Adjuvant Strategies in Selective Spinal Anesthesia for Knee Arthroscopy: Efficacy and Safety of Dexmedetomidine, Magnesium Sulphate, and Fentanyl with Low-Dose Hyperbaric Bupivacaine

Tarek Yousef Gaafar[(1)] , Salwa Hassan Waly[(1)] , Mostafa Ibrahim Ramadan[(1)] , Kareem Mohamed Abdel Azeem [(2)]

(1) Anesthesia, Intensive Care and Pain Management Department, Faculty of Medicine, Zagazig University

(2) MBBCh Faculty of Medicine, Zagazig University

Corresponding authors: Kareem Mohamed Abdel Azeem

Received: 1 November 2024, **Accepted:** 25 November 2024, **Published:** 30 November 2024

Abstract

Background: Knee arthroscopy is one of the most frequently performed orthopedic procedures, requiring reliable anesthesia with rapid onset, optimal analgesia, hemodynamic stability, and minimal side effects. Selective spinal anesthesia (SSA) using low-dose hyperbaric bupivacaine has gained attention as a technique that provides effective anesthesia with faster recovery and reduced motor block, enabling early mobilization and shorter hospital stay. However, the main challenge with low-dose spinal anesthesia is insufficient block duration and variable quality, which may limit its utility in procedures of intermediate length. To overcome these limitations, several intrathecal adjuvants have been studied, including opioids, α2-adrenergic agonists, and NMDA receptor antagonists.

Dexmedetomidine, a highly selective α2-adrenergic receptor agonist, has been reported to significantly prolong the duration of sensory and motor block when added to intrathecal bupivacaine, while providing stable hemodynamics and sedation without major respiratory depression. Magnesium sulphate, by acting as a non-competitive NMDA receptor antagonist and calcium channel blocker, enhances the quality of spinal anesthesia, although its slower onset and concerns about neurotoxicity remain under evaluation. Fentanyl, a lipophilic opioid, is among the most widely used intrathecal adjuvants, improving intraoperative analgesia and reducing the need for supplemental systemic opioids, but its use may be limited by side effects such as pruritus, nausea, and risk of respiratory depression.

Comparative evaluation of these agents as adjuvants to low-dose hyperbaric bupivacaine in SSA for knee arthroscopy is crucial, as the choice directly influences block characteristics, patient satisfaction, safety, and postoperative recovery. The available evidence suggests that dexmedetomidine provides the most consistent prolongation of block and superior analgesic efficacy compared to magnesium sulphate and fentanyl, although each agent has distinct pharmacological advantages and limitations.

This review aims to provide a comprehensive analysis of the pharmacological properties, clinical efficacy, and safety profiles of dexmedetomidine, magnesium sulphate, and fentanyl when used as intrathecal adjuvants to low-dose hyperbaric bupivacaine in selective spinal anesthesia for knee arthroscopy. By critically evaluating current literature, this article highlights optimal strategies for maximizing anesthetic efficacy while minimizing adverse effects, and outlines future directions for clinical research in this evolving field.

Keywords: *Selective Spinal Anesthesia , Knee Arthroscopy, Dexmedetomidine, Magnesium Sulphate, and Fentanyl with Low-Dose Hyperbaric Bupivacaine*

Introduction

Knee arthroscopy is a minimally invasive orthopedic procedure performed widely for diagnostic and therapeutic purposes, including meniscal repair, ligament reconstruction, and cartilage procedures. Despite its relatively short duration, effective anesthesia for knee arthroscopy must provide rapid onset, adequate sensory block, stable hemodynamics, optimal postoperative analgesia, and early ambulation to facilitate enhanced recovery pathways. Traditionally, general anesthesia or conventional spinal anesthesia with standard doses of local anesthetics has been employed. However, these approaches may be associated with undesirable side effects such as prolonged motor block, urinary retention, postoperative nausea and vomiting, and delayed discharge, which are particularly disadvantageous in ambulatory settings [1,2].

Selective spinal anesthesia (SSA) using reduced-dose hyperbaric bupivacaine has emerged as an attractive alternative. By limiting the spread of local anesthetic to the targeted dermatomes, SSA ensures sufficient surgical anesthesia while minimizing motor impairment and systemic complications. This technique is particularly suited for knee arthroscopy, where lower extremity anesthesia with early recovery is paramount [3]. However, the main limitation of low-dose spinal anesthesia is its relatively short duration and occasionally inadequate analgesic intensity for procedures extending beyond 45–60 minutes. To address this limitation, the addition of intrathecal adjuvants has been extensively explored [4].

Adjuvants such as opioids, α2-adrenergic agonists, and NMDA receptor antagonists are used to enhance block quality, prolong analgesia, and improve intraoperative hemodynamic stability. Among these, fentanyl, dexmedetomidine, and magnesium sulphate have received significant attention. Fentanyl, a lipophilic opioid, synergistically enhances the effect of local anesthetics but is associated with dose-dependent side effects including pruritus and respiratory depression [5]. Dexmedetomidine, a highly selective α2-agonist, provides profound analgesia and sedation, prolongs block duration, and preserves respiratory function, though concerns regarding bradycardia and hypotension exist [6]. Magnesium sulphate, by antagonizing NMDA receptors and modulating calcium influx, improves intraoperative and postoperative analgesia, although its clinical role remains less established compared to fentanyl and dexmedetomidine [7].

Despite numerous trials comparing these agents individually, there remains a lack of consensus on the optimal adjuvant for selective spinal anesthesia in knee arthroscopy. Some studies highlight dexmedetomidine as superior for prolonging analgesia and maintaining hemodynamic stability, whereas others support the utility of fentanyl for rapid intraoperative analgesia or magnesium for enhancing block quality with minimal sedation. These variable findings highlight the need for a comprehensive synthesis of evidence.

The aim of this review is to critically evaluate the efficacy and safety of dexmedetomidine, magnesium sulphate, and fentanyl as intrathecal adjuvants to low-dose hyperbaric bupivacaine in selective spinal anesthesia for knee arthroscopy. By comparing pharmacological profiles, mechanisms of action, clinical outcomes, and adverse effect profiles, this article seeks to provide guidance for optimizing anesthetic strategies in this common orthopedic procedure. Furthermore, the review identifies gaps in current literature and highlights areas requiring future research to refine evidence-based practice in this evolving field. [8,9]

Selective Spinal Anesthesia

Selective spinal anesthesia (SSA) is a modification of conventional spinal anesthesia in which a lower dose of local anesthetic is used with the goal of producing a restricted and targeted neural blockade. Unlike traditional spinal anesthesia, which may result in extensive sensory and motor block, SSA provides anesthesia limited to the dermatomes relevant for the surgical procedure. This technique is especially useful for knee arthroscopy, where anesthesia confined to the lower limb is sufficient, while preservation of motor function and faster postoperative recovery are desired [10].

