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REVIEW: Intrathecal Neostigmine for Post-Cesarean Analgesia: Balancing Analgesic Efficacy Against Nausea and Vomiting—A Current Concept Review

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ABSTRACT

Cesarean delivery is followed by clinically important acute pain, but analgesic intensity must be balanced against maternal nausea, sedation, delayed mobilization, impaired oral intake, and disruption of early recovery. Intrathecal neostigmine is a reversible acetylcholinesterase inhibitor that increases spinal acetylcholine and augments cholinergic antinociception. Early human and obstetric trials established a reproducible analgesic and opioid-sparing signal. In a post-cesarean dose-ranging trial, 10-100 mcg of intrathecal neostigmine reduced 24-hour morphine consumption and hourly morphine requirement for approximately 10 hours. In another randomized trial, 25 mcg produced analgesia broadly comparable with 100 mcg of intrathecal morphine, but nausea and/or vomiting occurred in 73.7% of patients.

This efficacy-to-tolerability mismatch remains the central limitation. A perioperative/peripartum meta-analysis found approximately fivefold higher odds of nausea/vomiting, whereas an obstetric neuraxial systematic review found nearly ninefold higher odds of nausea after intrathecal neostigmine. More recent comparative evidence, including a 2026 network meta-analysis, confirms that neostigmine-containing combinations can show analgesic activity, but certainty is generally low and does not neutralize the direct emetic signal. Dose reduction, altered baricity, combination strategies, and antiemetic prophylaxis may modify adverse effects, yet no contemporary trial has established a reliably favorable therapeutic window.

Meanwhile, the comparator standard has advanced: low-dose intrathecal morphine within scheduled nonopioid multimodal analgesia is effective, extensively studied, and embedded in modern PROSPECT and enhanced-recovery recommendations. Current evidence therefore supports intrathecal neostigmine as a mechanistically informative but investigational adjunct rather than routine post-cesarean therapy. Future trials should test ultra-low-dose combinations against contemporary enhanced-recovery regimens using patient-centered composite outcomes such as adequate analgesia without nausea/vomiting, excessive sedation, or delayed mobilization.

1. Introduction

Pain after cesarean delivery is common, dynamic, and clinically consequential. A high-quality analgesic strategy must support coughing, mobilization, infant care, feeding, sleep, and recovery while minimizing opioid exposure and treatment-related adverse effects. Contemporary procedure-specific recommendations therefore emphasize a multimodal foundation: low-dose long-acting neuraxial opioid when appropriate, scheduled acetaminophen/paracetamol and a

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nonsteroidal anti-inflammatory drug (NSAID), dexamethasone where suitable, and rescue opioid rather than routine high-dose systemic opioid therapy (1-3). Within that framework, the value of any neuraxial adjunct is determined not only by its ability to lower pain scores or opioid consumption, but by whether it improves the overall maternal recovery experience.

Intrathecal neostigmine is an instructive example of this distinction. By inhibiting acetylcholinesterase in the spinal compartment, neostigmine increases endogenous acetylcholine at neuraxial cholinergic synapses and can produce antinociception without acting as an opioid. Early dose-finding work in humans established spinal analgesic activity, but also identified nausea and vomiting as prominent dose- and distribution-sensitive adverse effects (4-6). Obstetric studies subsequently confirmed both sides of this pharmacology: measurable postoperative analgesia and opioid-sparing benefit on one hand, and clinically important emesis on the other (7-10).

The central question is therefore no longer whether intrathecal neostigmine can provide analgesia. It can. The more relevant question is whether the incremental analgesic benefit is large and reliable enough to compensate for nausea, vomiting, autonomic effects, sedation or restlessness, and uncertainty regarding a practical therapeutic window in patients undergoing cesarean delivery. This narrative Current Concept Review discusses the mechanistic rationale, pivotal obstetric studies, route-specific tolerability, and the place of intrathecal neostigmine within contemporary enhanced-recovery analgesia, with emphasis on the clinical balance between analgesic benefit and treatment burden.

