INTRODUCTION

Bile is produced by the liver to perform many functions, including elimination of waste processed by the liver and digestion of fat. Bile is temporarily stored in the gallbladder situated underneath the liver before it reaches the small bowel.

A gallstone is a crystalline concretion formed within the gall bladder by accretion of bile components. These calculi are formed in the gallbladder but may distally pass into other parts of the biliary tract such as the cystic duct, common bile duct, pancreatic duct or the ampulla of Vater.[1]

Concretions in the gallbladder are called gallstones. Gallstones are present in about 5% to 25% of the adult western population. Between 2% and 4% become symptomatic within a year. Symptoms include pain related to the gallbladder (biliary colic), inflammation of the gallbladder (cholecystitis), obstruction to the flow of bile from the liver and gallbladder into the small bowel resulting in jaundice (yellowish discolouration of the body usually most prominently noticed in the white of the eye, which turns yellow), bile infection (cholangitis), and inflammation of the pancreas, an organ that secretes digestive juices and harbours the insulin-secreting cells that maintain blood sugar level (pancreatitis). Rarely, in cases of severe inflammation, gallstones may erode through the gallbladder into adherent bowel potentially causing an obstruction termed gallstone ileus.[1]

Presence of gallstones in the gallbladder may lead to acute cholecystitis, an inflammatory condition characterized by retention of bile in the gallbladder and often secondary infection by intestinal microorganisms, predominantly Escherichia coli, Klebsiella Enterobacter, and Bacteroides species.[2] Presence of gallstones in other parts of the biliary tract can cause obstruction of bile ducts, which can lead to serious conditions such as ascending cholangitis or pancreatitis. Either of these two conditions can be life-threatening and are therefore considered to be medical emergencies.[3]

Cholelithiasis is the most common affliction of the hepatobiliary system and cholecystectomy is the commonest surgical intervention. Ever since the operative management of gallstones dawned on the surgical arena, it has been in a state of continuous evolution, exactly parallel to the evolution of surgical techniques and technical armamentarium.

➢ History and evolution of laparoscopic cholecystectomy (LC)

- **Stal Pert Von Der Weil**[4] had the first interaction of gallstones and surgery at 1687 while operating upon a patient of peritonitis, found gallstones during performing the surgery and he decided to remove the gallbladder as well.[4]

- **Carl Johann Langenbuch**[5] developed the technique of open cholecystectomy a century ago. This technique received little recognition but later became the gold standard for the definitive management of symptomatic cholelithiasis.[5]

- **Mirizzi**[6] 66 years ago made a major change in the operation and introduced the technique of cholangiography for the detection of common bile duct stones.[6]

- **Prof Dr Med Erich Mühe of Böblengen,**[7] in Germany in 1985 introduced LC and it was proved to be a new era in the management of cholelithiasis. Since the performance of the first LC, this procedure overtook open cholecystectomy as the treatment of choice in cholelithiasis.[7]

- **In March 1987 Dr. Mühe**[8] was completing a gynecologic laparoscopy on a woman who was also suffering from symptomatic gall stones, he shifted his laparoscope to the subhepatic area. Upon finding a comparatively free and supple gallbladder, he decided to remove it laparoscopically, instead of opening it up. He performed the procedure successfully and the patient recovered without complications.[8]

- **In September 1992, a National Institute of Health (NIH) consensus conference** concluded that LC was the treatment of choice for cholelithiasis.[9]

- The conventional LC was done by four ports; a 10mm optical port at umbilicus, a 10mm and a 5mm port in epigastrium and in the midclavicular line, respectively for the surgeon to work, and a 5mm port in the midaxillary line at the umbilical level for the assistant to retract the gallbladder fundus.

- **In 1995 Dr. Slim**[10] made many refinements including reduction in the port size and number. He did first LC safely with only three ports.[10] Some surgeons have argued that the fourth trocar may not be necessary and the surgery can be performed safely without its use.[11]

- **In 1997** with further evolution of the technique and increase in surgical experience, some surgeons tried LC via two ports only. This required the introduction of transabdominal sutures through the anterior abdominal wall for retracting the gallbladder while dissection.[12]

- **In 2001** it was the era of single port laparoscopy.[13] It required a singl incision **(single –incision laparoscopic cholecystectomy SILC)** and the use of a special port called the **R-port**.[13] The R-Port is a Tri-port that allows the ingress of three 5mm instruments through a single port.[13]

- **In 2001** for a few surgeons, this was not enough, and no scar laparoscopy came into being called **NOTES (natural orifice transluminal endoscopic surgery)**.[13] This entails the use of natural orifices for the removal of the diseased organ. NOTES is an area of new development with potential advantages for patients. However, technical and ethical challenges involved in perforation and closure of a healthy organ, as seen in transgastric access, and lack of comprehension of physiopathology of these approaches have not allowed wide clinical use.

- **In March 2006**, a 43-year-old female patient with symptomatic cholelithiasis was submitted to elective NOTES using a colonoscope, endoscopic graspers, and vaginal platform instruments.[14] Gallbladder can be removed through transanal, transvaginal, transcolonic and transgastric access with flexible endoscopic instruments, but these techniques are still under development.[14]

- **In 2010 Dr. Chalkoo and his collegue at Government Medical College, Srinagar**, **India** made developments in refining the open approach to make it less invasive. For example, they made a technique, (the Chalkoo innovation)[15], in which we make an oblique 2.5 cm long incision in the right hypochondrium and perform cholecystectomy using retractors.

- In this approach, the cystic artery and cystic duct are tied with sutures using two long Kelly forceps. The results of this procedure are comparable to the LC and it is recommend wherever laparoscopy is not available, feasible or the patient cannot afford it.[15]

- **In the last five years** with the era of robotics, robotic and assisted LC is now being performed successfully in experimental animals and volunteers and likely to have a good future.[16-19] Even though surgeons have come far in the surgical management of gallstones, the field is still open for innovation.

➢ Advantages of LC over open cholecystectomy.[20, 21]

1) Decrease wound size

Most of the trauma of an open cholecystectomy is inflicted because the surgeon must have a wound large enough to give adequate exposure for safe dissection. This was decreased by laparoscopy by more access to target site.

2) Decrease wound complications as infection, dehiscence, bleeding, herniation and nerve entrapment

The wound often causes morbidity, by decreasing the size of the wound there is less liability to encounter complications as infection, bleeding, dehiscence and nerve injury or entrapment.

3) Decrease wound pain

Pain of the wound prolongs recovery time, and by reducing mobility, contributes to an increased incidence of pulmonary collapse, chest infections and deep vein thrombosis. Mechanical and human retractors cause additional trauma. Body wall retractors tend to inflict localized damage that may be as painful as the wound itself.

In contrast during laparoscopy the retraction is provided by low pressure pneumoperitoneum, providing a diffuse force applied gently and evenly over the whole body wall causing minimal trauma.

4) Improved mobility

By decreasing trauma and pain to the wound, patients can regain their activity and ability of rapid ambulation postoperatively. Rapid recovery after LC and increasing experience with its postoperative course has led to progressively shorter postoperative stays and recent trend of true ambulatory LC without an overnight admission which is called outpatient laparoscopic cholecystectomy (OPLC).[22-24]

5) **Decrease fluid and heat loss**

Exposure of any body cavity to the atmosphere also causes morbidity through cooling and fluid loss by evaporation. During open cholecystectomy, exposure of the peritoneum to the atmosphere leads to fluid loss by evaporation according to the size of the wound. Fluid loss should be calculated and corrected during operation. In the contrary during LC incisions are too small to provide area of exposure to peritoneum, so there much less fluid and heat loss.

6) **Decrease postoperative adhesions**

Incidence of postoperative adhesions has been reduced by the use of laparoscopy because there is less damage to delicate serosal coverings. In handling intestinal loops, surgeon and assistant disturb peristaltic activity of the gut and provoke adynamic ileus.

7) **Economic benefits**

Shorter hospital stay and less side effects in postoperative periods leads to early return to work and normal activity. Shorter hospital stay provide less expenses needed during the course of postoperative period and decrease nosocomial complications like infections.

➢ Operative technique of LC:

1) Insertion of trocars and starting pneumoperitoneum

- Laparoscopic surgery starts with the intraperitoneal insufflation through a veress needle inserted into a small infra-umbilical incision or through the umbilicus itself.
- An electronic variable flow insufflator terminates flow when a preset intra-abdominal pressure has been reached (12-14 mmHg).
- A cannula then is inserted in place of the needle to provide and maintain insufflation adequate for surgery.
- A video laparoscope is inserted through the cannula and operative field is visualized by high-resolution television camera and monitor systems.[25, 26]
- Patient position is turned into head up (anti trendelenburg) with left lateral tilting.

2) Diagnostic laparoscopy

- The operator places the laparoscope at the umbilicus. Mandatory inspection of viscera beneath the trocar rules out injury, no matter how simple insertion has been.[27]

- Surgeon inspects the liver to rule out any abnormality, evaluates the status of the gall bladder (GB), the presence of any adhesions, or any other pathology.

- The surgeon places the high epigastric port at the level of the liver edge so that it is at the level of xiphisternum or between xiphoid and costal margin on the patient's right.[28, 29]

- The midclavicular (MCL) port is usually placed high up, lateral to the GB, and should be placed on a trajectory as if one were trying to impale the GB.

- The most lateral port should be at the anterior axillary line and is used for the fundus grasper. It is important to grasp the most floppy portion of dome of the fundus with an atraumatic grasper and not to grasp too much tissue, because that makes it difficult to pull the GB up over liver edge, a maneuver that allows for better traction on the GB.[30]

- The fundus then needs to be pulled over the edge of liver and retracted toward the mid clavicular line, or even more laterally toward the right shoulder. More medial retraction closes the triangle of Calot, whereas traction toward the right shoulder tends to open this triangle up.[30]

3) Exposure of the Calot's triangle

- Once retraction of the GB fundus has been established, the GB must be retracted in an appropriate fashion to splay open Calot's triangle. The GB body just proximal to the infundibulum must be retracted laterally, at a right angle to the CBD. This retraction is imperative to open up a suitable window and allows for progressive distraction of the GB and cystic duct from the common bile duct.[30]

- The anterior and posterior peritoneum overlying Calot's triangle is incised, usually with the L-hook, and the space is teased open from lateral to medial by gently pulling the peritoneum and fatty tissue away from the GB. This process invariably leaves small bands of tissue that can safely be divided by the L-hook.[30, 31]

- A blunt dissecting tool spreading the tissues apart, usually used parallel to the cystic duct/artery, can hasten this dissection and reveal small tethering bands or lymphatics that can

be divided by the L-hook. None of these divided structures should be large enough to be considered to be a major duct or vessel (cystic duct, cystic artery, CBD, right hepatic artery).

- Mass division or clipping of any large clump of tissue or duct structure should not occur. Eventually, using this technique, the entire window must be opened.

- Opening this window allows for the critical view. Occasionally, the cystic artery is divided early. This procedure allows for more distraction of the GB laterally and opens the window even wider, lengthening the cystic duct and enlarging the safety zone for dissection.[32]

- The window is open when all tissue except for the cystic artery and cystic duct has been divided in the triangle of Calot, and the dissection has been performed so that there is separation of the GB well onto the liver bed, precluding the possibility that any ductal structure could reenter the liver.[32]

4) Extent of dissection

- Extent of dissection before division of cystic artery and cystic duct is the most important feature of LC. In every case a funnel must be seen and exposed (ie, the normal tapering of GB from body to infundibulum to cystic duct).[33]

- The window, in which the triangle of Calot is found, must be opened well onto the liver bed using the techniques described earlier to ensure that tubular structures do not head back into the liver.