The concept of SSA relies on reducing both the volume and concentration of the local anesthetic while ensuring that the patient's positioning, baricity of the solution, and injection technique facilitate precise spread within the subarachnoid space. By achieving selective sensory block, SSA minimizes unnecessary

blockade of adjacent dermatomes and reduces side effects such as urinary retention, hypotension, and delayed ambulation, which are more commonly associated with conventional spinal anesthesia [11].

Hyperbaric solutions, particularly hyperbaric bupivacaine, are commonly used in SSA because their distribution in cerebrospinal fluid is highly influenced by gravity, allowing controlled block height based on patient positioning. This property makes SSA more predictable and safer in procedures confined to lower extremities. In knee arthroscopy, SSA with low-dose hyperbaric bupivacaine has demonstrated faster discharge readiness and higher patient satisfaction compared to both general anesthesia and higher-dose spinal anesthesia [12].

An additional benefit of SSA is its application in high-risk patients, such as those with cardiopulmonary comorbidities or elderly individuals, where minimizing the extent of sympathetic block reduces the risk of hemodynamic instability. Furthermore, SSA allows better postoperative analgesic strategies by facilitating early ambulation and participation in rehabilitation protocols, which is crucial in orthopedic day-care surgeries [13].

Despite these advantages, SSA may be associated with challenges such as shorter block duration, potential for inadequate anesthesia in longer procedures, and technical variability related to the precise distribution of local anesthetic. These limitations highlight the importance of intrathecal adjuvants, which can prolong block duration, enhance analgesic quality, and maintain hemodynamic stability, thereby expanding the utility of SSA in knee arthroscopy and other intermediate-duration procedures [14].

Factors Affecting Success of Selective Spinal Anesthesia

The success of selective spinal anesthesia (SSA) depends on multiple interrelated factors, including patient-related variables, technical aspects of the block, and the pharmacological properties of the local anesthetic and adjuvants used. Achieving a reliable sensory block with minimal motor impairment requires careful attention to these determinants [15].

Patient characteristics play a pivotal role in determining block spread and efficacy. Age, height, weight, and spinal anatomy influence cerebrospinal fluid (CSF) volume and distribution, which in turn affect local anesthetic dispersion. Elderly patients often require smaller doses due to decreased CSF volume and increased sensitivity of neural tissue, while obese patients may present challenges in positioning and needle placement, potentially affecting the predictability of the block [16].

Technical considerations are equally critical. Needle type, gauge, bevel orientation, and injection speed influence the initial spread of the local anesthetic within the subarachnoid space. Pencil-point needles, such as Whitacre or Sprotte, are often preferred for SSA due to their lower risk of post-dural puncture headache and more controlled drug delivery. Patient positioning during and after injection—sitting, supine, or lateral—greatly influences the cephalad spread of hyperbaric solutions, making positioning a key determinant of block selectivity [17].

Pharmacological factors are also essential to success. The baricity of the solution largely dictates the direction and extent of spread. Hyperbaric bupivacaine is commonly chosen for SSA because gravitational effects can be used to restrict block height to desired dermatomes. Dose adjustment is critical; excessive reduction may lead to incomplete or patchy anesthesia, whereas even a modest overdose may compromise selectivity and prolong motor block, reducing the benefits of SSA [18].

Finally, **adjuvant selection** significantly impacts block success. Agents such as fentanyl, dexmedetomidine, and magnesium sulphate enhance the quality of anesthesia by prolonging block duration and improving intraoperative analgesia, thereby compensating for the limitations of low-dose bupivacaine alone. However, the choice of adjuvant must balance efficacy with safety, since each has distinct side-effect profiles that may influence patient outcomes [19].

In summary, optimizing SSA requires an individualized approach, integrating patient assessment, meticulous technique, careful dosing, and appropriate adjuvant selection. When these factors are harmonized, SSA offers reliable anesthesia with rapid recovery, making it particularly advantageous for ambulatory procedures like knee arthroscopy [20].

Technique and Mechanism of Action

The technique of selective spinal anesthesia (SSA) is a modification of standard spinal anesthesia designed to achieve a restricted block tailored to the surgical site. For knee arthroscopy, the goal is to provide adequate sensory block confined to the lower limb dermatomes while minimizing motor blockade and systemic side effects. This is accomplished through precise needle placement, careful dosing of hyperbaric bupivacaine, and judicious use of adjuvants [21].

Technique begins with patient positioning, usually sitting or lateral decubitus, to optimize anatomical access and facilitate desired drug spread. After sterile preparation and local infiltration, a fine-gauge spinal needle (25–27G Whitacre or Sprotte) is introduced into the subarachnoid space at the L3–L4 or L4–L5 interspace. The choice of hyperbaric bupivacaine allows gravitational manipulation of block height, and patient positioning immediately after injection (supine, with or without leg elevation) determines cephalad spread. A low dose of bupivacaine (5–7.5 mg) is typically used for SSA in knee arthroscopy, significantly lower than conventional spinal doses (10–15 mg), thereby limiting block extent and duration [22].

Adjuvants such as fentanyl, dexmedetomidine, or magnesium sulphate are frequently co-administered intrathecally to improve block quality, prolong analgesia, and reduce intraoperative discomfort without prolonging recovery time. The combination of low-dose bupivacaine with an adjuvant enhances the selectivity of the block, ensuring adequate surgical conditions while maintaining rapid functional recovery [23].

Mechanism of action involves the synergistic interaction between local anesthetics and adjuvants at the spinal cord level. Bupivacaine, a long-acting amide local anesthetic, acts by reversibly binding to voltage-gated sodium channels, thereby inhibiting depolarization and nerve impulse conduction. This results in blockade of both sensory and motor fibers, with a higher sensitivity of small-diameter sensory fibers explaining the relative selectivity of analgesia at low doses [24].

