INTRODUCTION

Pain is defined as an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage [(1)].

Pain is a personal, subjective experience that involves sensory, emotional and behavioural factors associated with actual or potential tissue injury. What patients tell us about their pain can be very revealing, and an understanding of how the nervous system responds and adapts to pain in the short and long term is essential if we are to make sense of patients' experiences. The wide area of discomfort surrounding a wound, or even a wound that has healed long ago, such as an amputation stump, is a natural consequence of the plasticity of the nervous system. An understanding of the physiological basis of pain is helpful to the sufferer, and the professionals who have to provide appropriate treatment [(2)].

There is individual variation in response to pain, which is influenced by genetic makeup, cultural background, age and gender. Certain patient populations are at risk of inadequate pain control and require special attention. These include:

1. Paediatric patients.
2. Geriatric patients.
3. Patients with difficulty in communicating (due to critical illness, cognitive impairment or language barriers) [(3)].

Effective pain management is now an integral part of modern surgical practice. Postoperative pain management not only minimises patient suffering but also can reduce morbidity and facilitate rapid recovery and early discharge from hospital which can reduce hospital costs [(3)].

Pain pathway:

Peripheral Transmission:

Peripheral transmission of pain consists of production of electrical signals at the pain nerve endings (**Transduction)** followed by propagation of those signals through the peripheral nervous system **(Transmission)** [(4)].

Transduction:

The primary sensory structure that accomplishes transduction is the nociceptor. Most nociceptors are free nerve endings that sense heat, mechanical and chemical tissue damage. Several types are described:

1) ***Mechanoreceptors***, respond to pinch and pinprick,

2) ***Silent nociceptors***, which respond only in the presence of inflammation.

3) ***Polymodal mechanoheat nociceptors***. The last are most prevalent and respond to excessive pressure, extremes of temperatures (>42 °C and < 18 °C), and algogens (pain producing substances). Polymodal nociceptors are slow to adapt to strong pressure and display heat sensitization [(4)] (Figure 1).

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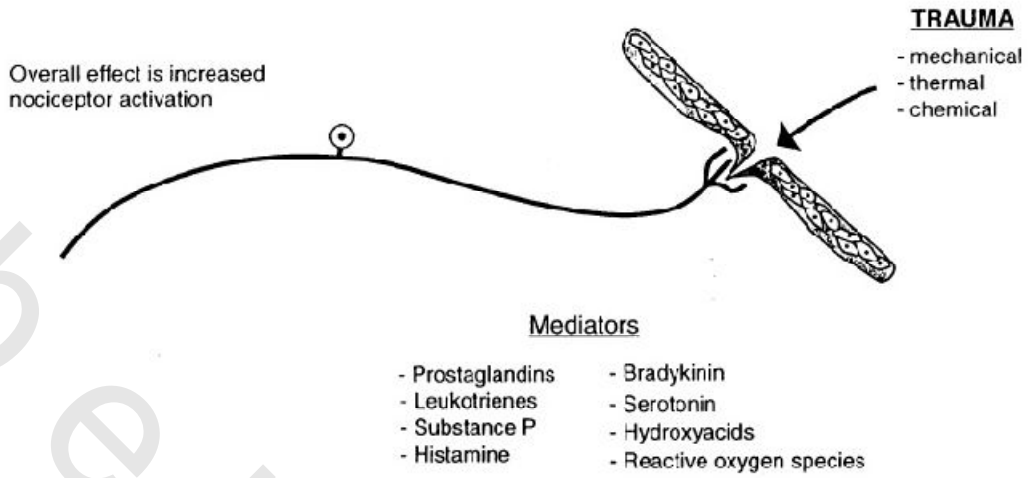

Figure 1: Representation of the transduction process and the mediators of inflammatory processes that lead to peripheral sensitization [(5)].

Transmission:

Pain impulses are transmitted by two fiber systems. The presence of two pain pathways explains the existence of two components of pain:

A) Fast, sharp and well localized sensation (*first pain*) which is conducted by Aδ fibers. Aδ fibers are myelinated, 2 – 5 μm in diameter and conduct at rates of 12 – 30 m/s.

b) A duller slower onset and often poorly localized sensation (*second pain*) which is conducted by C fibers. C fibers are unmyelinated, 0.4 – 1.2 μm in diameter and conduct at rates of 0.5 to 2 m/s [(6)].

Both fiber groups end in the dorsal horn of the spinal cord. Aδ fibers terminate predominantly on neurons in laminas I and V, whereas the dorsal root C fibers terminate in laminas I and II. The synaptic junctions between these first order neurons and the dorsal horn cells in the spinal cord are sites of considerable plasticity. For this reason the dorsal horn has been called a gate, where pain impulses can be "gated" i.e., modified [(7)].

Second-order neurons are either nociceptive-specific or wide dynamic range (WDR) neurons. Nociceptive-specific neurons serve only noxious stimuli and are arranged somatotopically in lamina I and have a discrete somatic receptive field; they are normally silent and respond only to high threshold noxious stimuli [(8)]. WDR neurons receive both noxious and non-noxious afferent input from Aβ, Aδ and C fibers. Differentiation between noxious and innocous stimuli occurs by ahigher frequency of WDR neuron discharge to noxious stimuli. WDR neurons are most abundant in lamina V [(9)].

Central Transmission:

The axons of most of the second order neurons cross the midline at the anterior commissure to the contralateral side of the spinal cord to ascend as Spinothalamic tract ending in the thalamus, reticular formation, nucleus raphe magnus and the periaqueductal gray. This ascending tract can be divided into lateral and medial:

a) The lateral Spinothalamic (neospinothalamic) tract projects mainly to the ventral posterolateral nucleus of the thalamus and carries discriminative aspects of pain, such as location, intensity, and duration.

b) The medial Spinothalamic (paleospinothalamic) tract projects to the medial thalamus and is responsible for mediating the autonomic and unpleasant emotional perception of pain [10] (figure 2).

