INTRODUCTION

The choice of anaesthesia for caesarean section is determined by multiple factors, including the indication for the operation, its urgency, parturient desire and the skills of the anaesthetist and the surgeon.[1]

There are many indications for general anaesthesia, some of which are failed regional anaesthesia, conditions where regional anaesthesia is contraindicated, maternal request and life-threatening foetal compromise when there might not be adequate time to perform a regional technique. In the past, general anaesthesia was considered to be the technique of choice. However, the proportion of caesarean sections performed under general anaesthesia has dropped significantly. In the United States, general anaesthesia is used for less than 5% of elective caesarean deliveries. For emergency deliveries, the rate varies between 15 and 30%. [2, 3]

There are some significant risks associated with general anaesthesia: The main risk to the mother involves the fact that the anaesthesiologist must secure and control the ability to breathe; airway problems are more common in pregnancy than in the general population due to anatomical and physiological changes during pregnancy. Some anatomic changes that may affect the obstetric airway include upper airway oedema, breast enlargement and excessive weight gain. [4]

Pulmonary aspiration is one of the concerns of general anaesthesia in obstetric patients. Risk factors for increased risk of aspiration include a prolonged gastric emptying time in labour, increased intra-abdominal pressure due to the gravid uterus and relaxation of the lower oesophageal sphincter due to hormonal changes. [5]Also, general anaesthesia affects the newborn at least a small amount. When giving the mother general anaesthesia for caesarean section, the obstetrician will try to deliver the baby as quickly as possible to minimize the amount of anaesthesia that the baby receives. The anaesthesia that the baby receives does wear off fairly quickly, but initially the baby might be sleepy, less active. [6]

Regional anaesthesia is the most popular form of anaesthesia for caesarean section due to avoiding risks of general anaesthesia, for better postoperative pain relief and also for keeping the woman awake to see her baby just after birth.[7] Approximately 95% of caesarean sections are performed under regional analgesia in United States, nearly evenly split between spinal and epidural analgesia.[8] Although this can be achieved by spinal or epidural anaesthesia, spinal anaesthesia is a simple technique with low failure rate, rapid onset and low drug dose.[9]

Obvious disadvantages of spinal anaesthesia are the inability to extend the block if the original block height is deemed to be inadequate or if the surgery takes longer than predicted. It is therefore vital to ensure adequate block before commencing surgery as a failure to do so could result in patient discomfort, conversion to general anaesthesia and possible medicolegal implications. Also, spinal anaesthesia may cause other complications such as hypotension, shivering, neurologic complications, technical difficulties as well as the potential for post- dural puncture headache. [10, 11]

Spinal anaesthesia in caesarean section:

Anatomy of the vertebral column and spinal canal

The vertebral column represents elastic and flexible bony structure consisting of 33 vertebrae: 7 cervical, 12 thoracic, 5 lumbar, 5 sacral and 4 coccygeal vertebrae. [12] In adult life, the sacral and coccygeal vertebrae are fused together. The cervical, thoracic and lumbar are independent and although firmly connected by articulations and ligaments, allow limited amount of movement on one another. [13]

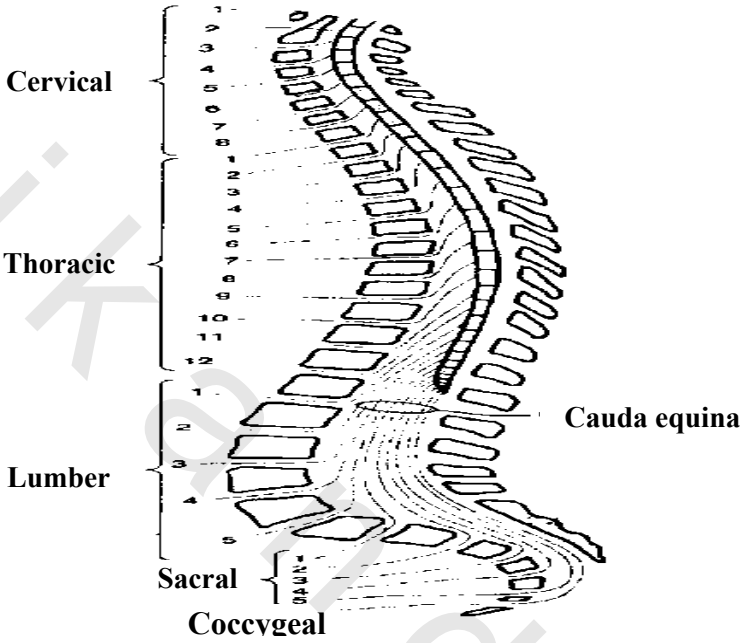

Figure (1): Vertebral column. [14]

Midline spinal puncture pierces the skin, subcutaneous fat, supraspinous ligament, inter spinous ligament, the ligamentum flavum and the dura, while in the lateral spinal approach only the skin, subcutaneous fat, skeletal muscle, ligamentum flavum and the dura are encountered.[10]

