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# Perioperative Multimodal Analgesia Overview: Review Article

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## ABSTRACT

**Background:** Multimodal analgesia refers to the use of several medications, often started preoperatively that target multiple loci along the pain pathway. Multimodal therapy attempts to modify the inflammatory response to surgery or decrease the immediate or long-term consequences of tissue injury and the pain that ensues. Such an approach may theoretically improve pain control, limit the dose and adverse effects of any one drug, and reduce opioid requirements. In most practice, the combination of acetaminophen and nonsteroidal inflammatory drugs (NSAIDs) is the basis for multimodal postoperative analgesia for most patients who are without contraindications. However, while there are data suggesting efficacy of multimodal analgesic therapy in adults.

**Objective:** Assessment of roles and benefits of perioperative multimodal analgesia.

**Methods:** Multimodal, and analgesia were all looked for in PubMed, Google scholar, and Science direct. References from relevant literature were also evaluated by the authors, but only the most recent or complete study from January 2000 to May 2021 was included. Due to the lack of sources for translation, documents in languages other than English have been ruled out. Papers that did not fall under the purview of major scientific investigations, such as unpublished manuscripts, oral presentations, conference abstracts, and dissertations, were omitted.

**Conclusion:** Combined use of multimodal opioid sparing analgesics such as Paracetamol, NSAIDs, Gabapentin, Dexmedetomidine, the clinical neurologic evaluation can be maintained while the patient receives the benefits of a scalp block for pain management and opioid reduction.

**Keywords:** Multimodal, Analgesia, Zagazig University.

## INTRODUCTION

Multimodal analgesia refers to the use of several medications, often started preoperatively, that target multiple loci along the pain pathway. Multimodal therapy attempts to modify the inflammatory response to surgery or decrease the immediate or long-term consequences of tissue injury and the pain that ensues [(1)] (Fig. 1).

Such an approach may theoretically improve pain control, limit the dose and adverse effects of any one drug, and reduce opioid requirements. In most practice, the combination of acetaminophen and nonsteroidal inflammatory drugs (NSAIDs) is the basis for multimodal postoperative analgesia for most patients who are without contraindications. However, while there are data suggesting efficacy of multimodal analgesic therapy in adults [(2)], an opioid sparing effect remains difficult to prove in children [(3)].

A 2017 systematic review of the literature on analgesic efficacy of systemic nonopioid analgesics found evidence of clinical analgesic efficacy (i.e., decrease in narcotic use and postoperative pain) for acetaminophen, NSAIDs, dexamethasone, ketamine, clonidine, and dexmedetomidine, but insufficient or no available data on the benefits of other medications [(4)]. Opioid sparing effects are difficult to demonstrate partly because of variability in dose and intervals of administration, drug combinations, variety of surgical procedures, age and patient population, follow-up duration, and outcome measures in existing studies [(5)].

Insufficient analgesia during the early perioperative phase is theorized to play a role in the progression of acute postsurgical pain to chronic postsurgical pain [(6)]. It makes sense to pharmacological target pain pathways outside of opioid receptors, as there are many different types of pain pathways, and the effects of a multimodal strategy are believed to be synergistic rather than additive. These measures can start before surgery and continue through the perioperative period, the intensive care unit, the regular ward, and the patient's time spent recovering at home. The Enhanced Recovery after Surgery (ERAS) procedures can also make use of them [(7)].



