

Efficacy, Safety And Patient Satisfaction Of A Simple Combination Of Readily Available Medications (Shiv-mix) For Perioperative Analgesia, Hemodynamic Stability And Postoperative Recovery Profile: Case Series And Narrative On Opioid Free Anaesthesia (OFA) In Spine Surgeries

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Abstract

Opioid-free anesthesia (OFA) is an emerging technique, is a boon especially for limited resource settings (LRS) where opioids availability is limited for perioperative pain management. The current study presents use of a combination of easily available medication as part of multimodal analgesia. These medications are easily available to any physician and our experience demonstrates that in addition to providing satisfactory analgesia, use of this combination also provides better hemodynamic stability and excellent post-operative recovery.

Introduction

The ultimate goal of any surgical treatment is to attain an uneventful recovery from anaesthesia and surgery for a better quality of life and outcomes without any associated complications and sequelae. Our goals can be achieved only with concurrent suitable anaesthesia. Greater than 80% of surgical patients experience pain [1], the under treatment of which can result in a variety of undesirable consequences and remains a considerable challenge worldwide [2] especially in limited resource settings. Poorly controlled acute pain remains one of the most undesirable consequences after surgery. Significant number of patients undergoing surgery experience moderate to severe pain, with a majority of them expressing dissatisfaction with their pain management. Advances in multimodal analgesia (MMA) have largely replaced conventional opioid-based mono-therapy, but continued reliance on opioids to manage postoperative pain may at least partly explain the inadequacy of conventional acute pain management. Despite widespread attention to the hazards of opioid agents, opioid misuse remains a leading cause of many postoperative

complications. For many patients with a long-term opioid misuse disorder, the first episode of opioid consumption can be traced to the perioperative period [3]. More recently, concerns about impaired healing [4], immunosuppression [5] and worsening of oncologic outcomes [6] with systemic opioids have been reported. In addition to these, perioperative cognitive dysfunction and opioid induced hyperalgesia remain concerns with any opioid-based technique [7, 8]. These risks mandate strategies to minimize and eliminate perioperative opioid exposure wherever possible. There are multiple opportunities for the anesthesiologist, surgeon, and institution to reduce opioid exposure and minimize patient harm. MMA has been consistently demonstrated to minimize opioid consumption and related side effects. Balanced anaesthesia with multimodal analgesia is harmonious use of combination of agents to produce a desired effect with minimal side effects of individual agents. This implies a full understanding of physiology and pharmacology. It necessitates a thorough clinical knowledge of the methods of administration and requires the ability to

manage the patient before, during, and after the administration of anaesthesia.

Opioid-free anaesthesia (OFA) is a technique in which intraoperative opioid is either not used or used sparingly via any route, including systemic, neuraxial, or tissue infiltration. OFA technique relies on combinations of nonopioid agents and adjuncts that include agents like Propofol, NSAIDs, Dexmedetomidine, Lidocaine, Dexamethasone, magnesium sulphate, ketamine and miscellaneous other medications to produce three desirable outcomes i.e anaesthesia, analgesia and sympatholysis. In contrast to OFA, traditional anaesthetic protocols rely mainly on perioperative opioids along with traditional anaesthetic agents to achieve these three conditions. OFA is an emerging technique which is a boon especially for limited resource setups where opioids for management of peri-operative pain are not readily available and hemodynamic stability remains a major concern for the perioperative physicians. The current study presents multimodal analgesia using medications that are easily available in most rural and limited resource centres.

Results from case reports and prospective studies are accumulating to support OFA as a tool that offers the following advantages:

- 1) Comparative intraoperative anaesthetic conditions to opioid-containing regimens [9].

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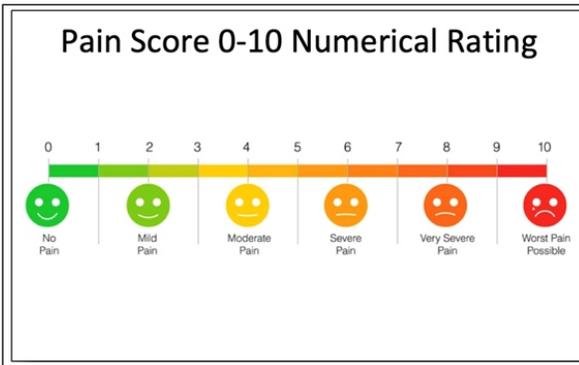