Adjuvants enhance this mechanism via distinct pathways. Fentanyl binds to μ-opioid receptors in the substantia gelatinosa of the dorsal horn, amplifying nociceptive inhibition. Dexmedetomidine acts at presynaptic and postsynaptic α2-adrenergic receptors to suppress norepinephrine release and hyperpolarize interneurons, prolonging sensory and motor blockade. Magnesium sulphate antagonizes NMDA receptors and modulates calcium channels, thereby reducing central sensitization and enhancing block depth. Together, these mechanisms support prolonged analgesia, stable hemodynamics, and reduced need for systemic analgesics [25].

Overall, the technique of SSA capitalizes on low-dose bupivacaine to achieve selective neural blockade, while adjuvants potentiate its action to ensure adequate duration and quality for procedures like knee arthroscopy. Proper technique and understanding of drug mechanisms are therefore essential to maximize efficacy and safety of this approach [26].

Pharmacology of Hyperbaric Bupivacaine

Bupivacaine is a long-acting amide local anesthetic widely used in neuraxial anesthesia due to its favorable balance of sensory and motor block. When prepared as a hyperbaric solution by adding dextrose, its density becomes greater than cerebrospinal fluid (CSF), allowing gravitational control of its spread within the subarachnoid space. This property makes hyperbaric bupivacaine particularly suitable for selective spinal anesthesia (SSA), where precise dermatomal restriction is essential [27].

Physicochemical properties of bupivacaine significantly influence its clinical profile. Being highly lipophilic, bupivacaine readily penetrates nerve membranes, producing potent and prolonged sodium channel blockade. Compared with lidocaine, it has a slower onset but a much longer duration of action, which explains its widespread use in lower limb orthopedic surgeries. The addition of dextrose (usually 8%) increases baricity, allowing anesthesiologists to manipulate block height through patient positioning, a cornerstone of SSA [28].

Mechanism of action involves reversible blockade of voltage-gated sodium channels in the axonal membrane, preventing depolarization and propagation of action potentials. Sensory fibers, particularly small-diameter unmyelinated C fibers and thinly myelinated Aδ fibers, are more sensitive to blockade than larger motor fibers, allowing selective analgesia at lower doses. At higher concentrations, motor

blockade and sympathetic blockade also occur, but SSA relies on minimizing these effects through reduced dosing [29].

Pharmacokinetics of intrathecal bupivacaine are influenced by dose, baricity, CSF dynamics, and patient posture. Hyperbaric solutions distribute predictably according to gravity, providing more reliable control of block extent compared to isobaric preparations. The duration of sensory block with standard intrathecal doses ranges from 90 to 180 minutes, but with low-dose hyperbaric solutions used in SSA, the block may be shorter, necessitating the use of adjuvants to prolong clinical effectiveness [30].

Adverse effects of bupivacaine are dose-dependent. Higher doses may cause profound hypotension due to sympathetic blockade, urinary retention, and delayed ambulation. Cardiotoxicity, though rare with intrathecal doses, is a known risk with systemic absorption. By contrast, low-dose hyperbaric bupivacaine used in SSA provides significant safety advantages by reducing sympathetic block and minimizing systemic side effects, particularly beneficial for day-case surgeries such as knee arthroscopy [31].

In summary, hyperbaric bupivacaine combines reliable spinal blockade with the ability to tailor spread by patient positioning. Its pharmacological profile makes it an ideal agent for SSA, provided that block duration is optimized through adjunctive agents like dexmedetomidine, magnesium sulphate, or fentanyl [32].

Pharmacology of Dexmedetomidine

Chemical Structure

Dexmedetomidine is a highly selective α2-adrenergic receptor agonist, belonging to the imidazole subclass of sedative-analgesic drugs. Structurally, it is the dextrorotatory enantiomer of medetomidine, with a chemical formula of C13H16N2 and a molecular weight of 200.28 g/mol. Its stereoselectivity accounts for its higher α2:α1 receptor affinity ratio (approximately 1600:1), making it more specific than clonidine, thereby reducing unwanted α1-mediated cardiovascular effects [33].

Clinical Pharmacology

Dexmedetomidine exerts its effects by binding to presynaptic α2 receptors in the locus coeruleus and dorsal horn of the spinal cord. Presynaptic binding inhibits norepinephrine release, resulting in reduced sympathetic outflow, sedation, and analgesia. Postsynaptic binding causes neuronal hyperpolarization, enhancing analgesic effects and prolonging sensory and motor blockade when used intrathecally [34].

Pharmacokinetically, dexmedetomidine exhibits rapid distribution and a terminal half-life of about 2–3 hours when administered intravenously. It undergoes extensive hepatic metabolism via glucuronidation and cytochrome P450-mediated hydroxylation, with inactive metabolites excreted renally. When administered intrathecally, systemic absorption is minimal, but local spinal cord receptor activity prolongs analgesia significantly. The major pharmacodynamic effects include sedation, anxiolysis, analgesia, and reduced anesthetic and opioid requirements, with bradycardia and hypotension being the most notable adverse effects [35].

Clinical Applications

Dexmedetomidine has multiple clinical applications in anesthesia and critical care. Intravenously, it is widely used for sedation in intensive care units, procedural sedation, and as an adjunct to general anesthesia. In regional anesthesia, particularly spinal anesthesia, it has demonstrated efficacy in prolonging block duration, enhancing postoperative analgesia, and improving patient satisfaction [36].

As an intrathecal adjuvant, dexmedetomidine prolongs both sensory and motor blockade when combined with bupivacaine, without causing respiratory depression. It provides stable hemodynamics and facilitates smooth perioperative sedation, which may reduce the need for supplemental sedatives during knee arthroscopy. Several randomized controlled trials have shown that intrathecal dexmedetomidine prolongs the duration of analgesia more consistently than fentanyl or magnesium sulphate, making it an increasingly preferred adjuvant for SSA [37].

Dexmedetomidine's role in SSA is particularly valuable in ambulatory orthopedic procedures, where minimizing opioid consumption and enhancing recovery profiles are critical. However, its use requires

careful monitoring for bradycardia and hypotension, particularly in elderly or hemodynamically unstable patients [38].

Pharmacology of Magnesium Sulphate

Pharmacology

Magnesium sulphate is an inorganic salt with diverse pharmacological actions, widely used in anesthesia, obstetrics, and critical care. Its mechanism is primarily mediated through antagonism of N-methyl-D-aspartate (NMDA) receptors and blockade of voltage-dependent calcium channels. By inhibiting calcium influx into presynaptic nerve terminals, magnesium reduces the release of excitatory neurotransmitters such as glutamate and substance P, thereby attenuating nociceptive transmission. This unique action makes magnesium a potential analgesic adjuvant in neuraxial anesthesia [39].

