"A RANDOMIZED PLACEBO CONTROLLED TRIAL TO ASSESS POST OPERATIVE ANALGESIA AFTER INTRAPERITONEAL INSTILLATION OF 0.5% BUPIVACAINE IN LAPAROSCOPIC CHOLECYSTECTOMY"

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This is to certify that the dissertation entitled **"A RANDOMIZED PLACEBO CONTROLLED TRIAL TO ASSESS POST OPERATIVE ANALGESIA AFTER INTRAPERITONEAL INSTILLATION OF 0.5% BUPIVACAINE IN LAPAROSCOPIC CHOLECYSTECTOMY"** is a bonafide research work done by **THE CANDIDATE REG NO. BH0108007** in the Department of General Surgery, Jawaharlal Nehru Medical College, Nehru Nagar, Belgaum – 590 010.

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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 cholecystectomy is characterized by reduced postoperative pain, many patients still complain of moderate abdominal and shoulder pain during the first 48 hours. The objective of this study was to compare effect of intraperitoneal instillation of 0.5% bupivacaine versus saline for post-operative analgesia in laparoscopic cholecystectomy.

Methodology

36 adult patients admitted to department of surgery posted for elective laparoscopic cholecystectomy in KLES Dr. Prabhakar Kore Hospital & MRC, Belgaum between age group 18 to 60 years of ASA-1 and ASA-2. 36 patients undergoing elective laparoscopic cholecystectomy were prospectively randomized into 2 groups. **Group (A) – Study group:** Patients received 20 ml 0.5% bupivacaine intraperitoneally at gall bladder bed and under right and left hemidiaphragm at the end of surgery through laproscope port in trendelenburg position. **Group (B) - Placebo group:** Patients received 20 ml normal saline intraperitoneally at the same location. The evaluation of postoperative pain was done at fixed time interval according VAS. Analgesic requirements were analyzed. Shoulder tip pain was also assessed.

Results

Mean pain scores upto 12 hours after surgery were lower in group (A)compared to group (B). This difference was statistically significant ($p<0.05$). The incidence of shoulder tip pain was not significant. 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, bupivacaine is effective in preventing pain over the first 12h after laparoscopic cholecystectomy when intraperitoneally instilled at the end of surgery and also reduces the analgesic requirement.

Key words

Laparoscopic cholecystectomy; Bupivacaine; Post operative pain relief;

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INTRODUCTION

With the expanding role of ambulatory surgery and the need to facilitate an earlier hospital discharge, improving postoperative pain control has become an increasingly important issue.[1]

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

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

Perioperative analgesia has traditionally been provided by opioid analgesics. However, extensive use of opioids is associated with a variety of perioperative side effects, such as ventilatory depression, drowsiness and sedation, postoperative nausea and vomiting, pruritis, urinary retention, ileus and constipation, thus can delay hospital discharge. In addition, it has been suggested by the Joint Commission on Accreditation of Health Organizations that excessive use of postoperative opioids analgesics leads to decrease patient satisfaction.[5]

In addition the use of conventional method of administration of intramuscular opioids in standard prescribed doses, may be too large (causing side effects), or too small (causing inadequate analgesia).Therefore, surgeons and anaesthesiologists are increasingly turning to non-conventional techniques as adjuvant for managing pain during perioperative period to minimize the adverse effects of analgesic medications.[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]

Intraperitoneal instillation of local anaesthetic in combination with general anaesthesia has been investigated in several interventional studies during laparoscopic cholecystectomy. 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, parietal or shoulder pain.[7]

By evaluating the pathophysiology of pain it is shown that we can prevent or reduce pain by blocking the nociceptors before their stimulation by use of local anaesthetics.[8] Bupivacaine 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, a more so to the right upper quadrant and right shoulder tip. The cause of this pain is thought to be related to abdominal muscle distension during laparoscopic procedure, irritative effects of residual carbon dioxide in the abdominal cavity and prolonged elevation of diaphragm by pneumoperitoneum.

Decrease in postoperative pain after infiltration of local anaesthetics into the operative wound have been observed among patients who undergo herniorhaphy and gynecological procedures.[9,10] Postoperative catheter infusion of bupivacaine into the subcostal incision during open cholecystectomy has been shown to decrease atelectasis, and reduce narcotic usage[11]. Continuous postoperative infusion of local anaesthetic agent into the abdominal wounds has reduced both postoperative pain and narcotic requirements.[12,13]

Bupivacaine has a half-life of 2.5 to 3.5 hours and has been reported to provide pain control for an average of six hours.[14] The margin of safety of the bupivacaine needed for analgesia is wide. Thus, pain relief and patient comfort during the early postoperative period becomes increasingly important, as the need for analgesic may delay discharge.

Several studies have described pain according to the presumed mechanism: visceral pain, which can theoretically be blocked by intraperitoneal instillation, and parietal pain, which can be blocked by port site infiltration.[10,12,13]

Present study was designed to evaluate the effect of intraperitoneal instillation of 0.5% bupivacaine for pain relief following laparoscopic cholecystectomy.

OBJECTIVES

The objectives of the present study were;

1. Comparing the effect of intraperitoneal instillation of 0.5% bupivacaine versus saline for post-operative analgesia in laparoscopic cholecystectomy.
2. To assess the need of rescue analgesics in post-operative period in both groups.
3. To assess shoulder tip pain postoperatively.

REVIEW OF LITERATURE

Laparoscopy is the process of inspecting the abdominal cavity through an endoscope. Initially, gynecologists used these instruments to diagnose pelvic pain, holding the rigid telescope in one hand and looking through it with the naked eye, it was possible to manipulate a second instrument in the abdominal cavity to move abdominal structures, aspirate cysts, and apply clips to fallopian tubes for sterilization. As small video cameras became available in the 1980s, the surgeon was able to use both hands to position surgical instruments, while one or more assistants could contribute to the procedure by sharing the same view as the surgeon.[15]

Laparoscopy is becoming one of the most common surgical procedures performed on outpatient basis. Technical advances in the field of endoscopic surgery such as the miniaturization of instruments, the use of gasless endoscopy, and the use of more efficient lighting techniques, will help to reduce surgical trauma and discomfort and thereby widen the scope of laparoscopy.[16]

Laparoscopic surgery is one of the most obvious forms of minimally invasive surgery. There is no doubt that such an approach reduces pain and immobility in the postoperative period because of significantly reduced skin and muscle wounds. Recovery occurs sooner, and hospital stays are reduced. There are disadvantages to laparoscopic surgeries as well. Surgical times may be longer, especially during the learning phase. Laparoscopic surgery can complicate the anaesthetic management and introduce new and serious complications that do not exist or are rare with the traditional approach.[16]

The first cholecystectomy was performed by Langenbuch on July 15, 1882 in Berlin.[17] One hundred and four year later in 1985, Muhe performed the first laparoscopic cholecystectomy and the following year he presented to the German Surgical Congress but was greeted with outright hostility.

The first laparoscopic cholecystectomy recorded in the medical literature was performed in March 1987 by Mouret, in Lyon, France. Subsequently the technique was perfected by Dubois, Perrisat and Reddick and in a very short period it became the gold standard operation for conditions of the gall bladder.

Various series have demonstrated that the laparoscopic approach leads to a reduction in postoperative pain and diminished postoperative hospitalization and disability.

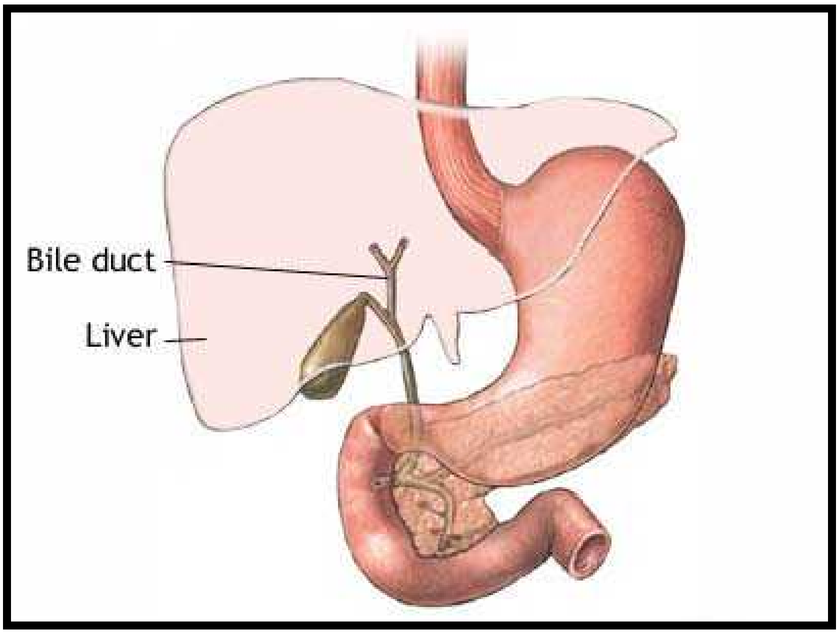


Fig. 1. Anatomy of gall bladder

The gallbladder is located in the abdomen, on the right side, underneath the liver. The gallbladder stores bile produced by the liver and delivers it to the first part of the small intestine (duodenum), where it aids in the digestion of fat.

Procedure of laparoscopic cholecystectomy

Position

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

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

Part preparation and draping done in the standard manner.

Access to peritoneal cavity

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

Closed pneumoperitoneum

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

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

Insufflation of the peritoneal cavity is then continued at an initial inflow rate of about 1l/min. if this process proceeds smoothly without significant change in the cardiovascular changes, the insufflators can be switched to high flow to allow complete filling of the peritoneal cavity to a pressure of approximately 10 to 15 mmHg. At this point the veress needle is withdrawn. During the insufflation all quadrants of the abdomen are percussed to confirm uniform distension.