Figure 1: Numerical Rating Scale (NRS)

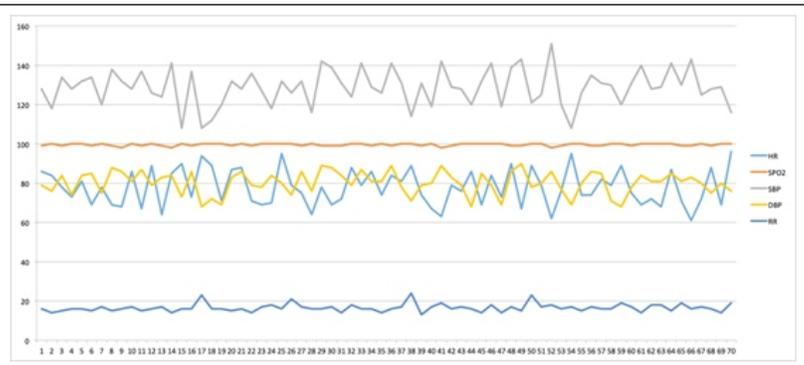


Figure 2: Pre-induction Haemodynamics

- 2) Improved postoperative analgesia with opioid-sparing effects [10].
- 3) Shorter duration of stay in the post anesthesia care unit (PACU) and shorter length of hospital stay [11].
- 4) Reduced postoperative nausea and vomiting (PONV) [11], and
- 5) Higher patient satisfaction [12].

OFA has further been proposed to be especially valuable in patients at high risk of opioid-related complications, including those with chronic pain conditions, opioid misuse disorder, and obstructive sleep apnea. In the present study 70 patients posted for different neurosurgical procedures at a limited resource centre were included and analyzed to study the effect of the combination of intravenous medications used peri-operatively for better hemodynamic stability and improved pain score and good postoperative outcomes.

Material and methods

The study was carried out using a defined mixture of non-opioid medications in patients undergoing elective neurosurgical procedures (laminectomy, discectomy, and/or micro discectomy). We included 70 patients presenting for surgery between June 2018 and May 2019.

Anaesthesia was induced in all patients with propofol and tracheal intubation facilitated with atracurium after the test mixture was administered over 20 min before induction of anaesthesia. Hemodynamic parameters were continuously recorded and analyzed during induction and at regular intervals intra-operatively. Emergence time and pain score and recovery profile at the end of surgery was also recorded.

Inclusion criteria

1. Adults between age 18- 60 yrs
2. ASA-1 and 2 physical status scheduled for elective spine surgery under general anaesthesia.

Exclusion criteria

1. Refusal to give consent
2. Patients for whom any component of mixture was contraindicated
3. History or family history of malignant hyperthermia
4. ASA physical status-III or higher were excluded
5. Patients having history of convulsions, meningitis, infections, anemia (Hb% <9 gm/dl) or any congenital heart disease
6. Patients having hepatic, renal or neuromuscular disease
7. Patients having respiratory system disease
8. Patients having respiratory system disease

Preanesthetic checkup

All patients included in this case series were selected after a thorough pre-anesthetic check-up and had all routine investigations. Six hours preoperative fasting for solids and four hours for clear fluids was ensured in all patients as preparation for general anesthesia. During the preoperative visit, verbal consent was obtained for their inclusion in this study and were informed and explained in detail by the anesthesiologist regarding the use of OFA and how numerical rating scale (NRS) would be used to assess their pain in the post-op period. They were also informed that

interview would be held before their discharge to assess their satisfaction with the care and pain management.

Anaesthetic technique

Preoperatively, patients were educated on the use of the numeric rating scale (NRS) to report pain and how pain scores translated to additional analgesic administration in the post-op anaesthesia care unit (PACU). All the patients were monitored continuously and data analyzed for heart rate (HR), non-invasive blood pressure (NIBP), End tidal carbon dioxide (ETCO₂), oxygen saturation (SpO₂), ECG changes before induction. The parameters were recorded at induction, 5 minutes, 15 minutes 30 minutes 45 minutes, 60 minutes and 90 minutes after induction. They were also recorded following extubation of trachea and at 30 minutes in the recovery area.

