International Journal of Progressive Sciences and Technologies (IJPSAT)
ISSN: 2509-0119.

https://ijpsat.org/
Vol. 47 No. 2 November 2024, pp. 508-534

The Application of Adjuvants in Spinal and Epidural Anaesthesia

Arbnor Ukaj[1]. Zamira Qerkezi Ukaj*[2]

[1]Head of Urgency department of Prizren
Prizren 20000, Kosova
arbnori.uka@gmail.com

[2]Dentist at 'Orthodent' private clinic in Prishtina
Prishtina 10000, Kosova
zamira.q1994@gmail.com

Corresponding Author: Zamira Qerkezi Ukaj

Abstract – Introduction: Spinal and epidural anesthesia are applied during regional anesthesia and analgesia, both during and after surgical interventions. The main advantage of these two methods lies in their low rate of complications and side effects. Adjuvants are agents used to prolong the effect of local anesthetics and simultaneously reduce potential side effects. Adjuvants can be opioids or non-opioids.
Objective of the Study: The aim of this study is to analyze the application of adjuvants in spinal and epidural anesthesia. It also explores the benefits and possible side effects of different types of adjuvants.
Materials and Methods: This study is part of a literature review, using secondary sources from credible articles. These sources were drawn from PubMed, MedLine, and The American Journal of Medicine.
Results: Experimental research on adjuvants from two groups—opioid and non-opioid has been analysed. The adjuvants studied include clonidine, morphine, sufentanil, fentanyl, and dexmedetomidine. The data from these experiments have been compared and discussed in detail regarding the adjuvants introduced at the beginning of this topic. Certain adjuvants were not studied due to a lack of literature.
Conclusion: Based on the literature review and recent international research findings, we conclude that the use of adjuvants in spinal and epidural anesthesia, in combination with local anesthetics, has contributed to extending the duration of the sensory-motor block in patients undergoing specific surgical procedures. This approach also aids in reducing postoperative pain and minimizes the side effects of local anesthetics when administered in combination with adjuvants.

Keywords – Anaesthesia, Spinal, Epidural, Anesthetic, Adjuvants, Opioid, Non-Opioid

1. Introduction

1.1. Application and Characteristics of Spinal Anesthesia

Spinal anesthesia is one of the types of neuraxial anesthesia [1]. Neuraxial anesthesia involves the administration of a local anesthetic near the nerve roots originating from the central nervous system, specifically from the spinal cord. As a neuraxial anesthesia technique, spinal anesthesia allows for the injection of a local anesthetic into the subdural space, located between the dura mater and the arachnoid membrane [2]. This area is known as the subdural space. Within this space, sterile cerebrospinal

fluid circulates, bathing and cleansing both the spinal cord and the brain. The average production of cerebrospinal fluid is about 500 ml in an adult [3].

1.1.1. History of Spinal Anesthesia

Spinal anesthesia has been in use since 1900 [2]. Before this method became widespread, the only techniques used were local anesthesia methods, specifically the infiltration of the skin and mucous membranes. In 1884, Carl Koller first used cocaine as a local anesthetic on a patient [2,3]. Similar injections were initially performed on animals; for instance, cocaine was used as an injected anesthetic in a dog by neurologist James Corning [2]. The development of spinal anesthesia is associated with surgeon Augustus Bier, who administered intrathecal cocaine injections to six patients undergoing surgery. This was the first regional anesthetic technique, introduced in 1898 in Germany [4]. Since then, spinal anesthesia has steadily gained popularity, supported by advancements in spinal needle design. Today, spinal anesthesia has evolved in every aspect, including equipment, knowledge of anatomy and physiology, and the growth of clinical expertise [2,3].

1.1.2. Anatomy of the Spine and Physiology of Spinal Anesthesia

For spinal anesthesia to be successful, it must be administered in the correct position, and the physician should have a sufficient understanding of spinal anatomy [2,4]. In spinal anesthesia, it is essential for the anesthetic to be delivered into the intrathecal (subarachnoid) space in the appropriate dose [4,5].

The spinal column is divided into five segments: cervical, thoracic, lumbar, sacral, and coccygeal (Figure 1) [5,6,7].

International Journal of Progressive Sciences and Technologies (IJPSAT)
ISSN: 2509-0119.

https://ijpsat.org/
Vol. 47 No. 2 November 2024, pp. 508-534

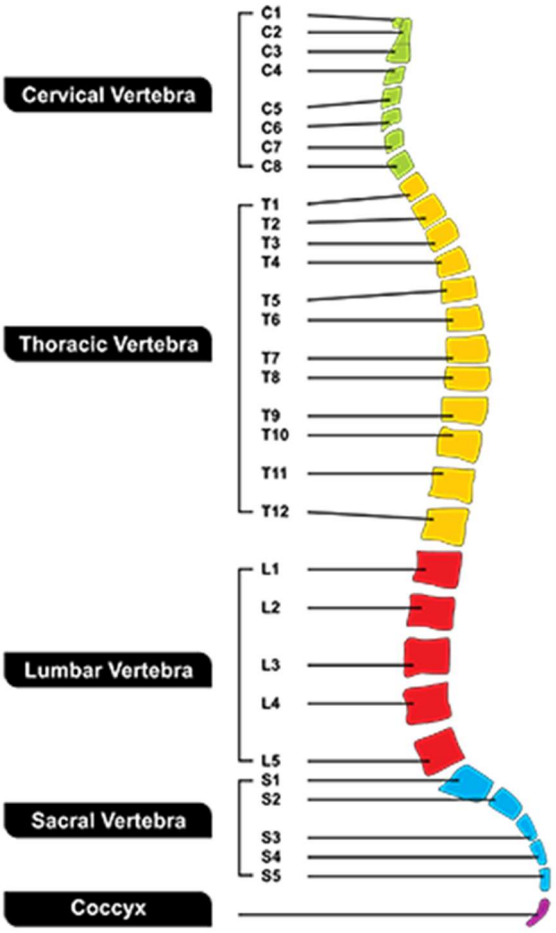

Figure 1: Segments of the Spinal Column [2]

There are various sizes of spinal needles, ranging from 16 to 30 gauge, as well as different designs: sharp-tipped (Quincke) and blunt-tipped (Whitacre) [17]. For spinal anesthesia, both the median and paramedian approaches can be used [17]. In spinal anesthesia, the needle is inserted between the lumbar vertebrae, piercing the dura mater and reaching the subarachnoid space. To access this space, the needle must pass through several layers of tissue and ligaments, which include the skin, supraspinous ligament, interspinous ligament, and ligamentum flavum. Since the spinal cord (conus medullaris) typically ends at the L1 or L2 level of the spinal column, the needle must be inserted below this level, between the L3-L4 or L4-L5 spaces, to avoid damaging the spinal cord [17,22].

International Journal of Progressive Sciences and Technologies (IJPSAT)
ISSN: 2509-0119.

https://ijpsat.org/
Vol. 47 No. 2 November 2024, pp. 508-534

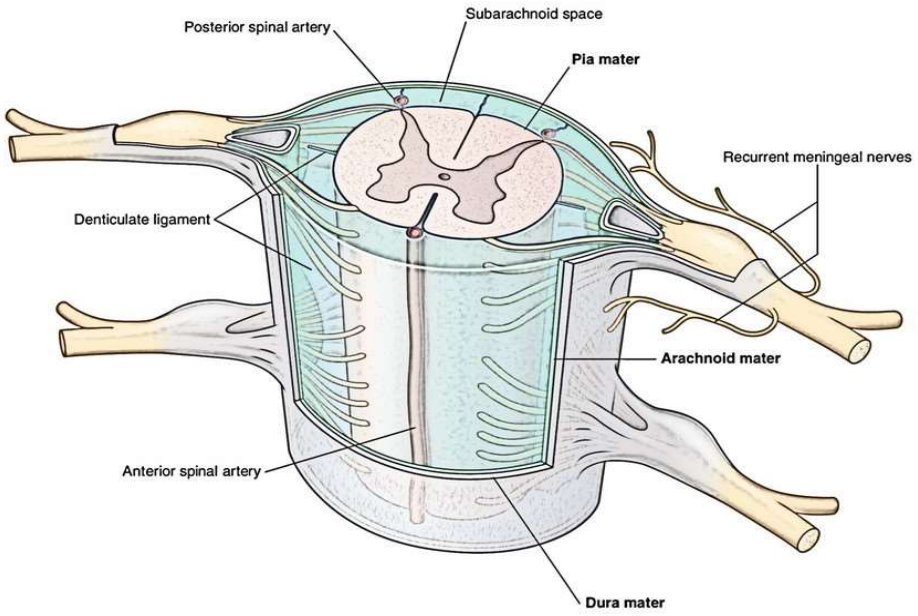

Figure 2: Details of the Subarachnoid Space Required for Spinal Anesthesia [2]

Patient positioning is essential for the success of the procedure and can influence the spread of the anesthetic after administration. There are three different positions commonly used: seated, lateral decubitus, and prone [5, 6, 17]. The seated and lateral decubitus positions are the most commonly employed.

Seated Position – The patient sits at the edge of the table with their back facing the physician, legs hanging off the end of the table, and feet resting on a stool [17,22,29]. The patient should round their shoulders and upper back forward (kyphosis). This posture helps to open the intervertebral spaces.

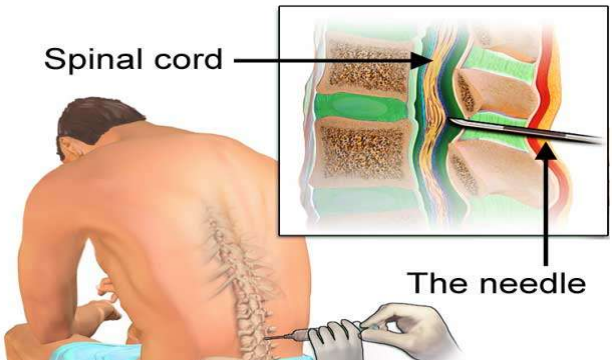

Figure 3: Seated Position [45]

Lateral Decubitus Position – In this position, the patient lies on their side with their back at the edge of the bed, facing the physician [29]. The patient should round their shoulders and keep their legs flexed.

