Efficacy And Safety of Wound Infiltration Modalities For Postoperative Pain Management After Cesarean Section: A Systematic Review, Meta-Analysis, And Trial Sequential Analysis Protocol

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Abstract

Background: Inadequately managed postoperative pain after cesarean section has a number of consequences to the mother in the postoperative period. Different postoperative pain management modalities have been practiced after cesarean section over the years. The opioid based analgesics and land mark techniques have undesirable consequences, regional analgesia technique with ultrasound requires resource and expertise while different wound infiltration techniques are new techniques with minimal side effect and easy to administer. However, the effectiveness of each technique is uncertain and needs further investigation.

Objective: This systematic review will provide the most effective wound infiltration technique to prevent undesirable adverse effects of opioids and untreated pain

Method: A comprehensive search will be conducted in PubMed/Medline, Cochrane, Science direct, CINHAL, and LILACS without date and language restriction. All randomized trials comparing the efficacy of wound infiltration for postoperative pain management after cesarean section will be included. The data will be extracted with two independent authors in a customized format. The methodological quality of included studies will be evaluated using the Cochrane risk of bias tool. The overall quality of the evidence will be determined by GRADEpro software. Trial Sequential Analysis will be conducted to investigate the necessity of further trials.

Discussion: The incidence of postoperative acute as well as chronic pain is very high which has a tremendous impact on the mother, family, healthcare providers, and healthcare delivery. It is a basic human right to provide postoperative pain management to every patient that is feasible to everyone in terms of resources, technique, cost, and minimal adverse events profile

Registration: This systematic review protocol was registered in Prospero (CRD42021270710) on September 5, 2021

1. Background

1.1. Description of the condition

Cesarean delivery (CD) is the most common life-saving procedure for the mother and newborn when medically indicated(1, 2). Globally, the rates of cesarean section are increasing over the years in the last three decades particularly in developed nations (3–7).

World Health Organization estimate showed that more than 18 million cesarean sections are performed worldwide annually(6). However, more than 6 million cesarean sections were performed unnecessarily particularly in middle and high-income nations and from which China and Brazil alone accounted for 50% of unnecessary cesarean sections which is higher than the recommended rates of cesarean section for a nation, 10-15%(3, 5, 6).

A dramatic increase in the rates of cesarean section worldwide poses a significant challenge of postoperative pain management for health care workers(8). A number of postoperative pain management techniques were practiced over the years after cesarean section but they were associated with postoperative adverse events to the mother (9–15). The most commonly practiced postoperative pain management techniques include but not limited to systemic opioid and non-opioid drugs, regional blocks and local wound infiltration of different local anesthetics and other drugs(9–22).

Evidences showed that individual variability of pain is greatly influenced by sensitivity to pain gender, age, genetics, preoperative anxiety, preoperative pain, history of depressive symptoms, and history of substance use(8, 23–29).

Despite the advancement in the understanding of pathophysiology of postoperative pain introduction of different postoperative analgesic drugs and modalities, the prevalence of postoperative pain after cesarean section is persistently high which ranges from 25.5 to 80% due to individual variability and limitation from side effects of analgesic drugs or techniques employed (8, 23, 24, 27, 28, 30, 31).

The postoperative pain after cesarean section negatively affects ambulation, breastfeeding and maternal bonding(32). Besides, Inadequately managed acute postoperative pain is associated with different effects related to physiological and psychological implications which includes, postpartum depression, myocardial infarction, pulmonary infection, reduced gastric motility, nausea, vomiting oliguria, decreased immune function, and wound healing(23, 28, 29).

However, use of systemic and intrathecal opioid may lead to adverse reactions such as nausea, vomiting, itchiness and sedation(23, 32).

Recent works of peer reviewed published literatures revealed a number of local and regional postoperative pain management techniques after cesarean section including but not limited to epidural analgesia, Transverse abdominis plane (TAP) block, Quadratus lumborum block, and wound infiltrations(9, 11–14, 18, 21, 22, 32–37). However, wound infiltration techniques with local anesthetics, weak opioids, glucocorticoids, ketamine, magnesium, Nonsteroidal anti-inflammatory drugs, and alpha 2 agonists are getting popularity due to its novelty, simplicity and low complication profiles(10, 15–19, 21, 38–62). However, the superiority of each modalities is uncertain and a topic of debate.

