RESEARCH PAPER

Nalbuphine versus Butorphanol as Intrathecal Adjuvants to Bupivacaine in Spinal Anesthesia: A Systematic Review of Efficacy and Safety

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Abstract

Background

Combining opioids with hyperbaric bupivacaine at the intrathecal level is a widely used approach for lengthening how long a spinal block lasts and sharpening how well it controls pain afterward. Nalbuphine and butorphanol, two agents with a mixed agonist-antagonist profile, have attracted growing clinical interest, since each controls pain well while keeping typical opioid complications — among them pruritus and respiratory depression — comparatively rare. Still, which of the two performs better overall, weighing both effectiveness and safety, has not been firmly settled.

Objective

The aim here was to systematically weigh how intrathecal nalbuphine stacks up against intrathecal butorphanol, in terms of both effectiveness and safety, when either is added to hyperbaric bupivacaine for patients having surgery under spinal block.

Methods

The search covered six databases — PubMed/MEDLINE, Embase, Scopus, Web of Science, the Cochrane Library, and Google Scholar — for literature through 2026. Eligible studies were RCTs or prospective comparative trials that pitted the two drugs directly against each other intrathecally. Data pulled from each covered how quickly and for how long sensory and motor block set in, how long postoperative pain relief lasted, the interval before a first rescue dose was needed, hemodynamic readings, and side effects, all brought together through qualitative synthesis.

Results

Across the included studies, both nalbuphine and butorphanol reliably improved spinal anesthesia quality relative to bupivacaine used alone. Nalbuphine tended to extend postoperative pain relief further, prolong sensory block, and push back the point at which patients needed rescue analgesia. Butorphanol provided adequate intraoperative anesthesia, though its analgesic effect wore off somewhat sooner in most trials. Side-effect rates — covering hypotension, bradycardia, nausea, vomiting, pruritus, respiratory depression, and urinary retention — stayed low and roughly matched between arms, and hemodynamics held steady with both agents.

Conclusion

Taken together, the evidence indicates that both nalbuphine and butorphanol are safe, effective choices as intrathecal adjuvants to hyperbaric bupivacaine. Nalbuphine, however, appears to have an edge in postoperative analgesia while carrying a similar safety profile, which makes it the more attractive option when longer pain relief is the goal. Confirming this with confidence will require larger, multicenter trials using standardized dosing.

Keywords: Spinal anesthesia; Intrathecal nalbuphine; Intrathecal butorphanol; Hyperbaric bupivacaine; Postoperative analgesia; Opioid adjuvants; Systematic review.

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INTRODUCTION

Among regional techniques, spinal anesthesia remains one of the most frequently chosen for lower-abdominal, pelvic, perineal, and lower-limb procedures, largely because it acts quickly, produces dense neural block, relaxes muscles reliably, and carries a favorable safety record (1,2). Set against general anesthesia, it brings several advantages: less intraoperative blood loss, a lower rate of postoperative nausea and vomiting, faster return of bowel function, fewer thromboembolic events, and

solid postoperative pain control (3,4). One drawback, though, is that local anesthetics such as hyperbaric bupivacaine act only briefly, so postoperative analgesia often runs out early and rescue analgesics must be given sooner than would be ideal (5).

Researchers have looked at a range of intrathecal adjuvants as a way around this problem—additions meant to stretch out sensory blockade, sharpen anesthesia quality, cut postoperative pain, and reduce how much systemic analgesic a patient later needs (6). The adjuvant list includes opioids, α2-adrenergic agonists, ketamine, magnesium sulfate, neostigmine, and midazolam (7); of these, opioids have been studied the most, since they work together with local anesthetics to boost analgesia without adding much to sympathetic or motor block (8).

The analgesic action of intrathecal opioids comes from their binding to receptors in the substantia gelatinosa of the spinal cord's dorsal horn, which blocks the passage of nociceptive signals and reduces neurotransmitter release (9). Pairing these opioids with hyperbaric bupivacaine has become a well-established way to sharpen intraoperative anesthesia while extending postoperative pain relief (10). That said, conventional μ-agonists such as morphine and fentanyl often bring pruritus, nausea, vomiting, urinary retention, heavy sedation, and respiratory depression along with them—problems that have pushed the field toward safer alternatives (11,12).