International Journal of Progressive Sciences and Technologies (IJPSAT)
ISSN: 2509-0119.

https://ijpsat.org/
Vol. 47 No. 2 November 2024, pp. 508-534

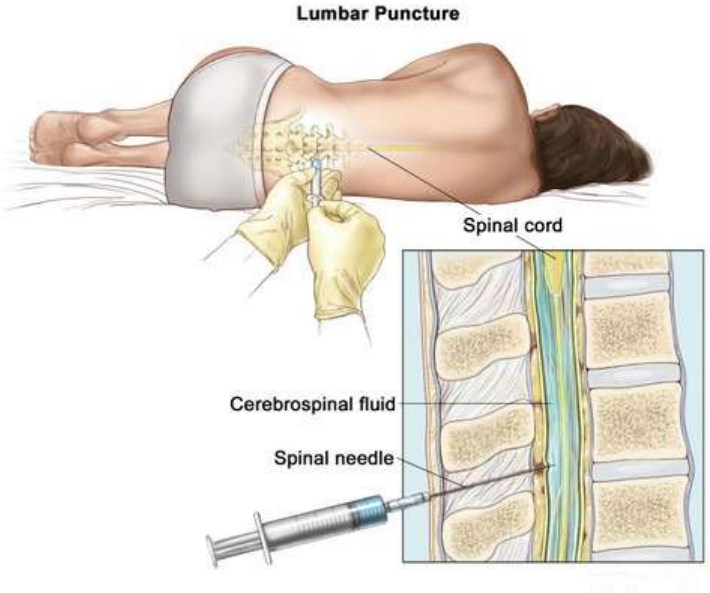

Figure 4: Lateral Decubitus Position [46]

Prone Position – The patient is positioned face down, with their back turned up in a "knife-edge" position [29].

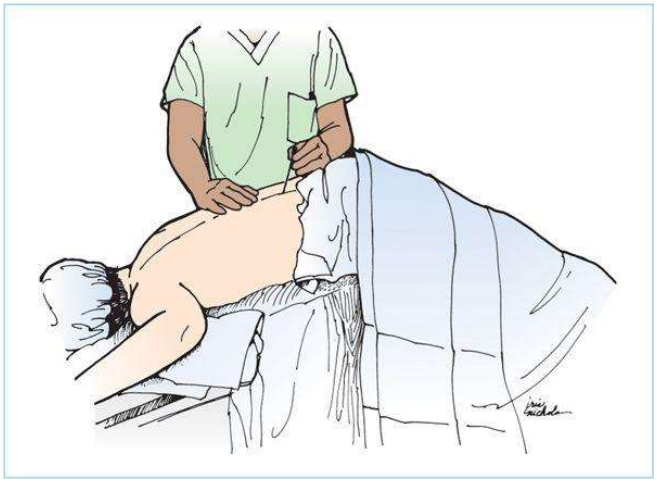

Figure 5: Prone Position [47]

1.1.3. Indications for Spinal Anesthesia

Spinal anesthesia is a technique that is commonly applied, either as a sole method or in combination with analgesia and general anesthesia [6, 29]. It is most frequently used for operations below the umbilicus; however, the use of spinal anesthesia has recently expanded to include some operations above the umbilicus as well as for postoperative analgesia [1, 2, 29]. Cases where spinal anesthesia is utilized include [22, 29]:

- Orthopedic surgery
- Vascular surgery in the legs
- Endovascular repair of aortic aneurysms
- Hernias (inguinal or epigastric)
- Hemorrhoidectomy
- Nephrectomy and cystectomy in combination with general anesthesia
- Transurethral resection of the prostate and transurethral resection of bladder tumors
- Hysterectomy using various techniques
- Cesarean section
- Management of pain during labor and vaginal delivery

Spinal anesthesia is a very good alternative for patients with severe respiratory diseases, such as COPD, as its application in these patients avoids the potential consequences of respiratory deterioration due to intubation and ventilation [1].

.1.4. Contraindications for Spinal Anesthesia

The contraindications for spinal anesthesia can be absolute or relative [1, 2, 3].

Absolute Contraindications [1, 29]:

- Patient does not give consent
- High intracranial pressure
- Infection at the injection site (meningitis)

Relative Contraindications [1, 2, 29]:

- Existing neurological diseases
- Severe dehydration
- Risk of hypotension due to advanced age in patients (40-50 years)
- Obesity
- Urgent surgeries
- Chronic hypertension
- Alcohol consumption
- Thrombocytopenia
- Coagulopathy

1.1.5. Possible Complications of Spinal Anesthesia

Although the possibility of complications is very low, some complications that may occur include: patients may experience back pain after the effect of spinal anesthesia wears off; another potential complication is headaches, dizziness, and nausea [1, 2, 5]. Total spinal anesthesia can also occur, which is a dangerous complication. Other complications include neurological injuries, spinal hematoma, and arachnoiditis.

International Journal of Progressive Sciences and Technologies (IJPSAT)
ISSN: 2509-0119.

https://ijpsat.org/
Vol. 47 No. 2 November 2024, pp. 508-534

1.1.6. Clinical Importance of Spinal Anesthesia

The development of spinal anesthesia has many benefits for patients that general anesthesia cannot provide. For example, spinal anesthesia has made it possible to perform major surgical operations on awake patients [1, 2]. This is a significant benefit for women giving birth, as it allows them to bond with their newborn during the cesarean section while remaining awake. Spinal anesthesia offers numerous advantages for surgeries performed at the lumbar segment of the spinal column and reduces the need for opioid use in these procedures [2]. Patients receiving this type of anesthesia regain bowel function much more quickly and begin physical therapy processes sooner after surgery.

1.2. Application and Characteristics of Epidural Anesthesia

Epidural anesthesia is a regional anesthesia method in which medication is administered into the epidural space surrounding the spinal cord [6, 10]. This technique is ideal for managing perioperative pain, meaning it is used before, during, and after surgical procedures. It is also a preferred technique for childbirth operations, allowing the mother to remain awake during delivery [10, 17]. The development of this type of anesthesia has led to reduced exposure of the human body to other agents, thereby decreasing the possibility of side effects. Furthermore, the benefits of this method have increased, such as lowering cortisol levels, reducing the risk of pulmonary embolism and deep vein thrombosis after surgeries, expediting the return of bowel function postoperatively, and shortening the time patients need to spend in the hospital [10, 11, 12, 29].

1.2.1. History of Epidural Anesthesia

The use of epidural anesthesia began in 1885 when James Corning, an American neurologist, decided to inject cocaine into the subarachnoid space, intending to perform spinal anesthesia [11]. However, his injection occurred in the epidural space of a male volunteer, making it an epidural anesthesia procedure without the neurologist's knowledge. The first known use of epidural anesthesia was in the early 20th century when Jean Sicard and Fernand Cathelin injected cocaine into the epidural space during genitourinary and neurological procedures [11, 12].

1.2.2. Anatomy of the Spinal Column and Physiology of Epidural Anesthesia

Epidural anesthesia is applied in the epidural space of the spinal column [12, 15]. Epidural anesthesia has a broader application than spinal anesthesia. Epidural blocks can be performed at the lumbar (most common), thoracic, and cervical levels, while sacral blocks are referred to as caudal blocks [11, 15, 29]. Standard epidural needles are sized 17-18 gauge. The blunt tip facilitates the penetration of the ligamentum flavum without penetrating the dura mater. The needle is inserted into the skin, passes through the ligamentum flavum, and must be halted before puncturing the dura [29].

There are two techniques to determine the passage of the needle into the epidural space [12]:

1. Loss of Resistance Technique - This is the preferred method [12]. The needle with the stylet inside passes through the subcutaneous tissue until it enters the interspinous ligament, where a resistance increase is observed. The stylet is removed, and 2 ml of solution or air is injected [12, 29]. If the needle tip is still in the ligament, attempting to inject the solution meets with resistance. The needle is advanced deeper, millimeter by millimeter, attempting to inject the solution each time. When in the epidural space, the resistance is lost, and the solution or air is injected [12, 13].

2. Hanging Drop Technique - After entering the spinous ligament, the stylet is removed. This technique requires the initial portion of the needle to be filled with solution, allowing it to remain as a hanging drop [10, 11, 12]. The needle is advanced deeper, millimeter by millimeter, attempting to inject the solution each time. Upon reaching the epidural space, negative pressure is created, thus drawing the hanging drop into the needle.

International Journal of Progressive Sciences and Technologies (IJPSAT)
ISSN: 2509-0119.

https://ijpsat.org/
Vol. 47 No. 2 November 2024, pp. 508-534

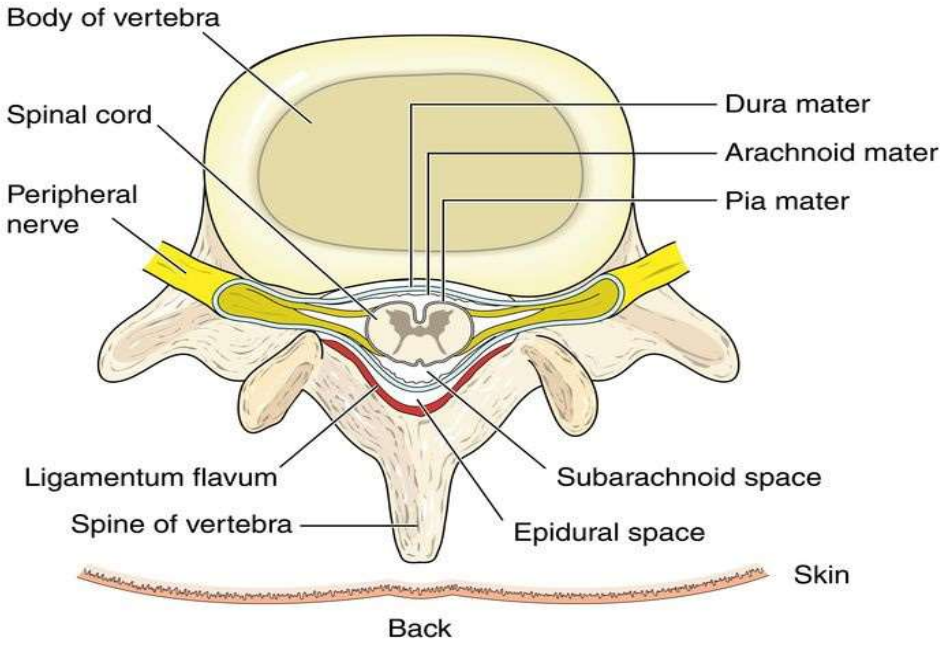

Figure 6: Details of the epidural space [13]

To reach this space, the patient must sit or lie in a lateral decubitus position, so that the epidural anesthetic can be injected [12]. It is advised that the patient forms a curve in the back, as this facilitates the exposure of the vertebral spaces. To inject the agent, physicians use three methods: epidural needles, loss of resistance syringes, and epidural catheters [10]. The latter are used for continuous anesthesia or when prolonged epidural anesthesia is necessary. Once the agent is injected, the effect begins to manifest after 10-20 minutes [11,12,29]. Epidural anesthesia can numb or block the sensation of pain in a specific part of the body.

1.2.3. Indications for Epidural Anesthesia

Epidural anesthesia is beneficial for surgical cases such as operations in the thoracic segment, major abdominal surgeries, and procedures on the spinal column [14,17,29]. Epidural anesthesia is also useful for managing pain during and after surgical sessions [14]. For certain groups of individuals, it is a much more favorable method, as it reduces surgical risks and the likelihood of morbidity, for example, in patients with ischemic heart disease [10]. Additionally, epidural anesthesia lowers the risks associated with pulmonary complications during surgery.

