

**Review Article**

**Novel concepts of analgesia for post operative pain: Multimodal analgesia**

**Safiya I Shaikh\* and Bheemas B Atlapure**

*Department of Anesthesiology, Karnataka Institute of Medical Sciences, Hubli 5800022, India*

**\*Correspondence Info:**

Dr. Safiya I Shaikh,  
Professor and HOD,  
Department of Anaesthesiology,  
Karnataka Institute of Medical Sciences, Hubli 5800022, India  
E-mail: [ssafiya11@yahoo.com](mailto:ssafiya11@yahoo.com)

**Abstract**

The concept of multimodal analgesia was introduced more than a decade ago as a technique to improve analgesia and reduce the incidence of opioid related adverse events. Multimodal analgesia is achieved by combining different analgesics that act by different mechanisms and at different sites in the nervous system resulting in additive or synergistic analgesia with lowered adverse effects of sole administration of individual analgesics. The analgesic benefits of controlling post-operative pain are generally maximized when a multimodal strategy to facilitate the patient's convalescence is implemented.

Principles of multimodal strategy include control of post-operative pain to allow early mobilisation, early enteral nutrition, education and attenuation of the perioperative stress response through the use of regional anaesthetic techniques and a combination of analgesic agents (i.e multimodal analgesia). The adaptation of multimodal ( or balanced) analgesic techniques as the standard approach for prevention of pain in the ambulatory setting is one of the keys to improving the recovery process after day care surgery.

An aggressive multimodal perioperative analgesic regimen that provides effective pain relief has minimal side effects is intrinsically safe and can be managed by the patient and their family members away from a hospital or surgical center. The approach that combines the consideration of peripheral and central treatment of pain possibly in combination with pre-emptive analgesia, may contribute eventually to a post-operative course without pain and one that provides for very early mobilization and restoration of function with subsequent reduction in post-operative morbidity and hospital stay.

**Keywords:** Multimodal analgesia; post-operative pain; opioids; Adjuvants

**1. Introduction**

The experience of pain is complex, multifaceted and "an unpleasant sensory and emotional experience" as defined in part by the International Association for the study of pain.<sup>1</sup> It is a personal, subjective experience that involves sensory, emotional and behavioural factors associated with actual or potential tissue injury.<sup>2</sup> Only by considering all concomitant factors can physicians provide optimal treatment.<sup>3</sup>

Multimodal analgesia is achieved by combining different analgesics that act by different mechanisms and at different sites in the nervous system resulting in additive and synergistic analgesia with lowered adverse effects of sole administration of individual analgesics.<sup>4</sup> Principles of a multimodal strategy include control of post operative pain to allow early mobilization, early enteral nutrition & attenuation of perioperative stress response through the use of regional anaesthetic techniques and multimodal analgesia.

Post operative pain, especially when poorly controlled, may produce a range of detrimental acute & chronic effects.<sup>5</sup> Chronic pain is a potential adverse outcome from surgery. It is costly to society in terms of suffering & disability.<sup>6</sup> The analgesic benefits of controlling postoperative pain are generally maximised when a multimodal strategy to facilitate the patients convalescence is implemented.<sup>7</sup> Pain involves multiple mechanisms that ideally require treatment using a multimodal analgesic technique.<sup>8</sup>

**2. Peripheral acting analgesics**

Local anaesthetics have been used for several decades for wound infiltration but their application & efficacy has been documented mostly in relatively minor or moderate procedures. The effect on postoperative pain is rather short lasting, emphasizing the severe need for more long lasting drugs.<sup>9</sup> Sodium channel blocking drugs are usually used in the management of both acute and chronic pain. When dealing with postoperative pain, local anaesthetics such as lidocaine and bupivacaine are mostly preferred.<sup>10</sup>

Local anaesthetics block sodium channels, thereby preventing transmission of nerve impulse along the axonal fibre. This is a local effect at the site of injection.<sup>11</sup>

Local anaesthetic solutions delivered through an epidural or perineural route are the most important treatments for decreasing incident pain, hormonal stress and sympathetic responses during and after surgery.<sup>12,13</sup> The best results are achieved when local anaesthetic solutions are infused neuraxially with lipophilic opioids such as sufentanil and fentanyl at adequate concentrations.<sup>14,15</sup>

**3. Techniques in post operative pain management**

One approach for multimodal analgesia is the use of regional anaesthesia and analgesia to inhibit the neural conduction from the surgical site to the spinal cord & decrease spinal cord sensitization.<sup>16</sup>