Nalbuphine, a synthetic opioid, acts as a κ-receptor agonist while antagonizing μ receptors (13). This dual agonist-antagonist profile lets it deliver solid spinal analgesia while capping the risk of respiratory depression, which is what makes it an appealing intrathecal adjuvant (14). A number of randomized trials support this, showing that intrathecal nalbuphine lengthens both sensory block and postoperative analgesia without destabilizing hemodynamics or raising the rate of opioid-related side effects (15,16).

Butorphanol works on a similar mixed principle, acting predominantly at κ receptors with partial agonist-antagonist activity at μ receptors (17). Its intrathecal use has grown because it lengthens and improves spinal anesthesia while causing less respiratory depression than pure μ-agonists (18). Clinical evidence indicates that it extends postoperative analgesia, improves comfort, and delivers satisfactory intraoperative anesthesia with few complications (19).

Given their favorable safety records and analgesic effectiveness, both drugs have become recognized alternatives to conventional intrathecal opioids (20). They share a κ-agonist mechanism, but differences in receptor affinity, potency, duration of action, and side-effect profile could still shape how each performs clinically when given intrathecally (21). That uncertainty is why anesthesiologists continue to debate which agent gives better postoperative pain relief without compromising safety.

Over the past decade, a series of randomized trials have directly compared intrathecal nalbuphine with butorphanol as bupivacaine adjuvants in orthopedic, lower-abdominal, gynecological, and urological surgery (22,23). Outcomes assessed have included onset and duration of sensory and motor block, duration of effective postoperative analgesia, time to first rescue analgesic, hemodynamic stability, sedation, and opioid-related adverse events (24). Findings across these trials have not always agreed, largely because of differences in dosing, patient populations, anesthetic technique, and how outcomes were measured (25).

Bringing together data from many trials is exactly what a systematic review is meant to do, offering a fuller picture of how two treatments compare on effectiveness and safety (26). Careful appraisal of the pooled evidence can surface consistent patterns, flag where uncertainty remains, and steer clinical decisions toward what the evidence actually supports (27). For intrathecal opioid adjuvants specifically, a review weighing nalbuphine against butorphanol could help anesthesiologists select the drug best suited to optimizing perioperative analgesia while keeping adverse effects to a minimum (28).

MATERIALS AND METHODS

Study Design

This review was conducted in line with the **Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020)** guidelines, with the goal of tracking down, critically weighing, and pulling together evidence on intrathecal nalbuphine measured against intrathecal butorphanol as bupivacaine adjuvants in spinal anesthesia.

Eligibility Criteria

Inclusion Criteria

- Randomized controlled trials (RCTs).
- Prospective, comparative clinical trials.
- Adult surgical patients (age 18 or above) receiving spinal anesthesia.
- A direct head-to-head comparison of intrathecal nalbuphine and intrathecal butorphanol.
- Hyperbaric bupivacaine used as the local anesthetic agent.
- Studies reporting on one or more of the following outcomes:
    - Onset of sensory block
    - Onset of motor block
    - Duration of sensory block
    - Duration of motor block
    - Duration of postoperative analgesia

    - Time to first rescue analgesia
    - Hemodynamic parameters
    - Adverse events
- Full-text articles available in English.

Exclusion Criteria

- Preclinical or laboratory-based studies.
- Narrative reviews, other systematic reviews, and meta-analyses.
- Individual case reports or case series.
- Conference abstracts without complete data.
- Editorials and letters to the editor.
- Pediatric studies.
- Studies assessing epidural or intravenous nalbuphine or butorphanol.
- Studies lacking a direct comparison between nalbuphine and butorphanol.
- Duplicate publications.

Information Sources

Searches were carried out across the following electronic databases:

- PubMed/MEDLINE
- Embase
- Scopus
- Web of Science
- Cochrane Library
- Google Scholar

Reference lists from the eligible studies were manually checked as well, to catch any relevant publications the database searches might have missed.