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

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

The cystic pedicle is exposed by grasping the gallbladder fundus which is lifted in a lateral direction and rolled backwards to expose the subhepatic pouch. A second atraumatic grasper is applied to the neck which is lifted upwards and anteriorly. The cystic pedicle outlines the margins of the triangle of Calot and contains between its superior and inferior leaves the cystic duct (usually anteriorly), the cystic artery (above and behind the duct) and the cystic lymph node of Lund which is loosely applied to the neck of the gallbladder between the duct and artery.the prominent anterior free edge of the cystic pedicle is formed as the peritoneum folds over the cystic duct.the dissection of the pedicle is carried out using scissors, or atraumatic graspers and the superior leaf of the pedicle is divided. Once the cystic duct and artery are well exposed, the cystic duct is clipped at the gallbladder end and cut followed by the cystic artery. The dissection is carried out between the loose fibrous layer which separates the gallbladder from the subjacent fascia covering the liver bed. Once separation of gallbladder is complete, the organ is held and extracted through the upper 10 mm port. Care is taken to avoid spillage of contents into the peritoneal cavity. After this final inspection is done to look for any oozing, heamostasis is achieved. All ports are removed under vision after decompressing the abdominal cavity to evacuate the carbon dioxide. Ports are closed using vicryl for the rectus sheath and skin using ethilon. Sterile dressing applied.

Definition of pain

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

Magnitude of the problem

Many factors influence the occurrence, intensity, quality and duration of postoperative pain like the site, nature and duration of operation, type of incision (thoracic and upper abdominal operations are associated with the most severe pain), the preoperative psychological, physical and pharmacological preparation of the patient, added to this the anaesthetic management and the quality of post operative care.[19]

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 is recognized

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

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).

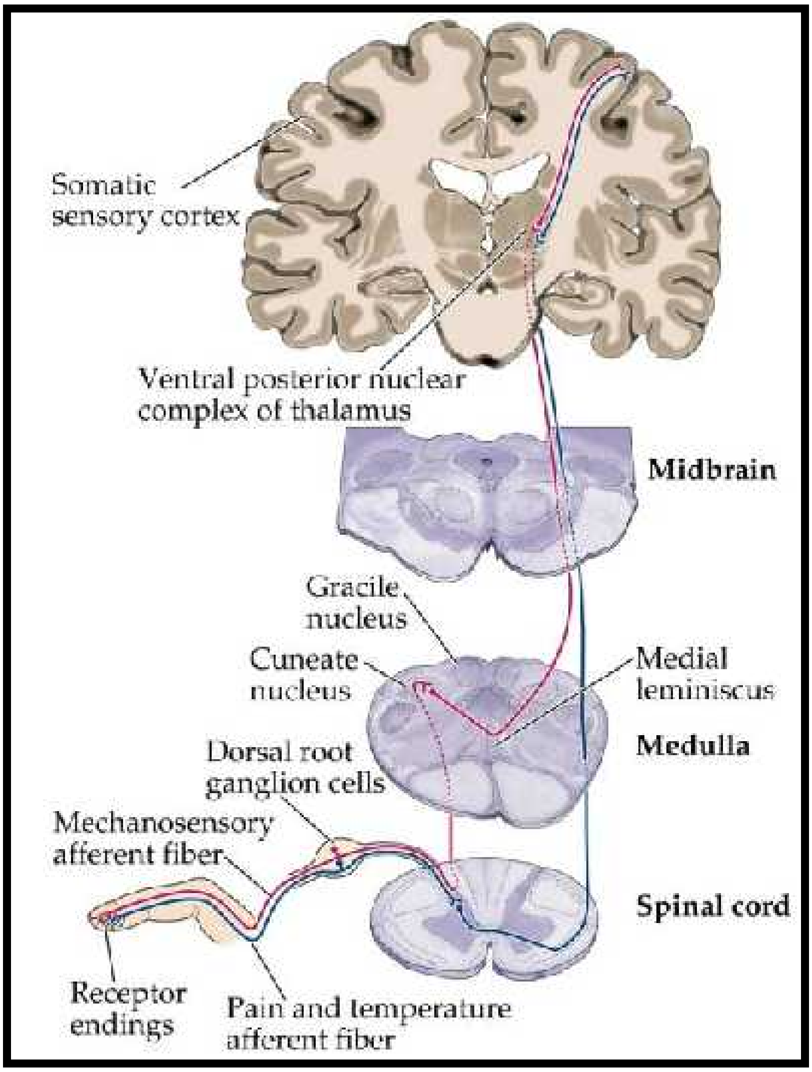


Fig. 2. Pain pathway

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 substantia gelatenosa) 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 spinothalamic tract that send its fibers to the thalamus, the reticular formation, nucleus raphe and periaquiductal 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]

Preemptive analgesia

Preemptive analgesia is defined as what is administered before surgical incision that prevent the development of central sensitization from incisional injury and inflammatory injuries (that is, intraoperative and postoperative periods). The combination of experimental data and positive clinical trials strongly suggests that preemptive analgesia is a clinically relevant phenomenon. Maximum benefit is observed when there is complete blockade of noxious stimuli.[25]

Pain after laparoscopy

Pain occurs after laparoscopy, but is usually less and shorter than that caused by the same surgical procedure made possible by laparotomy. The reduction in pain has made the early discharge from the hospital possible, provided that the control of the residual pain is adequate and that the drugs or techniques used for analgesia are safe enough.[7]

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

Pain after laparoscopy may be transient or it may persist for at least two days. After laparoscopic cholecystectomy, visceral pain was found to predominate in the first 24 hours, whereas shoulder pain, minor on the first day, increased and becomes significant on the following day.[26]

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 (pneumoperitoneum). There is statistically significant correlation between the width of the gas bubble and pain score, and this pain can be reduced by the aspiration of the gas under the diaphragm.[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 intraabdominal pH

The phrenic nerves may be damaged by the acid milieu created by the dissolution of CO_2. The intraperitoneal pH when CO_2 gas is insufflated has been measured at 6.0 immediately postoperatively. On the first postoperative day, the pH rises to 6.4 to 6.7, and on the second postoperative day to 6.8 to 6.9. Thereafter it normalizes to above 7.0.[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 anaesthesia 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 anaesthesia will be required, minimal side effects are anticipated, and the use of local anaesthesia 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 cholecystectomy. The intensity of pain after laparoscopic cholecystectomy peaks within the first four to eight hours, has been reported to be unbearable upto the first postoperative morning in one third of the patients. It involves three different components with different intensity, time course and pathophysiological mechanisms. These pain components are incisional pain (parietal pain component); deep intraabdominal pain (visceral pain component) and shoulder tip pain (presumed referred visceral pain.) The intensity of visceral pain dominates in the immediate postoperative period.

Effects of postoperative pain

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

Acute pain is typically associated with neuroendocrine stress response that is proportional to pain intensity, and it has been hypothesized that a reduction in surgical stress responses (endocrine, metabolic and inflammatory) will lead to a reduced incidence of postoperative organ dysfunction and thereby lead to an improved outcome. The latter suggests that effective postoperative pain management is not only human but a very important aspect of postoperative care.[35]

a. Cardiovascular effects

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

Although a variety of factors may contribute to the development of postoperative myocardial ischemia, including hypothermia, anaemia, anxiety, and tracheal intubation / suctioning, responses to poorly controlled pain play a prominent role. In this regard, activation of sympathoadrenal, and neuroendocrine 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. Gastrointesinal effects

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

<u>Single dimension methods</u>

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

<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]

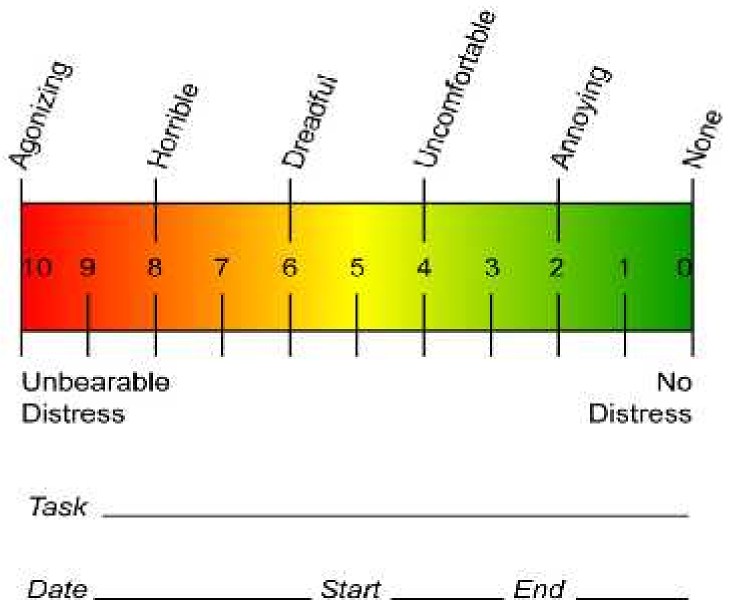


Fig. 3. Visual analogue scale

MANAGEMENT OF POSTOPERATIVE PAIN

Prophylactic measures

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

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

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

ACTIVE MEASURES

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

1. Systemic analgesics and adjuvant drugs.
2. Local infiltration and field block.
3. Regional analgesia with local anaesthetics.
4. Regional analgesia with epidural or intrathecal opioids.
5. Regional analgesia with combined local anaesthetics and opioids
6. Electrical analgesia achieved with transcutaneous electrical stimulation or electroacupuncture.[4]

1. Systemic analgesics and adjuvant

Drugs

a. Narcotics

Exogenously administered opioids produce analgesia by mimicking the actions of endogenous opioid peptides (enkephalins, B-endorphins and dynorphins) at specific receptors within the CNS. Pharmacological studies led to the proposal of five classes of opioid receptors. Each receptor mediates a spectrum of pharmacologic effects.

All opiates in clinical use produce analgesia via the same molecular mechanism that is, binding to G-protein coupled opioid receptors with subsequent inhibition of adenylate cyclase, activation of inwardly rectifying K-channels, and inhibition of voltage-gated Ca-cahnnels, all of which decrease neuronal excitability.[43]

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.