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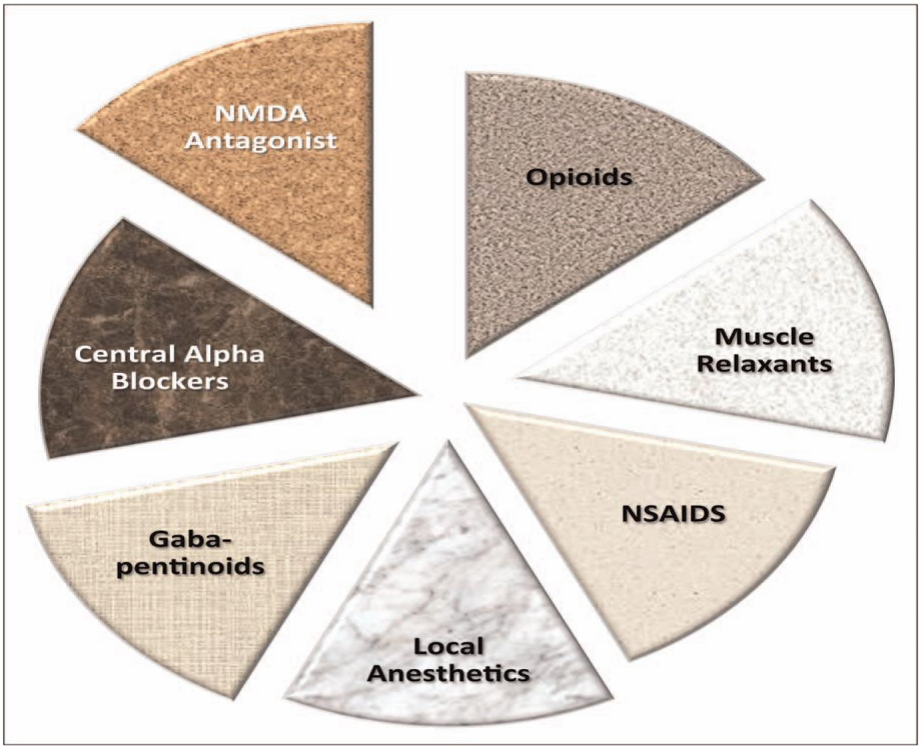


**Figure (1):** Relief from pain using a number of different approaches. Multiple pharmacologic medications are employed to alleviate pain more effectively while reducing the risk of adverse reactions (particularly opioids) [8].

**BUPIVACAINE**

First identified in 1957, bupivacaine is a powerful local anesthetic (LA) with distinguishing features among the amide group of local anesthetics. Procedures including regional anesthesia, epidural anesthesia, spinal anesthesia, and local infiltration all rely on local anesthetics. By raising the threshold for electrical excitation. Local anesthetics often prevent nerve cells from generating an action potential [9].

When LAs bind $Na^+$ channel and limit $Na^+$ permeability necessary for the action potential, local analgesia occurs, allowing nerve impulses to be transmitted along the axon without pain. All forms of voltage-gated $Na^+$ channels, but especially the open form, are sensitive to the inhibition of open-channel local anesthetics. Vascular smooth muscle relaxes as a result of decreased or eliminated conduction due to $Na^+$ channel blockage [10].

There are three available strengths of bupivacaine, each with their own set of benefits and risks. Epidural anesthesia/analgesia for labor pain, a caudal block, spinal anesthesia (injection into the CSF to provide anesthesia for orthopedic surgery, abdominal surgery, or caesarean delivery), and local infiltration (post-operative analgesia) are the most common routes of administration (anesthesia and analgesia below the umbilicus, usually for pediatric surgery) [11].

**Adverse effects**

Procedure, tissue vascularity, area, number of blocked segments, depth or length of anesthesia required, and patient health all play a role in determining the optimal bupivacaine dose. Antidepressants, blood thinners, and monoamine oxidase inhibitors may not work as well with bupivacaine if taken at the same time. Allergic responses to local anesthetics are uncommon [12]. Infection at the injection site, obstetric paracervical block, obstetric anesthesia at 0.75% concentration, intravenous regional anesthesia, and intra-articular continuous infusion are all contraindications. Caution should be exercised when administering to patients who have an allergy to sulfites, who have impaired liver function (the liver clears amides), who have impaired kidney function, who have impaired cardiac function, who have heart block, who are hypovolemic or hypotensive, or who are elderly, frail, and acutely ill[13].

**Dexmedetomidine**

**Mechanism of Action:**

Alpha agonist dexmedetomidine has calming, anxiety-reducing, hypnotic, pain-relieving, and sympathetic effects. By blocking alpha receptors in the brainstem, it reduces norepinephrine secretion and causes the aforementioned effects. It is 1600 times more selective for the alpha2 receptor than the alpha1 receptor [14]. When compared to another alpha agonist, clonidine, which has a selectivity of only 20 to 1, this selectivity becomes even more impressive. We don't know for sure how dexmedetomidine works to lengthen the duration of a peripheral nerve block, but it seems to do so by inhibiting cation currents in the nerve endings themselves (a perineural mechanism) rather than in the central nervous system [14].