Search Strategy

Search terms combined MeSH headings with free-text keywords, applied singly and in Boolean combination (AND/OR):

- "Nalbuphine"
- "Butorphanol"
- "Intrathecal"
- "Spinal anesthesia"
- "Subarachnoid block"
- "Hyperbaric bupivacaine"
- "Opioid adjuvant"
- "Regional anesthesia"

Example search string:

("Nalbuphine" AND "Butorphanol") AND ("Intrathecal" OR "Spinal anesthesia") AND ("Bupivacaine" OR "Subarachnoid block")

Study Selection

Every record pulled from the searches went into reference-management software for de-duplication, after which two reviewers independently screened titles and abstracts. Studies that passed this first screen were then read in full against the eligibility criteria, and any disagreement between reviewers was talked through until both sides agreed.

Data Extraction

From each included trial, the following was logged:

- First author
- Year of publication
- Country
- Study design
- Sample size
- Type of surgery
- Nalbuphine dose
- Butorphanol dose
- Bupivacaine dose
- Onset of sensory block
- Onset of motor block
- Duration of sensory block
- Duration of motor block
- Duration of postoperative analgesia
- Time to first rescue analgesia
- Hemodynamic parameters
- Adverse events
- Major conclusions

Outcome Measures

Primary Outcomes

- Duration of postoperative analgesia.
- Time to first rescue analgesic.

Secondary Outcomes

- Onset of sensory blockade.
- Onset of motor blockade.
- Duration of sensory blockade.
- Duration of motor blockade.
- Hemodynamic stability.
- Incidence of hypotension.
- Incidence of bradycardia.
- Incidence of nausea and vomiting.
- Incidence of pruritus.
- Sedation scores.
- Respiratory depression.
- Urinary retention.
- Shivering.
- Patient satisfaction.

Quality Assessment

RCT quality was judged using the **Cochrane Risk of Bias (RoB 2)** tool, working through the domains listed below, and each trial ended up rated low risk, some concerns, or high risk of bias overall.

- Randomization process.
- Deviations from intended interventions.
- Missing outcome data.
- Outcome measurement.
- Selection of reported results.

Data Synthesis

Because the synthesis was qualitative, findings were laid out in summary tables alongside a narrative account. Study by study, the review compared onset and duration of sensory/motor block, length of analgesia, need for rescue medication, hemodynamic shifts, and adverse effects, looking for patterns that held up consistently and differences that mattered clinically between the two drugs.

RESULTS

The database searches turned up 286 articles in total. Once duplicates were removed and titles, abstracts, and full texts had been screened, 11 randomized controlled trials covering 770 patients satisfied the inclusion criteria and were carried forward into this review.

Surgical settings across the 11 trials spanned lower-abdominal, gynecological, orthopedic, urological, and lower-limb procedures, all performed under spinal block, with nalbuphine and butorphanol compared head-to-head as bupivacaine adjuvants in each.

Broadly, spinal anesthesia quality and postoperative pain control improved with either drug, and in the majority of trials, how quickly sensory and motor function became blocked was about the same regardless of which opioid was used.

The real separation showed up in how long effects lasted: nalbuphine groups saw longer sensory block, longer motor block, and longer analgesia than butorphanol groups, and also went noticeably further before a first rescue dose was required — all pointing toward more durable pain control.

Pulling this together, both opioids hold up as effective and safe additions to intrathecal hyperbaric bupivacaine, and nalbuphine's advantage in analgesic duration and sensory-block length doesn't appear to trade off against a worse safety record.

DISCUSSION

As a regional technique, spinal anesthesia continues to be a mainstay for lower-abdominal, pelvic, perineal, gynecological, urological, and lower-limb surgery, thanks to its fast onset, dense sensory and motor block, good muscle relaxation, and effective postoperative pain control, all while sidestepping many of general anesthesia's complications (1,2). Its main constraint is that hyperbaric bupivacaine's action is fairly short-lived, which is why intrathecal adjuvants are used to extend postoperative analgesia without putting patient safety at risk (3). Mixed κ-agonists such as nalbuphine and butorphanol have drawn particular interest among these adjuvants because of their favorable analgesic profile and lower respiratory-depression risk relative to pure μ-agonists (4,5).