- Cystic duct must be dissected or visualized to the extent that when the lowest clip is placed on it a clearly tubular structure is seen below it; this prevents the inadvertent clipping of a tented CBD. One must be dogmatic about these dissection principles to minimize the risk for CBD injury.[33]

5) Removal of the gall bladder

- Once cystic duct is clipped and transected, removal of GB from the liver bed is facilitated by to-and-fro retraction. This process allows sequential dissection first of peritoneum, next layer of tissue on the medial aspect of GB, and then lateral aspect. Back and forth, each layer should be taken along a wide swath.[31]

- Routine extraction is through the umbilical port. If the GB is friable, or has a hole, it must be placed in a bag to avoid bile leakage or stone spillage.[31]

➢ Anaesthesia for LC

Preoperative evaluation

Patients should be assessed by anaesthetic team. It is crucial in identifying and stratifying risk to ascertain the level of perioperative care required, and also each individual's suitability for surgery. Detailed history taking and examination of the patients should be done. Investigations are done according to the patient general condition.

Premedications: benzodiazepines like midazolam are commonly used in LC to provide anxiolysis and amnesia. Antiemetic drugs like ondansetron and prokinetic drugs like metoclopramide are mandatory for prevention of postoperative nausea and vomiting.

a) General anaesthesia:

Monitoring: standard monitoring including ECG, non invasive blood pressure, oxygen saturation and endtidal capnoghraphy is mandatory during the surgery. Changes in the haemodynamics and endtidal capnography are detected and corrected.

Induction: intravenous anaethetic agents like thiopentone, propofol and etomidate may be used. Propofol, however, does have the advantage of producing less postoperative nausea and vomiting (PONV).[34]

Analgesics: Opioid supplementation like fentanyl is the most appropriate to prevent stress response after intubation. A major advantage of fentanyl is that doses sufficient to attenuate cardiovascular responses can be used without the risk of postoperative respiratory depression and delayed recovery. However, postoperative analgesia should be considered.

Preemptive analgesic techniques using nonopioids such as acetaminophen, non steroidal anti-inflammatory drugs, α 2-agonists, and N-methyl D-aspartate antagonists proved to be of benefit in multimodal analgesia and ambulatory surgery where rapid recovery is the

aim. Non-opioids are increasingly used during laparoscopy to decrease opioid requirements and avoid delayed recovery.[35]

Muscle relaxation: atracurium and cisatracurium make it feasible to reverse residual neuromuscular block even if the last increment of a drug was given within the previous 5 to 10 minutes. Some anesthesiologists avoid the use of reversal drugs because it has been suggested that they increase the incidence of PONV.[36] However, others have not found an increase in PONV associated with the use of neostigmine and glycopyrrolate to reverse residual neuromuscular block.[37] More importantly, even minor degrees of residual neuromuscular block can produce distressing symptoms, such as visual disturbances, facial and generalized weakness, and the inability to sit without assistance.[38] These symptoms can be present despite signs of clinical recovery from neuromuscular block and can prolong the recovery process. These findings should present an incentive to minimize the use of neuromuscular blocking drugs in ambulatory anesthesia. When they are used, however, reversal drugs should be administered in appropriate doses without hesitation.

Control of the airway**:** general anesthesia with endotracheal intubation and controlled ventilation is certainly the safest technique, it is recommended for inpatients and for long laparoscopic procedures.

General anesthesia without intubation can be performed safely and effectively with a ProSeal laryngeal mask airway (LMA) in nonobese patients.[39] LMA is as effective as an endotracheal tube for positive pressure ventilation without clinically important gastric distension in nonobese and obese patients.[39] However, it should be restricted to short procedures performed using low IAP and small degrees of tilt. It results in less sore throat and might be proposed as a safe alternative to endotracheal intubation. Furthermore, it allows controlled ventilation and accurate monitoring of endtidal capnography.[40]

Endotracheal intubation is still preferred due to decreased thoracopulmonary compliance during pneumoperitoneum resulting in airway pressures exceeding 20 cm H2O. Because the LMA cannot guarantee an airway seal above this pressure, its use for controlled ventilation should be limited to healthy, thin patients.

Nasogastric tube is used to deflate the stomach from the air that may be entered during induction and ventillation. Also to eavacuate the stomach from any food remnants that provide a clear field for performing the surgery.

Maintenance of anaesthesia: inhalational agents like isoflurane, sevoflurane and desflurane are used to maintain level of anaesthesia.

Mechanical ventilation: Adjusted to maintain endtidal carbondioxide (etco2) at approximately 35 mm Hg by increasing minute ventilation about 15% to 25%. In patients with chronic obstructive pulmonary disease (COPD) and in patients with a history of spontaneous pneumothorax or bullous emphysema, an increase in respiratory rate rather than tidal volume is preferable to avoid increased alveolar inflation and reduce the risk of pneumothorax.[41]

Recovery and postoperative care: Haemodynamic monitoring should be continued in the postanaesthesia care unit. Hemodynamic changes induced by the pneumoperitoneuum, and more particularly the increased systemic vascular resistance, outlast the release of pneumoperitoneuum.

Despite the reduction in postoperative pulmonary dysfunction, partial pressure of arterial oxygen ($PaO_{2)}$ still decreases after LC. Increased oxygen demand is observed after laparoscopy. Although laparoscopy tends to be considered a minor surgical procedure, oxygen should be administered postoperatively, even to healthy patients.

Finally, prevention and treatment of nausea, vomiting, and pain are important, particularly after outpatient laparoscopic procedures.

b) **Regional anaesthesia**, namely epidural and spinal anaesthesia, have the advantages of reducing the metabolic and hemodynamic responses, as well as reducing the need for postoperative sedatives and narcotics.[42] Yet patient cooperation, an experienced skilled surgeon, reduced intra-abdominal pressure and a high level of anaesthesia for complete muscle relaxation and prevention of diaphragmatic irritation, are necessary to guarantee the success of regional anaesthesia.[43]

I) Epidural anaesthesia

- It is considered as a safe alternative to general anesthesia for outpatient laparoscopy without associated respiratory depression because the respiratory control mechanism remains intact, allowing patients to adjust their minute ventilation and, therefore, maintaining an unchanged etco2.[44]

- An epidural catheter is introduced at T10/11 intervertebral space by loss of resistance technique, and titration by a bolus of 0.5% bupivacaine is administered to achieve the desired level of sensory block. Depending on the patient's pain threshold and the segmental level of analgesia achieved, incremental doses of 2 ml of 0.5% bupivacaine to maintain the level of the sensory block between T4 and L5. Opioids may be added to bupivacaine as fentanyl, alfentanil, pethidine or morphia.

- Patients can breathe spontaneously. No nasogastric tube is inserted but provided that fasting hours is about 10 hours to avoid presence of food remnants. Low-pressure (10 mmHg) pneumoperitoneum is created. LC is performed according to the standard technique.

- Shoulder pain, which is secondary to diaphragmatic irritation that results from abdominal distension, is incompletely alleviated using epidural anesthesia alone. Extensive sensory block (T4 through L5) is necessary for surgical laparoscopy and may also lead to discomfort. Epidural administration of opiates and/or clonidine might help to provide adequate analgesia.[45]

II) Spinal anaesthesia Spinal anesthesia is the simplest and most reliable of the regional anesthesia techniques. It has become more common in ambulatory practice with the introduction of fine-gauge pencil-point needles.

It can be used for LC without major impairment of ventilation. LC has been successfully performed using spinal anesthesia in COPD patients.

The metabolic response is reduced by spinal anesthesia. Spinal anesthesia reduces the need for sedatives and narcotics, produces better muscle relaxation, and can be proposed for laparoscopic procedures.

Shoulder-tip pain from diaphragmatic irritation and discomfort from abdominal distention are incompletely alleviated using spinal anesthesia alone. Extensive sensory block (T4-L5) is necessary for surgical laparoscopy and may also lead to discomfort.

- **Technique:**

All patients should receive preload solution 10-15 mL/kg before starting intratheccal injection. Standard monitoring is mandatory to record the hemodynamic changes during spinal anaethesia. The puncture is usually performed at L_{2-3} interspace using a 25 gauge or less spinal needle. The volume of the anaethetic agent is adjusted according to the level needed and the patient height. It varies from 3 to 4 ml of bupivacaine. Adding novel adjuvants in the subarachnoid space prolongs the analgesic effect and also allows reduction in the total dose of local anaesthetic used. Novel adjuvants studied to date include: opioids, clonidine, magnesium, ketamine, midazolam and dexmeditomidine.[46-49] After injection, patient lies in the supine position till the level of sensory block reached T4. When sensory block reached T4 dermatome and Bromage score 3 (patients can not flex ankle, knees or hip).[50] surgery is allowed to start. Oxygen supplement is given throughout the procedure.

- **<u>Choice of the anaesthetic technique for laparoscopic cholecystectomy:</u>**

General anaesthesia is the most common technique used. It was thought to be the safest technique to prevent aspiration during surgery. It provide complete level of anaesthesia and muscle relaxation.

Disadvantages of general anaesthesia include side effects of the drugs used like hypersensitivity, hypotension, nausea and vomiting, respiratory depression and malignant hyperthermia. Sore throat is common after endotracheal intubation and nasogastric tube insertion. Patients having respiaratory problems or hepatic patients have high risk of undergoing general anaethesia.

Epidural anaethesia: avoids complications of general anaesthesia such as side effects of drugs and sore throat after intubation but it is a difficult technique and it requires special skills to be done. Its block is delayed and need time to reach the level needed of blockage.

Systemic toxicity of local anaesthetic agent, migration of the epidural catheter or infection are major complications that may accompany epidural anaesthesia.[44]

- **Spinal anaesthesia**: is a less invasive technique and has lower complication and mortality rates compared with general anaesthesia.[51-54]

- It provides intraoperative analgesia and muscle relaxation in conscious and compliant patients without any systemic drugs that makes it preferred in patients with liver or kidney diseases.[52]

- It avoids the risks of hypoxia or hypercapnia accompanied with general anaethesia.[54, 55]

- It provides more dense block and more rapid onset than epidural anaesthesia with avoiding complications of catheter insertion.