1.2.4. Contraindications for Epidural Anesthesia

Relative Contraindications [10]:

- Aortic stenosis

- Anatomical deformities of the spinal column

- Pulmonary hypertension

Absolute Contraindications [10,14]:

- Patient refusal

- Local infection at the injection site

- Bacteremia

- Increased intracranial pressure

- Therapeutic anticoagulation

- Hemorrhagic diathesis

1.2.5. Possible Complications of Epidural Anesthesia

Although the safety provided by epidural anesthesia has significantly improved in recent years, there are still some complications that may manifest during the use of this type of anesthesia. These complications have a low probability of occurrence but are significant [15,29].

- Dizziness and nausea
- Hypotension
- Meningitis
- Epidural hematoma
- Epidural abscess
- Nerve injury with possible neuropathy – paresis is extremely rare
- Bronchospasm
- Post-surgical headache
- Transient neurological syndrome

1.2.6. Clinical Importance of Epidural Anesthesia

This method is one of the safest anesthesia techniques, which reduces the risks that surgical procedures may pose to individuals. It is of high importance in pediatric anesthesia, as some substances are thought to cause neurological complications in younger age groups [10,12,17].

Figure 7 illustrates a comparison between spinal anesthesia and epidural anesthesia, detailing the injection of anesthetic in both cases.

International Journal of Progressive Sciences and Technologies (IJPSAT)
ISSN: 2509-0119.

https://ijpsat.org/
Vol. 47 No. 2 November 2024, pp. 508-534

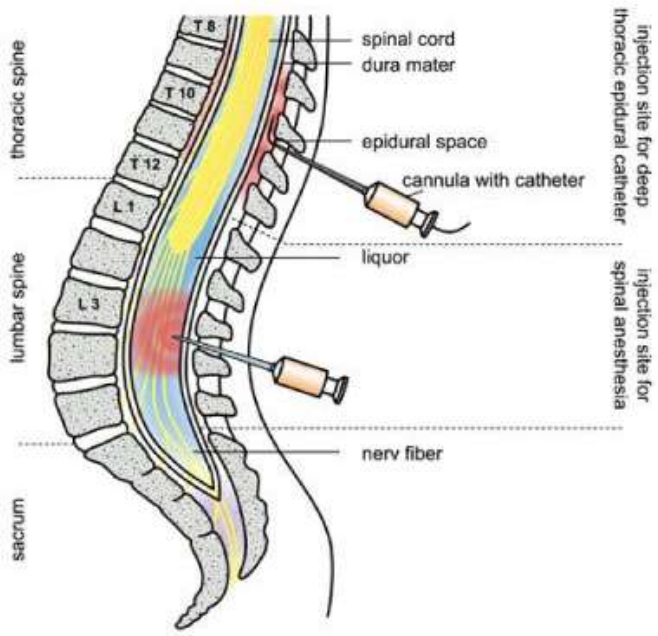

Figure 7: Spinal anesthesia and epidural anesthesia [15]

1.3. Local Anesthetics

The most commonly used local anesthetics for anesthesia include: lidocaine, bupivacaine, tetracaine, mepivacaine, ropivacaine, levobupivacaine, and chloroprocaine [17,29].

1.3.1. Mechanism and Site of Action of Local Anesthetics

Local anesthetics block the transmission of nerve impulses by inhibiting the passage of sodium ions through the selective ionic channels in the neuronal membrane [22]. Sodium channels have a specific receptor for local anesthetics, which is located on the inner side of the channel. They do not affect the transmembrane resting potential or the threshold potential value [22,29].

Local anesthetics are weak bases; therefore, over 50% of the drug remains in a non-ionized and lipophilic form [17]. If the pH of the tissue where the anesthetic is injected is acidic, the fraction of the ionized anesthetic increases. This is why the action of the local anesthetic diminishes when it is injected into metabolically different tissues with an acidic pH [17].

International Journal of Progressive Sciences and Technologies (IJPSAT)
ISSN: 2509-0119.

https://ijpsat.org/
Vol. 47 No. 2 November 2024, pp. 508-534

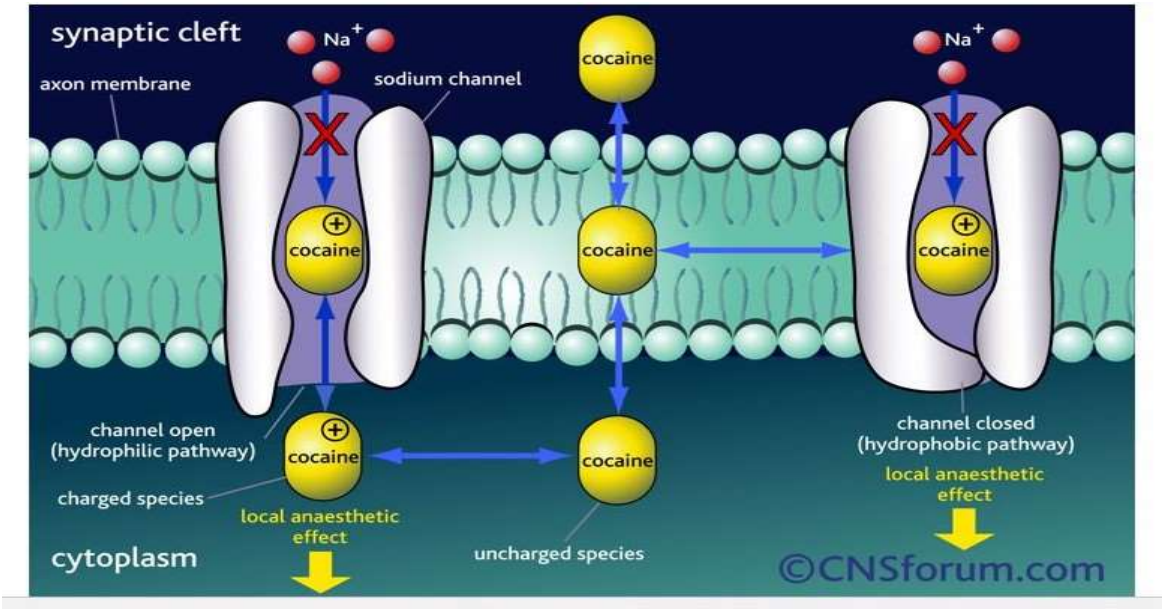

Figure 8: Mechanism of Action of Local Anesthetics and Site of Action [48]

Duration of Action of Local Anesthetics

The duration of action of an anesthetic is related to its lipid solubility [17,29]. Local anesthetics with higher lipid solubility have a longer action because they are more difficult to eliminate from the bloodstream.

1.3.2. Pharmacokinetics of Local Anesthetics

Since local anesthetics are applied or injected very close to the site where their action is required, their pharmacokinetics play an important role in their elimination and toxicity.

The absorption of a local anesthetic injected into the systemic circulation depends on the vascularization of the tissue and is determined by three factors: the site of injection, the presence of vasoconstriction, and the properties of the local anesthetic [17,22,29].

Distribution depends on the amount taken up by the organs, which is determined by tissue perfusion, tissue/blood coefficient, and tissue mass [17].

Metabolism and excretion depend on their chemical structure [17].

1.3.3. Pharmacodynamics of Local Anesthetics

Due to the blockade of sodium channels affecting the continuation of action potentials throughout the body, local anesthetics can exhibit systemic toxicity [17].

Action on the Cardiovascular System

Generally, all local anesthetics cause depression of the myocardial automatism and reduce the duration of the refractory period. At high doses, they can also lead to depression of contractility and a decrease in conductivity [17].

Action on the Central Nervous System (CNS)

The central nervous system is particularly sensitive to the toxicity of local anesthetics [17,22]. Early signs of toxicity that have

International Journal of Progressive Sciences and Technologies (IJPSAT)
ISSN: 2509-0119.

https://ijpsat.org/
Vol. 47 No. 2 November 2024, pp. 508-534

been observed during patient monitoring include numbness, tongue paresthesia, and dizziness. Sensitive complaints may include tinnitus and blurred vision. Additionally, tonic-clonic seizures may also occur [17,22].

Table 1: Types of Local Anesthetics and Their Characteristics [17,22,29]

Local Anesthetics	Application	Concentration	Maximum Dosage (mg/kg)	Duration of Neuroaxial Block
Chloroprocaine	Epidural, Infiltration, Peripheral Nerve Block	1%, 2%, 3%	12	0.5h - 1h
Cocaine	Topical	4%, 10%	3	0.5h - 1h
Procaine	Spinal Anesthesia, Infiltration, Peripheral Nerve Block	1%, 2%, 10%	12	0.5h - 1h
Tetracaine	Spinal, topical	0.2%, 0.3%, 0.5%, 1%, 2%	3	1.5 - 6h
Bupivacaine	Epidural, Spinal, Infiltration, Peripheral Nerve Block	0.25%, 0.5%, 0.75%	3	1.5h - 8h
Lidocaine	Epidural, Spinal, Infiltration, Peripheral Nerve Block, Intravenous Regional, Topical Anesthesia	0.5%, 1%, 1.5%, 2%, 4%, 5%	4.5 7 (with epinephrine)	0.75h - 2h
Mepivacaine	Epidural, Infiltration, Peripheral Nerve Block	1%, 1.5%, 2%, 3%	4.5 7 (me epinephrine)	1h - 2h
Ropivacaine	Epidural, Spinal, Peripheral Nerve Block	0.2%, 0.5%, 0.75%, 1%	3	1.5h - 8h

1.4. Adjuvants and Their Role

Adjuvants are medications that enhance the efficacy or potency of other drugs when administered simultaneously [16]. Although they are beneficial in the management of acute and chronic pain, the use of local anesthetics is limited by their duration of action and dose-dependent adverse effects on the central nervous system and cardiovascular system [17]. Neuroaxial adjuvants are used to improve or prolong analgesia and to reduce the side effects of local anesthetics, which may occur when dealing with high doses of a single local anesthetic agent [18]. In addition to their dose-sparing effects, adjuvants are also used to increase the onset speed of nerve block, improve quality, and extend the duration of nerve blockade [16,17].

A wide variety of drugs have been used for both neuroaxial and peripheral nerve blocks [18]. Adjuvants are broadly classified into non-opioids and opioids. Non-opioids include: α2-adrenoceptor agonists (clonidine and dexmedetomidine),

International Journal of Progressive Sciences and Technologies (IJPSAT)
ISSN: 2509-0119.

https://ijpsat.org/
Vol. 47 No. 2 November 2024, pp. 508-534

acetylcholinesterase inhibitors (neostigmine), midazolam, magnesium, sodium bicarbonate, and opioids, which comprise lipophilic agents (fentanyl and sufentanil) and hydrophilic agents (morphine) [19,20,21]. By adding these adjuvants, the dose of local anesthetics, such as bupivacaine, can be reduced, thus decreasing its side effects, such as myocardial depression, hypotension, bradycardia, heart block, and ventricular arrhythmias [17]. Alpha-2 adrenergic agonists like clonidine have expanded the horizons of regional anesthesia [17]. The co-administration of clonidine and local anesthetics in epidural anesthesia has been used in abdominal surgeries, total knee replacement surgeries, labor analgesia, chronic pain management, and cancer pain treatment [22].