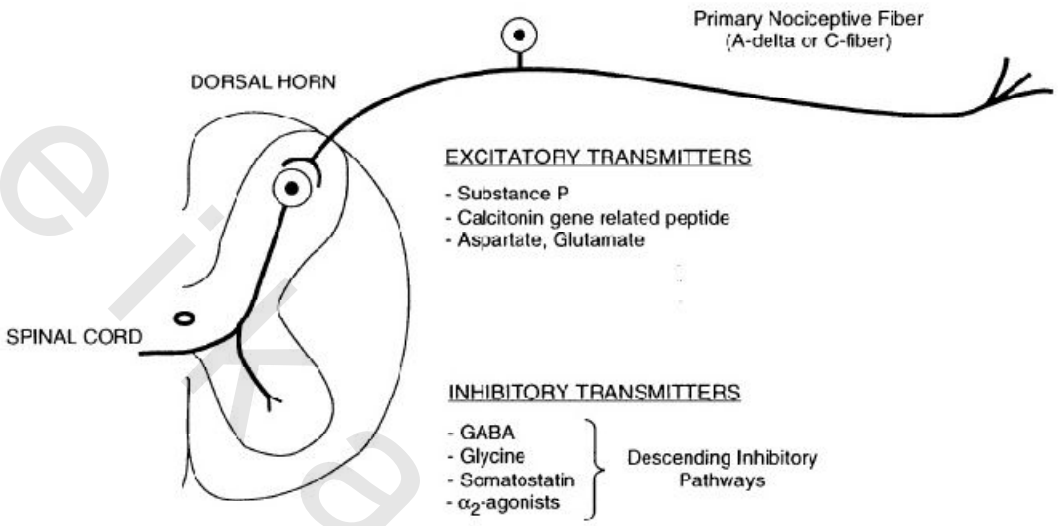

Figure 2: Representation of the transmission process by primary afferent (A-delta and C) fibers from periphery to the dorsal horn of the spinal cord[10].

Perception:

The third order neurons are located in the thalamus and project to somatosensory areas II and I in the post-central gyrus and superior wall of the Sylvain fissure. Perception and discrete localization of pain take place in these cortical areas. Some fibers project to the anterior cingulated gyrus and are likely to mediate the suffering and emotional components of pain [11].

Modulation:

Modulation of pain occurs peripherally at the nociceptor, in the spinal cord, or in supraspinal structures. This modulation can either inhibit or facilitate pain [11].

Peripheral modulation:

Nociceptors and their neurons display sensitization following repeated stimulation. Sensitization of nociceptors results in a decrease in threshold, an increase in frequency response, a decrease in response latency and spontaneous firing even after cessation of the stimulus (after discharges) [11].

This primary hyperalgesia is mediated by release of algogens like histamine, bradykinin, prostaglandin E2 (PGE2) and leukotriene from damaged tissues.

Secondary hyperalgesia or neurogenic inflammation is manifested by the triple response of flare, local oedema and sensitization to noxious stimuli. It is primarily due to antidromic release of substance P (sP) from collateral axons of primary afferent neurons. Substance P degranulates histamine and serotonin, vasodilates blood vessels, causes tissue oedema and induces formation of leukotrienes [12].

Central modulation:

This can either facilitate or inhibit pain.

A) The Facilitatory mechanisms are:

1) Windup and sensitization of second order neurons.

2) Receptive field expansion

3) Hyper excitability of flexion responses.

Neurochemical mediators of central sensitization include sP, cholecystokinin, angiotensin, alanin, L-glutamate and L-aspartate. These substances trigger changes in membrane excitability by interacting with G-protein coupled receptors, activating intracellular second messengers, which in turn phosphorylate substrate proteins [12].

B) Inhibitory mechanisms can be either Segmental or Supraspinal.

1) ***Segmental inhibition*** consists of activation of large afferent fibers subserving epicritic sensation inhibitory WDR neuron and spinothalamic activity. Glycine and γ-amino butyric acid (GABA) are amino acids that function as inhibitory neurotransmitters. Segmental inhibition appears to be mediated by $GABA_b$ receptor activity, which increases K^+ conductance across the cell membrane [12].

2) ***Supraspinal inhibition*** occurs whereby several supraspinal structures send fibers down the spinal cord to inhibit pain at the level of the dorsal horn. These include periaqueductal gray, reticular formation, and nucleus raphe magnus (NRM) [12].

Axons from these structures act pre-synaptically on the primary afferent neurons and post-synaptically on second-order neurons (or interneurons). These inhibitory pathways utilize monoamines, such as noradrenaline and serotonin, as neurotransmitters and terminate on nociceptive neurons in the spinal cord as well as on spinal inhibitory interneurons which store and release opioids [13].

Noradrenaline mediates this action through α 2 receptors. The endogenous opiate system acts via encephalin and β-endorphins. These mainly act presynaptically whereas the exogenous opiates act postsynaptically (figure 3) [13,14].

