Systematic Review and Meta-analysis Article
http://mjiri.iums.ac.ir
Medical Journal of the Islamic Republic of Iran (MJIRI)

Med J Islam Repub Iran. 2025 (9 Jul);39.92. https://doi.org/10.47176/mjiri.39.92

The Role of Preemptive Perioperative Analgesia in Prevention of Chronic Phantom Pain: A Systematic Review and Meta-analysis

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Received: 23 Feb 2025 Published: 9 Jul 2025

Abstract

Background: Phantom limb pain (PLP) is a debilitating condition leading to the experience of pain in a limb that has been amputated. Pharmacological interventions have been proposed to prevent chronic PLP. However, results of these interventions are still controversial. This systematic review and meta-analysis clarifies the effectiveness of preemptive pharmacological interventions in prevention of chronic phantom pain by evaluating incidence and intensity of PLP, residual limb pain (RLP), quality of life (QoL), depression, and anxiety.

Methods: We systematically searched the PubMed, Embase, Scopus, Web of Science, and Cochrane Library databases for published randomized clinical trials with the outcomes of incidence and intensity for PLP, RLP, QoL, depression, and anxiety in amputation candidates due to any reason. We used the Risk of Bias tool (ROB2) to assess the quality of evidence. Relative risks and mean differences were calculated by a fixed-effects model, and sensitivity analysis was conducted post-hoc for risk of bias. We presented the results using the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) tables.

Results: Overall, 20 studies were found to address outcomes of interest at 6 months or longer. In 18 studies, intervention was planned for lower limb amputations. Peripheral vascular disease was the most studied cause for amputation. Intervention showed a mean reduction of 0.63 (0.10- 1.15) in 6-month intensity of PLP with low certainty of evidence. Evidence for Ketamine, Gabapentin, Valproic Acid, Calcitonin, Amide local anesthetics such as bupivacaine via epidural and perineural catheters did not support reduction in PLP.

Conclusion: Imprecision due to small sample sizes, inadequate blinding, and publication bias downgraded the quality of evidence in this clinical scenario. Overall, preemptive perioperative pharmacological interventions do not seem to prevent phantom pain or stump pain compared with conventional perioperative pain control methods. Further robust studies are required for the effectiveness of Memantine in the prevention of chronic PLP.

Keywords: Phantom Limb Pain, Residual Limb Pain, Prevention, Systematic Review, Meta-analysis

Conflicts of Interest: None declared
Funding: None

Cite this article as: Abrishami R, Azh N, Farhang Ranjbar M, Motamedgorji N. The Role of Preemptive Perioperative Analgesia in Prevention of Chronic Phantom Pain: A Systematic Review and Meta-analysis. *Med J Islam Repub Iran.* 2025 (9 Jul);39:92. https://doi.org/10.47176/mjiri.39.92

Introduction

Patients with phantom limb pain (PLP) experience a debilitating pain in a limb that has been amputated. The condition is distinct from residual limb pain (RLP or stump pain) and could impact mental health and the quality of life (QoL) of amputees (1). While the exact cause of this phenomenon is not clear, the peripheral nervous system

↑What is "already known" in this topic:
Several interventions have been proposed to reduce the risk of developing chronic phantom pain post-amputation. These interventions aim to modify risk factors such as preoperative pain scores or acute postoperative phantom limb pain (PLP) and residual limb pain (RLP) that are presumed to predict and modify the incidence and intensity of phantom pain.

→What this article adds:
Our study aims to clarify the effectiveness of different perioperative pharmacological interventions in the prevention of chronic PLP through a systematic review and meta-analysis of the literature. Our findings help optimize the perioperative interventions for amputation candidates, as well as provide insights into the risk factors and underlying mechanisms of chronic PLP.

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undergoes changes including the formation of neuromas, abnormal spontaneous activity, and changes in ion channels, which have been associated with postamputation limb pain. These changes may result in the generation and transmission of pain signals to the central nervous system. Moreover, the central nervous system changes, including cortical reorganization, occur after amputation and can lead to alterations in the sensory and motor representation of the amputated limb. This reorganization may contribute to the perception of pain in the phantom limb (2, 3).

Epidemiological studies indicate that regardless of the cause, the prevalence of PLP ranges from 46% to as high as 86% with 2 peaks at 1 month and 1 year postoperatively (4-7). Several studies have proposed risk factors such as preoperative pain scores or postoperative PLP and RLP to predict the incidence of chronic phantom pain (8-10). However, it is unclear whether modifying these factors by controlling preoperative pain can decrease the risk of developing PLP (4, 11). Non-steroidal anti-inflammatory drugs (NSAIDs), opioids, anticonvulsants, antidepressants, N-methyl-d-aspartate (NMDA) receptor antagonists, and local amide anesthetics have been tested in different dosages, forms, and delivery routes and have shown contradicting results in the prevention settings (12-14). This systematic review and meta-analysis was conducted to help clarify the effectiveness of current perioperative interventions in prevention of chronic phantom pain by evaluating incidence and intensity of PLP, RLP, QoL, depression, and anxiety.

Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline was applied to our study (15).

Databases and Selection Process

We systematically searched PubMed, Embase, Scopus, Web of Science, and Cochrane Library databases. The search terms were designed by a bioinformatic librarian and a team of clinical epidemiologists and medical doctors. Appendix 1 shows the search terms and syntax used. We retrieved studies up to February 9, 2025. Two independent authors screened the retrieved articles for relevance, and relevant articles were screened by abstract and full text. Ultimately, 20 studies were included in the systematic review. This systematic review is registered in the PROSPERO database under the code CRD42023385291, with a detailed description of the search strategy.

Study Eligibility

We applied the following criteria for eligibility: Published randomized clinical trials, which assessed the perioperative pharmacological interventions' effectiveness for prevention of chronic PLP in both adults and children, compared with placebo or other conventional medications. The primary outcomes of our study were the incidence or intensity of chronic PLP and RLP reported using numerical or visual rating scales at a minimum of 6 months. Where available, we also recorded QoL, depression, and anxiety as secondary outcomes.

The interventions included epidural anesthesia combinations, peripheral nerve catheters, anti-epileptics, opioids, NMDA receptor agonists, and other conventional medications in all dosages and forms. Subgroup analyses were planned for interventions, sharing a similar setting based on duration, mode of action, dosage, delivery route, or demographics, but were not required.

We excluded studies that evaluated acute (under 6 months) phantom pain, nonpharmacological interventions such as mirror therapy and cognitive behavioral therapy, complex regional pain syndrome, fibromyalgia, and chronic postsurgical pain syndromes. We also excluded articles for which we could not obtain an English or full-text version.

Data Extraction

We recorded study characteristics such as author and year, study population and settings, participants' eligibility criteria, interventions and their dosage and follow-up length, measured outcomes, and source of funding. We summarized the data on the incidence and intensity of PLP and RLP, as well as the QoL, depression, and anxiety scores in a unified form presented as a study characteristics and effect estimates table for individual studies. Any disagreements were resolved by discussion. PlotDigitizer was used to quantify graph data for graphs without available values (16).

Quality Assessment and Evidence Certainty

We assessed the randomized control trials (RCTs) for their quality and limitations in study design or execution using the Cochrane tool for assessment of risk of bias (ROB2). ROB2 specifically addresses outcomes rather than the quality of the whole study, which makes it ideal for self-reported and subjective outcomes like pain (17). Additionally, we used the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) approach to assess the overall certainty of evidence for every outcome in the summary of findings tables (18).

Statistical Reporting and Meta-analysis

Our meta-analyses were set to estimate the relative risk (RR) of developing phantom pain and stump pain when additional analgesic measures were added to conventional pain control methods. Meta-analysis of inverse-variances with fixed-effect model was used for Epidural amide anesthetics, Perineural Catheter infusion of amide anesthetics, and Memantine. Difference in delivery routes, mechanisms of action, and population age were the main heterogeneity sources. We performed heterogeneity tests and meta-analyses using Review Manager 5.4.1 (19). The variance between the selected studies and the I^2 test was used concurrently to investigate the statistical heterogeneity for the meta-analyses. The Funnel plot diagram and Egger's test were used to check for publication bias. Finally, to assess the effect and adjust for study limitations, we conducted post-hoc sensitivity analyses excluding studies with high or some concern for risk of bias.

To report the results, dichotomous data were summarized as risk ratios (RR) with 95% confidence intervals (CI), and

[DOI: 10.47176/mjiri.39.92]

continuous data as mean differences (MD) and 95% CI or standardized MDs. As for ordinal outcomes, we reported the median and first and third quartiles.

We took several statistical solutions to decrease imprecision of the meta-analyses and thus, improve the certainty of evidence:

First, we transformed all dichotomous and continuous effect estimates into the natural log of odds ratio or standardized mean difference and analyzed their pooled effect estimates as the RR or the MD using inverse variances through the method proposed by Chinn et al (20). This allowed us to increase our information size, producing effect estimates from both continuous and dichotomous data. All included studies that reported dichotomous results used a numerical rating scale with a similar cutoff for significant pain (being ≥3 out of 10). The similarity in scales satisfied the assumption for pooling dichotomous and continuous data (20-22).

We also noticed that all the interventions were administered at the beginning of the studies and for a short period, so that "time" did not affect the integrity of interventions. This assumption allowed us to safely pool per-protocol results with intention-to-treat results without the risk of overestimation or requiring additional adjustment measures (23). This solution effectively increased the certainty of evidence by procuring a larger information size for the analyses at longer time points where loss to follow-up was a major limiting factor.