- It also provides potent postoperative analgesia with lesser consumption of systemic opioid than general anaesthesia.[52]

- Spinal anaesthesia provides adequate level of analgesia for a few hours after completion of surgery due to the existing activity of injected agents in the subarachnoid space.[56]

- There are also beneficial effects of neuraxial blockage on the cardiovascular system including amelioration of the hypercoagulable state associated with surgery, sympathectomy mediated increase in blood flow, improved oxygenation, and suppression of the neuroendocrine stress response to surgery.[54] Clinically significant alterations in pulmonary physiology are usually minimal with the neuraxial blockage produced by spinal anesthesia.[57]

- For patients with coronary artery disease, a decreased stress response and blockage of the sympathetic cardiac accelerator fibers that arise at T1-T4 translate into less perioperative ischemia and therefore reduced morbidity and mortality.[57]

- Neuraxial blockage may also reduce the incidence of venous thrombosis and pulmonary embolism in high risk patients.[57]

➢ Physiological changes during LC:

Cardiopulmonary changes during laparoscopy are complex and depend on the interaction of the patient's pre-existing cardiopulmonary status, the anaesthetic technique and several surgical factors including intra-abdominal pressure (IAP), carbon dioxide (CO2) absorption, patient position and duration of the surgical procedure. Although, physiological changes are well tolerated by most healthy patients, they could have adverse consequences in the elderly and patients with limited cardiopulmonary reserve.[58]

1) **Cardiovascular changes:**

Hemodynamic changes observed during laparoscopy result from the combined effects of pneumoperitoneum, patient position, anesthesia, and hypercapnia from the absorbed CO_2. In addition to these pathophysiologic changes, reflex increase of vagal tone and arrhythmias can also develop.

a) Reduction of cardiac output: Peritoneal insufflation to IAPs higher than 10 mm Hg induces significant alterations of hemodynamics. The decrease in cardiac output is proportional to the increase in IAP.[59] Cardiac output has also been reported to be increased or unchanged during pneumoperitoneum.[60, 61] These discrepancies might be caused by differences in rates of CO_2 insufflation.[61]

However, most studies have shown a fall of cardiac output (10% to 30%) during peritoneal insufflation whether the patient was placed in the head-down or head-up position.[62, 63]

b) Reduction of the venous return: a decrease in venous return is observed after a transient increase in venous return at low IAPs (<10 mm Hg) this is due to caval compression.[64]

The fact that atrial natriuretic peptide concentrations remain low despite increased pulmonary capillary occlusion pressure during pneumoperitoneum further suggests that abdominal insufflation interferes with venous return.[65] The reduction in venous return and cardiac output can be attenuated by increasing circulating volume before the pneumoperitoneum is produced.

c) Pooling of blood in the legs and an increase in venous resistance. The decline in venous return, which parallels the decrease in cardiac output is confirmed by a reduction in left ventricular end-diastolic volume measured using transesophageal echocardiography.[65] It can be prevented by intermittent sequential pneumatic compression device, or by wrapping the legs with elastic bandages.[66]

d) increased systemic resistance: compression over the abdominal aorta leading to increase systemic resistance and after work. All studies describe an increase in systemic vascular resistance during existence of pneumoperitoneum. This increase in afterload is not a reflex sympathetic response to decreased cardiac output. Systemic vascular resistance was reported to be increased in studies where no decrease in cardiac output was found. Although the normal heart tolerates increases in afterload under physiologic conditions, the increases in afterload produced by the presence of a pneumoperitoneum can be deleterious to patients with cardiac disease.(67)

The increase in systemic vascular resistance is affected by patient position. The Trendelenburg position attenuates this increase; the head-up position aggravates it. The increase in systemic vascular resistance can be corrected by administration of vasodilating anesthetic agents, such as isoflurane, or direct vasodilating drugs, such as nitroglycerin or nicardipine.

e) Heart rate remains unchanged or increased only slightly.(68)

f) Cardiac filling pressure rises during peritoneal insufflation. The paradoxical increase of this pressure can be explained by the increased intrathoracic pressure associated with pneumoperitoneum.(68)

g) Ejection fraction of the left ventricle, assessed by echocardiography, does not appear to decrease significantly when IAP increases to 15 mm Hg.(68)

h) Cardiac Arrhythmias during Laparoscopy

Arrhythmias during laparoscopy have several causes. The increased $PaCO_2$ may not be the cause of arrhythmias occurring during laparoscopy. Arrhythmias do not correlate with level of partial pressure of arterial carbondioxide and may develop early during insufflation, when high $PaCO_2$ is not present.(69)

Reflex increases of vagal tone may result from sudden stretching of the peritoneum. Bradycardia, cardiac arrhythmias, and asystole can develop. Vagal stimulation is accentuated if the patient is taking β-blocking drugs. These events are easily and quickly reversible.(70)

Treatment consists of interruption of insufflation, atropine administration, and deepening of anesthesia after recovery of the heart rate.

Cardiac irregularities occur most often early, during insufflation, when pathophysiologic hemodynamic changes are the most intense. For this reason, arrhythmias may also reflect intolerance of these hemodynamic disturbances in patients with known or latent cardiac disease. Gas embolism can also result in cardiac arrhythmias.[71]

2) Increase in the Partial Pressure of Arterial Carbon Dioxide (PaCO2).

During uneventful CO_2 pneumoperitoneum, the $PaCO_2$ progressively increases to reach a plateau 15 to 30 minutes after the beginning of CO_2 insufflation in patients under controlled mechanical ventilation during laparoscopic cholecystectomy in the head-up position[72, 73] Any significant increase in $PaCO_2$ after this period requires a search for a cause independent of or related to CO_2 insufflation, such as CO_2 subcutaneous emphysema. The increase in $PaCO_2$ depends on the IAP.[74]

During laparoscopy with local anesthesia, $PaCO_2$ remains unchanged but minute ventilation significantly increases.[44] Although mean gradients between $PaCO_2$ and the end-tidal carbon dioxide tension ($PETCO_2$) do not change significantly during peritoneal insufflation of CO_2, individual patient data regularly show variations of this difference during pneumoperitoneum.[75, 76] $PaCO_2$ increase more in ASA class II and III patients than in ASA class I patients. These findings have been documented in patients with COPD.[77, 78]

3) <u>Pulmonary changes:</u>

- **Peak inspiratory and mean airway pressures** are increased which can cause alveolar barotraumas. This increase is due to increased intrathoracic pressure and upword movement of the diaphragm during insufflations.[79]
- **Functional residual capacity and total lung capacity:** Increased IAP displaces the diaphragm upward and decreases functional residual capacity and total lung capacity resulting in basal atelectasis and increased airway pressures.[80]

- **Minute ventilation** is increased to maintain normocarbia and increases peak airway pressures. These pulmonary changes are compounded with those caused by changes in position.[80]

- LC is unique in that a change in body position from Trendelenburg when establishing pneumoperitoneum to reverse Trendelenburg during dissection of the gall bladder and other structures is necessary to avoid inadvertent bowel injury and to provide optimum exposure.[20]

4) <u>Renal changes:</u>

- Renal vein compression increases venous resistance, which impairs venous drainage. This appears to be the major cause of renal impairment.[81]

- Renal artery vasoconstriction is induced by the sympathetic nervous and renin-angiotensin systems, which are stimulated by the fall in cardiac output.[80]

- These changes result in progressive reduction in both glomerular perfusion and urine output.

Oliguria generally develops at intraabdominal pressure of approximately 15 mmHg.[80]

5) <u>Hepatic changes:</u>

The liver's ability to remove lactic acid is impaired by increases of intraabdominal pressure as small as 10 mmHg. This occurs even in the presence of a normal cardiac output and mean arterial blood pressure.[80]

Hepatic and portal blood flow decreases with abdominal insufflations to 14 mm Hg. A reduction in portal venous blood flow during pneumoperitoneum may lead to hepatic hypoperfusion and acute hepatocyte injury. Portal hypoperfusion can lead to transient elevation of liver enzymes.

6) <u>Central nervous system changes:</u>

Intracranial pressure (ICP) : transiently increases during the short-lived elevation of intraabdominal pressure that occurs with coughing, defecating, or emesis.[80] ICP similarly appears to be elevated in the presence of sustained increase intra abdominal pressure which occurs during laparoscopic cholecystectomy can lead to a critical decrease in cerebral perfusion and progressive cerebral ischemia.

7) Postoperative Nausea and Vomiting (PONV):

PONV can lead to delayed postanaesthesia care unit (PACU) and recovery room discharge and unanticipated hospital admission, thereby increasing medical costs. The etiology and consequences of PONV are complex and multifactorial, with patient-, medical- and surgery-related factors.[82]

- **Risk factors**:

a) Patient factors:

Female Gender had been identified as the strongest independent predictor for postoperative nausea, vomiting. The reason for increased female susceptibility to nausea and vomiting is unclear but persists well after menopause and most of the rest of a woman's life.[83]

History of PONV, Motion Sickness, or Migraine: Susceptibility to emetogenic stimuli varies among individuals according to history of PONV, history of motion sickness and history of migraine. Clearly, patients with a history of PONV were at higher risk for experiencing PONV. Indeed, the use of PONV history as a single predictor has been associated with a sensitivity of less than 50% to identify patients at risk for PONV.[84]

Age: In adults, although the incidence of PONV decreases with age, it has not always been a strong risk factor. In children with age of 3 years or older is associated with an increased risk for PONV.[84, 85]

b) Anaesthetic technique:

Opioids: Regardless of whether opioids are used intraoperatively or postoperatively, the available evidence suggests that the dose of opioid, rather than type, is one of the main predictors (or causes) for PONV.[86, 87]

Propofol and Inhaled Anaesthetics: Propofol is widely believed to have antiemetic properties.[88, 89] There are no differences in PONV among the volatile anesthetics isoflurane, enflurane, and sevoflurane. They all increase the incidence of PONV.[90, 91]

General anesthesia: is associated with a significantly higher incidence of PONV in comparison with regional anaesthesia.[92]

Duration of Anesthesia: There is a co-linearity between the duration of anesthesia and the postoperative nausea and vomiting.[93]

c) Surgical procedures

laparoscopic surgery and peritoneal irritation increases the tendency of PONV. Other surgeries like ear surgery, retinal surgery and strabismus surgery are associated with PONV.[93]

- **Prevention**

Selective 5-hydroxytryptamine (serotonin) receptor 3 (5-HT_3) antagonists such as ondansetron 4 mg (0.1 mg/kg in children), granisetron 0.01–0.04 mg/kg, and dolasetron 12.5 mg (0.035 mg/kg in children) are also extremely effective in preventing PONV and in treating established PONV.[94, 95]

It should be noted that unlike ondansetron, which is usually effective immediately, dolasetron requires 15 min for onset. An orally disintegrating tablet (ODT) preparation of ondansetron (8 mg) may be useful for treatment and prophylaxis against postdischarge nausea and vomiting. Metoclopramide, 0.15 mg/kg intravenously, is somewhat less effective but is a good alternative to 5-HT_3 antagonists. 5-HT_3 antagonists are not associated with the acute extrapyramidal (dystonic) manifestations and dysphoric reactions that may be encountered with metoclopramide or phenothiazine-type antiemetics.[96]

Transdermal scopolamine is effective but can be associated with troublesome side effects in some patients, such as exacerbating glaucoma, urinary retention, and difficulty in visual accommodation.[97]

8) <u>Postoperative Pain:</u>

Postoperative pain is variable in duration, intensity and character and is the main factor delaying discharge of patients undergoing day-care procedures including laparoscopy and hence adding to hospital cost.[80]

Even within the same type of procedure, pain after laparoscopic surgery may vary in quality and localization and is reported in several trials to be incisional, intra-abdominal or referred (shoulder tip).[80]

- The etiology is complex including

  a) somatic pain due to damage to abdominal wall structures.

  b) visceral pain trauma and inflammation and peritoneal irritation because of CO2 entrapment beneath the hemidiaphragms.[98]

Postoperative pain may be transient and most of the time lasts for 24 hours and sometimes even up to 3 days. Intensity of pain is more immediately after surgery and less after 24 hours.[98]