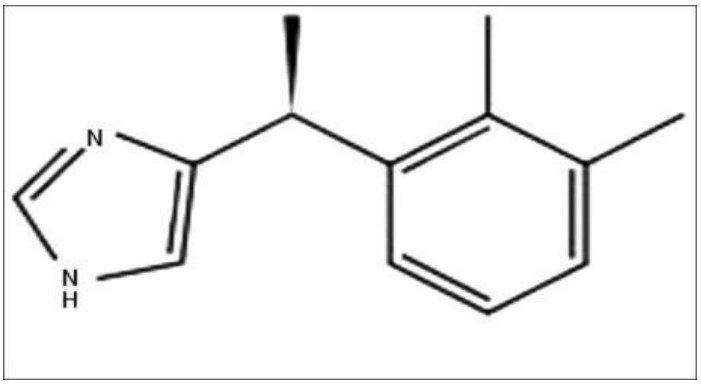


**Figure (2):** Chemical structure of dexmedetomidine [(15)].

Dexmedetomidine has analgesic effects via a variety of pathways. These include spinal, supraspinal, and peripheral activities. However, dexmedetomidine's analgesic efficacy is debated. Tolerance plateaus at dosages greater than 0.5 g/kg in a model of ischemia pain in healthy volunteers. While analgesia was observed throughout a wide range of plasma concentrations (0.5-8.0 ng/ml), the impact appeared to be dose-dependent[(16)].

Many clinical trials have confirmed dexmedetomidine's opioid-sparing efficacy. Pain following laparoscopic tubal ligation can be efficiently managed with a dexmedetomidine dose of 0.4 g/kg, however the resulting sleepiness and bradycardia may be less than ideal for the patient in the postoperative period. In a recent meta-analysis of 21 randomized studies, dexmedetomidine was found to be more beneficial than remifentanil for general anesthesia in terms of reducing pain scores within the first 24 hours after surgery, as well as reducing postoperative vomiting, nausea, as well as shivering [(17)].

The neuraxial administration of dexmedetomidine exerts analgesic effects on both localised and systemic pain. Dexmedetomidine given neuraxially reduces postoperative pain and increases the duration of analgesia, but it also increases the risk of bradycardia, according to a meta-analysis of 16 randomized controlled studies [(18)].

Dexmedetomidine has also been studied for its possible use in the treatment and prevention of neuropathic pain. Using a rat model of spinal nerve ligation-induced neuropathic pain, researchers found that injecting dexmedetomidine locally reduced pain perception in an antiallodynic fashion [(19)].

The usual dosage range for sedation in intensive care units is between 0.2 and 0.7 mcg/kg per hour. Although a higher dose of 1.5 mcg/kg per hour may be necessary to reach the appropriate amount of drowsiness, this is safe and effective. It is doubtful that doses greater than 1.5 mcg/kg per hour yield any further therapeutic benefit in the absence of increasing side effects; yet, doses up to 2.5 mcg/kg per hour have been documented. Renal or hepatic impairment does not necessarily necessitate dosage modifications, but they should be addressed, especially in the case of hepatic impairment. Although the manufacturer suggests no more than a 24-hour course, lengthier courses have been shown to be safe and effective. A loading dose of 0.5–1.0 mcg/kg is available for use by clinicians; however, this is normally avoided in patients who are highly vulnerable, such as those in critical care or those with compromised hemodynamics [(20)].

Hypertension, bradycardia, and hypotension are the most prevalent unintended reactions to dexmedetomidine. The activation of alpha receptor subtypes in vascular smooth muscles can lead to an increase in blood pressure (hypertension). Slow dosing or skipping the loading dosage is an effective way to prevent hypertension, which is rarely medically necessary. Stimulation of presynaptic alpha receptors causes a decrease in norepinephrine release, which contributes to hypotension and bradycardia by decreasing the central sympathetic outflow. These issues persist regardless of who is in charge of the country [(21)]. For the most part, dexmedetomidine can be used safely and effectively. Patients with preexisting bradycardia or hypotension should take caution, as the drug may make their conditions worse. Level B evidence suggests dexmedetomidine may aggravate myocardial dysfunction, therefore it should be taken with caution in patients with established heart failure [(22)].