**3.1 Pre-emptive- preventive analgesia**

The concept of pre-emptive analgesia has its origins in the idea that painful stimuli if not prevented by administration of preoperative analgesic drugs could lead to spinal sensitization resulting in increased pain intensity & duration after surgery. At the beginning, intensive pain therapy & analgesia

must be continued using step-down techniques that involve a change in drugs or route of administration (i.e. from the epidural and intravenous routes to per oral administration).<sup>17</sup> The main goals of preventive analgesia are to decrease pain after tissue injury to prevent spinal sensitization & to reduce the inflammatory or chronic pain.<sup>18</sup>

### 3.2 Drugs in postoperative pain management

#### Systemic analgesics:

**Opioids:** Opioids play an important role in the acute treatment of moderate to severe pain in the early postoperative period. Their effects can be summarised as hyperpolarisation of first & second order sensory neurons with inhibition of synaptic transmission. They act by binding to  $\mu$  receptors, which initially results in increased G protein activity; this, in turn, leads to  $K^+$  efflux and inhibition of  $Ca^{2+}$  influx into the cell. Opioids also stimulate the supraspinal descending inhibitory system, which further increases the hyperpolarisation of second order neurons by releasing 5HT & glycine.<sup>19</sup>

Opioids can be used in different ways: i.e intravenous, intramuscular, subcutaneous, transmucosal, epidural, intrathecal, transdermal. The most common route of post operative systemic opioid analgesic administration is intravenous. When the most important source of nociceptive stimuli is visceral pain, good results may be achieved by intrathecal administration of small doses of opioids.<sup>20</sup>

Patient Controlled analgesia (PCA) optimizes delivery of analgesic opioids and minimizes the effects of pharmacokinetic and pharmacodynamic variability in individual patients.

**Controlled release opioids:** Its preoperative administration leads to adequate plasma concentrations for postoperative analgesia and hyperalgesia treatment following short surgery (1-2 hr).<sup>21</sup> Controlled release opioids are an optimal choice for step down analgesia in the late postoperative & rehabilitation periods following orthopaedic surgical procedures.<sup>22</sup>

**Tramadol:** Tramadol enhances inhibitory effects on pain transmission at the spinal level blocking nociceptive signal transduction both by opioid & monoaminergic mechanisms.

**Non-opioids:** Opioid analgesics are replaced by a combination of non opioid analgesic drugs with diverse modes of action as part of a multimodal approach. Non opioid analgesics are increasingly being used before, during & after surgery to facilitate the recovery process especially after ambulatory surgery because of their anaesthetic and analgesic sparing effects & their ability to reduce post operative pain( with movement), opioid analgesic requirement and side effects thereby shortening the duration of the hospital stay.

Non-opioid drugs used in postoperative pain management can be classified as

- 1) NSAID's and COX-2 inhibitors
- 2) Acetaminophen (Paracetamol)
- 3) Adjuvants:
  - a) Alpha-2 adrenergic agonists: 1) clonidine 2) Dexmedetomidine
  - b) N-methyl-D-aspartate antagonists (Anti hyperalgesic drugs)
    - ketamine
    - Dexamethorphan
    - magnesium
  - c) Gabapentin type drugs
    - Gabapentin
    - pregabalin
  - d) Glucocorticoids:
    - Dexamethasone
  - e) Newer drugs:
    - Capsaicin
    - Glyceryl trinitrate
    - cholinergic drugs: nicotine
  - f) local anaesthetics

**NSAID'S & Cyclooxygenase 2 selective inhibitors:** NSAID's are known to achieve pain relief by their effect on COX1 & COX2 with the various NSAID's differing in the proportion to which they inhibit COX-1 & COX-2. They are acid compounds with analgesic, antipyretic & anti-inflammatory properties via inhibition of prostaglandin synthesis. Prostaglandins, including  $PGE_2$  are responsible for reducing the pain threshold at the site of injury resulting in central sensitization and a lower pain threshold in the surrounding uninjured tissue. NSAID's are administered orally, parenterally or by the rectal route.

They provide moderate postoperative analgesia and thereby have a significant opioid sparing effect of 20-30% after major surgery.<sup>23</sup> This may be of clinical importance as NSAID's may reduce the incidence of opioid related side effects ( respiratory depression, sedation, nausea & vomiting, paralytic ileus, urinary bladder dysfunction & possibly sleep disturbances). Since the COX-2 enzyme, the primary target of NSAID's is inducible it is not found in damaged tissues until a few hours following the onset of a noxious stimulus. This could explain the lack of efficacy of pre-emptive administration of these drugs.