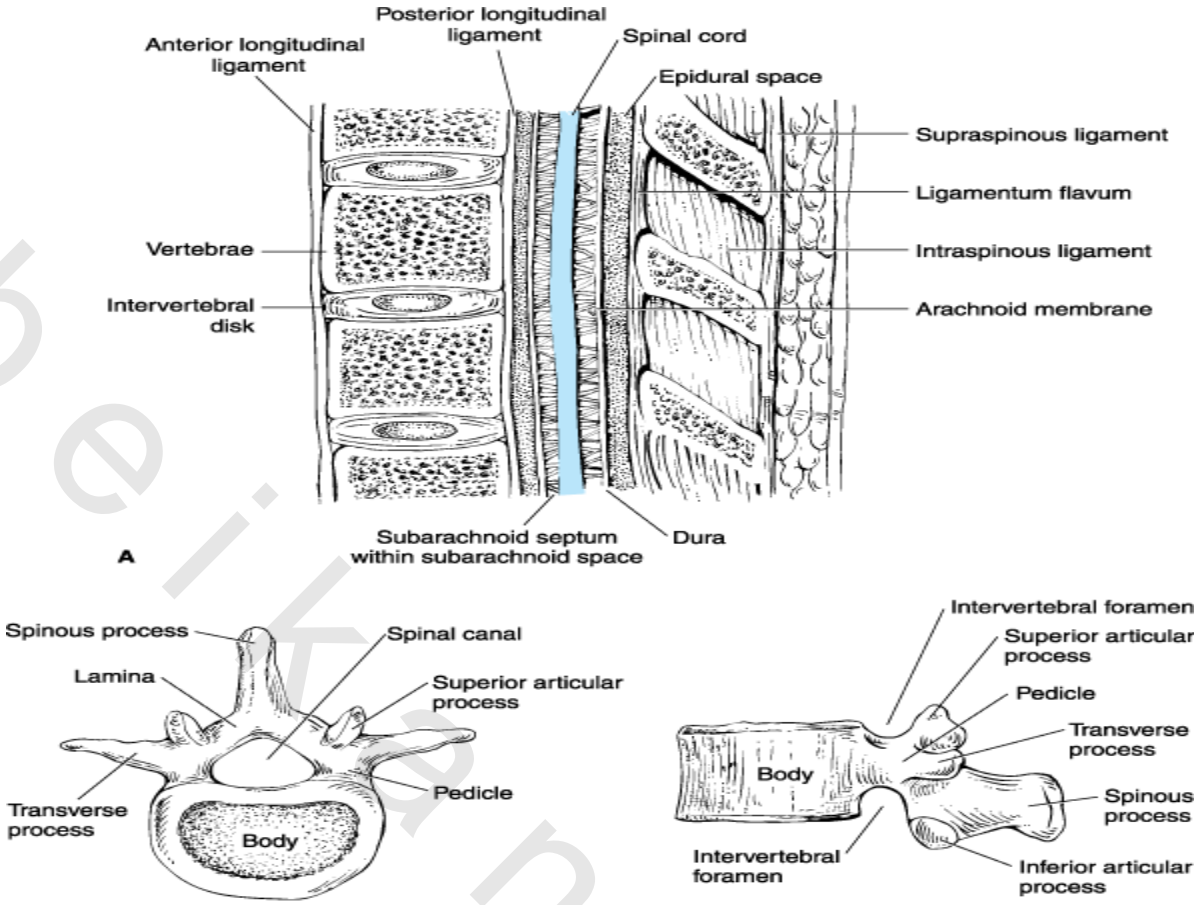

Figure (2): Anatomy of lumbar vertebrae. [15]

The spinal canal

The spinal canal extends from the foramen magnum to the sacral hiatus and is formed anteriorly by bodies of the vertebrae, laterally by pedicles and posteriorly by laminae. Between the bony vertebrae the intervertebral discs and the ligaments joining the laminae and spines comprise additional boundaries; the only openings in the canal are the intervertebral foraminate, which permit the passage of the segmental nerves and blood vessels. [16]

The canal contains the spinal cord, which is about 45 cm long. It is continuous with the medulla oblongata above and tapers into conus medullaris below, from which a thread like structure, the filum terminale, continues to be attached to the coccyx. [17]

Up to the third month of intrauterine life the cord extends the full length of the canal, but thereafter the vertebrae grow much more rapidly and in the newborn ،the cord usually terminates at the lower border of the third lumbar vertebra. In adult life, the cord usually ends at the level of the disc between the first and the second lumbar vertebra. [10]

The contents of the spinal canal are arranged in laminated manner, and the various compartments are considered as series of cylinders within each other. [16]

The spinal cord has three covering membranes or meninges which from within outwards are pia mater, arachnoid mater, and dura mater. The dural covering of the brain is a double membrane between whose walls lies on the cerebral venous sinuses. [10]

Physiological changes in anatomy of epidural and subarchnoid spaces in pregnancy:

The epidural space in pregnant women might be reduced due to engorgement of veins in the extra-dural space, compression of the subarachnoid space, and reduction in the volume of cerebrospinal fluid. Engorgement of veins in the extra-dural space and increased pressure are secondary to the increased intra-abdominal pressure, which causes compression of the inferior vena cava and consequent reduction in the volume of cerebrospinal fluid. Thus, it is more difficult to predict the extension of the blockade when using the same dose of local anaesthetics in obese and non-obese pregnants. [18, 19]

Besides, it is known that the need of local anesthetic in spinal anaesthesia is lower in pregnants especially obese. Mechanisms suggested for this include pregnancy-specific hormonal changes, which affect the action of neurotransmitters in the spinal column, increased permeability of neural membranes. Also, exaggerated lumber lordosis may increase cephaled spread of L.As. [18, 19]

Physiological changes during pregnancy:

Pregnancy and delivery are associated with vast physiological changes. Those related to pulmonary and cardiovascular systems are of fundamental importance to anaesthesiologist. [20]

Respiratory system: [20]

To accommodate the increased O2 demand and requirement for carbon dioxide elimination, pregnancy is associated with an increase in the respiratory minute volume and work of breathing. The most impressive change in maternal lung dynamics is a decrease in functional residual capacity (FRC), which at term may have changed by as much as 20% of pr e pregnancy values. Minute ventilation increases by 45% primarily as a result of an increase in the tidal volume because the respiratory rate is essentially unchanged. There is a liability to rapid development of hypoxia as result of decreased FRC and increased oxygen consumption. [20]

