietal peritoneum were infiltrated with 8 ml of drug/saline.

In each remaining two Trocar sites, 5 ml of drug/saline was infiltrated in similar manner.

The residual $CO_2$ was evacuated carefully at the end of surgery by manual compression of the abdomen with open trochars.

Post operatively the patients were assessed for pain utilizing visual analogue scale (VAS). The time of arrival in the postoperative recovery ward was defined as zero hour postoperatively. Pain intensity was measured at fixed time interval. The patients dose of rescue analgesia were assessed at every half hourly for first 6 hrs and then at 10, 18,24 hours.

**VAS Score**

Visual analogue scale consists of a 10 cm scale representing varying intensity of pain from 0 (no pain) to 10 (worst pain).

Rescue analgesics Inj. diclofenac 75 mg IM, was given when VAS was more than 4 postoperatively, which was given by the ward staff who were unaware of the nature of the intraoperative analgesia

The doses of post operative analgesia for breakthrough pain was assessed. Pain assessment was done by the investigator, who was blind to the group allocation of the patient and to any postoperative analgesia administered.

# RESULTS

The objective of the present study was to compare the effect of peri portal infiltration of 0.75% Ropivacaine for pain relief following laparoscopic Appendicectomy. The study was carried out in Dept of Surgery, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum between the periods January 2011 to December 2011.

The study included 60 patients of ASA grade I and II in the age group of 16 to 80 years. Each group consisted of 30 patients divided by computer generated randomization table as;

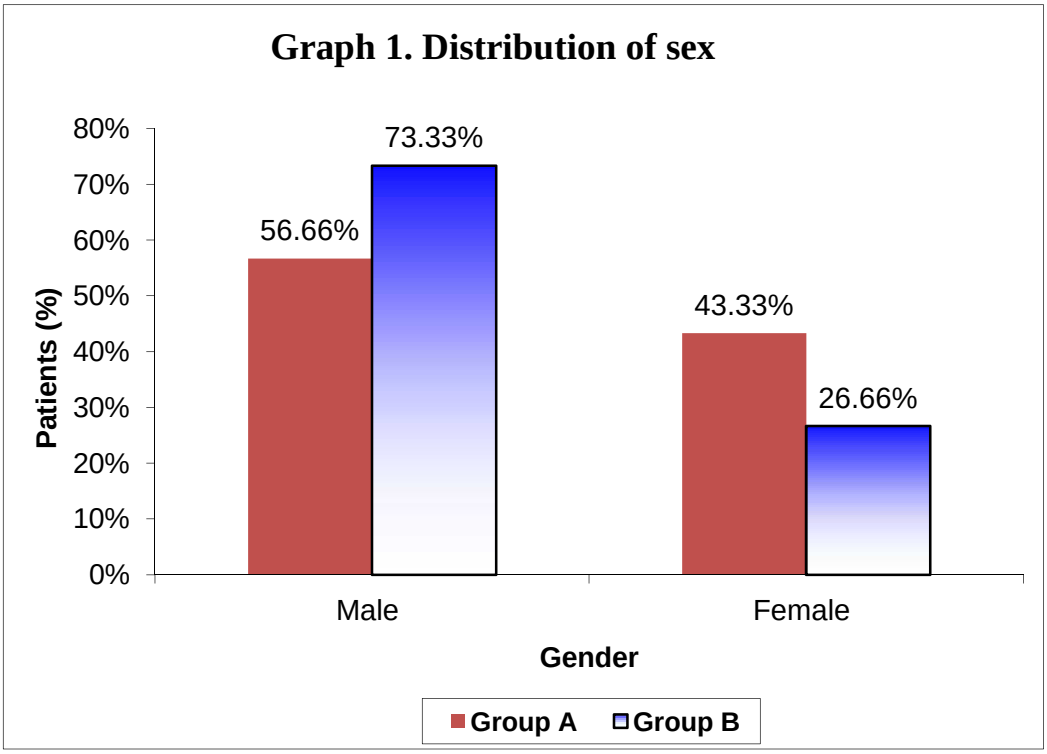
Group A - Ropivacaine group (n=30)

Group B - Saline group (n=30)

Data was collected in both groups and observations of the analyzed data are presented in the tabular form as follows.

**Table 1. Distribution of sex**

| Groups | Male | | Female | |
|---|---|---|---|---|
| | Number | Percentage | Number | Percentage |
| Group A | 17 | 56.66 | 13 | 43.333 |
| Group B | 22 | 73.33 | 8 | 26.66 |

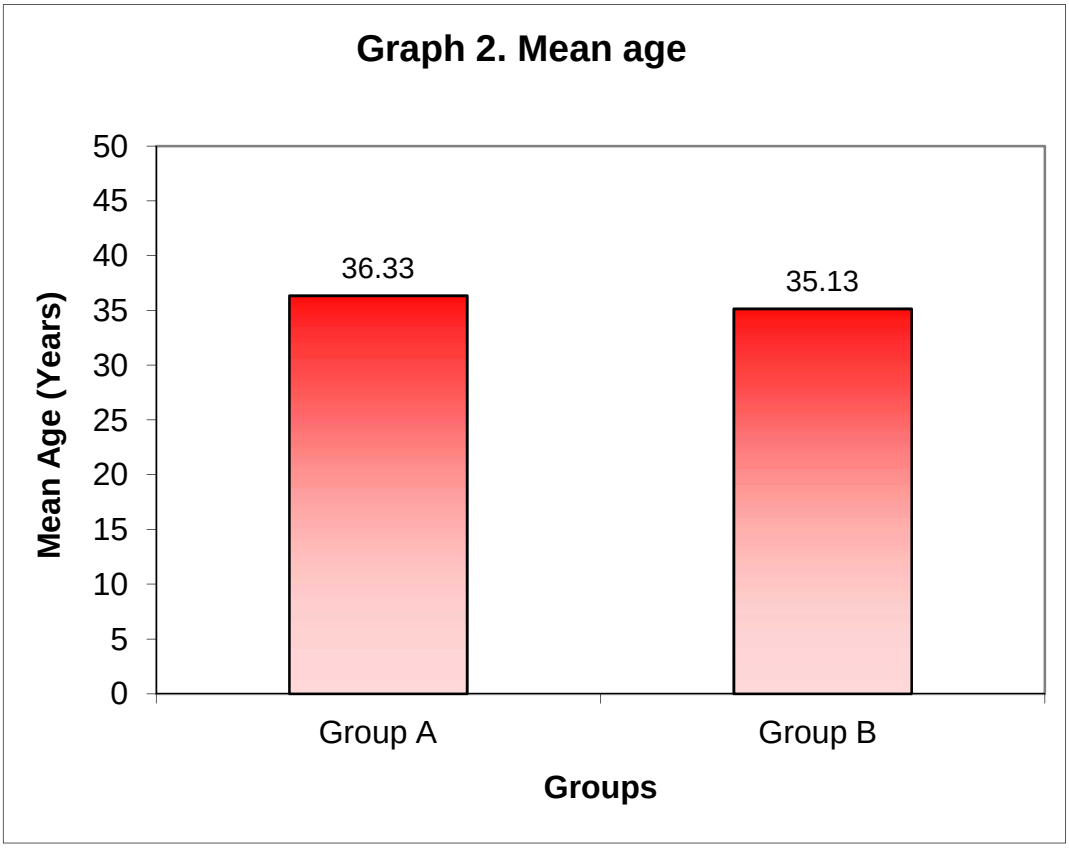



The distribution of sex was similar in both the groups with 56.66% males and 43.33% females in Group A and 73.33 % males and 26.66% females in Group B. Both the groups were comparable with p value of 0.176.