**Acetaminophen (Paracetamol):** Paracetamol has antipyretic and analgesic properties, but it is devoid of anti-inflammatory effects. It has an inhibitory action on central COX 2 & COX 3 enzymes, which would explain its antipyretic activity. The analgesic effect seems to be due to activation of descending serotonergic inhibitory pathways as well as inhibition of NO synthases. It is metabolised in the liver primarily by glucuronidation & sulfation.<sup>24,25</sup>

When paracetamol and NSAIDs are administered by an intravenous route they show sparing effects on opioid consumption (about 25% and 30% respectively); This effect begins 4 hours after their first administration and its synergistic.<sup>26,27</sup>

**Adjuvant:** Adjuvant drugs are defined as substances that may improve pain treatment & pain control, but they are not commonly defined as analgesics.

**Alpha-2 adrenergic agonists:** Alpha-2 adrenergic activation represents an intrinsic pain control network of the central nervous system. The alpha-2 adrenergic receptor has high density in the substantia gelatinosa of the dorsal horn in humans and that is believed to be the primary site of action by which alpha-2 adrenergic agonists can reduce pain.<sup>16</sup>

**Clonidine:** Clonidine is originally classified as an antihypertensive drug with negative chronotropic activity but has antinociceptive properties as well. In the spinal cord, clonidine acts at alpha-2 adrenergic receptors to stimulate acetylcholine release, which acts at both muscarinic & nicotinic receptor subtypes with analgesic effects.<sup>17</sup>

Low doses of clonidine proved to be a useful adjunct analgesic given neuraxially & in combination with peripheral nerve blocks.<sup>28</sup>

**Dexmedetomidine:** Dexmedetomidine is a relatively new, highly selective alpha-2-agonist. Dexmedetomidine, when used as an adjunct can reduce postoperative morphine consumption in various surgical settings using various routes such as intravenous.<sup>29,30,31</sup>

**N-methyl-D-Aspartate antagonists( Antihyperalgesic drugs):** With the discovery of the N-methyl-D-Aspartate(NMDA) receptor & its links to nociceptive pain transmission and central sensitization, there has been renewed interest in utilizing non competitive NMDA receptor antagonists such as ketamine, dextromethorphan, magnesium ions as potential antihyperalgesic agents.

**Ketamine:** Ketamine is the most commonly used antihyperalgesic drug. It acts as an antagonist of NMDA receptors. Perioperative administration of 2-10 µg/kg/min following a loading dose of 0.5 mg/kg decreases hyperalgesia and allodynia after thoracic and abdominal surgery, although doses may vary depending on the overall duration & amount of exposure to short acting opioids.<sup>32,33</sup>

Routes of administration include oral, intravenous, intramuscular, subcutaneous, epidural, transdermal and intraarticular.

Clinical use of ketamine can be limited due to psychomimetic adverse effects such as hallucinations, excessive sedation and bad dreams. Other common adverse effects are dizziness, blurred vision and nausea & vomiting.<sup>32</sup> It can be used in subanaesthetic doses as an adjunct to provide postoperative pain relief in opioid dependent patients.<sup>33</sup>

**Dextramethorphan:** Dextramethorphan has a similar mechanism of action with a lower affinity for the NMDA receptor. Following oral administration, it is rapidly absorbed from the gut and crosses the blood brain barrier.<sup>34</sup>

**Magnesium:** Magnesium ion was the first agent discovered to be an NMDA channel blocker. Since magnesium crosses the blood brain barrier with difficulty in humans, it is not clear whether its therapeutic effects are related to NMDA antagonism in the central nervous system.

**Gabapentin type drugs:** Pregabalin and gabapentin bind to voltage gated calcium channels in the spinal cord and brain. Both drugs are used for seizures and neuropathic pain. One advantage of pregabalin in clinical use is that it has higher bioavailability than gabapentin and linear pharmacokinetics. The gabapentinoid compounds have been used as part of multimodal analgesic in the postoperative period.<sup>16</sup>

**Glucocorticoids:** Glucocorticoids including dexamethasone, have been used to reduce inflammation and postoperative pain in surgical procedures.<sup>35</sup>

**Dexamethasone:** Dexamethasone is a synthetic glucocorticoid with high potency and a long duration of action (half life: 2 days), and has low mineralocorticoid activity.<sup>36</sup>

#### Newer drugs:

- Capsaicin: Capsaicin (8-methyl-N-vanillyl-6-nonemamide)(TRPV-1 agonist) is a non narcotic alkaloid acting peripherally at unmyelinated C-fiber nerve endings.<sup>37</sup>
- Glyceryl trinitrate: The organic nitrates such as glyceryl trinitrate(GTN) act as nitric oxide donors.<sup>38</sup>
- Cholinergic drugs: Acetylcholine may cause analgesia through direct action on spinal cholinergic muscarinic receptors M1 & M3 and nicotinic receptor subtypes.
- Tapentadol: It is a new receptor agonist with 18 times more affinity than morphine and it also inhibits the noradrenaline uptake considering potency

