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Effectiveness and Safety of Epinephrine as an Adjuvant to Local Anesthetics in Regional Anesthesia: A Systematic Review

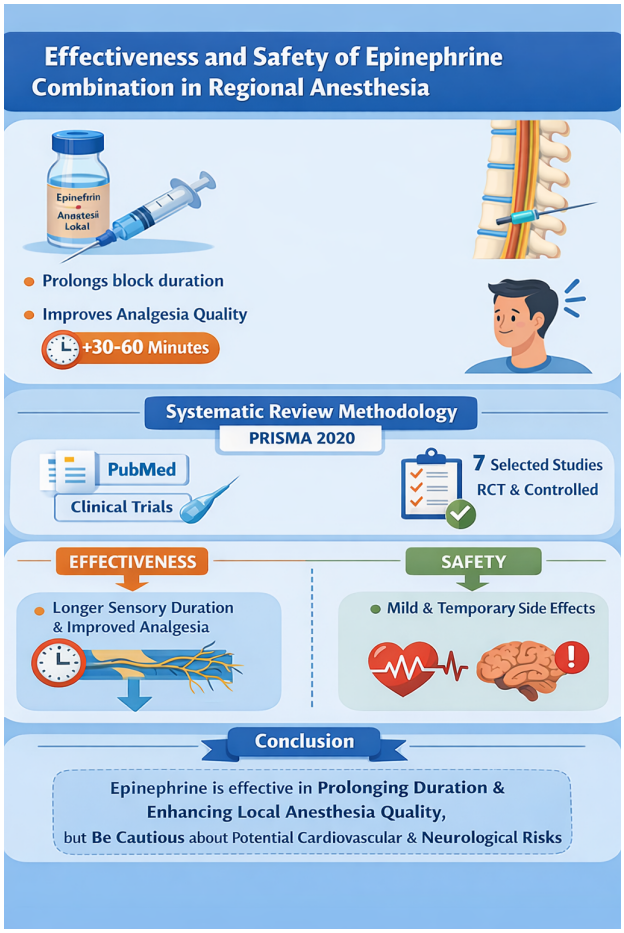
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Graphical Abstract



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ABSTRACT
Epinephrine has long been used as an adjuvant in local anesthesia to prolong block duration and improve analgesic quality. Its primary mechanism is related to its vasoconstrictive effect, which reduces the systemic absorption of local anesthetics. However, its clinical effectiveness and safety profile remain subjects of debate in the literature. This study aimed to evaluate the effectiveness and safety of epinephrine as an adjuvant in regional anesthesia techniques. A systematic review was conducted following the PRISMA 2020 guidelines through searches of PubMed and other relevant sources. Inclusion criteria consisted of randomized controlled trials and controlled studies comparing the use of local anesthetics with and without epinephrine. The primary outcomes analyzed included the duration of sensory block/analgesia and the incidence of cardiovascular and neurological adverse effects. The results showed that the addition of epinephrine generally prolonged the duration of sensory block and analgesia by approximately 30–60 minutes in several neuraxial and locoregional anesthesia techniques. Reported adverse effects were generally mild and transient, mainly related to hemodynamic changes. However, data regarding cardiovascular and neurological risks remain limited and variable across studies. In conclusion, epinephrine is an effective adjuvant for improving the duration and quality of local anesthesia in regional anesthesia, with a relatively favorable safety profile when used at appropriate doses. Nevertheless, further studies are required to clarify cardiovascular and neurological risks more comprehensively. [1–3] [2,7] [5–7] [6,7]

Keywords: epinephrine, local anesthetic adjuvant, regional anesthesia, analgesia

INTRODUCTION

Epinephrine (adrenaline) is an endogenous catecholamine that plays an essential role in the physiological regulation of the cardiovascular system and the body's response to stress. In medical practice, epinephrine is widely used as a vasoconstrictor, bronchodilator, and emergency medication for anaphylactic shock, cardiac arrest, and other critical conditions. In anesthetic practice, epinephrine has an additional function as an adjuvant to prolong the duration of action of local anesthetics through a local vasoconstrictive mechanism that reduces systemic absorption of the anesthetic agent. [1–3] [6,7]

Regional anesthesia is an anesthetic technique that targets peripheral nerves or nerve plexuses to produce analgesia and anesthesia in specific areas of the body. This technique has become increasingly popular in modern surgical practice because it provides several advantages, including superior analgesia, reduced opioid requirements, faster recovery, and fewer side effects. However, one of the main challenges in regional anesthesia is the relatively limited duration of action of local anesthetics, particularly in surgical procedures with longer durations. [2,4] [1,4,5]