**Table 2. Mean age**

| Groups | Age (Years) | |
|---|---|---|
| | **Mean** | **S.D.** |
| Group A | 36.33 | 13.66 |
| Group B | 35.13 | 13.05 |

p= 0.006 (not significant).




The mean age in group A was 36.33 ± 13.66 and in group B it was 35.13 ± 13.05 years which was comparable in both the groups (p=0.006 ).Mean age of group one is more as compared to group two the difference is not statistically significant .Male and female distribution between the two groups does not differ(p=0.176)

**Table 3. Comparison of hemodynamic parameters**

| Parameters | Group A | | Group B | | p value |
|---|---|---|---|---|---|
| | Mean | S.D. | Mean | S.D. | |
| Pulse rate (/min) | 83.26 | 9.758 | 77.9 | 14.77 | 0.107 |
| SBP (mm Hg) | 109.93 | 10.05 | 118.3 | 12.88 | 0.07 |
| DBP (mm Hg) | 70 | 8.71 | 75.6 | 8.97 | 0.06 |
| Respiratory Rate (/min) | | | 14.44 | 1.04 | 0.787 |

The mean pulse rate in group A is 83.2+ or _ 9.75 per minute and in group B it was 77.9 ± 14.77 per minute.

The mean systolic blood pressure was 109.9 ± 10.05 mm Hg in group A and 118.3 ± 12.88 mm Hg in group B.

The diastolic blood pressure in group A was 70 ± 8.71 mm Hg and in group B it was 75.6 ± 8.97.

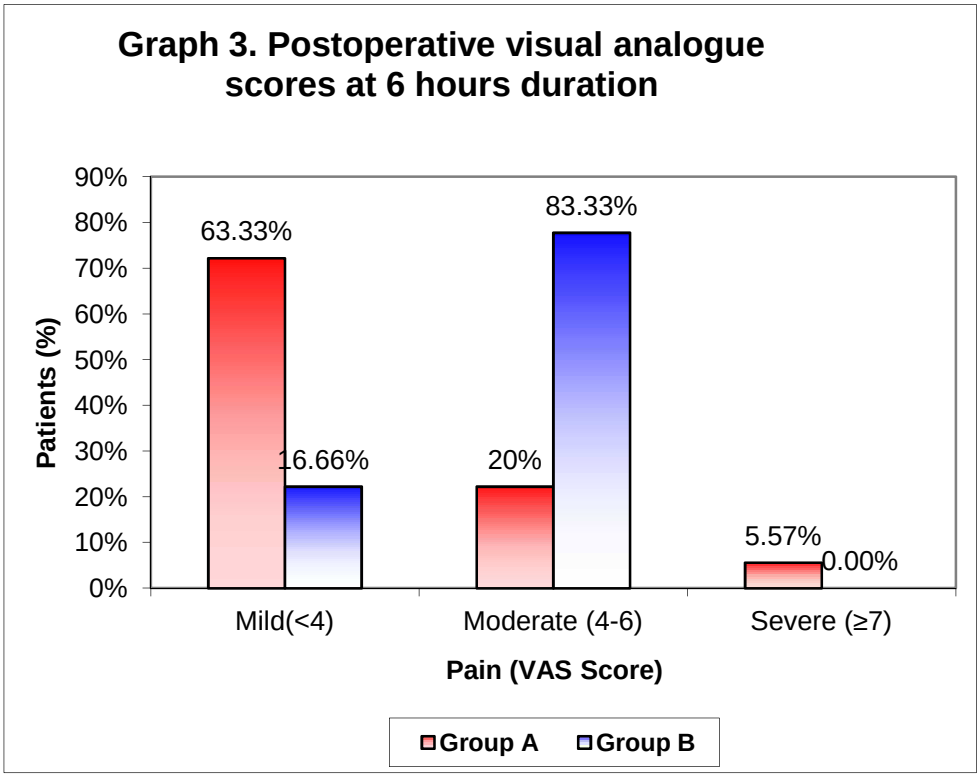
The respiratory rate in groups A and group B was 14.61 ± 2.38 per minute and 14.44 ± 1.04 per minutes respectively.

All these haemo dynamic parameters in group A and group B were comparable in both the groups and statistically not significant (p>0.05)

**Table 4. Postoperative visual analogue scores at 6 hours duration**

| Pain (VAS Score ) | Groups | | | | p value |
|---|---|---|---|---|---|
| | Group A | | Group B | | |
| | No. | % | No. | % | |
| Mild (≤4) | 24 | 80 | 5 | 16.66 | |
| Moderate (4-6) | 6 | 20 | 25 | 83.33 | |
| Severe (≥7) | 0 | 0.00 | 0 | 0.00 | |
| Mean VAS Scores | 1.8±1.6 | | 4.6±1.61 | | <0.001* |

*Statistically significant

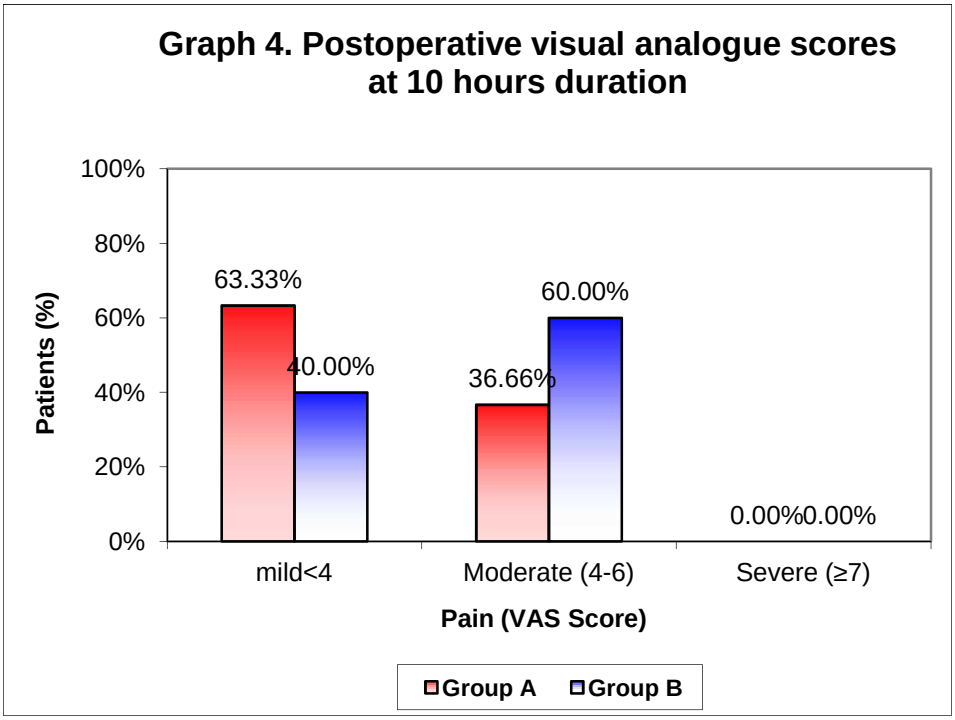



In group A, at six hour duration, significantly more number of patients (63.33%) experienced mild pain (VAS scores ≤ 3) compared to 83.33% patients in Group B who had moderate pain (VAS scores 4 to 6) (p=<0.001).