Results

Included Studies

Our primary query of the 5 databases retrieved 28,325 articles, of which 10,792 were duplicates. A total of 68 records were nominated for full-text evaluation. Finally, we included 20 studies. Figure 1 summarizes the systematic search results (24).

Risk of Bias

Figure 2 present the risk of bias assessed for each study using the ROB2 tool. Epidural interventions suffered from a poor method of randomization, as well as assessors not being blinded to the allocations. Among studies using perineural catheters (PNC) to deliver drugs, the study by Bosanquet et al was open-label, and Reuben et al did not adequately describe the follow-up process. The study by Schley et al in the memantine group does not provide a CONSORT (Consolidated Standards of Reporting Trials) diagram and allocation process details as a part of deviations from intended with the new ROB2 tool. The report by Wang et al is unclear regarding the outcome assessors that were masked from the intervention in the gabapentin group (25). Makkar et al did not describe their random sequence

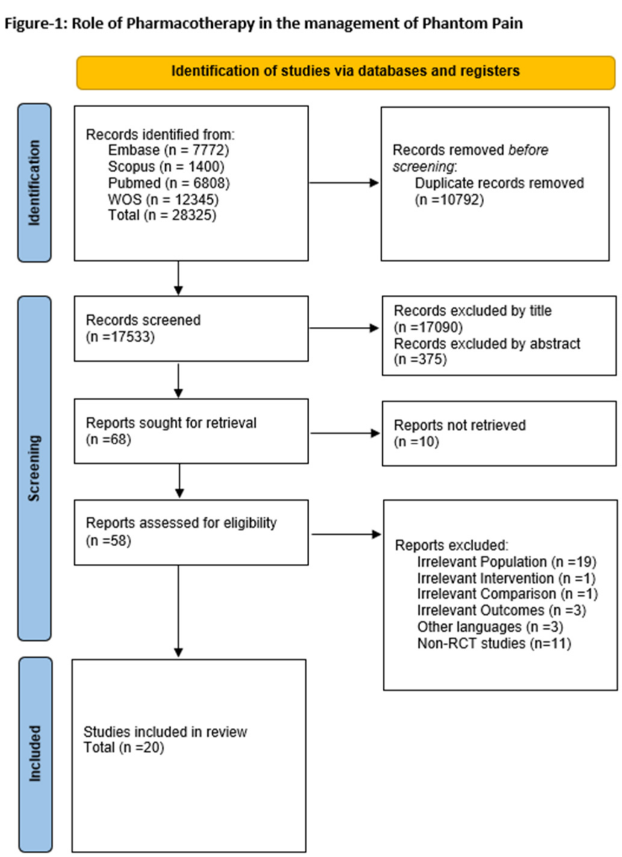

Figure 1. PRISMA flowchart of included studies

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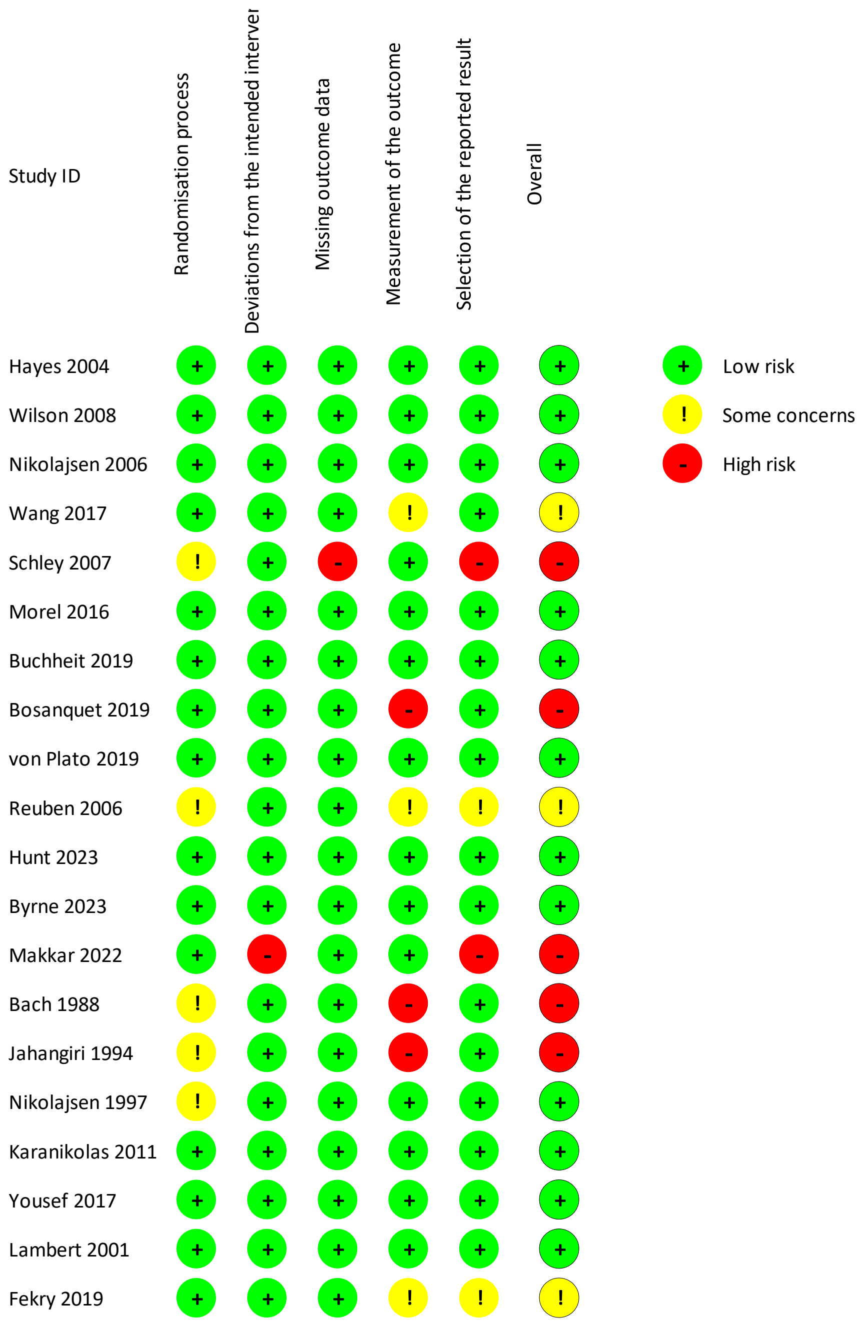