Pharmacokinetics and Pharmacodynamics

When administered intravenously, magnesium has a distribution half-life of approximately 2.5–4 hours and is excreted renally in unchanged form. It does not undergo hepatic metabolism. Therapeutic plasma concentrations typically range from 2 to 4 mEq/L, while higher levels may induce toxicity such as hypotension, respiratory depression, and cardiac conduction abnormalities. After intrathecal administration, systemic absorption is minimal, and its action is predominantly localized to the spinal cord, where it modulates synaptic transmission through NMDA receptor blockade [40].

Pharmacodynamically, magnesium potentiates the analgesic and anesthetic effects of local anesthetics by preventing central sensitization and reducing neuronal hyperexcitability. It does not produce motor block on its own but prolongs the duration of sensory block when used in combination with intrathecal agents such as bupivacaine. The onset of action may be slower compared to other adjuvants, but it provides prolonged analgesic benefits without respiratory depression [41].

Clinical Pharmacology

Magnesium sulphate has several established clinical roles, including treatment of eclampsia, prevention of arrhythmias, and management of severe asthma. In anesthesia, its intravenous use reduces anesthetic and opioid requirements, stabilizes hemodynamics, and provides perioperative analgesia. Intrathecally, magnesium has been studied as an adjuvant to local anesthetics in spinal anesthesia for lower limb surgeries, cesarean sections, and orthopedic procedures. Clinical trials suggest that it prolongs the duration of sensory block and postoperative analgesia when combined with bupivacaine, though the evidence is less robust compared to fentanyl and dexmedetomidine [42].

Safety remains a consideration with intrathecal magnesium use. Animal studies raised concerns about potential neurotoxicity, but human studies at clinically used doses have not demonstrated significant adverse neurological outcomes. However, the slower onset of block and variability in efficacy compared to other adjuvants limit its routine use in spinal anesthesia. Nevertheless, in SSA for knee arthroscopy, magnesium may provide an opioid-sparing effect and prolongation of analgesia, making it a potential alternative in selected patients [43].

Pharmacology of Fentanyl

Pharmacology

Fentanyl is a synthetic lipophilic opioid belonging to the phenylpiperidine class. It is a potent μ-opioid receptor agonist, approximately 50–100 times more potent than morphine. Its high lipid solubility allows rapid penetration across the blood-brain barrier, contributing to its fast onset of action. The primary site of action for fentanyl is the substantia gelatinosa of the dorsal horn of the spinal cord, where it binds to μ-receptors and inhibits nociceptive neurotransmission by reducing presynaptic calcium influx and enhancing postsynaptic potassium efflux, leading to neuronal hyperpolarization [44].

Pharmacokinetics and Pharmacodynamics

After intravenous administration, fentanyl demonstrates rapid redistribution from plasma to highly perfused tissues, with a distribution half-life of 13 minutes and a terminal elimination half-life of 2–4 hours. It undergoes hepatic metabolism primarily via CYP3A4-mediated N-dealkylation to inactive metabolites, excreted renally. Its pharmacokinetics are characterized by high lipophilicity, resulting in fast onset and relatively short duration of effect after single doses [45].

When administered intrathecally, fentanyl produces analgesia by direct activation of spinal opioid receptors, with rapid onset due to its lipophilicity. Its duration of action is limited (approximately 2–4 hours) because of redistribution and systemic absorption, but it synergistically enhances the effects of local anesthetics, allowing for lower doses of bupivacaine to be used while maintaining block quality [46]. Pharmacodynamically, fentanyl provides profound analgesia, especially for visceral and somatic pain, but does not produce motor block. Its adverse effects include pruritus, nausea, vomiting, urinary retention, and dose-dependent respiratory depression, though the risk is lower with intrathecal administration compared to systemic routes. Hemodynamic effects are generally minimal due to lack of sympathetic blockade [47].

Clinical Pharmacology

Fentanyl is widely used in perioperative and critical care settings for analgesia, sedation, and as an adjunct to regional anesthesia. In spinal anesthesia, intrathecal fentanyl has been shown to improve intraoperative analgesia, reduce shivering, and decrease the need for supplemental sedatives or systemic opioids. When added to low-dose bupivacaine in SSA for knee arthroscopy, fentanyl improves block quality and prolongs early postoperative analgesia, although the duration is generally shorter compared to dexmedetomidine [48].

Intrathecal Role of Fentanyl

Intrathecal fentanyl has been extensively studied as an adjuvant to spinal anesthesia. Its lipophilic nature ensures rapid onset, making it especially useful for short procedures such as arthroscopy, cesarean delivery, and urologic surgeries. The combination of low-dose hyperbaric bupivacaine with intrathecal fentanyl produces dense sensory block with minimal prolongation of motor block, facilitating early ambulation and discharge in outpatient procedures [49].

However, side effects remain a concern. Pruritus is the most frequently reported adverse effect, occurring in up to 60% of patients. Respiratory depression, although rare at low intrathecal doses (10–25 μg), requires vigilance, particularly in elderly or opioid-sensitive patients. Despite these limitations, intrathecal fentanyl remains a safe and effective adjuvant, especially when the goal is to enhance intraoperative analgesia without excessively prolonging recovery [50].

Comparative Efficacy with Hyperbaric Bupivacaine

The addition of intrathecal adjuvants to low-dose hyperbaric bupivacaine has been shown to enhance the efficacy of selective spinal anesthesia (SSA), particularly in procedures such as knee arthroscopy where short- to intermediate-duration analgesia with early recovery is essential. Comparative evaluation of dexmedetomidine, magnesium sulphate, and fentanyl highlights differences in their impact on block characteristics, hemodynamic stability, sedation, and recovery profiles [51].

Hemodynamic stability is a critical consideration in SSA. Fentanyl, due to its lack of sympathetic blockade, has minimal effects on blood pressure and heart rate, thereby providing stable intraoperative hemodynamics. Dexmedetomidine, while effective in prolonging block duration, may induce bradycardia and hypotension through sympatholysis, particularly in elderly or volume-depleted patients. Magnesium sulphate exerts mild vasodilatory effects but generally maintains stable hemodynamics at intrathecal doses used clinically [52].

Analgesic efficacy and block duration differ significantly among the adjuvants. Dexmedetomidine consistently provides the longest prolongation of sensory and motor block, often extending postoperative analgesia by 2–4 hours beyond that of fentanyl or magnesium. Fentanyl, while offering rapid onset of dense analgesia, has a shorter duration, typically 90–150 minutes, limiting its utility for longer procedures but making it ideal for ambulatory cases. Magnesium sulphate prolongs sensory block modestly, with less impact on motor block, offering a balance between efficacy and recovery [53].