Routes of administration

There is a wide inter-subject and intra subject variability in the relationships of opioid dose, serum concentration, and analgesic response in the treatment of postoperative pain; for example, intramuscularly administered narcotics may result in a wider variability in serum drug concentration than other intravenously administered one, on the other hand , 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]

Intravenous patient controlled analgesia

A significant improvement in postoperative analgesia was the development of appropriate delivery system that allows the use of intravenous patient controlled analgesia (IVPCA). Pumps used allow the patient to inject a small bolus of an intravenous opioid drug whenever he or she feels pain, thus maintaining the analgesic book level in the appropriate range, 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. 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]

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]

Transdermal opioids (Fentanyl patches) provide 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]

Peripheral opioid analgesia

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. 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]

Pharmacological properties of narcotics

CNS effects

Opioid eliminates pain, depresses respiration, suppresses cough, stimulates the third nerve nucleus causing miosis and stimulates the chemoreceptor trigger zone causing nausea and vomiting.[47]

Haemodynamic effects

Opioids cause bradycardia and decrease the sympathetic tone.[37]

Smooth muscle effects

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

Non-steroidal anti-inflamatory drugs (NSAID) block the synthesis of prostaglandins by inhibition of the enzyme cyclo-oxygenase. Cyclo-oxygenase enzyme catalyzes the conversion of arachidonic acid to the cyclic endoperoxide, which are the precursors of prostaglandins. Prostaglandins mediate several components of the inflammatory response including fever, pain and vasodilatation. NSAID differ in potency with respect to their analgesic, anti-inflammatory and antipyretic properties.[25]

NSAIDs have traditionally been used to relieve pain after minor surgery or have been prescribed two or three days after major surgery when the more powerful analgesics have been withdrawn. 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]

The three major problems associated with NSAID therapy are

1. Gastropathy
2. Impaired hemostasis
3. Nephrotoxicity

All are directly related to inhibition of prostaglandin synthesis. 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.

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 undergoing laparoscopic cholecystectomy or inguinal 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.

Dexmedetomidine is a pure alpa 2-agonist that also reduces postoperative pain and opioid analgesic requirement. However, its use was associated with increased postoperative sedation and bradycardia.[52]

f. 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 cholecystectomy surgery. 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 bupivacaine 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

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. Continuous segmental epidural block

The dosing regimen for epidural analgesia can be controlled by the patient. This is the technique of “patient-controlled epidural analgesia (PCEA)”. With this technique an adequate sensory block must first be initiated with a bolus injection(s). The block is then maintained either by demand injections alone or by a background infusion plus demand injections signaled by the patient as soon as there is a recurrence of minimal or undesired discomfort. Advantages of this technique include the ability to minimize drug dosage, flexibility and benefits of self administration, and reduced demand on professional time. The used pump must be able to give a continuous set infusion rate, to give demand doses with set lockout periods, and to limit a total dose over a set period of time.

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 injection may be single, intermittent, or a continuous infusion. 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]

Bupivacaine has been the most widely used local anaesthetic for interpleural analgesia. A dose of 20 ml of 0.25% in a normal adult provides analgesia lasting for three to five hours after cholecystectomy.

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]

Contraindications to interpleural catheter placement are those conditions that make the risk of lung puncture and/or local anaesthetic toxicity unacceptably high. For example, pleural effusion, pleural fibrosis, pleura inflammation (recent pneumonia), lung malignancy, and anticoagulation and bleeding diathesis.[4]

The chief complications of interpleural analgesia are pneumothorax and local anaesthetic toxicity. Other complications of the technique include hemothorax, Horner’s syndrome and, rarely, pleural effusions.[20]

c. Intraperitoneal analgesia

Intraperitoneal instillation of local anaesthetics 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 intraperitoneal local anaesthetics is mediated by local peritoneal effects rather than by systemic absorption. Addition of adrenaline to intraperitoneal local anaesthetic 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]

Variable analgesic effects of periportal infiltration of local anaesthetics, infiltration of the periportal parietal peritoneum, intraperitoneal spraying, subdiaphragmatic space, and into the subhepatic space covering the area of the hepatoduodenal ligament have been reported. Some to them failed to show analgesic effects. When 240 mg of lignocaine or 100 mg of bupivacaine are injected intraperitoneally, the time required to reach peak plasma levels are similar to the time required in other forms of regional applications of these drugs. The difference in the time required to reach peak plasma concentration for lignocaine (30 minutes) bupivacaine (60 minutes) may be related to the increased protein binding capabilities of bupivacaine and its sequestration in the peritoneal adipose tissue. With application of bupivacaine 0.25% the maximum plasma concentrations, ranging from 0.35 to 2.1 mgL^{-1}, were found after 5 to 30 minutes. However no clinical signs of neuro- or cardiovascular toxicity were observed.[58]

Local anaesthetic instillation (bupivacaine) 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 (a 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 oipiods, possibly due to reduction of vascular uptake.

4. Regional analgesia with combined local anaesthetics and opioids

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

5. 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]

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]

PHARMACOLOGY OF LOCAL ANAESTHETICS

Structure activity relationship of local anaethetics

Local anaesthetics consist of lipophilic group, usually a benzene ring, separated from a hydrophilic group, usually a tertiary amine, by an intermediate chain which includes an ester or amide linkage. Local anaesthetics are weak bases that usually carry a positive charge at the tertiary amine group at physiologic pH. The nature of the intermediate chain is the basis of classification of local anaesthetics into amide or ester. Local anaesthetics act by penetrating lipoprotein cell membrane in the non-ionized state. In order to make them suitable for injection, the non-ionized base has to be converted to the ionized state by injecting them in an acid solution as the hydrochloric salt so, tertiary amine group becomes quaternary and then they become water soluble and suitable for injection.

Structural activity relationship

a. Potency

An increase in the lipid solubility and/or increase in the molecular weight increase the potency of local anaesthetic. For example, adding a butyl group to mepivacaine (less potent local anaesthetic) converts it into bupivacaine (more potent local anaesthetic).

Potency is affected by:

1. <u>Fiber size:</u> The smaller unmyelinated fibers (e.g. sensor C fibers) are more effectively blocked than the large myelinated fibers (motor A fibers).

2. pH: Acidic pH antagonize the block.
3. Frequency of nerve stimulation: Access of local anaesthetic to Na channels is enhanced by repeated opening of those channels.

b. Speed of onset of action

And this depends on:

1. pKa of the drug: Local anaesthetics with pKa closer to the physiologic pH have a higher concentration of the non-ionized free base that can cross the nerve cell membrane.
2. Molecular weight: Local anaesthetics with smaller molecular weight have more rapid onset of action.

c. Duration of action

It depends on the aromatic group which affect the plasma protein binding. The higher the plasma protein binding the slower the clearance and thus the higher the duration of action. Also, higher protein binding increase the duration of affection of the local anaesthetic to the Na channels and thus prolong the action.

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 anaesthetics prevent the depolarization of the nerve membrane and so prevent conduction of impulses.[61]

PHARMACOKINETICS OF LOCAL ANAESTHETICS

1. Absorption

Factors that affect the absorption of local anaesthetic are:

a) ***Site of injection:*** Highly vascular tissues show increase in the systemic absorption of local anaesthetic 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 anaesthetic for example, lignocaine.
c) ***Type of local anaesthetic:*** Local anaesthetics with high tissue binding are more slowly absorbed e.g. etidocaine.[20]

2. Distribution

Distribution of local anaesthetics 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 anaesthetic in the blood.

3. Metabolism

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

Amide local anaesthetics 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 anaesthetics 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]

BUPIVACAINE

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

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

Melting point: 258°C

pH: Solutions containing epinephrine has a pH of about 3.5

pKa: 8.1

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

Molecular formula: $C_{18}N_2OH28HCl$.

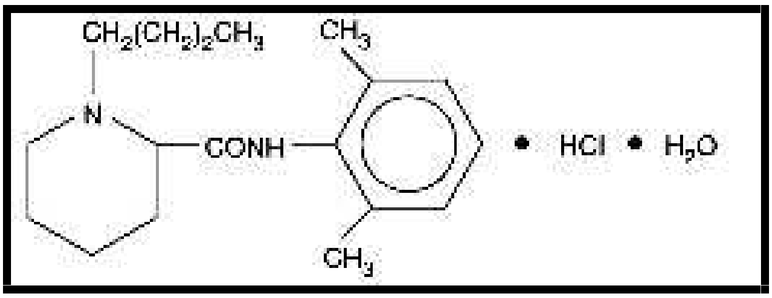


Fig. 4. Chemical structure :bupivacaine

Physiochemical properties

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

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

Anaesthetic properties

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

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

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

Toxic effects of local anaesthetics

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

1. Central nervous system:

The early symptoms of toxicity are numbness of the tongue and circumoral region, tinnitus and are encountered most frequently in patients on intravenous antiarrhythmic therapy. Thus, central stimulation followed by depression, hysterical behavior, vertigo, tremor, convulsions, and respiratory failure may occur.[61]

2. Cardiovascular system

Local anaesthetics directly depress myocardial conduction and myocardial contractility in a dose-dependent manner, leading to hypotension, bradycardia, pallor, and sweating. This type of intoxication may be due to a rapid absorption of the drug.[62]

3. Respiratory depression

This may progress to apnea from medullary depression or respiratory muscle paralysis.[62]

4. Allergic phenomena

Allergy rarely takes the form of bronchospasm, urticaria or angioneurotic edema. It is well documented in association with the use of ester linked agents, including dermatitis in personnel handling procaine. Allergy to amide linked agents is extremely rare.[63]

5. Drug interactions

Non-depolarizing muscle relaxant blockade is potentiated by local anaesthetics. Pseudocholinesterase inhibitors can lead to decrease metabolism of ester local anaesthetics. Cimetidine and propranolol decrease hepatic blood flow and lidocaine clearance. Opioids and adrenergic agonists potentiate local anaesthetic pain relief.

