

## REVIEW ARTICLE

## REGIONAL ANESTHESIA

# Shifts in the use of adjuncts for regional anesthesia, aligning practice with evidence: a comprehensive review

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## ABSTRACT

In regional anesthesia, there has been an evolution in the development of adjuncts to evidence-based practice that improve patient outcomes. This intensive review aims to discuss the historical perspective of adjuncts, including how they came into play in the practice of anesthesia, and reduce complications by refining efficacy. The traditional adjuncts, opioids and alpha-2 adrenergic agonists, have been employed for many years to prolong analgesia/anesthetic time, but their use is associated with significant side effects like respiratory depression and bradycardia. Newer adjuncts such as liposomal bupivacaine and magnesium have the potential to provide long-acting alternatives with less systemic toxicity. Alternatively, the review in question provides a critical assessment of the treatment efficacy and safety profile of these agents, helping to elucidate how clinical practice patterns are evolving. This study further emphasizes the need for ensuring that anesthesia protocols are current and incorporate updated research to keep patient safety in mind, while minimizing potential side-effects and improving outcomes. Future directions include ongoing research on and optimization of anesthesia adjuncts, as well as instilling a collaborative mindset among healthcare providers to incorporate the most updated high-quality evidence in their clinical practice.

**Keywords:** Adjuncts; Alpha-2 adrenergic agonists; Anesthesia safety; Corticosteroids; Evidence-based practice; Liposomal bupivacaine, Magnesium; Opioids; Pain management; Regional anesthesia

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## 1. INTRODUCTION

One of the most important techniques in modern anesthetic practice is regional anesthesia, which involves blocking sensation in a specific area of the body, allowing for pain-free surgical procedures while

maintaining full consciousness. Methods include the epidural, spinal, and peripheral nerve blocks, but among these, interventional techniques are particularly prevalent in orthopedic surgery and obstetric care. Regional techniques have been associated with decreased postoperative complications, shorter recovery

times, and fewer systemic side effects compared to general anesthesia.<sup>1</sup> This extensive range of benefits has reflected their extensive use in clinical practice and is vitally important for individualized care delivery. Regional anesthesia has changed dramatically in recent years. As the field advances, patients would also be well served by advancing adjuncts— those powerful interventions that amplify pain relief and recovery. No matter who you are — a practitioner or a patient, it is equally important to understand how these adjuncts work.

This review will look at the evolving use of adjuncts in regional anesthesia, from historical views to contemporary innovations. The function of adjuncts to regional anesthesia is in the process of change, with new formulations being offered that aim at improving their efficacy and prolonging the action on nerve conduction.<sup>2</sup> Adjuncts, including opioids and non-opioids, have been used traditionally to improve the quality of anesthesia, reduce the dose of local anesthetics needed, and counteract side effects such as hypotension and respiratory depression. This review provides an overview of contemporary adjunct use in critically ill patients and emphasizes the need to align clinical practice with the best available evidence. It seeks to steer future research and clinical decision-making, ensuring that our practice remains as safe and effective as possible with an aim to best practice.

## 2. Historical Context

Much has changed in the use of adjuncts for regional anesthesia over the years. Originally, when it came to surgical procedures, clinicians used to provide local anesthetics only. Though, as practice grew the demand for better pain management was recognized. In the early days of regional anesthesia, some experimentalists tried to add many compounds to local anesthetics. The advent of opioids was a dramatic step forward, giving rise to potent analgesia and enhancing patient comfort.

This is the situation up until the mid-20th century, or so, when new pharmacological agents were introduced (i.e., clonidine and corticosteroids). These were augmented by progress in the understanding of drug pharmacodynamics and the innovation of more efficient delivery systems. This development led to a change in clinical view, with early experience of the successes and disappointments with early adjuncts resulting in rethinking their role. However, a growing understanding of the physiology underlying mechanism-based anesthetic care has facilitated re-purposing existing adjuncts to improve effect and brought clinical practice more in keep with both expanding knowledge of mechanisms and emerging stronger evidence.<sup>3</sup>

## 3. Commonly Used Adjuncts

Subsequently, the utility of adjuncts in RA has become an important component in nerve blocks with better efficacy and duration of action, ultimately benefiting patients. Fentanyl and morphine are potent analgesics which be frequently added to local anesthetics for use as opioids.<sup>4</sup> They act by binding to opioid receptors in the central nervous system, synergistically decreasing pain and prolonging the block. Nevertheless, opioids are associated with potential risks, including respiratory depression and pruritus as well as gastrointestinal side effects (e.g., opioid-induced ileus), necessitating close patient monitoring.<sup>5</sup>