1.4.1. Opioid Adjuvants

Opioids act as agonists at opioid receptors that are widely distributed throughout the body, including the brain (cerebral cortex, thalamus, hypothalamus, amygdala, basal ganglia, brainstem), spinal cord, and non-nervous tissues, such as the gastrointestinal tract [19,23]. The four main classes of opioid receptors are: mu, kappa, delta, and nociceptin, all of which are coupled with inhibitory G protein receptors [23]. Each opioid has a different affinity for these receptor classes, and each class is associated with specific therapeutic effects and side effects. Analgesia from the administration of neuraxial opioids is primarily mediated by pre- and postsynaptic binding to mu-opioid receptors in the gelatinous substance of the posterior horn of the spinal cord [24]. Activation of presynaptic receptors in primary afferent neurons that carry nociceptive information results in a decrease in permeability through calcium channels.

This reduces signaling between the primary afferent neuron and the secondary neuron in the dorsal horn. The binding of postsynaptic opioid receptors in secondary afferent neurons results in hyperpolarization and a reduced propagation of action potentials.

Intrathecal Opioids

Intrathecal opioids potentially act as ligands on opioid receptors in three different areas to produce analgesia [25]:

- They have direct access to the dorsal horn of the spinal cord (their primary site of action).

- They are transported supraspinally through the cerebrospinal fluid (CSF), mainly modulating the inhibition of pain pathways.

- A small amount of the opioid diffuses into the epidural space due to subsequent systemic absorption, resulting in analgesia.

ntrathecal opioids undergo minimal metabolism within the CSF [19,20,25]. The onset and duration of analgesia and the rate of opioid diffusion depend on lipid solubility [22]. Highly lipid-soluble opioids, such as fentanyl and sufentanil, rapidly distribute into the spinal cord and bind to dorsal horn receptors [26]. This results in a rapid onset of analgesia with minimal cephalad spread and a low risk of respiratory depression; however, the duration of analgesia is relatively short. Morphine is poorly soluble in lipids (hydrophilic) and binds to dorsal horn receptors very slowly, resulting in a slow onset of anesthesia but with a longer duration of analgesia [27].

Epidural Opioids

After epidural administration, variable amounts (depending on which opioid is used) will distribute through the dura mater and arachnoid membrane, into the subarachnoid space, to bind to opioid receptors in the dorsal horn of the spinal cord [28]. Lipid solubility is the most important factor affecting the rate of diffusion and the subsequent onset and duration of analgesia. Lipophilic opioids such as fentanyl and sufentanil rapidly diffuse through the dura mater into the CSF compared to hydrophilic opioids like morphine [17,22,28]. Lipophilic opioids produce a rapid onset of analgesia, which has a short overall duration. After epidural distribution, opioid levels in the CSF peak at 6 minutes for sufentanil, 20 minutes for fentanyl, and 1-4 hours for morphine [23].

The epidural space is highly vascularized, resulting in significant absorption of opioids through the epidural venous plexus into the systemic circulation [22,23]. Systemic opioids reach the central nervous system and bind to receptors in brain areas that modulate pain perception and response. Epidural administration of sufentanil, fentanyl, and morphine produces plasma opioid

International Journal of Progressive Sciences and Technologies (IJPSAT)
ISSN: 2509-0119.

https://ijpsat.org/
Vol. 47 No. 2 November 2024, pp. 508-534

levels similar to those observed after intramuscular injection of comparable doses [23,25,27]. Lipophilic opioids, such as sufentanil and fentanyl, are absorbed more quickly and are therefore more likely to cause early respiratory depression [22]. For epidural dosing, plasma levels peak in less than 5 minutes for sufentanil, 5-10 minutes for fentanyl, and 10-15 minutes for morphine [23].

Appropriate Doses

The suitable dose depends on the type of opioid (potency, efficacy, lipid solubility), the indication for use, the addition of other adjuvants, patient condition factors, and the method of administration (Table 2) [29]. Intrathecal drugs have direct access to the central nervous system (CNS) and require relatively small doses for analgesic effect compared to epidural dosing [21]. Intrathecal doses are usually approximately 1/10 of the epidural dose [23].

In neuroaxial anesthesia, both opioids and alpha-2 receptor agonists have beneficial effects [29]. Intrathecal fentanyl and sufentanil not only improve postoperative analgesia but also allow for a reduction in the local dose of the anesthetic. When clonidine or dexmedetomidine were added to intrathecal local anesthetics, the regression of sensory-motor block increased, which was dose-dependent, and postoperative analgesia was prolonged. The potential of intrathecal clonidine compared to dexmedetomidine appears to be 10:1 [23]. In peripheral nerve blocks, when opioids were combined with local anesthetics, no significant improvement in analgesia was reported compared to systemic controls in most studies, except for buprenorphine. Specific factors, such as the type of local anesthetics, the block of upper or lower limbs, are important for its effectiveness. Other adjuvants, apart from low-dose neostigmine, have little significance for neuroaxial anesthesia [29].

Opioids and alpha-2 receptor agonists are important as neuroaxial adjuvants to improve the quality of perioperative and postoperative analgesia in high-risk patients and in the application of outpatient procedures [22,29]. However, in peripheral nerve blocks, the benefits are only found when clonidine is added to local anesthetics under specific circumstances.

Table 2: Ideal Doses for Neuroaxial Opioids [36]

DRUG	INTRATHECAL DOSE	EPIDURAL LOADING DOSE
Fentanyl	10-25µg	50-100µg
Sufentanil	2.5-10µg	10-50µg
Morphine	50-300µg	2-5mg
Diamorphine	300-400µg	2-3mg
Pethidine	Not recommended	25-50mg

Efficacy

Neuroaxial opioids mainly differ in their potential for action, onset, duration of action, and side effects [23,29]. The choice of opioid depends on the indication for neuroaxial analgesia (e.g., labor analgesia, cesarean section, postoperative analgesia), as well as the addition of other adjuvants to achieve analgesia, whether epidural or spinal [28, 29]. Opioids can also be used alone, but are more often used as adjuncts to local anesthetics, with which they have a synergistic effect. When used alone, the benefit of the

International Journal of Progressive Sciences and Technologies (IJPSAT)
ISSN: 2509-0119.

https://ijpsat.org/
Vol. 47 No. 2 November 2024, pp. 508-534

more lipophilic adjuvant is limited by a short duration of effect and dose-related side effects. The most commonly used neuroaxial opioids include morphine, diamorphine, fentanyl, and sufentanil [23,28,29].

Peripheral Pain Mechanisms and Analgesia

In the late 1980s, evidence began to accumulate that the antinociceptive effects of opioids might be mediated by peripheral opioid receptors located on sensory neurons [29]. Some studies suggest that a significant portion of the analgesic effects produced by systemically administered opioids may be mediated by peripheral opioid receptors [22,29].

Research over the past three decades has confirmed the existence of opioid receptors and other excitatory and inhibitory peptide receptors on afferent nerve terminal nerve endings in peripheral tissues [29]. All three classic subtypes of opioid receptors have been demonstrated in peripheral tissues at afferent nerve terminals.

Several clinical studies demonstrate peripheral analgesia with opioids, such as intra-articular injection of opium for knee surgery. One study concluded that morphine had a certain but not satisfactory benefit that lasted 24 hours, surpassing any expected systemic effect [27].

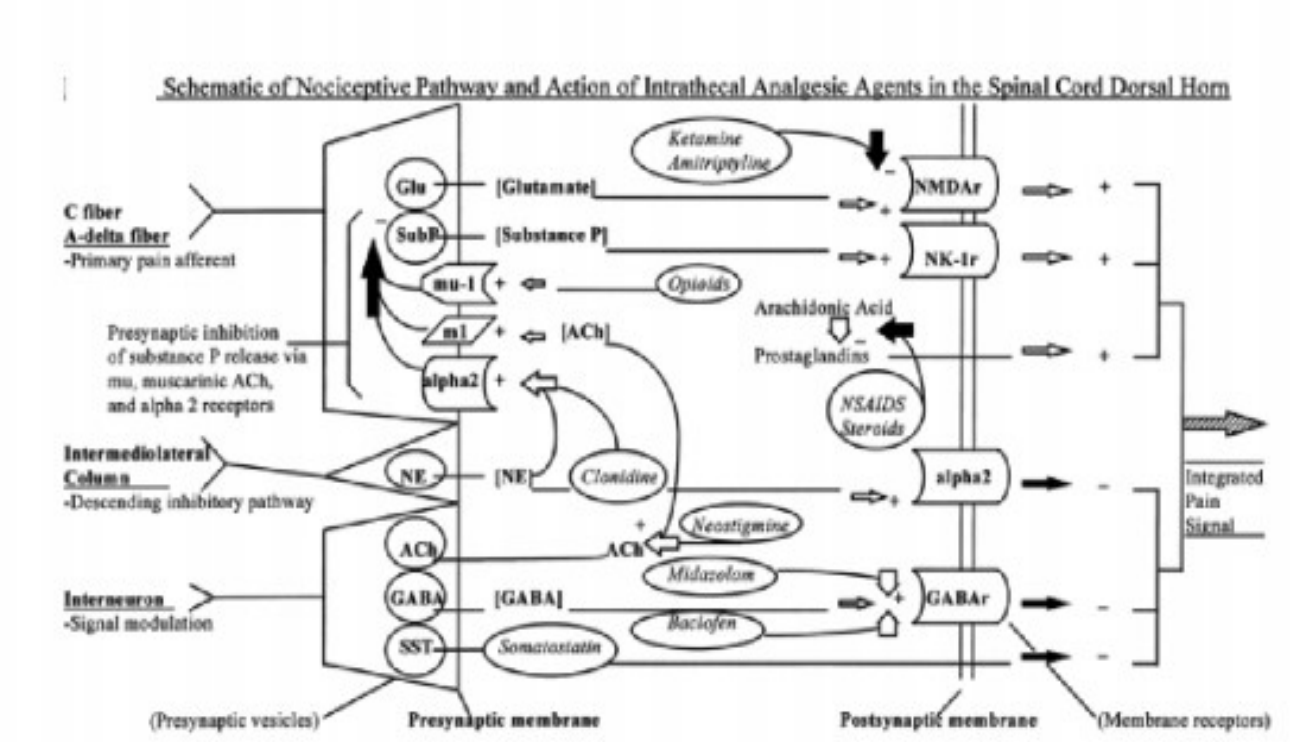

Figure 9: Pathways of Pain Transmission [27]

Neurotoxicity

The neurotoxicity of adjuvants administered alongside local anesthetics remains a significant concern [30]. Many of the adjuvants have not been thoroughly studied with rigorous research that would demonstrate their safety in children at various stages of development. Williams et al. compared clonidine, buprenorphine, dexamethasone, and midazolam, finding that at clinically significant concentrations, these agents were less neurotoxic to mouse neurons than ropivacaine [31].