**Table 5. Postoperative visual analogue scores at 10 hours duration**

| Pain (VAS Score ) | Groups | | | | p value |
|---|---|---|---|---|---|
| | Group A | | Group B | | |
| | No. | % | No. | % | |
| Mild (≤4) | 19 | 63.33 | 12 | 40 | |
| Moderate (4-6) | 11 | 36.66 | 18 | 60 | |
| Severe (≥7) | 0 | 0.00 | 0 | 0.00 | |
| Mean VAS scores | 1.8±2.05 | | 3.1±2.43 | | 0.026* |

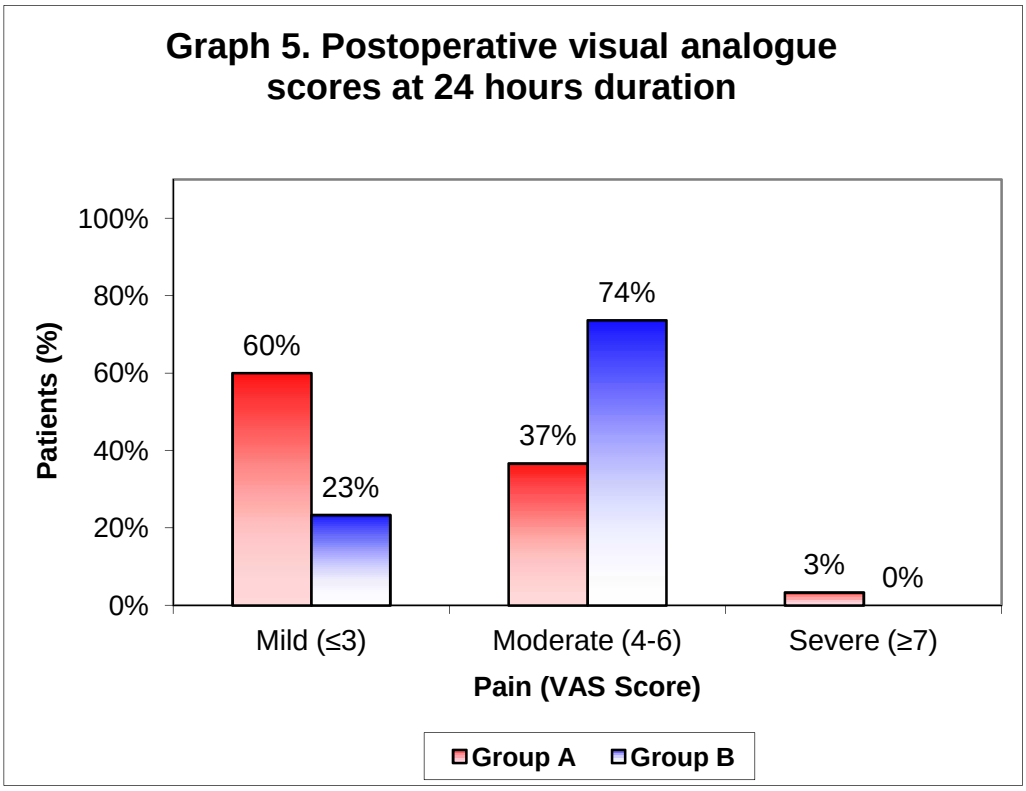
*Statistically significant




At 10 hour duration, majority of patients in group A (63.33%) experienced mild pain and 36.66% patients had moderate pain. In Group B majority of the patients had (60%) moderate pain and 40% patients had mild pain. This difference was statistically significant (p=0.026). None of patient in both group A and B reported severe pain.

**Table 6. Postoperative visual analogue scores at 24 hours duration**

| Pain (VAS Score ) | Groups | | | | p value |
|---|---|---|---|---|---|
| | Group A | | Group B | | |
| | No. | % | No. | % | |
| Mild (≤4) | 18 | 60 | 7 | 23.33 | |
| Moderate (4-6) | 11 | 36.66 | 23 | 73.66 | |
| Severe (≥7) | 1 | 3.33 | 0 | 0.00 | |
| Mean VAS Scores | 2.4±2.75 | | 3.9±2.35 | | 0.02* |



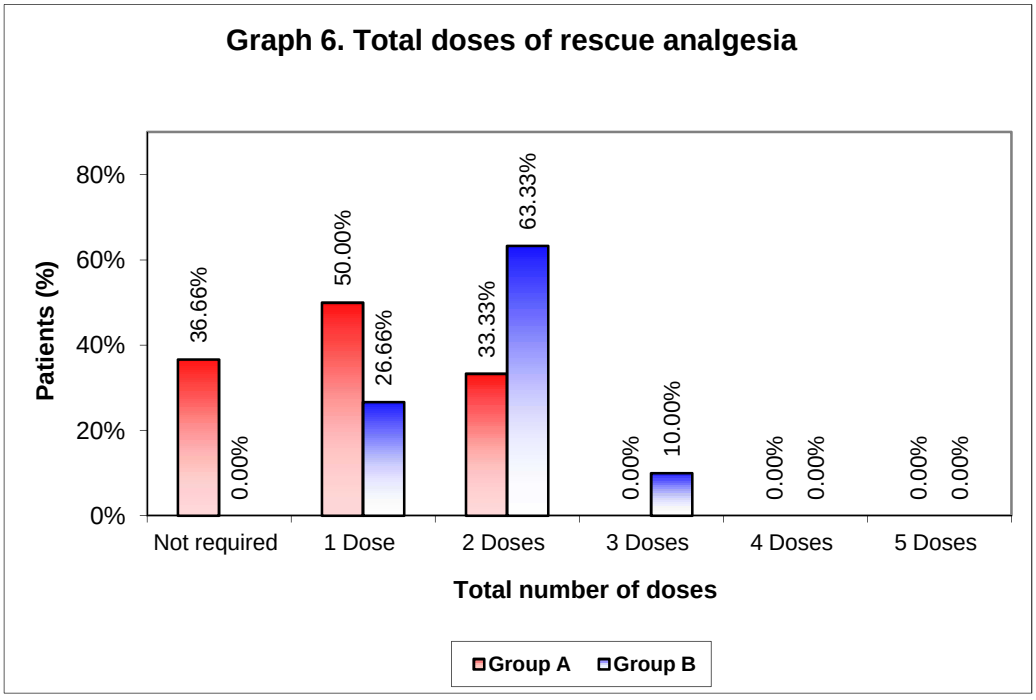

At 24 hour duration,60% patients in group A and23% patients in group B experienced mild pain and this difference was statistically not significant (p=0.020).

At each time of observation, mean VAS of group 2 is significantly more as compared to group1 with p value being p=0.0001 (statistically significant )

**Table 7. Total doses of rescue analgesia**

| Total number of doses | Group A | | Group B | |
|---|---|---|---|---|
| | Number | Percentage | Number | Percentage |
| Not required | 11 | 36.66 | 0 | 0.0 |
| 1 Dose | 15 | 50 | 8 | 26.66 |
| 2 Doses | 4 | 33.33 | 19 | 63.33 |
| 3 Doses | 0 | 0.0 | 3 | 10 |
| 4 Doses | 0 | 0.0 | 0 | 0 |
| 5 Doses | 0 | 0.0 | 0 | 0 |

p=0.0001 statistically significant




In this study among patients with group A majority of the patients (50%) required one dose of rescue analgesia whereas in group B majority of the patients (63.33%) required three doses of rescue analgesia. This difference was statistically significant (0.0001).