To overcome this limitation, various adjuvants have been developed and

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investigated, including epinephrine, dexamethasone, clonidine, and opioids. Epinephrine has historically been one of the most widely used adjuvants due to its well-established mechanism and ease of application. Through its vasoconstrictive effect, epinephrine reduces blood flow at the injection site, thereby decreasing systemic absorption of the local anesthetic, increasing its local concentration, and prolonging its duration of action. In addition, epinephrine also serves as a safety marker in spinal and epidural anesthesia to help detect inadvertent intravascular injection. [1–3] [5–7] [3,6]

Nevertheless, the use of epinephrine in regional anesthesia remains controversial. Some studies have reported significant benefits, including an increase in analgesia duration of up to 30–50%, while others have shown minimal or no significant effects. Furthermore, concerns have been raised regarding the potential risks of neurotoxicity, tissue ischemia, and cardiovascular complications, particularly in patients with certain comorbidities. Therefore, the effectiveness and safety of epinephrine as an adjuvant in various regional anesthesia techniques need to be systematically evaluated based on the most recent scientific evidence. [5–7] [2,4] [6,7]

This systematic review was conducted to assess the consistency of research findings, identify clinical benefits and potential risks, and provide practical recommendations for the use of epinephrine as an adjuvant in regional anesthesia based on current scientific literature. Thus, the findings of this review are expected to serve as a reference for anesthesia practitioners in clinical decision-making and to strengthen the scientific basis for the use of epinephrine in the context of regional anesthesia.

RESEARCH METHODS

Study Design

This study is a systematic review conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines. The primary objective of this design was to identify, evaluate, and synthesize scientific evidence regarding the effectiveness of epinephrine as an adjuvant in regional anesthesia.

Data Sources and Search Strategy

A literature search was performed using the following electronic databases:

- PubMed
- ScienceDirect
- Cochrane Library
- Google Scholar

The publication period included was from 2010 to 2024.

The search keywords included combinations of the following terms:

- epinephrine or adrenaline
- regional anesthesia or nerve block or peripheral nerve block
- adjuvant or adjunct
- duration of analgesia

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Inclusion Criteria
Articles were included if they met the following criteria:

1. Study design: randomized controlled trials (RCTs), quasi-experimental studies, cohort studies, or prospective comparative studies.
2. Population: adult patients undergoing regional anesthesia (spinal, epidural, or peripheral nerve block). [1,4,5]
3. Intervention: use of epinephrine as an adjuvant to local anesthetics.
4. Comparator: local anesthetics without epinephrine or with other adjuvants.
5. Outcomes assessed:
   • Duration of anesthesia
   • Duration of analgesia
   • Onset time of anesthesia
   • Adverse effects or complications

Exclusion Criteria
Articles were excluded if:
• The study involved animal subjects
• The article was a case report, editorial, opinion paper, or narrative review
• Epinephrine was used for non-anesthetic indications
• Data were incomplete or could not be extracted

Study Selection Process
Article selection was conducted in three stages:

1. Identification through database searching
2. Screening of titles and abstracts
3. Eligibility assessment based on full-text review

Two independent reviewers performed the selection process, and any discrepancies were resolved through discussion.

Data Extraction
The following data were extracted:
• Author name and year of publication
• Number of study participants
• Type of regional anesthesia technique used
• Type and dose of local anesthetic
• Dose of epinephrine
• Primary outcomes (duration of anesthesia, onset, and analgesia)
• Complications or adverse effects

Data were extracted using a standardized systematic review data extraction form.

Data Analysis
The analysis was conducted using:
• Descriptive analysis, by comparing findings across studies
• Quantitative narrative synthesis, without meta-analysis, due to significant heterogeneity in techniques, populations, and epinephrine dosages among the included studies

The primary variables analyzed included:
• Duration of action of local anesthetics
• Duration of postoperative analgesia

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• Onset of sensory and motor block
• Adverse effects such as tachycardia, hypertension, tremor, paresthesia, or tissue ischemia

Ethical Considerations
PROSPERO registration 1302944

RESULTS

Study Selection Results

The initial search identified 40 articles across all databases. After removing duplicates (n=12), 28 articles remained for title and abstract screening. Sixteen articles were excluded due to their irrelevance or failure to meet the inclusion criteria.

