Opioids in Spinal Anaesthesia

Physicians have been using opioids over three thousand years in clinical practice for analgesia. Still they are the most potent drugs in analgesic armamentarium for treating acute perioperative pain. They have also their strong role in different techniques of anaesthesia now a days. It is claimed that the intrathecal administration of opioids is century old[1]. However it was not until 1970s that researchers have to know that these agents exert their effect by binding with specific receptors. Intrathecal opioids were first administered to human subjects in 1979[2]. Since then they are used to provide analgesia for various surgical procedures.Three advances in the later part of the last century established the foundation of opioids role in neuroaxial analgesia and anesthesia. In 1968 'gate control theory' was proposed by Melzack and Wall[3]. It stated that the spinal cord was a potential target area for modulation of nociception. This proposition leads to the discovery of opioid receptors by Pert and Snyder in 1973[4]. They also identified the dorsal horn opioid receptors by radiological techniques. In 1976 Yakush and Rudy[5] succeeded to demonstrate that nociceptive stimuli can be modulated by direct action of opioids on the spinal cord. A great work was in 1979 when Wang and colleagues used intrathecal morphine and successfully provided analgesia to a small group of cancer patients. Another study published in the Lancet in the same year. It was suggested by the authors that the analgesic effect was directly mediated by morphine joining specific opioid receptors located in the substantia gelatinosa of Rolando present in the dorsal horn cells of the spinal cord[6].

There are three main types of opioid receptors including mu, kappa, and delta. All opioids produce analgesia by binding with opioid receptors. These receptors are present in brain, spinal cord, primary afferent neurons and non neuronal tissues and they have their variable affinities for different types. They produce different therapeutic responses and adverse effects. Intrathecally mu opioid receptors provide the primary site of action and are present in lamina I and II (substantia gelatinosa) of the dorsal horn. Opioids follow the same molecular mechanism.The agonists bind to G-protein coupled pre and post synaptic opioid receptors which inhibits adenylate cyclase[7]. That mediates increased potassium and decreased calcium channel. Ultimately the intracellular calcium level falls which inhibits the release of excitatory neurotransmitters substance P and glutamate and there is a reduction in neuronal excitation. Though the post-synaptic numbers are less than the presynaptic receptors they play a vital role in controlling the endogenous opioid containing interneurons. Several other target sites have been proposed for different opioids. These are local anaesthetic like effects on sensory C fibers (fentanyl), increase in CSF level of adenosine (morphine) causing hyperpolarization of nerve fibers and a calcium independent mechanism in dorsal horn neurons which counters the knowledge of damping down of neuronal activity in the context of an analgesic effect [8]. Studies have also shown that intrathecal opioid not only act through spinal specific mechanism. They also provide their analgesic effects at distant sites via bulk CSF flow to the supra spinal areas and also via systemic vascular absorption followed by bind to higher centers.

Though the mechanism of action of intrathecal opioids is the same, their pharmacodynamics those include onset, duration of action, intensity and degree of cephalad spread differ. Spinal cord bioavailability describes the differences [9, 10]. The ability of the intrathecal opioids to reach to their specific intrathecal sites depends on their lipophilicity. Lipophilicity is inversely related with bioavailability at spinal sites. There by hydrophilic opioid agonists (morphine, diamorphone) have a greater bioavailability at spinal cord level than lipophilic agents (fentanyl, sufentanyl). The lipophilic opioids provide rapid onset, potent analgesia but shorter duration of action. If commonly used lipophilic agent fentanyl is considered, it has been found that only 8% of the

intact drug can bind ultimately to the receptor sites in the grey matter[11]. The CSF level starts to fall with concomitant increase in both epidural and plasma level. Studies have shown also that the clearance rate of fentanyl (27 ml/kg/min) is ten times higher than that of morphine (2.8 ml/kg/min) [9].