**Table 8: Comparision of Mean VAS Scores at 6 , 10 . 24 hrs duration in both the groups**:

| | 6 hrs | 10 hrs | 24 hrs |
|---|---|---|---|
| Group A | 1.8±1.62 | 1.8±2.05 | 2.4±2.75 |
| Group B | 4.6±1.61 | 3.1±2.43 | 3.9±2.35 |
| P values | <0.001* | 0.026* | 0.020* |

*= statistically significant

# DISCUSSION

Although minimal invasive surgery is characterized by reduced pain, it is not painless. Patients undergoing laparoscopic Appendicectomy suffer considerable pain on the day of surgery frequently requiring narcotic analgesia.

Pain after laparoscopic Appendicectomy comprises of several components.[64] The parietal pain is due to placement of trocars through the abdominal wall. The visceral pain is because of intraperitoneal dissection and insufflation of $CO_2$ resulting in distension of abdominal wall and prolonged elevation of diaphragm leads to shoulder tip pain.[26,27,28] The parietal pain is superficial and can be located by the patient on the other hand visceral pain is dull, more diffuse in nature and difficult to locate. Studies show that blocking receptors before nociceptive stimulation eliminates the onset of pain. Visceral pain can theoretically be blocked by intraperitoneal instillation; and parietal pain can be blocked by portside infiltration.[65,66]

Our study was done to know analgesic efficacy of periportal infiltration of Ropivacaine versus periportal infiltration of saline for postoperative analgesia following laparoscopic Appendicectomy.

Despite the large variation in the pain scores, differences in mean pain scores between the study and placebo group during the first six hours and 12 hours were found to be statistically significant. Although we expected the effect of the local anaesthetic to wear off after the period of six to eight hours, there was no increase in the pain score at 24 hours postoperatively in the patients who received Ropivacaine. For the placebo group pain scores peaked immediately and was maximum during the first 12 hours after the surgical procedure and thereafter declined to the level comparable to that for the Ropivacaine group by 24 hours postoperatively. Therefore, the main effect of Ropivacaine in this study seems to have been in amelioration of pain peak occurring during the initial 12 hours after the surgical procedure.

We have shown that preemptive periportal infiltration of 0.75% Ropivacaine at the begining of laparoscopic Appendicectomy significantly reduced abdominal pain scores, and this was confirmed by the lower total dose of diclofenac 23 doses compared to 55 doses given in placebo group, which were given postoperatively, and the longer time for the first requested analgesia in the study group. Hence on an average, every person in study group received 0.7 dose of rescue analgesia where as every person in pacebo group received on an average of 1.8 doses of rescue analgesia.

Similar study done by Pavlidis et al for laparoscopic cholecystectomy and laproscopic inguinal hernia repair found that pain score and analgesic dose required were lower in Ropivacaine group.[8]

Goldstein a et al compared 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.[64]

Local anaesthetics infiltration has been found to be effective for post operative analgesia in other laparoscopic surgeries.

Pappas-Gogos et all conducted a randomized double blind controlled trial of preincisional and intraperitoneal ropivacaine plus normal saline infusion for post operative pain relief after laproscopic cholecystectomy which concludes that Preincisional local infiltration plus intraperitoneal infusion of ropivacaine at the beginning of Laproscopic Cholecystectomy combined with normal saline infusion at the end of the procedure is a safe and valid method for reducing pain after Laproscopic Cholecystectomy.[67]

Cha SM et al , conducted a study on Peritrocal and Intra peritoneal Ropivacaine for Laproscopic Cholecyctectomy in 80 patients which

concluded that peritrocal infiltration of ropivacaine significantly decreases parietal pain and intraperitoneal instillation of ropivacaine significantly decreases the visceral and shoulder tip pain. Their effects are additive with respect to the total pain.[57]

The effect of pre emptive and post operative application of local anaesthetics in laparoscopic surgery was studied and concluded that pre emptive application of local anaesthetics reduces the post operative pain and analgesic requirements after laparoscopic fundoplication better than laparoscopic herniorraphy.[72]

There are a few other studies in which local anaesthetic infiltration has failed to show the efficacy. These failure could be because of use of lower dosage, lower concentration or uneven infiltration at various sites, variations in surgical technique, general anaesthesia, differences in infiltration technique and post operative care.[68,73,74]

Randomized control studies on effect of periportal local anaesthetic infiltration in laparoscopic surgeries on overall pain.

Table:9

| Study | Pavlidis et al | Thue Bisgard et al-1999 | Cha SM et al-2011 | Di Pace MR et all-2009 | Present Study |
|---|---|---|---|---|---|
| No of patients: (Treatment/ Control gr) | 75 (LC)+20(LIHR)/ 75 (LC)+20(LIHR) | 25/25(LC) | 20\20\20\20(LC) GrA:Peritrocal+Intraperitoneal Saline GrB:Peritrocal saline+Intraperitoneal Ropivacaine GrC:Peritrocal Ropivacaine+Intra peritoneal Saline GrD:Peritrocal Ropivacaine+Intraperitoneal Ropivacaine | 10/10/10(All Laproscopic surgeries) GrA : Peritrocal Ropivacaine GrB : Peritrocal ropivacaine+intra peritoneal Ropivacaine GrC : No analgesic | 30/30 (LA) |
| Ropivacaine(%/volume) | (10mg/ml) **Preincisional infiltration** Total-20ml 7ml-10mm ports 3ml-5mm ports | 0.75%-for infiltration 2% for instillation ***After incision:*** 24ml periportal infiltration ***After surgery(before closure):*** 34ml instillation+infiltration to gall bladder | 0.75%-for infiltration 2% for instillation ***Post operative infiltration and instillation*** | 0.75%-for infiltration 2% for instillation ***Post operative infiltration and instillation*** | ***Preincisional infiltration*** 0.75%-total 20ml in all ports 10 ml-umbilical port 5ml- each port |
| Overall pain | P<0.05.No analgesia was required in 41% of LC patients and 85% of LIHR in study gr. | Overall pain($p<0.01$) Incisional pain:($p<0.05$) | Significantly ↓VAS Scores in GrC from 2 to 24hrs and Gr D from 2 to 12 hrs for parietal pain | . Six and 12 hours postoperatively, the abdominal parietal pain was significantly higher ($P < 0.0005$) in group C than in the other two groups, both treated with an infiltration at the trocar sites | Significantly ↓ in first 6 to 12 hrs ($p<0.05$) post operatively |
| Comments | Total analgesic requirement reduced significantly in study group | Median morphine requirement was 0 at first 3 hrs($p<0.05$) with Ropivacaine No of patients requiring supplementary analgesia also significantly reduced with ropivacaine($p<0.05$) TNS also significantly reduced. | Peritrocal infiltration significantly reduces parietal pain and its effects are additive with intraperitoneal instillation with respect to overall pain | combination of local infiltration and intraperitoneal instillation of ropivacaine is more effective for pain relief in children after laparoscopic surgery | main effect of Ropivacaine in this study seems to have been in amelioration of pain peak occurring during the initial 12 hours after the surgical procedure.. Total doses of rescue analgesia used significantly reduced in Ropivacaine group |

NS - No significant difference between study and control group.

p < 0.05 - Statistically significant difference between study and control group.

