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Chloroprocaine for Spinal or Epidural Anesthesia

Rapid Review

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Abbreviations

AMSTAR	A Measurement Tool to Assess Systematic Reviews
CP	chloroprocaine
LA	local anesthesia
MA	meta-analysis
NMA	network meta-analysis
RCT	randomized controlled trials
RR	risk ratio
SR	systematic review
TNS	transient neurologic symptoms

Key Messages

- Compared to alternative local anesthetic drugs, chloroprocaine may result in a shorter or equal onset of sensory and motor blocks and recovery from sensory and motor blocks.
- Compared to alternative local anesthetic drugs, chloroprocaine has a shorter time to unaided ambulation, time to independent urination, and time to discharge.
- Chloroprocaine may have better or equal clinical effectiveness than alternative drugs for spinal or epidural local anesthesia.
- Compared to alternative local anesthetic drugs, chloroprocaine may cause higher rates of adverse events. However, due to inconsistency in evidence, it was difficult to draw any firm conclusions in this regard, suggesting further investigation for decision-making.
- We did not find any evidence regarding the cost-effectiveness of chloroprocaine compared to other local anesthetic drugs and evidence-based guidelines for using chloroprocaine for patients requiring spinal or epidural anesthesia that met the inclusion criteria for the present review.

Context and Policy Issues

Spinal and epidural anesthesia are procedures to deliver local anesthetics in or around the spine (lumbar level) that numb parts of the body to block pain.[1] For epidural local anesthesia (LA), the drug is injected around the spinal cord into the epidural space, just outside the sac of cerebrospinal fluid (CSF). A small tube (catheter) is often left in place to receive more anesthetic drugs during or after the procedure if required. For spinal LA, the drug is injected into the CSF around the spinal cord only once (without a catheter placed) and rapidly begins to take effect.[1] Overall for LA, anesthetics with rapid onset and fast regression (recovery or resolution) of sensory and motor blocks that allow for a quick recovery and fast discharge with minimal side effects are preferred.[2]

Because of the unique short duration of action, intense block, fast resolution of both sensory and motor blocks, quick recovery, and suitability for day-case surgery, lidocaine has an attractive pharmacokinetic profile for spinal anesthesia.[2,3] However, due to concerns about lidocaine's adverse events (AEs), such as hypotension, urinary retention, and transient neurologic symptoms (TNS), its widespread clinical use has been limited.[2,4] The symptoms of TNS can appear within a few hours up to 24 hours after full recovery and may last up to 2 to 5 days.[3] These symptoms consist of pain originating in the gluteal region and radiating to both lower extremities. Irrespective of dose or concentration, all forms of lidocaine are associated with TNS, and the cause of this painful condition is still unknown.[3]

Bupivacaine, introduced in the 1960s, is the most commonly used alternative to lidocaine. As an alternative, bupivacaine has a lower incidence of TNS but may have a longer recovery duration.[5] In addition, bupivacaine might cause unpredictable, dose-dependent levels of LA and lead to complications, such as hemodynamic instability (insufficient blood flow in the body)[3] and urinary retention.[6]

Chloroprocaine (CP) is a derivative of procaine indicated for spinal and epidural neuraxial anesthesia with a rapid onset of action and elimination by plasma cholinesterase metabolism.[7] The obstetric setting is the most common application for CP, where it is used to provide fast-onset epidural anesthesia for urgent or emergent Caesarean delivery.[7] Due to concerns about neurotoxicity related to preservatives, CP was withdrawn from the market in the 1980s; and reintroduced into clinical practice in 2004 with a new formulation without preservatives.[3] Recently, the preservative-free 2-CP has regained popularity because of its desirable pharmacokinetic properties, such as very fast onset, a quick recovery time, and lower incidence of TNS.[3,8]

Due to a shortage of raw materials and a combination of corporate decisions by the CP manufacturer, preservative-free CP was removed from the market in Canada in 2012.[9] CP is still manufactured and broadly available in the US and Europe under the trade names Clorotekal, Nesacaine, and Ampres.[10] According to the Canadian Anesthesiologists' Society (CAS),[11] Health Canada–approved the importation of preservative-free CP to Canada in January 2021, but accessibility is limited by foreign supply.[10] Given supply challenges, the question arises as to whether CP should be preferred over alternatives for spinal or epidural LA. With respect to recent changes to the use of chloroprocaine in Canada, it is unclear if chloroprocaine should be included in regular formulary use. This report aimed to summarize and critically appraise available evidence of the clinical effectiveness and cost-effectiveness of CP compared to alternative anesthetic drugs used for spinal or epidural LA, as well as the evidence-based guidelines for using CP for patients requiring spinal or epidural LA.

Research Questions

1. What is the clinical effectiveness of chloroprocaine for patients requiring spinal or epidural local anesthesia?
2. What is the cost-effectiveness of chloroprocaine for patients requiring spinal or epidural local anesthesia?
3. What are the evidence-based guidelines for the use of chloroprocaine for patients requiring spinal or epidural local anesthesia?

Methods

Literature Search Methods

An information specialist conducted a literature search on key resources including MEDLINE, the Cochrane Database of Systematic Reviews, the International HTA Database, the websites of Canadian and major international health technology agencies, as well as a focused internet search. The search approach was customized to retrieve a limited set of results, balancing comprehensiveness with relevancy. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. Search concepts were developed based on the elements of the research

questions and selection criteria. The main search concepts were epidural anesthesia, spinal anesthesia, and chloroprocaine. No filters were applied to limit retrieval by study type. The search was completed on March 27, 2023 and limited to English-language documents published since January 1, 2018.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first screening level, titles, and abstracts were reviewed, and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in, were duplicate publications, or were published before January 1, 2018.

Critical Appraisal of Individual Studies

One reviewer critically appraised systematic reviews (SRs) using a Measurement Tool to Assess Systematic Reviews (AMSTAR-2) tool[12] and randomized controlled trials (RCTs) using the Downs and Black checklist.[13] For SRs with network meta-analysis (NMA), both AMSTAR[12] and a Questionnaire to Assess the Relevance and Credibility of an NMA[14] were used. Summary scores were not calculated for the studies; the strengths and limitations observed among the included studies were summarized and described narratively in Appendix 3.

Summary of Evidence

Quantity of Research Available

A total of 93 citations were identified in the literature search. Following the screening of titles and abstracts, 79 citations were excluded and 14 potentially relevant articles from the electronic search were retrieved for full-text review. No potentially relevant publication was identified from the grey literature search for full-text review. Fourteen publications[2-4,6,15-24] met the selection criteria and were included in this report.

Appendix 1 presents the PRISMA[25] flow chart of the study selection. Additional references of potential interest are provided in Appendix 5.

Summary of the Study Characteristics

Fourteen peer-reviewed publications[2-4,6,15-24] including 2 SRs with NMA,[3,21] 1 SR with MA,[2] and 11 RCTs[4,6,15-20,22-24] were included in this report. Given the diversity of the 3 included SRs in terms of population, intervention, comparator, and outcome (i.e., PICO components), except for 1 RCT included in 2 SRs,[2,3] no more overlaps were identified in the 3 SRs.[2,3,21]

Additional details regarding the characteristics of the included publications are provided in Appendix 2 (Table 2 and Table 3).

Table 1: Selection Criteria

Criteria	Description
Population	Patients (any age) requiring spinal or epidural local anesthesia
Intervention	Chloroprocaine (any dose)
Comparator	**Q1 and Q2:** Alternative anesthetic drugs used for spinal or epidural local anesthesia (e.g., bupivacaine, lidocaine, mepivacaine, ropivacaine, procaine, tetracaine) **Q3:** Not applicable
Outcomes	**Q1:** Clinical effectiveness (e.g., pain relief, duration of pain relief, time to ambulation, length of stay, patient satisfaction, health-related quality of life) and safety (e.g., complications, rate of adverse events, mortality) **Q2:** Cost-effectiveness (e.g., cost per quality-adjusted life-year gained, incremental cost-effectiveness ratio) **Q3:** Recommendations regarding the best use of chloroprocaine for spinal or epidural local anesthesia (e.g., appropriate administration, patient population, appropriate dose)
Study designs	Health technology assessments, systematic reviews, randomized controlled trials, economic evaluations, evidence-based guidelines

Study Design

Of the 14 peer-reviewed publications[2-4,6,15-24] that met the selection criteria for this report, 11 were RCTs.[4,6,15-20,22-24]

The other 3 publications were SRs consisting of 1 SR with NMA based on a graph theoretical approach within a frequentist framework for indirect and mixed comparisons,[3] 1 SR with NMA using Bayesian statistical analysis for direct and indirect comparisons,[21] and 1 SR with MA using a random effect model for statistical analysis.[2]

Country of Origin

Systematic Reviews

The authors of 2 SRs with NMA[3,21] and 1 SR with MA[2] were based in the UK, US, and Switzerland, respectively.

