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**Drugs used for pain management in gastrointestinal surgery and its implication**

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**Abstract**

Pain is the predominant symptom troubling patients. Pain management is one of the most important aspect in the management surgical patients leading to early recovery from surgical procedure or in patients with chronic diseases or malignancy. Various groups of drugs are used for dealing this, however they have their own implications in the form of adverse effects and dependence. In this article we have tried to review the concerns of different pain relieving medicines used in gastrointestinal surgery postoperatively and for malignant and chronic diseases.

**INTRODUCTION**

Pain is the most common symptom with which the patients usually present to the emergency room.[1] Previously it was thought to be a subjective term which could only be quantified by the patient experiencing the pain. As the 20<sup>th</sup> century advanced, there has been a change in the understanding of pain, its causes, assessment and management. <sup>1</sup> The International Association for the study of pain defines it as, "An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage." [2] Acute pain which was once thought to be of short duration, is a more complex and unpleasant experience having cognitive, emotional and sensory response to tissue trauma caused after surgery[3], which is reported by nearly 80% people in post operative period. Most of these patients report

moderate pain, and severe or extreme pain is reported by about 20%-40% patients.[4,5] There was a time when the surgeons were feared for conducting surgeries because of pain it induced to the patients making them apprehensive, so much so that patients feared the scalpels and escaped the dreadful, yet sometimes, life saving surgeries.

### **Chronicle of pain management**

As the modern scientific knowledge brought improvement in the surgical techniques, pain management also became an area of interest. For thousands of years hashish, mandrake, opium and alcohol has been used to produce analgesia during surgical procedures. In a failed attempt in 1845, Horace Wells brought to the limelight, the use of Nitrous Oxide as an anaesthetic agent. William TH Warren successfully removed a soft tissue tumour without pain from a young man's neck in 1846, making use of Ether. Soon chloroform and ether were being used world over for the painless surgeries. William Halsted made use of regional anaesthesia to produce field blocks for painless surgery which was followed by development of Spinal and Epidural anaesthesia by 1920. Sodium Thiopental was used to produce the similar pain free experience by 1934. And the progress in pain management became more and more significant in the coming times making the surgery a painless and pleasant experience to the patients.

Despite the advances in this field, and numerous studies showing the superiority of one approach over the other, pain management in surgical patients is still not absolute, but evolving.[6,7] It occurs that the acute pain must subside once the obnoxious stimulus is stopped and healing occurs, but a poorly managed pain can lead to loss of function, poor mobility & recovery, increased risk of post operative complications and chronicity. Evidence based studies have lead to formulation of guidelines which have been updated time to time which include the preoperative planning and patient education, perioperative pain management using pharmacological and nonpharmacological methods emphasising that the pain management is a complex process which has got significant implications over patient's quality of life.[8] Despite all the advancements in this field the incidence of severe acute postoperative pain has

remained unchanged over last 30 years, at about 20%.[9] Opioid use in the pain management has led to an opioid abuse epidemic such as chronic pancreatitis, malignancy etc, thus making it all the more important to make use of alternative multiple modalities in the pain management. This can include non-opioid medications, neuraxial analgesic techniques, and intravenous lignocaine. Beside this the minimal invasive techniques are supposed to cause less pain as compared to traditional open surgery. But the studies haven't produced any consistent results favouring a particular approach.[10] World health organisation has developed a analgesic step ladder where for mild pain non opioid plus option adjuvant is used; for mild to moderate pain weak opioid plus non-opioid and adjuvant analgesic is used; for moderate to severe pain a strong opioid plus non-opioid and adjuvant analgesic is used. It advises to move one step up when pain is intense.

### Search Strategy

All authors did an online search on PubMed, Google Scholar and Cochrane Database using of relevant articles. Further, the articles' reference lists were also searched for additional appropriate studies. The keywords used for searching were "post operative pain"; "pain management"; "Analgesia"; "acute pain"; "pain score"; "pain after GI surgery"; "spinal anaesthesia"; "epidural anaesthesia"; "intra venous anaesthesia"; "regional anaesthesia". The search was limited to publications in English literature. All the authors had an agreement that the articles selected for the minireview were relevant.