Sedation profiles also distinguish the agents. Dexmedetomidine produces a unique sedative state resembling natural sleep, which many patients find pleasant. This sedation can reduce intraoperative anxiety but requires close monitoring for bradycardia. Fentanyl does not produce significant sedation at intrathecal doses, whereas magnesium is generally devoid of sedative effects when administered intrathecally [54].

Recovery characteristics are essential in knee arthroscopy, where early ambulation and discharge are prioritized. Fentanyl, by providing good analgesia without prolonging motor block, facilitates rapid recovery and short hospital stay. Dexmedetomidine, though superior in prolonging analgesia, may delay discharge in ambulatory settings due to extended motor block and sedation. Magnesium sulphate offers a middle ground, extending analgesia modestly without significant delay in mobilization [55].

In summary, dexmedetomidine is most effective in prolonging block and analgesia, fentanyl provides rapid onset and faster recovery, while magnesium sulphate offers moderate prolongation with a favorable safety profile. The optimal choice depends on surgical duration, patient comorbidities, and institutional emphasis on fast-track recovery [56].

Safety and Adverse Effects

The safety of intrathecal adjuvants is a key determinant of their clinical acceptability. Although dexmedetomidine, magnesium sulphate, and fentanyl enhance the efficacy of selective spinal anesthesia (SSA), each carries distinct adverse effect profiles that must be carefully considered when used in combination with low-dose hyperbaric bupivacaine [57].

Dexmedetomidine is generally well tolerated but can cause dose-dependent **bradycardia and hypotension** due to central sympatholysis and reduced norepinephrine release. These hemodynamic changes are usually manageable with fluid resuscitation or vasopressors, though they may pose risks in elderly or cardiac-compromised patients. Sedation, while often beneficial intraoperatively, can sometimes delay discharge in ambulatory procedures. Importantly, dexmedetomidine does not depress respiration, making it safer than opioids in terms of airway management [58].

Magnesium sulphate is considered relatively safe at intrathecal doses used in clinical trials, though concerns regarding potential **neurotoxicity** have been raised based on animal studies. Human data, however, have not demonstrated significant adverse neurological sequelae at doses of 50–100 mg. Systemically, excessive magnesium levels may cause hypotension, flushing, and cardiac conduction abnormalities, but these are rare with intrathecal administration due to minimal systemic absorption. Its most frequent drawback in SSA is the **slower onset of anesthesia** and occasional reports of inadequate block density compared to other adjuvants [59].

Fentanyl is associated with a well-recognized spectrum of opioid-related adverse effects. The most common is **pruritus**, occurring in up to 60% of patients, especially in obstetric populations. Other side effects include nausea, vomiting, urinary retention, and **dose-dependent respiratory depression**, which, although uncommon at intrathecal doses of 10–25 µg, remains a concern, particularly in elderly or opioid-sensitive patients. Despite these risks, fentanyl is often preferred for its rapid onset, dense block, and minimal effect on motor recovery [60].

Comparative studies suggest that **dexmedetomidine** has fewer incidences of pruritus and nausea compared with fentanyl, but is more likely to cause bradycardia and hypotension. **Magnesium sulphate** appears to have the most favorable safety profile, with minimal systemic side effects, but its clinical utility is limited by inconsistent efficacy. Thus, safety considerations strongly influence adjuvant selection, particularly in high-risk patient groups or in ambulatory knee arthroscopy where rapid recovery and minimal side effects are paramount [61].

Evidence from Clinical Trials and Meta-Analyses

Randomized trials in ambulatory knee arthroscopy established that **low-dose hyperbaric bupivacaine combined with intrathecal fentanyl** yields reliable anesthesia with fast-track recovery. Korhonen et al. showed that **3 mg hyperbaric bupivacaine + 10 µg fentanyl** provided adequate surgical conditions and discharge suitability with minimal side effects, supporting the SSA concept for outpatient arthroscopy. Subsequent work comparing low-dose bupivacaine with or without an opioid confirmed longer time to first analgesic request and favorable recovery when fentanyl is added to the intrathecal mixture. These early trials cemented fentanyl's role as a rapid-onset adjuvant for knee arthroscopy under SSA. [62,63]

The **magnesium story** in knee arthroscopy began with Buvanendran et al., who performed the first prospective human RCT demonstrating that **intrathecal magnesium (50 mg) significantly prolonged**

fentanyl analgesia for arthroscopic knee surgery without neurologic complications. Additional randomized studies in lower-limb surgery reported prolonged sensory block and delayed first analgesic request when magnesium was combined with bupivacaine (often alongside fentanyl), albeit with a generally slower onset of anesthesia. Together, these trials suggest that magnesium can extend analgesia and reduce early rescue analgesic needs, though heterogeneity in dosing and co-adjuvants persists. [64–66]

Intrathecal dexmedetomidine has accumulated robust evidence from meta-analyses across spinal anesthesia indications, consistently showing prolongation of sensory and motor block and extended postoperative analgesia when added to bupivacaine. Contemporary systematic reviews (including network/meta-analyses) report meaningful increases in block duration and reduced shivering, with no clear signal of excess hypotension or bradycardia at low intrathecal doses in pooled data, although individual RCTs warrant vigilance for bradycardia. Overall, dexmedetomidine demonstrates a larger effect size for prolonging analgesia than fentanyl or magnesium in most pooled analyses. [67–69]

When head-to-head comparisons are considered, RCTs in low-dose spinal anesthesia (lower-limb cohorts) indicate that 5 μg dexmedetomidine may produce longer sensory block and analgesia than 25 μg fentanyl, while maintaining acceptable hemodynamics—albeit with higher rates of bradycardia in some series. For knee arthroscopy specifically, studies comparing intrathecal vs intra-articular dexmedetomidine show both routes improve analgesia, though intra-articular administration can reduce systemic exposure and still provide meaningful pain relief. These data support dexmedetomidine as a potent adjuvant, with route and dose tailored to setting and recovery goals. [70,71]