This review drew together 11 RCTs and 770 patients comparing the two drugs as bupivacaine adjuvants. Both agents markedly improved the quality of spinal anesthesia and postoperative pain relief, but when the evidence was pooled, nalbuphine consistently came out ahead on duration of both postoperative analgesia and sensory block, without giving up ground on safety relative to butorphanol.

Nearly every trial agreed on one thing: how fast the block set in, whether sensory or motor, was much the same with either drug. That tracks pharmacologically, since how quickly bupivacaine itself takes effect owes more to its own physicochemical properties than to whichever opioid rides along with it, so neither agent meaningfully shifted the timing of block onset (6,7) — a result that lines up with earlier work showing opioid adjuvants sharpen analgesia without materially speeding up or slowing down how fast local anesthetics act (8).

Onset aside, duration told a different story: nalbuphine consistently kept sensory block going longer than butorphanol did, and that longer block carried over into better postoperative analgesia and a longer wait before rescue medication was needed. The likely explanation lies in pharmacology—nalbuphine binds spinal κ-receptors with high affinity and stays attached in the dorsal horn longer, keeping nociceptive signaling suppressed for longer (9,10). Those properties are probably what make it especially useful for procedures expected to cause moderate-to-severe postoperative pain.

Motor block duration also ran a bit longer with nalbuphine, which is worth noting clinically since prolonged motor block can, in principle, hold back early ambulation in some patient groups. In practice, though, the increase reported across the trials was small and was not tied to later discharge or lower satisfaction, and most authors judged it an acceptable trade-off given how much postoperative analgesia improved (11,12).

How well postoperative pain is managed strongly shapes both recovery and patient satisfaction. Almost every trial in this review found that nalbuphine patients stayed pain-free notably longer, delaying the point at which rescue analgesia was first needed. Cutting down analgesic requirements this way matters clinically—it means less opioid use overall, more patient comfort, easier early mobilization, and potential support for enhanced-recovery pathways (13,14).

Butorphanol was not ineffective, to be clear—it improved postoperative pain relief meaningfully compared with bupivacaine alone, largely through κ-receptor agonism paired with partial μ-antagonism, giving decent visceral and somatic analgesia with minimal respiratory depression (15). But head-to-head, the trials in this review generally had it running out sooner than nalbuphine, which points to nalbuphine being the better choice when the goal is longer-lasting pain relief.

Hemodynamic stability is another factor to weigh here, since sympathetic block from spinal anesthesia can predispose patients to hypotension and bradycardia. On this front, both drugs performed reassuringly well—intraoperative heart rate, systolic and diastolic pressure, and mean arterial pressure stayed comparable between groups, suggesting that

neither opioid meaningfully worsens sympathetic blockade at the doses typically used intrathecally (16,17).

Safety, in general, looked good for both drugs across the pooled studies—hypotension, bradycardia, nausea, vomiting, urinary retention, shivering, and pruritus were all uncommon and similarly distributed between groups. None of the trials reported clinically significant respiratory depression, which underscores the safety edge that mixed agonist-antagonist opioids hold over conventional μ-agonists like morphine (18,19).

Of all the risks tied to intrathecal opioids, respiratory depression is the one clinicians worry about most. Because of their mixed receptor pharmacology, both nalbuphine and butorphanol show a ceiling effect on respiratory depression, cutting the risk of this potentially serious complication while still delivering effective analgesia (20)—a feature that makes them especially appealing for elderly patients or those with limited cardiopulmonary reserve.

Sedation, where reported, stayed mild in both arms—arguably a plus during regional anesthesia, since light sedation eases anxiety without compromising spontaneous breathing or airway reflexes, and none of the trials recorded sedation severe enough to need airway support or intensive monitoring (21).

Patient satisfaction has become a widely used marker of anesthetic quality, and most of the reviewed studies found it higher with nalbuphine, driven mainly by its longer analgesic duration and lower need for rescue medication. Better postoperative comfort in turn tends to support earlier mobilization and greater overall satisfaction with perioperative care (22).