Alpha-2 adrenergic agonists such as clonidine and dexmedetomidine, although not only developed for pain control, have become important drugs in regional anesthesia due to their analgesic effects as well as through the central (dexmedetomidine) and peripheral receptors.<sup>6</sup> Clinically, these agents decrease opioid requirement and enhance the quality of the block without proper safety precautions against hypotension, bradycardia, with possible extreme sedation. Most corticosteroids, especially dexamethasone, although known for their anti-inflammatory effect and prolongation of anesthesia action. Although effective, it can lead to hyperglycemia and potential neurotoxicity with repeated doses. Furthermore, local anesthetic additives such as sodium bicarbonate and epinephrine facilitate rapid block onset times while prolonging duration, with the added benefit of limiting systemic absorption of local anesthetics using vasoconstrictors like epinephrine. New agents, including liposomal bupivacaine and magnesium, demonstrate strong indications for expanded adjunct selection, with recent trials providing insight towards optimizing RA techniques.<sup>7,8</sup>

### 3.1. Opioids as adjuncts

Opioids (fentanyl, morphine) are frequently added to local anesthetics during regional anesthesia to provide prolonged postoperative analgesia. They act by binding to opioid receptors, specifically the  $\mu$ -receptors, located in the dorsal horn of the spinal cord and peripherally on nerve endings.<sup>9</sup> Opioids exert some of the local anesthetic effects through sodium channel blockade, and at a molecular level, release of neurotransmitters involved in pain transmission, notably substance P and glutamate, is inhibited by opioids. It results in a Na<sup>+</sup> blockade of nerve fibers. Receptor stabilization prevents the artificially high Na concentrations and membrane behavior, causing a blockade for a long time (more than 4 hours), which is good as it will give long-lasting sensory blockade and relief from pain. Applies the opioid directly to the site of action; with minimal

systemic absorption possible, there are smaller effects of common opioid related systemic side effects (such as respiratory depression and sedation).

There are several beneficial effects, as the nerve plexus or ganglion delivers opioids locally, improving opioid interaction with local anesthetics. The more effective modulation of pain pathways by this combined approach translates to an overall greater analgesic effect that allows less use of systemic opioids. But even though opioids may have a favorable safety profile, they can still lead to a lot of unwanted side effects — and such is particularly the case when used regionally. The most common side effects reported are pruritus, nausea, and urinary retention. There is also a risk of opioid-induced respiratory depression (particularly at larger doses), sedation, and possible hyperalgesia from the opioids. So opioids help a lot in prolonging the duration and in better the quality of regional anesthesia, but keep that in mind as side effects if giving very high dose.<sup>10</sup>

### 3.2. Alpha-2 adrenergic agonists

For adjuncts in regional anesthesia techniques alpha-2 adrenergic agonists, clonidine and dexmedetomidine have been seen to increase the duration of analgesia. They act through direct stimulation of alpha-2 receptors in the central and peripheral nervous system, preventing norepinephrine release and hence decreasing sympathetic outflow.<sup>11</sup> This results in hyperpolarization of nerve cells and subsequently increased action potential duration, explaining that at a molecular level, local anesthetic sodium channel blockade and nerve fibre desensitization are prolonged. This cumulatively serves to slow down the onset, and at the same time increase the extent and duration of sensory blockade with subsequent prolongation in live nerve conduction, so nociceptive input continues its blockade longer. Alpha-2 agonists further potentiate the analgesic mechanism by direct CNS inhibition of nociceptive afferent pathways and increased nerve conduction blockade via pre-synaptic alpha 2 receptor blockade.<sup>12</sup>

Alpha-2 adrenergic agonists are also quite good for the reduction of systemic side effects. They act by direct application to the nerve plexus or ganglion, reducing systemic absorption and thereby the side effects profile of sedation and hypotension commonly observed with systemic administration. Because they produce local effects, the doses of required topical anesthetics or opioids are less than those for systemic application and therefore provide local pain control. Adjuvants additively improve the quality of regional anesthesia but are not exempt from side effects. Regardless of the support for a more balanced pharmacological profile, bradycardia and hypotension, as well as excessive sedative effects, are still major concerns, which

necessitate proper step-by-step optimization of pharmacologic therapy with close monitoring in patients with pre-existing cardiovascular conditions.<sup>13</sup>