Capillary engorgement of mucosa and oedema of the orophyranx, larynx, and trachea may result in a difficult intubation. [20]

Cardiovascular system: [21]

Cardiac output increases from the fifth week of pregnancy and reaches its maximum levels (approximately 40% of non pregnant values) at 32 weeks. It is due to an increase in the heart rate and the more important factor is the stroke volume. Changes in heart rate are difficult to quantify but it is thought that approximately 20% increase in heart rate present by fourth week of pregnancy. Tachyarrhythmias are more common especially later in pregnancy as a result of both hormonal and autonomic factors. [21]

Hematologic system: [22]

Maternal blood volume begins to increase early in pregnancy as a result of changes in osmoregulation and the renin- angiotension system causing sodium retention and increasing the total body water by 8.5 litters (L). By term, blood volume increases up to 45% whereas red cell volume increase by only 30%, this differential increase leads to physiological anemia of pregnancy. A state of hypercoaguability exists in pregnancy with an increased level of most coagulation factors mainly fibrinogen and factor VII. [22]

Gastrointestinal system: [23]

Although progesterone relaxes smooth muscles, it impairs esophageal and intestinal motility during pregnancy. It has recently been suggested that gastric emptying is not always delayed in pregnant woman, however risk of aspiration remains when caesarean section is done under general anaesthesia. [23]

Central nervous system: [22]

From early pregnancy, when neuroaxial anaesthesia is administered women require less local anaesthetic than non pregnant women to reach a given dermatomal sensory level because the epidural veins become congested secondary to increase in intra abdominal pressure and epidural space becomes narrower. [22]

Renal system: [21]

It undergoes many changes in pregnancy, mainly because of the effect of progesterone and the mechanical effects of compression of the gravid uterus. Urea, creatinine and uric acid clearance all increase. Renal plasma flow and glomerular filtration rate (GFR) both also increase rapidly. Glycosuria is common finding in pregnancy. [21]

Effect of spinal analgesia on maternal physiology: [24]

In pregnancy there are haemodynamic changes in the form of: [24]

- Cardiac output rises by 30-40% gradually till the time of delivery.
- Blood volume increases by 15-45%, with relative anaemia
- Blood pressure slightly decreases as pregnancy progresses.

These are accompanied with changes in peripheral blood distribution; the uterus enlarges in size with growth of foetus and placenta. At full term the uterus contains about one-sixth of the mother`s blood volume. The result of such an increase of peripheral blood volume with a concomitant decrease in central blood volume may worsen hypotension during spinal analgesia. [24]

Even with the same level of spinal analgesia, hypotension is greater in pregnant than non pregnant women. Moreover, the gravid uterus affects the circulation by its weight compressing the inferior vena cava and partially obstructing the aorta. [18] This will diminish the venous return to the heart, also the arterial blood supply to the pelvic organ and lower extremities are decreased, but the clinical manifestations of compression vary individually according to the degree of the obstruction as well as the degree of

compensation. Decreased venous return due to mild to moderate inferior vena cava obstruction can be compensated by an increase in heart rate. (24)

Only when such compensatory mechanism is attenuated, cardiac output decreases dramatically and supine hypotension occurs, 10% of women show severe hypotension in supine position in late pregnancy. (24)

Pulmonary ventilation mechanisms are little changed even at full term. The elevation of diaphragm during the last trimester tends to decrease the vital capacity but is compensated by widening of the subcostal angle. (24)

Effect of spinal analgesia on the fetus:

Spinal analgesia has no direct effect on the fetus, but indirectly it impairs maternal circulation to the placenta to an extent causing reduction of oxygen supply across the placenta, but this impairment to the placental circulation, rarely reaches a point that fetal oxygenation is handicapped. (24)

Complications of spinal analgesia in obstetric:

1. Hypotension

Hypotension represents incidence of about 55–100%, so it is the most frequent complication. Moreover, hypotension is hazardous for the mother and the baby as it can cause loss of consciousness, aspiration. (25) Hypotension after spinal anaesthesia occurs mainly due to sympathetic block which depend on the height of block. (10)

This sympathectomy causes venous and arterial vasodilation, but because of the large amount of blood in the venous system (approximately 75% of the total volume of blood), the venodilation effect predominates as a result of the limited amount of smooth muscle in venules; in contrast, the vascular smooth muscle on the arterial side of the circulation retains a considerable degree of autonomous tone. After neuraxial block–induced sympathectomy, if normal cardiac output is maintained, total peripheral resistance should decrease only 15% to 18% in normovolamic healthy patients. (15)

Pregnant women have an elevated resting sympathetic tone and thus increased effects of sympathetic blockade. This also leads to decreased sensitivity to vasopressors, secondary to downregulation of adrenergic receptors and increased synthesis of endothelium-derived vasodilators during pregnancy. Spinal anaesthesia abolishes labor pain, which can decrease maternal blood pressure. (15)

Pregnant women have increased sensitivity (i.e. increased peak block height and block duration) to spinal anaesthesia, due to a combination of reduced volume of spinal cerebrospinal fluid (CSF) and enhanced neural susceptibility to local anaesthetics. Aortocaval compression by the gravid uterus, if present, further contributes to hypotension.(15)

2. Postdural Puncture Headache (PDPH)

PDPH is a common complication of spinal analgesia. Parturient constitutes the highest risk category, the reported incidence in these patients varying between 0 and

30%.The risk of PDPH is less with epidural anaesthesia, but it occurs in up to 50% of young patients following accidental meningeal puncture with large-diameter needles. The headache 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., diplopia, tinnitus) and nausea and vomiting are also present. The headache is believed to result from the loss of CSF through the meningeal needle hole, resulting in decreased beyond the 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 that are seen occasionally. [26, 11]