### Pathophysiology of pain

Central nervous system receives the information about tissue damage after the nociceptors are activated due to trauma.[11] The classical mechanism of pain involves conversion of the energy from noxious stimulus into sensory receptors called signal transduction.[11] These signals are then transmitted to the spinal cord and brain where these signals are perceived as pain.[12] This results in modulation of the nociceptive

response at the spinal cord level through the inhibitory or facilitatory response from the brain.[13] The neurotransmitters thus released, such as, enkephalins and endorphins inhibit the release of neurotransmitters involved in pain transmission. The pharmacological agents act at these different steps to produce the analgesic effects.[14] The pain management should begin before surgery with a thorough assessment of the patients allowing the optimal pain management techniques to be used and, helps to alleviate the patient anxiety and fears about post operative pain, as some of them might be using opioids for complex pain syndromes preoperatively.[15]

### **Pain assessment**

Thorough patient education and perioperative intervention (Table: 1&2) allows advanced planning including the patients with comorbidities which may subject the patients to significant side effects of the drugs used.[16] It allays the fear of post operative pain in the patient and allows the healthcare professionals to predict the types of patients who are about to have significant pain problem after surgery. Young females who smoke and have anxiety or depression and people already using opioids before the surgery are particularly at risk of having significant post operative pain.[17] Major emergency abdominal surgeries are also a risk factor for significant post operative pain.[18] Studies have proved that all these factors are associated with persistent post operative pain.[19]

Underassessment of the pain has been found to be the leading cause of under treatment of the pain. Therefore, the American Pain Society has included, "Pain as the 5<sup>th</sup> vital sign". Thus, it is as important to assess the pain as the other four vital signs. Pain has also been included as the 5<sup>th</sup> vital sign in the National Pain Management Strategy by the Veterans Health Administration.[22] Various one-dimensional and multidimensional tools for pain assessment have been developed to be used in different situations. One-dimensional tools like, Numeric Rating scale (NRS), Visual Analog Scale (VAS) and Categorical Scales using simple visual or verbal descriptors of pain are good for assessing the acute pain of fixed origins like post operative pain.[23]

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Multidimensional tools like, Initial Pain Assessment tool, Brief Pain Inventory (BPI)[24] and McGill Pain Questionnaire (MPQ) are important tools for assessing more complex and chronic pain.[25] Clinically Aligned Pain Assessment (CAPA) includes comfort, change in pain, pain control, functioning and sleep; thus can be used in perioperative period. Pain assessment in mentally disabled people, people suffering from dementia and those unable to verbalize can be assessed with Pain In Advanced Dementia (PAINAD), Dolopus-2, Critical care Pain Observation Tool (CPOT) and Behavioural Pain Scale (BPS).[26-28] Patients should be continuously monitored for any pain severe than mild, which needs treatment on priority.

### Pharmacologic treatment

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Post operative pain management is an integral part of the enhanced recovery after surgery (ERAS) protocols. Traditionally for abdominal surgery Epidural Analgesia (EA) or Intravenous Patient-Controlled Analgesia (IVPCA) based on opioids, has been used. It has good pain control but has a significant drug associated morbidity which hampers the achievement of the goal of early Drinking, Eating and Moving (DrEaMing).[29] There is no single drug which has got the ideal pain management properties, hence a multimodal approach towards reaching a perfect analgesia is favoured. It involves the use of various drugs acting at the different levels of pain pathway to achieve a better control.[30] As in evidence-based PROcedure-SPECific Pain Management (PROSPECT) guidelines, these different drugs used, thus effectively lower the total analgesic dose and the associated side effects.[31]

Pain treatment can be pharmacological or nonpharmacological in the multimodal treatment strategy.[32] Commonly used pharmacological agents are:

**Non opioid analgesics:** Non-Steroidal Anti-Inflammatory Drugs (NSAID) including Aspirin and other salicylic acid derivatives, work by inhibiting prostaglandin production responsible for pain and inflammation.[33] They could be selective cyclooxygenase-2 (COX-2) inhibitors like celecoxib or, nonspecific cyclooxygenase inhibitors like Aspirin, Ibuprofen and Naproxen.[34-36] Major concern is renal toxicity and

gastritis. Paracetamol is another NSAID used for the mild to moderate pain management. It has a significant opioid sparing effect in multimodal analgesia approach. When used intravenously for pain prophylaxis, it lowers the incidence of pain associated nausea and vomiting. It has been proven safe at the therapeutic dosage in different studies.[37,38] Major concern is the hepatotoxicity at the significantly higher dosage.[39]

**Opioid analgesics:** mu opioid agonists (morphine like agonists) and agonist-antagonist opioids are the cornerstone of treating moderate to severe pain. They can be further classified as natural, synthetic or semi-synthetic opioids. Many people report opioid related adverse effects (ORADE) in the immediate post operative period like dizziness, vomiting, nausea, constipation, dry mouth, dependence, pruritus *etc.* Development of ORADE leads to a prolonged hospital stay. Many a times the drugs when prescribed beyond the recommended post operative period are misused and sold to other people.[40] These patients need continuous monitoring as they are liable to develop respiratory depression, drug tolerance, drug dependence and addiction when used over a long period. Patients who have a preoperative history of prolonged pain, use of benzodiazepines, anxious personality and history of drug addiction are more liable to develop drug dependence and addiction.[41] Such type of patients are liable to have withdrawal effects in the post operative period so they should be maintained on minimal opioid dosage and supplemented with other types of analgesics and use of regional anaesthesia techniques.[42]

**Adjuvant analgesics or co-analgesics** include a wide variety of drugs mainly used for purposes other than pain relief, but with some analgesic properties. Commonly used ones are Gabapentinoids, magnesium, lignocaine IV, Ketamine, Antidepressants like Selective Serotonin Reuptake Inhibitors (SSRI) and Anti-Epileptic drugs.[32]

**Ketamine** is a dissociative anaesthetic, which when used for acute pain relief in perioperative settings may reduce the morphine consumption and pain intensity.[43] It prevents the development of persistent post surgical pain in the patients. Although it is not a part of the ERAS protocols but it may reduce the morphine consumption when

used in multimodal analgesia.[44] Adverse effects include amnesia, psychosis, hypertension, depression, impaired coordination and judgement, depression, respiratory complications *etc.*

**Gabapantenoids** act on the ascending as well as descending pathway of pain perception decreasing nociception.[45] They have been found to be effective in the post operative pain management and have a morphine sparing effect in multimodal analgesia.[43,46] They prevent the development of persistent post surgical pain but they have an abuse potential and can lead to addiction and death. Various other side effects include ataxia, angioedema, suicidal tendency, viral infections, nystagmus, constipation, weight gain *etc.* They should be used with caution in patients with previous history of drug abuse or addiction.[47]

### **Alpha -2 agonists**

Drugs like Clonidine and Dexmedetomidine can be used to decrease the opiate use in the perioperative period either orally, intravenously, intrathecally, or as a transdermal patch.[48] When they are used for nerve blocks, they produce prolonged analgesic effect, but they are associated with hypotension and sedation therefore patients require strict perioperative monitoring when these drugs are used.[49]

**Lignocaine infusion:** Although the current ERAS guidelines included Intra-Venous lignocaine infusion for post operative pain relief in colorectal surgery, there has not been evidence sufficient enough to support this practise anymore.[50] Studies have found insufficient evidence that it helps in post operative pain, ileus, nausea or vomiting.[51]

**Magnesium:** Intravenous Magnesium has been found to be useful in post operative pain management and has a morphine sparing effect under multimodal post op analgesia protocols.[52] It has been demonstrated to prolong the effect of nerve blocks and spinal anaesthesia.[53]

**Neuraxial blocks:** Epidural Analgesia (EA), uses local anaesthetics along with adjuncts ,such as morphine, Buprenorphine, Tramadol, Fentanyl,Hydroxy morphine,