### 3.3. Corticosteroids as adjuncts

Recently, corticosteroids have received widespread interest as adjuvants to regional anesthesia.<sup>14</sup> This anti-inflammatory quality is crucial in providing relief from pain and swelling. Because of their ability to provide a prolonged duration local anesthetic effect, systemic administration of adjuncts like corticosteroids (such as dexamethasone) with regional anesthesia is commonly practiced. Their mechanism of action is by their anti-inflammatory activity, which mediates the inhibition of pro-inflammatory cytokines and mediators, thus reducing perineural inflammation and prolonging nerve blockade duration. Corticosteroids may also prolong the action of local anesthetics by stabilizing nerve cell membranes on a molecular level, enhancing sodium channel blockade, and reducing the excitability of nerve fibers, which again contributes to a prolonged nerve desensitization. Minimizing systemic absorption of the corticosteroid from the local deposit to the nerve plexus or ganglion lowers the risk of systemic side effects, including hyperglycemia and immunosuppression. It also potentiates analgesia by weakening effects on pain pathways, especially by decreasing peripheral and central sensitization, when used in combination with local anesthetics; the result is improved anesthesia that lasts longer. On the other hand, although corticosteroids are known to extend analgesic duration, their use is associated with an increased incidence of hyperglycemia in diabetic patients, and concerns about neurotoxicity upon repetitive or high-dose administration, where careful judgment should be exercised before using it.<sup>15</sup>

### 3.4. Miscellaneous additives

The value of additives to local anesthetics remains one of the most impressive ways of increasing efficacy in regional anesthesia. For many years, additives such as sodium bicarbonate and epinephrine have been used in regional anesthesia to prolong the duration of action and effectiveness of the local anesthetics. The higher pH of the local anesthetic solution produced by sodium bicarbonate increases the fraction of drug in its lipid-soluble, unionized form; this allows rapid penetration into nerve cell membranes, resulting in more effective blockade of sodium channels. This speeds up the onset of anesthesia and duration by keeping the nerve fiber desensitized.<sup>16</sup> However, epinephrine behaves rather like a vasopressor, allowing blood flow to decrease at the injection location to lower systemic absorption of the local anesthetic and to lengthen its local action, in contrast to epinephrine, which serves only as a vasoconstrictor.<sup>17</sup> This vasoconstrictive function also

serves to reduce systemic absorption of local anesthetics, thereby limiting the exposure of surrounding tissues to the drug and minimizing potential accompanying complications – enhancing the overall safety profile. Both of them allowed targeted drug delivery to the nerve plexus or ganglion, and furthered specific interaction with local anesthetics, respectively strengthening their effect on pain pathways. However, they pose risks when used as sodium bicarbonate can cause hypercapnia, and epinephrine may induce hypertension, tachycardia, or tissue ischemia due to inappropriate use.<sup>18, 19</sup>

## 4. Emerging adjuncts

Liposomal bupivacaine and magnesium are emerging adjuncts that have been studied for their effects on PNB analgesia. Liposomal bupivacaine achieves a longer duration of analgesia by utilizing a paucity-releasing strategy, which slowly eludes the bupivacaine to sodium channels, providing an extended nerve block and desensitizing nerve fibers.<sup>20</sup> In comparison, magnesium blocks N-methyl-D-aspartate (NMDA) receptors, leading to a decrease in calcium influx within neurons, permitting the local anesthetics to act by modifying pain pathways and prolonging sodium channel blockade.<sup>21</sup> The idea is, both agents are formulated to limit systemic absorption, with the result that fewer side effects occur. Not only does liposomal bupivacaine release a pharmacologically active drug for a longer duration of time with minimal systemic toxicity, but the magnesium further inhibits NMDA receptors, relieving many of the local anesthetic-sparing properties; mixing them allows synergism to that end. These adjuvants also enhance site-specific delivery via transient physical interactions with local anesthetics that allow them to be "steered" towards the target nerve plexus or ganglion, thereby improving pain control more efficiently. Nevertheless, undesirable side effects such as hypotension (magnesium) and possible local tissue reactions in the form of bupivacaine spilling (liposomal bupivacaine use) are still issues to keep in mind that demand vigilance to obtain an appropriate balance between efficacy and safety.

## 5. Evidence-Based Evaluation

The efficacy of adjuncts in league with anesthetic blocks has been thoroughly studied by clinical trials and meta-analyses, concentrating largely on the block duration, analgesia, and adverse effects. In a recent double-blinded study, adjuncts such as clonidine and dexamethasone were shown to significantly prolong nerve block duration and enhance postoperative pain management.<sup>22</sup> Meta-analyses show that most adjuncts are associated with reduced supplemental analgesia and lower pain scores, but the effect of an adjunct on secondary

outcomes is largely dependent on the adjunct used and clinical situation.<sup>23</sup> While adjuncts are typically felt to be safe, rare but potentially fatal cardiovascular sequelae associated with agents like epinephrine have been described domestically and abroad.