Synthesizing the comparative efficacy: fentanyl offers fast onset and excellent intraoperative comfort but shorter postoperative analgesia; dexmedetomidine provides the most consistent prolongation of block and analgesia (with sedative synergy), and magnesium confers modest prolongation and potential opioid-sparing effects with a favorable safety signal but greater heterogeneity in effect size. Importantly, meta-analyses focused on arthroscopy also suggest benefits from peri- or intra-articular magnesium or dexmedetomidine regimens; while not intrathecal, these reinforce the drugs' analgesic potential around knee arthroscopy and can complement SSA strategies. [72–75]

Overall, contemporary evidence supports tailoring the adjuvant to procedure length and recovery priorities in knee arthroscopy: dexmedetomidine when prolonged analgesia is paramount; fentanyl when rapid recovery and minimal sedation are prioritized; and magnesium when an opioid-sparing profile with acceptable prolongation is desired, acknowledging variability in onset and trial heterogeneity. [67–75]

Conclusion

Selective spinal anesthesia (SSA) using low-dose hyperbaric bupivacaine represents a valuable technique for knee arthroscopy, offering rapid onset, reliable block, and faster recovery compared with conventional spinal anesthesia. However, the inherent limitation of short duration necessitates the use of intrathecal adjuvants to optimize efficacy and prolong postoperative analgesia.

Among the studied agents, **dexmedetomidine** emerges as the most effective in prolonging sensory and motor block, enhancing postoperative analgesia, and providing intraoperative sedation. Its limitations, however, include potential bradycardia and hypotension, particularly in vulnerable patient groups. **Fentanyl**, on the other hand, provides rapid and dense analgesia with minimal prolongation of motor block, making it ideal for short procedures and outpatient surgery, though pruritus and respiratory depression remain important side effects. **Magnesium sulphate** offers moderate prolongation of sensory block with a favorable safety profile and opioid-sparing effect, though its slower onset and inconsistent efficacy limit widespread adoption.

Comparative clinical trials and meta-analyses suggest that **no single adjuvant is universally superior**, and the optimal choice depends on the clinical scenario. For longer procedures or when postoperative pain control is a priority, dexmedetomidine is advantageous. For ambulatory settings requiring rapid recovery, fentanyl remains a reliable choice. Magnesium sulphate serves as a promising alternative where opioid-related adverse effects must be avoided.

Overall, intrathecal adjuvants significantly enhance the performance of low-dose hyperbaric bupivacaine in SSA for knee arthroscopy, each with distinct advantages and limitations. Tailored use based on patient comorbidities, surgical duration, and recovery requirements provides the best outcomes. Future research should focus on defining optimal dosing strategies, exploring combination regimens, and evaluating long-term safety to refine adjuvant use in SSA.

References

1. Gupta A, Axelsson K, Thörn SE, et al. Low-dose bupivacaine spinal anesthesia for knee arthroscopy: effect on recovery and discharge. *Anesth Analg*. 2005;100(5):1483-1488.
2. Liu SS, McDonald SB. Current issues in spinal anesthesia. *Anesthesiology*. 2001;94(5):888-906.
3. Van Zundert AAJ, Stultiëns G, Jakimowicz JJ, et al. Segmental spinal anesthesia for cholecystectomy in a patient with severe lung disease. *Br J Anaesth*. 2006;96(4):464-466.
4. Choi DH, Park SH, Song IA. Intrathecal adjuvants for neuraxial anesthesia: a review of randomized clinical trials. *Korean J Anesthesiol*. 2017;70(5):547-560.
5. Ben-David B, Solomon E, Levin H, Admoni H, Vaida S. Intrathecal fentanyl with small-dose dilute bupivacaine: better anesthesia without prolonging recovery. *Anesth Analg*. 1997;85(3):560-565.
6. Al-Mustafa MM, Abu-Halaweh SA, Aloweidi AS, et al. Intrathecal dexmedetomidine prolongs spinal anesthesia. *Anesth Analg*. 2009;108(2):482-487.
7. Arcioni R, Palmisani S, Tigano S, et al. Combined intrathecal and epidural magnesium sulfate supplementation of spinal anesthesia to reduce postoperative analgesic requirements. *Anesth Analg*. 2007;104(5):1261-1269.
8. Ture H, Uckunkaya N, Ozkan B, et al. Comparison of spinal anesthesia with intrathecal fentanyl or fentanyl plus low-dose bupivacaine in outpatient arthroscopic knee surgery. *Acta Anaesthesiol Scand*. 2001;45(1):19-23.
9. Kumar A, Sharma DK, Datta B. Comparative evaluation of intrathecal dexmedetomidine and fentanyl as adjuvants to low-dose bupivacaine for knee arthroscopy. *J Anaesthesiol Clin Pharmacol*. 2017;33(4):496-502.
10. Van Zundert AAJ, Stultiëns G, Jakimowicz JJ, et al. Segmental spinal anesthesia for cholecystectomy in a patient with severe lung disease. *Br J Anaesth*. 2006;96(4):464-466.
11. Kuusniemi KS, Pihlajamäki KK, Pitkänen MT. Low-dose bupivacaine spinal anesthesia for outpatient knee arthroscopy. *Reg Anesth Pain Med*. 1999;24(6):594-598.
12. Breebaart MB, Sermeus LA, Vercauteren MP, et al. Selective spinal anesthesia for outpatient arthroscopic knee surgery: a randomized controlled trial. *Anesth Analg*. 2003;96(6):1631-1634.
13. Ben-David B, Miller G, Gavriel R, Gurevitch A. Low-dose bupivacaine-fentanyl spinal anesthesia for surgical repair of hip fracture in the elderly. *Anesthesiology*. 2000;92(1):6-10.
14. Choi DH, Park SH, Song IA. Intrathecal adjuvants for neuraxial anesthesia: a review of randomized clinical trials. *Korean J Anesthesiol*. 2017;70(5):547-560.
15. Brull R, Macfarlane AJ, Chan VW. Spinal, epidural, and caudal anesthesia. In: Miller RD, Cohen NH, Eriksson LI, eds. *Miller's Anesthesia*. 8th ed. Philadelphia, PA: Elsevier; 2015:1684-1720.
16. Carpenter RL, Hogan QH, Liu SS, Crane B, Moore J. Lumbosacral cerebrospinal fluid volume is the primary determinant of sensory block extent and duration during spinal anesthesia. *Anesthesiology*. 1998;89(1):24-29.
17. Pitkänen MT, Aromaa U. Technical aspects and complications of spinal anesthesia. In: Wildsmith JAW, Armitage EN, eds. *Principles and Practice of Regional Anaesthesia*. Edinburgh: Churchill Livingstone; 1993:129-148.
18. Kuusniemi KS, Pihlajamäki KK, Pitkänen MT. Low-dose bupivacaine spinal anesthesia for outpatient knee arthroscopy. *Reg Anesth Pain Med*. 1999;24(6):594-598.
19. Gupta S, Kaur M, Gupta R, et al. Comparative evaluation of intrathecal dexmedetomidine, fentanyl, and magnesium sulphate as adjuvants to low-dose hyperbaric bupivacaine for lower limb surgeries. *Anesth Essays Res*. 2016;10(3):437-442.
20. Breebaart MB, Vercauteren MP, Hoffmann VL, et al. Selective spinal anesthesia in day-case knee arthroscopy: randomized controlled trial comparing different doses of bupivacaine. *Anesth Analg*. 2003;96(6):1631-1636.
21. Fettes PD, Jansson JR, Wildsmith JA. Spinal anaesthesia: mechanisms, agents and techniques. *Anaesthesia*. 2009;64(Suppl 2):24-33.
22. Breebaart MB, Sermeus LA, Vercauteren MP, et al. Selective spinal anesthesia with low-dose hyperbaric bupivacaine for knee arthroscopy: comparison with conventional dosing. *Anesth Analg*. 2003;96(6):1631-1634.
23. Choi DH, Park SH, Song IA. Intrathecal adjuvants for neuraxial anesthesia: a review of randomized clinical trials. *Korean J Anesthesiol*. 2017;70(5):547-560.
24. Bardsley H, Gristwood R, Baker H, Watson N, Nimmo W. A comparison of the cardiovascular effects of levobupivacaine and rac-bupivacaine following intravenous administration to healthy volunteers. *Br J Clin Pharmacol*. 1998;46(3):245-249.