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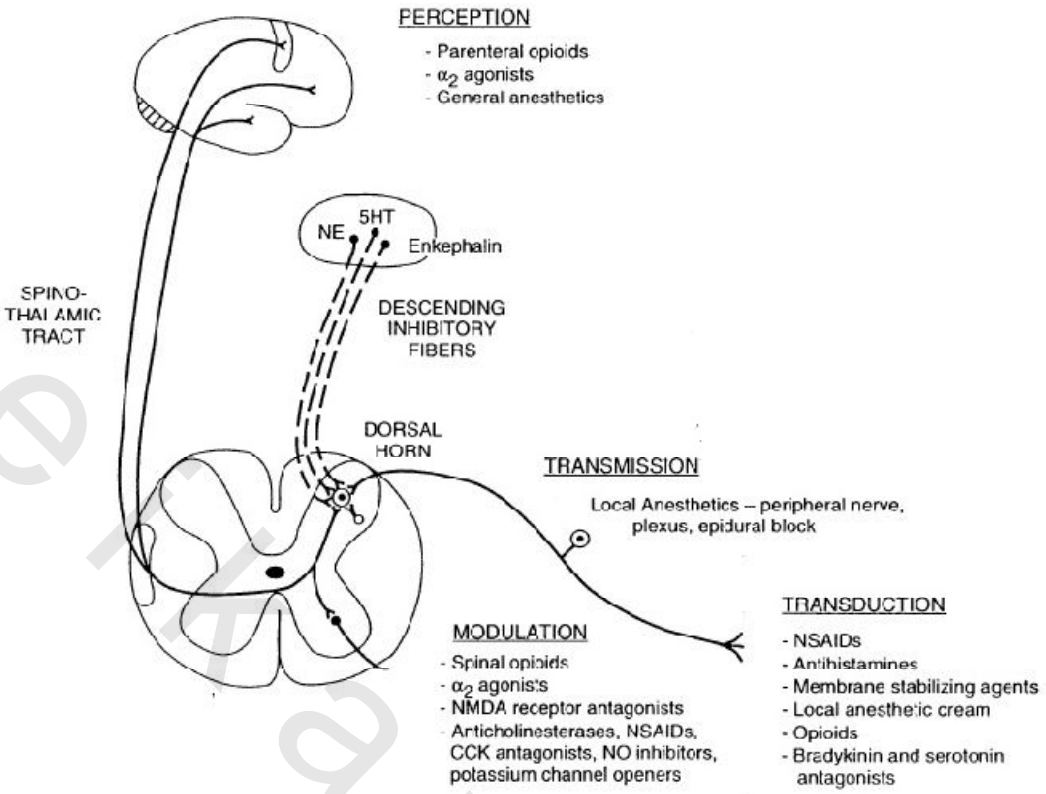

Figure 3: Diagrammatic representation of the four processes involved in the sensory pathway: transduction, transmission, perception, and modulation [13].

Classification of pain:

Pain can also be classified according to pathophysiology (e.g., nociceptive or neuropathic pain), etiology (e.g., postoperative or cancer pain), the affected area (e.g., headache or low back pain), or duration (acute or chronic pain). Such classifications are useful in the selection of treatment modalities and drug therapy [15].

Nociceptive pain is caused by activation or sensitization of peripheral nociceptors, specialized receptors that transduce noxious stimuli. Neuropathic pain is the result of injury or acquired abnormalities of peripheral or central neural structures [15].

Acute pain:

Acute pain can be defined as pain that is caused by noxious stimulation due to injury, a disease process, or the abnormal function of muscle or viscera. It lasts less than three months. It is usually nociceptive. Nociceptive pain serves to detect, localize, and limit tissue damage [16].

Chronic pain:

Chronic pain is defined as pain that persists beyond the usual course of an acute disease or after a reasonable time for healing to occur; more than 3 months. Chronic pain may be nociceptive, neuropathic, or mixed [17].

Somatic Pain:

Somatic pain can be further classified as superficial or deep. Superficial somatic pain is due to nociceptive input arising from skin, subcutaneous tissues, and mucous membranes. It is characteristically well localized and described as a sharp, pricking, throbbing, or burning sensation [18].

Visceral Pain:

The visceral form of acute pain is due to a disease process or abnormal function of an internal organ or its covering (e.g., parietal pleura, pericardium, or peritoneum) [18].

Post operative pain (POP):

Postoperative pain control is generally best managed by anaesthesiologists, because they offer regional anaesthetic techniques as well as pharmacological expertise in analgesics. Concerns over increased cost may be unjustified because some studies have demonstrated lower mortality and morbidity, as well as reduced hospital costs [19].

Adverse effects of post operative pain:

Cardiovascular effects:

Cardiovascular effects are often prominent and include hypertension, tachycardia, enhanced myocardial irritability, and increased systemic vascular resistance. Cardiac output increases in most normal persons but may decrease in patients with compromised ventricular function. Because of the increase in myocardial oxygen demand, pain can aggravate or precipitate myocardial ischemia [20].

Respiratory effects:

An increase in total body oxygen consumption and carbon dioxide production necessitates a concomitant increase in minute ventilation. The latter increases the work of breathing, particularly in patients with underlying lung disease [20].

Pain due to abdominal or thoracic incisions further compromises pulmonary function because of guarding (splinting). Decreased movement of the chest wall reduces tidal volume and functional residual capacity; this promotes atelectasis, intrapulmonary shunting, hypoxaemia, and, less commonly, hypoventilation. Reductions in vital capacity impair coughing and the clearing of secretions [20].

Gastrointestinal and urinary effects:

Enhanced sympathetic tone increases sphincter tone and decreases intestinal and urinary motility, promoting ileus and urinary retention, respectively. Hypersecretion of gastric acid can promote stress ulceration, and together with reduced motility, potentially

predisposes patients to severe aspiration pneumonitis. Nausea, vomiting, and constipation are common. Abdominal distention further aggravates loss of lung volume and pulmonary dysfunction [21].

Immune effects:

The stress response produces leukocytosis with lymphopenia and has been reported to depress the reticuloendothelial system. The latter predisposes patients to infection [22].

General sense of well-being:

The most common reaction to pain is anxiety. Sleep disturbances are also typical. When the duration of the pain becomes prolonged, depression is not unusual. Some patients react with anger that is frequently directed at the medical staff[23].

Pharmacological options of pain management:

1. NSAIDS:

Oral NSAIDs have long been used for treating nonsurgical pain syndromes because of their well-known anti-inflammatory, antipyretic and analgesic properties. When parenteral preparations of NSAIDs (e.g., ketorolac, ketoprofen, diclofenac) became available, these drugs were more widely used in the management of acute perioperative pain [24].

NSAIDs block the synthesis of prostaglandins by inhibiting cyclooxygenase (COX) types I and II, thereby reducing production of mediators of the acute inflammatory response. By decreasing the inflammatory response to surgical trauma [24].

NSAIDs have been alleged to reduce peripheral nociception. Studies also suggest that the central response to painful stimuli is modulated by NSAID-induced inhibition of prostaglandin synthesis in the spinal cord [23].