--- - Not evaluated.

Gr - Group

VAS - visual analogue score.

TNS -Total Nausea Scores

LC - Laproscopic Cholecystectomy

LIHR - Laproscopic Inguinal Hernia Repair

LA - Laproscopic Appendicectomy

In the study by Bisgaard et al.,a combination of incisional and intra-abdominal infiltration and instillation with Ropivacaine significantly reduced over all pain ,morphine requirements and Nausea during the first three post operative hours after Laproscopic Cholecystectomy.[64]

In above table it could be seen that,

In a study done by Di Pace MR et al,it is observed that abdominal parietal pain was significantly higher (P < 0.0005) in group C than in the other two groups, both treated with an infiltration at the trocar sites. Rescue analgesic treatment was significantly higher in group C, if compared to groups A and B 12 hours after the operation .Hence, this study demonstrated that local infiltration significantly reduces the parietal pain and combination of local infiltration and intra peritoneal instillation of ropivacaine is more effective for pain relief in children

after laparoscopic surgery than the administration of ropivacaine only at the trocar sites.[70]

In a study conducted by Callesen et al reported reduced abdominal pain and reduced Nausea and vomiting following combined port site infiltration and peritoneal instillation with ropivacaine after Laproscopic sterilization , a procedure which is associated with significant post operative pain .In Ropivacaine group,abdominal pain scores were significantly lower in the first 4 hrs.($p<0.00001$),use of morphine was less($p<0.001$)and fewer patients had Nausea in the first 72 hrs($p<0.05$).There were no signs off anaesthetic toxicity.[71]

Ropivacaine is a relatively safer drug and a local infiltration of ropivacaine is less likely to cause any side effects unless it is accidentally injected intravascularly.

Ropivacaine is well tolerated, and has less potential for CNS toxicity and cardiovascular toxicity than Bupivacaine. Ropivacaine has lower affinity for cardiac sodium channels and a more rapid release from them compared to bupivacaine.this reduces the risk of accumulation and cardiac toxicity.[Arlock1988]. Ropivacaine interferes less with myocardial calcium channels and the ATP synthesis in mytochondria,

altogether resulting in less negative ionotropism and less of arrhythmias than with bupivacaine.[75]

Ropivacaine has better CNS and CVS tolerability than bupivacaine.[76]In double blind cross over volunteer studies[76], The mean Ropivacaine dose to maximum tolerable CNS effects was 12-25% larger than that of bupivacaine.The mean tolerated total venous plasma concentration after ropivacaine was higher than after bupivacaine in the study.[76,77]

Our study showed modest overall analgesic effect during the first 12 hours. There was also no shoulder tip pain. The use of local anaesthetic infiltration, as in our study, for efficacious postoperative analgesia should allow widespread use in laparoscopic surgery.

**Limitation of the study:**

1. Study was conducted in comparision with placebo

**Future scope of the study**:

1. Since the study was carried out with only periportal infiltration and was found to be significantly effective, the study combining both periportal infiltration and intraperitoneal instillation of ropivacaine can be carried out for better results.

2. In our study, Ropivacaine was compared with placebo .A study can be carried out comparing Ropivacaine with much routinely used drug bupivacaine .

# CONCLUSION

Ropivacaine is found to be significantly effective in preventing post operative pain over the first 12 hours after laparoscopic Appendicectomy when infiltrated periportally before the start of laproscopy i.e preemptively. Periportal infiltration of Ropivacaine has significantly reduced the need for diclofenac compared with pacebo. Port site infiltration is safe and effective procedure with very minimal side effects. Infiltration of local anesthetics should be considered in all patients undergoing laparoscopic procedures. Ropivacaine is better choice as compared to bupivacaine and other local anesthetics because of fewer side effects and better sensory blockade and preemptive application is better as the receptors are blocked before the sensitization and hence onset of pain is prevented.

# SUMMARY

Laparoscopic Appendicectomy is one of the simple, safest and most common laproscopic surgeries performed. Even though, laproscopic surgery involves less surgical trauma as compared to open surgery, post operative pain especially in early post operative period is the most frequent complaint. Now days, there are various techniques available to combat this early post operative pain. Pain after laparoscopic Appendicectomy can be either incisional or visceral pain.

There will be $CO_2$ entrapment beneath the hemidiaphragms, leading to damage to abdominal wall structures, the induction of visceral trauma and inflammation, and peritoneal irritation. Reduction in surgical stress responses is the main cause for decrease in the incidence of postoperative organ dysfunction and thereby to an improved outcome. Acute pain is typically associated with neuroendocrine stress response that is proportional to the intensity of pain. This suggests that effective postoperative pain management is very important aspect of postoperative care. Uncontrolled postoperative pain is the worst post operative complication and has an adverse sequel of delayed resumption of normal pulmonary function, restriction of mobility (thus contributing to thromboembolic complications), nausea and vomiting, increase in the systemic vascular resistance, cardiac work, and myocardial oxygen consumption through an increase in the catecholamine release induced by the stress response.

It was suggested that periportal infiltration of local anaesthetic may provide an effective postoperative parietal pain relief after laparoscopic Appendicectomy. Unfortunately, studies in which local anaesthetics have been used in this setting have provided conflicting results. Most of these initial studies have used small doses of

Ropivacaine. By contrast, other recent studies that have used larger doses and concentrations have demonstrated that periportal infiltration of Ropivacaine can be effective. Ropivacaine, an amide local anaesthetic has a reduced systemic and cardiac toxicity as compared with ropivacaine which was evaluated by several studies.

In our study we compared the effect of periportal infiltration of normal saline versus periportal infiltration of Ropivacaine on the postoperative pain following laparoscopic Appendicectomy. The demographic data and duration of surgery were similar in both groups. Patients receiving periportal infiltration of Ropivacaine showed significantly lower pain scores ($p<0.05$).

The dose of diclofenac given as rescue analgesia postoperatively was significantly less in the Ropivacaine group ($p<0.0001$)

So, we believe that periportal Ropivacaine administration is more effective than saline in controlling postoperative abdominal pain. Hence we recommend its use as a part of multimodal analgesic technique for laparoscopic Appendicectomy.

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# ANNEXURE I - CONSENT FORM

**YOUR PARTICIPATION**

You Mr/Mrs/Ms. _____ I.P. No. _____ are being asked to be a participant in the research study titled "A RANDOMISED PLACEBO CONTROLLED TRIAL TO ASSESS POST OPERATIVE ANALGESIA WITH PERIPORTAL INFILTRATION OF 0.75% ROPIVACAINE IN LAPAROSCOPIC APPENDICECTOMY".

A one year randomized controlled trial conducted by Dr. _____ Postgraduate Student, Department of General Surgery, JNMC, Belgaum. You are eligible after looking into inclusion criteria. You read this form and ask any questions you may have before agreeing to participate.