2. Mechanistic basis of intrathecal neostigmine

2.1 Spinal cholinergic antinociception

The dorsal horn contains a functionally relevant cholinergic system that modulates nociceptive processing. Neostigmine is a quaternary ammonium acetylcholinesterase inhibitor; when placed intrathecally, it reduces acetylcholine breakdown within the cerebrospinal fluid (CSF) and spinal cord environment. Human phase-I work showed that intrathecal neostigmine can increase CSF acetylcholine from very low baseline concentrations to more than 100 pmol/mL within minutes, providing a direct pharmacodynamic bridge between drug administration and enhanced cholinergic signaling (4,5). Muscarinic mechanisms are considered central to analgesia, with additional nicotinic interactions and modulation of inhibitory interneuronal systems contributing to the net antinociceptive effect (6).

This mechanism is attractive in obstetric anesthesia because it is opioid-independent. In theory, an effective nonopioid spinal adjunct could prolong analgesia while reducing systemic opioid exposure, pruritus, and respiratory monitoring burden. The difficulty is that cholinergic activation is not confined to a single desired spinal circuit. The same neuraxial exposure that promotes analgesia can activate pathways associated with nausea, vomiting, bradycardia, sweating, intestinal activity, restlessness, and sedation. The clinical problem is therefore one of anatomic and pharmacologic selectivity rather than absence of analgesic pharmacology.

2.2 Baricity, rostral spread, and the therapeutic-index problem

Early human safety studies demonstrated that nausea intensity after intrathecal neostigmine depends on dose, injectate characteristics, and distribution within CSF (4). Hyperbaric solutions and positional control were explored to limit cephalad drug migration, reflecting a plausible mechanism in which rostral exposure increases emetogenic cholinergic signaling. However, intrathecal drug spread is intrinsically variable and depends on baricity, patient position, dose/volume, injection characteristics, and patient anatomy (36). For a drug with a narrow separation between desired spinal analgesia and unpleasant

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supraspinal effects, this variability is clinically important.

The resulting therapeutic-index problem can be expressed simply: a lower dose may reduce nausea but also reduce the reliability of analgesia, whereas a higher dose may strengthen or prolong block characteristics without proportionally improving postoperative benefit. Several studies suggest that analgesic gain can plateau while adverse effects continue to accumulate. That pattern is particularly unfavorable in cesarean delivery, where patients are awake and often highly sensitive to intraoperative nausea, vomiting, dizziness, and sedation.

3. Clinical evidence in cesarean delivery

3.1 Dose-ranging post-cesarean evidence

Krukowski and colleagues performed the pivotal post-cesarean dose-response trial in 24 healthy term patients randomized to intrathecal placebo or neostigmine 10, 30, or 100 mcg before epidural lidocaine anesthesia (7). Neostigmine reduced 24-hour morphine consumption from 82 ± 7 mg in the placebo group to approximately 50 ± 8 mg when neostigmine groups were considered together, and hourly morphine use was reduced for roughly 10 hours. Importantly, the study did not demonstrate a clear dose-response across 10-100 mcg. The signal was therefore clinically interesting but pharmacologically awkward: substantial opioid-sparing occurred, yet simply increasing the dose did not predictably improve analgesia.

The trial also illustrates an interpretive limitation that remains relevant. A reduction in morphine consumption is valuable only if the replacement intervention does not impose a comparable or greater recovery burden. In the intrathecal neostigmine literature, nausea and vomiting became that competing burden. The small sample size also limited confidence regarding uncommon maternal or neonatal adverse outcomes; absence of a detected fetal signal in a small trial should not be interpreted as proof of broad fetal safety.

3.2 Neostigmine versus intrathecal morphine and low-dose combinations

Chung and colleagues randomized 79 term parturients to spinal bupivacaine with saline, neostigmine 25 mcg, morphine 100 mcg, or a combination of neostigmine 12.5 mcg plus morphine 50 mcg (8). The 25-mcg neostigmine regimen produced analgesic efficacy broadly similar to 100 mcg of intrathecal morphine, confirming that low-dose spinal neostigmine can be clinically active. However, nausea and/or vomiting occurred in 73.7% of patients receiving neostigmine 25 mcg. The combination arm suggested a potentially useful concept: two mechanistically different drugs at reduced doses might provide longer analgesia with less pruritus than full-dose morphine and possibly less severe emesis than higher-dose neostigmine.