➢ Alternatives to CO2 pneumoperitoneum

New approaches have been investigated to reduce pathophysiologic consequences of CO2 pneumoperitoneum

a) Inert gas

Insufflation of inert gas (e.g., helium, argon) instead of CO_2 avoids the increase in $PaCO_2$ from absorption, consequently, hyperventilation is not required.[99, 100]

Also, the ventilatory consequences of the increased intra abdominal pressure persist. The hemodynamic changes produced by pneumoperitoneum using inert gas are similar to those observed with CO_2. However, the use of these gases accentuates the decrease in cardiac output, whereas the increase in arterial pressure is attenuated.[100, 101] Unfortunately, the low blood solubility of the inert gases raises the issue of safety in the event of gas embolism.[102]

b) Gasless Laparoscopy

Another alternative is gasless laparoscopy. The peritoneal cavity is expanded using abdominal wall lift obtained with a fan retractor. This technique avoids the hemodynamic and respiratory repercussions of increased IAP and the consequences of the use of CO_2.[103, 104]

Renal and splanchnic perfusion is not altered.[105] Port-site metastases after laparoscopic surgery for cancer are reduced after gasless laparoscopy.[106] This technique, therefore, is appealing for patients with severe cardiac or pulmonary disease. However, gasless laparoscopy compromises surgical exposure and increases technical difficulty.[106] Combining abdominal wall lifting with low pressure CO_2 pneumoperitoneum (5 mm Hg) may improve surgical conditions.[106]

➢ Low pressure laparoscopy:

The above mentioned changes have led to suggestion of low-pressure pneumoperitoneum (< 12 mmHg) for laparoscopic cholecystectomy in cases of uncomplicated symptomatic gallstones as a recommended procedure as long as an adequate exposure is obtained with this technique.

Only when no adequate exposure of the surgical field is achieved, should a surgeon consider elevating the pneumoperitoneum pressure a higher value providing good exposure.[107]

Studies were made comparing between low pressure pneumoperitoneum versus high pressure pneumoperitoneum and there were no differences in the incidence of surgical complications or surgeon satisfaction between the two methods.[108-110]

➢ Advantages of low pressure laparoscopy:

It has the advantage of avoiding physiological changes during laparoscopy and much less shoulder pain postoperative.[111, 112] This technique will lead to improve patient satisfaction, decrease postoperative stay, decrease postoperative opioid usage and improve postoperative ampulation and recovery.[111, 112]

SUBARACHNOID BLOCKADE

Anatomical considerations

Vertevral column

There are 7 cervical, 12 thoracic and 5 lumbar vertebrae. The sacrum comprises 5, and the coccyx 4 fused segments.[113] The adult spine presents four curvatures: those of the cervical and lumbar zones are convex forwards (lordosis), those of the thoracic and sacral regions are concave (kyphosis). The former are postural, the latter are produced by the actual configuration of the bones themselves.[114] [figure. 1]

Spinal cord is continuous with the medulla oblongata above and tapers into the conus medullaris below, from which a thread like structure, the filum terminale, continues to be attached to the coccyx.[115]

Spinal Cord

- **Neuroanatomy:**

In the first-trimester fetus, it extends from the foramen magnum to the end of the spinal column. Thereafter, vertebral column lengthens more than spinal cord.

At birth, it ends at about the level of third lumbar vertebra.

In the adult, the caudad tip of spinal cord typically lies at the level of first lumbar vertebra. However, in 30% of individuals spinal cord may end at T12, while in 10% it may extend to L3.[116]

A sacral spinal cord has been reported in an adult.[116] Flexion of vertebral column causes the tip of spinal cord to move slightly cephalad.

Spinal cord gives rise to 31 pairs of spinal nerves, each composed of an anterior motor root and a posterior sensory root. Roots are in turn composed of multiple rootlets.[117]

The portion of spinal cord that gives rise to all of the rootlets of a single spinal nerve is called a cord segment. The skin area innervated by a given spinal nerve and its corresponding cord segment is called a dermatome. The intermediolateral gray matter of T1 through L2 spinal cord segments contains cell bodies of preganglionic sympathetic neurons.[118]

These sympathetic neurons run with the corresponding spinal nerve to a point just beyond intervertebral foramen where they exit to join the sympathetic chain ganglia.

Spinal nerves and their corresponding cord segments are named for the intervertebral foramen through which they run.[117]

In the cervical region, spinal nerves are named for the vertebra forming the caudad half of intervertebral foramen; for example, C4 emerges through an intervertebral foramen formed by C3 and C4. In the thoracic and lumbar region, nerve roots are named for the vertebrae forming the cephalad half of intervertebral foramen; for example, L4 emerges through an intervertebral foramen formed by L4 and L5. Because spinal cord ends between L1 and L2, the thoracic, lumbar, and sacral nerve roots run increasingly longer distances in the subarachnoid space to get from their spinal cord segment of origin to the intervertebral foramen through which they exit.[117] Those nerves that extend beyond the end of spinal cord to their exit site are collectively known as the cauda equina.

- **Coverings:**

It has three covering membranes or meninges arranged from inner aspect outwards as pia, arachonoid and dura mater.[119] Dural covering of the brain is a double membrane between which lie the cerebral venous sinuses.[120] [figure. 2]

It normally extends from the foramen magnum to the lower border of L1 vertebra in adults. Therefore, performing a lumbar (subarachnoid) puncture below L1 in an adult avoids potential needle trauma to the cord; damage to the cauda equina is unlikely as these nerve roots float in the dural sac below L1 and tend to be pushed away (rather than pierced) by an advancing needle.[115, 121]

Lumbar puncture:

Spinal anaesthesia should be performed only after appropriate monitors are applied and in a setting where equipment for airway management and resuscitation are immediately available. Before positioning the patient, all equipment for spinal block should be ready for use, for example, local anesthetics mixed and drawn up, needles uncapped and so on. Preparing all equipment ahead of time will minimize time required to perform the block and thereby enhance patient comfort.

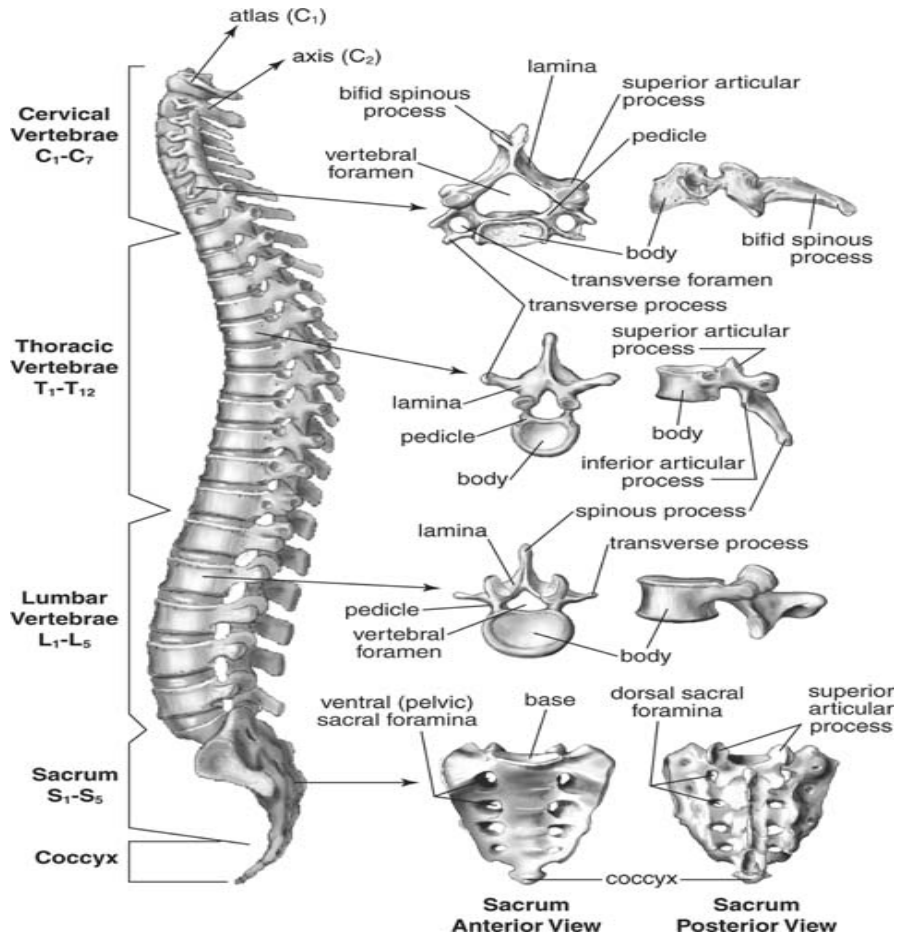

Figure (1): The vertebral column and the common features of the vertebrae.[121]

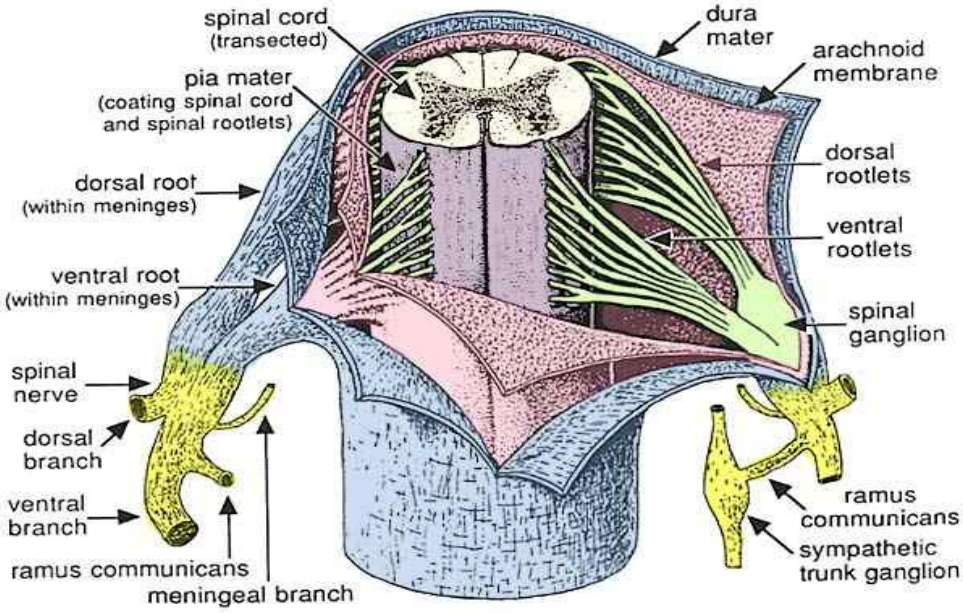

Figure (2): segment of the spinal cord and its coverings.[119]

Position

Poor positioning can turn an otherwise easy spinal anesthetic into a challenge for both anesthesiologist and patient.

Lateral position:

Spinal needles are most often inserted with the patient in lateral decubitus position However, both the prone jackknife and sitting positions offer advantages under specific circumstances.

Sitting position:

it is often easier to identify the midline with the patient sitting. In addition, sitting position allows one to restrict spinal block to sacral dermatomes (saddle block) when using hyperbaric local anesthetic solutions.[122]

In lateral decubitus position [figure. 3], patient lies with the operative side down when using hyperbaric local anesthetic solutions and with the operative side up when using hypobaric solutions, thus assuring that the earliest and most dense block occurs on the operative side.