Treatment of toxicity

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

A study done in 2000 while comparing intraperitoneal 0.5% bupivacaine, 0.75% ropivacaine and saline instillation for postoperative pain relief found that local anaesthetics gave significantly good pain relief with ropivacaine being better than bupivacaine in both analgesia and opioid sparing effect.[64]

Many other studies during intraperitoneal instillation of 0.5% bupivacaine with or without adrenaline for postoperative pain relief in patients undergoing laparoscopic cholecystectomy, laparoscopic pelvic surgery and diagnostic laparoscopy. They concluded that locally instilled bupivacaine produces significant postoperative analgesia and the requirement of analgesics was reduced.[8,65,66,67]

In another study authors studied the effect of intraperitoneal local anaesthesia for postoperative pain relief for two different type of surgeries and showed that local anaesthetic was effective in reducing pain in laparoscopic fundoplication rather than laparoscopic hernia repair.[68]

Though all these studies proved that local instillation of bupivacaine is effective in postoperative pain relief, few earlier studies have different opinion. Studies conducted to assess postoperative analgesic effect of locally instilled bupivacaine in laparoscopic cholecystectomy patients reported that there is no significant postoperative pain relief in these patients.[7,69]

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 2009 to December 2009 on 36 patients with posted for elective laparoscopic cholecystectomy.

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 2009 to December 2009.

Source of data

Patients admitted in Department of Surgery, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum posted for elective laparoscopic cholecystectomy in between age group 18 to 60 years.

Method of collection of data

Sample size

Present study was conducted on 36 adult patients of either sex between age group 18 to 60 years of ASA-1 and ASA-2 undergoing elective laparoscopic cholecystectomy.

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

Considering p1 = 80; p2 = 20; P = 50

$Z\alpha = 2.33$

$Z\beta = 1.28$

d = 60

n = 36

Randomization

A total of 36 patients divided into two groups of 18 patients each randomly by computer generated randomization sheet.

Selection criteria

Inclusion criteria

- Adult patients with age between 18 to 60 years of both sexes.
- Patients undergoing elective laparoscopic cholecystectomy ASA-1 and ASA-2 grade.

Exclusion criteria

- Patients refusal.
- ASA grade III and IV.

- History of previous abdominal surgery.
- Patients with
    - Allergy to protocol drug.
    - Conversion to open cholecystectomy is done for any reason.
    - Drain is placed.

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 cholecystectomy 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 18 patients each randomly using computer randomization table.

Group A (Study group): Patients received 20 ml 0.5% bupivacaine intraperitoneally at gall bladder bed and under right hemidiaphragm at the end of surgery through laparoscope port in trendlenburg position.

Group B (Placebo group): Patients received 20 ml normal saline intraperitoneally 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.

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. A nasogastric tube was introduced and the patient was placed in a head up position in order to provide optimum conditions for laparoscopic surgery. General anaesthesia was maintained by controlled mechanical ventilation with a 0.5 to 1% 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 intraperitoneal and sub diaphragmatic 0.5% bupivacaine 20 ml at the end of surgery before the trochars were withdrawn; a total of 100 mg, after instillation patient was maintained in trendlenburg position for five minutes for the drug to stay at the injected site. Patients in group B received intraperitoneal and subdiaphragmatic saline (20 ml) at the end of surgery before the trochars were withdrawn and trendlenburg position was given for five minutes. The surgeon was blinded for the nature of the solution used.

The residual CO_2 was evacuated carefully at the end of surgery by manual compression of the abdomen with open trochars. The nasogastric tube was removed after recovery from anaesthesia.

Post operatively the patients were assessed for pain utilizing visual analogue scale (VAS). The time of arrival in the postoperative ward was defined as zero hour postoperatively. Pain intensity was measured at fixed time interval. The patients dose of rescue analgesia were assessed at 6, 12, 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 six postoperatively, which was given by the ward staff who were unaware of the nature of the intraoperative analgesia.

The time from the end of surgery until the first requested analgesia was recorded, and the doses of postoperative 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.

Patients were deemed ready for discharge from the hospital when they were afebrile, oral nutrition was tolerated without discomfort and bowel function (defined as presence of good intestinal sound or first passage of flatus) had returned.

Statistical analysis

The data was analysed using rates, ratios and percentages. The data was compared using student unpaired 't' test and Mann Whitney test.

RESULTS

The objective of the present study was to compare the effect of intraperitoneal instillation of 0.5% bupivacaine for pain relief following laparoscopic cholecystectomy. The study was carried out in Dept of Surgery, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum between the period January 2009 to December 2009.

The study included 36 patients of ASA grade I and II in the age group of 18 to 60 years. Each group consisted of 18 patients divided by computer generated randomization table as;

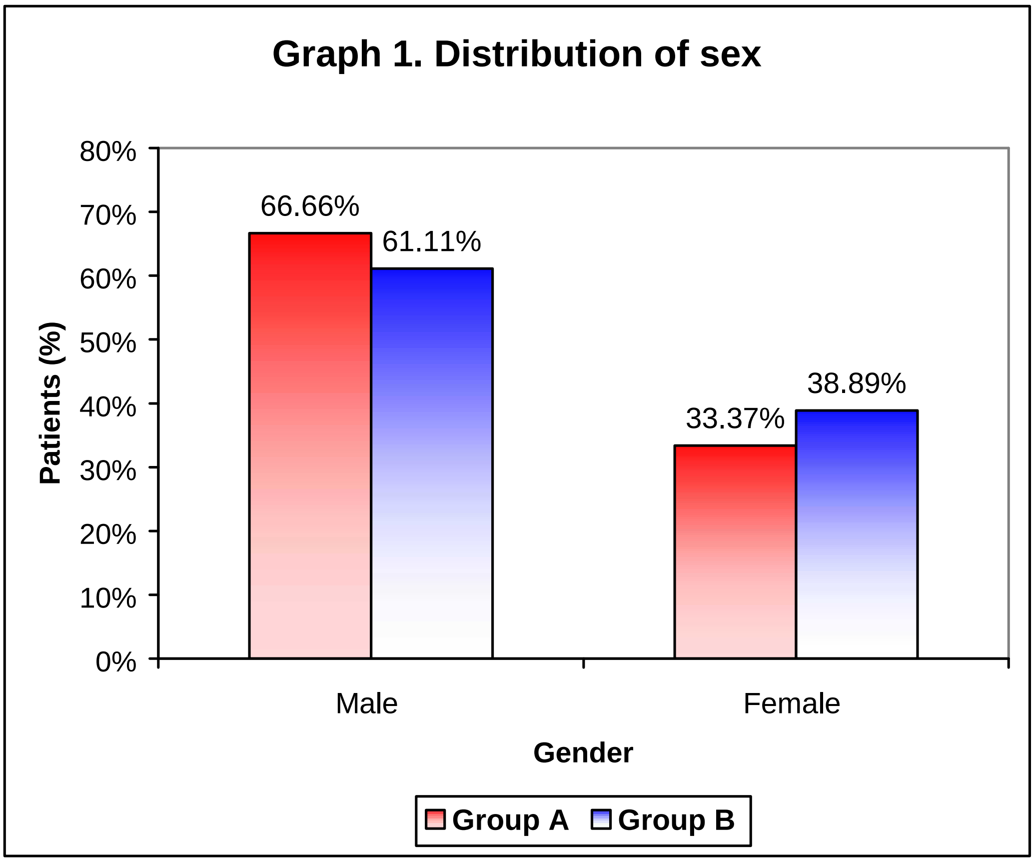
Group A - Bupivacaine group (n=18)

Group B - Saline group (n=18)

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	12	66.66	6	33.37
Group B	11	61.11	7	38.89

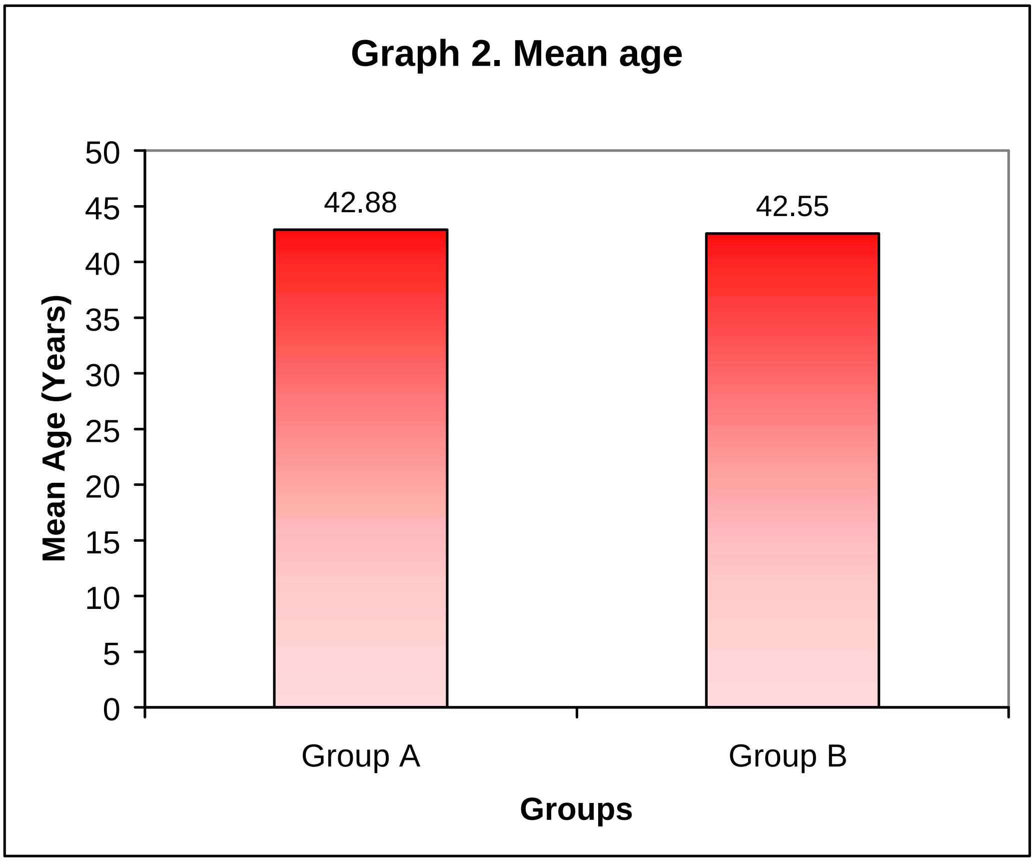


The distribution of sex was similar in both the groups with 66.66% males and 33.37% females in Group A and 61.11% males and 38.89% females in Group B. Both the groups were comparable. The male to female ratio was 2:1 in group A and 1.57:1 in Group B.