That combination hypothesis remains pharmacologically credible but clinically unproven. The study was small, conducted before current enhanced-recovery bundles, and was not designed to establish noninferiority on a modern patient-centered outcome such as pain control without nausea/vomiting, rescue antiemetic use, excessive sedation, or delayed mobilization. In current practice, an adjunct that only reduces opioid consumption is not sufficient; it must improve net recovery.

3.3 Higher-dose and combination spinal strategies

Pan and colleagues examined intrathecal neostigmine 50 mcg, clonidine 150 mcg, and their combination with bupivacaine for cesarean anesthesia, demonstrating that neostigmine can enhance spinal anesthetic and postoperative analgesic effects and that cholinergic and alpha-2-adrenergic pathways can interact (9). Such synergy is mechanistically useful but also illustrates a recurring problem: combining neuraxial adjuncts may improve block characteristics while introducing competing adverse-effect profiles such as hypotension, sedation, bradycardia, or emesis.

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A later randomized study of 90 elective cesarean patients compared bupivacaine alone with bupivacaine plus intrathecal neostigmine 75 or 150 mcg (10). Neostigmine prolonged sensory and motor block and postoperative analgesia, but nausea and vomiting increased in a dose-related manner. These higher doses therefore magnified the central trade-off rather than solving it. A longer block is not automatically a better post-cesarean outcome if it delays functional recovery or is accompanied by severe gastrointestinal symptoms.

Table 1. Pivotal obstetric evidence defining the efficacy-tolerability trade-off of neuraxial neostigmine.

Study	Design/regimen	Analgesic signal	Adverse effects and current interpretation
Krukowski et al., 1997 (7)	n=24; placebo vs IT neostigmine 10, 30, 100 mcg	24-h morphine reduced (82 ± 7 mg placebo vs ~50 ± 8 mg pooled neostigmine); hourly morphine reduction for ~10 h; no clear dose-response.	Demonstrates real opioid-sparing, but small sample and uncertain therapeutic window.
Chung et al., 1998 (8)	n=79; saline, neostigmine 25 mcg, morphine 100 mcg, or neostigmine 12.5 + morphine 50 mcg	Neostigmine 25 mcg broadly comparable with morphine 100 mcg; low-dose combination prolonged analgesia.	Nausea/vomiting in 73.7% with neostigmine 25 mcg. Combination concept promising but inadequately validated.
Pan et al., 1998 (9)	Cesarean spinal anesthesia; bupivacaine with neostigmine 50 mcg, clonidine 150 mcg, both, or control	Neostigmine and clonidine enhanced spinal anesthetic/analgesic effects; combination suggested mechanistic synergy.	Adjunct stacking can add hypotension, sedation or emetic burden; not a modern recovery-centered regimen.
Hye et al., 2010 (10)	n=90; bupivacaine alone or + neostigmine 75 or 150 mcg	Longer sensory/motor block and postoperative analgesia.	Dose-related nausea/vomiting; high-dose strategy is poorly aligned with rapid recovery.
Ho et al., 2005 (11)	Meta-analysis of 19 perioperative/peripartum studies	Delayed rescue analgesia by ~168 min and improved pain measures.	Nausea/vomiting OR 5.0 (95% CI 3.4-7.3); bradycardia and agitation/restlessness also increased. Authors judged disadvantages greater than modest benefit.
Cossu et al., 2015 (12)	Systematic review of neuraxial neostigmine in obstetric anesthesia/analgesia	Reduced local-anesthetic consumption; no fetal harm signal detected in available trials.	Intrathecal route increased nausea OR 8.99 (95% CI 4.74-17.05); epidural route did not show the same nausea signal.
Ollosu et al., 2026 (22)	Network meta-analysis; 166 cesarean RCTs, 14,925 patients, 32 intrathecal strategies	Several morphine-containing combinations, including some with neostigmine, ranked favorably for duration/opioid reduction.	Evidence certainty generally very low to low; broad network results do not erase the specific emesis signal of intrathecal neostigmine.

CI, confidence interval; h, hour(s); IT, intrathecal; mcg, microgram(s); OR, odds ratio; RCT, randomized controlled trial.