Despite the overall tilt toward nalbuphine, a few caveats deserve attention when interpreting these results. Nalbuphine doses across the studies ranged roughly 0.4–1 mg and butorphanol doses roughly 25–50 μg, and the trials also varied by surgery type, patient characteristics, and pain/block assessment methods—differences that could partly explain the minor inconsistencies seen in reported outcomes (23).

Methodological quality of the included RCTs was mostly adequate, though several trials had fairly small sample sizes, and most were single-center studies conducted in India—a pattern that limits how confidently these findings can be generalized to other populations and healthcare settings (24).

A further limitation is inconsistency in outcome measurement: the studies used different pain scales, sensory-block assessment methods, and rescue-analgesic protocols, and these methodological gaps make direct quantitative comparison difficult and limit the scope for pooled statistical analysis (25).

Even with these constraints, multiple RCTs pointing the same way strengthens the case that intrathecal nalbuphine keeps postoperative analgesia going longer than butorphanol does, without sacrificing comparable hemodynamic stability or safety — a consistency that backs nalbuphine's use as a routine, effective spinal-anesthesia adjuvant.

Going forward, larger multicenter trials should test standardized doses of both drugs across a broader range of surgical populations, track longer-term postoperative outcomes, capture patient-reported recovery quality, and weigh cost-effectiveness—work that would help settle which intrathecal opioid best supports perioperative analgesia and surgical recovery.

On balance, this review suggests both drugs have real value as intrathecal opioid adjuvants, though the current evidence tips toward nalbuphine for its stronger postoperative analgesia alongside an equally good safety record—which is why it comes across as the preferred adjuvant to hyperbaric bupivacaine in many clinical settings.

The growing use of intrathecal opioid adjuvants reflects an ongoing push to get more out of spinal anesthesia—namely, longer postoperative analgesia without more adverse events. Bupivacaine alone gives reliable surgical anesthesia, but its analgesic effect typically fades within a few hours, leaving patients with early pain and a greater need for opioids. That is the practical reason combining it with intrathecal adjuvants has become standard practice, aimed at better comfort, lower postoperative opioid use, and smoother enhanced recovery (31,32).

Compared with conventional μ-agonists, nalbuphine and butorphanol both carry pharmacological advantages, since each acts predominantly at κ receptors while behaving as an antagonist or partial agonist at μ receptors. That receptor profile delivers strong spinal analgesia while cutting down substantially on respiratory depression, pruritus, and the more severe complications typically tied to morphine and fentanyl (33,34)—a picture this review's findings reinforce for mixed agonist-antagonist opioids used in neuraxial anesthesia generally.

Nalbuphine's edge in postoperative analgesia likely traces back to its pharmacodynamics: a strong pull toward κ receptors sitting in the dorsal horn's substantia gelatinosa, where it curbs the release of pain-signaling chemical messengers, substance P and glutamate among them. Damping down nociceptive transmission this way lowers central sensitization and stretches analgesia out past what the local anesthetic alone would provide (35); and since nalbuphine antagonizes μ receptors at the same time, it keeps

most of the usual opioid side effects at bay while still holding pain in check.

Butorphanol earns its place too, working through κ-receptor activation to deliver real spinal analgesia, and the evidence shows it does lengthen and sharpen spinal block compared with local anesthetic given alone. Even so, most of the studies here found its postoperative analgesia ran shorter than nalbuphine's. The gap was modest in a few trials, but the direction was consistent—nalbuphine came out ahead on duration of pain relief and the interval before rescue analgesia was needed (36).

Time to first rescue analgesic was tracked in nearly every study, and for good reason—it is a direct proxy for how long effective analgesia actually lasts and carries real implications for postoperative pain management. Nalbuphine patients generally went longer before needing supplemental analgesics, which in turn can mean fewer opioid-related side effects, better patient satisfaction, and easier engagement with early mobilization and rehabilitation (37).

Nalbuphine's longer sensory block is another clinically meaningful benefit—maintaining adequate block through the early postoperative window supports better comfort, a smaller stress response to surgery, and lower pain scores. Blunting nociceptive input during this window may also lower the odds of central sensitization and chronic postsurgical pain developing, though none of the included trials tracked long-term pain outcomes directly. Even so, good early analgesia is recognized as an important piece of overall surgical recovery (38).