Table 2. Mean age

Groups	Age (Years)	
	Mean	**S.D.**
Group A	42.88	10.27
Group B	42.55	9.97

p=0.276 (Not significant).

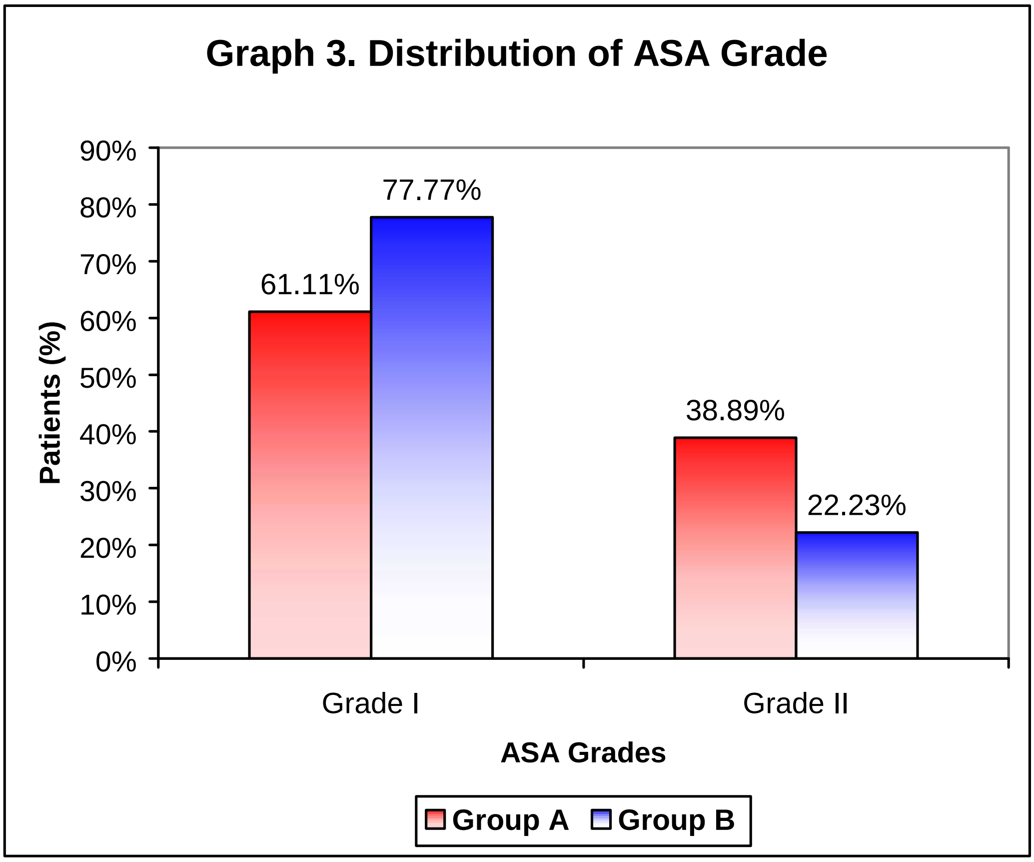


The mean age in group A was 42.88 ± 10.27 and in group B it was 42.55 ± 9.97 years which was comparable in both the groups (p=0.276).

Table 3. Distribution of ASA Grade

Groups	ASA I		ASA II	
	Number	**Percentage**	**Number**	**Percentage**
Group A	11	61.11	7	38.89
Group B	14	77.77	04	22.23

p=0.393 (Not significant).



Distribution of patients according to ASA I and II grade was 61.11% and 38.89% in Group A compared to 77.77% and 22.23% in group B respectively. This difference was statistically not significant (p=0.393).

Table 4. Comparison of hemodynamic parameters

Parameters	Group A		Group B		p value
	Mean	S.D.	Mean	S.D.	
Pulse rate (/min)	82.78	9.85	82.67	5.49	0.966
SBP (mm Hg)	126.33	12.47	125.44	9.12	0.808
DBP (mm Hg)	80.78	9.31	77.89	6.77	0.294
Respiratory Rate (/min)	14.61	2.38	14.44	1.04	0.787

The mean pulse rate in group A was 82.78 ± 9.85 per minute and in group B it was 82.67 ± 5.49 per minute.

The mean systolic blood pressure was 126.33 ± 12.47 mm Hg in group A and 125.44 ± 9.12 mm Hg in group B.

The diastolic blood pressure in group A was 80.78 ± 9.31 mm Hg and in group B it was 77.89 ± 6.77.

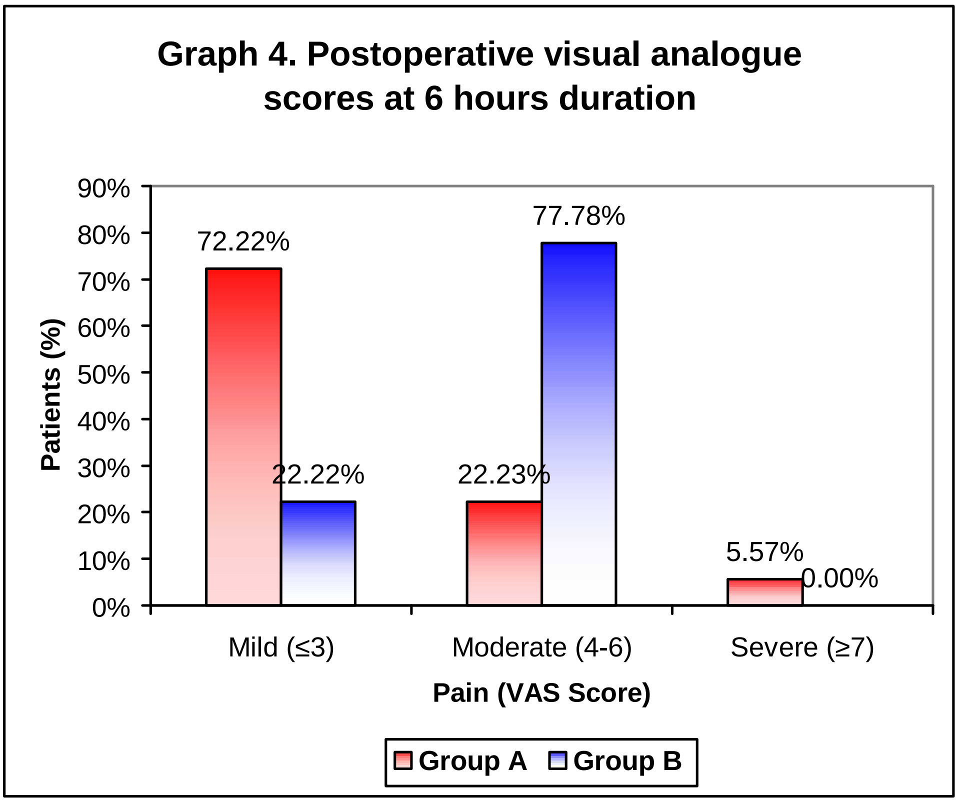
The respiratory rate in groups A and group B was 14.61 ± 2.38 per minute and 14.44 ± 1.04 per minutes respectively.

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

Table 5. Postoperative visual analogue scores at 6 hours duration

Pain (VAS Score)	Groups				p value
	Group A		Group B		
	No.	%	No.	%	
Mild (≤3)	13	72.22	4	22.22%	
Moderate (4-6)	4	22.22	14	77.78	0.0079*
Severe (≥7)	1	5.56	0	0.00	

*Statistically significant

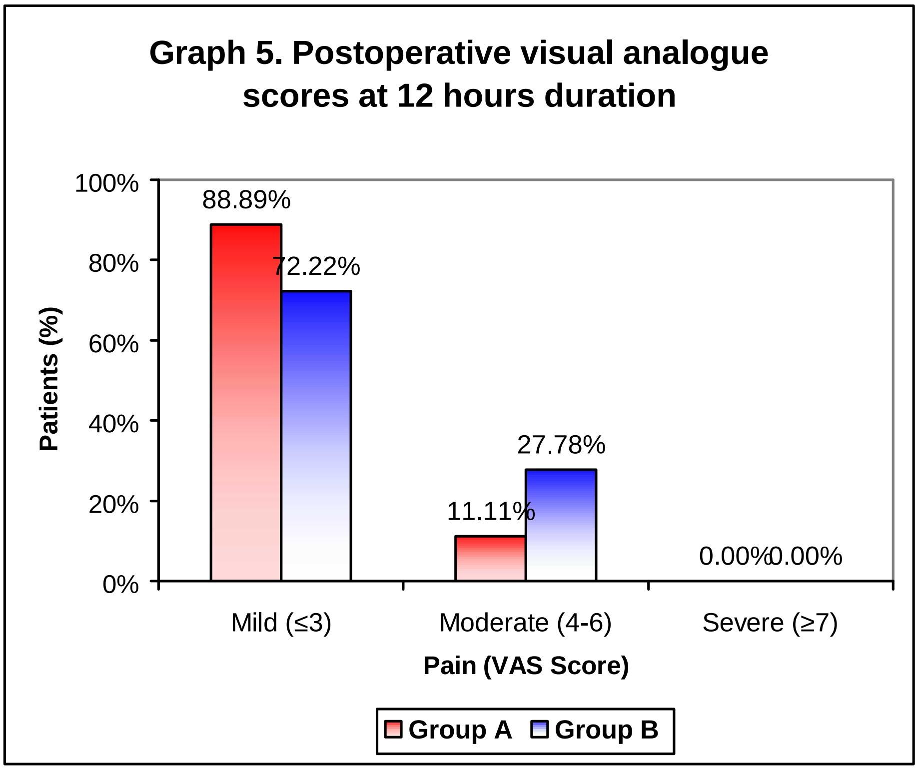


In group A, at six hour duration, significantly more number of patients (72.22%) experienced mild pain (VAS scores ≤ 3) compared to 77.78% patients in Group B who had moderate pain (VAS scores 4 to 6) (p=0.0079). One patient (5.57%) in group A reported severe pain.