An intravenous line was secured in the preoperative area. After shifting the patient to operation theatre and attaching all the monitors, injection Glycopyrrolate 0.2 mg and Injection midazolam 1 mg IV was administered. Following this shiv mix-3 (1gm IV Paracetamol, 100mg Lignocaine and 10mmols of MgSO₄) was infused over 20

Table 1: Types of Surgeries		Table 2 c: Demography, Age and Weight					
Types of Surgery	N	N	Min	Max	Mean	SD	
Spine Discectomy	66	Age	70	18	65	40.66	12.758
Spine Tumor	2	Weight	70	51	81	63.54	6.292
Cranioplasty	1	Table 3: Emergence and Recovery Characteristics					
Removal of implant	1	Coughing	0/70				
Table 2 a: Demography, Male:Female Ratio		Breathe holding	0/70				
	Numbers	Percentage	Laryngospasm	0/70			
Male	40	57.1	Bronchospasm	0/70			
Female	30	42.9	Excitement	0/70			
Total	70	100	Requirement for Analgesia	1/70			
Table 2 b: Demography, ASA Grade		Table 4: Post-op Complications					
ASA Grade	Numbers	Percentage	Nausea	0/70			
ASA-1	53	75.7	Vomiting	0/70			
ASA-2	17	24.3	Shivering	0/70			
Total	70	100	Arrhythmia	0/70			
			Desaturation	0/70			

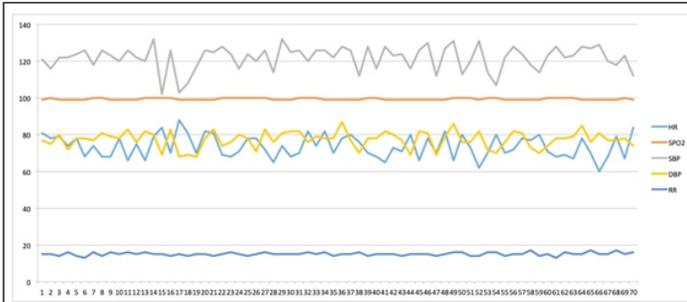


Figure 3: Haemodynamics after the Shiv mix

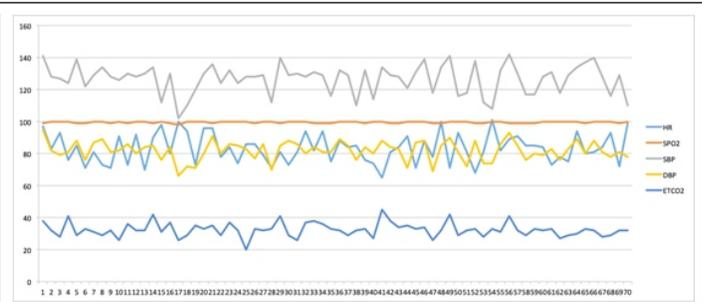


Figure 4: Haemodynamics at laryngoscopy and intubation

minutes. During this period, a nasal cannula was applied and oxygen insufflated @ 2L/min which was increased to 15 L/min at induction of anaesthesia. After 20mins and completion of the infusion, Induction of anaesthesia was commenced by incremental administration of propofol (1.5 to 2 mg/kg IV, titrated to apnea) after ascertaining positive pressure ventilation using Bain's breathing system injection Atracurium 0.5 mg/kg body weight was administered for securing tracheal intubation. Intravenous Dexamethasone 8 mg after induction of anaesthesia and Injection Diclofenac 75 mg in a drip were also administered as part of multimodal analgesia. Painting and draping followed after appropriate position of the patient according to the proposed surgery.

Anesthesia was maintained with Isoflurane in Oxygen and Nitrous Oxide mixture. Mechanical ventilation was achieved with a tidal volume of 6–8 ml/kg and respiratory rate of 8–14 titrated to an end-tidal carbon dioxide between 30–35 mm Hg. Muscle relaxation was maintained with intermittent administration of Inj atracurium in a dose 0.1 mg/kg.

Blood pressure was assessed noninvasively every 5 minutes throughout the procedure, and heart rate was recorded continuously. In all patients, elevations in mean arterial pressure (> 100) and/or heart rate 15% above baseline (or higher) was treated with labetalol (10 mg bolus intravenously) and/or propofol (up to a 20 to 30 mg bolus), and/or increased concentration of inhaled anesthetics.