Motor block duration matters too in spinal anesthesia, since a prolonged block could theoretically slow ambulation. What was seen with nalbuphine, though, was a modest extension that did not harm postoperative recovery in practice, and most authors treated it as an acceptable trade-off given the analgesic and comfort gains. Still, for ambulatory surgery where rapid recovery is the priority, the adjuvant choice should probably be tailored to the specific procedure and the institution's own protocols (39).

Hemodynamic stability continues to be a key concern with spinal anesthesia, given that sympathetic block can trigger hypotension and bradycardia, especially in elderly or cardiovascularly compromised patients. Across the reviewed trials, both nalbuphine and butorphanol showed strong cardiovascular safety, with neither altering heart rate, blood pressure, or mean arterial pressure any more than the other—evidence that neither opioid worsens the sympathetic block already induced by hyperbaric bupivacaine, and that both can be used safely in well-selected patients (40).

Adverse effects tied to opioid use were consistently uncommon across this review's evidence base—nausea, vomiting, pruritus, urinary retention, shivering, hypotension, and bradycardia all occurred rarely and mildly, and none of the RCTs reported respiratory depression severe enough to need ventilatory support. That reinforces the established pharmacological edge that mixed κ-agonist/μ-antagonist opioids hold over traditional μ-agonists.

Sedation gets close attention in regional anesthesia because too much of it can threaten airway protection and slow recovery. Here, sedation stayed mild in both groups, with no patient needing airway intervention or intensive monitoring—and mild intraoperative sedation can arguably work in a patient's favor, easing anxiety without giving up spontaneous breathing or airway reflexes.

Patient satisfaction now ranks as one of the important quality markers in perioperative care, and the higher scores reported with nalbuphine mostly trace back to its longer analgesia, later need for rescue medication, and greater comfort during recovery. Good postoperative pain control, more broadly, shapes patient experience for the better—earlier mobilization, better sleep, and stronger alignment with enhanced-recovery pathways all follow from it.

Even though the balance of evidence favors nalbuphine, some limitations temper that conclusion. Most trials were small, single-center studies, which cuts into statistical power and limits how broadly the results can be applied, and there was considerable variation across studies in drug doses, surgical procedures, pain-assessment methods, rescue protocols, and follow-up length. Standardizing these variables in future work would make cross-study comparison easier and strengthen the overall evidence base.

What is needed next are large, multicenter RCTs using standardized doses of both drugs across varied surgical populations, plus additional work on recovery quality, functional outcomes, patient-reported measures, cost-effectiveness, and long-term postoperative pain—all of which would sharpen understanding of where these agents best fit in modern anesthetic practice.

Taking the evidence as a whole, both nalbuphine and butorphanol qualify as effective, safe intrathecal adjuvants to hyperbaric bupivacaine. But the RCTs consistently point to nalbuphine offering better postoperative analgesia, longer sensory block, a later need for rescue analgesia, higher patient satisfaction, and comparable safety—which together make it the preferred adjuvant across a wide range of surgical procedures performed under spinal anesthesia.

CONCLUSION

Both intrathecal nalbuphine and intrathecal butorphanol emerge from this review as effective, safe choices for pairing with hyperbaric bupivacaine during spinal anesthesia. Each one sharpens spinal block quality, stretches out postoperative analgesia, keeps intraoperative vital signs steady, and carries a low rate of opioid-related side effects.

Between the two, nalbuphine consistently came out ahead clinically—longer sensory block, more prolonged postoperative analgesia, and a significantly later need for rescue analgesics than butorphanol. Yet this stronger analgesic punch did not cost anything on safety: rates of hypotension, bradycardia, nausea, vomiting, pruritus, urinary retention, and heavy sedation all stayed low, and no included study reported clinically significant respiratory depression.

That said, most of the supporting evidence comes from single-site trials with fairly small cohorts and dosing and assessment approaches that varied from study to study. Turning these conclusions into firm, evidence-based recommendations for routine practice will require well-designed multicenter RCTs built around standardized intrathecal dosing and uniform outcome measures.

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