Compared to the partial opioid agonist tramadol, diclofenac produced better postoperative pain relief with fewer side effects after orthopaedic surgery and when administered as an adjuvant, ketorolac was associated with improved postoperative analgesia and patient comfort compared to fentanyl and the partial opioid agonist, dezocine[24].

When diclofenac (1 mg/kg IV) was administered before arthroscopic surgery, it was associated with similar pain scores to fentanyl (1 μg/kg IV) [25].

Despite the obvious benefits of using NSAIDs in the perioperative period, controversy still exists regarding their use because of the potential for gastrointestinal mucosal damage, renal tubular and platelet dysfunction [26].

2. Opioids:

Moderate postoperative pain should be treated with oral opioids either on an as-needed (PRN) basis or on a fixed schedule. They are commonly combined with oral COX inhibitors; combination therapy enhances analgesia and decreases side effects [27].

Opioid analgesia is achieved at a specific blood level for each patient for a given pain intensity. Patients with severe pain typically continue to report pain until the analgesic blood level reaches a certain concentration above which the patient experiences analgesia and the severity of pain rapidly diminishes. That point is referred to as the minimum effective analgesic concentration (MEAC). Small increases above this point produce a large increase in analgesia [(27)].

Intra-operative use of large bolus doses or continuous infusions of potent opioid analgesics may actually increase postoperative pain as a result of their rapid elimination and/or the development of acute tolerance [(28)].

Extensive use of opioids is associated with a variety of perioperative side effects [e.g., ventilatory depression, drowsiness and sedation, postoperative nausea and vomiting (PONV), pruritus, urinary retention, ileus, constipation] that can delay hospital discharge[(28)].

3. N-methyl d-aspartate (NMDA) Antagonists:

The NMDA receptor in its resting state is 'blocked 'by a magnesium 'plug'. Priming of the NMDA receptor by co-release of glutamate and other peptides, leads to removal of the magnesium plug and subsequent calcium influx into the cell. This leads to secondary events, such as immediate early gene induction, production of nitric oxide (NO), activation of a number of messengers, including phospholipases, polyphosphoinosites [IP3, DAG], cGMP, eicosanoids and phospholipase C [(29)].

The 2nd messengers act directly to change the excitability of the cell or involve production of oncogenes which may lead to long term alterations in cell excitability and response. Prolonged stimulation through sustained and excitotoxic glutamate release may result in cell death [(29)].

Anaesthesia for total knee arthroplasty:

Total knee arthroplasty (TKA) is a common surgical procedure in the elderly and is associated with severe pain after surgery and a high incidence of chronic pain. Several factors are associated with severe acute pain after surgery, including psychological factors and severe preoperative pain [(30)].

The primary indication for total knee arthroplasty (ie, total knee replacement) is relief of significant, disabling pain caused by severe arthritis. Night pain is particularly distressing. If dysfunction of the knee is causing significant reduction in the patient's quality of life, this should be taken into account .Correction of significant deformity is an important indication but is rarely used as the primary indication for surgery [(30)].

Anatomy of the knee [(31)]:

The knee is the largest joint in the body and having healthy knee is required to perform most every day activities. The knee is made up of lower end of the thighbone (femur), the upper end of the shinebone (tibia), and the knee cap (patella). The ends of these three bones where they touch are covered with articular cartilage, a smooth substance that protect the bones and enable them to move easily [(31)].

The menisci are located between the femur and tibia. These c-shaped wedges act as 'shock absorber' that cushion the joint .Large ligaments hold femur and tibia together and provide stability. The long thigh muscles give the knee strength. All the remaining surfaces of the knee are covered by thin linig called the synovial membrane. These membrane releases a fluids that lubricates the cartilage, reducing friction to nearly zero in a healthy knee. Normally, all of these components work in harmony. But disease or injury can disrupt these harmony result in pain, muscle weakness, and reduced function [31].

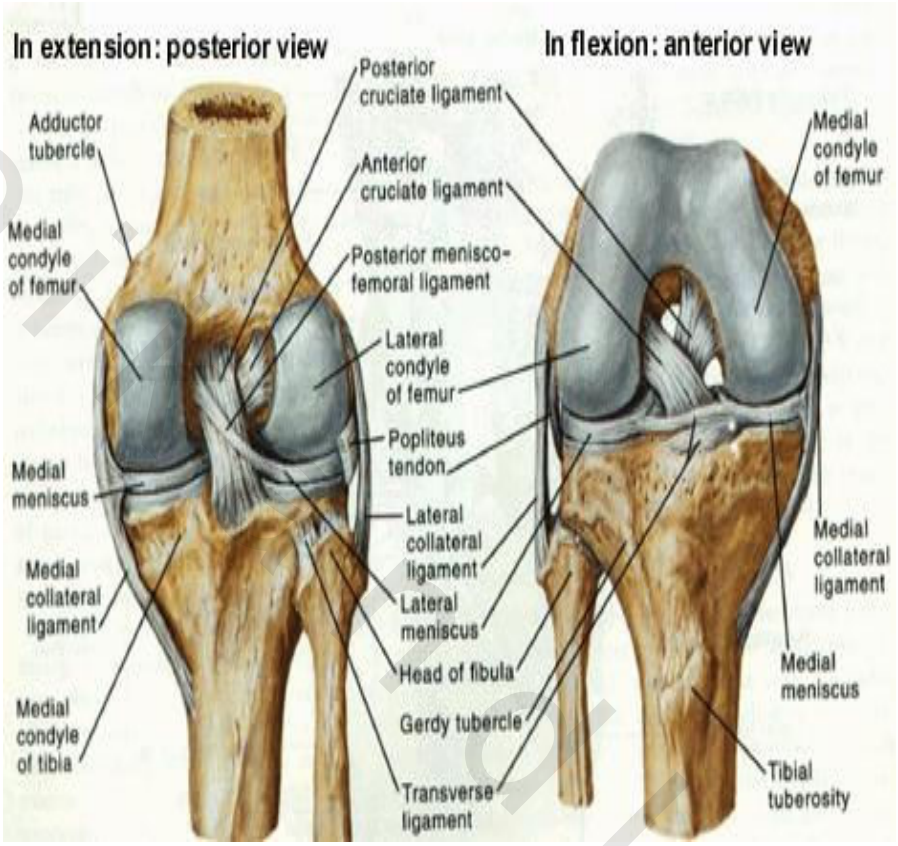

Figure (4): Normal knee anatomy [32].