Primary Studies

Eleven RCTs[4,6,15-20,22-24] were conducted by authors from India,[4,6,16,18,20,22,23] China,[24] Netherlands,[15] Belgium,[17] and US.[19]

Patient Population

Systematic Reviews

In 1 SR and NMA[21] on the choice of local anesthetic for epidural Caesarean section, RCTs on women with epidural Caesarean section were selected for review. Of the 24 RCTs included, 5 RCTs used 2-CP 3% epidurally for surgical anesthesia.

In 1 SR and NMA[3] to compare lidocaine with other types of local anesthetics in the frequency of TNS after spinal LA, RCTs and quasi-RCTS on adults undergoing surgery were considered for review. Of 24 RCTs, 2 RCTs[26,27] used 2-CP for spinal LA.

In 1 SR and MA[2] to compare the clinical outcomes of spinal 2-CP with low-dose bupivacaine, 4 RCTs on adults with lower extremity and abdominal surgery were included.

Primary Studies

Patients with various types of surgeries received spinal[4,6,15-20,22,23] or epidural[24] LA, including different ambulatory surgeries,[16] perineal surgery or gynecological procedures,[4,6,22] knee arthroscopy,[15,17,24] ureteroscopic lithotripsy surgery,[20] inguinal hernia repair surgery,[18] lower abdominal or lower limb surgeries,[23] and women undergoing cervical cerclage surgery.[19]

Interventions and Comparators

Systematic Reviews

In the SR and NMA by Reschke et al. (2020)[21] to rank the speed of onset of the 6 local anesthetics for epidural Caesarean section, 2-CP 3% was compared with bupivacaine 0.5%, lidocaine 2%, lidocaine 2% plus bicarbonate, l-bupivacaine 0.5%, and ropivacaine 0.75%.

In the SR and NMA by Forget et al. (2019),[3] the frequency of TNS with lidocaine was compared with other types of LA, including 2-CP, bupivacaine, prilocaine, mepivacaine, procaine, ropivacaine, and levobupivacaine.

In the SR and MA by Saporito et al. (2019),[2] the clinical outcomes of spinal 2-CP (40 or 50 mg) were compared with low-dose bupivacaine (less than 10 mg).

Primary Studies

Intervention: Except for 1 study with epidural LA,[24] spinal LA was used in all primary studies.[4,6,15-20,22,23] The studies used various percentages and doses of CP for LA consisting of 1-CP 1% (40 mg),[6,20] 2-CP 1% (30 mg),[4,22] CP 1% (50 mg),[17] 2-CP 1% (40 mg),[15,16,23] 2-CP 1% (40 mg) combined with saline (0.025 mg);[18] 2-CP 3% (30 mg),[24] or 2-CP 3% (50 mg) combined with fentanyl (0.015 mg).[19]

Comparators: The interventions that were compared with CP were: bupivacaine 5% with different doses (10 mg,[6,16] 20 mg,[20] 15 mg,[4] or 10.5 mg[18]), prilocaine 2% (50 mg),[17] levobupivacaine 5% (15 mg),[22] prilocaine 2% (40 mg),[15] lidocaine 2% (30 mg),[24] 2-CP (40 mg) combined with fentanyl (0.025 mg),[18] 2-CP 1% (40 mg) combined with buprenorphine (0.06 mg);[23] or hyperbaric bupivacaine 0.75% (9 mg) combined with fentanyl (0.015 mg).[19]

Outcomes

Systematic Reviews

The outcome measures in 2 SRs with NMA[3,21] and 1 SR with MA[2] were speed of anesthesia onset and AEs,[21] presence of TNS,[3] onset time, block duration, time to ambulation, and time to discharge[2] after spinal or epidural LA with CP compared to other drugs.

Primary Studies

The outcome measures used in the primary studies were the onset of sensory block,[6,15,16,18-20,23,24,28] resolution (recovery or regression) of sensory block,[6,15,17-20,23,24,28] onset of motor block,[4,16,18,20,23,28] resolution of motor block,[4,6,16,18-20,23,24,28] time to maximum sensory block,[6] time to unaided ambulation,[16,20,23,28] time to independent

urination (spontaneous voiding),[4,15,17,20,23,28] time for first analgesic dose,[23] time to discharge,[15,16,19,20] patient satisfaction,[19] TNS,[19] and other AEs (hypotension or urinary retention).[4,17,18,24]

Patients underwent spinal anesthesia in the sitting position at the L3-L4[4,6,15-19,22,23] or L4-L5[16,19,20,23] interspace (lumbar level) in the sitting position for the spinal LA, and L2–L3 interspace in the supine position for epidural LA.[24] In all selected primary studies,[4,6,15-20,22-24] patients were placed supinely following injection, and the sensory level was assessed every few minutes (e.g., 2 minutes) to pinprick until a constant level was achieved for 2 consecutive tests. Motor block was assessed every few minutes (e.g., 2 minutes) using the Bromage score (0 = no block, full straight leg raise possible; 1 = unable to raise straight leg, 2 = unable to flex knee but able to flex ankle; and 3 = no motor movement, complete motor block).[29]

In 1 study,[19] patients were telephoned on the first postoperative day and asked to rate their satisfaction with the anesthetic (complete, adequate, or inadequate) and report any complaints of TNS (e.g., abnormal sensations such as hypoesthesia or dysesthesia in the gluteal region and radiating to the lower extremities), back pain, or headache.

Summary of the Critical Appraisal

SRs

Of the 14 studies included in this report, 3 were SRs (Table 4) consisting of 2 SRs with NMA[3,21] and 1 SR with MA.[2] We used the AMSTAR-2 checklist[12] to evaluate the quality of SRs and determine whether the most important elements of the SR methodology were reported. In addition, we used the Questionnaire to Assess the Relevance and Credibility of NMAs[14] to assess the strengths and limitations of the 2 SRs with NMA[3,21] (Table 5). This questionnaire consists of 26 questions related to the relevance (i.e., the usefulness of NMA to inform health care decision-making) and credibility (including 5 subdomains: indirect comparison or NMA, analysis, reporting quality, and transparency, interpretation, and conflict of interest) of NMAs.[14]

The strengths of the 3 SRs were in defining the research question and inclusion and exclusion criteria, describing the study design of the selected primary studies, using a comprehensive literature search strategy, conducting study selection and data extraction in duplicate, using a satisfactory tool for assessing the risk of bias (RoB) in primary studies, and reporting potential sources of conflict of interest. In 2 SRs,[2,21] the systematic search protocol was established before the conduct of the review. Two SRs[2,21] did not list excluded studies and justify the exclusions. The SR with NMA[21] on the choice of local anesthetic for epidural Caesarean section had several limitations. The authors did not adequately describe the selected primary studies, investigate publication bias (small study bias) and discuss its potential impact on the outcomes, interpret the potential impact of RoB in primary studies included in MA, and describe heterogeneity observed in MA results. For the NMA,[21] the authors used the Markov Chain Monte Carlo algorithm to derive inferences from the random-effects Bayesian network, the Metmeta package to evaluate the assumptions of transitivity (i.e., the similarity of treatment effect distribution across primary studies) and consistency (of direct and indirect estimates), and meta-regression to assess the interactions of 2 covariates with the onset of surgical LA. The NMA[21] was limited in including sufficient detail about the rationale for the use of random effects, conducting within-study randomization and assessing agreement in treatment effects (consistency) in

statistical methods, assessing and discussing heterogeneity with subgroup analyses, and if all pairwise contrasts between interventions were reported along with measures of uncertainty.

Forget et al. (2019)[3] conducted an SR with NMA to determine the frequency of TNS in adult surgical patients after spinal LA with lidocaine compared to other types of LA. Due to expected methodological and clinical heterogeneities across the included studies resulting in varying effect sizes between studies of pairwise comparisons, the authors used an inverse variance weighting for summary statistics and a random-effect model for statistical analyses. The included studies were analyzed based on a graph theoretical approach within a frequentist framework, and the competing treatments were ranked by P scores. The planned subgroup analyses were not conducted due to the low number of TNS events.

Both SRs with NMA,[3,21] especially the Reschke et al. (2020) study,[21] didn't provide enough details from a statistical method standpoint, which made it challenging to evaluate this evidence. The NMA by Reschke et al. (2020)[21] did not include sufficient detail about Bayesian statistical analyses, and the paper did not cite standard methods for NMA. Likewise, the graph theoretical approach referenced by Forget et al. (2019)[3] did not appear to be a standard approach to NMA, and the authors did not provide adequate detail to explain the implications of this approach.