Injection Ondansetron 4 mg was administered intravenously half an hour before expected completion of the surgery. Fluids were infused according to fasting and maintenance requirements. Muscle relaxation was reversed with combination of inj. Neostigmine 0.05 mg/kg and inj glycopyrrolate 0.01 mg/kg at the onset of return of reflexes and some voluntary movements after oropharyngeal suctioning.

All procedures were performed by a single surgeon with extensive experience in neurosurgery.

For spine surgeries, after induction of general anaesthesia, patients were positioned prone on a radiolucent table with Wilson frame.

Postoperative care

Pain control, level of alertness, and vital signs were monitored in the PACU. Patients were permitted oral intake once patients were fully awake from anaesthesia. Patients with reported NRS scores ≤ 4 were treated with Shiv Mix 1 (Paracetamol 1gm and 25-50mg Tramadol), and/or non-pharmacotherapies (including ice, distraction, and position changes). For those with NRS scores 5–7, patients received 50-mg additional doses of tramadol if needed; and for those with NRS scores 8–10, patients received incremental doses of 50mcg of fentanyl. Further escalation of opioids required assessment by the anesthesiologist. Readiness for discharge from the PACU was determined when patients achieved a modified Aldrete score ≥ 9 .

Data Collection

Data on demographics, intraoperative metrics, and recovery were collected and included age, sex, ASA class, smoking status, type of surgery, and duration of surgery, time to recovery from anaesthesia (defined as the interval from the end of surgery to the transition of care from the anesthesiologist to the PACU nurse), NRS scores, and opioid consumption.

Parameters recorded and analyzed

1. Preoperative hemodynamic parameters
2. Laryngoscopy and intubation response
3. Cardiorespiratory parameters during induction and at regular intervals
4. Emergence time
5. Duration of surgery
6. Recovery profile at the end of surgery by assessing Eye opening / Purposeful

movements (hand grip)/Cough and gag reflex

7. PONV

Emergence time was defined as the time from discontinuation of anaesthetics to extubation of the trachea. Time between intubation and extubation of trachea was taken as anaesthesia time. Patients were followed up post operatively for 30 minutes. Any side effects or complications were recorded. Patients were shifted to the ward after stabilization of all vitals and oxygen saturation. Post-operative pain was managed by Shiv Mix -1 (Paracetamol 1gm with 25-50mg of Tramadol) every 6 hourly.

Postoperative pain scores were measured using the numerical rating scale (NRS).

A numerical rating scale (NRS) requires the patient to rate their pain on a defined scale. For example, 0–10 where 0 is no pain and 10 is the worst pain imaginable (Fig-1). Commonly used NRS are 11 point (0–10)

Results

In the present case-series, we studied perioperative hemodynamic, induction and recovery characteristics of Shiv Mix-3 in 70 patients between 18-60 years of age undergoing various neurosurgical procedures under general anaesthesia. Short procedures associated with little post-operative pain, Individuals where difficult intubation or ventilation are anticipated, Procedures where rapid emergence is particularly desirable in terms of more rapid awakening and ability to obey commands in longer cases.

After analysis of the data, it was found that:

1. Most of the surgical procedures were of 2-3 Hours duration. The types of surgeries are described in Table-1
2. Demographic parameters in the study population are depicted in Table 2a, b and c.
3. There was minimal response to laryngoscopy and intubation in all patients Fig 2, 3 and 4
4. Patients in all age groups were

hemodynamically stable throughout the period of observation.

5. We found extremely stable hemodynamics during entire surgical procedure.

6. Recovery times were not found to be prolonged. Only one patient (no 19) required 50mcg of Fentanyl as additional analgesia in the PACU. Recovery characteristics were commendably devoid of any additional requirements for analgesics. Table-3

7. PONV and shivering was noticeably a rare phenomenon in patients whose surgery was conducted using this regimen. Table-4

In the study it is evident that the preoperative use of shiv mix-3 is an excellent combination that provides better perioperative hemodynamic stability and post-operative pain score with lack of common complications like PONV and shivering. There was a clinically significant decrease in time to readiness for discharge from the PACU associated with OFA as patients were awake and comfortable without any associated complications seen with the routine use of opioids.