The incidence of PDPH decreases with increasing age and with the use of small-diameter spinal needles with non cutting tips to less than 3%.[27, 28] Inserting cutting needles with the bevel aligned parallel to the long axis of the meninges has also been shown to decrease the incidence of PDPH. [28] PDPH is usually self-limiting and spontaneous resolution may occur in few days. Therefore, many authors recommend approximately 24 h of conservative therapy. Various pharmacological (e.g. Methylxanthines, ACTH, Caffeine) and interventional measures (e.g., epidural saline/dextran) are available to treat PDPH; epidural blood patch (EBP) has a 96–98% success rate and has been recognized as the definitive treatment for PDPH. [29, 30, 31]

3. Backache

Back pain in women during pregnancy is up to 76%. Also, has been cited in one study as the most common reason for patients to refuse future spinal block. [32] The etiology of backache is not clear, although needle trauma, local anaesthetic irritation, and ligamentous strain secondary to muscle relaxation have been offered as explanations. [33]

4. Needle breakage, infection, haematoma and oedema.

Infections such as epidural abscess or meningitis are extremely rare. Infection may be exogenous in origin and be caused by the contamination of equipment or pharmacologic agents or by colonization of the catheter. Endogenous spread may occur from a site of infection elsewhere in the body. [34]

The incidence of neurologic injury resulting from haematoma associated with neuraxial anaesthesia is very low, with estimates of 1 in 150,000 and 1 in 220,000 for epidural and spinal anaesthesia, respectively. A review of 61 cases of spinal haematoma associated with spinal or epidural anaesthesia reported evidence of haemostatic abnormality in 68% of patients and difficult or bloody placement of needles and catheters in 25% of cases. In 15 of the reported cases the patients received spinal anaesthesia, with the remaining 46 receiving epidural anaesthesia. [34]

5. Hearing Loss

Lamberg et al. [35] demonstrated that a transient (1 to 3 days) mild decrease in hearing acuity (>10 decibel) is common after spinal analgesia, with an incidence of roughly 40% and a 3:1 female-to-male predominance. [36]

6. Systemic Toxicity

Toxicity occurs due to overdosage or intravascular injection of the local anaesthetic. The signs are excitement, disorientation, twitches, convulsions and perhaps apnea with severe cardiac depression. [37]

7. Total Spinal Anaesthesia

Total spinal anaesthesia occurs when local anaesthetic spreads high enough to block the entire spinal cord and occasionally the brainstem during either spinal or epidural analgesia. 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, and fluids as necessary to support the cardiovascular system, plus oxygen and controlled ventilation. If the cardiovascular and respiratory consequences are managed appropriately, total spinal block will resolve without sequelae. [38, 39]

8. Neurologic Injury

Persistent parasthesias and limited motor weakness are the most common injuries, although paraplegia and diffuse injury to cauda equina roots (cauda equina syndrome) do occur rarely. Injury may result from direct needle trauma to the spinal cord or spinal nerves, from spinal cord ischemia, from accidental injection of neurotoxic drugs or chemicals, from introduction of bacteria into the subarachnoid or epidural space, or very rarely from epidural haematoma. [40]

The mechanism by which local anaesthetics produce cauda equina syndrome is not yet clear; however, in vitro evidence suggests that local anaesthetics can produce excitotoxic damage by depolarizing neurons and increasing intracellular calcium concentrations.[41]Other studies demonstrate that local anaesthetics can cause neuronal injury by damaging neuronal plasma membranes through detergent like actions[42,43]or by activation of phospholipase-C which results in a decrease in membrane-cytoskeleton adhesion. It is also unclear as yet whether adjuncts added to local anaesthetics (e.g., epinephrine) contribute to cauda equina syndrome. [44]

9. Transient Neurologic Symptoms

In addition to cauda equina syndrome, the occurrence of transient neurologic symptoms (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 analgesia and was first proposed as a recognizable entity by Schneider et al.[45]All local anesthetics have been shown to cause TRI, although the risk appears to be greater with lidocaine than other local anesthetics.[46, 47]

Pain from TRI is not trivial, with the majority of patients rating it as moderate (visual analogue scale = 4 to 7/10). The pain usually resolves spontaneously within 72 hours, but a few patients have required up to 6 months. [48]

10. Nausea and vomiting

Nausea and vomiting are common side effects in parturients undergoing caesarean delivery performed under spinal anaesthesia can be very unpleasant to the patients. The reported incidence of nausea and vomiting during caesarean performed under regional anaesthesia varies from 50% to 80% when no prophylactic antiemetic is given. [49]

Nausea and vomiting are commonly associated with hypotension, bradycardia and high sensory block (T5 and above). It is usually corrected as the blood pressure is restored to normal. Persistent nausea and vomiting are treated by antiemetics. [49]

11. Urine retention

Not more common after spinal than after general anaesthesia and usually yields to neostigmine 0.5 mg. IM. [50]

Intrathecal local anaesthetics act on the neurons of the sacral spinal cord segments (S2–S4) by blocking the transmission of the afferent and efferent action potentials on the nervous fibers from and to the bladder. The sensation of urgency to void disappears 30–60 s after intrathecal injection of local anaesthetics, but a dull feeling of tension on maximal filling of the bladder persists. Bladder analgesia is due to the block of the transmission of the afferent nerve fibers from the bladder to the micturition center in the brain. [50, 51]

The detrusor contraction (detrusor block) is completely abolished 2–5 min after the injection of spinal anaesthesia, and its recovery depends on the duration of sensory block above the S2 and S3 sacral segment. [50]