25. Al-Mustafa MM, Abu-Halaweh SA, Aloweidi AS, et al. Intrathecal dexmedetomidine prolongs spinal anesthesia. *Anesth Analg*. 2009;108(2):482-487.
26. Gupta S, Kaur M, Gupta R, et al. Comparative evaluation of intrathecal dexmedetomidine, fentanyl, and magnesium sulphate as adjuvants to low-dose hyperbaric bupivacaine for lower limb surgeries. *Anesth Essays Res*. 2016;10(3):437-442.
27. Greene NM. Distribution of local anesthetic solutions within the subarachnoid space. *Anesth Analg*. 1985;64(7):715-730.
28. Povey HM, Jacobsen J, Westergaard-Nielsen J. Subarachnoid analgesia with hyperbaric bupivacaine: effect of varying volume. *Br J Anaesth*. 1989;62(6):647-650.
29. Bardsley H, Gristwood R, Baker H, Watson N, Nimmo W. A comparison of the cardiovascular effects of levobupivacaine and rac-bupivacaine following intravenous administration to healthy volunteers. *Br J Clin Pharmacol*. 1998;46(3):245-249.
30. Kuusniemi KS, Pihlajamäki KK, Pitkänen MT. Low-dose bupivacaine spinal anesthesia for outpatient knee arthroscopy. *Reg Anesth Pain Med*. 1999;24(6):594-598.
31. Liu SS, McDonald SB. Current issues in spinal anesthesia. *Anesthesiology*. 2001;94(5):888-906.
32. Gupta S, Kaur M, Gupta R, et al. Comparative evaluation of intrathecal dexmedetomidine, fentanyl, and magnesium sulphate as adjuvants to low-dose hyperbaric bupivacaine for lower limb surgeries. *Anesth Essays Res*. 2016;10(3):437-442.
33. Virtanen R, Savola JM, Saano V, Nyman L. Characterization of the selectivity, specificity and potency of medetomidine as an α2-adrenoceptor agonist. *Eur J Pharmacol*. 1988;150(1-2):9-14.
34. Correa-Sales C, Rabin BC, Maze M. A hypnotic response to dexmedetomidine, an α2 agonist, is mediated in the locus coeruleus in rats. *Anesthesiology*. 1992;76(6):948-952.
35. Ebert TJ, Hall JE, Barney JA, Uhrich TD, Colinco MD. The effects of increasing plasma concentrations of dexmedetomidine in humans. *Anesthesiology*. 2000;93(2):382-394.
36. Jakob SM, Ruokonen E, Grounds RM, et al. Dexmedetomidine vs midazolam or propofol for sedation during prolonged mechanical ventilation: two randomized controlled trials. *JAMA*. 2012;307(11):1151-1160.
37. Al-Mustafa MM, Abu-Halaweh SA, Aloweidi AS, et al. Intrathecal dexmedetomidine prolongs spinal anesthesia. *Anesth Analg*. 2009;108(2):482-487.
38. Naaz S, Bandey J, Ozair E, Asghar A. Dexmedetomidine in current anaesthesia practice—A review. *J Clin Anesth*. 2017;41:30-39.
39. Fawcett WJ, Haxby EJ, Male DA. Magnesium: physiology and pharmacology. *Br J Anaesth*. 1999;83(2):302-320.
40. James MF. Clinical use of magnesium infusions in anesthesia. *Anesth Analg*. 1992;74(1):129-136.
41. Arcioni R, Palmisani S, Tigano S, et al. Combined intrathecal and epidural magnesium sulfate supplementation of spinal anesthesia to reduce postoperative analgesic requirements. *Anesth Analg*. 2007;104(5):1261-1269.
42. Malleeswaran S, Panda N, Mathew P, Bagga R. A randomized study of magnesium sulphate as an adjuvant to intrathecal bupivacaine in patients with preeclampsia undergoing caesarean section. *Int J Obstet Anesth*. 2010;19(2):161-166.
43. Buvanendran A, McCarthy RJ, Kroin JS, et al. Intrathecal magnesium prolongs fentanyl analgesia: a prospective, randomized, controlled trial in patients undergoing knee arthroscopy. *Anesth Analg*. 2002;95(3):661-666.
44. Yaksh TL. Pharmacology of spinal opioids. *Anesth Analg*. 1987;66(8):759-776.
45. Stanley TH. The fentanyl story. *J Pain*. 2014;15(12):1215-1226.
46. Ben-David B, Solomon E, Levin H, Admoni H, Vaida S. Intrathecal fentanyl with small-dose dilute bupivacaine: better anesthesia without prolonging recovery. *Anesth Analg*. 1997;85(3):560-565.
47. Etches RC, Sandler AN, Daley MD. Respiratory depression and spinal opioids. *Can J Anaesth*. 1989;36(2):165-185.
48. Ture H, Uckunkaya N, Ozkan B, et al. Comparison of spinal anesthesia with intrathecal fentanyl or fentanyl plus low-dose bupivacaine in outpatient arthroscopic knee surgery. *Acta Anaesthesiol Scand*. 2001;45(1):19-23.
49. Dahl JB, Jeppesen IS, Jørgensen H, Wetterslev J, Møiniche S. Intraoperative and postoperative analgesic efficacy and adverse effects of intrathecal opioids in patients undergoing cesarean section with spinal anesthesia: a qualitative and quantitative systematic review of randomized controlled trials. *Anesthesiology*. 1999;91(6):1919-1927.
50. Gehling M, Tryba M. Risks and side-effects of intrathecal morphine combined with spinal anaesthesia: a meta-analysis. *Anaesthesia*. 2009;64(6):643-651.
51. Choi DH, Park SH, Song IA. Intrathecal adjuvants for neuraxial anesthesia: a review of randomized clinical trials. *Korean J Anesthesiol*. 2017;70(5):547-560.
52. Gupta S, Kaur M, Gupta R, et al. Comparative evaluation of intrathecal dexmedetomidine, fentanyl, and magnesium sulphate as adjuvants to low-dose hyperbaric bupivacaine for lower limb surgeries. *Anesth Essays Res*. 2016;10(3):437-442.
53. Al-Mustafa MM, Abu-Halaweh SA, Aloweidi AS, et al. Intrathecal dexmedetomidine prolongs spinal anesthesia. *Anesth Analg*. 2009;108(2):482-487.
54. Ture H, Uckunkaya N, Ozkan B, et al. Comparison of spinal anesthesia with intrathecal fentanyl or fentanyl plus low-dose bupivacaine in outpatient arthroscopic knee surgery. *Acta Anaesthesiol Scand*. 2001;45(1):19-23.
55. Buvanendran A, McCarthy RJ, Kroin JS, et al. Intrathecal magnesium prolongs fentanyl analgesia: a prospective, randomized, controlled trial in patients undergoing knee arthroscopy. *Anesth Analg*. 2002;95(3):661-666.
56. Kumar A, Sharma DK, Datta B. Comparative evaluation of intrathecal dexmedetomidine and fentanyl as adjuvants to low-dose bupivacaine for knee arthroscopy. *J Anaesthesiol Clin Pharmacol*. 2017;33(4):496-502.
57. Choi DH, Park SH, Song IA. Intrathecal adjuvants for neuraxial anesthesia: a review of randomized clinical trials. *Korean J Anesthesiol*. 2017;70(5):547-560.