Discussion

The WHO recommends a multimodal approach to the treatment of pain. Currently, a multimodal approach to postoperative analgesia is recommended. Targeting on central sensitization, preventive analgesia may be beneficial for reducing incidence and severity of both acute and chronic postoperative pain. As a part of preventive analgesia, preemptive analgesia involves the preoperative administration of analgesics so that they are effective intraoperatively and prevent central sensitization before exposure to painful stimuli.

Preemptive analgesia is defined as a treatment that is initiated before surgery in order to prevent the establishment of central sensitization evoked by the incisional and inflammatory injuries occurring during surgery and in the early postoperative period [13]. Owing to this 'protective' effect on the nociceptive system, preemptive analgesia has the potential to be more effective than a similar analgesic treatment initiated after noxious stimuli (surgical incision). As a consequence, preemptive analgesia can reduce immediate postoperative pain and also prevent the development of persistent post surgical and chronic pain by decreasing the altered central sensory processing [14].

There are many compelling reasons to avoid opioids in any surgical patient. Recognized

important side effects include respiratory depression and/or obstruction, nausea, vomiting, constipation and ileus, urinary retention, sedation, and cognitive dysfunction. Recent data has also linked opioids to increased wound complications. Specific populations of surgical patients that may be even more likely to benefit from OFA include patients with obesity and/or obstructive sleep apnea and those suffering from chronic pain.

Although gaining prominence in other surgical subtypes, procedure-specific data for the efficacy of OFA is not yet in evidence for spine surgery. Kim et al. described the use of OFA in a patient undergoing a 2-level posterior lumbar fusion; they used dexmedetomidine and lidocaine infusions and concluded possible improved analgesia in the first 24 hours after surgery [15]. A second report described a fully opioid-free anesthetic and analgesic regimen in a patient undergoing multilevel thoracolumbar spine fusion, featuring erector spinae plane block and comprehensive MMA.

The results of this study suggest that OFA with comprehensive MMA is associated with lower opioid consumption in the perioperative period, without adverse effects on postoperative pain scores, opioid requirements, or recovery.

What are the shiv mix

These are combination of readily available medication that are easily available and used in the peri-operative period to achieve analgesia, haemodynamic stability and prevent development of post-op persistent pain and hyperalgesia. The common components of these mixes include; paracetamol, tramadol, lignocaine and magnesium sulphate.

MIX-1:

This was described by the author (SKS) a while ago and combines low dose Tramadol (25-50mg) with IV Paracetamol 1Gm in 100mls. This is not a new concept, combination of Paracetamol and Tramadol as oral preparation has been in the market for a long time.

Our experience with this mix has shown that when we combined low Dose IV Tramadol with IV Paracetamol, it not only achieved excellent analgesia, since the drugs were delivered slowly over 20-30mins, the incidence of PONV and shivering was extremely low in these cases. This was

because of 3 following reasons that we identified

1. Using Low Dose of Tramadol, 25mgs (in small built patients and females) or 50mgs in others. These low doses were enough to produce equivalent analgesia and at the same time reduced the side effects of using larger dose of tramadol esp PONV.

2. Combining with IV Paracetamol (100mls) would be administered as an infusion over 20-30mins. With Tramadol, PONV is associated with higher dose and quicker administration, slow infusion reduced this risk.

3. Paracetamol itself is known to prevent PONV. This has been proven in a meta-analysis by Apfel [16].

MIX-2:

This is a lot more recent mix. In this 1Gm IV Paracetamol (100mls) is combined with 100mg Lignocaine (1.5mg/kg) and 8.0mmols or 2.0 Gms (40-50mg/kg) of MgSO₄.

This was basically designed to prevent laryngoscopic response to Intubation. Laryngoscopy is a painful procedure and Intubation of trachea is a noxious stimulus. Combining these 3 agents and administering it 15-20 mins before Intubation prevents any hemodynamic perturbations associated with laryngoscopy and tracheal intubation, as well as provide analgesia for the surgical procedure.

In cases where opioid like Fentanyl is available and used for obtunding laryngoscopic and intubation response, this mix can be used as part of MMA, it can be given intra-op instead of pre-induction.

MIX-3:

For Short Day Case procedures Mix-1 and 2 can be combined (3rd Mix). In this mix, 100mg Lignocaine, 8.0 mmols/2.0 Gms MgSO₄ and 25-50 mg Tramadol are mixed in 1Gm Paracetamol (100mls) for infusion over 15-20mins soon after induction or it can be given even before induction and intubation of trachea.