Primary Studies

The Downs and Black Checklist[13] used for critical appraisal of the included primary studies consists of 5 sections (Table 6): reporting, external validity, internal validity, confounding, and power. In the following paragraphs, the strengths and weaknesses of the included primary studies are described in each of the 5 sections.

Reporting: The items clearly described in the 11 RCTs[4,6,15-20,22-24] were: study objectives, main outcomes, characteristics of the patients, interventions, main findings of the study, estimated random variability in data for main outcomes, and the distributions of principal confounders. All studies reported funding sources. The typical examples of confounders in RCTs (e.g., sex, age, and disease characteristics)[30] were clearly described in the selected studies. The rate of AEs was a secondary outcome measure in 5 studies[4,17-19,24] and not an outcome measure in 6 studies.[6,15,16,20,22,23]

External Validity: Staff, places, and facilities reported in the studies were representative of the procedures provided to patients. All studies reported receiving no specific funding. It was unclear if the patients who were asked to participate in the study were representative of the entire population recruited (i.e., poor reporting of the source of the population).

Internal Validity: All RCTs were double-blinded, except for 2 studies[16,18] that were not blind to those measuring the outcomes or were unclear. The main outcome measures and statistical tests (except for one study)[22] used for data analysis were clearly described in the studies.

Confounding: Patients were randomized to intervention groups, and randomization was concealed from patients and staff. Patients in different intervention groups were recruited from the same population, but it was unclear whether participants were recruited over the same period of time. Data collection was conducted during ambulatory surgery, and there was no loss of patients for follow-up.

Power: Of the 11 selected RCTs, sample size and power calculation were reported in 8 studies.[4,15-19,22,23] In 3 studies,[6,20,24] it was unclear if they were sufficiently powered to detect clinically significant effects.

Additional details regarding the strengths and limitations of the included publications are summarized in Appendix 3.

Summary of Findings

We identified 14 studies including 2 SRs with NMA,[3,21] 1 SR with MA,[2] and 11 RCTs[4,6,15-20,22-24] regarding the clinical effectiveness of CP for patients with spinal or epidural LA. We did not find any studies that met the inclusion criteria regarding the cost-effectiveness of CP compared to other local anesthetics or evidence-based guidelines for using CP for patients requiring spinal or epidural LA.

Appendix 4 presents the main outcomes of the included studies.

Onset of Sensory Block

In 1 SR and NMA[21] on the choice of local anesthetic for epidural Caesarean section, the mean onset of surgical LA from fastest to slowest was: lidocaine 2% with bicarbonate; 2-CP 3%; lidocaine 2%; ropivacaine 0.75%; bupivacaine 0.5%; bupivacaine 0.5% (Table 7).

The onset of sensory block was reported in 9 RCTs (Table 8).[6,15,16,18-20,23,24,28] Four studies found that the onset of sensory block for CP was significantly shorter compared to bupivacaine,[6,20] levobupivacaine,[22] and prilocaine.[15] In 1 study, the onset of sensory block for CP combined with saline was also shorter compared to both CP combined with fentanyl and bupivacaine.[18] In 3 studies, the sensory block onset with CP was similar to bupivacaine,[16] prilocaine,[23] and lidocaine.[24] Likewise in 1 study,[19] the onset of sensory block was similar for CP combined with fentanyl and bupivacaine combined with fentanyl.

Onset of Motor Block

In 1 SR and MA,[2] 2-CP had a shorter motor block onset compared to a low dose (10 mg or less) of hyperbaric bupivacaine (Table 10).

Motor block onset was reported in 9 RCTs.[4,6,15,16,18,20,23,24,28] Four studies found the onset of motor block was significantly shorter for CP compared to bupivacaine[4,6,20] and prilocaine.[15] This measure was also shorter for CP combined with saline compared to both CP combined with fentanyl and bupivacaine.[18] While, 4 studies found similar results for CP relative to bupivacaine,[16] prilocaine,[23] levobupivacaine,[22] and lidocaine.[24]

Resolution of the Sensory Block

The resolution of sensory block was reported in 7 RCTs.[6,16,18-20,22,23] This measure was significantly shorter for CP compared to bupivacaine,[6,20] prilocaine,[17] and levobupivacaine;[22] as well as for CP combined with fentanyl compared to bupivacaine combined with fentanyl[19] and for CP combined with saline compared to both CP combined with fentanyl and bupivacaine.[18] In 1 study, the CP sensory block resolution was similar to prilocaine's.[23]

Resolution of the Motor Block

Motor block resolution was reported in 10 RCTs.[4,6,15,16,18-20,22-24] Seven studies found a significantly shorter resolution of the motor block for CP compared to bupivacaine,[4,6,16,20] prilocaine,[15] levobupivacaine,[22] and lidocaine.[24] One study also reported a shorter motor block resolution for CP combined with saline compared to both CP combined with fentanyl and bupivacaine.[18] However, 2 studies[19,23] found no difference in the motor block resolution for CP compared to other alternatives, including CP compared to prilocaine,[23] and CP combined with fentanyl compared to bupivacaine combined with fentanyl.[19]

Time to Maximum Sensory Block

Time to maximum sensory block was reported in 3 RCTs.[6,19,22] This measure was found to be shorter for CP compared to bupivacaine in 1 study,[6] and was reported similar for CP and levobupivacaine[22] and CP combined with fentanyl and bupivacaine combined with fentanyl[19] in 2 studies.[19,22]

Time to Discharge

In 1 SR and MA,[2] time to discharge was significantly shorter for 2-CP compared to low-dose hyperbaric bupivacaine (Table 10).

Time to discharge was reported in 4 RCTs,[15,16,19,20] all confirming a shorter time to discharge for CP compared to bupivacaine[16,19] and prilocaine,[15] as well as for CP combined with fentanyl compared to bupivacaine combined with fentanyl.[19]

Time to Unaided Ambulation

In 1 SR and MA,[2] a significantly shorter time to ambulation was reported for 2-CP compared to low-dose hyperbaric bupivacaine (Table 10).

Time to unaided ambulation was reported in 4 RCTs,[16,20,22,23] 3 demonstrated a shorter time to unaided ambulation for CP compared to bupivacaine[16] and levobupivacaine,[22] and 1 showed no significant difference between CP and prilocaine.[23]

Time to Independent Urination

Time to unaided ambulation was reported in 6 RCTs,[4,15,17,20,22,23] all confirming a shorter time to independent urination for CP compared to bupivacaine,[4,20] prilocaine,[15,17,23] and levobupivacaine.[22]

Patient Satisfaction

Patient satisfaction was reported in 1 study,[19] demonstrating no difference between CP combined with fentanyl and bupivacaine combined with fentanyl.

Adverse Events

In 1 SR with NMA[21] on the choice of local anesthetic for epidural Caesarean section, l-bupivacaine 0.5% was least likely to cause hypotension and 2-CP 3% was most likely to cause hypotension. Loss of surgical LA requiring intra-operative supplementation was most likely after 2-CP 3% and least likely after ropivacaine 0.75% (Table 7).

In 1 SR with NMA[3] to compare lidocaine with other types of LA, the risk ratio (RR) of TNS was 80% to 90% lower for bupivacaine, levobupivacaine, prilocaine, procaine, and ropivacaine compared to lidocaine. The RR of TNS for 2-CP and mepivacaine did not differ from lidocaine (Table 11).

In RCTs included in the present report, AEs were reported in 5 studies[17-19,24] showing no difference between CP with both prilocaine[17] and lidocaine[24] in hypotension and with bupivacaine in TNS[19] and urinary retention.[18] In addition, in 1 RCT, no patient with hypotension was reported with CP, while 20% was reported in patients anesthetized with bupivacaine.[4]

Limitations

All publications selected for this report focused on CP's clinical effectiveness for patients requiring spinal or epidural anesthesia. We did not find any publications that met the inclusion criteria on the cost-effectiveness of CP compared to other types of LA and evidence-based guidelines for using CP for patients requiring spinal or epidural anesthesia.

Of the 11 RCTs,[4,6,15-20,22-24] more than half of the studies (n = 7, 64.0%) were conducted by authors in India,[4,6,16,18,20,22,23] and other studies were carried out in China,[24] Netherlands,[15] Belgium,[17] and the US.[19] We did not find any relevant studies conducted in Canada, which might be influenced, at least in part, by the withdrawal of preservative-free CP from the market in Canada in 2012.[9] Thus, the generalizability of these findings to the cross-Canada context is uncertain.