4. Nausea and vomiting: the principal tolerability limitation

4.1 Magnitude and consistency of the emetic signal

The most influential evidence synthesis is the meta-analysis by Ho and colleagues, which examined intrathecal neostigmine as an adjunct across perioperative and peripartum settings (11). Across 19 studies, intrathecal neostigmine improved some pain outcomes and delayed rescue analgesia, but the improvement was modest relative to adverse effects. The odds of nausea/vomiting were approximately fivefold higher (OR 5.0, 95% CI 3.4-7.3). Bradycardia requiring atropine and agitation/restlessness were also increased. The authors concluded that the disadvantages outweighed the minor analgesic improvement.

The obstetric-specific systematic review by Cossu and colleagues reached a similar route-dependent conclusion (12). Intrathecal neostigmine markedly increased nausea (OR 8.99, 95% CI 4.74-17.05), whereas epidural administration did not show the same increase (OR 0.97 in the cited analysis). This contrast is important because it argues against interpreting nausea as a generic property of any neuraxial neostigmine exposure. Instead, it supports a distribution-dependent mechanism in which intrathecal delivery creates higher or less controllable central cholinergic exposure.

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For cesarean delivery, nausea and vomiting have unusually high clinical salience. They can arise intraoperatively from spinal hypotension, uterotonics, visceral traction, uterine exteriorization, anxiety, or opioid exposure; adding a strongly emetogenic neuraxial adjunct compounds an already multifactorial risk environment. Contemporary Enhanced Recovery After Cesarean guidance specifically emphasizes antiemetic prophylaxis and prevention of spinal hypotension as core intraoperative interventions (38). In an awake patient, severe nausea or vomiting can be more distressing than a modest difference in pain score. It may also delay oral intake and mobilization and increase rescue antiemetic use. Nausea should therefore be treated as a competing recovery outcome and potential treatment failure, not as a minor side effect.

4.2 Can prophylactic antiemetics modify the risk?

Modern antiemetic prophylaxis is substantially better developed than it was during the pivotal neostigmine trials. Multimodal postoperative nausea and vomiting (PONV) guidance supports risk-adapted prophylaxis, and 5-hydroxytryptamine-3 (5-HT3) antagonists and dexamethasone are widely used in cesarean pathways (17-19). In women receiving intrathecal morphine, 5-HT3 antagonists reduce nausea/vomiting and pruritus, and a 2024 network meta-analysis suggested that combinations such as a 5-HT3 antagonist plus dexamethasone rank well for prophylaxis of neuraxial-morphine-associated PONV (18,19).

However, these data cannot simply be extrapolated to intrathecal neostigmine. Opioid-associated PONV and cholinergic neostigmine-associated nausea are not pharmacologically identical, and no contemporary cesarean trial has shown that a standardized antiemetic bundle reliably converts intrathecal neostigmine into a favorable net-benefit intervention. Antiemetic prophylaxis may attenuate symptoms, but it also adds medication, cost, and potential adverse effects while leaving the underlying therapeutic-index problem unresolved. A future trial could test this hypothesis; current evidence is insufficient to use prophylaxis as a rationale for routine intrathecal neostigmine.

4.3 Comparison with intrathecal morphine

Intrathecal morphine is not free of adverse effects. Dose-ranging evidence shows a trade-off between longer analgesia and more nausea/vomiting or pruritus as the dose rises, and contemporary meta-analysis confirms increased nonpulmonary adverse effects such as PONV, pruritus, and urinary retention (15,16,20). The crucial distinction is that intrathecal morphine has a far larger evidence base, standardized low-dose regimens, well-described monitoring recommendations, and integration into enhanced-recovery pathways (1,2,15,23). Its risks can therefore be anticipated, monitored, and mitigated within established protocols.

By contrast, the intrathecal neostigmine literature never established a similarly robust low-dose therapeutic window. Even a 25-mcg dose produced very high nausea/vomiting in one cesarean RCT (8). This means that "opioid-free" does not automatically mean "better tolerated." The relevant comparator is not systemic morphine from older trials, but contemporary low-dose neuraxial morphine embedded within scheduled nonopioid analgesia.