Innervation of the knee joint:

Innervation of the knee joint is derived from femoral nerve via the branch to vastus medialis (anterior aspect of the joint capsule), sciatic nerve via genicular branches of both tibial and common peroneal components (posterior aspect of the joint capsule and all of the intra-articular structures), and obturator nerve by a branch from its posterior division that accompanies the femoral artery through adductor magnus into the popliteal fossa. Cutaneous innervation of the anterior aspect of the knee is supplied by the femoral nerve. The obturator nerve supplies the skin on the medial aspect of the knee in less than 40% of people[33].

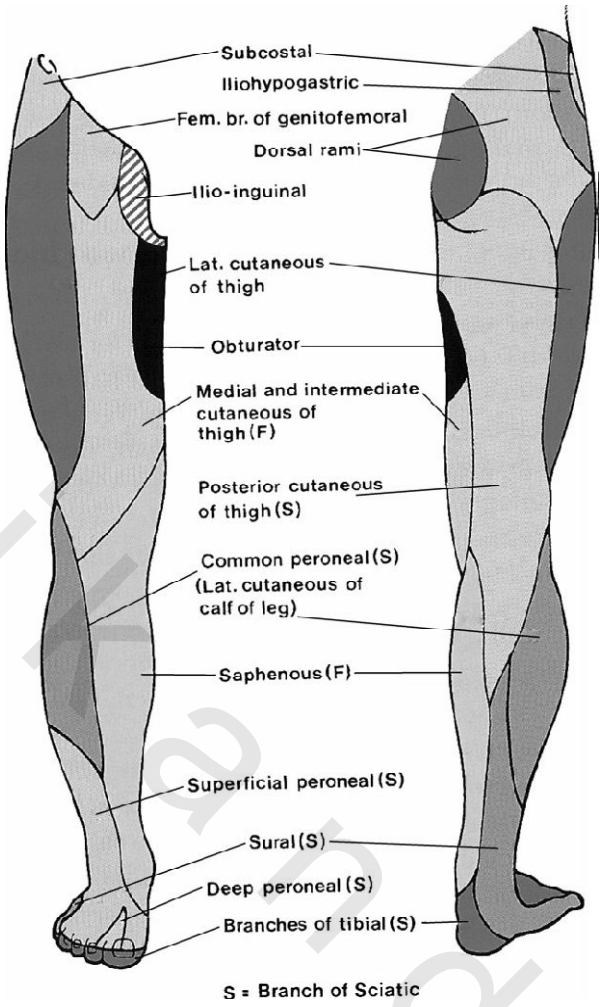

Figure (5): Innervation of the lower limb[33].

Surgical Alternatives to Arthroplasty:

A number of operative procedures should be considered in patients with degenerative disease of the knee. Arthroscopic debridement is sometimes indicated in mild degenerative joint disease with mechanical symptoms and recurrent persistent effusions [34].

Proximal tibial valgus osteotomy should be reserved for patients with medial tibiofemoral compartment disease, stable collateral ligaments, and a correctable varus deformity of the knee joint. Similarly, a distal femoral varus osteotomy can be considered for patients with lateral tibiofemoral compartment disease, stable collateral ligaments, and a valgus deformity of the knee joint [34,35].

Assesment for total knee arthroplasty surgery:

Preoperative medical evaluation of the patient includes the following:

Most patients are elderly, and commonly have associated problems such as hypertension, ischaemic heart disease, chronic obstructive pulmonary disease (COPD) or renal disease. Younger people presenting for joint replacement surgery often suffer from

rheumatoid arthritis, severe osteoporosis or obesity. Presentation for revision of previous replacement surgery is increasingly common [(36)].

Patients with ischemic heart disease, congestive heart failure, and chronic obstructive airway disease should be evaluated by a medical specialist or anaesthetist. Patients with significant peripheral vascular disease should be seen by a vascular surgeon [(37)].

Medical evaluation - Patients must have good cardiopulmonary function to withstand anaesthesia and to cope with a blood loss of 1000-1500 mL over the perioperative period; routine preoperative electrocardiography should be performed on elderly patients [(38)].

Blood loss is often considerable. Pre-donation of one unit of blood in the anaesthetic room, using acute normovolaemic haemodilution, is useful if the patient has an adequate starting haemoglobin level. Fluid balance should be guided by surgical blood loss, central venous pressure trends (where available), pulse, blood pressure and urine output, with the aim of maintaining normovolaemia.[(39)]

Antibiotics and antithrombotic prophylaxis are administered approximately 30 minutes before the incision is made. Mechanical antithromboembolic devices (e.g., stockings, foot pumps) are used intraoperatively [(40)].

Intraoperative Management:

The duration of total knee arthroplasty tends to be shorter than hip replacement; patients remain in a supine position, and blood loss is limited by the use of a tourniquet. Cooperative patients usually tolerate a regional technique with intravenous sedation. Bone cement implantation syndrome following insertion of a femoral prosthesis is possible, but is less likely than during hip arthroplasty [(40)].

Choice of anaesthetic:

Total knee arthroplasty (TKA) may be performed with the patient under regional or general anaesthesia. Which of these is used depends partly on the medical condition of the patient, although cardiovascular outcomes, cognitive function, and mortality rates associated with regional and general anaesthesia have not been proved to be significantly different[(40)].

Who have regional anaesthesia have been shown to develop fewer perioperative deep vein thrombosis (DVTs). Whether this has an overall positive benefit for the patient is not known [(41)].