In 3 SRs with MA or NMA,[2,3,21] except for 1 primary study[27] included in 2 SRs,[2,3] no overlapping studies were identified in the 3 SRs.[2,3,21] Likewise, the 9 RCTs included in the review varied widely in terms of population characteristics (e.g., patients with perineal surgery,[4,6,22,24] gynecological procedure,[6] cervical cerclage surgery,[19] ureteroscopic lithotripsy surgery,[20] knee arthroscopy,[15,17] inguinal hernia repair surgery,[18] general ambulatory surgeries,[16] lower abdominal or lower limb surgeries[23]), CP percentage (e.g., 1%,[4,6,15-18,20,22,23] 3%,[19,24]) and dosage (e.g., 30 mg,[4,22,24] 40 mg,[6,15,16,18,20,23] 50 mg,[17,19]) used, and the comparators (spinal bupivacaine 5% [10 mg,[6,16] 10.5 mg,[18] 15 mg,[4] or 20 mg[20]], bupivacaine 0.75% [9 mg],[19] prilocaine 2% [40 mg[15] or 50 mg[17]], levobupivacaine 5% [15 mg],[22] 2-CP 1% [40 mg] combined with buprenorphine [0.06 mg],[23] and epidural lidocaine 2% [30 mg][24]). This variation in relevant evidence limits how much the findings can be effectively synthesized.

The 2 SRs with NMA,[3,21] especially the SR by Reschke et al. (2020),[21] didn't provide adequate statistical details, which made evaluating this evidence challenging. Overall, this NMA[21] had several methodological limitations that make the strength of the conclusions less certain. The 9 RCTs selected for this review did not have serious methodological concerns, except for not clearly describing the source of the study population and if the patients in intervention and control groups were recruited over the same period of time.

In the SR and NMA by Forget et al. (2019),[3] only 2[26,27] out of the 24 RCTs included in the NMA used 2-CP for spinal LA.[26] This NMA reported similar RRs of TNS for 2-CP to lidocaine. In another SR with NMA,[21] loss of surgical anesthesia requiring intra-operative supplementation and hypotension during Caesarean section

were more likely with 2-CP 3% compared to other local anesthetics. However, the RCTs[17-19,24] included in the present report showed no difference between CP with alternative drugs for spinal LA in hypotension,[17,24] TNS,[19] and urinary retention.[18] In addition, the rate of hypotension with CP was zero compared to 20% with bupivacaine in 1 RCT.[4] Given the inconsistency in the literature, it was difficult to draw a conclusion about the rate of AEs with CP relative to alternative drugs for LA, suggesting further studies are needed.

Conclusions and Implications for Decision- or Policy-Making

The studies selected for this report supported better or equal clinical effectiveness for CP compared to other alternatives for spinal or epidural LA on several outcomes. For example, several studies found a shorter time for the onset of sensory block,[6,15,20-22] the onset of motor block,[2,4,6,15,20] recovery from the sensory block,[6,17-20,22] and recovery from motor block[4,6,16,18,20,22,24] with CP compared to alternative drugs for LA. In addition, in all studies reporting time to unaided ambulation[2,16,20,22,23] (except 1 study with similar results for CP and prilocaine),[23] time to independent urination,[4,15,17,20,22,23] and time to discharge,[2,15,16,19,20] CP was associated with a shorter time relative to other local anesthetics. Thus, it could be concluded that CP may result in better or equal clinical effectiveness compared to alternative drugs for spinal or epidural LA.

However, due to inconsistency in evidence, it was difficult to draw any firm conclusions about the safety of CP for spinal or epidural LA, corroborating the need for additional studies to assist with decision-making. In addition, the publications included in this report represented a broad range of study populations by country of origin, mostly by authors based in India. Thus, the extent to which studies from other cultures might contribute to the cross-Canada context remains unclear and requires further research.

We did not find any publications regarding the cost-effectiveness of CP compared to other types of LA or evidence-based guidelines for the use of CP for patients requiring spinal or epidural LA that met the inclusion criteria for this review.

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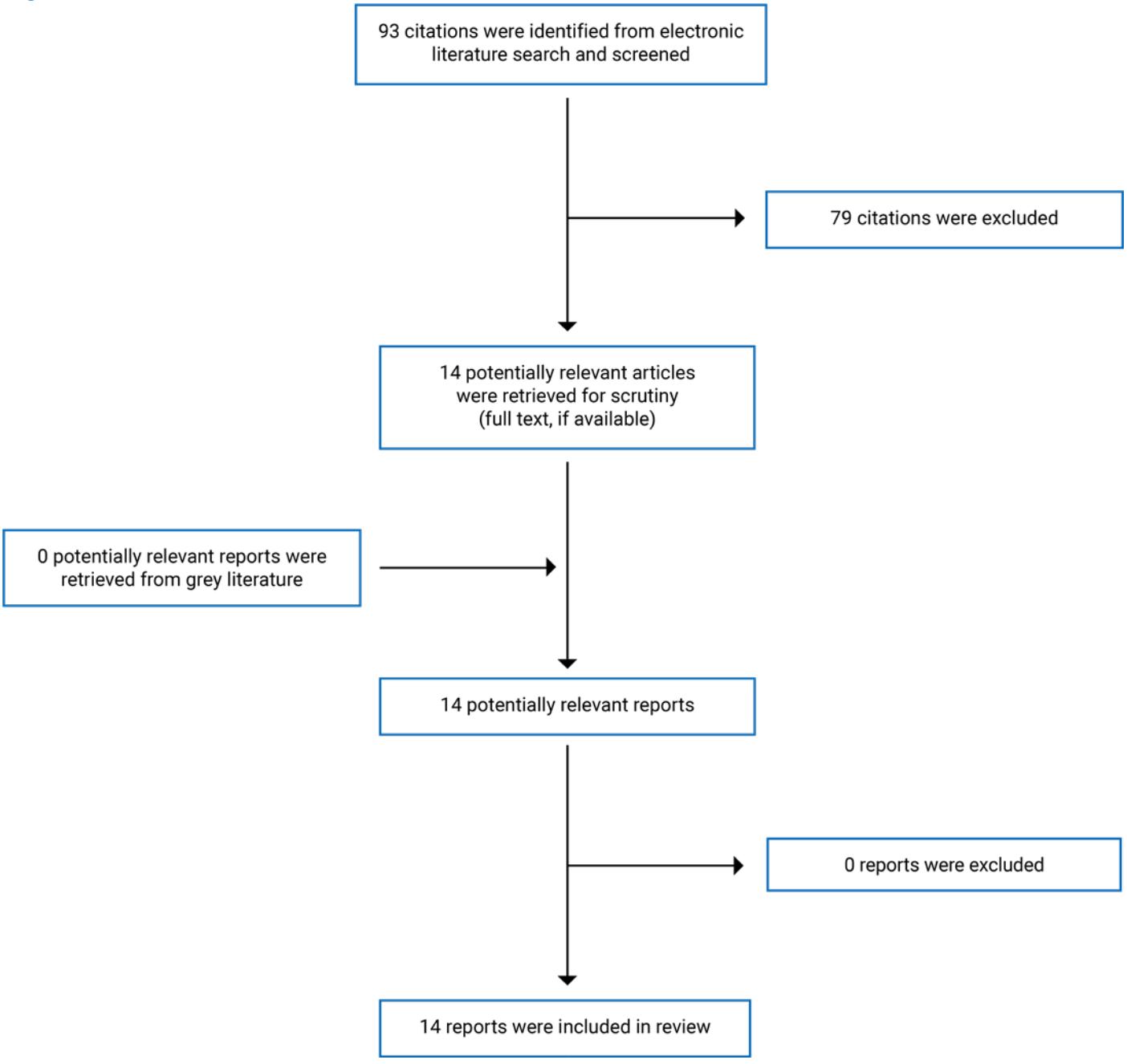
Appendix 1: Selection of Included Studies

Figure 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Note that this table has not been copy-edited.

Table 2: Characteristics of the Included Systematic Reviews (SRs)

Study citation, country, objective, funding source	Study designs and the number of primary studies included	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
Reschke et al. (2020)[21] US Funding source: No funding	Design: SR with NMA Total studies included: 24 RCTs Total studies relevant to this review: 5 RCTs on 2-CP 3%	Population included: 1,280 women with epidural Caesarean section Age in all included studies: NR Sex: Female Exclusion criteria: NR	Interventions included: Epidural 2-CP 3% Comparator: • Bupivacaine 0.5% • Lidocaine 2% • Lidocaine 2% combined with bicarbonate • L-bupivacaine 0.5% • Ropivacaine 0.75%	Outcome measure: • Speed of anesthesia onset • Adverse events (AE) Follow-up: Intra-operative follow-up (no long-term follow-up postoperation)
Forget et al. (2019)[3] UK Funding source: No funding	Design: SR with NMA Total studies included: 24 RCTs and quasi-RCTS Total studies relevant to this review: 2 RCT on 2-CP	Population included: 2,226 adults undergoing surgery Age in all included studies: NR Sex: NR Exclusion criteria: • Studies used meperidine as a sole spinal local anesthesia, or combinations of local anesthetics and opioids. • Studies in which spinal anesthesia was combined with epidural analgesia	Interventions included: Spinal lidocaine Comparator: Other local anesthetics • 2-CP • Bupivacaine • Prilocaine • Mepivacaine • Procaine • Ropivacaine and levobupivacaine	Outcome measure: Presence of transient neurologic symptoms (TNS) Follow-up: 24 hours postspinal anesthesia
Saporito et al. (2019)[2] Switzerland Funding source: No funding	Design: SR with MA Total studies included: 4 RCTs Total studies relevant to this review: 4 RCTs on 2-CP	Population included: Adults with lower extremity and abdominal surgery Age in all included studies: NR Sex: NR Exclusion criteria: Studies with poor methodological quality.	Interventions included: Spinal 2-CP Comparator: Low-dose bupivacaine (10 mg or less)	Outcome: • Resolution of motor block • Time to ambulation • Time to discharge Follow-up: Intra-operative follow-up (no long-term follow-up postoperation)

CP = chloroprocaine; MA = meta-analysis; NMA = network meta-analysis; NR = not reported; RCT = randomized controlled trial; SR = systematic review.