5. Mechanism-to-clinical-value model

6. Route-specific considerations: intrathecal versus epidural neostigmine

A separate body of obstetric evidence suggests that epidural neostigmine can reduce local-anesthetic or opioid requirements with much less nausea than intrathecal administration. Roelants and colleagues explored epidural neostigmine, including combinations with other neuraxial agents, for labor analgesia (13,27). Ross and colleagues found that adding epidural neostigmine to

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patient-controlled epidural labor analgesia reduced hourly bupivacaine requirement by approximately 19%-25% without increasing nausea, although mild sedation remained possible (28). This route effect is consistent with slower or more segmental neuraxial exposure.

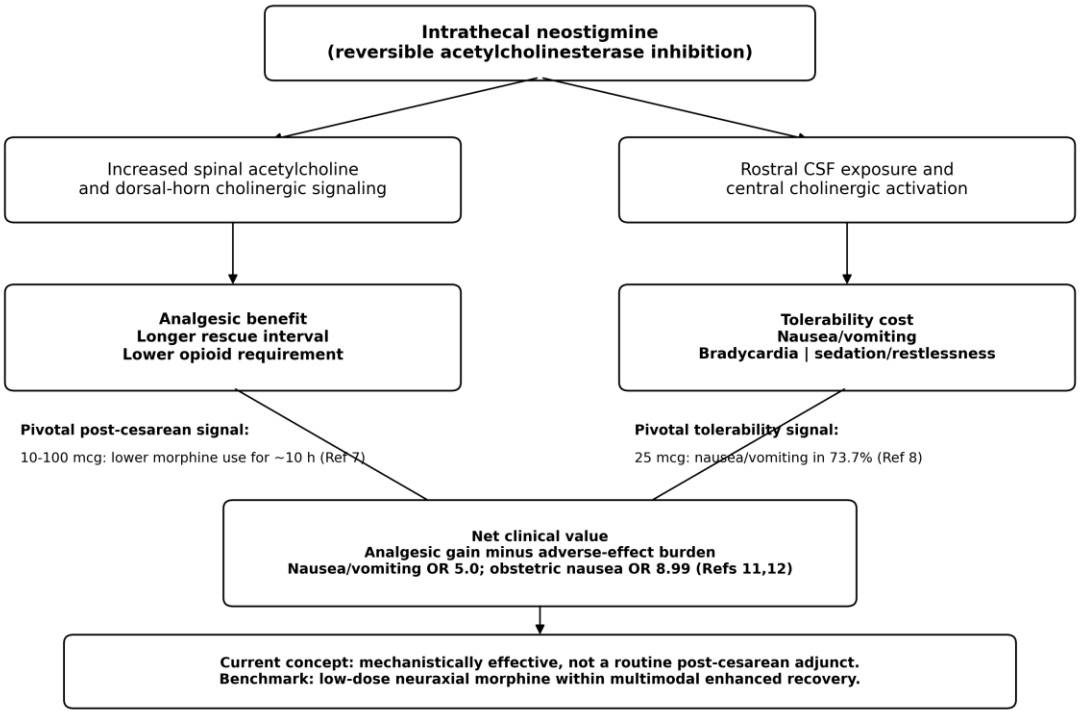

Figure 1. Mechanism-to-clinical-value model for intrathecal neostigmine after cesarean delivery. Analgesic efficacy is real, but the net benefit is constrained by cholinergic adverse effects, especially nausea/vomiting. OR values are from Refs 11 and 12. Figure created by the authors for this review.