Magnesium sulphate

Magnesium, which is the second most abundant intracellular cation, has numerous functions in human physiology including activation of enzymes, protein synthesis, regulation of vasomotor tone, neurotransmission and signaling [17]. Magnesium also acts as a non-competitive antagonist of N-methyl-D-aspartate

(NMDA) glutamate receptors which are involved in pain perception and the persistence of postoperative pain [18,19]. Magnesium sulphate (MgSO₄) is used as a pharmacological agent in a variety of clinical situations: tachyarrhythmia, myocardial and neuronal ischemia, asthma, spasmophilia, pre-eclampsia, tocolysis and post-anaesthesia shivering.

Lignocaine

Lignocaine is unique in that it has been shown to improve enhanced recovery after surgery (ERAS) outcomes; early ambulation and feeding, early fitness for discharge, and increased patient satisfaction [20]. Lignocaine is a widely available and commonly used local anaesthetic. When administered intravenously, it demonstrates antihyperalgesic properties that improve acute postoperative pain. Lignocaine is one of the components of Mix-2 and 3.

Steroids, dexamethasone

Glucocorticoids have a number of beneficial properties in a surgical setting. In addition to being antiemetic, they are anti-inflammatory, analgesic, antipyretic, and antiallergic. Glucocorticoids reduce prostaglandin synthesis by inhibiting both phospholipase enzyme and cyclooxygenase Type II and by decreasing the products of cyclooxygenase-2, but have only a minor effect on cyclooxygenase-1 [21]. They also modulate the inflammatory response by inhibiting tumor necrosis factor-alpha, interleukin1 beta, interleukin 6, C-reactive protein, and leukocyte receptors [22]. We use IV dexamethasone 2mls (4mg/ml) after induction of anaesthesia in almost all our cases and it forms important part of the MMA.

Difference from other of a regimens

A major difference between our OFA

regimen and published reports is that we did not include dexmedetomidine. As a centrally acting alpha-2 adrenergic receptor agonist, dexmedetomidine decreases adrenergic outflow and blunts the sympathetic-adrenal response to surgical stimulation. These actions promote intraoperative hemodynamic stability, making dexmedetomidine a frequent opioid substitute in OFA.

Dexmedetomidine also has analgesic properties: One meta-analysis concluded that dexmedetomidine reduced early postoperative pain scores and opioid consumption when administered intraoperatively to patients receiving general anaesthesia in mixed surgical cohorts. However, a more recent systematic review of the analgesic benefits of dexmedetomidine for abdominal surgery was less optimistic, concluding that the majority of studies were of mixed quality and most compared dexmedetomidine to placebo. A meta-analysis of dexmedetomidine as an adjunct in spine surgery confirmed an opioid-sparing effect—both intra- and postoperatively—but failed to find additional benefits, including PONV.

Ellen M. Soffin et al also noticed that OFA within an ERAS pathway for lumbar spinal decompression represents an opportunity to minimize perioperative opioid exposure without adversely affecting pain control or recovery [23].

Conclusion

The described OFA regimen is a good mixture in attenuating laryngoscopic and intubation response. Hemodynamic stability is maintained and the incidence of common complications like PONV and shivering are non-existent and less worrisome. In most of the patients anaesthesia was reversed in a pain free state. This multimodal OFA for anaesthesia proved to be safe, effective and

satisfactory for the conduct of wide variety of neurosurgical cases in our clinical practice.

With this case series we can confidently concluded that use of Shiv-mix is an excellent combination of medication that are readily available and can be used safely in patients for analgesia and for maintaining haemodynamic stability during laryngoscopy and intubation and, in the peri-operative period. The use of this combination is also associated with lesser commonly encountered postoperative complications like PONV and shivering.

Limitations of this case series

More robust randomized controlled trials would be required to fully appreciate the benefits of this combinations of readily available drugs esp in limited resource centres. It would also be beneficial to study their role for opioid free or opioid sparing anaesthesia (OFA or OSA) in prevention of persistent post-operative surgical pain and chronic pain.

Clinical relevance

A good perioperative condition can be obtained without use of opioids by practicing opioid free multimodal analgesia. Shiv-mix is a very good example of the use of readily available drugs that can be used to provide stable hemodynamics and adequate perioperative analgesia in limited resource settings and in areas where opioids may not be readily available for managing peri-operative pain.

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