Table 3: Characteristics of Included Randomized Controlled Trials (RCTs)

Study citation, design, country, objective, funding source	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
Agrawal et al. (2022)[6] Country: India Funding source: No funding.	Patient with short-duration elective ambulatory perineal surgery or gynecological procedure. Number of patients (n), Age in year, mean (SD), range: Total: 120, NR, 18 to 60 • 1-CP: 60, 38.26 (13.44), NR • Bupivacaine: 60, 38.48 (11.82), NR Sex: number of males, n (%) Total: 88 (75.44) • 1-CP: 46 (76.67) • Bupivacaine: 42 (70.00) Inclusion criterion: • Age of 18 to 60 years • ASA grade of I or II Exclusion Criteria: • Sensitive or allergic to local anesthetics • Neurologic diseases • Those with no indication of spinal LA	Intervention: Spinal 1-CP 1% (40 mg) Comparator: Spinal bupivacaine 5% (10 mg)	Outcomes: • Onset and resolution of sensory block • Onset and resolution of motor block • Time to maximum sensory block Follow-up: During surgery and before discharge
Lee et al. (2022)[19] Country: US Funding source: No funding	Women undergoing cervical cerclage surgery. Number of patients (n), Age in year, mean (SD), range: Total: 41, NR, NR • 2-CP: 22, 33.00 (4.00), NR • Bupivacaine: 19, 34.0 (6.00), NR Sex: number of males, n (%) Total: 41 (100) Inclusion criterion: • Age of 18 years or older • Indication for cervical cerclage Exclusion Criteria: • Contraindications to neuraxial anesthesia • Allergy to LA, para-aminobenzoic acid allergy or the presence of atypical cholinesterase • Neurologic diseases	Intervention: Spinal 2-CP 3% (50 mg) combined with fentanyl (0.015 mg) Comparator: Spinal hyperbaric bupivacaine 0.75% (9 mg) combined with fentanyl (0.015 mg)	Outcomes: • Onset and resolution sensory block • Resolution motor block • Time to discharge • Patient satisfaction • TNS Follow-up: 1 day (phone call on the first postoperative day)
Sugumar et al. (2022)[20] Country: India	Patients with ureteroscopic lithotripsy surgery. Number of patients (n), Age in year, mean (SD), range:	Intervention: Spinal CP 1% (40 mg) Comparator: Spinal bupivacaine 5% (20 mg)	Outcomes: • Onset and resolution of sensory block • Onset and resolution of motor block

Study citation, design, country, objective, funding source	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
Funding source: No funding.	Total: 60, NR, 18 to 50 • CP: 30, 31.20 (7.53), NR • Bupivacaine: 30, 32.20 (5.55), NR Sex: number of males, n (%) Total: 35 (58.33) • CP: 17 (56.66) • Bupivacaine: 18 (60.00) Inclusion criterion: • Age of 18 to 50 years • ASA grade of I or II Exclusion Criteria: • Contraindications to neuraxial block and patient refusal. • Psychiatric and/or neurologic diseases • Lactating or pregnant women		• Time to discharge • Time to unaided ambulation • Time to independent urination Follow-up: During surgery and before discharge
Guntz et al. (2021)[17] Country: Belgium Funding source: No funding.	Patients with knee arthroscopy. Number of patients (n), Age in year, mean (SD), range: Total: 80, NR, 18 to 80 • CP: 40, NR, NR • Bupivacaine: 40, NR, NR Sex: number of males, n (%) NR Inclusion criterion: • Age of 18 to 80 years • ASA grade between 1 to 3 • BMI = 20 to 30 Kg/m^2 • Height = 155 to 190 cm Exclusion Criteria: • Contraindications to neuraxial block and patient refusal.	Intervention: Spinal CP 1% (50 mg) Comparator: Spinal hyperbaric prilocaine 2% (50 mg)	Outcomes: • Resolution of sensory block • Time to independent urination • AE (hypotension, bradycardia) Follow-up: During surgery and before discharge
Tiwari et al. (2021)[18] Country: India Funding source: No funding.	Male patients with inguinal hernia repair surgery. Number of patients (n), Age in year, mean (SD), range: Total: 102, NR, 18 to 65 • 2-CP: 34, NR, NR • 2-CP + saline: 34, NR, NR • Bupivacaine: 34, NR, NR Sex: number of males, n (%) Total: 102 (100) Inclusion criterion: • Age of 18 to 65 years	Intervention: Spinal 2-CP 1% (40 mg) combined with saline (0.025 mg) Comparator: Spinal • Bupivacaine 5% (10.5 mg) • 2-CP (40 mg) combined with fentanyl (0.025 mg)	Outcomes: • Onset and resolution of sensory block • Onset and resolution of motor block • AE (urinary retention) Follow-up: During surgery and before discharge

Study citation, design, country, objective, funding source	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
	• ASA grade of I or II Exclusion Criteria: • Spine deformity, localized sepsis, raised intracranial pressure, and patient refusal. • Cardiovascular, hepatic, coagulation, psychiatric, and/or neurologic diseases.		
Bhaskara et al. (2020)[22] Country: India Funding source: No funding.	Patients who underwent perianal surgeries. Number of patients (n), Age in year, mean (SD), range: Total: 60, NR, 18 to 55 • CP: 30, NR, NR • Levobupivacaine: 30, NR, NR Sex: number of males, n (%) NR Inclusion criterion: • Age of 18 to 55 years • ASA grade of I or II • BMI = 19 to 26 Kg/m^2 • Height = 155 to 190 cm Exclusion Criteria: • Allergy or intolerance to LA • Neurologic disease	Intervention: Spinal CP 1% (30 mg) Comparator: Spinal levobupivacaine 5% (15 mg)	Outcomes: • Onset and resolution of sensory block • Onset and resolution of motor block • Time to unaided ambulation • Time to independent urination Follow-up: During surgery and before discharge
Singh et al. (2020)[16] Country: India Funding source: No funding.	Patients who underwent ambulatory surgeries. Number of patients (n), Age in year, mean (SD), range: Total: 60, NR, 18 to 60 • 2-CP: 30, 60.00 (10.00), NR • Bupivacaine: 30, 55.00 (12.00), NR Sex: number of males, n (%) Total: 22 (36.66) • 2-CP: 10 (33.33) • Bupivacaine: 12 (40.00) Inclusion criterion: • Age of 18 to 60 years • ASA grade of I or II Exclusion Criteria: • Allergy or intolerance to LA • Atypical plasma cholinesterase deficiency, patients on oral anticoagulant therapy, and/or neurologic disorders	Intervention: Spinal 2-CP 1% (40 mg) Comparator: Spinal hyperbaric bupivacaine 5% (10 mg)	Outcomes: • Onset of sensory block • Onset and resolution of motor block • Time to unaided ambulation • Time to discharge Follow-up: During surgery and before discharge