12. Shivering

Shivering like tremor in patient given neuroaxial analgesia is always preceded with core hypothermia and vasoconstriction (above the level of the block). [52] The incidence is 20–70% in women receiving neuraxial blockade for labour or CS. This incidence is more in spinal anaesthesia than in epidural anaesthesia. [29]

The local anaesthetic blocks the inhibitory pathway in the brain and thus produces excitatory signs such as shivering.[52] It is uncomfortable for the patients and may interfere with monitoring of electrocardiogram, blood pressure (BP) and oxygen saturation.[53] It also increase oxygen consumption, lactic acidosis and carbon dioxide production.[54] It has been shown to increases the metabolic rate by up to 400%.[55] Treatment modalities have included covering the patient with blankets, application of radiant heat and warming the operating room suits. The use of warm local anaesthetic solutions stored at 23°C or warm intravenous fluid has met varying degrees of success. [56]

Thermoregulation

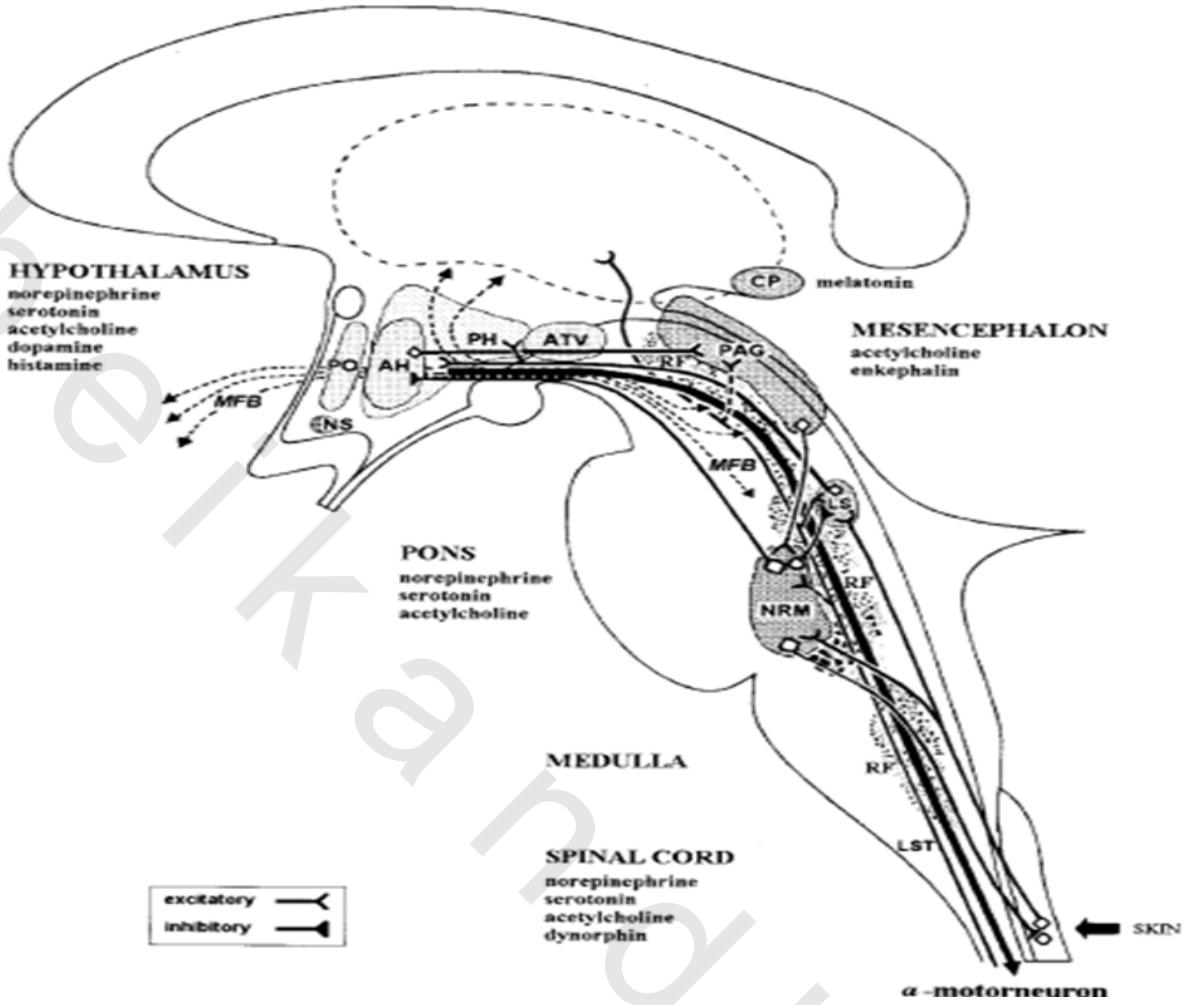

Figure (3): Neural pathways in the control of shivering.[55]

Afferent input

Temperature information is obtained from thermally sensitive cells throughout the body. Cold-sensitive cells are anatomically and physiologically distinct from those that detect warmth. Warm receptors increase their firing rates when temperature increases, while cold receptors do so when temperature decreases. [57]

Cold signals travel primarily by Aδ nerve fibers and warm information by unmyelinated C fibers, although some overlap occurs. C fibers also detect and convey pain sensation, which is why intense heat cannot be distinguished from sharp pain.[58]

Most ascending thermal information traverses the spinothalamic tracts in the anterior spinal cord, but no single spinal tract is critical for conveying thermal information. The hypothalamus, other parts of the brain, deep abdominal and thoracic tissues and the skin surface each contribute to roughly 20% of the total thermal input to the central regulatory system. [59]

Central control

Temperature is regulated by central structures (primarily the hypothalamus) that compare integrated thermal inputs from skin surface, neuraxis and deep tissues with threshold temperatures for each thermoregulatory response. It is likely that some regulatory responses can be mounted by spinal cord alone. [60]

