EDITORIAL VIEW

Management of opioid induced postoperative ileus: the current scenario

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ABSTRACT

Persistent postoperative ileus causes significant discomfort to a surgical patient. Not only it increases hospital stay or leads to rehospitalization, it involves significant cost of treatment and morbidity in some unfortunate patients. No single intervention, drug or perioperative protocol has been found to be successful. The strategy has to be multimodal. Early enteral feeds, active ambulation, physiotherapy, use of minimally invasive surgical techniques so as to reduce bowel handling, judicious use of narcotics, good perioperative pain relief using a multimodal approach are the strategies that when applied together has better outcomes. Peripherally acting opioid antagonists have been successfully used but are very costly. Perioperative intravenous lidocaine infusion along with other strategies appears promising.

Key words: Opioid analgesics; Ileus; Colorectal surgery; Postoperative; Morphine; Lidocaine; Alvimopan; Methylnaltrexone; Oliceridine

Citation: Nair AS. Management of opioid induced postoperative ileus: the current scenario. Anaesth Pain & Intensive Care 2016;20(4):380-382

Received: 27 Dec 2016; **Reviewed:** 28 Dec 2016; **Accepted:** 28 Dec 2016

INTRODUCTION

Postoperative ileus (POI) is a common problem encountered after surgeries involving the gastrointestinal tract, genitourinary tract and retroperitoneum. POI leads to significant patient discomfort, prolonged hospital stay, increased cost of treatment, re-exploration, deep vein thrombosis and hospital acquired infections. POI is a multifactorial entity. The factors responsible are bowel handling, release of inflammatory mediators, electrolyte imbalance, use of opioids perioperatively, late enteral feeds etc. Interventions or strategies that have been known to enhance recovery are minimally invasive surgical technique, use of epidural analgesia, early enteral feeds, correction/ optimization of electrolyte imbalance, early mobilization and ambulation, use of prokinetics and laxatives. Although the mentioned strategies, when implemented together, have found a reasonable outcome, none of these works alone in relieving POI.[1]

Perioperative intravenous (IV) lidocaine infusion has been found to be very effective in many studies involving patients who underwent laparoscopic and open surgeries where the return of bowel activity was found very early compared to patients who were managed without lidocaine. Peripherally acting opioid receptor antagonists are now US-FDA approved and acts selectively on the opioid receptors present in the intestines without antagonizing the central effects. Alvimopan and methyl naltrexone are the 2 drugs in this group. When it is started at the time of surgery, the opioid induced POI can be addressed. However, the other mechanical and metabolic factors need to be addressed along with the reversing agents.[2]

Lidocaine, a promising drug in ileus:

Lidocaine is a class Ib anti-arrhythmic drug, which has been used quite successfully in gastrointestinal cases. Intravenous infusion of lidocaine when used as an infusion perioperatively has been shown to

reduce post-operative pain, has facilitated early recovery of bowel function and a reduced hospital stay.[3] A loading dose of 1.5 mg/kg during induction, a maintenance dose of 2 mg/kg intraoperatively and 1 mg/kg postoperatively for 24 hours has shown promising results. In the meta-analysis by Ventham et al, they described lidocaine as a multi-dimensional drug which reduces postoperative pain, leads to less opiate consumption, less nausea and vomiting and promotes early recovery of bowel function.[4] Kranke et al conducted a review to assess the efficacy of IV lidocaine in alleviating postoperative pain and its role in early bowel recovery, the results of which were published in Cochrane Database Systematic Review. The study involved 45 trials with 2802 participants. They found low to moderate evidence in using lidocaine IV for postoperative pain. They also found limited evidence in the role of lidocaine in promoting early gastrointestinal recovery, reduced length of hospital stay, and opioid requirements perioperatively.[5]

The peripherally acting opioid antagonists:

Alvimopan is an orally available, peripherally acting μ receptor antagonist (PAM-OR) which is approved by US-FDA for perioperative use after bowel resections and anastomosis. It has affinity to the peripheral opioid receptors. Unlike naloxone, it does not cross blood brain barrier. Therefore, the systemic analgesia provided by μ-agonists e.g. fentanyl, morphine, remifentanil, is not affected.[6] The FDA has approved 15 doses of alvimopan, a dose of 12 mg preoperatively orally followed by 12 mg twice daily for 7 days. Before the year 2008, alvimopan was also used in patients having constipation due to long term oral opioids for cancer and non-cancer pain. Long term alvimopan use was found responsible for serious cardiovascular events like myocardial infarction. Therefore, the drug was banned for use in patients with opioid induced constipation and was approved for perioperative use only. Traut et al reviewed the regularly used prokinetics and other drugs which were used in relieving post-operative ileus. They found that 6 randomized controlled trials supported the use of perioperative alvimopan.[7]

The problem with alvimopan is that it can be procured only by hospitals who are enrolled in EASE® (ENTEREG® Access Support and Education) Program after which the drug can be procured by REMS (Risk Evaluation and Mitigation Strategy) of US-FDA. This is a complicated affair. Above all, the drug is very costly (the cost of 15 doses of alvimopan is around $930).[8] The drug has not been approved for use in pediatric surgical patients.

Methylnaltrexone is a peripherally acting opioid receptor antagonist which is available for subcutaneous use. It has been used successfully in cancer patients with opioid induced constipation at a dose of 12 mg subcutaneously once daily or 0.15 mg/kg once daily in patients less than 40 kg. The treatment is continued till the constipation is relieved.[9] Like alvimopan, methylnaltrexone also doesn't cross blood brain barrier. But unlike alvimopan, it has been successfully used in pediatric patients suffering with opioid induced ileus 0.15 mg/kg once daily subcutaneously).[10] A 12 mg vial costs 48$ and a kit of 7 vials is available for around 336$. The meta-analysis by Siemens et al described methylnaltrexone as a safe and effective drug for use in patients with opioid induced constipation.[11]

The ongoing research:

Lot of research is going on to develop opioids which can provide systemic analgesia, devoid of peripheral effects like constipation and dependence. Once a μ-agonist drug is administered, the β-arrestin-2 type of receptors get recruited which are responsible for the undesirable peripheral side effects of opioids.[12] TRV130 or oliceridine is such an agent which is developed with that idea which is in an investigational stage. Chemically it is a μ-receptor G protein pathway selective modulator (μGPS.[13] Due to its β-arrestin-2 inhibitory properties when administered IV, oliceridine could be the future of perioperative opioid therapy once it gets approval for clinical use.[14]

CONCLUSION

Although peripherally acting opioid receptor antagonists appear promising and effective, these are very costly for regular clinical use. It limits its routine use. Lidocaine is a safe, cost effective option with other desirable effects and negligible side effects. The preventive strategies should be multimodal. Early enteral feeds, multimodal postoperative analgesia (non-steroidal anti-inflammatory drugs whenever there is no contraindication, epidural analgesia and judicious use of opioids), correction of electrolyte imbalance, early mobilization and ambulation, less handling of gut during surgeries by using a minimally invasive (laparoscopic or robotic) along with opioid antagonists and lidocaine in selected cases can facilitate early bowel activity, early discharge and an overall lesser cost of treatment.

Conflicts of interest: NIL

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