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Original Contribution

Programmed intermittent peripheral nerve local anesthetic bolus compared with continuous infusions for postoperative analgesia: A systematic review and meta-analysis☆

Matthew A. Chong, MD *[,1], Yongjun Wang, BScPharm [2], Shalini Dhir, MD [3], Cheng Lin, MD [4]

Department of Anesthesia and Perioperative Medicine, Western University, London, Ontario, Canada

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ABSTRACT

Study objective and background: The role of the programmed intermittent bolus (PIB) technique for infusion of local anesthetics in continuous peripheral nerve blockade (CPNB) remains to be elucidated. Randomized controlled trials (RCTs) on PIB versus continuous infusion for CPNB have demonstrated conflicting results and no systematic review or meta-analysis currently exists. We aimed to delineate via systematic review with meta-analysis if there is any analgesic benefit to performing PIB versus continuous infusion for CPNB.
Design: We conducted a systematic review and random-effects meta-analysis of RCTs.
Data sources: We searched Medline, Embase, and the Cochrane Library without language restriction from inception to 2-May-2017.
Eligibility criteria: Included RCTs had to compare PIB to continuous infusion in adult surgical patients receiving any upper or lower limb CPNB for postoperative analgesia. VAS pain scores were the primary outcome. The Cochrane Risk of Bias Tool with GRADE methodology was utilized to assess evidence quality.
Results: Nine RCTs (448 patients) met the inclusion criteria. Two studies performed upper limb blocks and the rest lower limb blocks. Five RCTs activated the CPNB with long-acting local anesthetic and only five used multi-modal analgesia. PIB modestly reduced VAS pain scores at 6 h (−14.2 mm; 95%CI −23.5 mm to −5.0 mm; $I^2 = 82.5\%$; $p = 0.003$) and 12 h (−9.9 mm; 95%CI −14.4 mm to −5.4 mm; $I^2 = 12.4\%$; $p < 0.001$), but not at later time points. There were no other meaningful differences in the rest of the outcomes, apart from more residual motor block with PIB (OR 4.27; 95% CI 1.08–16.9; $p = 0.04$; NNTH = 8). GRADE scoring ranged from low to very low.
Conclusions: The existing evidence demonstrates that PIB does not meaningfully reduce VAS pain scores in CPNB. This systematic review provides important information about the limitations of existing studies. Future studies should reflect contemporary practice and focus on more painful operations.

1. Introduction

Continuous infusions of local anesthetics are widely utilized in regional anesthesia to provide catheter-based postoperative analgesia after painful surgeries [1]. Recently, there has been high interest in a novel infusion strategy termed the programmed intermittent bolus (PIB) technique. PIB differs from continuous infusion insofar as the hourly block volume is given as a bolus, rather than infused continuously. Such bolus administration is thought to result in better spread of local anesthetic around the targeted nerves [2]. Indeed, benefits of PIB have been demonstrated for labor analgesia, where PIB results in better patient satisfaction and less local anesthetic consumption [3].

Despite the clinical effectiveness of PIB in labor analgesia, the evidence for this technique in regional anesthesia is unclear. Numerous randomized controlled trials (RCTs) have been performed and they have demonstrated conflicting results as to whether PIB is superior to

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* Corresponding author at: Department of Anesthesia & Perioperative Medicine, University Hospital (London Health Sciences Centre), 339 Windermere Road, C3-108, London, Ontario N6A 5A5, Canada.
E-mail addresses: matthew.chong@lhsc.on.ca (M.A. Chong), Shalini.Dhir@sjhc.london.on.ca (S. Dhir).
[1] Contribution: MC conceived the idea for the meta-analysis, designed the search strategy, selected study articles, performed the risk of bias assessment, extracted the data, performed the data analysis, created the figures/tables, and prepared the manuscript.
[2] Contribution: YW assisted with the data extraction and manuscript preparation.
[3] Contribution: SD reviewed and edited the manuscript.
[4] Contribution: CL selected study articles, extracted data, performed the risk of bias assessment, and revised the final manuscript.

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continuous infusion in the setting of continuous peripheral nerve blockade (CPNB) for postoperative analgesia [4,5]. The elucidation of whether or not PIB is of benefit is important: on one hand, PIB may result in better patient outcomes, as suggested by the benefits in the labor analgesia literature; on the other hand, PIB requires specialized pumps that are capable of giving the automated boluses and, therefore, may be costly to adopt [6]. Finally, we are not aware of any existing systematic review and meta-analysis that synthesizes the evidence for PIB in regional anesthesia. Therefore, given this gap in the literature and clinical equipoise, we designed and conducted a systematic review and meta-analysis of RCTs to elucidate the effect of PIB on patient centered outcomes in CPNB for postoperative analgesia. Based on the benefits in the labor analgesia literature, we hypothesized that PIB would result in better analgesia with less local anesthetic and rescue opioid consumption.