Efferent responses

The body responds to thermal perturbations (body temperature differing from the appropriate threshold) by activating effector mechanisms that increase metabolic heat production or alter environmental heat loss. Each thermoregulatory effector has its own threshold and gain, so there is an orderly progression of responses and response intensities in proportion to the need. In general, energy efficient effectors such as vasoconstriction are maximized before metabolically costly responses such as shivering are initiated. [61]

Effectors determine the ambient temperature range that the body will tolerate while maintaining a normal core temperature. When specific effector mechanisms are inhibited (e.g. shivering prevented by administration of muscle relaxants), the tolerable range is decreased. Still, temperature will remain normal unless other effectors cannot compensate for the imposed stress. [62]

Quantitatively, behavioral regulation (e.g. dressing appropriately, modifying the environmental temperature, assuming positions that oppose skin surfaces, and voluntary movement) is the most important effector mechanism. Cutaneous vasoconstriction is the most consistently used autonomic effector mechanism. Nonshivering thermogenesis increases metabolic heat production (measured as whole body oxygen consumption) without producing mechanical work. Metabolic heat is lost primarily through convection and radiation from the skin surface, and vasoconstriction reduces this loss.[63]

Decreased muscle mass, neuromuscular diseases, and muscle relaxants all inhibit shivering, which increases the minimum tolerable ambient temperature. Similarly, anticholinergic drugs inhibit sweating, which decreases the maximum tolerable temperature. [64]

Hypothermia

Hypothermia is common during regional anaesthesia and may be nearly as severe as general anaesthesia. Core temperature typically decreases 0.5˚C to 1.0˚C shortly after induction of anaesthesia. However, the vasodilatation induced by regional anaesthesia only slightly increases cutaneous heat loss. Furthermore, metabolic heat production remains constant or increases because of shivering thermogenesis. This rapid decrease in core temperature, similar to that noted after induction of general anaesthesia, also results from an internal core-to-peripheral redistribution of body heat.[65, 66]

Subsequent hypothermia is simply due to heat loss exceeding metabolic heat production. Not only is the vasoconstriction threshold centrally impaired by regional anaesthesia, but more importantly, vasoconstriction in the legs is also directly prevented by nerve block.[67]

Epidural anaesthesia and spinal anaesthesia each decreases the thresholds triggering vasoconstriction and shivering (above the level of the block) by about 0.6˚C. Also, regional anaesthesia blocks all thermal inputs from blocked regions, which in the typical case is primarily cold information. The brain may then interpret decreased cold information as relative leg warming. Because skin temperature is an important input to the thermoregulatory control system, leg warming proportionately decreases the vasoconstriction and shivering thresholds. Painful stimulation slightly increases vasoconstriction thresholds. Consequently, thresholds are somewhat lower when surgical pain is prevented by simultaneous local or regional anaesthesia. Furthermore, the reduction in thresholds is proportional to the number of spinal segments blocked. [68, 69]

Neuraxial anaesthesia is frequently supplemented with sedative and analgesic medications. With the exception of midazolam, all significantly impair thermoregulatory control. Such inhibition may be severe when combined with the intrinsic impairment produced by regional anaesthesia and other factors, including advanced age and preexisting illness.[70]

The vasoconstriction and shivering thresholds are reduced by regional anaesthesia and further reduced by adjuvant drugs and advanced age. Even once triggered, the gain and maximum response intensity of shivering are about half normal. Finally, behavioral thermoregulation is impaired. The result is that cold defenses are triggered at a lower temperature than normal during regional anaesthesia, defenses are less effective once triggered, and patients frequently do not recognize that they are hypothermic. Because core temperature monitoring remains rare during regional anaesthesia, substantial hypothermia often goes undetected in these patients.[71, 72]

Shivering-like tremors in patients given neuraxial anaesthesia are always preceded by core hypothermia and vasoconstriction (above the level of the block). The risk of shivering during neuraxial anaesthesia is markedly diminished by maintaining strict normothermia. However, there is a distinct incidence of low-intensity, shivering-like tremors that occur in normothermic patient and is not thermoregulatory. [73]

Shivering during neuraxial anaesthesia can sometimes be treated by warming patient skin. Such warming increases cutaneous thermal input to the central regulatory system, thus increasing the degree of core hypothermia tolerated. Because the entire skin surface contributes 20% to the thermoregulatory control and the lower part of the body contributes about 10%, patient skin warming is likely to compensate for only small reductions in core temperature. [74]

Pharmacotherapy of shivering

Potent antishivering properties have been attributed to numerous drugs. These drugs are substances of several classes including biogenic monoamines, cholinomimetics, cations, endogenous peptides and possibly N-methyl-D-aspartate (NMDA) receptor antagonists. All these appear to modulate central thermoregulatory control mechanisms. 5-hydroxytryptamine (5-HT) causes shivering and vasoconstriction and a concomitant rise in core temperature, while norepinephrine and epinephrine lower the normal resting temperature and attenuated the hyperthermia induced by 5-HT. The balance between the modulatory 5-HT and norepinephrine inputs may be responsible for short and long term thermoregulatory adaptive modifications of the shivering threshold.[75, 76]

Serotonin (5-Hydroxytryptamine)

Serotonin is a biological amine found in the brain and spinal cord, has a role in neurotransmission and studies suggested that the serotonergic system has a role in control of post anaesthetic shivering. [77]5-hydroxytryptamine may influence both heat production and heat loss pathways. [56]Granisetron (1mg), Ondansetron (4 and 8 mg) and dolasetron (1mg.kg $^{-1}$), 5-HT $_3$ antagonists have been effectively used in treatment of postoperative shivering**.**