The back should be at edge of the table so that the patient is within easy reach. Patient's shoulders and hips are both positioned perpendicular to the bed to help prevent rotation of the spine. Knees are drawn to the chest, neck is flexed, and patient is instructed to actively curve the back outward. This will spread spinous processes apart and maximize the size of the interlaminar foramen. It is useful to have an assistant who can help the patient maintain this position. Using iliac crests as a landmark [figure. 4], the interspaces are identified and the desired interspace chosen for needle insertion.[123, 124]

Interspaces above L2-3 are avoided to decrease risk of hitting spinal cord with the needle. Some find it helpful to mark spinous processes flanking the desired interspace with a skin marker. This obviates the need to reidentify the intended interspace after the patient is prepped and draped.

Patient is prepared with an appropriate antiseptic solution and drapped. All antiseptic solutions are neurotoxic, and care must be taken not to contaminate spinal needles or local anesthetics with the prepared solution.

Spinal needle is passed through the following structures [Figure. 5]: skin, subcutaneous tissue, supraspinous and interspinous ligaments, ligamentum flavum, and dura mater.[115] On puncturing the dura, a characteristic 'give' is often appreciated. On removal of the stylet from the needle, cerebrospinal fluid (CSF) should appear at the hub of the needle.

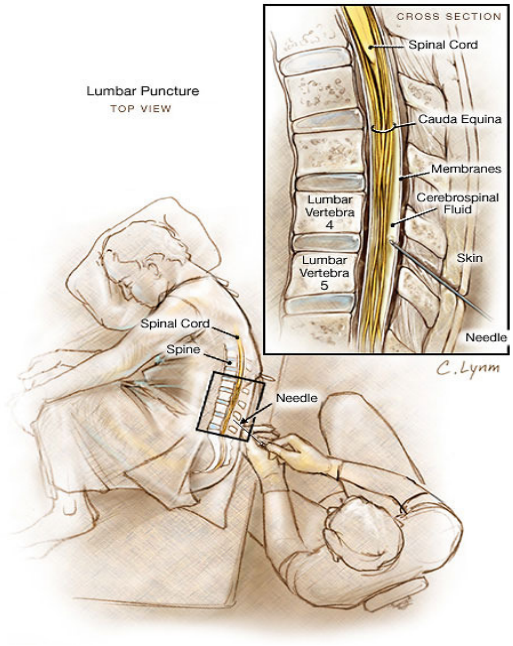

Figure (3): Lumbar puncture in the lateral position [Top view].[125]

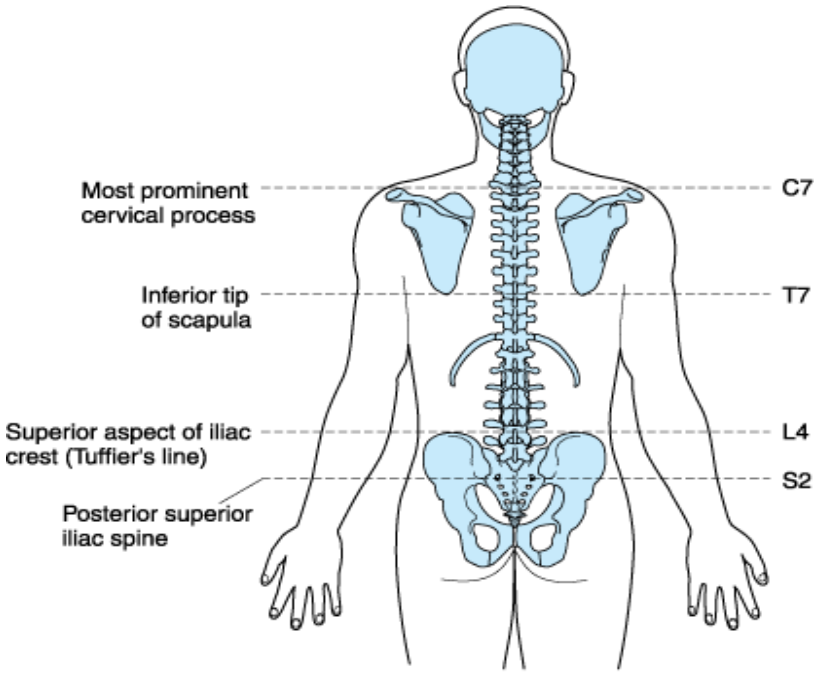

Figure (4): Surface landmarks for identifying spinal levels. [113]

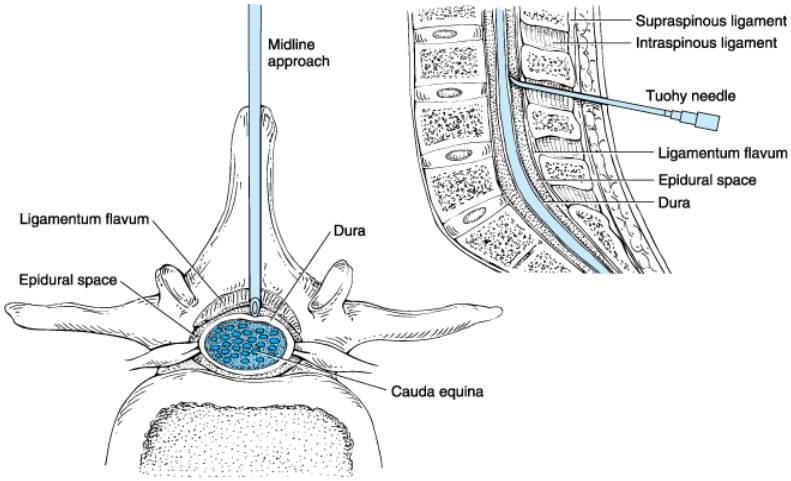

Figure (5): Structures pierced by an advancing spinal needle in the midline approach.[115]

Midline Approach

For the midline approach to the subarachnoid space, skin overlying the desired interspace is infiltrated with a small amount of local anesthetic to prevent pain when inserting the spinal needle. One should avoid raising too large a skin wheal because this can obscure palpation of the interspace, especially in obese patients.

Additional local anesthetic is then deposited along the intended path of spinal needle to a depth of 1 to 2 inches. This deeper infiltration provides additional anesthesia for spinal needle insertion and helps identify the correct path for the spinal needle.

Spinal needle or introducer needle is inserted in the middle of the interspace with a slight cephalad angulation of 10 to 15 degrees [figure. 6]. The needle is then advanced, in order, through the subcutaneous tissue, supraspinous ligament, interspinous ligament, ligamentum flavum, epidural space, dura mater, and finally arachnoid mater.Ligaments produce a characteristic sensation as the needle is advanced through them, and the anesthesiologist should develop the ability to distinguish a needle that is advancing through the high-resistance ligaments from one that is advancing through lower-resistance paraspinous muscle.

This will allow early detection and correction of needles that are not advancing in the midline. Penetration of dura mater produces a subtle loss of resistance that is most easily detected with pencil-point needles. Detection of dural penetration will prevent inserting the needle all the way through subarachnoid space and contacting vertebral body.

In addition, learning to detect dural penetration will allow one to insert the spinal needle quickly without having to stop every few millimeters and remove the stylet to look for CSF at the needle hub.

If bone is encountered during needle insertion, anesthesiologist must develop a reasoned, systematic approach to redirecting the needle. Simply withdrawing the needle and repeatedly reinserting it in different directions is not appropriate. When contacting bone, depth should be immediately noted and the needle redirected slightly cephalad. If bone is again encountered at a greater depth, then the needle is most likely walking down the inferior spinous process and it should be redirected more cephalad until subarachnoid space is reached. If bone is encountered again at a shallower depth, then the needle is most likely walking up the superior spinous process and it should be redirected more caudad.[126]

If bone is repeatedly encountered at the same depth, then the needle is likely off the midline and walking along vertebral lamina [figure 6].

Changes in needle direction should be made in small increments because even small changes in needle angle at the skin may result in fairly large changes in position of the needle tip when it reaches the spinal meninges at a depth of 4 to 6 cm.[127, 128]

If the patient experiences a paresthesia, it is important to determine whether the needle tip has encountered a nerve root in epidural space or in subarachnoid space. When paresthesia occurs, immediately stop advancing the needle, remove the stylet, and look for CSF at the needle hub.[128]

The presence of CSF confirms that the needle encountered a cauda equina nerve root in the subarachnoid space and the needle tip is in good position. Given how tightly packed the cauda equina nerve roots are, it is surprising that all spinal punctures do not produce paresthesias. If CSF is not visible at the hub, then paresthesia is probably resulted from contact with a spinal nerve root traversing the epidural space. This is especially true if paresthesia occurs in the dermatome corresponding to the nerve root that exits vertebral canal at the same level that spinal needle is inserted. In this case the needle has most likely deviated from midline and should be redirected toward the side opposite paresthesia. Occasionally, pain experienced when the needle contacts bone may be misinterpreted by the patient as a paresthesia and the anesthesiologist should be alert to this possibility.[129]

Once the block is placed, strict attention must be paid to the patient's hemodynamic status with blood pressure and/or heart rate supported as necessary. Block height should also be assessed early by temperature sensation. Temperature sensation is tested by wiping the skin with alcohol and may be preferable to pin prick because it is not painful. If, after a few minutes, the block is not rising high enough or is rising too high, the table may be tilted as appropriate to influence further spread of hypobaric or hyperbaric local anesthetics.

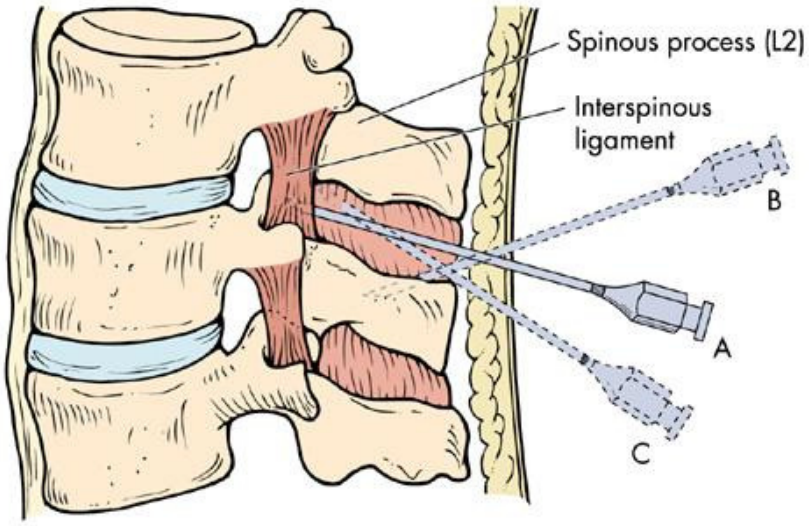

Figure 6. Midline approach to the subarachnoid space. The spinal needle is inserted with a slight cephalad angulation and should advance in the midline without contacting bone (A). If bone is contacted, it may be either the caudad (B) or the cephalad spinous process (C).[126]

Paramedian Approach

It is useful in situations where the patient's anatomy does not favor midline approach, e.g., inability to flex the spine or heavily calcified interspinous ligaments. This approach can be used with the patient in any position and is probably the best approach for the patient in prone jackknife position.[129]