Studies conducted on comparative trials have shown that dexamethasone has demonstrated superiority over other adjuncts in duration of blocks, pain control and some studies showing that adding another type of the available accelerants like clonidine to dexamethasone gave a better effect than using it as single agent.<sup>14, 24</sup> However, the mixing of adjuvants can raise safety concerns such as adverse events in people who are more vulnerable like those who are elderly or have multiple comorbidities. The safety profile must be meticulously evaluated when utilizing amiodarone for special populations such as the elderly, who are vulnerable to hypotension and bradycardia; pediatric patients, who may cause torsade de pointes; and comorbid patients who necessitate dosing adjustments to avoid complications. Accordingly, treatment planning must be individualized in order to balance efficacy versus safety.<sup>25</sup>

## 6. Shifts in the Use of Adjuncts

Regional anesthesia is changing. Studies over the past few years reveal a much higher rate of reliance on adjuncts. Evidence-based providers who choose to use adjuncts alongside other therapies.<sup>26</sup> The decreasing use of conventional adjuvants, such as epinephrine and opioids in regional anesthesia, is based on the evidence from updated guidelines that have reported their side effects.<sup>25</sup> While epinephrine is a pre-septic ischemic condition and should have become the drug of choice to constrict blood vessels, it has been associated with problematic cardiovascular effects—especially in patients with existing heart disease—and opioids carry significant concerns for side effects like respiratory depression (in addition to nausea) while possibly increasing relative dependence. These concerns have led to changes in prescription practice under the updated guidelines with a preference for more effective and safer alternatives, especially among the high-risk groups.

In contrast, newer adjuncts such as dexmedetomidine, magnesium, and liposomal formulations have enjoyed success arising from their increased safety profile and efficacy. Advantages of dexmedetomidine are its sedative and analgesic effects without the risk of respiratory depression as with opioids, whereas magnesium potentiates the other block-modifying factors without major side effects.<sup>27</sup> The time frame for pain relief is increased when the drugs are administered in liposomal formulations. Recent agent utilization

varies by region according to local practices, guidelines, regulatory approvals, institutional policies, and experience with some agents, resulting in different patterns of adjunct use among regions.

## 7. Aligning Clinical Practice with Evidence

Difficulties associated with incorporating adjuncts into anesthetic practice include institutional inertia to change, practitioner unfamiliarity or reticence, and infrastructure and regulatory obstacles. Also, newer adjuvants may prove to be of higher cost and be less widely available; therefore, uptake of agents like dexmedetomidine or liposomal formulations could be relatively slow in low-resourced areas as well. Overcoming these barriers will require targeted educational and training programs for anesthesiologists to keep pace with the best research practices. Special evidence-based clinical guidelines or clinical pathways and standard operating procedures (SOPs) prepared are another way to make use of them in day-to-day practice.

The input of anesthesia societies and other professional organizations is a critical pathway in helping new evidence-based adjuncts gain acceptance by updating practice guidelines based upon the latest science and research. First, clinical outcomes are so few and far between it is hard to evaluate all cases done, and getting feedback from patients allows a data-driven decision process of when to use adjuncts, which we believe should be the norm in anesthesia departments.

## 8. Future Directions

Aligning clinical practice with evidence is crucial in enhancing patient outcomes. This approach ensures that the latest research informs anesthesia techniques and adjuncts used during procedures. Practitioners should remain vigilant, continuously updating their knowledge base as new studies emerge. Relying on outdated methods can hinder efficiency and effectiveness in managing pain. Engagement in multidisciplinary collaboration fosters a culture of shared learning. Anesthesiologists, surgeons, and nurses working together can tailor strategies based on collective insights. Moreover, utilizing data from patient experiences helps refine protocols. Understanding what works best in real-world scenarios bridges the gap between theory and practice. Regular training sessions focused on current evidence equip practitioners to implement new findings seamlessly into their routines. Such efforts lead to improved anesthetic care, ensuring every patient receives optimal treatment tailored to their individual needs.<sup>28</sup>

## 9. CONCLUSION

Clinical practice should align with evidence to improve patient outcomes. New research drives the development of anesthesia techniques and adjuncts. Traditional approaches can hinder productivity and efficiency. Interdisciplinary collaborations foster a culture of collaborative learning, allowing providers, surgeons, and nurses to plan interventions based on collective knowledge. Data on patient experiences is used to develop protocols. Regular practice with current evidence allows for easy implementation in daily routines, leading to better anesthetic care and optimal therapy options for each patient.

## 10. Conflict of interest

The authors declare no conflict of interest.

## 11. Authors contribution

MAZ: Main Concept

AA: Conduction of the study work

AK: Manuscript editing

PA: Literature Search

HMFI: Proof reading

MAR: Final Review

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