International Journal of Progressive Sciences and Technologies (IJPSAT)
ISSN: 2509-0119.

https://ijpsat.org/
Vol. 47 No. 2 November 2024, pp. 508-534

Intraoperative Analgesia

Opioids are usually added to local anesthetics for surgeries performed with epidural and spinal anaesthesia [30].

Epidural Analgesia during Labor

Opioids have a synergistic effect with local anesthetics [29,30]. This allows for the use of lower doses of local anesthetics, which in turn reduces the frequency and severity of maternal hypotension and motor blockade. Epidural opioids improve the quality of analgesia and decrease the number of epidural failures due to segmental blocks [30]. Various opioids can be used; however, those with low lipid solubility, such as morphine, are associated with delayed respiratory depression and should be used cautiously.

Fentanyl is the most commonly used adjuvant for labor analgesia [30]. Intrathecal opioids are also effective for labor analgesia; however, no single intrathecal drug can reliably provide analgesia for the entire duration of labor.

Specific Opioids:

- Fentanyl: Fentanyl is a highly potent lipophilic phenylpiperidine derivative [23,29,30]. It has a rapid onset of action (5 minutes intraspinal, 10 minutes epidural) and a relatively short duration of action due to redistribution (2-4 hours intraspinal and epidural). Its terminal half-life is approximately 190 minutes, and if repeated in high doses, it may result in accumulation. Due to its high lipid solubility, it quickly binds to receptors in the dorsal horn of the spinal cord after neuroaxial administration. Epidural bolus doses can lead to early respiratory center depression due to systemic absorption. Its rapid onset is beneficial for labor analgesia and urgent cesarean delivery; however, its short duration limits its analgesic effect postoperatively after a single dose with spinal anesthesia.

- Sufentanil: Sufentanil is an extremely potent lipophilic phenylpiperidine derivative [23,30]. It has a faster onset (2-3 minutes intraspinal, 4-6 minutes epidural) and a shorter duration of action compared to fentanyl (1-3 hours intraspinal and epidural). Its analgesic potential is 5-7 times greater than fentanyl, and it is 1600 times more lipid-soluble than morphine. Its terminal elimination half-life is shorter than fentanyl's (150 minutes), making accumulation less likely. Like fentanyl, the intraspinal administration of sufentanil for postoperative analgesia is limited by its short duration of action.

- Morphine: Morphine is a hydrophilic phenanthrene derivative and is approximately 100 times less potent than fentanyl [23,27,29,30]. Its onset is slow compared to lipophilic opioids (15 minutes intraspinal, 30 minutes epidural), and it has a significantly longer duration of action (approximately 12-24 hours). The half-life of elimination is approximately 170 minutes. Intrathecal morphine binds slowly to receptors in the dorsal horn of the spinal cord due to its poor lipid solubility, and free opioid in CSF can migrate to the supraspinal space, leading to delayed respiratory depression. Neuraxial morphine has been shown to be effective, providing similar improvements in the quality of analgesia for labor pain, cesarean delivery, and is more effective than a single dose of fentanyl in providing postoperative pain relief [23,27,29,30]. Unfortunately, both intraspinal and epidural morphine are associated with a higher incidence of nausea, vomiting, itching, urinary retention, sedation, and delayed respiratory depression compared to fentanyl.

In the context of postoperative analgesia after cesarean delivery, both forms of anesthesia have been applied where a single dose of morphine was given. Morphine applied via intraspinal and epidural anesthesia has been shown to have a high analgesic effect; at doses greater than 100µg (intraspinal) and 3.75mg (epidural), it is associated with an increased incidence of side effects (especially pruritus).

- Diamorphine: Diamorphine is primarily used in the United Kingdom. It is a lipophilic semi-synthetic opioid, about twice as potent as morphine [23,30]. It is a product that is converted to its more active metabolites (morphine and 6-monoacetylmorphine) through deacetylation in the liver and nervous tissue. Diamorphine is 280 times more lipid-soluble than morphine, so delayed respiratory depression is less common. The incidence of nausea and vomiting is significantly lower than that of morphine. Diamorphine has a rapid onset of action (<10 minutes) and a long duration of action (10-20 hours intraspinal and epidural). It has a similar efficacy to fentanyl when used for intraoperative analgesia. It is commonly used for pain relief after cesarean surgery. The duration and quality of analgesia produced by intraspinal diamorphine are similar to that produced by epidural diamorphine;

International Journal of Progressive Sciences and Technologies (IJPSAT)
ISSN: 2509-0119.

https://ijpsat.org/
Vol. 47 No. 2 November 2024, pp. 508-534

however, the incidence of itching is higher with intraspinal administration. Although the epidural administration of mixtures of bupivacaine and diamorphine has been shown to provide better analgesia for operative labor.

Unwanted Effects

The unwanted effects of neuraxially administered opioids may potentially result from the spread of the opioid in the cerebrospinal fluid (CSF) or from systemic absorption from the epidural space, which can lead to adverse effects similar to those observed after parenteral administration [29]. Intraspinal and more hydrophilic opioids are more likely to cause side effects due to the migration of the substance, while epidural and lipophilic opioids are more likely to cause side effects due to systemic absorption. Most side effects are dose-related and result from interactions with opioid receptors. The classical side effects of neuraxial opioids include:

- **Pruritus (itching).** Itching is the most common side effect of neuraxial opioids [22,29]. It occurs within the first few hours and is usually localized to the face, neck, and thorax. The mechanism for itching is not fully understood, but it is thought to be mediated by the cephalic migration of the opioid, which binds to opioid receptors in the trigeminal nucleus. It is more common when using poorly lipid-soluble agents (for example, there is a 70% incidence of itching with intrathecal morphine compared to 10% for fentanyl). Histamine-1 receptor antagonists may be helpful, although itching is not mediated by histamine release. Opioid receptor antagonists, such as naloxone, are most effective in managing itching but may reduce analgesic effects.
- **Nausea and vomiting.** The incidence of nausea and vomiting associated with neuraxial opioids is reported to be between 20-50% [22,29]. It is more common in females. It is thought to be mediated by the cephalic migration of the opioid to the chemoreceptor trigger zone, where opioids may act as a partial agonist at dopamine-2 receptors.
- **Urinary retention.** The incidence of urinary retention is approximately 30-40% [22,29]. It is more common in young males when morphine is administered intraspinally. It is mediated by opioid receptors in the sacral spinal cord.
- **Respiratory depression.** This is potentially the most serious side effect caused by neuraxial opioids. The incidence after neuraxial administration is similar to that of opioids administered parenterally [29]. Factors that increase the risk of respiratory depression include high doses of opioids, elderly patients, concurrent use of sedative and analgesic medications, lack of opioid tolerance, and the presence of comorbid factors (e.g., sleep apnea and pulmonary diseases).

1.4.2. Sodium Bicarbonate

Sodium bicarbonate can be used to expedite the onset of action of epidural lidocaine [30,32]. It is not commonly used with other neuraxial agents. For epidural lidocaine to exert its effects, the extraneural local anesthetic must diffuse across the nerve membrane to enter the voltage-gated sodium channels, which reversibly block sodium channel permeability. Lidocaine exists as a weak base [30]. Only the unionized form is lipid-soluble and can easily distribute throughout the lipid portion of nerve membranes. The more alkaline the solution, the greater the fraction of unionized lidocaine.

Adding 8.4% sodium bicarbonate to lidocaine raises the pH, thereby increasing the fraction of the un-ionized form [32]. This allows a greater amount of local anesthetic to diffuse across the nerve membrane. The permitted dose of this adjuvant is 1ml of 8.4% NaHCO3 for every 10ml of lidocaine (Table 3) [30].

Alkalinization of the lidocaine solution results in a faster onset of nerve block; improved depth of the block may also increase the spread of the epidural block [32]. This is especially useful for epidural anesthesia in obstetric surgeries when urgent cesarean delivery is required. The increase in the fraction of the unionized form will allow the local anesthetic to diffuse into the spinal nerves in the epidural space as well as assist diffusion through the dura and arachnoid to reach the subarachnoid space. This may accelerate the onset of the block by 2-5 minutes [30].

International Journal of Progressive Sciences and Technologies (IJPSAT)
ISSN: 2509-0119.

https://ijpsat.org/
Vol. 47 No. 2 November 2024, pp. 508-534

Table 3: Ideal Doses of Adjuvants for Local Anesthesia [30]

Drug	Bolus Dose (mcg/kg)	Infusion (mcg/kg/hr)
Morphine	10-30 (> 50 leads to excessive side effects)	3-8
Hydromorphone	3 -4	2-4
Fentanyl	0.2-1.0 (max. 50 mcg/hr)	0.5-1.0
Clonidine	0.5-2	0.1-0.2
Ketamine	500 – 1000 (max: 100 **mg**)	NA
Butophanol	20 - 40 (lessens opioid side effects)	
Sodium Bicarbonate	1 mg/ml of lidocaine 0.1 mg/ml of bupivacaine, ropivacaine or levobupivacaine	NA

1.4.3. Vasoconstrictors

Vasoconstrictors act as agonists at G-protein-coupled receptors located in the smooth muscle of blood vessels [23,29,30]. Ligand binding stimulates phospholipase C, resulting in calcium influx and vasoconstriction of blood vessels. This reduces vascular absorption of the local anesthetic and maintains a higher concentration at the nerve roots for a longer period. This can significantly prolong the duration of the blockade, especially in highly vascular areas such as the epidural space. Epinephrine is the most commonly used vasoconstrictor adjunct for local anesthetics. The ideal dose of this adjuvant is 1:200,000 (5 µg/ml of an epidural solution) [30].

- Efficacy

The reduction of vascular absorption of the local anesthetic to maintain a higher concentration at the nerve root results in improved quality of motor block and extended duration of the blockade [23,29]. Delayed vascular absorption decreases plasma levels of local anesthetics and therefore increases the risk of systemic toxicity of the local anesthetic. This allows the safe use of higher doses of some agents when combined with epinephrine; i.e., the maximum recommended dose of lidocaine when used alone is 4 mg/kg compared to 7 mg/kg when combined with epinephrine 1:200,000 [30]. This is useful in extensive procedures or when repeated doses of lidocaine are required. The addition of epinephrine to lidocaine or chloroprocaine for use in the epidural space has been shown to reduce systemic absorption by approximately 30% and significantly extend the duration of the nerve block [29,30]. Agents with high lipid solubility, such as bupivacaine, bind more to tissues and have less systemic absorption compared to less soluble agents. The addition of epinephrine to bupivacaine for use in the epidural space reduces systemic absorption by about 10-20% and is less effective in prolonging the block compared to lidocaine [29,30]. Most local anesthetics have intrinsic vasodilatory properties at low doses. Ropivacaine is an exception, as it has mild vasoconstrictive properties, and the addition of epinephrine has minimal effect on reducing systemic absorption or prolonging the nerve block [23,30].