Table 6. Postoperative visual analogue scores at 12 hours duration

Pain (VAS Score)	Groups				p value
	Group A		Group B		
	No.	%	No.	%	
Mild (≤3)	16	88.89	13	72.22	
Moderate (4-6)	2	11.11	5	27.78	0.0302*
Severe (≥7)	0	0.00	0	0.00	

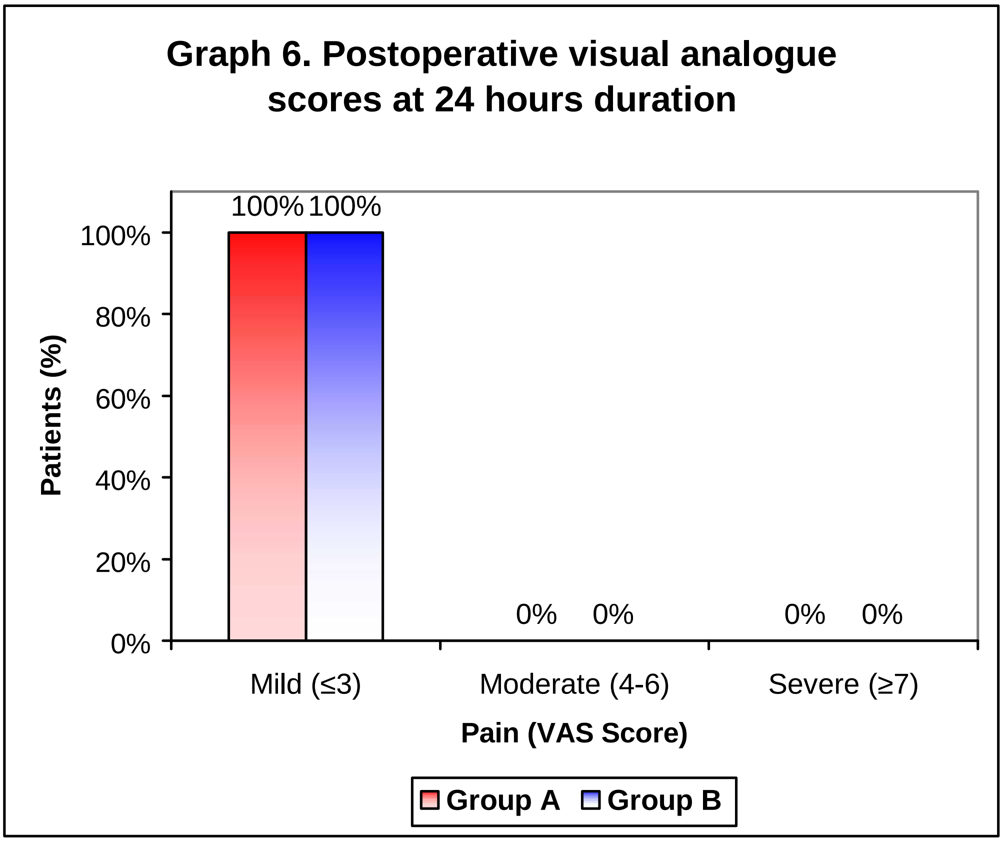
*Statistically significant



At 12 hour duration, majority of patients in group A (88.89%) experienced mild pain and 11.11% patients had moderate pain. In Group B majority of the patients had (72.22%) mild pain and 27.78% patients had moderate pain. This difference was statistically significant (p=0.0079). None of patient in both group A and B reported severe pain.

Table 7. Postoperative visual analogue scores at 24 hours duration

Pain (VAS Score)	Groups				p value
	Group A		Group B		
	No.	%	No.	%	
Mild (≤3)	18	100	18	100	
Moderate (4-6)	0	0.00	0	0.00	0.7397
Severe (≥7)	0	0.00	0	0.00	



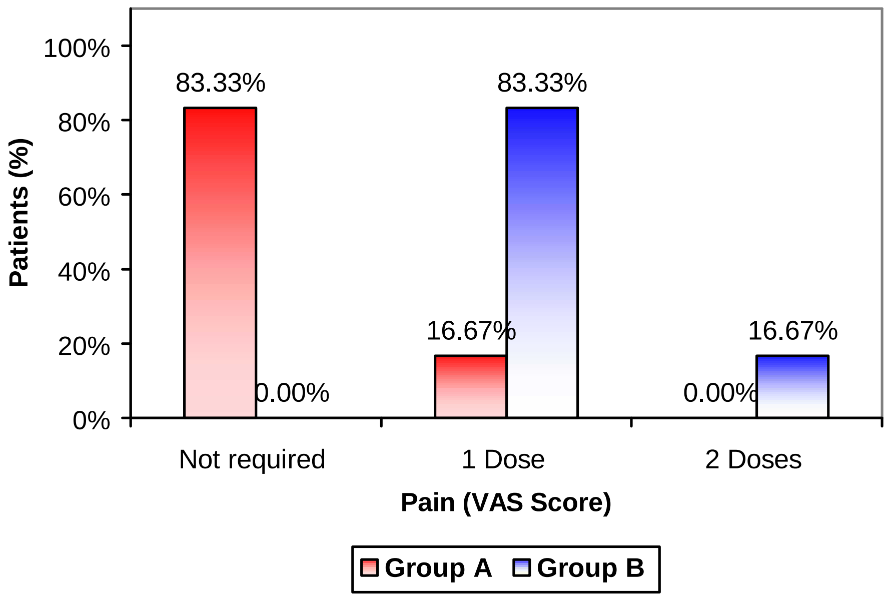
At 24 hour duration, all patients (100%) in group A and group B experienced mild pain and this difference was statistically not significant (p=0.7397). None of patient in both group A and B reported moderate and severe pain.

Table 8. Doses of rescue analgesia within the first 6 hours

Doses	Group A		Group B	
	Number	Percentage	Number	Percentage
Not required	15	83.33	0	0.00
1 Dose	03	16.67	15	83.33
2 Doses	00	0.00	3	16.67

p=0.0001 Statistically significant

Graph 7. Doses of rescue analgesia within the first 6 hours



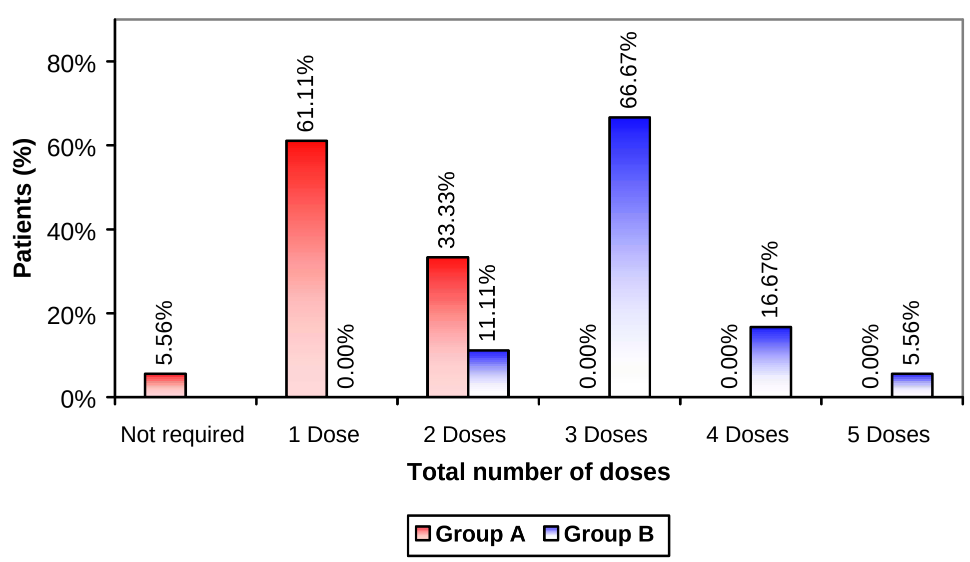
In this study among patients with group A majority of the patients (83.33%) did not require any doses of rescue analgesia within first six hours whereas in group B majority of the patients (83.33%) required one dose of rescue analgesia. This difference was statistically significant (0.0001).