Regional Anaesthesia:

Anaesthetic and analgesic relief after TKA traditionally has been provided through neuraxial (spinal or epidural) techniques, along with intravenous patient-controlled analgesia (PCA) using opioids. These approaches provide substantial anaesthesia and analgesia, respectively, often of several hours' duration. However, the side effects of these techniques, and of the opioids administered, make their use somewhat undesirable. These drawbacks have led to a shift toward redefining the effectiveness and utility of regional anaesthesia, specifically, of peripheral nerve blocks (PNBs) in intraoperative anaesthesia and postoperative analgesia [(41)].

Regional anaesthetic techniques have been shown to offer several advantages over general anaesthesia for this type of surgery. Regional anaesthesia is associated with less intra- and post-operative blood loss due to reductions in mean arterial pressure and venodilatation. Venous thromboembolic complications are reduced by 50% when central neuraxial block is compared with general anaesthesia in patients who have not received antithrombotic prophylaxis. Experimental evidence suggests that this results from attenuation of the pro-thrombotic effects of the stress response[(42).]

1) Spinal anaesthesia:

The most common anaesthesia recommended for total knee replacements is spinal anaesthesia. Spinal anaesthesia is quick, reliable, and simple to perform. The recovery profile and analgesia in the immediate post-operative period, combined with the ability to co-administer long acting intrathecal opioids make spinal anaesthesia, in several ways, the optimal anaesthetic technique [(43)].

2) Peripheral nerve blocks:

The use of either single shot or continuous peripheral nerve blocks is becoming increasingly popular for post-operative analgesia following lower limb arthroplasty. Current evidence supports earlier and improved rehabilitation when peripheral nerve blocks are used to provide post-operative analgesia. They can provide excellent analgesia with minimal motor block. This facilitates early and more effective joint mobilization and physiotherapy, while limiting reflex muscle spasm. In addition, they avoid the systemic side effects associated with continuous epidural analgesia (hypotension, urinary retention) and PCA morphine (sedation, PONV)[(44)].

Continuous peripheral nerve blocks provide prolonged sensory nerve block and analgesia when compared with single shot blocks. This has been demonstrated for femoral, lumbar plexus, and sciatic nerve blocks. In order to minimize motor block in the postoperative period, low concentration local anaesthetic solutions should be used, although the optimal concentration to maximize analgesia and minimize motor block is not yet known. The typical rate of local anaesthetic infusion is between 5 and 10 ml/h (per block). The insertion of continuous peripheral nerve catheters requires a greater level of expertise and can be both time consuming and technically challenging. Good local anaesthetic skin infiltration and an appropriate level of sedation are important to minimize patient discomfort and anxiety when performing these procedures in awake patients. We strongly recommend that peripheral nerve blocks are not carried out in patients under general anaesthesia to minimize the risk of accidental intra-neural or intravenous injection[(45)] .

a. Femoral nerve block:

Femoral nerve block has a high success rate and carries a low risk of complications. However, proximal spread of local anaesthetic to the other branches of the lumbar plexus is unreliable. Single shot femoral nerve block using a long acting amide local anaesthetic will provide analgesia to the anterior aspect of the knee for up to 24 h, although the incidence of profound motor block of the quadriceps muscles will be unacceptably high if large volumes of concentrated local anaesthetic agents are used [(46)].

a. Sciatic nerve block:

Pain behind the knee is a problem for a significant proportion of patients who only receive femoral nerve block because all of the intra-articular structures are innervated by the tibial nerve. The benefit of adding a sciatic nerve block to a femoral nerve block has become the subject of debate in regional anaesthesia circles.The advantage of improved analgesia in some patients may be offset by the extra time taken to perform the procedure, the potential for greater motor block and concerns regarding early detection of surgically induced sciatic nerve injury post-operatively [(46)] .

Single shot sciatic nerve block combined with femoral nerve block will provide analgesia for up to 24 h. When performing the block using a nerve stimulator, success rates are highest if inversion(tibial and peroneal nerve) or plantar flexion (tibial nerve) ofthe foot are elicited [(47)].

b. Lumbar plexus block:

It has been suggested that lumbar plexus block may be better than femoral nerve block because it blocks the femoral, obturator, and lateral femoral cutaneous nerves more reliably. Continuous lumbar plexus block is a logical and effective technique that has been shown to improve analgesia and facilitate earlier mobilization following total knee arthroplasty compared with single shot lumbar plexus block[(48)].

c. Obturator nerve block:

The addition of a separate obturator block to a femoral or lumbar plexus block is contentious. Femoral nerve block has been shown to spare the obturator nerve in as many as 50% of patients, contrasting with lumbar plexus block when the obturator nerve is missed in 10% of patients [(49)].

d. The 3 in 1 block:

An alternative to these individual blocks is the 3-in-1 block which theoretically blocks the three nerves by a single injection (femoral, lateral cutenous nerve, obturator nerve), provided sufficient volume of local anesthetic is injected [(50,51)].

For knee arthroscopy the 3-in-1 block provides a greater degree of muscle relaxation and a longer postoperative analgesia than the femoral nerve block alone. To provide complete anaesthesia for the knee, a sciatic nerve block must accompany the 3-in-1 block. Combined 3-in-l/sciatic nerve blocks for knee arthroscopy provides excellent intraoperative and postoperative analgesia and reduces postoperative complication rates. For postoperative pain management following open-knee procedures, the 3-in-1 block is an excellent adjunct to general anaesthesia[(52)].

3) Intrarticular Anaesthesia:

Knee arthroscopy is performed in many centers using intraarticular local anaesthetics with monitored anaesthesia care. Volumes of 50 to 60 mL of a local anaesthetic solution (ie, bupivacaine 0.25%) are required to ensure sufficient surgical anesthesia. Even with those high volumes, plasma levels remain 10 to 15 times below a nontoxic plasma level. This is presumably due to slow absorption through the synovia and considerable washout

of the local anaesthetic after the arthroscopy. Furthermore, peak serum bupivacaine concentrations can be reduced by adding epinephrine and injecting the local anaesthetic solution after tourniquet inflation [53].