**NSAIDs**

Inhibition of the enzyme cyclooxygenase is central to the anti-inflammatory effects of NSAIDs (COX). Arachidonic acid is converted into thromboxanes, prostaglandins, and prostacyclins by cyclooxygenase. This deficiency in eicosanoids is thought to be responsible for the therapeutic effects of NSAIDs. Nonsteroidal anti-inflammatory drugs (NSAIDs) are controversial for use in neurosurgery. NSAIDS reduce pain and inflammation by blocking the production of prostaglandins. In the absence of bleeding disorders or renal abnormalities, diclofenac has been recommended for use [(6)].

**COX-2 inhibitors**

Since selective COX-2 inhibitors targeted inflammatory mediators and sidestepped platelet dysfunctions, they were met with much fanfare upon their introduction. After a craniotomy, intravenous parecoxib, morphine, and scalp blocks were used to help with the discomfort. However, these studies have shown no noteworthy variations in analgesia. Improved analgesia and fewer opioid-related adverse effects were achieved by combining rofecoxib with oral oxycodone [(23)].

**Paracetamol (Acetaminophen)**

Pain and fever can be treated with acetaminophen, which is a non-opioid analgesic and antipyretic.

Paracetamol, or acetaminophen, is an acetanilide derivative with the chemical formula C8H9NO2 (Fig. 3). It can be used alone for mild to moderate pain, or in conjunction with an opioid analgesic for severe pain [(24)].

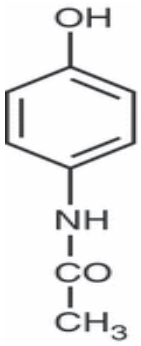


**Figure (3):** Chemical structure of paracetamol [(25)].

Acetaminophen might only inhibit the COX pathway in the brain and spinal cord, but in other parts of the body it would have no effect. Acetaminophen inhibits COX activity, however it does so in a way that does not involve binding to the enzyme's active site (where COX-1 or COX-2 enzymes would be bound). Although it has not been demonstrated in people, acetaminophen may also suppress a splice version of COX-1 known as COX-3 [(26)]. Acetaminophen's analgesic and antipyretic effects are attributed, at least in part, to its ability to reduce COX pathway activity and hence suppress synthesis of prostaglandins in the central nervous system. It is possible that the analgesic qualities arise from a stimulating influence on the descending serotonergic pathways in the central nervous system (CNS). In addition to its analgesic effects, acetaminophen or one of its metabolites, such as AM 404, may also have anti-inflammatory and pain-relieving effects by activating the cannabinoid system [(27)] (Fig 4).

**Perioperative use of paracetamol**

Postoperative morphine consumption is reduced by 20% in the first 24 hours after major surgery when paracetamol is added to morphine patient-controlled analgesia (PCA), although this is not accompanied by a reduction in morphine-related side effects [(28)]. The results of two systematic studies, one of which found that adding an NSAID to paracetamol enhanced postoperative analgesia compared to paracetamol alone, and the other of which found no evidence of benefit, are inconsistent with one another. However, the number of papers that could be included in either review was quite low. In comparison to opioids, its effectiveness as a main treatment for treating post-craniotomy pain is low. Guidelines currently advocate acetaminophen for usage as an adjuvant analgesic because of its opioid-sparing properties [(29)]. Specifically, there appears to be no difference in the analgesic efficacy of oral and intravenous forms of acetaminophen, according to the available evidence [(30)].