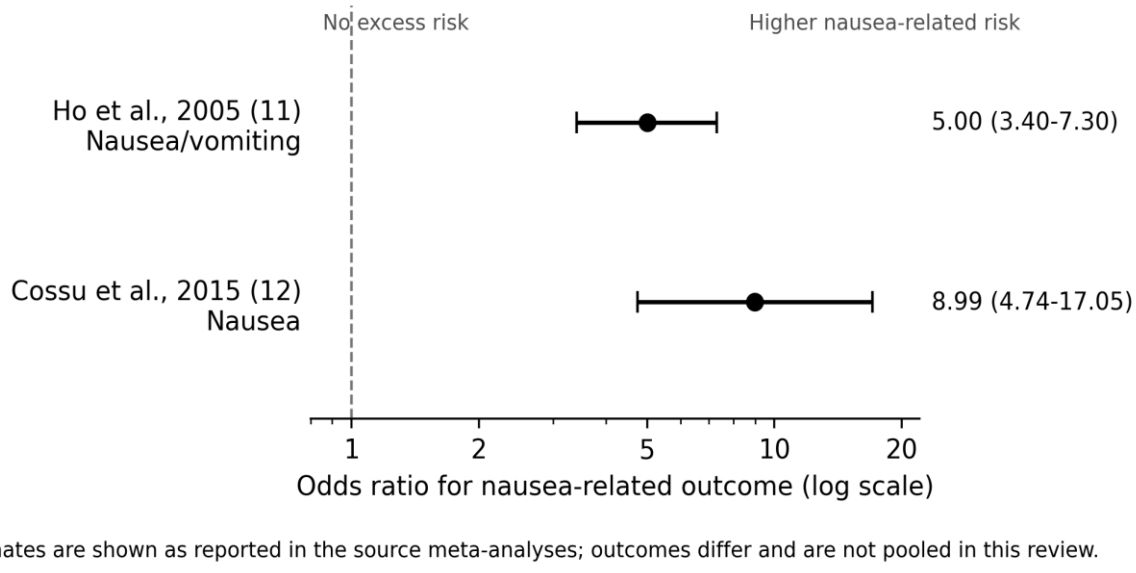

Figure 2. Magnitude of the nausea-related safety signal associated with intrathecal neostigmine in evidence syntheses. Ho et al. reported an odds ratio (OR) of 5.0 (95% CI 3.4-7.3) for nausea/vomiting across perioperative and peripartum studies (11). Cossu et al. reported an OR of 8.99 (95% CI 4.74-17.05) for nausea with intrathecal neostigmine in obstetric neuraxial studies (12). The outcomes and study sets are not identical; estimates are displayed for clinical context and are not pooled in this review.

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After cesarean delivery, Kaya and colleagues found that epidural neostigmine produced modest analgesia without increasing nausea but caused mild sedation, particularly at higher doses (29). Alkan and Kaya similarly reported reduced 24-hour local-anesthetic requirement after single-dose epidural neostigmine, although morphine produced a longer time to first analgesic request (30). These studies support the biologic importance of drug distribution, but they should not be used to "rescue" intrathecal neostigmine. Epidural and intrathecal administration are distinct interventions with different dose ranges, kinetics, and safety profiles.

7. Intrathecal neostigmine in contemporary post-cesarean analgesia

One reason early intrathecal neostigmine results can appear more attractive than they do today is that post-cesarean analgesia has improved. Current procedure-specific recommendations emphasize intrathecal morphine 50-100 mcg (or an appropriate long-acting neuraxial opioid alternative) plus scheduled acetaminophen/paracetamol and an NSAID, with dexamethasone and rescue opioid as appropriate (1). When long-acting neuraxial opioid is not used, wound infiltration or fascial-plane blocks become more important. Enhanced-recovery statements likewise prioritize multimodal opioid-sparing analgesia, early mobilization, oral intake, functional recovery, and standardized management of adverse effects (2,24).

This modern framework changes the evidentiary threshold for adding a new intrathecal adjunct. A study must show more than a statistically significant reduction in morphine consumption; it should demonstrate a clinically meaningful improvement in pain, opioid exposure, function, or recovery quality without increasing nausea/vomiting, sedation, hypotension, pruritus, urinary retention, respiratory risk, or treatment complexity. A 2026 network meta-analysis of intrathecal adjuncts for cesarean delivery illustrates both the breadth of available options and the generally low certainty of many indirect comparisons (22). Some morphine-neostigmine combinations ranked favorably for analgesic outcomes, but network rankings should not supersede direct, repeated evidence of neostigmine-associated emesis. In benefit-harm terms, a high rank for duration of analgesia cannot compensate for a clinically important increase in a patient-centered adverse outcome.