**RESEARCH BEING DONE**

To compare Post operative analgesia with periportal infiltration of 0.75% ropivacaine and placebo in laparoscopic appendicectomy

**Purpose of the research**

- To study the postoperative analgesic effect of 0.75% Ropivacaine following Periportal infiltration in laparoscopic Appendicectomy

**Procedures involved**

You will be randomly allocated either into group A or group B, if you are in group A you will receive 20ml 0.75% Ropivacaine periportally around the port sites at the start of surgery before the insertion laparoscope port and if you are in group B

you will receive 20 ml normal saline periportally at the same location. Post operative pain will be assessed with visual analogue scale at 6 hrs, 12 hrs and 24 hrs.

**Potential risks and discomforts**

- No serious side effects.

**Benefits of taking part in this research**

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

**Other option**

**Decline from participation**

You have the option to decline from participation in the study without any discrimination and you will be treated as per the existing protocol for your condition.

**New information**

All information collected during the study from participant will be told as and when required.

**Privacy and confidentiality**

Privacy of individual will be respected and any information about you or provided by you during the study will be kept strictly confidential.

**Injury as a result of participation**

There will neither be any compensation to or for the patient and his or her relatives nor there any monetary benefits for the damage incurred.

**Costs of participation in this research**

Participation is free of cost.

**Reimbursement for any expenses for participation in research**

No reimbursement for any of your expenditures

**Withdrawal or be removed**

To start with as the participation was voluntary so is the decision to withdraw. Such a step will not alter the participant's management by any staff in hospital. Researcher can remove you from the study if circumstances arise.

Signature of the participant or legally authorized person

| | |
|---|---|
| Participants name: | Witness name: |
| Signature: | Signature: |
| Date: | Place: |

# ANNEXURE - II

## PROFORMA / QUESTIONNAIRE TO BE USED FOR DATA COLLECION

**The proposed proforma / questionnaire to be used for data collection for the study tilted "TO EVALUATE THE ANALGESIC EFFICACY OF PERIPORTAL INFILTRATION OF 0.75%ROPIVACAINE VS PLACEBO FOR POST OPERATIVE PAIN RELIEF FOLLOWING LAPROSCOPIC APPENDICECTOMY, A DOUBLE BLINDED RANDOMIZED CONTROL TRIAL, HOSPITAL BASED STUDY" is as:**

**PATIENT DETAILS:**

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

**NAME:** **D.O.S:**

**SEX:** **D.O.D:**

**AGE:**

**OCCUPATION:**

**ADDRESS:**

Chief Complaints: YES / NO duration

PAIN ABDOMEN: ☐ ☐

SITE OF PAIN -

- RIGHT ILIAC FOSSA ☐

TYPE OF PAIN: ☐ RADIATING

THROBBING / PRICKING TYPE / DULL ACHING TYPE

☐ ☐ ☐

INTENSITY:

| MILD | MODERATE | SEVERE |
|---|---|---|
| | | |

FEVER: YES / NO

DURATION -

DEGREE OF FEVER--

| MILD | MODERATE | SEVERE |
|---|---|---|
| | | |

TYPE OF FEVER----

| CONTINUOUS | INTERMITTENT | SPIKING |
|---|---|---|
| | | |

Past History:

GENERAL EXAMINATION:

BUILT AND NOURISHMENT:

WEIGHT:

PULSE:

BP:

R/R:

TEMPERATURE:

| | |
|---|---|
| PALLOR | |
| ICTERUS: | |
| CYANOSIS: | |
| CLUBBING | |
| LYMPHADENOPATHY | |
| EDEMA | |

SYSTEMIC EXAMINATION:

PER ABDOMEN - TENDERNESS YES/NO

- RIGHT ILIAC FOSSA
- AROUND UMBILICUS
- BOWEL SOUNDS

| | NORMAL | ABNORMAL FINDINGS: |
|---|---|---|
| RESPIRATORY- | | |
| CVS- | | |
| CNS- | | |

INVESTIGATIONS:

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

FBS : ( )

Blood Urea ( )

Sr. Creatinine ( )

Urine :

Routine

Microscopy

GROUP: GROUP A / GROUP B

| | |
|---|---|
| | |

| | | | | |
|---|---|---|---|---|
| | | | | |

OPERATION DETAILS: -

DATE OF SURGERY:
NAME OF SURGERY: LAPROSCOPIC APPENDICECTOMY

ANAESTHESIA: GENERAL ANAESTHESIA

DURATION OF SURGERY:

ASSESSMENT OF POST OPERATIVE PAIN - VISUAL ANALOGUE SCALE

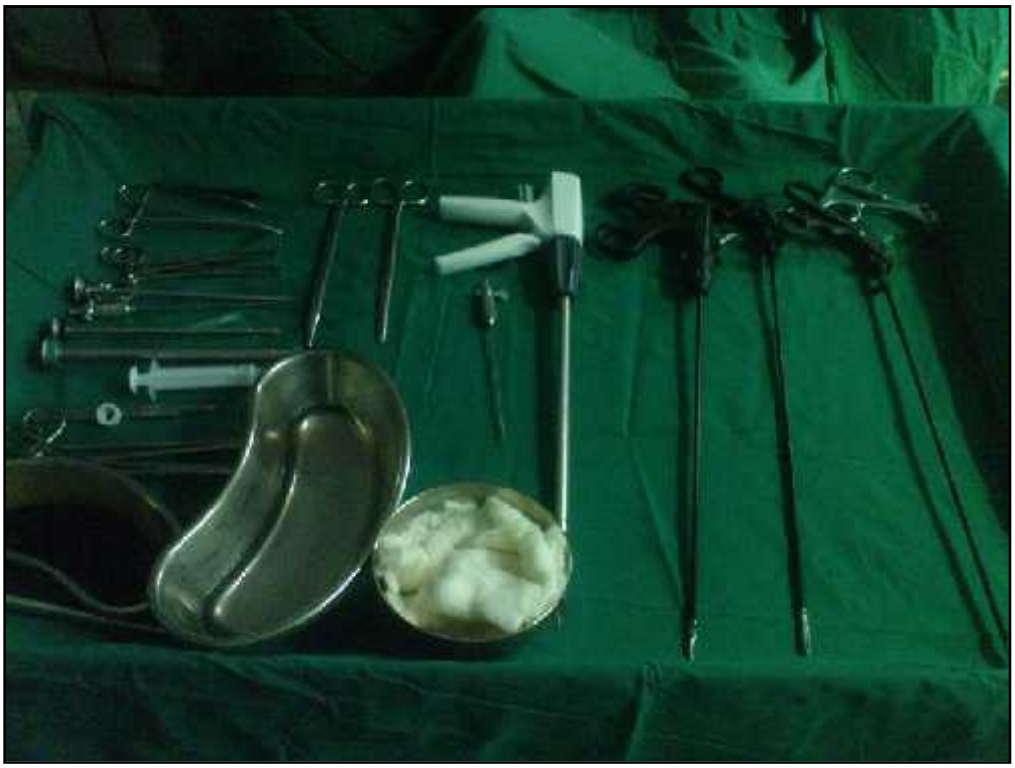
Postoperative pain according to visual analogue score during post operative period at the end of:

| 0 min | 6hrs | 10hrs | 24 hrs |
|---|---|---|---|
| | | | |

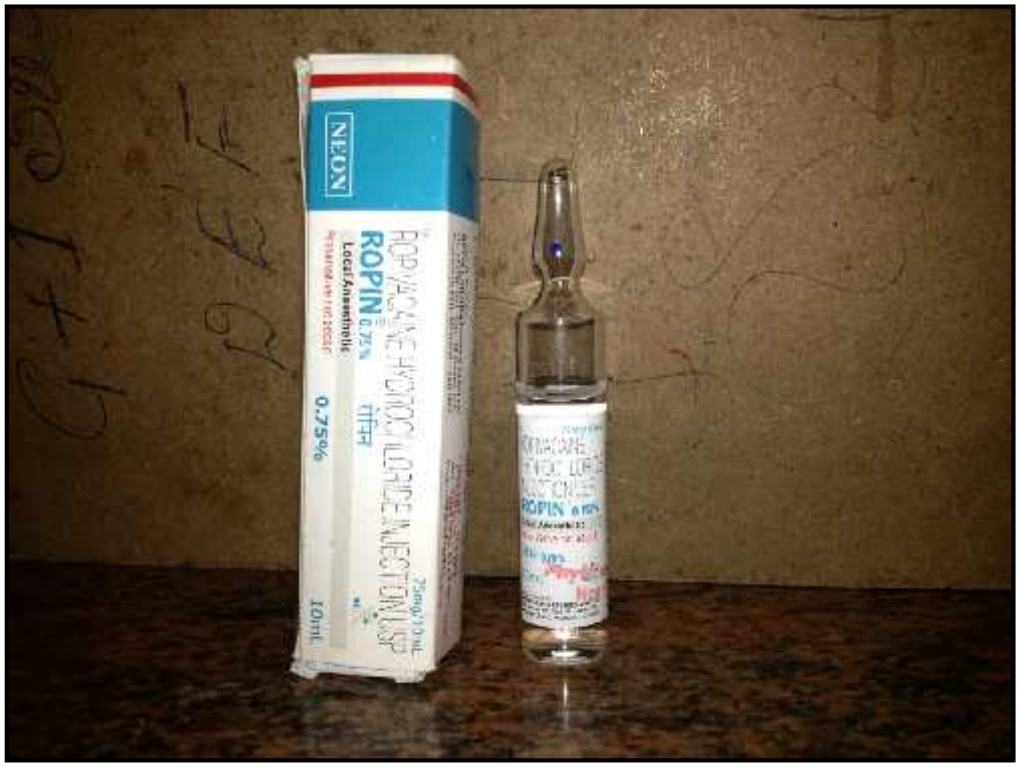
# ANNEXURE – III
# PHOTOGRAPHS

**Photograph 1. Monitor, gas insufflator, light source**

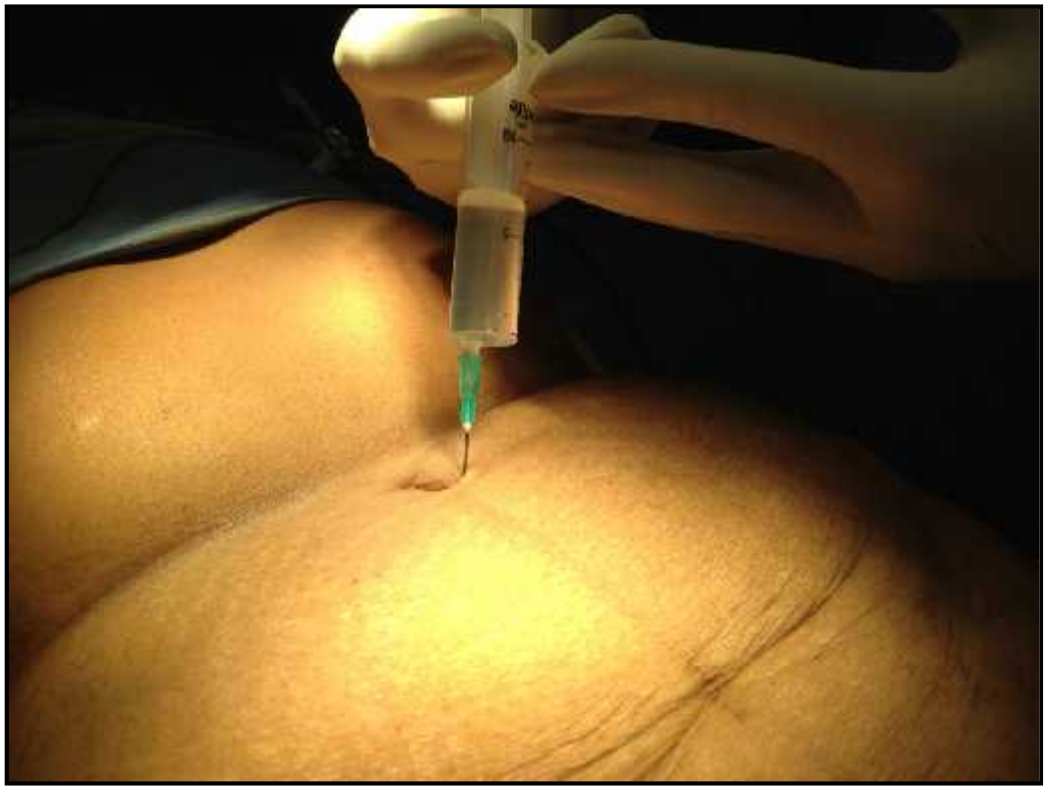
**Photograph 2. Laparoscopic instruments**



**Photograph 3. Ropivacaine ampoules**




**Photograph 4.Preemptive periportal infiltration**



# ANNEXURE – IV

## KEY TO MASTER CHART

| | | |
|---|---|---|
| ASA | : | American Society of Anesthesiologists |
| DBP | : | Diastolic Blood Pressure |
| F | : | Female |
| IP NO. | : | Inpatient number |
| M | : | Male |
| min | : | Minute |
| mm Hg | : | Millimeter of mercury |
| N | : | No |
| PR | : | Pulse Rate |
| RA | : | Rescue Analgesia |
| SBP | : | Systolic Blood Pressure |
| Sl. No. | : | Serial Number |
| VAS | : | Visual Analogue Scale |
| Y | : | Yes |