Table 9. Total doses of rescue analgesia

Total number of doses	Group A		Group B	
	Number	Percentage	Number	Percentage
Not required	1	5.56	0	0.0
1 Dose	11	61.11	0	0.0
2 Doses	6	33.33	2	11.11
3 Doses	0	0.0	12	66.67
4 Doses	0	0.0	3	16.67
5 Doses	0	0.0	1	5.56

p=0.0001 statistically significant

Graph 8. Total doses of rescue analgesia

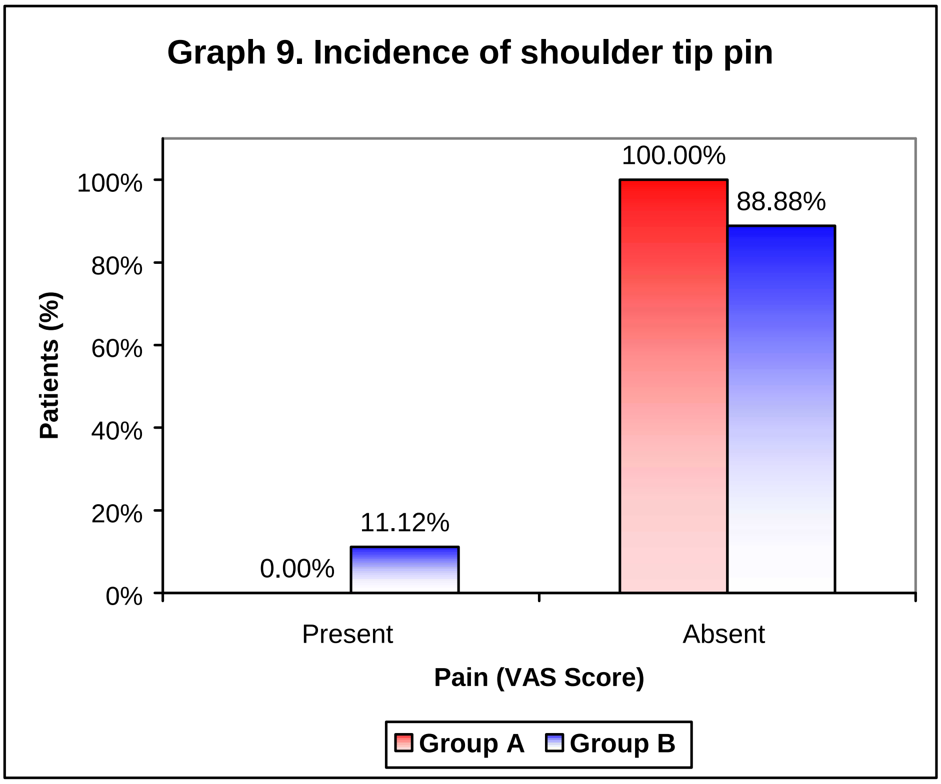


In this study among patients with group A majority of the patients (61.11%) required one dose of rescue analgesia whereas in group B majority of the patients (66.67%) required three doses of rescue analgesia. This difference was statistically significant (0.0001).

Table 10. Incidence of shoulder tip pin

Groups	Present		Absent	
	Number	**Percentage**	**Number**	**Percentage**
Group A	0	0.0	18	100.0
Group B	2	11.12	16	88.88

p=0.1456



In group A shoulder tip pain was reported in 11.12% and not reported in 88.88% patients. In group B all the patients (100%) reported shoulder tip pain. However this difference was statistically not significant.

DISCUSSION

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

Pain after laparoscopic cholecystectomy 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 intraperitoneal bupivacaine versus intraperitoneal saline for postoperative analgesia following laparoscopic cholecystectomy and is similar to other studies that were concerned with postoperative analgesia following laparoscopic surgeries by local anaesthetic instillation intraperitoneally.

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 bupivacaine. 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 bupivacaine group by 24 hours postoperatively. Therefore, the main effect of bupivacaine 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 intraperitoneal instillation of 100 mg of bupivacaine at the end of laparoscopic cholecystectomy significantly reduced abdominal pain scores, and this was confirmed by the lower total dose of diclofenac 23 doses compared to 57 doses given in placebo group, which was given postoperatively, and the longer time for the first requested analgesia in the study group.

The incidence of shoulder tip pain, was absent in bupivacaine group.

Similar study done by Shalan H et al for laparoscopic pelvic surgery, found that pain score and analgesic dose required were lower in bupivacaine 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]

Bhardwaj et al, conducted study in patients undergoing laparoscopic cholecystectomy. He instilled 20 ml 0.5% bupivacaine only at the end of surgery in the trendelburg position. Post operatively they assessed for vital signs (heart rate, blood pressure and respiratory rate), pain scores (VAS, VRS and shoulder pain) and analgesic consumption.[67] They found that it reduced post operative cholecystectomy pain and analgesic consumption.

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

Local anaesthetics instillation has been found to be effective for post operative analgesia in other laparoscopic surgeries. Intraperitoneal bupivacaine can significantly decrease post operative pain and the need for additional analgesics in gynaecological laparoscopic surgeries. A systematic instillation is likely to be cost effective because it decreases resource utilization for the treatment of postoperative pain and emesis.[70,71]

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 instillation has failed to show the efficacy. These failure were could be because of use of lower dosage, lower concentration or because the entire dose was instilled under right hemidiaphragm.[68,73,74]

We observed that shoulder pain was less in patients receiving bupivacaine but with no statistical significance. Pasqualucci et al. demonstrated a statistically significant effect on surgical metabolic endocrine response (glucose and cortisol) and on postoperative pain scores by instillation of bupivacaine 100 mg after creation of pneumoperitoneum and 200 mg at the end of surgery.[75]

Randomized control studies on effect of Intraperitoneal local anaesthetic instillation in laparoscopic cholecystectomy on shoulder tip and overall pain.

Study	No of patients Treatment /control	Bupivacaine % vol	Over all pain	Shoulder pain	Comments
Chundrigar et al 1993[68]	28/30	0.25% 20 ml	P<0.05	NS	Significant at 1h and 2h post op
Pasqualucci et al 1994[75]	14/14/14	0.5% 20 ml preop +20 ml postop	P<0.05	--	Sig at 4hr in pregroup and upto 24 hrs in pre and post group.
Pasqualucci et al 1996[76]	30/30/30/30	0.5% 20 ml preop, 0.5%20ml postop, 0.5% 20 ml pre and post op.	P<0.05	--	Significant pre+post>post> pre
Szem etal 1995[77]	26/29	0.1% 100ml intraop	P<0.05	NS	Significant upto 6hrs
Mraovic etal 1997[78]	40/40	0.5% 15 ml preop +15 ml postop	P<0.05	--	Significant at 4 and 8hrs.
Weber et al 1997[79]	50/50	0.5% 10 ml postop	P<0.05	--	Significant at 2, 6 and 12 hrs.
Tsimoyannis et al 1998[79]	50/50	0.25% 30 ml postop	--	P<0.05	Pain score lowers upto 12 hrs
Raetzell et al 1995[73]	12/12	0.25% 50ml postop	NS	NS	Evaluated at day 1, 2, 3.
Rademaker et al 1994[80]	15/15/15	0.25% 20ml postop (lidocaine)	NS	NS	Evaluated at 1,2 and 4hrs
Sheinin et al 1995[74]	20/20/20	0.15% 100ml postop	NS	NS	Evaluated at day 1-7
Present study	18/18	0.5% 20 ml post op.	P<0.05	NS	Significant upto 12 hrs

NS - No significant difference between study and control group.

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

--- - Not evaluated.

Of the 10 randomized controlled trails comparing bupivacaine or lidocaine with saline; wherein, in all trials the local anaesthetic was administered in the right subdiaphragmatic or gall bladder region in concentrations between 0.1% and 0.5%, 10 and 100 mL at the beginning of the procedure, at the end, or both . Seven of the 10 trials found improved pain relief for at least one of the evaluated pain measures. In seven trials, overall pain scores were significantly reduced compared with the control patients. In most studies, pain scores were only reduced early postoperatively (two to eight h) however, in two trials, reductions lasted up to 24 h.[75,76] In the three other trials;[73,74] no effect on pain scores was observed.

Results from reports of intraperitoneal local anaesthetic after laparoscopic surgery revealed weak evidence for an effect on postoperative pain. Especially after laparoscopic cholecystectomy, the evidence was not compelling, and the clinical significance, at least regarding pain scores, was questionable. The differences between results in the various RCTs are difficult to explain[57] whereas our study showed a statistically significant effect in relieving post op pain.

Local anaesthetics are associated with toxicity which is dose related. Thus the amount of local anaesthetics used may be of importance. Intraperitoneal instillation of 100 mg of bupivacaine did not result in toxic plasma concentration,[81] as also 300 mg.[75] Expression of neurological toxicity is a function of the cerebral concentration of local anaesthetic and its rate of increase; it is thus, caused by a direct intravascular injection or a rapid absorption. The maximal tolerated dose before manifestation of central nervous system toxicity is

12% to 25%.[82,83] Based on these studies we conducted our study with 100 mg bupivacaine, and there were no signs of any toxicity found.

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

CONCLUSION

To conclude, bupivacaine is effective at preventing pain at wake-up and over the first 12 hours after laparoscopic cholecystectomy when intraperitoneally instilled at the end of laparoscopy. Our study showed, instillation of 100 mg bupivacaine significantly reduced the need for diclofenac compared with saline. This technique is simple, safe, and without adverse effects. As postoperative pain is unpredictable, local anaesthetics should be considered for instillation in all patients at the end of laparoscopic procedures. Bupivacaine is better choice because of its higher efficacy and larger safety margin.

SUMMARY

Laparoscopic cholecystectomy is the preferred surgical technique for uncomplicated cholecystectomy, because of an improved postoperative course. Although laparoscopic cholecystectomy, compared with the open procedure, may be associated with diminished surgical trauma and shortened convalescence, early postoperative pain after laparoscopic procedures is a frequent complaint. Furthermore, the fact that laparoscopic cholecystectomy is performed on a fast-track basis, emphasizes the importance of improving early postoperative pain. Pain after laparoscopic cholecystectomy may vary in quality and localization and is reported in several trials to be incisional, intraabdominal, or referred (shoulder tip).

The etiology is complex, including damage to abdominal wall structures, the induction of visceral trauma and inflammation, and peritoneal irritation because of CO_2 entrapment beneath the hemidiaphragms. 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 to an improved outcome. The latter suggests that effective postoperative pain management is not only human but a very important aspect of postoperative care. Uncontrolled postoperative pain has an adverse sequel of delayed resumption of normal pulmonary function, restriction of mobility (thus contributing to thromboembolic complications), nausea and vomiting, increase in the systemic vascular resistance,

cardiac work, and myocardial oxygen consumption through an increase in the catecholamine release induced by the stress response.

It was suggested that intraperitoneal injection of local anaesthetic may provide an effective block of postoperative visceral pain after laparoscopic cholecystectomy. 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 bupivacaine or of lidocaine. By contrast, other recent studies that have used larger doses and concentrations have demonstrated that intraperitoneal bupivacaine can be effective. Bupivacaine, an amide local anaesthetic has a reduced systemic and cardiac toxicity which was evaluated by several studies in doses as large as 300–375 mg for instillation and no clinical evidence of toxicity was observed.