The current BJA Education review of obstetric neuraxial adjuncts lists intrathecal neostigmine as "not recommended," while recognizing an epidural dose range and characteristic adverse effects including bradycardia, nausea/vomiting, and sedation (14). The 2021 PROSPECT cesarean guideline explicitly did not recommend intrathecal neostigmine because of adverse-effect concerns (21). The updated 2026 PROSPECT recommendations center on low-dose intrathecal morphine/diamorphine plus multimodal nonopioid therapy and do not include intrathecal neostigmine among recommended strategies (1).

8. The ultra-low-dose combination hypothesis

The most plausible remaining hypothesis is not high-dose neostigmine monotherapy, but an ultra-low-dose combination strategy. Nonobstetric studies explored intrathecal neostigmine dose-response and combinations with morphine; later work included single-digit microgram neostigmine added to morphine (31-35). In obstetric spinal analgesia, however, adding neostigmine 10 mcg to bupivacaine, clonidine, and sufentanil did not prolong labor analgesia and increased nausea/vomiting, illustrating that combination therapy does not automatically improve the therapeutic index (26). By contrast, the cesarean study by Chung et al. suggested that 12.5 mcg of neostigmine combined with 50 mcg of morphine could extend analgesia while reducing exposure to each drug (8). Together, these findings keep the low-dose combination concept biologically plausible but clinically unsettled.

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Table 2. Net clinical value of intrathecal neostigmine relative to contemporary post-cesarean analgesic strategies.

Strategy	Main analgesic advantage	Characteristic liabilities	Current role
Intrathecal neostigmine	Opioid-independent spinal analgesia; can reduce rescue opioid use.	High and dose/distribution-sensitive nausea/vomiting; possible bradycardia, restlessness or sedation; uncertain optimal dose.	Investigational; not supported for routine post-cesarean use.
Intrathecal morphine 50-100 mcg	Long-duration analgesia with the strongest cesarean evidence base.	Pruritus, PONV, urinary retention; respiratory depression is uncommon but requires risk-based monitoring.	Reference neuraxial strategy within contemporary multimodal pathways when not contraindicated.
Epidural neostigmine	Can reduce local-anesthetic/opioid requirement with less nausea than intrathecal dosing.	Modest analgesia; sedation at some doses; catheter-dependent and off-label context.	Separate research/adjunct concept; does not validate intrathecal use.
Regional blocks/wound techniques	Useful opioid-sparing option when long-acting neuraxial opioid is omitted.	Technique-dependent; may add procedure time and local-anesthetic exposure.	Recommended alternative in selected patients/pathways.
Scheduled acetaminophen + NSAID (+ dexamethasone where appropriate)	Foundational multimodal analgesia; reduces opioid need and supports recovery.	Drug-specific contraindications (e.g., NSAID renal/bleeding considerations).	Routine core of enhanced-recovery post-cesarean analgesia.

NSAID, nonsteroidal anti-inflammatory drug; PONV, postoperative nausea and vomiting.

Nevertheless, a pharmacologic possibility is not a clinical indication. Ultra-low-dose regimens have not been tested adequately against a contemporary comparator that includes prophylactic antiemetics, vasopressor-based prevention of spinal hypotension, scheduled acetaminophen/NSAID therapy, early mobilization, and standardized rescue treatment. They also have not established a reproducible "analgesia without nausea" endpoint. Until such evidence exists, the combination hypothesis should be regarded as a research question rather than a practice recommendation.

9. Clinical implications

For routine elective cesarean delivery, the evidence does not support substituting intrathecal neostigmine for low-dose intrathecal morphine, nor adding neostigmine solely to reduce morphine consumption. Contemporary guidelines, accumulated tolerability data, and validated multimodal alternatives favor established strategies (1,2,14,21,24,25,38). A recent multidisciplinary consensus addressing pain management in pregnant patients with opioid-use disorder likewise notes that the benefits of neuraxial neostigmine remain unclear and that severe nausea/vomiting may limit its use in pregnant people with or without opioid-use disorder (37). Accordingly, intrathecal neostigmine should be framed as an investigational neuraxial adjunct rather than an opioid-sparing substitute with established routine utility.