**GROUP - A**

| Sl.No. | IP No | Age(yrs) | Sex | ASA grade | pulse rate | SBP | DBP | VAS Score | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | 6 hrs | 10 hrs | 24 hrs | RA | RA <6hrs |
| 1 | 446384 | 28 | M | ASA 1 | 92 | 110 | 70 | 0 | 0 | 4 | 1 | 0 |
| 2 | 387431 | 33 | M | ASA 1 | 82 | 110 | 70 | 2 | 0 | 0 | 0 | 0 |
| 3 | 446165 | 32 | M | ASA 1 | 86 | 114 | 70 | 0 | 0 | 0 | 0 | 0 |
| 4 | 444988 | 33 | M | ASA 1 | 92 | 110 | 70 | 0 | 4 | 0 | 1 | 0 |
| 5 | 443641 | 70 | M | ASA 2 | 72 | 110 | 70 | 0 | 0 | 0 | 0 | 0 |
| 6 | 441493 | 21 | F | ASA 1 | 72 | 100 | 60 | 0 | 0 | 2 | 0 | 0 |
| 7 | 439361 | 19 | F | ASA 1 | 92 | 110 | 70 | 0 | 0 | 0 | 0 | 0 |
| 8 | 391436 | 16 | M | ASA 1 | 98 | 120 | 80 | 4 | 4 | 0 | 1 | 0 |
| 9 | 408324 | 33 | M | ASA 1 | 92 | 114 | 70 | 2 | 0 | 0 | 0 | 0 |
| 10 | 412518 | 26 | M | ASA 1 | 88 | 120 | 80 | 3 | 0 | 0 | 0 | 0 |
| 11 | 423766 | 38 | M | ASA 1 | 72 | 110 | 70 | 2 | 0 | 3 | 0 | 0 |
| 12 | 423842 | 27 | F | ASA 1 | 84 | 110 | 70 | 0 | 0 | 2 | 0 | 0 |
| 13 | 419757 | 33 | F | ASA 1 | 92 | 110 | 70 | 0 | 0 | 4 | 1 | 0 |
| 14 | 420488 | 40 | M | ASA 1 | 82 | 140 | 90 | 0 | 3 | 0 | 0 | 0 |
| 15 | 420828 | 32 | M | ASA 1 | 90 | 110 | 70 | 3 | 0 | 0 | 0 | 0 |
| 16 | 407370 | 34 | M | ASA 1 | 82 | 120 | 80 | 3 | 3 | 6 | 1 | 0 |
| 17 | 422297 | 32 | F | ASA 1 | 84 | 90 | 50 | 0 | 4 | 6 | 1 | 0 |
| 18 | 421824 | 38 | F | ASA 1 | 82 | 130 | 90 | 3 | 6 | 3 | 1 | 0 |
| 19 | 422806 | 22 | M | ASA 1 | 72 | 110 | 70 | 4 | 4 | 0 | 2 | 1 |
| 20 | 411592 | 27 | M | ASA 1 | 88 | 100 | 70 | 2 | 0 | 6 | 1 | 0 |
| 21 | 419757 | 18 | F | ASA 1 | 92 | 90 | 50 | 3 | 3 | 6 | 1 | 0 |
| 22 | 403077 | 38 | F | ASA 1 | 78 | 110 | 70 | 2 | 4 | 0 | 1 | 0 |
| 23 | 404671 | 50 | F | ASA 1 | 74 | 110 | 70 | 3 | 4 | 4 | 2 | 1 |
| 24 | 413073 | 20 | M | ASA 1 | 83 | 110 | 60 | 2 | 0 | 6 | 1 | 0 |
| 25 | 420824 | 29 | M | ASA 1 | 92 | 100 | 70 | 4 | 4 | 10 | 2 | 1 |
| 26 | 398369 | 29 | F | ASA 1 | 92 | 110 | 70 | 4 | 4 | 4 | 2 | 1 |
| 27 | 414768 | 29 | F | ASA 1 | 92 | 100 | 70 | 4 | 4 | 0 | 1 | 1 |
| 28 | 403437 | 28 | F | ASA 1 | 82 | 110 | 60 | 0 | 4 | 4 | 1 | 0 |
| 29 | 435654 | 28 | M | ASA 1 | 59 | 100 | 70 | 0 | 0 | 4 | 1 | 0 |
| 30 | 441385 | 29 | F | ASA 1 | 60 | 110 | 70 | 4 | 0 | 0 | 1 | 1 |

## GROUP - B

| Sl No | IP No | Age | Sex | ASA grade | PR | SBP | DBP | VAS Score | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | 6 hrs | 10 hrs | 24 hrs | RA | RA<6 hrs |
| 1 | 443286 | 31 | F | ASA 1 | 92 | 110 | 70 | 4 | 4 | 6 | 2 | 1 |
| 2 | 407370 | 40 | M | ASA 1 | 82 | 120 | 90 | 6 | 0 | 4 | 2 | 1 |
| 3 | 403437 | 21 | F | ASA 1 | 98 | 110 | 70 | 6 | 6 | 0 | 2 | 1 |
| 4 | 408324 | 33 | M | ASA 1 | 82 | 120 | 90 | 6 | 0 | 4 | 3 | 1 |
| 5 | 422708 | 55 | M | ASA 1 | 92 | 130 | 80 | 0 | 4 | 6 | 3 | 1 |
| 6 | 410666 | 69 | F | ASA 2 | 84 | 140 | 90 | 4 | 6 | 6 | 3 | 1 |
| 7 | 423429 | 46 | M | ASA 2 | 92 | 140 | 90 | 7 | 3 | 6 | 2 | 1 |
| 8 | 425158 | 35 | M | ASA 1 | 98 | 110 | 70 | 6 | 0 | 4 | 1 | 1 |
| 9 | 425216 | 60 | F | ASA 2 | 92 | 140 | 70 | 6 | 6 | 0 | 2 | 1 |
| 10 | 426208 | 26 | M | ASA 1 | 94 | 110 | 70 | 6 | 6 | 0 | 2 | 1 |
| 11 | 428015 | 26 | M | ASA 1 | 92 | 110 | 70 | 6 | 6 | 0 | 2 | 1 |
| 12 | 429340 | 27 | M | ASA 1 | 84 | 110 | 70 | 4 | 4 | 6 | 1 | 1 |
| 13 | 430160 | 36 | M | ASA 1 | 84 | 100 | 70 | 6 | 3 | 4 | 1 | 1 |
| 14 | 428016 | 30 | M | ASA 1 | 92 | 110 | 70 | 6 | 6 | 6 | 2 | 1 |
| 15 | 419091 | 19 | M | ASA 1 | 97 | 110 | 70 | 4 | 4 | 4 | 2 | 1 |
| 16 | 428503 | 31 | M | ASA 1 | 92 | 110 | 70 | 6 | 0 | 0 | 1 | 1 |
| 17 | 431968 | 48 | M | ASA 2 | 84 | 140 | 90 | 4 | 4 | 6 | 2 | 1 |
| 18 | 436524 | 32 | F | ASA 1 | 68 | 130 | 70 | 4 | 0 | 6 | 2 | 1 |
| 19 | 437167 | 29 | F | ASA 1 | 62 | 120 | 90 | 4 | 0 | 5 | 2 | 1 |
| 20 | 436732 | 45 | M | ASA 2 | 64 | 110 | 70 | 4 | 4 | 0 | 1 | 1 |
| 21 | 466746 | 32 | M | ASA 1 | 62 | 110 | 70 | 6 | 0 | 4 | 2 | 1 |
| 22 | 453292 | 33 | M | ASA 1 | 60 | 120 | 70 | 6 | 0 | 4 | 2 | 1 |
| 23 | 454653 | 49 | M | ASA 2 | 65 | 140 | 90 | 4 | 6 | 0 | 1 | 1 |
| 24 | 454744 | 18 | M | ASA 1 | 60 | 110 | 70 | 2 | 4 | 6 | 1 | 1 |
| 25 | 455369 | 16 | M | ASA 1 | 58 | 100 | 70 | 3 | 4 | 4 | 1 | 1 |
| 26 | 455558 | 54 yrs | M | ASA 2 | 62 | 140 | 90 | 4 | 6 | 6 | 2 | 1 |
| 27 | 457320 | 18 | M | ASA 1 | 58 | 110 | 70 | 3 | 4 | 4 | 2 | 1 |
| 28 | 458258 | 29 | F | ASA 1 | 65 | 110 | 70 | 2 | 4 | 6 | 2 | 1 |
| 29 | 460120 | 31 | F | ASA 1 | 60 | 120 | 70 | 4 | 0 | 6 | 2 | 1 |
| 30 | 460442 | 35 | M | ASA 1 | 64 | 110 | 70 | 6 | 0 | 4 | 2 | 1 |