Spinous process forming lower border of the desired interspace is identified. The needle is inserted 1 cm lateral to this point and is directed toward the middle of interspace by angling it 45 degrees cephalad with just enough medial angulation 15 degrees to compensate for lateral insertion point. The first significant resistance encountered should be the ligamentum flavum.[130]

Bone encountered prior to ligamentum flavum is usually the vertebral lamina of the cephalad vertebra and the needle should be redirected accordingly. An alternative method is to insert the needle perpendicular to the skin in all planes until the lamina is contacted. The needle is then walked off the superior edge of the lamina and into the subarachnoid space. The lamina provides a valuable landmark that facilitates correct needle placement; however, repeated needle contact with periosteum can be painful.[130]

PHYSIOLOGY

Physiological effects of Subarachnoid Blockade:

Neurological effects:

Site of Action

Neural blockade can potentially occur at any or all points along the neural pathways extending from the site of drug administration to the interior of spinal cord.[131]

The studies concluded that neural pathways within the spinal cord were largely intact during spinal anesthesia and that spinal nerve rootlets were the principal site of neural blockade.[132, 133]

Interestingly, human studies demonstrate that are maintained during epidural anesthesia, although amplitudes are decreased and latencies increased. This contrasts with spinal block in which evoked potentials are completely eliminated and supports the clinical impression that epidural block is generally less dense than that achieved with spinal anesthesia.[134]

Differential Nerve Block

Differential block refers to a clinically important phenomenon in which nerve fibers subserving different functions display varying sensitivity to local anesthetic blockade. In vivo sympathetic nerve fibers appear to be blocked by the lowest concentration of local anesthetic followed in order by fibers responsible for pain, touch, and motor function.[135]

This observation has led to the widely held belief that differences in sensitivity to local anesthetic blockade is explained solely by differences in fiber diameter, with smaller diameter neurons exhibiting greater sensitivity than larger diameter neurons. While the mechanism for differential block in spinal anesthesia is not known, it is clear that fiber diameter is not the only, or perhaps not even the most important, factor contributing to differential block.[135, 136]

Differential block occurs with both peripheral nerve blocks and central neuraxial blocks. In the peripheral nervous system, differential block is a temporal phenomenon with

sympathetic block occurring first followed in time by sensory and motor block. In contrast, with spinal and epidural anesthesia differential block is manifest as a spatial separation in the modalities blocked. This is seen most clearly with spinal anesthesia where sympathetic block may extend as many as 2 to 6 dermatomes higher than pin-prick sensation which in turn extends 2 to 3 dermatomes higher than motor block.[137]

This spatial separation is believed to result from a gradual decrease in local anesthetic concentration within the CSF as a function of distance from the site of injection.[137]

Another important neurophysiologic aspect of central neuroaxial block is that it produces sedation,[138] potentiates the effect of sedative hypnotic drugs,[139, 140] and markedly decreases minimum alveolar concentration (MAC).[141]

Cardiovascular effects:

Cardiovascular side effects, principally hypotension and bradycardia, are arguably the most important and most common physiologic changes during spinal anesthesia.

I) Hypotension:

- Blockade of sympathetic efferents is the principal mechanism by which spinal anaesthesia produces cardiovascular derangements. As would be expected, incidence of significant hypotension is generally related to the extent of sympathetic blockade, which in turn parallels block height.[142]

- Hypotension during spinal anesthesia is the result of both arterial and venodilation. Venodilation increases volume in capacitance vessels, thereby decreasing venous return and right-sided filling pressures.[143, 144]

- This fall in preload is thought to be the principal cause of decreased cardiac output during high spinal anesthesia. Arterial dilation during spinal anesthesia results in significant decreases in total peripheral resistance.[145]

Role of Bezold-Jarisch Reflex (BJR) in reducing spinal induced hypotension.[146, 147]

It is named after Albert Von Bezold and Adolf Jarisch Junior. It involves a variety of cardiovascular and neurological processes which can cause bradycardia and hypotension.

Prolonged upright posture results in some degree of pooling of blood in the lower extremeties that can lead to diminished intracardiac volume. The resultant hypotension is sensed in the carotid sinus baroreceptors which send signals to increase cardiac rate and contractility. However pressure receptors in the wall and trabeculae of the left ventricle sends signals that trigger paradoxical bradycardia and decreased contractility resulting in more bradycardia and hypotension.[146, 147]

Components of the reflex:

- **Receptors:**

- This reflex is mediated by serotonin receptors (5HT3 subtype) within the wall of the ventricle in response to systemic hypotension.[147]

- **pathway**

- Serotonin receptors in the wall of the underfilled left ventricle due to hypotension are stimulated, it send signals to high-pressure C-fiber afferent nerves. This lead to reflex stimulation of the vagus nerve that triggers paradoxical bradycardia and decreased contractility, resulting in additional and relatively sudden arterial hypotension.[148]

- The bradycardia reaction to acetic acid veratril in the cardiac pacemaker region was first described by von Bezold. Jarisch identified the reaction as a chemoreceptor reflex via the vagus nerve, relayed in the nucleus tractus solitarius.

- **Outcome**

The result of stimulation of BJR is more hypotension and sinus bradycardia.[149] The BJR has been suggested as a possible cause of profound bradycardia and circulatory collapse after spinal anesthesia.[150, 151] Many studies were done to prevent or reduce spinal induced hypotension.[152-154]

Ondansetron has been safely used to blunt the BJR resulting in less bradycardia and less hypotension first in animals and later in humans undergoing spinal anesthesia.[155, 156] It prevented the serotonin-induced BJR, suppressed venodilatation, augmented venous return to the heart and resulted in lesser reductions in SBP and MAP.[157] Blockade of the 5-HT3 receptor antagonizes the BJR induced by serotonin.[157]

Treating hypotension:

Treatment of hypotension secondary to spinal block must be aimed at the root causes: decreased cardiac output and/or decreased peripheral resistance.

1) Bolus intra venous fluids administration has often been advocated as a means of restoring venous return and thus cardiac output during central neuraxial blockade. However, the effectiveness of this therapy in normovolemic patients is controversial.

Prehydrating patients with 500 to 1,500 mL of crystalloid does not reliably prevent hypotension, but it has been shown to decrease the incidence of hypotension during spinal anesthesia in some studies.[158]

Crystalloid preloading of patients before central neuraxial blocks may benefit some patients, this practice cannot be relied on to prevent clinically significant hypotension in all or even most patients. The reason for this is that increasing preload can only increase stroke volume, which has limited ability to restore blood pressure if heart rate or systemic vascular resistance remains low.[158]

Colloids offer an interesting alternative to crystalloids for preloading before central neuraxial blocks.[159] the volume of crystalloids needed to treat hypotension usually is 3-4 times that of colloids. Also colloids do not interfere with the oncotic pressure of the plasma which make them better in cases of hypoalbuminemia.[159]

2) Vasopressors are a more reliable approach to treating hypotension secondary to central neuraxial blockade.[160] Ephedrine and phenylephrine are the drugs most commonly used to treat hypotension.[160]

- **Ephedrine** boluses of 5 to 10 mg increase blood pressure by restoring cardiac output and peripheral vascular resistance.[161]

- **Phenylephrine** it is a selective α_1-adrenergic receptor agonist. It is commonly used as a vasopressor to increase the blood pressure in unstable patients with hypotension, especially

resulting from septic shock. Such use is common in anesthesia or critical-care practices; it is useful in counteracting the hypotensive effect of epidural and subarachnoid anesthetics.[161]

- **Dopamine** may be preferable to ephedrine for long-term infusion because tachyphylaxis can develop to repeated ephedrine boluses.[162]

II) Bradycardia:

Incidence and risk factors: Bradycardia occasionally occurs with a reported incidence of 10% to 15%. As with hypotension, the risk of bradycardia increases with increasing block height.[145]

Additional risk factors associated with bradycardia include age younger than 50 years, ASA 1 physical status, and concurrent use of beta blockers.[163]

Mechanism of bradycardia:

- Blockade of the sympathetic cardioaccelerator fibers originating from T1-4 spinal segments is often suggested as the cause. The fact that bradycardia is more common with high blocks supports this mechanism. However, significant bradycardia sometimes occurs with blocks that are seemingly too low to block cardioaccelerator fibers.[164]
- Another factor leading to bradycardia after spinal anaethesia is Reverse Bainbridge reflex. As venous return decreases, the pressure in the superior and inferior vena cava decrease. This results in an decrease in the pressure of the right atrium, which inhibit the atrial stretch receptors (low pressure receptor zones). These receptors in turn signal the medullary control centers to decrease the heart rate (Bradycardia).[165, 166]

  Decreasing the heart rate serves to collect more blood the right atrium which serves to deliver it to the ventricle to maintain cardiac output. This continues until right atrial blood pressure returns to normal levels, upon which the heart rate increases to its original level.[165]

Respiratory effects:

- **Spinal blocks to midthoracic levels** have little effect on pulmonary function in patients without preexisting lung disease. Drugs used perioperatively for sedation during spinal block likely have a larger impact on pulmonary function than the block per se.[167]
- In particular, lung volumes, resting minute ventilation, dead space, arterial blood gas tensions, and shunt fraction show little or no change during spinal anesthesia. Interestingly, the ventilatory response to hypercapnia is actually increased by spinal and epidural block.[168]
- **High blocks** associated with abdominal and intercostal muscle paralysis can impair ventilatory functions requiring active exhalation. For example, expiratory reserve volume, peak expiratory flow, and maximum minute ventilation may be significantly reduced by high spinal and epidural blocks. The negative impact of high blocks on active exhalation suggests caution when using spinal or epidural anesthesia in patients with obstructive pulmonary disease who may rely on their accessory muscles of respiration to maintain adequate ventilation.[169, 170]

Gastrointestinal effects:

- The gastrointestinal effects of spinal anesthesia are largely the result of sympathetic blockade. Abdominal organs derive their sympathetic innervation from T6-L2.[171]
- Blockade of these fibers results in unopposed parasympathetic activity by way of the vagus nerve. Consequently, secretions increase, sphincters relax, and the bowel becomes constricted.[171]
- Nausea is a common complication of spinal anesthesia. The etiology is unknown but an increased incidence of nausea during spinal anesthesia is associated with blocks higher than T5, hypotension, opioid premedication, and a history of motion sickness.[163]

Endocrine-Metabolic effects:

Stress response

- Surgery produces numerous endocrine and metabolic changes, including increased protein catabolism and oxygen consumption as well as increases in circulating concentrations

of catecholamines, growth hormone, renin, angiotensin, thyroid-stimulating hormone, endorphin, glucose, and free fatty acids.[172]

- The mechanisms responsible for stress response are complex and incompletely understood. However, afferent sensory information from the surgical site plays an important role in initiating and maintaining these changes. Not surprisingly, spinal anesthesia have been shown to inhibit many of endocrine metabolic changes associated with stress response.[173]

- The inhibitory effect is greatest with lower abdominal and lower extremity procedures and least with upper abdominal and thoracic procedures. The salutary effect of spinal anesthesia is believed to result from blockade of the afferent sensory information that helps initiate the stress response.[173]

Urinary system effects:

Renal blood flow is maintained during central block by auto-regulation mediated by local tissue factors. Therefore, urine production is unaffected. Urine retention due to S_{2-4} blockade may be produced because urinary bladder is innervated by these segments. [174]

Hepatic effects:

Blood flow to the liver decreases in direct proportion to the decrease in mean arterial blood pressure because liver extracts more oxygen from arterial inflow, however, it tends not to become ischemic and liver enzymes are usually not affected.[174]

Complications of Spinal Anaesthesia

I) Complications related to needle placement

1) Failed spinal anaesthesia:

It may occur due to improper position of the patient, obese patients or anatomical anomalies in the vertebral column.