If intrathecal neostigmine is studied, several safeguards are conceptually important. The formulation must be appropriate for neuraxial research, local regulatory and ethics requirements must be satisfied, and the protocol should specify dose, baricity, injectate volume, patient position, antiemetic prophylaxis, vasopressor management, rescue criteria, maternal hemodynamic monitoring, and neonatal outcomes. Because many neuraxial adjuncts are used outside formal labeling, a research protocol should not treat "commonly studied" as equivalent to "approved" or "standard of care" (14).

Clinical interpretation should also prioritize what matters to the patient. A 20%-30% reduction in rescue opioid requirement may be unattractive if it is purchased at the cost of severe nausea, vomiting, sedation, or a prolonged motor block. Conversely, a modest analgesic improvement could be worthwhile if achieved without additional symptoms. The proper endpoint is therefore net benefit, not analgesia in isolation.

10. Future research priorities

- **Use a contemporary active comparator.** Future trials should compare an ultra-low-dose neostigmine combination with low-dose intrathecal morphine-based

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enhanced recovery, not with placebo or obsolete high-opioid regimens.

- **Make "analgesia without toxicity" the primary outcome.** Composite endpoints should include acceptable pain control, no moderate/severe nausea or vomiting, no rescue antiemetic, no excessive sedation, and timely mobilization/oral intake.
- **Standardize confounders of cesarean nausea.** Vasopressor protocols, uterotonic administration, uterine handling, fluid strategy, and antiemetic prophylaxis should be protocolized so drug-related emesis can be distinguished from background obstetric causes.
- **Test pharmacokinetic hypotheses directly.** Dose, baricity, injectate volume, position, and CSF spread should be linked to both analgesia and emesis rather than inferred retrospectively.
- **Report maternal and neonatal safety consistently.** Trials should include hemodynamics, neurologic symptoms, motor recovery, sedation, feeding/mobilization milestones, Apgar/umbilical measures where appropriate, and post-discharge recovery.
- **Separate intrathecal from epidural questions.** The better nausea profile of epidural neostigmine is mechanistically informative but should be studied as a distinct intervention with its own comparator and outcomes.

11. Limitations of this narrative review and the evidence base

Most direct intrathecal neostigmine cesarean trials are small, single-center studies conducted before current enhanced-recovery practice, routine multimodal PONV prophylaxis, phenylephrine-based prevention of spinal hypotension, and standardized low-dose neuraxial opioid protocols. Doses, baricity, local-anesthetic regimens, anesthetic techniques, definitions of nausea/vomiting, rescue treatments, and follow-up windows vary substantially. Several mechanistic and dose-response observations derive from nonobstetric populations, and the available obstetric evidence is underpowered for rare neurologic or neonatal harms. As a narrative Current Concept Review, this article was not designed as a PRISMA-guided systematic review and did not use duplicate screening, a formal risk-of-bias instrument, or quantitative evidence grading. It should therefore be read as a clinically focused synthesis rather than an exhaustive evidence inventory. These limitations reduce certainty about the exact dose-response relationship and leave open the possibility of a narrow ultra-low-dose niche. They do not, however, negate the repeated, quantitatively large, and route-specific intrathecal nausea signal observed across trials and evidence syntheses.

12. Conclusion

Intrathecal neostigmine demonstrates an important principle in perioperative pharmacology: efficacy and clinical utility are not synonymous. Spinal acetylcholinesterase inhibition can reduce post-cesarean pain and opioid requirements, and low-dose combinations may produce pharmacologic synergy. Yet intrathecal neostigmine has never achieved a reliably favorable therapeutic index because nausea and vomiting are frequent, sometimes severe, and strongly linked to dose and neuraxial distribution. The burden is especially relevant in awake cesarean patients, for whom comfort, alertness, oral intake, mobility, and early recovery are central outcomes.

Against the contemporary standard of low-dose neuraxial morphine plus scheduled nonopioid multimodal analgesia, routine intrathecal neostigmine offers insufficient net advantage. Its most appropriate present role is investigational: a mechanistically compelling adjunct that should advance only through trials capable of demonstrating patient-centered analgesic benefit without an unacceptable emetic, sedative, hemodynamic, or motor-recovery cost. The research target should no longer be simply "less morphine," but a clinically meaningful increase in the probability of good analgesia with intact function and freedom from nausea and vomiting.

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Conflicts of interest
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