2. Methods

This systematic review and meta-analysis complies with the PRISMA statement [7]. Our institutional research ethics board does not require approval for systematic reviews and meta-analyses, as no data is being collected from patients. The clinical question, study inclusion criteria, outcomes, and analysis plan were defined a priori.

2.1. Literature search

Ovid Medline, Embase, and the Cochrane Library were searched from inception to 2 May 2017 without language restriction for RCTs meeting the following inclusion criteria.

2.2. Study selection criteria

2.2.1. Population

Studies had to recruit adult surgical patients receiving any CPNB with catheter placement. Neuraxial blockade was not considered part of the scope of the review. Furthermore, we did not include studies recruiting healthy volunteers, such as subjects who volunteer to have a nerve catheter placed without undergoing surgery.

2.2.2. Intervention and control

To be included, the trial had to compare PIB to continuous infusion for delivery of the local anesthetic solution. The dosing of the local anesthetic had to be mathematically similar (e.g. 5 mL per hour in the continuous arm versus 10 mL every 2 h in the PIB arm was considered acceptable). We excluded studies where the local anesthetic solution volume or dose differed between study arms or where the patient was relied upon to administer the intervention boluses (e.g. the PIB was not truly programmed).

2.2.3. Outcomes

The primary outcome was visual analogue scale (VAS) pain scores on a 100 mm scale. Secondary outcomes included opioid and local anesthetic consumption, patient satisfaction, rescue analgesia requirement, side effects (e.g. nausea and vomiting), and block-related complications.

2.2.4. Search strategy

The full search strategy is available in the Appendix (Supplemental Digital Content 1, which lists search terms for each database). The search utilized a comprehensive combination of medical subject heading (MeSH) terms, free-text terms, and corresponding synonyms. The reference lists of included articles were manually searched for additional studies. We also queried the clinicaltrials.gov database for additional and on-going studies, but did not seek unpublished data.

2.3. Article screening and data extraction

All titles, abstracts, and full texts (where required to assess the study for inclusion) were reviewed in duplicate by MC and CL. Any disagreements were resolved by consensus with SD. Data from included studies were extracted independently onto standardized forms by MC, YW, or CL. Extracted data included important baseline demographic information of each study, information regarding assessment of the risk of bias of the study, and the pre-specified outcomes. To facilitate meta-analysis, medians, IQR, and range values were approximated into means and their corresponding standard deviation using methods suggested by the Cochrane Library [8]. Where necessary (e.g. data values not reported in text and only within graphs), numerical data were extracted from graphs by digital measurement. We attempted to contact principal investigators of included studies for additional information, where necessary.

2.4. Risk of bias evaluation

The Cochrane Risk of Bias Tool was utilized to appraise each included study's risk of bias by MC and CL and all discrepancies were resolved by consensus [9]. We considered studies to be at low risk of bias if they scored 3 or higher on these criteria: (1) appropriately generated the randomization sequence, (2) appropriate allocation concealment, (3) blinded study personnel and participants, and (4) blinded outcome assessors, and (5) reported data completely. Furthermore, the study had to demonstrate no significant selective reporting bias or other source of bias [9]. Finally, GRADE methodology was utilized to provide an overall appraisal of the quality of evidence underlying each outcome [10].

2.5. Statistical analysis

Statistical analysis was carried out in Stata (Version 13.1 by StataCorp, College Station, Texas). Standard summary measures were generated with the weighted mean difference (WMD) or standardized mean difference (SMD) for continuous data and odds ratios (ORs) for binary data, with their corresponding 95% confidence intervals (CIs) and an $\alpha = 0.05$. All analyses were carried out using a random-effects model. For multiple comparisons over time (e.g. VAS pain score data), a Bonferroni correction was applied. Furthermore, to account for heterogeneity in reporting of pain scores, we converted 10-point and ordinal pain scales to a 100 mm VAS. Only one study utilized an ordinal scale (3 points) that had to be converted in this manner [11]. The I^2 statistic was utilized to quantify heterogeneity. We interpreted an I^2 value of 0–25% as low heterogeneity, 25–50% as moderate heterogeneity, and >50% as high heterogeneity. The continuity correction was utilized for zero event studies [12]. A funnel plot was constructed for the primary outcome and Egger's regression performed to assess for statistical evidence of publication bias.

The pre-specified subgroup analyses included block technique (ultrasound-guided versus nerve stimulator versus landmark), type of local anesthetic (short-acting versus intermediate-acting versus long-acting), use of concurrent multimodal analgesia (e.g. acetaminophen and/or non-steroidal anti-inflammatory agents), study quality (high versus low risk of bias), block location (upper versus lower limb), usage of patient-controlled demand boluses (patient-controlled regional analgesia [PCRA]), and type of catheter (e.g. single versus multi-orifice).

3. Results

3.1. Literature search and study selection

Our search strategy initially captured 226 citations and 9 RCTs (448 patients) ultimately met the inclusion criteria (Fig. 1, PRISMA Flow Chart). Notable study exclusions included one RCT where the patients