- Side Effects

An increase in plasma epinephrine levels can be observed after neuraxial administration of local anesthetic solutions containing epinephrine [33,34]. Epinephrine is an agonist at both alpha and beta adrenoceptors and may cause tachycardia and hypertension in a dose-dependent manner. The use of epinephrine may not be advisable in patients with unstable angina, uncontrolled hypertension, or recent myocardial infarction [35]. Solutions containing epinephrine should be used cautiously in patients undergoing general anesthesia with halothane due to the risk of cardiac arrhythmias. The use of high doses of epinephrine in the epidural space may potentially increase the risk of spinal artery thrombosis; however, there is no definitive evidence for this. Solutions containing epinephrine should not be used in intraspinal and epidural anesthesia [33,34,35]. Solutions containing epinephrine should be used cautiously in patients receiving antidepressant medications. Additionally, caution should be exercised in women suffering from pre-eclampsia, as systemic absorption of epinephrine may further elevate blood pressure [29].

International Journal of Progressive Sciences and Technologies (IJPSAT)
ISSN: 2509-0119.

https://ijpsat.org/
Vol. 47 No. 2 November 2024, pp. 508-534

1.4.4. Clonidine

Clonidine is a partial alpha-2 adrenoceptor agonist that acts centrally [36]. Its analgesic effect is thought to be mediated by postsynaptic alpha-2 receptors (inhibitory receptors associated with G proteins) in the dorsal horn of the spinal cord, resulting in decreased nociceptive transmission. The ideal dose for epidural administration is 75-150µg as a bolus, while for spinal administration it is 30-60µg [30,36].

- Efficacy

When used as a neuraxial adjunct for pain relief after cesarean delivery and in orthopedic surgery, clonidine increases the duration of analgesia and anesthesia [36]. Obstetric studies have shown that for cesarean delivery with spinal anesthesia, intrathecal clonidine when administered at 30-60µg increases the duration of sensory block by approximately 30%, also delaying the onset of postoperative pain and reducing overall postoperative opioid requirements [29,35,36]. The addition of clonidine to opioids for postoperative analgesia as continuous epidural therapy reduces opioid requirements by between 20-60% [23]. Dosing regimens that include a bolus dose followed by continuous infusion appear to produce superior analgesia. Clonidine is a very useful adjuvant for epidural analgesia during surgeries. It has been shown to reduce the requirements for local anesthetics and has an analgesic effect when combined with 0.125% bupivacaine +/- fentanyl 2 µg/ml [36].

- Side Effects

Sedation, hypotension, and bradycardia are the main adverse effects of neuraxial clonidine [36]. Cardiovascular effects are usually observed within 15 to 30 minutes of epidural administration and can last up to 3 hours. Changes in blood pressure are dose-dependent. Clonidine does not produce respiratory depression but seems to increase the risk of nausea, vomiting, urinary retention, or itching when combined with other neuraxial opioids.

1.4.5. Neostigmine

Neostigmine acts by inhibiting acetylcholinesterase and preventing the breakdown of acetylcholine [29,36]. The increase in acetylcholine concentration makes binding available for muscarinic and nicotinic receptors in the dorsal horn of the spinal cord, providing analgesia without motor or sympathetic blockade. The ideal doses are 50-100µg as a bolus for epidural administration (for postoperative pain) and 300-500µg as a bolus for epidural administration (for labor analgesia) [23,36].

- Efficacy

Neostigmine administered intrathecally enhances analgesia through interaction with opioids administered systemically and neuraxially, but a high incidence of severe nausea and vomiting precludes its use via this route [36].

- Epidural

Epidural neostigmine provides modest analgesia in postoperative patients as evidenced by results contributing to a small reduction in pain and decreased opioid consumption [29,36]. The magnitude of this effect is similar to that achieved by simple analgesics. Epidural neostigmine also increases the duration and intensity of analgesia from systemic and neuraxial alpha-2 adrenoceptor agonists, opioids, and local anesthetics [36].

- Side Effects

Unlike intrathecal neostigmine, epidural neostigmine is not associated with an increased risk of nausea and vomiting; however, doses greater than 100µg have been associated with sedation [29]. It does not cause respiratory center depression or itching when used alone or even in combination with other neuraxial opioids [36].

1.4.6. Ketamine

Ketamine is a non-competitive NMDA receptor antagonist [36,37,38]. Its primary analgesic effect is mediated by antagonism of NMDA receptors located on secondary afferent neurons in the dorsal horn of the spinal cord. This reduces the transmission of nociceptive information in the spinal cord and plays an important role in preventing central sensitization, which encompasses all

chronic pain [37,38]. At high doses, it may have slight additional analgesic effects by binding to mu-opioid receptors. For intrathecal use, this adjuvant is not recommended, while for epidural use, a dose of 0.5-1.0 mg/kg is recommended [36].

- Efficacy

There are limited human studies on the use of intrathecal ketamine due to the potential risk of neurotoxicity from its chloride [30,37,38]. In a human study of intrathecal ketamine, doses above 50 mg resulted in local anesthetic effects [30]. Results from animal studies suggest that intrathecal administration of ketamine may cause complete sensory and motor block [29]. Numerous studies have evaluated the efficacy of epidural ketamine when used as a single agent or in combination with opioids and other local anesthetics for postoperative pain. Epidural ketamine appears to accelerate the onset of analgesia and prolong the duration of analgesia, particularly when combined with epidural morphine. When used as an adjunct to local anesthetics for postoperative pain, epidural ketamine has been shown to be effective in enhancing pain reduction and has an effect on reducing dosage [36].

- Side Effects

Reported side effects of epidural ketamine include sedation, headache, and transient back pain during injection with doses greater than 0.5 mg/kg [37,38]. No clinical trials have reported respiratory depression, hallucinations, cardiovascular instability, urinary bladder dysfunction, or neurological deficits when the epidural dose has been up to 1 mg/kg [37,38]. There is no increase in the incidence of nausea, vomiting, or itching when combined with neuraxial opioids.

1.4.7. Midazolam

Midazolam is a benzodiazepine and an agonist of the GABA-A receptor [30,39]. GABA-A receptors are ligand-gated receptors located throughout the central nervous system (CNS), and GABA is the main inhibitory neurotransmitter of the CNS [39]. The binding of GABA results in a change in the receptor's configuration, causing the opening of an ion channel that allows chloride ions to flow down their electrochemical gradient into the cell. This results in hyperpolarization of the neuron and a reduction in the propagation of the action potential. Benzodiazepines have their own binding site (called the benzodiazepine receptor) on the GABA-A receptor [29,36,39]. The effect of binding increases the frequency of chloride channel openings, enhancing the effects of GABA. The gelatinous substance of the dorsal horn of the spinal cord contains a high density of GABA-A receptors. Benzodiazepines likely mediate their analgesic effect by increasing the inhibition of nociceptive neurons in this area. The appropriate doses are 20 µg/kg (up to 2.5 mg) for intrathecal use, and 10-20 µg/kg/hour for up to 12 hours in the epidural [36,39].

-Efficacy

Intrathecal midazolam prolongs the duration of spinal anesthesia, reduces postoperative analgesic requirements, and decreases the incidence of nausea and vomiting [30,36,39]. Although there are limited studies, it has also been shown that epidural midazolam used as a continuous infusion for postoperative analgesia reduces postoperative analgesic requirements and the incidence of nausea and vomiting. In addition to local anesthetics, midazolam can be combined with other medications such as opioids, clonidine, and ketamine for additional anesthetic effects.

-Side Effects

There are limited studies evaluating the clinical safety of intrathecal midazolam [36,39]. The most serious side effect observed in animal studies is neurotoxicity. Doses up to 2.5 mg have not been shown to cause any neurological deficits in humans.

1.4.8. Dexmedetomidine

As valuable adjuncts to local anesthetics, α-2 receptor agonists possess sedative properties and analgesic actions at peripheral, spinal, and supraspinal levels [30,36,40]. Dexmedetomidine—an extremely selective α-2 receptor agonist—has been demonstrated to have a strong synergistic action with local anesthetics. Furthermore, when used via the epidural route, dexmedetomidine has shown numerous beneficial effects. It acts at both pre- and postsynaptic nerve terminals as well as in the central nervous system, reducing the release of norepinephrine, resulting in sedative, anxiolytic, analgesic, and sympatholytic effects. Dexmedetomidine causes dose-dependent bradycardia and hypotension [40].

International Journal of Progressive Sciences and Technologies (IJPSAT)
ISSN: 2509-0119.

https://ijpsat.org/
Vol. 47 No. 2 November 2024, pp. 508-534

The analgesic effect of dexmedetomidine is mediated at the spinal level [36,40]. In the dorsal root neuron, α-2 receptor agonists inhibit the release of substance P in the nociceptive pathway. By inhibiting norepinephrine release, α-2 receptors located in nerve endings may play a role in analgesia. Despite evidence of the supraspinal and peripheral actions of dexmedetomidine, the spinal mechanism tends to be considered the primary mechanism responsible for its potent analgesic effects [40].

Although the prolonged duration of sensory blockade with dexmedetomidine may improve postoperative pain management, delayed recovery of motor function may have its disadvantages and may be unsuitable for outpatient surgical procedures [29,40]. The decrease in heart rate caused by α-2 agonists may be explained by their central action, mediated by a reduction in synaptic output and enhanced norepinephrine release. Higher doses of epidural dexmedetomidine are recommended cautiously in long surgical procedures to avoid delayed motor recovery and unwanted side effects [30,40].

Alpha-2 adrenergic antagonists, such as clonidine and dexmedetomidine, are among the most widely used classes of adjuncts for local anesthesia.

2. Objective of the Study

The aim of this study is to define and differentiate spinal and epidural anesthesia. Additionally, the study places significant emphasis on the types of adjuvants and their application methods in spinal and epidural anesthesia. It is intended that the recommended doses of each adjuvant will be reviewed, and their efficacy will be evaluated. The study also aims to detail the potential side effects of each adjuvant and their ideal use in various situations.

3. Materials and Methods

Due to various limitations, this study was conducted solely based on secondary data. For the purposes of this work, a literature review methodology was used as the only primary approach. The literature was sourced from credible and globally recognized platforms such as PubMed, MedLine, The American Journal of Medicine, as well as local literature. The types of literature utilized for this study include scientific articles from reputable journals, professional books, and articles published in prestigious magazines.