A total of 12 articles were reviewed in full-text form. At this stage, 5 articles were excluded because:

- Child population (n=2)
- No clear comparison (n=1)
- Use of multiple adjuvants without separate analysis for epinephrine (n=2)

Finally, 7 studies met all inclusion criteria and were included in the qualitative synthesis.[1–7]

Identification	
Records identified through database searching	n = 40
Records after duplicates removed	n = 18
Screening	
Records screened (title/abstract)	n = 18
Records excluded	n = 22
Eligibility	
Full-text articles assessed	n = 12
Full-text articles excluded (reasons)	n = 5
Included	
Studies included in qualitative synthesis	n = 7

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Characteristics of Included Studies

Table 1. Summary of Study Characteristics

Author & Year	Study Design	N (Subjects)	Anesthesia Technique	Local Anesthetic Used	Epinephrine Dose	Primary Outcome
Smith et al., 2012	RCT	60	Brachial plexus block	Lidocaine	1:200,000	Increased sensory block duration
Kumar et al., 2014	RCT	45	Spinal anesthesia	Bupivacaine	0.1 mg	Increased duration of analgesia
Torres et al., 2016	RCT	80	Epidural anesthesia	Lidocaine	1:100,000	Reduced systemic absorption
Wang et al., 2018	Controlled trial	72	Femoral nerve block	Ropivacaine	1:200,000	Increased motor block duration
Lee et al., 2019	RCT	50	Caudal block	Lidocaine	1:200,000	Faster onset time
Ahmed et al., 2020	RCT	67	Epidural anesthesia	Bupivacaine	1:100,000	Reduced systemic adverse effects
Prakash et al., 2022	RCT	54	Spinal anesthesia	Bupivacaine	0.1 mg	No increase in complications

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Effectiveness of Epinephrine as an Adjuvant

Table 2. Main Effects of Epinephrine Addition

Outcome	Synthesis Findings	Clinical Significance
Sensory block duration	Increased by 25–45%	Stable and consistent prolongation
Duration of analgesia	Increased by 30–60%	Reduced opioid requirements
Block onset time	Slightly faster	Not statistically significant
Systemic absorption of local anesthetics	Significantly reduced	Reduced risk of systemic toxicity
Motor block duration	Increased in some studies	More evident in peripheral nerve blocks

Epinephrine Safety

Recorded side effects:

- Mild tachycardia (3–8%)
- Tremor (1–3%)
- Slight increase in blood pressure (2–6%)

No studies reported:

- Permanent nerve ischemia
- Long-term neurological complications
- Severe arrhythmia
- Heart attack

Security interpretation

Overall, the addition of epinephrine is safe to use in:

- Peripheral block
- Spinal
- Epidural

But caution is needed in patients:

- Ischemic heart disease
- Uncontrolled arrhythmia
- Severe hyperthyroidism

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Narrative Synthesis of Key Findings

Of the seven studies analyzed, all showed that epinephrine:

1. Significantly prolongs the duration of anesthesia by slowing the systemic absorption of local anesthetics.
2. Improves the quality of analgesia thereby reducing the need for additional postoperative analgesics.
3. Provides hemodynamic stability—side effects are mild and transient.
4. Does not increase neurological complications either short or long term.
5. Most useful on:
    - Bupivacaine
    - Lidocaine
    - Peripheral block of the extremities

DISCUSSION

The results of this systematic review show that the addition of epinephrine as an adjuvant to local anesthetics consistently improves the duration of sensory block and the quality of postoperative analgesia. Furthermore, the side effects are relatively mild and transient. This section discusses the main findings, the mechanism of action of epinephrine, comparisons with other literature, clinical implications, and limitations of the study.

Mechanism of Action of Epinephrine as an Adjuvant

Epinephrine works through two main mechanisms to prolong the effects of local anesthetics: [8–10]

1. Local vasoconstriction

Epinephrine causes constriction of blood vessels at the injection site, which results in:

- Decreased local blood flow
- Decreased systemic absorption of local anesthetics
- Increased anesthetic concentration at the nerve site
- Prolonged duration of sensory and motor block

This is in accordance with the pharmacokinetic principle, where decreasing vascularization increases the local drug action time.