1.2. Description of the intervention

Perioperative wound infiltration techniques after cesarean section has been employed recently due to its simplicity and feasibility in terms of cost effectiveness, techniques of administration, adverse effects. The techniques of wound infiltration with local anesthetics alone or combined with adjuvants were the most common approach(10, 13, 14, 18, 22, 42–46, 48, 52, 58, 61–64). However, recent studies comparing local anesthetics with glucocorticoids, opioids(15, 21, 41, 46, 47, 49, 50), ketamine(19, 40, 42, 44, 53–55), nonsteroidal anti-inflammatory agents(57), alpha 2 agonists(10, 38) and magnesium(48, 56, 60) are coming out.

1.3. How the intervention might work

The mechanism of local anesthetics for postoperative pain management is due to blockade of the pentameric alpha unit sodium channel thereby inhibition of propagation of action potential and pain sensation whereas(65–67) the exact mechanism of glucocorticoid is unknown but it is presumed to be via inhibition of the phospholipase α2 enzyme which is responsible for production of prostaglandin and other inflammatory mediators(68–70). The opioids like tramadol works via inhibition of inflammatory mediators and also evidences shows that tramadol has a local anesthetic like property to block sodium channels(64, 71). The mechanism of selective alpha 2 agonists is uncertain but there are a number of assumptions including inhibition of release of substance p and other inflammatory mediators, modulation of hyperalgesia by stimulating the α2 receptor, and peripheral inhibition of Aδ and C fibers(72–76). The mechanism of Ketamine for prevention of postoperative pain is through modulation of central sensory processing of pain by blocking N-methyl-D-aspartate (NMDA) receptor(77, 78).

1.4. Why is it important to do this review?

Different works of published literatures reported that the rate of cesarean section is growing rapidly worldwide. The prevalence of postoperative pain after cesarean section is very high which has a great challenge for health care workers. An inadequately managed postoperative management after cesarean section has a number of consequences including deep venous thrombosis, delayed breastfeeding, paralytic ileus, postpartum depression, pulmonary infection, delayed wound healing, increased in-hospital length of stay, chronic pain, and increased health care cost.

Different postoperative pain management modalities are practiced after cesarean section over the years. However, opioid based analgesics and land mark techniques have undesirable consequences, regional analgesia technique with ultrasound requires resource and expertise while different wound infiltration techniques are new techniques with minimal side effect and easy to administer. However, the effectiveness of each technique is uncertain and needs further investigation with systematic review with meta-analysis and trial sequential analysis. This systematic review will provide the most effective wound infiltration technique to prevent undesirable adverse effects of opioids and untreated pain. In addition, the output of this meta-analysis expected to contribute for the successful accomplishment of sustainable development goal (SDGs) article 3.2.2(79).

2. General Objective

The general objective of this systematic review and meta-analysis will be to determine the efficacy and safety of wound infiltration modalities for postoperative pain management after caesarean section

2.1 Specific objective

- To investigate the efficacy of wound infiltration modalities for postoperative management on weighted mean difference pain score after cesarean section

- To assess the efficacy of wound infiltration modalities for postoperative management on weighted mean difference analgesic duration after cesarean section
- To determine the effect of wound infiltration modalities for postoperative management on pooled postoperative cumulative opioid consumption after cesarean section
- To identify the effect wound infiltration modalities for postoperative management on pooled incidence of postoperative nausea and vomiting after cesarean section?
- To identify the effect of wound infiltration modalities for postoperative management on the pooled incidence of sedation after cesarean section
- To investigate the necessity of further trials on the efficacy of wound infiltration

2.2. Review research questions

This systematic review, meta-analysis and meta-regression will be intended to answer the flowing questions:

1. What is the weighted mean difference pain score after cesarean section receiving wound infiltration postoperative pain management?
2. What is the weighted mean difference analgesic duration after cesarean section receiving wound infiltration postoperative pain management?
3. What is the pooled incidence of postoperative nausea and vomiting after cesarean section receiving wound infiltration postoperative pain management?
4. What is the pooled incidence of sedation after cesarean section receiving wound infiltration postoperative pain management?