In our study we compared the effect of intraperitoneal saline versus intraperitoneal bupivacaine on the postoperative pain following laparoscopic cholecystectomy. The demographic data and duration of surgery were similar in both groups. Patients receiving intraperitoneal instillation of bupivacaine showed significantly lower visceral pain scores ($p<0.05$) .No significant difference was seen in shoulder tip pain in both groups.

The dose of diclofenac given as rescue analgesia postoperatively was less in the bupivacaine group ($p<0.0001$), meanwhile the time to first requested dose was significant between both groups ($p=0.0001$).

So, we believe that intraperitoneal bupivacaine administration is more effective than intraperitoneal saline in controlling postoperative abdominal pain.

Hence we recommend its use as a part of multimodal analgesic technique for laparoscopic cholecystectomy.

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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 INTRAPERITONEAL INSTILLATION OF 0.5% BUPIVACAINE IN LAPAROSCOPIC CHOLECYSTECTOMY".

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 INTRAPERITONEAL INSTILLATION OF 0.5% BUPIVACAINE AND PLACEBO IN LAPAROSCOPIC CHOLECYSTECTOMY

Purpose of the research

- To study the postoperative analgesic effect of 0.5% bupivacaine following intraperitoneal instillation in laparoscopic cholecystectomy

Procedures involved

You will be randomly allocated either into group A or group B, if you are in group A you will receive 20ml 0.5% bupivacaine intraperitoneally at the gall bladder bed and under right and left hemidiaphragm at the end of surgery through laparoscope port and if you are in group B you will receive 20 ml normal saline intraperitoneally 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 participants management by any staff in hospital. Researcher can remove you from the study if circumstances arise.

Whom to contact

For any information about the study during the study or after that may be collected from

- Principal, JNMC, Belgaum.
- Dr. ***** ****** Professor, Department of General Surgery, JNMC, Belgaum
- Dr. ****** ******* Postgraduate student in General Surgery, JNMC, Belgaum

Signature of the participant or legally authorized person

Participants name:	Witness name:
Signature:	Signature:
Date:	Place:

ANNEXURE II – PROFOMA

Title: A RANDOMISED PLACEBO CONTROLLED TRIAL TO ASSESS POST OPERATIVE ANALGESIA AFTER INTRAPERITONEAL INSTILLATION OF 0.5% BUPIVACAINE IN LAPAROSCOPIC CHOLECYSTECTOMY.

Patients Name	:	I.P. No.:
Age	:	Wt :
Sex	:	
Occupation	:	Date of operation:
Address	:	Surgeon :

Chief Complaints

Past History

HTN / D.M / Asthma / Epilepsy / Drug allergy

Drug therapy

Previous exposure to anaesthesia

Family History:

General Physical Examination

Pallor / Icterus / Clubbing / Lymphadenopathy / Odema

P.R: B.P:

R.R:

Systemic Examination:

a. R.S b. CNS

c. C.V.S d. GIT: Per abdomen

Investigations:

Hb

TC

DC

ESR

Blood Urea

Serum Creatinine

Serum electrolytes

Liver function tests

ECG

Chest X Ray

Pre operative physical status: ASA grade I II

Inclusion criteria

1. Patients in age group of 18 to 60 years of both sex.
2. ASA grade 1 and 2.

Exclusion criteria

1. ASA grade >2.
2. Patient refusal.
3. Patients who are allergic to the protocol drug.
4. Patients in whom conversion to open cholecystectomy is done for any reason.
5. Placement of drain intraoperatively.
6. Previous upper abdominal surgery.
7. Spillage of stone or bile intraoperatively.

Diagnosis:

Proposed surgery:

Patients will be allocated by random number table into group A and group B. All patients will receive alprazolam 0.5mg orally and ranitidine 150mg orally the previous night of surgery.

All patients will undergo similar general anaesthetic procedure. Pneumoperitoneum is produced by insufflation of carbon dioxide with the method of open laparoscopy using Hassan's cannula and four port laparoscopy is carried out with gas pressure maintained between 12-14mmhg in both cases and controls. The resected gall bladder is delivered from the epigastric port. After delivery of the gall bladder,

Group (A) – *study group* – patients will receive 20ml 0.5% bupivacaine intraperitoneally at the gall bladder bed and under right and left hemidiaphragm at the end of surgery through laparoscope port.

Group (B) – *placebo group* – patients will receive 20ml normal saline intraperitoneally at the same location at the end of the surgery.

In all cases, residual carbon dioxide is evacuated at the end of the procedure by compressing the abdomen. The closure of the umbilical port is done in two layers using vicryl, whereas the other port sites are closed in single layer.

Patients are cared for in the recovery room according to the standard protocol and then they are shifted to the postoperative ward. The time of arrival in the postoperative ward is defined as zero hour postoperatively. Pain intensity is measured at fixed time interval at 6 hrs, 12 hrs, 24 hrs respectively using visual analogue scale. Presence of shoulder pain is also assessed during the same interval.

Patients are given analgesia intramuscularly (diclofenac sodium 50mg) on request and the total number of doses of analgesia used is recorded in a standard proforma.

SHOULDER TIP PAIN: YES/NO

POSTOPERATIVE PAIN:

	Site	**Character**	**Duration**	**Pain score**
6 hrs				
12 hrs				
24 hrs				

ANALGESIC CONSUMPTION:

Analgesic	Dose	Time

PAIN SCORING: VISUAL ANALOUGE SCORE ON A SCALE OF 10.

0: **NO PAIN**

10: **MAXIMUM PAIN.**

score	0	1	2	3	4	5	6	7	8	9	10
Time											
6hrs											
12hrs											
24hrs											

Date :

ANNEXURE III – PHOTOGRAPHS

Photograph 1. Monitor, gas insufflator, light source

Photograph 2. Laparoscopic instruments

Photograph 3. Laparoscopic ports with instruments

Photograph 4. Gall bladder fossa - Site of drug instillation

Photograph 5. 0.5% Bupivacaine vial

ANNEXURE IV – MASTER CHART

Group A

Sl. No.	I. P. No.	Age (Years)	Sex	ASA Grade	Pulse Rate (/min)	Blood pressure (mm Hg)		Respiratory Rate (/min)	VAS Score			RA < 6 hours	RA	STP
						SBP	DBP		6 Hours	12 Hours	24 Hours			
1	308708	42	M	2	74	134	82	12	2	1	0	0	1	N
2	308708	55	F	2	76	146	94	13	0	2	0	0	1	N
3	308708	35	F	1	80	126	90	16	0	2	0	0	2	N
4	308708	50	M	1	92	130	82	16	0	3	0	0	2	N
5	308708	36	F	2	70	132	76	14	3	0	0	0	1	N
6	308708	29	M	1	88	112	70	14	4	1	0	0	1	N
7	308708	44	F	1	76	134	90	16	3	1	0	0	2	N
8	308708	22	F	1	106	110	74	20	4	2	1	0	1	N
9	308708	28	F	1	88	120	70	18	3	0	0	0	2	N
10	308708	33	F	1	86	110	70	13	2	2	0	0	2	N
11	308708	38	F	1	96	100	70	16	6	3	1	1	2	N
12	308708	52	M	1	88	128	82	13	7	4	1	1	1	N
13	308708	57	M	2	76	132	94	12	0	0	0	0	1	N
14	308708	48	F	2	72	140	90	14	0	1	0	0	1	N
15	308708	53	F	2	86	142	88	12	3	1	0	1	1	N
16	308708	45	F	2	72	122	70	12	0	5	0	0	1	N
17	308708	51	M	1	90	120	72	18	5	2	2	0	1	N
18	308708	54	F	1	74	136	90	14	0	1	0	0	0	N

Group B

Sl. No.	I. P. No.	Age (Years)	Sex	ASA Grade	Pulse Rate (/min)	Blood pressure (mm Hg)		Respiratory Rate (/min)	VAS Score			RA < 6 Hours	RA	STP
						SBP	DBP		6 Hours	12 Hours	24 Hours			
1	308938	30	F	1	84	114	72	13	6	2	0	1	2	N
2	310060	41	M	1	76	134	86	14	0	3	0	1	2	N
3	310541	46	F	1	90	120	72	14	4	2	0	1	3	N
4	310704	31	M	1	88	122	70	16	5	1	1	1	3	Y
5	310509	48	F	2	88	142	90	15	3	3	1	1	3	N
6	312967	55	F	1	78	132	84	16	5	2	1	1	3	N
7	314113	54	M	1	70	134	86	14	6	4	0	1	3	N
8	317686	30	M	1	86	124	82	15	6	2	0	2	3	N
9	322743	22	F	1	88	110	72	16	5	4	0	1	3	N
10	326135	57	M	2	84	130	80	14	4	2	0	2	5	N
11	327048	40	F	1	84	124	82	16	5	3	0	1	3	N
12	327164	45	F	1	80	110	70	14	5	1	0	1	3	N
13	331582	39	M	1	78	128	80	14	5	3	0	1	4	N
14	333683	56	M	1	80	124	72	13	3	1	0	2	4	N
15	334455	32	F	1	86	122	70	14	5	5	2	1	4	Y
16	337284	47	F	2	90	118	74	14	5	4	2	1	3	N
17	338102	48	F	1	80	132	86	13	0	4	0	1	3	N
18	346256	45	F	2	78	138	74	15	5	2	0	1	3	N

ANNEXURE IV - KEY TO MASTER CHART

ASA	:	American Society of Anesthesiologist
ASA	:	American society of anaesthesiologists
DBP	:	Diastolic Blood Pressure
F	:	Female
F	:	Female
IP NO.	:	Inpatient number
M	:	Male
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
STP	:	Shoulder tip pain
VAS	:	Visual Analogue Scale
Y	:	Yes