Study citation, design, country, objective, funding source	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
Khare et al. (2019)[4] Country: India Funding source: No funding.	Patients who underwent perianal surgeries. Number of patients (n), Age in year, mean (SD), range: Total: 90, NR, 18 to 60 • 2-CP: 45, 40.70 (14.00), NR • Bupivacaine: 45, 42.90 (12.40), NR Sex: number of males, n (%) Total: 68 (75.55) • 2-CP: 31 (68.88) • Bupivacaine: 37 (82.22) Inclusion criterion: • Age of 18 to 60 years • ASA grade of I or II Exclusion Criteria: • Allergy or intolerance to LA • Deformity, or cardiovascular, renal, or neurologic diseases	Intervention: Spinal 2-CP 1% (30 mg) Comparator: Spinal hyperbaric bupivacaine 5% (15 mg)	Outcomes: • Onset and resolution of motor block • Time to independent urination • AE (hypotension) Follow-up: During surgery and before discharge
Siddaiah et al. (2019)[23] Country: India Funding source: No funding.	Patients undergoing lower abdominal or lower limb surgeries. Number of patients (n), Age in year, mean (SD), range: Total: 90, NR, 18 to 60 • 2-CP: 45, 43.53 (12.70), NR • 2-CP combined with buprenorphine: 45, 45.64 (13.82), NR Sex: number of males, n (%) Total: 38 (42.22) • 2-CP: 19 (42.22) • 2-CP combined with buprenorphine: 19 (42.22) Inclusion criterion: • Age of 18 to 60 years • ASA grade of I or II Exclusion Criteria: • Contraindications to spinal LA and patient refusal. • Pregnant women	Intervention: Spinal 2-CP 1% (40 mg) Comparator: Spinal 2-CP 1% (40 mg) combined with buprenorphine (0.06 mg)	Outcomes: • Onset and resolution of sensory block • Onset and resolution of motor block • Time to unaided ambulation • Time to independent urination • Time for first analgesic dose Follow-up: During surgery and before discharge
Wesselink et al. (2019)[15] Country: The Netherlands Funding source: No funding.	Patients undergoing knee arthroscopy. Number of patients (n), Age in year, mean (SD), range: Total: 150, NR, 18 years and older • 2-CP: 75, 54.00 (12.50), NR • Prilocaine: 75, 49.80 (11.20), NR	Intervention: Spinal 2-CP 1% (40 mg) Comparator: Spinal prilocaine 2% (40 mg)	Outcomes: • Onset and resolution of sensory block • Resolution of motor block • Time to discharge

Study citation, design, country, objective, funding source	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
	Sex: number of males, n (%) Total: 85 (56.66) • 2-CP: 41 (54.70) • Prilocaine: 44 (58.70) Inclusion criterion: • Age of 18 years or older • ASA grade of I or II Exclusion Criteria: • Allergy or contraindications to neuraxial block and patient refusal. • Lower extremity neuropathy • Pregnant women		• Time to independent urination Follow-up: During the surgery and before discharge
Yang et al. (2019)[24] Country: China Funding source: No funding.	Patients undergoing knee arthroscopy. Number of patients (n), Age in year, mean (SD), range: Total: 80, NR, 18 to 60 • 2-CP: 40, 37.60 (7.50), NR • Lidocaine: 40, 41.30 (18.30), NR Sex: number of males, n (%) Total: 80 (56.66) • 2-CP: 21 (52.25) • Lidocaine: 23 (57.50) Inclusion criterion: • No endocrine or metabolic diseases or any nervous system disorders • No abnormalities in liver and kidney function, and no epidural puncture contraindications Exclusion Criteria: • Patients with unsmooth anesthesia operation or uncertain effects	Intervention: Epidural 2-CP 3% (30 mg) Comparator: Epidural lidocaine 2% (30 mg)	Outcomes: • Onset and resolution of sensory block • Resolution of motor block • AEs Follow-up: During the surgery and before discharge

AE = adverse events, ASA = American Society of Anesthesiologists, BMI = body mass index, CP = chloroprocaine, Kg/m^2 = kilogram per square metre, LA = local anesthesia, NR = not reported, SD = standard deviation.

Appendix 3: Critical Appraisal of Included Publications

Note that this table has not been copy-edited.

Table 4: Strengths and Limitations of Systematic Reviews Using a MeaSurement Tool to Assess Systematic Reviews 2 (AMSTAR 2)[12]

Checklist's items	Reschke et al. (2020)[21]	Forget et al. (2019)[3]	Saporito et al. (2019)[2]
1. Did the research questions and inclusion criteria for the review include the components of PICO?	Yes	Yes	Yes
2. Did the report of the review contain an explicit statement that the review methods were established before the conduct of the review and did the report justify any significant deviations from the protocol?	Yes	Yes	No
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Yes	Yes	Yes
4. Did the review authors use a comprehensive literature search strategy?	Yes	Yes	Yes
5. Did the review authors perform study selection in duplicate?	Yes	Yes	Yes
6. Did the review authors perform data extraction in duplicate?	Yes	Yes	Yes
7. Did the review authors provide a list of excluded studies and justify the exclusions?	No	Yes	No
8. Did the review authors describe the included studies in adequate detail?	No	Yes	Yes
9. Did the review authors use a satisfactory technique for assessing the RoB in individual studies that were included in the review?	Yes	Yes	Yes
10. Did the review authors report on the sources of funding for the studies included in the review?	Yes	Yes	Yes
11. If meta-analysis was performed did the review authors use appropriate methods for the statistical combination of results?	Unclear	Yes	Yes
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	Unclear	Yes	Yes
13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	No	Yes	Partially
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Partially	Yes	Partially
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	No	Yes	Yes
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes	Yes	Yes

NA = not applicable; PICO = population, intervention, comparator, outcome; RoB = risk of bias.

Table 5: Strengths and Limitations of Systematic Reviews with Network Meta-Analyses (NMA) Using a Questionnaire to Assess the Relevance and Credibility of NMA[14]

Checklist's items	Reschke et al. (2020)[21]	Forget et al. (2019)[3]
	Yes, No, or CNA	
Relevance		
1. Is the population relevant?	Yes	Yes
2. Are any critical interventions missing?	No	No
3. Are any relevant outcomes missing?	No	No
4. Is the context (e.g., settings and circumstances) applicable to your population?	Partially	Yes
Credibility: Evidence base		
5. Did the researchers attempt to identify and include all relevant RCTs?	Yes	Yes
6. Do the trials for the interventions of interest form one connected network of randomized controlled trials?	Yes	Yes
7. Is it apparent that poor-quality studies were included thereby leading to bias?	CNA	No
8. Is it likely that bias was induced by selective reporting of outcomes in the studies?	No	No
9. Are there systematic differences in treatment effect modifiers (i.e., baseline patient or study characteristics that impact the treatment effects) across the different treatment comparisons in the network?	CNA	No
10. If yes (i.e., there are such systematic differences in treatment effect modifiers), were these imbalances in effect modifiers across the different treatment comparisons identified before comparing individual study results?	CNA	NA
Credibility: Analysis		
11. Were statistical methods used that preserve within-study randomization? (No naive comparisons)	No	Yes[a]
12. If both direct and indirect comparisons are available for pairwise contrasts (i.e., closed loops), was agreement in treatment effects (i.e., consistency) evaluated or discussed?	No	CNA
13. In the presence of consistency between direct and indirect comparisons, were both direct and indirect evidence included in the network meta-analysis?	Yes	Yes
14. With inconsistency or an imbalance in the distribution of treatment effect modifiers across the different types of comparisons in the network of trials, did the researchers attempt to minimize this bias with the analysis?	CNA	Yes
15. Was a valid rationale provided for the use of random effects or fixed effect models?	No	Yes
16. If a random effects model was used, were assumptions about heterogeneity explored or discussed?	No	Yes
17. If there are indications of heterogeneity, were subgroup analyses or meta-regression analysis with prespecified covariates performed?	Yes	No
Credibility: Reporting quality and transparency		
18. Is a graphical or tabular representation of the evidence network provided with information on the number of RCTs per direct comparison?	Yes	Yes

Checklist's items	Reschke et al. (2020)[21]	Forget et al. (2019)[3]
	Yes, No, or CNA	
19. Are the individual study results reported?	Yes	Yes
20. Are results of direct comparisons reported separately from results of the indirect comparisons or network meta-analysis?	CNA	Yes
21. Are all pairwise contrasts between interventions as obtained with the network meta-analysis reported along with measures of uncertainty?	No	CNA
22. Is a ranking of interventions provided given the reported treatment effects and its uncertainty by the outcome?	Yes	Yes
23. Is the impact of important patient characteristics on treatment effects reported?	No	No
Credibility: Interpretation		
24. Are the conclusions fair and balanced?	CNA	Yes
Credibility: Conflict of interest		
25. Were there any potential conflicts of interest?	No	No
26. If yes, were steps taken to address these?	NA	NA

CAN = cannot answer; NA = not applicable; NR = not reported; RCTs = randomized controlled trials.