Local anaesthesia with intravenous sedation compared favorably with the other techniques: surgical time was not increased, a large variety of operative procedures were successfully completed, recovery time was significantly shortened, and patient satisfaction remained high. It was concluded that this technique may offer several advantages over other types of anaesthesia for knee arthroscopy, including improved cost effectiveness [54] .

General anaesthesia:

General anaesthesia is often used for major surgery, such as a joint replacement. General anaesthesia may be selected based on patient, surgeon, or anaesthesiologist preference, or if the patient unable to receive regional or local anaesthesia. Unlike regional and local anaesthesia, general anaesthesia affects the entire body. It acts on the brain and nervous system and renders the patient temporarily unconscious [55].

As with any anaesthesia, there are risks, which may be increased if the patients already have heart disease, chronic lung conditions, or other serious medical problems. General anaesthesia affects both the heart and breathing rates, and there is a small risk of a serious medical complication, such as heart attack or stroke. The tube inserted down into the throat may give a sore throat and hoarse voice for a few days. Headache, nausea, and drowsiness are also common [56].

A combination of anaesthetics:

The patient can have a combination of spinal or epidural anaesthesia and a general anaesthetia. The patient will gain the benefits of a spinal or epidural anaesthetia but will be unconscious during the operation. The general anaesthetia will be 'lighter' and the unpleasant after-effects of the general anaesthetia may be less [56].

Postoperative managment:

The patient undergoes recovery and is usually observed for a 24-hour period in a high-dependency ward. Adequate hydration and analgesia are essential in this time of high physical stress. Analgesia is provided through continuation of the intraoperative epidural, patient-controlled intravenous analgesia, or oral analgesia. Cryotherapy is used to reduce postoperative swelling and pain .The goals of postoperative pain management are to minimize discomfort and allow the patient to move with less pain in order to participate in physical therapy after surgery[57].

Good acute pain control can be provided with multimodal analgesia, including regional anaesthesic techniques. Studies have demonstrated that poor acute pain control after TKA is strongly associated with development of chronic pain, and this emphasizes the importance of attention to good acute pain control after TKA [58].

Due to very intense postoperative pain, systemic analgesia is most commonly carried out with opioids applied through a PCA pump. This therapy is only sufficient with high doses and is inevitably associated with side effects such as nausea, vomiting, sedation and often a respiratory depression [59].

On the other hand, regional anaesthesia ensures good postoperative therapy, reduces the consumption of opioids, decreases the incidence of PONV and provides more success in rehabilitation. In comparison with general anaesthesia, regional anaesthesia has shown a far smaller risk of postoperative thrombosis [60,61].

Injecting the local anaesthetic through the epidural catheter with or without opioids results in good analgesia, but has side effects such as hypotension, reduced capability of mobilisation and urinary retention. The major issue is the risk of epidural bleeding due to which lumbar epidural anaesthesia and analgesia are no longer recommended [62].

Many studies have shown that the peripheral blocks such as femoral and sciatic nerve blocks as well as combination of the two result in excellent analgesia [63]. In comparison with epidural blocks, these blocks have significant advantages, they block one extremity and there minor side effects compared with epidural blocks. If applied under US monitoring, these blocks can be used in anticoagulated patients (apart from anterior approach to sciatic nerve where deep blood vessels necessitate caution) [64].

It is well known that ultrasound guided nerve blocks have multiple advantages in comparison with nerve stimulation such as risk reduction of puncturing blood vessels, nerve injuries and decrease of local anaesthetic volume by at least 40–50% [65].

The use of peripheral nerve catheters has the advantage over single shot techniques and is considered as the technique of choice for postoperative analgesia after total knee replacement surgery. It enables prolongation of block duration and analgesia. The method of local anaesthetic administration can be continuous or bolus injections [66].

Most studies show that continuous application of local anaesthetic improves patients' recovery and enables earlier discharge, there are some studies with opposite results [67].

Medications, medication delivery systems, physical intervention and alternative methods can be combined to provide balanced analgesia with the fewest side effects for the patient. Often, some medications for pain are given before surgery. A cox-2 medication or opioid medication may be given for preemptive pain management. Preemptive medication acts to block pain impulses from the surgery to the central nervous system before the injury occurs [68].

Pain after discharge from hospital following TKA is currently poorly managed, and this is an area where increased resources need to be focused to improve early pain control. This is particularly as patients are often discharged home within 4–5 days after surgery[69].

Chronic pain after TKA in the elderly can be managed with both pharmacological and non-pharmacological techniques. After excluding treatable causes of pain, the simplest approach is with the use of acetaminophen combined with a short course of non-steroidal anti-inflammatory drugs (NSAIDs). Careful titration of opioid analgesics can also be helpful with other adjuvants such as the antidepressants or antiepileptic medications used especially for patients with neuropathic pain [69].

Topical agents may provide benefit and are associated with fewer systemic side effects than oral administration. Complementary psychological therapies may be beneficial for those patients who have failed other options or have depression associated with chronic pain [69].

Magnesium (Mg):

Magnesium (Mg) is a nutrient and is the 4th most abundant mineral in the body, after Sodium, Potassium and Calcium. It is the 2nd most abundant intracellular cation after Potassium. It is a physiological antagonist of Calcium at different voltage-gated channels. It activates about 300 enzymes in the body, many of which involve energy production. ATP is fully functional when chelated to Mg. Mg regulates Calcium entry into the cells [70].

Pharmacokinetics of magnesium:

Total body Mg^{2+} is about 310g (1000 mmol) and daily requirements 200 to 250mg/day. Normal serum Mg levels is 0.76 to 0.9 mmol/l.

Mg is absorbed and excreted in the GIT and kidneys. It is reabsorbed in the ascending loop of Henle. Serum [Mg^{2+}] provides a negative feedback to the Loop of Henle. Mg is maintained at a ratio of 1:5 with K^{+}.