Meperidine

Meperidine decreases the shivering threshold almost twice as much as vasoconstriction threshold and is not only an effective treatment for shivering, but clearly more effective than equi-analgesic concentrations of pure mu-receptors agonists. The antishivering activity of meperidine may be partially mediated by opioid kappa-receptors.[78]

Magnesium

Magnesium may be considered as physiologic calcium channel blocker. During cold exposure, magnesium concentration in plasma increases, and it decreases in heat-acclimatized volunteers. The possible physiological role in cold adaptation may thus explain the effectiveness of magnesium in decreasing the threshold of post anaesthetic shivering. Magnesium sulfate is a physiologically occurring competitive antagonist at NMDA-receptors and was found to stop post anaesthetic shivering. [79]

Ketamine

Ketamine is a competitive NMDA-receptor antagonist also inhibits post anaesthetic shivering. It probably modulates shivering at a number of levels, either by influencing the hypothalamus or via a beta-adrenergic effect of norepinephrine. In contrast to meperidine, ketamine may prevent shivering with mild changes in haemodynamic and respiratory parameters. Based on these potential effects, this agent could be useful in preventing intra- and postoperative anaesthetic-related shivering. [80]

Clonidine

Clonidine exerts its anti-shivering effects at three levels: Hypothalamus, locus coeruleus and spinal cord. At the hypothalamic level, it decreases thermoregulatory threshold for vasoconstriction and shivering, because hypothalamus has high density of α2 adrenoceptors and hence is effective in treating the established post anaesthetic shivering.[81,82] It also reduces spontaneous firing in locus coeruleusa pro-shivering centre in pons.[83] At the spinal cord level, it activates the α2 adrenoreceptors and release of dynorphine, norepinephrine and acetylcholine.[84]The depressor effects of these neurotransmitters at the dorsal horn modulate cutaneous thermal inputs.[85] Clonidine is highly lipid-soluble and easily crosses the blood-brain barrier.[86] Due to these merits, interaction at the α2 adrenoreceptors at spinal and supraspinal sites occurs within the central nervous system.[87]

Complications of mild intraoperative hypothermia

Coagulation is impaired by mild hypothermia (33-36 ^{0}C). The most important factor appears to be a cold-induced defect in platelet function. Interestingly, the defect in platelet function is related to local temperature, not core temperature. (88)

Hypothermia can contribute to wound infections both by directly impairing immune function and indirectly triggering thermoregulatory vasoconstriction, which in turn decreases wound oxygen delivery. It is well established that fever is protective and that infections are aggravated when naturally-occurring fever is inhibited. (89)

Furthermore, hypothermia delays wound healing and prolong the duration of hospitalization by 20%, even in patients without infection. (90)

Thermal comfort is markedly impaired by postoperative hypothermia. Patients, being asked years after surgery, often identify feeling cold in the immediate postoperative period as the worst part of their hospitalization, sometimes rating it worse than the surgical pain. (91)

Postoperative thermal discomfort is also physiologically stressful because it elevates blood pressure, heart rate, and plasma catecholamine concentrations. These factors presumably contribute to what may be the most important consequence of mild perioperative hypothermia; morbid myocardial outcomes. (92). As might be expected from the pharmacokinetic and pharmacodynamic effects of hypothermia, the duration of post anaesthetic recovery is significantly prolonged, even when temperature is not a discharge criterion. (93) Lastly, hypothermia causing shivering may be responsible for increased intracranial and intraocular pressure.(94)

Granisetron:

Granisetron is a selective serotonin 5-HT_3 receptor antagonist with little or no affinity for other serotonin receptors used as an antiemetic to treat nausea and vomiting following chemotherapy.(95-96)

Chemical sturure:

1-methyl-*N*- ((1*R*, 3r, 5S)-9-methyl-9-azabicyclo [3.3.1] non -3-yl)-1*H*-indazole-3-carboxamide. (97)

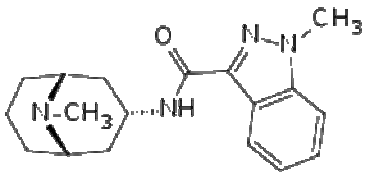

Figure (4): Chemical structure of Granisetron(97)

History:

It was developed by chemists working at the British drug company Beecham around 1988 and is available as a generic. It is produced by Roche Laboratories under the trade

name Kytril. The drug was approved in the United Kingdom in 1991 and in United States in 1994 by the FDA. [98]

Formulation:

Granisetron hydrochloride present in the form of tablets, injection and transdermal patch. Granisetron injection is clear, colorless, sterile, non pyrogenic, aqueous solution for intravenous administration. It is in 1&3 ml ampoules, each 1ml of aqueous solution contain 1.12mg granisetron hydrochloride equivalent to granisetron 1mg and sodium chloride, 9mg. PH ranges from 4.7 to 7.3.[98,99] It is compatible with dextrose 5% in sodium chloride 0.45 or 0.9 %. A granisetron transdermal patch was approved by the US FDA on September 12, 2008. [100]

Pharmacokinetics:

Mechanism of action:

Granisetron is a selective 5-hydroxytryptamine$_3$ (5-HT$_3$) receptor antagonist with little or no affinity for other serotonin receptors, including 5-HT$_1$; 5-HT$_{1A}$; 5-HT$_{1B}$/C; 5-HT$_2$; for alpha$_1$-, alpha$_2$-, or beta-adrenoreceptors; for dopamine-D$_2$; or for histamine-H$_1$; benzodiazepine; picrotoxin or opioid receptors. [101]