[a]"If item 11 is scored as a "no" resulting in a fatal flaw, the overall domain should be judged as fatally flawed and the network meta-analysis may have serious validity issues."[14]

Table 6: Strengths and Limitations of Randomized Controlled Trials Using the Downs and Black Checklist[13]

Checklist's items	Agrawal (2022)[6]	Lee (2022)[19]	Sugumar (2022)[20]	Guntz (2021)[20]	Tiwari (2021)[18]	Singh (2020)[16]	Bhaskara (2020)[22]	Khare (2019)[4]	Siddaiah (2019)[23]	Wesselink (2019)[15]	Yang (2019)[24]
Reporting											
1. Is the objective of the study clear?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2. Are the main outcomes clearly described in the Introduction or Methods?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
3. Are the characteristics of the patients included in the study clearly described?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
4. Are the interventions clearly described?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
5. Are the distributions of principal confounders in each group of subjects clearly described?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
6. Are the main findings of the study clearly described?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
7. Does the study estimate random variability in data for main outcomes?	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
8. Have all the important adverse events consequential to the intervention been reported?	NA	Partially[a]	NA	Partially	Partially	NA	NA	Partially	NA	NA	Partially
9. Have characteristics of patients lost to follow-up been described?	NA [b]	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
10. Have actual P values been reported for the main outcomes except for probability < 0.001?	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No

Checklist's items	Agrawal (2022)[6]	Lee (2022)[19]	Sugumar (2022)[20]	Guntz (2021)[20]	Tiwari (2021)[18]	Singh (2020)[16]	Bhaskara (2020)[22]	Khare (2019)[4]	Siddaiah (2019)[23]	Wesselink (2019)[15]	Yang (2019)[24]
External validity											
11. Is the source of funding clearly stated?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
12. Were subjects who were asked to participate in the study representative of the entire population recruited?	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
13. Were those subjects who were prepared to participate representative of the recruited population?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
14. Were staff, places, and facilities where patients were treated representative of the treatment most received?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Internal validity											
15. Was an attempt made to blind study subjects to the intervention?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
16. Was an attempt made to blind those measuring the main outcomes?	Yes	Yes	Yes	Yes	Unclear	No	Yes	Yes	Yes	Yes	Yes
17. If any of the results of the study were based on data dredging was this made clear?	No	No	No	No	No	No	No	No	No	No	No
18. Was the time period between intervention and outcome the same for intervention and control groups or adjusted for?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Checklist's items	Agrawal (2022)[6]	Lee (2022)[19]	Sugumar (2022)[20]	Guntz (2021)[20]	Tiwari (2021)[18]	Singh (2020)[16]	Bhaskara (2020)[22]	Khare (2019)[4]	Siddaiah (2019)[23]	Wesselink (2019)[15]	Yang (2019)[24]
19. Were the statistical tests used to assess the main outcomes appropriate?	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes
20. Was compliance with the interventions reliable?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
21. Were the main outcome measures used accurate (Valid and reliable)?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Internal validity – Confounding (selection bias)											
22. Were patients in different intervention groups recruited from the same population?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
23. Were study subjects in different intervention groups recruited over the same period of time?	Unclear	Yes	Unclear	Unclear	Yes	Unclear	Yes	Unclear	Unclear	Unclear	Unclear
24. Were study subjects randomized to intervention groups?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
25. Was the randomized intervention assignment concealed from patients and staff until recruitment was complete?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
26. Was there an adequate adjustment for confounding in the analyses from which the main findings were drawn?	Yes	Yes	Yes	Yes	Unclear	No	Yes	Yes	Yes	Yes	Yes
27. Were losses of patients to follow-up considered?	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

Checklist's items	Agrawal (2022)[6]	Lee (2022)[19]	Sugumar (2022)[20]	Guntz (2021)[20]	Tiwari (2021)[18]	Singh (2020)[16]	Bhaskara (2020)[22]	Khare (2019)[4]	Siddaiah (2019)[23]	Wesselink (2019)[15]	Yang (2019)[24]
Power											
28. Was the study sufficiently powered to detect clinically important effects where the P value for a difference due to chance is < 5%?	Unclear	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear

NA = not applicable.

[a]The rate of adverse events (AEs) was a secondary outcome measure in 5 studies.[4,17-19,24]

[b]No loss of follow-up was reported in the selected studies.

Appendix 4: Main Study Findings

Note that this table has not been copy-edited.

Table 7: Summary of Findings by Outcome — Summary of Evidence for Epidural Anesthesia for Caesarean Section in a Systematic Review and Network Meta-analysis by Reschke et al. (2020)[21]

Outcomes	Value with worst drug (OR or mean, 95% CrI)	Value with best drug (OR or mean, 95% CrI)	Relative effect (OR or mean, 95% CrI)	Number of women (number of trials)	Comments
Onset of surgical anesthesia	Bupivacaine 0.5% (19.8, 17.3 to 22.4) min	Lidocaine 2% (3.90, 1.8 to 6.0)	6.4 (3.3 to 9.7) min	1,280 (24)	Mean of onset for 2-CP 3% = 5.7 (3.0 to 8.3) min
Intra-operative hypotension	2-CP 3% (516, 438 to 594) per 1,000	l-bupivacaine 0.5% (315, 236 to 407) per 1,000	0.52 (0.20 to 1.26)	807 (14)	2-CP3% OR (CrI) vs. l-bupivacaine 0.5% = 0.84 (0.24 to 2.86)
Intra-operative supplementation	2-CP 3% (250, 112 to 569) per 1,000	Ropivacaine 0.75% (48, 19 to118) per 1,000	0.05 (0.00 to 0.76)	886 (15)	2-CP 3% OR (CrI) vs. Ropivacaine 75% = 0.05 (0.003 to 0.76)

CP = chloroprocaine; CrI = credible interval; OR = odds ratio.

[a]Credible interval (CrI) reflects the Bayesian 95% confidence interval showing a 95% probability that the true estimate lie within the interval.[31]

Table 8: Summary of Findings by Outcome of 5 Studies — Clinical Effectiveness of Chloroprocaine Compared to Alternative Local Anesthetics

	Agarwal et al. (2022)[6]			Lee et al. (2022)[19]			Sugumar et al. (2022)[20]			Guntz et al. (2021)[17]			Tiwari et al. (2021)[18]			
	Mean (SD)			Median (IQR)			Mean (SD)			Mean (SD)			Mean (SD)			
Variables	C (n = 60)	B (n = 60)	P	C + F (n = 60)	B + F (n = 60)	P	C (n = 30)	B (n = 30)	P	C (n = NR)	Pril (n = NR)	P	C + S (n = 34)	C + F (n = 34)	B (n = 34)	P
Onset of sensory block (min)	4.26 (1.64)	4.29 (1.92)	0.02	4 (2 to 6)	4 (2 to 8)	0.67	5.06 (0.82)	6.24 (1.07)	< 0.001	NR	NR	NR	2.68 (0.58)	4.04 (0.99)	3.59 (0.61)	< 0.001
Onset of motor block (min)	5.26 (0.29)	5.32 (0.46)	0.02	NR	NR	NR	6.83 (0.83)	8.84 (0.84)	< 0.001	NR	NR	NR	3.37 (0.66)	4.99 (1.01)	4.57 (0.79)	< 0.001
Resolution of sensory block (min)	153.06 (19.38)	194.32 (21.86)	< 0.001	143 (116 to 162)	198 (152 to 263)	0.002	66.80 (4.69)	191.50 (8.72)	< 0.001	169.0 (56.10)	248.0 (59.40)	< 0.001	100.68 (25.510	133.65 (8.71)	209.94 (51.76)	< 0.001
Resolution of motor block (min)	169.52 (19.76)	197.36 (21.39)	< 0.001	109 (88 to 148)	112 (97 to 143)	0.66	64.60 (5.88)	175.33 (9.09)	< 0.001	NR	NR	NR	92.56 (24.310	107.74 (11.52)	192.29 (47.56)	< 0.001
Time to maximum sensory block	12.06 (3.24)	13.38 (3.82)	0.01	T8	T8	0.56	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Time to discharge (min)	NR	NR	NR	158 (137 to 188)	229 (186 to 332)	0.005	211.0 (24.0)	441.60 (34.8)	< 0.001	NR	NR	NR	NR	NR	NR	NR
Time to unaided ambulation (min)	NR	NR	NR	NR	NR	NR	210.60 (24.24)	441.60 (34.80)	< 0.001	NR	NR	NR	NR	NR	NR	NR

Variables	Agarwal et al. (2022)[6]			Lee et al. (2022)[19]			Sugumar et al. (2022)[20]			Guntz et al. (2021)[17]			Tiwari et al. (2021)[18]			
	Mean (SD)			Median (IQR)			Mean (SD)			Mean (SD)			Mean (SD)			
	C (n = 60)	B (n = 60)	P	C + F (n = 60)	B + F (n = 60)	P	C (n = 30)	B (n = 30)	P	C (n = NR)	Pril (n = NR)	P	C + S (n = 34)	C + F (n = 34)	B (n = 34)	P
Time to independent urination (min)	NR	NR	NR	NR	NR	NR	2.84 (0.59)	5.53 (0.57)	< 0.001	203.00 (57.60)	287.30 (47.20)	< 0.001	NR	NR	NR	NR
Patient satisfaction	NR	NR	NR	16/1/0[a]	14/3/0	0.60	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
TNS	NR	NR	NR	0	0	1.00	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Hypotension	NR	NR	NR	NR	NR	NR	NR	NR	NR	0	2	0.329	NR	NR	NR	NR
Urinary retention	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	0	0	2	> 0.05

B = bupivacaine, C = chloroprocaine, F = fentanyl, IQR = interquartile range, L = levobupivacaine, Lid = lidocaine, NR = not reported, Pril = prilocaine, S = saline, SD = standard deviation, TNS = transient neurologic symptoms.