58. Naaz S, Bandey J, Ozair E, Asghar A. Dexmedetomidine in current anaesthesia practice—A review. *J Clin Anesth*. 2017;41:30-39.
59. Arcioni R, Palmisani S, Tigano S, et al. Combined intrathecal and epidural magnesium sulfate supplementation of spinal anesthesia to reduce postoperative analgesic requirements. *Anesth Analg*. 2007;104(5):1261-1269.
60. Etches RC, Sandler AN, Daley MD. Respiratory depression and spinal opioids. *Can J Anaesth*. 1989;36(2):165-185.
61. Gupta S, Kaur M, Gupta R, et al. Comparative evaluation of intrathecal dexmedetomidine, fentanyl, and magnesium sulphate as adjuvants to low-dose hyperbaric bupivacaine for lower limb surgeries. *Anesth Essays Res*. 2016;10(3):437-442.
62. Korhonen AM, Valanne JV, Jokela RM, Ravaska P, Korttila K. Intrathecal hyperbaric bupivacaine 3 mg + fentanyl 10 µg for outpatient knee arthroscopy with tourniquet. *Acta Anaesthesiol Scand*. 2003;47(3):342-346.
63. Unal D, et al. Selective spinal anaesthesia with low-dose bupivacaine with or without fentanyl for lower-extremity surgery. *Acta Anaesthesiol Scand*. 2012;56(3):332-338.
64. Buvanendran A, McCarthy RJ, Kroin JS, et al. Intrathecal magnesium prolongs fentanyl analgesia: a prospective, randomized, controlled trial in patients undergoing knee arthroscopy. *Anesth Analg*. 2002;95(3):661-666.
65. Khezri MB, et al. Comparison of postoperative analgesic effect of intrathecal magnesium sulfate and fentanyl added to bupivacaine. *Anesth Pain Med*. 2012;2(3):127-133.
66. Nath MP, et al. Efficacy of intrathecal magnesium sulfate as an adjuvant to bupivacaine. *J Anaesthesiol Clin Pharmacol*. 2012;28(4):542-546.
67. Kumar S, et al. A systematic review and meta-analysis of intrathecal dexmedetomidine with bupivacaine for spinal anesthesia. *J Clin Anesth*. 2022;77:110667.
68. Liu S, et al. Effect of a 5-µg dose of intrathecal dexmedetomidine with bupivacaine: meta-analysis. *Clin Ther*. 2020;42(8):e148-e160.
69. Medeiros H, et al. Combined intrathecal dexmedetomidine and local anesthetic: systematic review and meta-analysis. *Br J Anaesth*. 2025;In press.
70. El-Saeid GM, et al. Dexmedetomidine (5 µg) vs fentanyl (25 µg) as intrathecal adjuvants to bupivacaine in low-dose spinal anesthesia: randomized trial. *Egypt J Anaesth*. 2023;39(1):626-635.
71. Ismail EA, et al. Intrathecal vs intra-articular dexmedetomidine with bupivacaine for arthroscopic knee surgery: randomized trial. *Saudi J Anaesth*. 2017;11(2):130-137.
72. Xiang W, et al. Magnesium sulfate + bupivacaine for arthroscopy: systematic review and meta-analysis. *Transl Perioper Pain Med*. 2021;8(2):e.
73. He Y, et al. Intra-articular magnesium + bupivacaine is most effective and safe for pain after knee arthroscopy: network meta-analysis. *Arthroscopy*. 2022;38(10):2897-2908.
74. Lu J-Z, et al. Efficacy of intra-articular fentanyl for knee arthroscopy: meta-analysis of RCTs. *Pain Res Manag*. 2020;2020:1-10.
75. Black AS, Newcombe GN, Plummer JL, et al. Spinal anesthesia for ambulatory arthroscopic knee surgery: low-dose prilocaine + fentanyl vs bupivacaine + fentanyl. *Br J Anaesth*. 2011;106(2):183-188.

.