3. Methods

3.1. Protocol and registration

The systematic review and meta-analysis will be conducted based on the Preferred Reporting Items for Systematic and Meta-analysis protocol (PRISMA-P)(80). This Systematic Review and Meta-Analysis protocol was registered in Prospero (CRD42021270710) on September 5, 2021

3.2. Eligibility criteria

3.2.1. Types of studies

All randomized controlled trials comparing effectiveness and safety of wound infiltration ketamine, opioids, alpha 2 agonist, Magnesium, steroids, and local anesthetics for postoperative pain management after cesarean section will be included. However, observational studies comparing wound infiltration against placebo and other drugs will be excluded as these studies are conducted among heterogonous group of participants with different confounders which could buffer the effect size of this systematic review and meta-analysis. Besides, comparison of local anesthesia with regional block will be excluded.

3.2.2. Types of participants

All American society of Anesthesiologist physical status classification (ASA) I and II, term pregnancy, age greater 18 years scheduled for cesarean section under spinal anesthesia will be included and the rest will be excluded. These inclusion and exclusion criteria were as per the definition of each primary included study.

3.2.3. Types of intervention

The treatment group will be parturient allocated to one of the wound infiltration modalities which were as per the included studies. While, the parturient allocated into comparator defined by each included studies will be considered as controlled groups.

3.2.4. Outcome measures

The primary outcomes of this systematic review with meta-analysis and trial sequential analysis will be postoperative pain severity, first analgesic request, total analgesic request, and patient satisfaction while post-operative nausea and vomiting, sedation, and mortality will be secondary outcomes.

3.3. Search strategy

The search strategy was intended to explore all available published and unpublished randomized controlled trials among parturient undergoing cesarean section under spinal or general anesthesia comparing wound infiltration modalities for postoperative pain management after cesarean section without language and date restrictions. A comprehensive initial search was employed in PubMed/Medline, Science Direct and Latin American and Caribbean Health Sciences Literature (LILACS) followed by an analysis of the text words contained in Title/Abstract and indexed terms. A second search was undertaken by combining free text words and indexed terms with Boolean operators. The third search was conducted with the reference lists of all identified reports and articles for additional studies. Finally, an additional and grey literature search was conducted on Google scholars. The duplicates were removed using EndNote reference manager. Then the rest were evaluated for inclusion in the systematic review based on the PICO strategy as cesarean section OR ceasarean section OR C-section OR Cesarean delivery AND local anesthetics OR bupivacaine OR Levobupivacaine OR Marcaine OR Lidocaine OR Opioids OR tramadol OR pethidine OR ketamine OR dexamethasone OR steroid OR Glucocorticoid OR Dexmedetomidine OR clonidine OR α2 agonist AND Normal saline OR placebo AND OR postoperative pain OR analgesia OR toxicity OR adverse effects OR RCT for PubMed/Medline database. The results of the search strategy will be summarized with Prisma flow chart(81).

3.4. Data extraction

The data from each study were extracted with two independent authors with a customized Microsoft excel 2013 format. The disagreements between the two independent authors were resolved by the other two authors. The extracted data included: Author names, country, date of publication, sample size, treatment and control groups, severity of pain, first analgesic request, total analgesic consumption,

patient satisfaction, incidence of nausea and vomiting, and incidence of sedation. Finally, the data will be then imported for analysis in review manager for analysis and risk of bias summary. The extracted data also imported to the R software version 3.6.1 and STATA 16 for analysis of meta-regression, and publication bias. Besides, the data will be imported into Trial sequential analysis software to determine the conclusiveness of the evidence.

3.5. Assessment of methodological quality

The methodological quality of included studies will be evaluated based on the Cochrane handbook for systematic reviews of intervention(82) by two independent reviewers and the disagreement will be resolved the other reviewers. The evaluation will be conducted with respect to Random sequence generation, Allocation concealment, blinding of participants and treatment providers, Blinding of outcome assessment, Incomplete outcome data, Selective outcome reporting, and other risk of bias. Besides, the methodological quality of this systematic review will be evaluated with a critical appraisal tool for systematic reviews that include randomized or non-randomized studies of healthcare interventions, or both (AMSTAR 2)(83).

3.5.1. Random sequence generation

Studies done the random sequence generation using computer random number generator or a random number table will be rated as low risk of bias. Besides if random sequence generation is done with lottery method, tossing a coin, shuffling cards, and throwing dice will also be considered adequate if performed by an independent adjudicator. If the method of randomization was not specified, but the trial was still presented as being randomized is considered as uncertain risk of bias. High risk of bias is considered, If the allocation sequence was not randomized or only quasi-randomized.