2) Vasovagal attack:

It occurs in response to a trigger, with a stimulation of parasympathetic system over sympathetic one resulting in cardiac inhibition and bradycardia.

3) Backache

Although postoperative backache occurs following general anesthesia, it is more common following spinal anesthesia.[175] The etiology of backache is not clear, although needle trauma, local anesthetic irritation, and ligamentous strain secondary to muscle relaxation have been offered as explanations. As a needle passes through skin, subcutaneous tissues, muscle, and ligaments it causes varying degrees of tissue trauma. A localized inflammatory response with or without reflex muscle spasm may be responsible for postoperative backache.

Postoperative back soreness or ache is usually mild and self-limited, although it may last for a number of weeks. If treatment is sought, acetaminophen, nonsteroidal antiinflammatory medication, and warm or cold compresses should suffice. Although backache is usually benign, it may be an important clinical sign of much more serious complications, such as epidural hematoma and abscess.

4) Postdural Puncture Headache (PDPH)

Incidence

Postdural puncture headache is a common complication of spinal anesthesia with a reported incidence as high as 25% in some studies. Some studies have suggested that women are at greater risk of developing PDPH. However, if age differences are accounted for, there does not appear to be a gender difference in the incidence of PDPH. Folklore aside, remaining supine following meningeal puncture does not decrease the incidence of PDPH.[176]

Criteria of post dural puncture headache:

- It is characteristically mild or absent when the patient is supine, but head elevation rapidly leads to a severe fronto-occipital headache, which again improves on returning to the supine position. Occasionally cranial nerve symptoms (e.g., diploplia, tinnitis) and nausea and vomiting are also present.[177]

- It is believed to result from the loss of CSF through the meningeal needle hole resulting in decreased buoyant support for the brain. In the upright position the brain sags in the cranial vault putting traction on pain-sensitive structures. Traction on cranial nerves is believed to cause the cranial nerve palsies occasionally seen.

- Incidence of PDPH decreases with increasing age and with the use of small diameter spinal needles with noncutting tips.[178]

- A more likely explanation arises from the fact that dura mater is under longitudinal tension. Thus, a slit-like hole oriented perpendicular to this longitudinal tension will tend to be pulled open while a hole oriented parallel to this tension will be pulled closed.[179]

Treatment:

PDPH usually resolves spontaneously in a few days to a week for most patients. However, there are reports of PDPH persisting for months following meningeal puncture. Initial treatment is appropriately conservative if this meets the patient's needs. Bed rest and analgesics as necessary are the mainstay of conservative treatment. Caffeine has also been shown to produce short-term symptomatic relief.[180]

Patients who are unable or unwilling to await spontaneous resolution should be offered epidural blood patch. Epidural blood patch is believed to form a clot over the meningeal hole, thereby preventing further CSF leak while the meningeal rent heals. 10 to 20 mL of autologous blood is aseptically injected into epidural space at or near the interspace at which the meningeal puncture occurred. This is effective in relieving symptoms within 1 to 24 hours in 85% to 95% of patients.

5) **Neurologic Injury**

Multiple large series of spinal anaesthesia report that neurologic injury occurs in 0.03% to 0.1% of all central neuraxial blocks, although in most of these series the block was not clearly proven to be causative.[181]

a) Cauda equina syndrome

- Persistent paresthesias and limited motor weakness are the most common injuries, although paraplegia and diffuse injury to cauda equina roots do occur rarely.[181]

- Injury may result from direct needle trauma to the spinal cord or spinal nerves, spinal cord ischemia, accidental injection of neurotoxic drugs or chemicals, introduction of bacteria into the subarachnoid or epidural space, or very rarely epidural hematoma.[181]

b) Spinal cord or nerve root damage:

Either nerve roots or spinal cord may be injured. The latter may be avoided if the neuraxial blockade is performed below the termination of the conus (L1 in adults and L3 in children). Postoperative peripheral neuropathies can be due to direct physical trauma to nerve roots. Although most resolve spontaneously, some are permanent. Some of these deficits have been associated with paresthesia from the needle or complaints of pain during injection.

Damage to the conus medullaris may cause isolated sacral nerve dysfunction, including paralysis of the biceps femoris muscles; anesthesia in the posterior thigh, saddle area, or great toes; and loss of bowel or bladder function.

c) Spinal haematoma

Needle trauma to epidural veins often causes minor bleeding in the spinal canal, although this usually has no consequences. A clinically significant spinal hematoma can occur following spinal anaesthesia, particularly in the presence of abnormal coagulation or a bleeding disorder. The pathological insult to the spinal cord and nerves is due to the hematoma's mass effect, compressing neural tissue and causing direct pressure injury and ischemia. Symptoms include sharp back and leg pain with a motor weakness and/or sphincter dysfunction.

6) Meningitis:

Infection of the subarachnoid space can follow neuraxial blocks as the result of contamination of the equipment or injected solutions, or as a result of organisms tracked in from the skin.

7) Epidural abscess (EA)

Spinal epidural abscess is a rare but potentially devastating complication of neuraxial anesthesia. There are four classic clinical stages of EA, although progression and time course can vary. Initially, symptoms include back or vertebral pain that is intensified by percussion over the spine. Second, nerve root or radicular pain develops. The third stage is marked by motor and/or sensory deficits or sphincter dysfunction. Paraplegia or paralysis marks the fourth stage. Ideally, the diagnosis is made in the early stages. Prognosis has consistently been shown to correlate to the degree of neurological dysfunction at the time the diagnosis is made.

II) Exaggerated physiological responses

a) Total Spinal

Total spinal anesthesia occurs when local anesthetic spreads high enough to block the entire spinal cord and occasionally the brainstem during spinal anesthesia. Profound hypotension and bradycardia are common secondary to complete sympathetic blockade. Respiratory arrest may occur as a result of respiratory muscle paralysis or dysfunction of brainstem respiratory control centers. Management includes vasopressors, atropine, sedatives and fluids as necessary to support cardiovascular system, plus oxygen and controlled ventilation. If the cardiovascular and respiratory consequences are managed appropriately, total spinal block will resolve without sequelae.(182)

b) Urinary Retention

Local anesthetic block of S2–S4 root fibers decreases urinary bladder tone and inhibits the voiding reflex. Intrathecal opioids can also interfere with normal voiding. These effects are most pronounced in male patients. Urinary bladder catheterization should be used for all but the shortest acting blocks. If a catheter is not present postoperatively, close observation for voiding is necessary. Persistent bladder dysfunction can also be a manifestation of serious neural injury.

c) Palsy of the sixth cranial nerve:

This causes palsy of the external rectus muscle resulting in dipolpia. It occurs between the 5^{th} and the 11^{th} postoperative day. Its incidence is 1:300 and is associated with headache. Paralysis is never complete. It may be due to upset of hydrodynamics of CSF pressure causing stretching of the abducent nerve.(183)

III) Complications associated with drug toxicity:

a) Neurotoxicity of local anaethetics

Importantly, local anesthetics intended for intrathecal use can themselves be neurotoxic in concentrations used clinically.(184)

In particular, hyperbaric 5% lidocaine has been implicated as a cause of multiple cases of cauda equina syndrome following subarachnoid injection through small-bore catheters during continuous spinal anesthesia.(185)

Nerve injury is believed to result from pooling of toxic concentrations of undiluted lidocaine around dependent cauda equina nerve roots.

b) Transient Neurologic Symptoms (TNS)

Occurrence of TNS or transient radicular irritation (TRI) has also emerged as a concern following central neuraxial blockade. TRI is defined as pain, dysesthesia, or both in the legs or buttocks after spinal anesthesia and was first proposed as a recognizable entity by Schneider.[186] All local anesthetics have been shown to cause TRI although the risk appears to be greater with lidocaine than other local anesthetics.[187]

c) Pruritis:

Following an intrathecal block, pruritis has been seen in patients with peripheral neuropathy and with some intrathecal opioids.[188]

PHARMACOLOGY

Classification of antiemetics:

1) **Dopamine antagonists** act in the brain and are used to treat nausea and vomiting associated with neoplastic disease, radiation sickness, opioids, cytotoxic drugs and general anaesthetics. Side effects include muscle spasms and restlessness.
   a) Domperidone
   b) Olanzapine
   c) Droperidol, haloperidol, chlorpromazine, prochlorperazine. Some of these drugs are limited in their usefulness by their extra-pyramidal and sedative side-effects.
   d) Alizapride
   e) Prochlorperazine
   f) Metoclopramidealso acts on the GI tract as a pro-kinetic, and is thus useful in gastrointestinal disease; however, it is poor in cytotoxic or post-op vomiting. also a5-HT_3 receptor antagonists
2) **Neurokinin 1 (NK1) receptor antagonist**
   a) Aprepitant is a commercially available NK1 Receptor antagonist
   b) Casopitant is an investigational NK1 receptor antagonist
3) **Antihistamines (H_1 histamine receptor antagonists)** are effective in many conditions, including motion sickness, morning sickness in pregnancy, and to combat opioid nausea.
   a) Cyclizine
   b) Diphenhydramine
   c) Dimenhydrinate
   d) Doxylamine
   e) Meclizine

f) Promethazine can be administered via a rectal suppository for adults and children over 2 years of age.

g) Hydroxyzine

4) **Cannabinoids** are used in patients with cachexia, cytotoxic nausea, and vomiting, or who are unresponsive to other agents. These may cause changes in perception, dizziness, and loss of coordination.

a) Cannabis

b) Dronabinol.

5) **Benzodiazepines**

a) Midazolam is given at the onset of anesthesia has been shown in recent trials to be as effective as ondansetron.

b) Lorazepam is said to be very good as an adjunct treatment for nausea along with first line medications such as ondansetron.

6) **Anticholinergics**

Hyoscine (also known as scopolamine)

7) **Steroids**

Dexamethasone is given in low dose at the onset of a general anaesthetic is an effective antiemetic. The specific mechanism of action is not fully understood.

8) **5-HT_3 receptor antagonists:** block serotonin receptors in the central nervous system and gastrointestinal tract. As such, they can be used to treat post-operative and cytotoxic drug nausea & vomiting. They can also cause constipation or diarrhea, dry mouth, and fatigue.[189]

a) Dolasetron can be administered in tablet form or in an injection.

b) Granisetron can be administered in tablet, oral solution, injection or in a single transdermal patch to the upper arm.

c) Ondansetron is administered in an oral tablet form, orally dissolving tablet form, orally dissolving film, or in an IV/IM injection.

d) Tropisetron can be administered in oral capsules or in injection form.

e) Palonosetron can be administered in an injection or in oral capsules.

f) Mirtazapine is an antidepressant that also has antiemetic effects and is also a potent histamine H1 receptor antagonist.