Serotonin receptors of the 5-HT$_3$ type are located peripherally on vagal nerve terminals and centrally in the chemoreceptor trigger zone of the area postrema. During chemotherapy that induces vomiting, mucosal enterochromaffin cells release serotonin, which stimulates 5-HT$_3$ receptors. This evokes vagal afferent discharge, inducing vomiting. [102]

The antiemetic activity appears to be mediated both centrally (in medullary chemoreceptor trigger zone) and peripherally (in GI tract) via inhibition of 5-HT$_3$ receptors. It does not have much effect on vomiting due to motion sickness. This drug does not have any effect on dopamine receptors or muscarinic receptors**.** [100-102**)**

5-hydroxytryptamine may influence both heat production and heat loss pathways. Ondansetron and dolasetron which are 5-HT$_3$ antagonists have been effectively used in treatment of postoperative shivering. [103]

Dose:

For chemotherapy induced nausea and vomiting 10mcg/kg IV over 5 minutes, 30 minutes prior chemotherapy.

For prevention and treatment of postoperative nausea and vomiting 1 mg undiluted over 30 seconds, given before induction of anesthesia, or immediately before reversal of anesthesia; or after surgery. [104]

Absorption:

Bioavailability:

Dose of oral solution is bioequivalent to corresponding dose of oral tablets. [96]

Food:

Food has minimal effect on extent of absorption; may increase peak plasma concentration by 30 %.[96]

Distribution:

Extent:

Distributed freely between plasma and red blood cells. Not known whether granisetron distributed into milk. [95]

Plasma Protein Binding: Approximately 65 %.[95]

Elimination:

Metabolism:

Metabolized via N-demethylation and aromatic ring oxidation followed by conjugation; metabolism appears to be mediated by CYP3A subfamily. [95]

Elimination Route:

Excreted in urine as unchanged drug (11–12%) and metabolites (48–49%) and in feces as metabolites (34–38%). [95]

Interactions for Granisetron Hydrochloride:

Apparently metabolized by CYP3A; does not induce or inhibit CYP isoenzymes.[105,106]

Specific Drugs:

- Antineoplastic agents: No apparent interaction with emetogenic cancer chemotherapies. [105, 106]
- Ketoconazole: Inhibition of granisetron metabolism in vitro. [107]

Half-life:

- IV administration: Terminal half-life is approximately 9 hours in adult cancer patients or adults undergoing surgery. [95]
- Oral administration: Terminal half-life is approximately 6.2 hours in healthy adults. [95]

Medical uses:

Chemotherapy

It may be used for chemotherapy-induced nausea and vomiting and appears to work about the same as ondansetron. [107-109]

Post operative

A number of medications including granisetron appear to be effective in controlling post-operative nausea and vomiting (PONV). It is unclear if it is better than or worse than other agents like droperidol, metoclopramide, ondansetron or cyclizine. [110]

Other uses

5HT $_3$ antagonists have been found to decrease pain on propofol injection granisetron, although the spinal serotonergic mechanisms in pain modulation are complex, several studies have confirmed the role of 5-HT3 receptors in antinociception. [111-116]

- **Serotonin (5-Hydroxytryptamine)**, a biological amine found in the brain and spinal cord, [109] has a role in neurotransmission and studies suggest that the serotonergic system has a role in control of post anaesthetic shivering.[118]The 5-HT3 binding sites are abundant at the spinal level.[117]These receptors are located in the superficial laminae and substantia gelatinosa of the spinal cord. 5-hydroxytryptamine may influence both heat production and heat loss pathways.[112]

- Granisetron has antidepressant like action, due to 5-HT3 receptors sites are ligand gated ion channels which mediate the release of number of neurotransmitters. There are evidence suggesting the possible involvement of 5-HT3 receptors in depression. [119,120] Also, the 5-HT3 receptors found to modulate neuronal release of norepinephrine (NE). Therefore, other possible mechanism of antidepressant action may be increased release of NE due to blockade of 5-HT3 receptors. [121]

- Is a possible therapy for nausea and vomiting due to acute or chronic medical illness or acute gastroenteritis

- Treatment of cyclic vomiting syndrome although there are no formal trials to confirm efficacy.

Cautions for Granisetron Hydrochloride:

Contraindications:

- Known hypersensitivity to granisetron or any ingredient in the formulation or other 5HT3 blockers.[105,106]

General Precautions:

- Granisetron has been assigned to pregnancy category B by Food and Drug Approval (FDA). Animal studies using doses up to 146 times the normal human dose failed to reveal evidence of fetal harm. [105,106]

GI Precautions:

- Does not stimulate gastric or intestinal peristalsis; do not use as a substitute for nasogastric suction. [105,106]

- May mask progressive ileus and/or gastric distention when used in patients undergoing abdominal surgery or in those with chemotherapy-induced nausea and vomiting. [105,106]

Adverse Effects:

Usually side effects of granisetron appear with overdose up to 38,5mg, nervous system side effects have been reported the most frequently. These have included headache, dizziness, insomnia, anxiety, somnolence, asthenia, agitation, and stimulation. Granisetron-induced headache is generally mild. In clinical trials, headache typically resolved spontaneously or was relieved by analgesics. (122)

Gastrointestinal side effects have included nausea, constipation appears to be dose related with single dose 300mcg/kg, vomiting, diarrhea, abdominal pain, dyspepsia, flatulence, dry mouth, and taste disturbances. (122)

Hepatic side effects have been reported rarely, these have included elevations in serum transaminases (two times normal values).Acute pancreatitis has also been reported.(123)

Cardiovascular side effects have included hypertension in 1% of patients. Atrial fibrillation, angina pectoris, and syncope have been reported rarely. Hypotension, sinus bradycardia, A-V block, ventricular ectopy, QT prolongation, and ECG changes have been reported as well. (123)