#### Neuraxial techniques:

Spinal or epidural analgesia techniques in single or continuous forms can be used in postoperative pain management. The use of epidural anaesthesia & analgesia is an integral part of multimodal approach because of the superior analgesia & physiologic benefits conferred by epidural analgesia.<sup>39</sup>

Thoracic epidural analgesia with local anaesthetics & opioids for abdominal, thoracic & vascular surgery improves bowel recovery times while decreasing the risks of cardiovascular adverse events and of developing persistent pain.<sup>40</sup>

Maintenance techniques in epidural analgesia include:

Continuous infusion: An easy technique that requires little intervention. The cumulative dose of local anaesthetic is likely to be higher & side effects are more likely than with the other two techniques.

Intermittent top-up: Results in benefits due to frequent patient/staff contact but can produce a high staff workload & patients may have to wait for treatment.

Patient Controlled Epidural Analgesia(PCAE): This technique produces high patient satisfaction & reduced dose requirements compared with continuous infusion.

Continuous central neuraxial blockade is one of the most effective forms of postoperative analgesia, but is also one of the most invasive.

Continuous central neuraxial blockade can be achieved via two routes: Continuous epidural analgesia-the recommended first choice & continuous spinal analgesia should be limited to selected cases only as there is less experience with this technique.

- The tip of the catheter should be placed as close as possible to the surgical dermatomes: T<sub>6</sub>-T<sub>10</sub> for major intra-abdominal surgery and L<sub>2</sub>-L<sub>4</sub> for lower limb surgery.

## 4. Peripheral regional analgesia techniques

Peripheral regional analgesia techniques may have several advantages over systemic opioids (i.e., superior analgesia and decreased opioid related side effects). Also the side effects associated with central neuraxial blockade such as hypotension and wide motor blockade with reduced mobility & proprioception and complications such as epidural hematoma, epidural abscess & paraparesis can be avoided.

Continuous peripheral nerve blocks are being increasingly used since they provide more selective but still excellent postoperative analgesia with reduced need for opioids over an extended period. Patient controlled regional analgesia (PCRA) can also be used to maintain peripheral nerve block. A low basal infusion rate (Eg: 3-5 ml/hr) associated with small PCA boluses (Eg: 2.5-5 ml, lockout; 30-60 min) is the preferred technique.

#### Paravertebral blocks:

The evidence suggests that the use of paravertebral blocks provide effective postoperative pain control following breast & thoracic surgery as well as for inguinal hernia repair.<sup>41,42,43</sup> On their own, paravertebral blocks have been demonstrated to provide effective postoperative analgesia lasting upto 24 hrs.<sup>44</sup>

Infiltration technique:

Local anaesthetics can be administered.

- Intraarticular
- Intraperitoneal instillation
- Wound infiltration

Wound Infiltration:

Infiltrating local anaesthetics into the skin and subcutaneous tissue prior to making an incision maybe the simplest approach to analgesia. It is safe procedure.

#### Topical Application:

- Local anaesthetics:  
Lidocaine patches were applied to the wound area in the next two studies, and the evidence shows that these are particularly effective for wound pain when the patient coughs and they reduce the postoperative pain score at discharge.<sup>45</sup>
- Local Infiltration analgesia:  
The administration of large volumes of local anaesthetics with or without adjuvants into different tissue planes perioperatively is called local infiltration analgesia (LIA).<sup>46</sup>

Other Pharmacological techniques: A number of non-pharmacological methods of pain management may be used to alleviate postoperative pain.

- a) Electro-analgesic technique
  - Cryo-analgesia
  - Acupuncture
  - Relaxing therapy and distraction
  - Hypnosis
  - Meditation & Yoga
  - Herbal medicine

## 5. Conclusion

Postoperative pain is a complication of surgery, which in turn complicates recovery with functional impairment and drug related adverse effects. The multimodal approach may potentially decrease perioperative morbidity, reduce the length of hospital stay, and improve patient satisfaction without compromising safety. However, widespread implementation of these programs requires multidisciplinary collaboration, change in the traditional principles of postoperative care, additional resources, and expansion of the traditional acute pain service. Although a multipharmacologic approach may be universally recommended, drugs and their route of administration must be changed according to the type of surgery and hospital resources, and of course to the patient needs.

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