[a]Number of patients who rated their satisfaction with the anesthetics as 1 = complete, 2 = adequate, or 3 = inadequate.[19]

Table 9: Summary of Findings by Outcome of 6 Studies — Clinical Effectiveness of Chloroprocaine Compared to Alternative Anesthetic Drugs

	Singh et al. (2020)[16]			Bhaskara et al. (2020)[22]			Khare et al. (2019)[4]			Siddaiah et al. (2019)[23]			Wesselink et al. (2019)[15]			Yang et al. (2019)[24]		
	Mean (SD)			Mean (SD)			Mean (SD)			Mean (SD)			Median (IQR)			Mean (SD)		
Variables	C (n = 30)	B (n = 30)	P	C (n = 30)	L (n = 30)	P	C (n = 45)	B (n = 45)	P	C	Pril	P	C	Pril	P	C	Lid	P
Onset of sensory block (min)	5	7	> 0.05	2.27 (0.52)	3.37 (0.49)	< 0.001	NR	NR	NR	3.11 (1.53)	2.93 (0.94)	0.507	2 (2 to 4)	4 (2 to 6)	0.010	9.40 (92.2)	9.70 (3.10)	> 0.05
Onset of motor block (min)	8	9	> 0.05	1.43 (0.50)	1.57 (0.50)	0.302	3.70 (0.60)	4.10 (0.60)	0.001	4.69 (2.07)	4.16 (1.68)	0.182	120 (90 to 135)	165 (135 to 190)	<0.001	74.30 (15.1)	73.70 (21.1)	> 0.05
Resolution of sensory block (min)	NR	NR	NR	59.00 (8.75)	126.83 (20.1)	< 0.001	NR	NR	NR	67.47 (19.3)	72.0 (8.36)	0.153	NR	NR	NR	NR	NR	NR
Resolution of motor block (min)	88	150	< 0.05	50.67 (5.68)	181.00 (27.8)	< 0.001	71.16 (12.30)	160.7 (14.8)	< 0.001	67.16 (21.7)	70.84 (9.91)	0.303	60 (60 to 82)	75 (60 to 90)	0.004	76.10 (16.3)	85.90 (18.8)	< 0.05
Time to maximum sensory block	NR	NR	NR	T8 (T8 to T10)	T6 (T6 to T10)	0.536	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Time to discharge (min)	180	365	< 0.05	NR	NR	NR	NR	NR	NR	NR	NR	NR	222 (72)	282 (42)	<0.001	NR	NR	NR

Variables	Singh et al. (2020)[16]			Bhaskara et al. (2020)[22]			Khare et al. (2019)[4]			Siddaiah et al. (2019)[23]			Wesselink et al. (2019)[15]			Yang et al. (2019)[24]		
	Mean (SD)			Mean (SD)			Mean (SD)			Mean (SD)			Median (IQR)			Mean (SD)		
	C (n = 30)	B (n = 30)	P	C (n = 30)	L (n = 30)	P	C (n = 45)	B (n = 45)	P	C	Pril	P	C	Pril	P	C	Lid	P
Time to unaided ambulation (min)	130	220	< 0.05	88.33 (9.13)	206.67 (27.2)	< 0.001	NR	NR	NR	84.02 (18.9)	85.80 (8.06)	0.563	NR	NR	NR	NR	NR	NR
Time to independent urination (min)	160	350	< 0.05	79.83 (10.13)	152.3 226.9	< 0.001	199.40 (19.20)	464.9 (30.3)	< 0.001	204.42 (81.3)	269.42 (157)	0.016	198 (60)	258 (42)	<0.001	NR	NR	NR
Time for first analgesic dose	100	250	< 0.05	NR	NR	NR	NR	NR	NR	359.1 (253)	855.8 (667)	< 0.001	NR	NR	NR	NR	NR	NR
Patient satisfaction	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
TNS	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Hypotension	NR	NR	NR	NR	NR	NR	0	9	0.002	NR	NR	NR	NR	NR	NR	1	2	> 0.05
Urinary retention	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

B = bupivacaine, C = chloroprocaine, F = fentanyl, IQR = interquartile range, L = levobupivacaine, Lid = lidocaine, NR = not reported, Pr = prilocaine, S = saline, SD = standard deviation, TNS = transient neurologic symptoms.

Table 10: Summary of Findings by Outcome — Clinical Effectiveness of 2-Chloroprocaine Compared to Bupivacaine in a Systematic Review and Network Meta-analysis by Saporito et al. (2019)[2]

Outcomes	Pooled mean difference (min)	P value[a]
Motor block regression	−57.00	0.015
Sensory block regression	−140.30	< 0.001
Time to ambulation	−84.60	< 0.001
Time to discharge	−88.60	< 0.001
Onset time	−1.10	0.118

[a]Compared to a low dose bupivacaine, spinal 2-chloroprocaine was associated with significantly faster motor and sensory block regression, and shorter time to ambulation and discharge.

Table 11: Summary of Findings by Outcome — The Risk Ratio of Transient Neurologic Symptoms (TNS) After Spinal Local Anesthesia in a Systematic Review and Network Meta-Analysis by Forget et al. (2019)[3]

Local anesthetics	Number of studies included in the analysis	Risk ratio[a]	Confidence interval
Bupivacaine	12	0.16	0.09 to 0.28
2-chloroprocaine	2	0.09	0.01 to 1.51[a]
Mepivacaine	4	1.01	0.18 to 5.82
Levobupivacaine	2	0.13	0.02 to 0.69
Prilocaine	4	0.18	0.07 to 0.49
Procaine	2	0.14	0.04 to 0.52
Ropivacaine	2	0.10	0.01 to 0.78

[a]Risk ratio (or relative risk) is the ratio of the risk of an event (here transient neurologic symptoms [TNS]) in 2 or more groups.[32] According to Forget et al. (2019),[3] in local anesthesia with 2-chloroprocaine and Mepivacaine, the RR of TNS might be as high as 1.51 and 5.82, respectively, showing no difference with lidocaine.

Appendix 5: References of Potential Interest

The following publications were identified because they may provide additional information associated with this report.

Systematic Reviews

Alternative Research Question

Yung EM, Abdallah FW, Todaro C, Spence E, Grant A, Brull R. Optimal local anesthetic regimen for saddle block in ambulatory anorectal surgery: an evidence-based systematic review. *Reg Anesth Pain Med*. 2020 09;45(9):733-739.

Nonrandomized Controlled Trials

Bhaskara B, Shruthi S, Ramachandraiah R. A study to evaluate intrathecal 1% chloroprocaine and 0.5% levobupivacaine in perianal surgeries: a prospective randomized study. *Anesth Essays Res*. 2020;14(3):406-411. PubMed

Herndon CL, Martinez R, Sarpong NO, Geller JA, Shah RP, Cooper HJ. Spinal anesthesia using chloroprocaine is safe, effective, and facilitates earlier discharge in selected fast-track total hip arthroplasty. *Arthroplast Today*. 2020;6(3):305-308. PubMed

Mims SC, Zanolli NC, Fuller M, Habib AS. Intrathecal bupivacaine versus chloroprocaine for transvaginal cervical cerclage placement: a retrospective cohort study. *Int J Obstet Anesth*. 2022;50:103276. PubMed

Gebhardt V, Hausen S, Weiss C, Schmittner MD. Using chloroprocaine for spinal anaesthesia in outpatient knee-arthroscopy results in earlier discharge and improved operating room efficiency compared to mepivacaine and prilocaine. *Knee Surg Sports Traumatol Arthrosc.* 2019;27(9):3032-3040. PubMed

Gebhardt V, Kiefer K, Bussen D, Weiss C, Schmittner MD. Retrospective analysis of mepivacaine, prilocaine and chloroprocaine for low-dose spinal anaesthesia in outpatient perianal procedures. *Int J Colorectal Dis*. 2018;33(10):1469-1477. PubMed

Animal Studies

Walker SM, Malkmus S, Eddinger K, et al. Evaluation of neurotoxicity and long-term function and behavior following intrathecal 1% 2-chloroprocaine in juvenile rats. *Neurotoxicology*. 2022 01;88:155-167. PubMed