Mg homeostasis is under parathyroid hormone (PTH) and 1, 25 Dihydrocholecalciferol control, which increases gastrointestinal (GIT), bone, and renal re-absorption [71].

Mechanism of action of magnesium:

Magnesium is a Ca^{2+} antagonist. It competes with calcium to inhibit vasoconstriction. It blocks the NMDA receptor thus decreasing intracellular calcium. Magnesium inhibits Ryanodine receptors decreasing muscle contraction .Also directly inhibits catecholamine release from the adrenal medulla [72].

Physiologic effects of Magnesium [73]:

Cardiovascular system:

Magnesium improves cardiac output, coronary blood flow and coronary perfusion and reduces after load, due to vasodilatation. Magnesium changes excitatory threshold and intracellular ionic content causing less arrhythmias on reperfusion.It has a direct depressant effect on myocardial and vascular smooth muscle. Through decreased vascular tone, it decreases pulmonary vascular resistance. It slows the rate of impulse formation at the SA node and prolongs SA conduction, the PR interval and AV node refractory period [73].

Central nervous system:

Mg reduces the release of Acetylcholine at the NMJ (neuro muscular junction) by antagonizing calcium ions at the presynaptic junction causes reduced excitability of nerves. It Reverses cerebral vasospasm, therefore anticonvulsant [73].

Respiratory system:

Magnesium is an effective bronchodilator, but does not affect the respiratory drive. Respiratory failure may occur as a result of excessive muscle weakness [73].

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Musculoskeletal:

Magnesium is involved in terminating contraction, initiating relaxation in skeletal muscles. In combination with the effects above excessive plasma concentrations can cause muscle weakness [73].

Genitourinary:

Magnesium is a powerful tocolytic, decreasing uterine tone and contractility. Have mild diuretic properties [73].

Medical Applications and uses of Magnesium [74]:

Clinical use of magnesium sulphate in anaesthesia

1- Obstetric anaesthesia:

Magnesium can alter the pressor response to intubation in patients with gestational proteinuric hypertension. In a recent study magnesium sulphate (40 mg/Kg) was found to be superior to either lignocaine (1.5 mg/Kg) or alfentanil (10 μg/Kg) for the control of hypertensive response to intubation [75].

2- Cardiovascular anaesthesia:

It has also been shown to be as effective as propranolol, and more effective than verapamil in controlling the arrhythmias associated with adrenaline administration. Magnesium is a valuable antiarrhythmic agent, particularly for those arrhythmias associated with digitalis, hypokalemia, alcoholism and myocardial infarction [76]. A serum magnesium concentration of between 1.5-4mmol/L has been reported as both safe and effective in prevention and control of catecholamine-induced arrhythmias and for the control of the hypertensive response to endotracheal intubation.[75] A bolus dose of 2 g of magnesium sulphate administrated over 5 minutes is generally recommended, followed by an infusion rate of 1-2 g/h [77].

3- Phaeochromocytoma:

Magnesium effectively controls the release of catecholamine and hypertensive response at induction of anaesthesia, intubation of the trachea and during surgical stimulation [78].

4- Intrathecal magnesium sulphate:

Recent data indicates that intrathecal magnesium prolongs spinal opioid analgesia in humans and suggests that the availability of an intrathecal N-methyl-D-aspartate antagonist could be of clinical importance for pain management [79].

Therapeutic levels and toxicity:

Magnesium sulphate, the commercial preparation used in the parenteral form, has a molecular weight of 246, thus 7 g of this salt contains 98 mg of elemental magnesium (10% of the total weight) [80]. The normal plasma magnesium concentration is 0.75-1.0 m mol/L. A loading dose of approximately 16 mmol (4 g $MgSo_4$) is required to raise the plasma magnesium concentration by 1 m mol/L [81].

A serum magnesium concentration of between 1.5-4 mmol/L has been reported as both safe and effective in prevention and control of catecholamine induced arrhythmias and for control of the hypertensive response to intubation [82].

The patellar reflex disappears by the time the plasma magnesium level reaches 5mmol/L. It is the first sign of magnesium toxicity. Early signs and symptoms of magnesium toxicity include nausea, feeling of warmth, flushing, somnolence, diplopia, slurred speech and weakness [83].

When plasma levels rise above 5mmol/L, respiratory depression develops, and at 6 mmol /L or more, respiratory arrest occurs [84].

Manifestation of Mg toxicity[85]:

Cardiovascular:

Electrocardiograph changes with a magnesium sulfate overdose have included increased PR interval, increased QRS complex width and prolonged QT interval. The majority of adverse effects are associated with excessive serum levels. Rapid bolus infusions (i.e. 2 grams over 5 seconds) may cause cutaneous flushing and transient hypotension due to a direct vasodilating effect.

Bradyarrhythmias have occurred at levels above 5 mmol/L. Asystole has occurred at levels above 12 mmol/L. Intravenous calcium (5 to 10 mEq) quickly antagonizes the effects of magnesium[85].

Central nervous system:

As serum levels exceed 1.5 to 2 mmol/L, central nervous system depression, lethargy, confusion, disorientation, frank coma may occur.

Central nervous system depression may occur at higher levels; however, therapeutic serum magnesium levels attained for control of seizure during preeclampsia or eclampsia (2 to 4 mmol/L) have not been shown to be harmful to mother or infant.

Gastrointestinal:

Gastrointestinal side effects have included primarily diarrhea, nausea (Mg levels of 2 to 3 mmol/L), and rare cases of paralytic ileus (Mg levels greater than 3 mmol/L).

Treatment of toxicity:

Treatment with calcium gluconate intravenously plus the withholding of magnesium sulphate usually will reverse mild to moderate respiratory depression. For severe respiratory depression and arrest prompt endotracheal intubation and ventilation will prove life saving. With appropriate ventilation, cardiac action can be satisfactory even when plasma levels are very high [86].