It has also been suggested that lipophilic opioids have more affinity for white matter compared to hydrophilic agents who have more affinity for gray matter. This affinity can be explained by the cellular construction of the sites. White matter is composed of neuronal membranes and Schwann cells which contains 80% lipid while grey matter is more hydrophilic as it contains no myelin. This may explain the narrow band of segmental analgesia at the site of injection by the lipophilics versus the wider band of segmental analgesia by the hydrophilic agents. Another important pharmacokinetic aspect of intrathecal opioids is cephalad movement and crossing the BBB. Bulk flow of the drug, fluctuation of thoracic pressure and changes in brain volume related with cardiac cycle results in a net cephalad movement of injected intrathecal drugs. They may also access the brain stem through vascular system. The lipophilic agents readily crosses the BBB and posses the early respiratory depression. Hydrophilic agents carry the risk of delayed respiratory depression as they cross the BBB slowly[11].

Commonly the opioids are used intrathecally along with a local anaesthetic. It has been found that this combination provides better pain relief and associated with fewer side effects than when either drug is given alone. Though little is known about the effects of local anaesthetics on opioid receptor signaling it is known that they inhibit impulse transmission at the nerve root and dorsal root ganglia. This helps explaining segmental block [12]. A recent meta analysis has shown that the mixture decreases the median doses of local anaesthetics by 40%[13]. Other studies proved that morphine at a dose of 75-150microgram is optimal for single intrathecal administration which half of the safe dose when morphine alone is used[14]. This reduction of doses provides fewer side effects.

There are side effects of intrathecal opioids. Few classic dose dependent side effects are recorded. They are pruritus, nausea and vomiting, urinary retention, and respiratory depression. Sedation and somnolence and myoclonic activity are also recorded when used with continuous infusion[15].

Pruritus though mild becomes sometimes distressing to the patients and need interventions. Prophylactic use of opioid antagonists has been recommended to prevent the problem along with other side effects. Respiratory depression is a deleterious side effect which may lead to serious consequences from desaturation to respiratory arrest. So it is mandatory to monitor all the patients closely. They need not to nurse in a PACU or ICU. According to a Swedish guideline issued in1992 all patients having spinal opioids can be nursed in regular wards which is now practiced widely[16].

Although nausea is an unpleasant nuisance following opioid administration, intrathecal opioids are found to be reducing the occurrence. Researchers have reported a significant decrease in intraoperative nausea when 25μg fentanyl is added to a standardized spinal anaesthetic for caesarean delivery[17] .Urinary retention is a problem when hydrophilic opioids are used. There is no evidence that spinal opioids cause neurotoxicity[11]. It is also claimed that severe post operative hypothermia develops in a variety of surgical procedures including caesarean section. The mechanism is yet to know but it is frequently seen in unwarmed patients [18].

It is known that opioids are used alone or in combination for a lot of surgical procedures including day case surgery, orthopaedic, spine surgery, urogenital, abdominal and also obstetric surgery. The characteristics dictate their use in different procedures. It is understandable that fentanyl is suitable for day case surgeries. Morphine is licensed for arthoplasty. A larger dose of morphine can be used in spine surgeries. Post operative analgesia following laparoscopic cholecystectomy can be achieved with morphine for up to 24 hours. Diamorphone is available and used in some parts of the world and has established as a suitable alternative for morphine[11]. Pethidine is also used intrathecally but the risk of side effects are high [19]. Spinal opioids for caesarean delivery bear a special interest for anaesthesiologists. Probably fentanyl is the most widely used opioid for caesarean section. A combination of fentanyl

(20-30 μg) with commonly used local anaesthetic bupivacaine leads to a faster block for intraoperative and immediate postoperative analgesia without increasing the degree of motor blockade[10]. Bigger doses proved no extra effect although they did not appeared unsafe. Fentanyl has also shown less emetic activity than either morphine or pethidine.

Providing spinal anaesthesia with local anaesthetics may not be a difficult technique now days for the anaesthesiologists. Adding opioids may be newer for many across the world. Though complications have come down still they happen. Till date thousands of works have been done with different opioids for different surgical techniques. Gathering experiences from those and acquiring Knowledge of the opioid pharmacology is important to apply in one's own setting for better outcome and fewer complications.

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