4. Discussion

As mentioned earlier, clonidine has demonstrated efficacy in prolonging anesthesia duration in both spinal and epidural anesthesia cases. In instances where spinal anesthesia is utilized, clonidine has been shown to reduce postoperative pain and the need for opioid medications during the postoperative period [36]. In the case of epidural anesthesia, it also decreases the requirement for opioid use and exhibits analgesic effects. This is further corroborated by a study conducted by Prasad et al., who analyzed the effects of epidural clonidine in spinal anesthesia in patients undergoing gynecological surgical procedures [41]. This study randomly selected 60 participants, and the study design was blinded, meaning none of the participants were aware of the treatment they would receive. The study examined a combination of spinal and epidural anesthesia.

As observed, the use of clonidine in combined spinal-epidural anesthesia produced longer-lasting analgesia and extended the duration of sensory and motor blockade. The results showed a significant difference; for example, the group that received clonidine treatment began to experience sensory blockade on average 37.8 seconds after treatment (Table 4) [41]. In contrast, the other group experienced sensory blockade after an average of 50.3 seconds (Table 4). Additionally, the duration of analgesia in the clonidine-treated group was approximately 299 minutes, while for the other group, it was only 152 minutes (Table 4). Therefore, this confirms that the use of clonidine in spinal-epidural anesthesia nearly doubled the duration of sensory-motor blockade.

International Journal of Progressive Sciences and Technologies (IJPSAT)
ISSN: 2509-0119.

https://ijpsat.org/
Vol. 47 No. 2 November 2024, pp. 508-534

Table 4: Effect of Clonidine Use in Spinal-Epidural Anesthesia [41]

Outcome variables	Group C	Group S	*P*
Onset of sensory block at L_1 (s)	37.83±8.58	50.33±8.80	<0.001**
Time to Bromage 3 (s)	54.33±7.74	102.00±73.17	0.001**
Time to 2 segment regression (min)	193.67±19.82	109.33±18.56	<0.001**
Duration of motor block (min)	343.00±32.92	221.00±29.17	<0.001**
Total duration of analgesia (min)	299.00±43.38	152.50±21.04	<0.001**

**Clinically significant if $P < 0.05$

Another study by Braga examined the effects of three adjuvants, specifically morphine, clonidine, and sufentanil, in cesarean cases with spinal anesthesia [42]. This study involved 96 patients who were divided into four groups. The first group received no adjuvants, the second group received sufentanil, the third group received clonidine, and the fourth group received morphine. It has been previously noted that the use of morphine may be associated with severe side effects and may result in high analgesia [30,36]. Morphine provides a slower effect but has a longer duration. Sufentanil, on the other hand, is noted to provide a rapid effect, as it distributes quickly in the spine. However, the effect of sufentanil dissipates more quickly than, for example, morphine. The study by Braga demonstrated similar phenomena. Thus, the group that received morphine experienced motor blockade for more than two hours after the operation, confirming the effect of morphine on the duration of anesthesia (Table 5) [42]. Although the duration of anesthesia was longer in the group that received sufentanil, Braga states that this may occur due to the amount that was used. The common side effects of morphine were not present in this study. The study also confirmed that the addition of sufentanil and clonidine as adjuvants to the agent bupivacaine provides sufficient analgesia for cesarean operations.

Table 5: Effect of Different Adjuvants in Spinal Anesthesia [42]

	Group I	Group II	Group III	Group IV	p
Latency (min)*	6.00 ± 1.66 #	4.54 ± 1.95	4.16 ± 1.37	4.29 ± 1.23	< 0.01
Maximum Degree of Motor Block**					0.45
3	24	24	24	24	
Maximum Level of Sensory Block**					0.3
T2	02 (8.3%)	05 (20.8%)	02 (8.3%)	05 (20.83%)	
T4	18 (75.0%)	18 (75.0%)	17 (70.83%)	14 (58.34%)	
T6	03 (12.5%)	01 (4.16%)	04 (16.7%)	05 (20.83%)	
T8	01 (4.16%)	00 (0%)	01 (4.16%)	00 (0%)	
Time to Motor Block Recovery (min)*	149.45 ± 26.86	201.87 ± 42.60 ¶¶	177.66 ± 45.95	255.12 ± 73.32 ¶	< 0.001
Total Duration of Analgesia (min)*	148.37 ± 23.55	269.12 ± 58.67	138.69 ± 39.33	167.82 ± 40.52	< 0.01

We have highlighted the rapid effect of fentanyl, specifically 5-10 minutes, while for morphine, it takes about 10-15 minutes for the effect to manifest [29,30,36]. Shah analyzed the effects of these two adjuvants in surgeries below the umbilicus that utilize spinal-epidural anesthesia [43]. This study also confirms that fentanyl begins its action more quickly but has a shorter duration. In contrast, morphine lasts longer but is associated with serious side effects. We previously noted effects such as nausea, vomiting, and respiratory center depression. Shah confirmed similar results, with a particular emphasis on respiratory center depression in patients. Thus, the side effects of morphine are consistently confirmed by almost every study to be severe, even though it has the benefit of providing longer-lasting anesthesia.

We have also analyzed the application of dexmedetomidine, highlighting the benefits it offers in terms of the duration of anesthesia [36]. The greatest benefit is that it allows for easier management of pain following surgical procedures. Boules confirmed the same in his study, which examined the effect of dexmedetomidine in epidural anesthesia [44].

5. Conclusion

We have seen that spinal and epidural anesthesia differ based on the location where the anesthetic is injected. In the case of spinal anesthesia, the anesthetic is injected into the subarachnoid space located between the pia mater and the arachnoid mater, in the lumbar segment of the spinal column. One of the greatest benefits that spinal anesthesia offers is the possibility of performing the surgical procedure on awake patients. Epidural anesthesia is administered in the lumbar region of the spinal column. This type of anesthesia is ideal for managing pain after surgical procedures.

Adjuvants are agents used in conjunction with spinal and epidural anesthesia. The purpose of using adjuvants is to increase the duration of analgesia, especially when needed for longer surgical procedures, as well as to reduce the likelihood of side effects that may occur. Adjuvants can be divided into two major groups: opioids and non-opioids. Lipid solubility is the most important factor affecting the speed of diffusion and the onset and subsequent duration of analgesia.

Highly lipid-soluble opioids, such as fentanyl and sufentanil, distribute quickly to the spinal cord and bind to the receptors in the dorsal horn rapidly. This produces a quick onset of analgesia with minimal cephalad spread and a low risk of respiratory center depression; however, the duration of analgesia is relatively short.

Morphine is poorly soluble in lipids (hydrophilic) and is very slow to bind to the dorsal horn receptors, resulting in a slow onset of anesthesia but a longer duration of analgesia.

Intrathecal drugs have direct access to the central nervous system (CNS) and require relatively small doses for analgesic effect compared to epidural dosing. Intrathecal doses are usually approximately 1/10 of the epidural dose.

Opioids can be used alone, but they are more commonly used as adjuncts to local anesthetics, with which they have a synergistic effect. When used alone, the benefits of the more lipophilic adjuvant are limited by a short duration of effect and dose-related side effects. The most commonly used neuraxial opioids include morphine, diamorphine, fentanyl, and sufentanil.

Fentanyl is the most commonly used adjuvant for labor analgesia. Its rapid onset is beneficial for labor analgesia and urgent cesarean delivery; however, its short duration of action limits its analgesic effect postoperatively after a single dose with spinal anesthesia.

Neuraxial morphine has been shown to be as effective as fentanyl in improving the quality of analgesia for labor pain, cesarean delivery, and more effective than a single dose of fentanyl in providing postoperative pain relief [23,27,29,30]. Unfortunately, both intrathecal and epidural morphine are associated with a higher incidence of nausea, vomiting, pruritus, urinary retention, sedation, and delayed respiratory center depression compared to fentanyl.

Sodium bicarbonate can be used to accelerate the onset of action of epidural lidocaine. It is not usually used with other neuraxial agents.

Vasoconstrictors reduce the vascular absorption of local anesthetic and maintain a higher concentration at the nerve roots for a longer period. This can significantly prolong the duration of the block, especially in highly vascular areas such as the epidural space. Epinephrine is the most commonly used vasoconstrictor adjunct for local anesthetics.

When used as a neuraxial adjunct for pain relief after cesarean delivery and in orthopedic surgery, clonidine increases the duration of analgesia and anesthesia for cesarean delivery with spinal anesthesia. Clonidine given intrathecally at 30-60μg increases the duration of the sensory block by approximately 30%, also delaying the onset of postoperative pain and reducing overall postoperative opioid requirements.

Dexmedetomidine has been shown to have numerous beneficial effects when used via the epidural route. It acts on both pre- and postsynaptic nerve terminals and in the central nervous system, reducing the release of norepinephrine, with sedative, anxiolytic, analgesic, and sympatholytic effects.

This topic has explored experimental articles where various adjuvants have been applied in different surgical procedures. The results have been consistent with our theories regarding the applications of types of adjuvants, their duration, and their potential side effects. Since most adjuvants are still in the early stages, where much research is still needed to confirm their characteristics, the numerous experiments conducted have focused on adjuvants such as morphine, clonidine, sufentanil, dexmedetomidine, and fentanyl.

7. Summary

Introduction: The development of epidural and spinal anesthesia has brought great benefits to various surgeries. Spinal anesthesia is a process where the anesthetic agent is injected into the subarachnoid space located in the lumbar segment of the spine. Indications for this type of anesthesia include patient consent, performance in surgeries below the neck and umbilicus. Contraindications can be divided into absolute and relative, and some of them are non-approval of the patient, infection at the injection site, dehydration, etc. This type of anesthesia can have complications, such as back pain, headaches, neurological injuries, etc.

Epidural anesthesia is a process where the agent is injected into the epidural space through needles, syringes, or catheters. Indications for this type of anesthesia include patient approval, thoracic, and abdominal surgeries, etc. Contraindications are also divided into absolute and relative, such as hypertension, bacteremia, etc. Possible complications of the epidural include vomiting, meningitis, hypotension, etc.

The role of adjuvants in spinal and epidural anesthesia consists of prolonging the duration of nerve blockade and improving analgesia while contributing to the reduction of side effects caused by the exclusive use of anesthetics during anesthesia. There is a wide range of substances used as adjuvants, although most of them are still in the early stages of research, and there are insufficient clinical studies on their effects.

This paper elaborates on the two main groups of adjuvants, which are opioid and non-opioid adjuvants, showing their association, mechanisms of action, and clinical effects during their use in spinal and epidural anesthesia, as well as their possible side effects. The choice of adjuvant depends on the indication for neuraxial analgesia (e.g., labor analgesia, cesarean section, postoperative analgesia), and the addition of other adjuvants depends on whether we need to achieve analgesia epidurally or spinally.