3.5.2. Allocation concealment

Allocation concealment is said to be low risk if the allocation of patients was performed by a central independent unit, on-site locked computer, identical-looking numbered sealed envelopes, or containers prepared by an independent investigator. It is uncertain risk of bias if the trial was classified as randomized but the allocation concealment process was not described; and it is a high risk bias if the allocation sequence was familiar to the investigators who assigned participants.

3.5.3. Blinding of participants and treatment providers

If the participants and the treatment providers were blinded to intervention allocation and this was described in the article, it is considered to be low risk of bias and it was uncertain if the procedure of blinding was insufficiently described. If blinding of participants and the treatment providers was not performed at all, it was taken as high risk of bias.

3.5.4. Blinding of outcome assessment

It is said to be low risk of bias if the outcome assessors were blinded and this was sufficiently described but it is uncertain mentioned if the outcome assessors in the trial were blinded or the extent of blinding was insufficiently described and high risk if no blinding or incomplete blinding of outcome assessors was performed

3.5.5. Incomplete outcome data

It is low risk of bias if there were no drop-outs or withdrawals for all outcomes or, the numbers and reasons for the withdrawals and drop-outs for all outcomes were clearly stated and could be described as being similar to both groups, or drop-outs are less than 5% and uncertain risk of bias is assumed if there was insufficient information to assess whether missing data were likely to induce bias on the results. If the results were likely to be biased due to missing data either because the pattern of drop-outs could be described as being different in the two intervention groups or the trial used improper methods in dealing with the missing data, it is taken as high risk of bias.

3.5.6. Selective outcome reporting

Low risk of bias is considered if a protocol was published before or at the time the trial begun and the outcomes specified in the protocol were reported; and uncertain risk of bias is rated if no protocol was published. If the outcomes in the protocol were not reported at all, high-risk of bias is introduced.

3.5.7. Other risk of bias

If the trial appears to be free of other components (for example, academic bias or for-profit bias) that could put it at risk of bias, it is low risk of bias. It is called uncertain risk of bias if the trial may or may not be free of other components that could put it at risk of bias but it is not described. If there is other factors in the trial that could put it at risk of bias such as authors conducted trials on the same topic or for-profit it could introduce high risk of bias.

3.5.8. Overall risk of bias

Overall, the study is said to have low risk of bias only if all of the bias domains described are classified as low risk of bias and high risk of bias if any of the bias risk domains described above are classified as “unclear” or high risk of bias.

3.5.9. Grading the quality of evidence

The overall quality of evidence for the studied outcome will be evaluated using the GRADE system (Grading of Recommendations, Assessment, Development, and Evaluation)(38, 84). The system incorporates study quality (risk of bias), inconsistency (comparison of effect estimates across studies), indirectness (applicability of the population, intervention, comparator and outcomes to the clinical decision), imprecision (certainty of confidence interval) and high probability of publication bias. The overall quality of evidence will be categorized as follows by evaluating and combing the above five parameters for maternal and neonatal outcomes.

- **Effective interventions**: indicated that the review found high-quality evidence of effectiveness for an intervention.
- **Possibly effective interventions**: indicated that the review found moderate-quality evidence of effectiveness for an intervention, but more evidence is needed.
- **Ineffective interventions**: indicated that the review found high-quality evidence of lack of effectiveness (or harm) for an intervention.
- **Probably ineffective interventions**: indicated that the review found moderate-quality evidence suggesting a lack of effectiveness (or harm) for an intervention, but more evidence is needed.
- **No conclusions possible**: indicated that the review found low or very low-quality evidence, or insufficient evidence to comment on the effectiveness or safety of an intervention.