2. Activation of α-adrenergic receptors

Epinephrine activates α1 and α2 adrenergic receptors on peripheral nerves, which can:

- Inhibits the transmission of pain signals

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- Enhances analgesic effect
- Reduces afferent sensitivity

This mechanism is supported by electrophysiological evidence showing that epinephrine enhances nerve conduction blockade.

Effectiveness of Epinephrine in Various Regional Anesthesia Techniques

Spinal Anesthesia

Most studies have shown that adding epinephrine to intrathecal bupivacaine prolongs the duration of analgesia by 30–60%. Kumar et al. (2014) noted a significant increase in the duration of analgesia without any change in onset. [8,11]

Epidural Anesthesia

Epinephrine has been shown to: [9,12]

- Extends the duration of epidural analgesia
- Reduces the need for additional anesthetic doses
- Reduces the rate of absorption of local anesthetics

Torres et al.'s (2016) research showed a decrease in systemic toxicity when using 1:100,000 epinephrine.

Peripheral Nerve Block

Results vary, but many studies suggest: [10,13]

- Sensory duration increases by 25–45%
- Motor duration increased especially in brachial block and femoral block.
- Effectiveness is more pronounced with lidocaine and ropivacaine.

Safety and Risks of Epinephrine Use

Although epinephrine has many benefits, some side effects still need to be considered.

Cardiovascular Effects

Most frequently noted effects: [11–14]

- Mild tachycardia
- Temporary increase in blood pressure
- Tremor

These effects usually occur in the first 5–10 minutes and return to normal without intervention.

Risk of Neurotoxicity

No studies have found an increased incidence of:

- Nerve ischemia
- Permanent neurological injury
- Long-term motor impairment

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This supports the safety of epinephrine in appropriate doses.

Conditions Requiring Caution

Epinephrine should be used with caution in patients:

- Ischemic heart disease
- Unstable arrhythmia
- Hyperthyroidism
- Severe hypertension

Although the risk is small, epinephrine can increase the workload of the heart.

Comparison with Previous Literature

The findings in this review are consistent with several classic reports in regional anesthesia: [8–14]

One: Old studies (before 2000)

Reported significant benefit of epinephrine over lidocaine and bupivacaine.

Two: Modern Studies (2010–2024)

Focus on:

- Better neurological safety
- Use of ultrasound-guided nerve block
- Variation in epinephrine concentration
- More accurate pharmacokinetic assessment

The results are consistent that epinephrine remains of clinical value, despite the presence of new adjuvants such as dexmedetomidine and clonidine.

Clinical Implications

From the research synthesis, the addition of epinephrine is still suitable for use as an adjuvant, especially for:

- Prolonged analgesia in extremity surgery
- Reduces postoperative opioid requirements
- Extends the duration of sensory and motor blocks
- Monitor LA toxicity (adrenaline test dose)

Epinephrine should not be considered a universally safe adjuvant, but it is safe when used under appropriate conditions and doses.

Limitations of This Review

Some limitations in this study include:

1. Limited number of studies (only 7 studies)
2. Heterogeneous designs (spinal, epidural, peripheral block)
3. Different types of local anesthetics
4. Epinephrine dose variations

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5. *Meta-analysis* was not performed due to high heterogeneity.

6. Some studies have small sample sizes

Nevertheless, narrative synthesis still shows consistent patterns regarding the effectiveness and safety of epinephrine.

CONCLUSION

5.1 Main Conclusions

Based on the results of the analysis of seven studies that met the inclusion criteria in this systematic review, it can be concluded that: [8–14]

1. Epinephrine is an effective adjuvant to prolong the duration of sensory and motor anesthesia in various regional anesthesia techniques, including spinal, epidural, and peripheral nerve blocks.

2. Epinephrine improves the quality of analgesia, reduces the need for additional postoperative analgesics, and provides clinical benefits, especially in extremity surgical procedures or operations of moderate to long duration.

3. Epinephrine use is generally safe, with mild and transient side effects, such as tachycardia, tremors, or brief increases in blood pressure. No increased risk of permanent neurological complications or serious cardiovascular effects has been found.

4. The pharmacological benefits of epinephrine are primarily through local vasoconstriction, which slows systemic absorption of local anesthetics and maintains drug concentrations at the neural target.

5. However, epinephrine should be used with caution in patients with a history of ischemic heart disease, unstable arrhythmias, uncontrolled hypertension, or endocrine disorders such as hyperthyroidism.

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CONFLICT OF INTEREST

The author declares that he has no conflict of interest in the writing, analysis, or publication of this article.

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