The side effects of neuraxial administration of opioid adjuvants are potentially due to the spread of opioids in the cerebrospinal fluid (CSF) or through systemic absorption from the epidural space. The neurotoxicity of adjuvants administered in conjunction with local anesthetics remains a significant concern. Many of the adjuvants have not been fully scrutinized with rigorous research that would demonstrate their safety. It can be said that the application of adjuvants in spinal and epidural anesthesia has opened a new range for anesthesiology, contributing more benefits than harm to patients.

Purpose of the Study: The aim of this study was to analyze the applications of adjuvants in spinal and epidural anesthesia. The recommended doses, side effects, and benefits of each are analyzed. Additionally, spinal and epidural anesthesia is explained and reviewed to highlight the differences between these two methods.

Methodology: The methodology used for this study involved secondary sources; thus, it was a literature review with high credibility. These resources were taken from journals such as PubMed, MedLine, and The American Journal of Medicine.

Results: During the discussion, experimental studies were compared with the literature used, analyzing the effects of opioid and non-opioid adjuvants in different sessions with spinal or epidural anesthesia. Due to the lack of literature, only the following adjuvants were analyzed: opioid adjuvants, fentanyl, sodium bicarbonate, vasoconstrictors, clonidine, neostigmine, ketamine, midazolam, and dexmedetomidine.

Conclusion: Opioid adjuvants have been shown to establish a rapid onset of analgesia as they bind to dorsal horn receptors quickly. This speed results in a shorter duration of analgesia. Morphine has been seen to bind more slowly to dorsal horn receptors but results in a longer duration. Sodium bicarbonate has been observed to be used for the rapid onset of action of epidural lidocaine. Vasoconstrictors have been found to retain the effect of local anesthetic on nerve roots for a longer period. Clonidine has been shown to be useful for cesarean births with spinal anesthesia and orthopedic surgery, relieving postpartum pain. Dexmedetomidine exhibits beneficial effects when used epidurally.

REFERENCES

[1] Olawin MA, Das JM. Spinal Anesthesia. National Center for Biotechnology Information (NCBI). 2020. In: StatPearls [Internet].

[2] Chin A, Zundert AV. Spinal Anesthesia. NYSORA. 2020.

[3] Imbelloni LE. Spinal hemianesthesia: Unilateral and posterior. NCBI. Anesthesia, Essays and Researches. 2014; 8(3), 270-276.

[4] Lim GFS, Huether MJ, Brodland DG. Spinal Anaesthesia. ScienceDirect. Essentials of Pain Medicine and Regional Anesthesia. 2019; 566-574.

[5] Sengul G, Watson Ch. Spinal Cord. ScienceDirect. The Human Nervous Sytsem. 2012; 186-232.

[6] Carlson GD, Gorden C. Current developments in spinal cord injury research. The Spine Journal. 2002; 2(2), 116-128

[7] Spinal cord injury. Christopher & Dana Reeve Foundation. 2020.

[8] Vertebral Column. Basic Medical Key. 2020

[9] Spinal meninges. Earth's Lab. 2020

[10] Hernandez AN, Singh P. Epidural Anesthesia. National Center for Biotechnology Information (NCBI). 2020. In: StatPearls [Internet].

[11] Toledano RD, Velde MV. Epidural Anesthesia and Analgesia. NYSORA. 2020.

[12] Spinal, Epidural, and Caudal Anesthesia: Anatomy, Physiology, and Technique. Anesthesia Key. 2020.

[13] Dreyfuss P, Malanga G, Kapural L, Haid RW, Richeimer S. Cervical Epidural Injection. SpineUniverse. 2020.

[14] Tobias JD. Indications and Application of Epidural Anesthesia in a Pediatric Population Outside The Perioperative Period. SAGE Journals. Clinical Pediatrics. 1993; 32(2), 81-85.

[15] Green L. Schematic view of spinal and epidural anaesthesia. ResearchGate. 2010.

[16] Awate S, Babiuk LA, Mutwiri G. Mechanisms of Action of Adjuvants. PubMed Central. Frontiers in Immunology. 2013; 4: 114.

[17] Barash PG, Cullen BF, Stoelting RK. Clinical Anesthesia. 4th edition. Lippincott Williams & Wilkins Publishers. January 2011

[18] Simon JK, Edelman R. Clinical evaluation of adjuvants. ScienceDirect. Immunopotentiators in Modern Vaccines. 2006; 319-342

[19] Khan MIA, Walsh D, Dellan NB. Opioid and adjuvant analgesics: compared and contrasted. PubMed. The American journal of hospice & palliative care. 2011. 28(5), 378-383.

[20] Loveridge R, Patel S. Systemic non-opioid adjuvant analgesics: Their role in acute postoperative pain in adults. ScienceDirect. Trends in Anasthesia and Critical Care. 2014; 4(1), 10-18.

[21] Thiruvenkatarajan V, Wood R, Watts R, Currie J, Wahba M, Wijk RM. The intraoperative use of non-opioid adjuvant analgesic agents: a survey of anaesthetists in Australia and New Zealand. BMC Anesthesiology 19, 188. 2019.

[22] Euliano TY, Gravenstein JS, Gravenstein N, Gravenstein D. Essential Anesthesia-From Science to Practice. 2nd edition. University of Florida, College of Medicine, Gainesville, Florida, USA. 2011

[23] Christiansson L. Update on adjuvants in regional anaesthesia. ResearchGate. Periodicum Biologorum. 2009; 111(2).

[24] Swain A, Nag DS, Sahu S, Samaddar DP. Adjuvants to local anesthetics: Current understanding and future trends. NCBI. World Journal of Clinical Cases. 2017; 5(8), 307-323.

[25] Staikou C, Paraskeva A. The effects of intrathecal and systemic adjuvants on subarachnoid block. PubMed. Minerva anestesiologica. 2014; 80(1), 96-112

[26] Motiani P, Chaudhary S, Bahl N, Sethi AK. Intrathecal Sufentanil Versus Fentanyl for Lower Limb Surgeries - A Randomized Controlled Trial. NCBI. Journal of Anaesthesiology, Clinical Pharmacology. 2010; 26(4), 507-513

[27] Andoh T, Sugiyama K, Fujita M, Iida Y, Nojima H, Saiki I, Kuraishi Y. Pharmacological evaluation of morphine and non-opioid analgesic adjuvants in a mouse model of skin cancer pain. PubMed. Biological & pharmaceutical bulletin. 2008; 31(3), 520-530.

[28] Youssef N, Orlov D, Alie T, Chong M, Cheng J, Thabane L, Paul J. What epidural opioid results in the best analgesia outcomes and fewest side effects after surgery?: a meta-analysis of randomized controlled trials. PubMed. Anesthesia and analgesia. 2014; 119(4), 965-977.

[29] Morgan GE, Mikhail MS, Murray MJ. Clinical Anesthesiology. 4th edition. McGraw-Hill companies. 2006

[30] Corrie TM, Anderson MD. Adjuvants in Regional and Neuraxial Anesthesia: An Update. PedsAnesthesia. 2017.

[31] Knight JB, Schott NJ, Kentor ML, Williams BA. Neurotoxicity of common peripheral nerve block adjuvants. PubMed. Current opinion in anaesthesiology. 2015; 28(5), 598-604.

[32] Grof I, Bocsik A, Harazin A, Maria AR, Vizsnyiczai G, Barna L, Kiss L, Fur G, et al. The Effect of Sodium Bicarbonate, a Beneficial Adjuvant Molecule in Cystic Fibrosis, on Bronchial Epithelial Cells Expressing a Wild-Type or Mutant CFTR Channel. PubMed. International Journal of Molecular Sciences. 2020; 21(11), 4024.

[33] Biyani G, Chhabra A, Baidya DK, Anand RK. Adjuvants to local anaesthetics in regional anaesthesia – Should they be used? Part I: Pros. ScienceDirect. Trends in Anaesthesia and Critical Care. 2014; 4(1), 19-24.

[34] Mehta N, Aasima S, Qazi N. Adjuvant Drugs to Local Anesthetics. Intechopen.com. Topics in Local Anesthetics. 2020.

[35] Goma HM, Carrillo JC, Lugo V. Spinal Additives in Subarachnoid Anaesthesia for Cesarean Section. Intechopen.com. Topics in Spinal Anaesthesia. 2013.

[36] Khangure N. Adjuvant agents in neuraxial blockade. Anaesthesia tutorial of the week 230. 2011.

[37] Imani F, Varrassi G. Ketamine as Adjuvant for Acute Pain Management. NCBI. Anesthesiology and Pain Medicine. 2019; 9(6), 160-187.

[38] Subramaniam K, Subramaniam B, Steinbrook RA. Ketamine as adjuvant analgesic to opioids: a quantitative and qualitative systematic review. PubMed. Anesthesia and analgesia. 2004; 99(2), 482-495

[39] Dodawad R, Sumalatha GB, Pandarpurkar S, Jajee P. Intrathecal Midazolam as an Adjuvant in Pregnancy-Induced Hypertensive Patients Undergoing an Elective Caesarean Section: A Clinical Comparative Study. NCBI. Anesthesiology and Pain Medicine. 2016; 6(5), 38-55

[40] Bajwa SJ, Kulshrestha A. Dexmedetomidine: An Adjuvant Making Large Inroads into Clinical Practice. NCBI. Annals of Medical and Health Sciences Research. 2013; 3(4), 475-483

[41] Prasad R, Rao RS, Turai A, Prabha P, Shreyavathi R, Harsoor K. Effect of epidural clonidine on characteristics of spinal anaesthesia in patients undergoing gynaecological surgeries: A clinical study. NCBI. Indian Journal of Anaesthesia. 2016; 60(6), 398-402

[42] Braga AA, Frias JA, Braga FS, Poterio GB, Hirata ES, Torres NA. Spinal anesthesia for cesarean section. Use of hyperbaric bupivacaine (10mg) combined with different adjuvants. PubMed. Brazilian Journal of Anesthesiology. 2012; 62(6), 775-787

[43] Shah OM, Bhat KM. Comparison of the Efficacy and Safety of Morphine and Fentanyl as Adjuvants to Bupivacaine in Providing Operative Anesthesia and Postoperative Analgesia in Subumblical Surgeries Using Combined Spinal Epidural Technique. NCBI. Anesthesia, Essays and Researches. 2017; 11(4), 913-920

[44] Boules ML. Dexmedetomedine-As an Adjuvant to Epidural Analgesia: Comparison Between Different Doses. Journal of Pain and Relief. 2017; 7(2), 310-322

[45] Martin P. Lumbar Puncture (Spinal Tap). Nurseslabs. 2019.

[46] Spinal and Epidural Anesthesia. Quizlet. 2020.

[47] Nair H. Spinal Anasthesia. MD India. 2020.

[48] Tomin J. Differences in Local Anesthetic Effects of Optically Active Isomers of local Anesthetic Compounds. Biotechnology & Biotechnological Equipment Journal. 2006; 20(3), 9-14.