Clonidine, Dexmedetomidine or Diamorphine. Drugs like clonidine and Dexmedetomidine prolong the effect of the nerve block.[54] EA provides better analgesia after GI surgery with low incidence of ileus, pulmonary complications and analgesic requirements. It improves ileus and promotes food tolerance by reducing nausea and vomiting thus helping the patient in achieving an early state of DrEaMing.[55] EA is associated with high failure rate as compared to IVPCA and has a high complication rates like hematoma formation, hypotension, permanent harm in about 17.4 per 100000 patients with death reported in about 6.1 per 100000 patients.[56,57] ERAS guidelines also support the use of EA in esophagectomy and colorectal surgery.[58,59]

**Intrathecal analgesia:** A process in which the local anaesthetic agent, sometimes mixed with adjuncts, is instilled into the subarachnoid space to produce anaesthetic/analgesic effect which can last up to 24 hrs. It has high efficacy and low complication rate as compared to EA with permanent damage in about 2.2 per 100000 and death in about 1.2 per 100000 patients.[57]It reduces the opioid consumption and has low pain scores in laparoscopic colorectal surgery.[58] It can lead to respiratory depression hence will require strict monitoring. It has been included in the ERAS protocols for colorectal surgery.[60]

**Abdominal wall blocks:** They provide analgesia in abdominal surgery. Previously blind techniques were used but now ultrasonogram (USG) guidance has increased their popularity. They avoid the adverse effects of epidural and spinal analgesia like hypotension, motor block and the risk of neurological damage.USG should eliminate the complications but studies have failed to demonstrate so.[61]They could be of particular importance when the neuraxialblockade is contraindicated like in sepsis, coagulopathy, preexisting neurological deficit or when the patients decide against it. Catheters for infusion can be used to prolong the blockade.

Transversus Abdominis Plane block (TAP) can be performed blindly but USG guidance increases the precision (Fig 1a & 1b). It can be used in wide variety of surgeries including abdominal, urological, gynaecological, and obstetric surgeries. It

has the opioid sparing effect in multimodal analgesic approach.[62] It blocks the T7-L1 nerves. The subcostal TAP block aims to block the lower thoracic nerves including T6-T9. A study has found the USG guided posterior TAP block to be superior as compared to the lateral TAP block in lower abdomen incisions.[63]

Quadratus lumborum block (QLB): USG guided QLB block has been used in providing analgesia in midline laparotomy and laparoscopic procedures. It is a newer technique about which there is a less evidence about efficacy in abdominal surgery.[64]

Transversalis fascia plane (TFP) It blocks the lateral cutaneous branches of T12-L1, which are commonly missed by the TAP block. It has been successfully used in open appendectomy and inguinal hernia surgeries.[65]

Erector Spinae Plane block: ESP is a new technique where the LA is injected around the tip of T5 transverse process level depositing the drug deep to the erector spinae muscle. It can have analgesic effect in laparotomies. Recently it has been reported to be used successfully in laparoscopic ventral hernia repair.[66]

USG guided blocks are supposed to be safe as the needle tip can be directly visualised while injecting the drug, but studies have found peritoneal breach while the needle tip was being visualised during the try to infiltrate around the nerve bundles. Thus the needle should aim for the fascial planes rather than the nerve bundles. Systemic LA toxicity is a concern due to a large volume of the drug being used to infiltrate. The abdomen is well vascularised, so the absorption is fast. Thus, the less cardio toxic alternatives should be used.[67]

**Nonpharmacological techniques:** they have been used successfully for the management of chronic pain but recently they have been used in the acute post operative period also. The cognitive behavioural therapy, distraction techniques like music, aromatherapy, canine therapy and virtual reality has been used effectively in perioperative pain management. They decrease anxiety and help the patients in self-management.[9,68] These measures can be an area of future research for developing better methods of pain relief.

## **CONCLUSION**

Pain is the main symptom troubling patients and its management is one of the most important aspect for better outcomes and early recovery after surgery. Numerous drugs and procedures are used for the purpose of managing pain. World Health Organisation has advocated simple and valuable use of analgesic step ladder for pain management. However, inspite the advances in this field and various studies pain management in surgical patients is still not absolute and is still evolving.

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