➢ Serotonin

Serotonin, 5-hydroxytryptamine (5-HT), is present in large quantities in platelets and the GI tract (enterchromaffin cells and the myenteric plexus). It is also an important neurotransmitter in many areas of the central nervous system, including the retina, limbic system, hypothalamus, cerebellum, and spinal cord.[190, 191] It is formed by hydroxylation and decarboxylation of tryptophan. Monoamine oxidase inactivates serotonin into 5-hydroxyindoleacetic acid (5-HIAA).[192] Physiology of serotonin is very complex because there are at least seven receptor types, most with multiple subtypes. The 5-HT_3 receptor mediates vomiting and is found in the GI tract and the brain (area postrema).[192]

The 5-HT_{2A} receptors are responsible for smooth muscle contraction and platelet aggregation, the 5-HT_4 receptors in the GI tract mediate secretion and peristalsis, and the 5-HT_6 and 5-HT_7 receptors are located primarily in the limbic system where they appear to play a role in depression. Many antidepressant drugs bind 5-HT_6 receptors. All except the 5-HT_3 receptor are coupled to G proteins and affect either adenylyl cyclase or phospholipase C; the 5-HT_3 receptor is an ion channel.

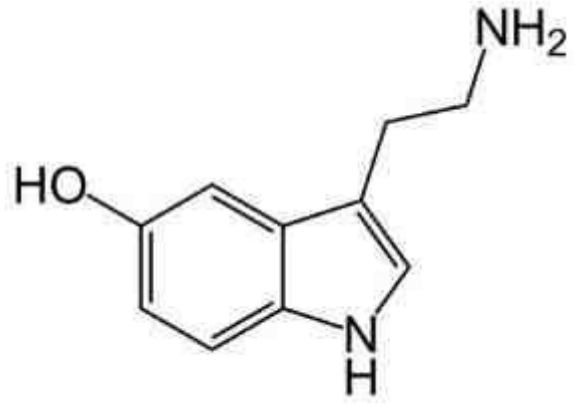

Figure 7: Chemical structure of serotonin.

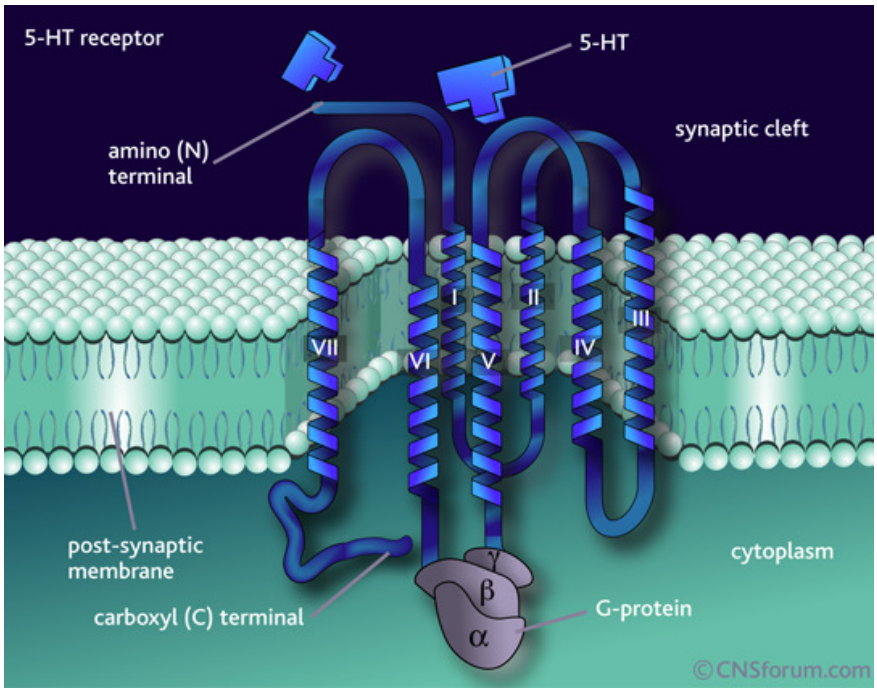

Figure 8: Types of serotonin receptors.

Effects:

Cardiovascular effects:

Except in the heart and skeletal muscle, it is a powerful vasoconstrictor of arterioles and veins. Its vasodilator effect in the heart is critically dependent on the endothelium. When the myocardial endothelium is damaged following injury, it produces vasoconstriction. Pulmonary and renal vasculatures are very sensitive to the arterial vasoconstrictive effects of serotonin. Modest and transient increases in cardiac contractility and heart rate may occur following serotonin release; reflex bradycardia often follows. Vasodilatation in skeletal muscle can subsequently cause hypotension.[193]

Respiratory effects:

It increases respiratory centre excitability and muscular electrical activity leading to contraction of smooth muscle with increased airway resistance. It increases respiratory indices, such as frequence, volume and lung ventilation per min. In addition the pH of blood shifted to alkalic and oxygen tension of the blood increased while CO2 tension of the blood decreased.[194]

Gastrointestinal effects:

Direct smooth muscle contraction (via 5-HT_2 receptors) and serotonin-induced release of acetylcholine in the myenteric plexus (via 5-HT_3 receptors) greatly augment peristalsis. Secretions are unaffected. 5-HT_3 receptors, which are located peripherally (abdominal vagal afferents) and centrally (chemoreceptor trigger zone of the area postrema and the nucleus tractus solitarius), appear to play an important role in the initiation of the vomiting reflex.

ONDANSETRON

A competitive serotonin type 3 receptor antagonist. It is effective in the treatment of nausea and vomiting caused by cytotoxic chemotherapy drugs, including cisplatin, and has reported anxiolytic and neuroleptic properties.[195] It has little effect on vomiting caused by motion sickness,[195] and does not have any effect on dopamine receptors or muscarinic receptors.[196] It is on the World Health Organization's List of Essential Medicines, a list of the most important medication needed in a basic health system.[197] The empirical formula is C18H19N3O representing a molecular weight of 293.4.[figure.7]

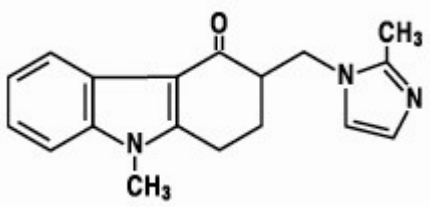

Figure (9): Chemical structure of ondansetron.[196]

Pharmacodynamics:

It is a highly specific and selective serotonin 5-HT_3 receptor antagonist, not shown to have activity at other known serotonin receptors and with low affinity for dopamine receptors. The serontonin 5-HT_3 receptors are located on the nerve terminals of the vagus in the periphery, and centrally in the chemoreceptor trigger zone of the area postrema. The temporal relationship between the emetogenic action of emetogenic drugs and the release of serotonin, as well as the efficacy of antiemetic agents suggest that chemotherapeutic agents release serotonin from the enterochromaffin cells of the small intestine by causing degenerative changes in the GI tract. The serotonin then stimulates the vagal and splanchnic nerve

receptors that project to the medullary vomiting center, as well as the 5-HT_3 receptors in the area postrema, thus initiating the vomiting reflex, causing nausea and vomiting.[198]

Pharmacokinetics:

Absorption: it is well absorbed from the gastrointestinal tract and undergoes some first-pass metabolism. Mean bioavailability in healthy subjects, following administration of a single 8-mg tablet, is approximately 56%.[199] Ondansetron systemic exposure does not increase proportionately to dose. The bio-availability is also slightly enhanced by the presence of food but unaffected by antacids.[200]

Protein binding: 70- 76% binding to plasma proteins. It has a halh life from 5-7 hours

Metabolism and clearance: It is extensively metabolized in humans, with approximately 5% of a radiolabeled dose recovered as the parent compound from the urine.[200] The primary metabolic pathway is hydroxylation on the indole ring followed by subsequent glucuronide or sulfate conjugation. Although some nonconjugated metabolites have pharmacologic activity, these are not found in plasma at concentrations likely to significantly contribute to the biological activity of ondansetron. Its half life is about 5.7 hours.[200]

In patients with mild-to-moderate hepatic impairment, clearance is reduced two folds and mean half-life is increased to 11.6 hours compared to 5.7 hours in normals.[201] In patients with severe hepatic impairment (Child-Pugh2 score of 10 or greater), clearance is reduced two to three folds and apparent volume of distribution is increased with a resultant increase in half-life to 20 hours.[201]

Elimination: Due to the very small contribution (5%) of renal clearance to the overall clearance, renal impairment was not expected to significantly influence the total clearance of ondansetron. However, ondansetron oral mean plasma clearance was reduced by about 50% in patients with severe renal impairment (creatinine clearance < 30 mL/min).[201]

Medical uses:

1) **Cancer treatment:** ondansetron is the primary drug used to treat and prevent and radiotherapy-induced nausea and vomiting.[202, 203]

2) **Postoperative nausea and vomiting:**

A number of medications including ondansetron appear to be effective in controlling postoperative nausea and vomiting (PONV).[204]

3) **Cyclic vomiting syndrome:**

It is one of several anti-emetic agents used during the vomiting phase of cyclic vomiting syndrome.[205]

4) **Gastroenteritis**:

Trials in emergency department settings support the use of ondansetron to reduce vomiting associated with gastroenteritis and dehydration.[206]

Adverse effects:

It is a well-tolerated drug with few side effects. Constipation, dizziness and headache are the most commonly reported side effects associated with its use.[207] Ototoxicity has also been reported if injected too quickly.[207]

QT prolongation:

The use of ondansetron has been associated with prolongation of the QT interval, which can lead to the potentially fatal heart rhythm known as Torsade de Pointes.[208]

The risk is also higher in patients taking other medicines that prolong the QT interval, as well as in patients with congenital long QT syndrome, congestive heart failure, and/or bradyarrhythmias.[209] As such, single doses of injectable ondansetron should not exceed 16 mg at one time. (Oral dosing recommendations remain intact, including the recommendation of a single 24 mg oral dose when indicated.) Electrolyte imbalances should be corrected before the use of injectable ondansetron. Patients are cautioned to seek immediate medical care if symptoms such as irregular heartbeat/palpitations, shortness of breath, dizziness, or fainting occur while taking ondansetron.[209]

➢ Values of ondansetron during spinal anaesthesia:

Reduction of shivering associated with spinal anaesthesia: Shivering is a very common during spinal anaesthesia. Increasing studies have reported ondansetron may have a preventive effect on shivering without any side effects.[210-213]

prevention of nausea and vomiting: Nausea and vomiting during spinal anesthesia is a common finding and may occur in up to 66% of patients. The usual drugs used for prevention or treatment of this important adverse effect have adverse effects such as intense sedation, dystonic reactions, restlessness, and extrapyramidal symptoms. Intravenous ondansetron has preventive effect of nausea and vomiting during spinal anesthesia.[214, 215]

Anti pruritic effect: Opioids are used as adjuvants to local anaesthetics intrathecally to increase analgesic effect of local anaesthetics. Administration of opioids is frequently associated with pruritus. The administration of 8 mg ondansetron intravenously is an effective treatment for spinally administered opioid induced pruritus.[216-218]

Reduction of spinal induced hypotension and bradycardia: Many studies were done to decrease the incidence of hypotension during spinal anaesthesia. Ondansetron pevent BJR and decrease the hypotension and bradycardia induced through this reflex by blocking serotonin receptors.[154-156]