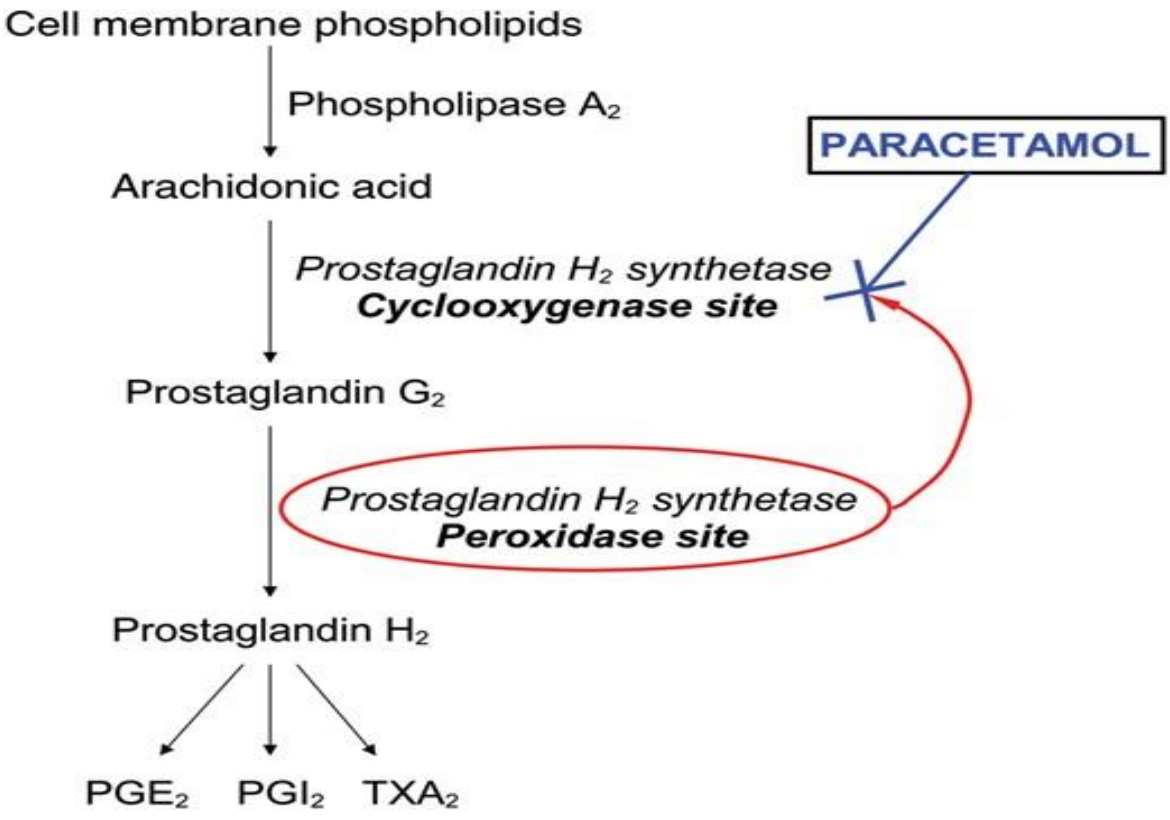


**Figure (4):** Role of paracetamol in inhibition of prostaglandin production [(31)].

**Gabapentin**

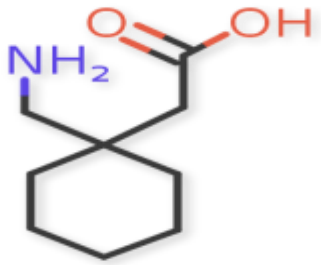


**Figure (5):** Structure of gabapentin [33].

To treat focal seizures and post-herpetic neuralgia, as well as peripheral neuropathic pain, gabapentin has been approved for use in the United States and the United Kingdom, respectively [32]. Gabapentin is an anticonvulsant that works by blocking voltage-gated $Ca2^{+}$ and $Na^{+}$ channels presynaptically, hence lowering synaptic transmission. In addition, gabapentin inhibits neurotransmitter release from presynaptic terminals by decreasing exocytosis [34].

Clinical research has shown that preoperative and postoperative gabapentin for craniotomy patients is more effective than placebo for reducing pain and nausea and reducing the need for opioids. After 24 hours, the reaction has waned; therefore, postoperative gabapentin must be taken continuously to keep the multimodal analgesia in effect [7].

Recently, **Zeng *et al.*** [35] in a randomised, placebo-controlled, double-blind study that was carried out at a single site. 122 individuals who were scheduled to have an elective craniotomy by either a suboccipital or subtemporal approach were split into two groups: those who received a placebo and those who were given gabapentin. Patients in the gabapentin group took 600 mg of the drug orally the night before surgery and again two hours before anesthesia was induced; those in the placebo group took vitamin B. The 24-hour postoperative pain score was the primary endpoint. Consequences such as nausea, vomiting, sedation, and the need for painkillers were tracked as secondary outcomes. Within 24 hours of surgery, gabapentin significantly reduced resting and active acute pain scores (P0.001 and P0.000, respectively).

## CONCLUSION

Combined use of multimodal opioid sparing analgesics such as Paracetamol, NSAIDs, Gabapentin, Dexmedetomidine, scalp block holds the potential for enhancing pain management and decreasing reliance on opioids without compromising the validity of a clinical neurologic evaluation.

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