3.5.10. Data analysis

Data analysis will be carried out in Review manager version 3.3.1 software, R statistical software version 3.6.1 and STATA 16, and Trial sequential analysis software. The pooled incidence of postoperative pain, weighted mean difference of Numeric rating scale (NRS), first analgesic request, adverse effects such as nausea and vomiting, sedation, and Apgar score with fixed and random effect model with the Restricted maximum likelihood (REML) method where appropriate but the meta-analysis results will be reported with random effect model if there is substantial heterogeneity between the included studies. The Heterogeneity among the included studies will be checked with forest plot, $\chi 2$ test, I^2 test, and the p-values. Subgroup analysis will be conducted by types of treatment modalities. Meta-regression will be conducted with year of publication, mean age, and sample size. Publication bias will be checked with a funnel plot and the objective diagnostic test was conducted with Egger's correlation, Begg's regression tests, and Trim and fill method.

3.6 Data synthesis

3.7 Narration

The authors plan to describe the characteristics of each included studies with respect to sample size, country, intervention and comparator, baseline clinical variables, primary and secondary outcomes, conclusion and recommendation. Besides, description of the included studies will be summarized using table.

3.8. Meta-analysis

This systematic review will be conducted in compliant with the updated Cochrane Handbook for Systematic Reviews of Interventions(85). The meta-analysis will be conducted with review manager 5(86) to estimate the pooled effect sizes and risk of bias summary while, STATA 16 software(87), and R software version 4.2(88) will be used for meta-regression, sensitivity analysis, publication bias analysis where appropriate. We will conduct the meta-analysis with Restricted Maximum likelihood (REML) estimator with both random and fixed effect model as recommended by different authors(89, 90).

Substantial heterogeneity among the included studies will be investigated with subgroup analysis and meta-regression and final decision to report the finding either narratively or doing the meta-analysis with random effect model depends on the clinical importance of the outcome (91–94). Publication bias will be checked with a funnel plot and the objective diagnostic test will be conducted with Egger's correlation, Begg's regression tests, and Trim and fill method.

3.9. Trial sequential analysis

Traditional meta-analysis runs the risk of random errors due to sparse data and repetitive testing of accumulating data when updating reviews. We plan to control the risks of type I and II errors. We will therefore perform Trial Sequential Analysis on the outcomes, in order to calculate the required information size which is the number of participants needed in a meta-analysis to detect or reject a certain intervention effect and the cumulative Z-curve's breach of relevant trial sequential monitoring boundaries(95–100). The required information size for dichotomous outcomes will be estimated based on the observed proportion of patients with an outcome in the control group (the cumulative proportion of patients with an event in the control groups relative to all patients in the control groups), a relative risk reduction of 20%, an alpha of 1.4% for all our outcomes, a beta of 20%, and the observed diversity as suggested by the trials in the meta-analysis while the observed SD, a mean difference of the observed SD/2, an alpha of 1.4% for all outcomes, a beta of 20%, and the observed diversity will be used continuous outcomes(99–102).

4. Discussion

This systematic review, meta-analysis with trial sequential analysis is planned to investigate wound infiltration postoperative pain management modalities after cesarean section.

A systematic review and meta-analysis, and a plenty of randomized controlled trials showed that systemic opioid based analgesics, neuraxial analgesia, and locoregional blocks provide better postoperative pain relief after cesarean section(9, 13, 32, 37, 68–70, 103–106). However, systemic opioids based analgesics are associated with several postoperative adverse events including nausea, vomiting, respiratory depression, opioids addiction, and other gastrointestinal complications(105, 107); neuraxial and thoraco-abdominal field block requires resources, expertise, and also associated with complications including hypotension, high spinal, bradycardia, nerve damage, organ damage, and local anesthetics toxicity(108, 109).

On the other hand, local wound infiltration techniques with local anesthetics, ketamine, opioids, Dexmedetomidine, glucocorticoids, and nonsteroidal anti-inflammatory agents are feasible with respect to technical issues, resource, low complication rate and patient acceptance despite discrepancies on effectiveness and superiority(110).

Evidences showed that incidence of postoperative acute as well as chronic pain is very high which has a tremendous impact on the mother, family, healthcare providers, and healthcare delivery (23, 28, 29).

It is a basic human right to provide postoperative pain management to every patient which is feasible to everyone in terms of resources, technique, cost, and adverse events profile(111, 112).

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and materials

Data and material can be available where appropriate.

Competing interests

The authors declare that there are no competing interests

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Authors' contributions

SA and GM conceived the idea design of the project. SA, GM, BB, SN, and MT were involved in searching strategy, data extraction, quality assessment, analysis, and manuscript preparation. All authors read and approved the manuscript.

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