Figure 2. Risk of Bias for prevention of phantom limb pain

generation process and only reported the per-protocol analysis (26).

Findings

We found 7 different perioperative interventions tried for preventing chronic phantom pain. Table 1 presents an overview of the effects estimates for the PLP incidence/intensity, stump pain incidence/intensity, mood disorders, and QoL (if reported) at 6 months to 1 year. Also, 19 out of 20 studies compared specific pharmacological interventions with either placebo or conventional analgesics—mostly based on the World Health Organization (WHO) analgesia ladder—whereas Lambert et al compared 2 routes of administration for the same medication (27). Wang et al studied a trial of gabapentin in children with malignant bone tumors (25), but the rest were conducted in adults, mostly undergoing amputation due to peripheral vascular disease (PVD).

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Table 1. Study Characteristics & Effect Estimates in Prevention of Phantom Limb Pain

Study ID	Settings	Intervention & Comparison	Duration	Long-term Outcomes (6 months to 1 year)	Effect Estimate [95% Confidence Interval]
Hayes 2004	Lower limb PVD, cancer, or chronic infection N=45	1. IV infusion, Ketamine 2. IV infusion, Normal saline + PCA	3 days postoperatively	PLP	RR= 0.66 [0.35 to 1.23]
				RLP	RR= 1.24 [0.54 to 2.86]
Wilson 2008	Lower limb PVD N=47	1. Epidural bupivacaine + Ketamine 2. Epidural bupivacaine + Normal saline	2-3 days postoperatively	PLP	RR= 1.49 [0.60 to 3.70]
				RLP	RR= 2.13 [0.65 to 7.04]
				The hospital anxiety scale	MD= 0.60 [-3.15 to 4.35]
				The hospital depression scale	MD= 1.20 [-2.67 to 5.07
Nikolajsen 2006	Lower limb PVD N=41	1. Gabapentin, Oral on days 13–30 2. Placebo	30 days postoperatively	PLP	RR= 1.18 [0.65 to 2.13]
				Phantom Pain Intensity- NRS	No significant difference
				Stump pain NRS	No significant difference
				Consumption of Opioids	No significant difference
				McGill Pain Questionnaire PLP	No significant difference
				McGill Pain Questionnaire RLP	No significant difference
Wang 2017	Lower limb malignant bone tumors N=45	1. Gabapentin, Oral 2. Placebo	30 days postoperatively	PLP* (incidence at 2 months)	RR= 0.56 [0.34 to 0.94]
Schley 2007	Upper limb traumatic amputation Brachial nerve trunk N=19	1. Memantine, Oral + PNC Ropivacaine 2. PNC Ropivacaine + Placebo	30 days postoperatively	PLP	MD= -6.30 [-12.02 to -0.58]
				Phantom pain prevalence	RR= 0.23 [0.03 to 1.66]
Morel 2016	Mastectomy, Brachial nerve trunk N=40	1. Memantine, Oral 2. Placebo	30 days Pre- and postoperatively	PLP	MD= -1.10 [-2.45 to 0.25]
				RLP	RR= 0.78 [0.36 to 1.68]
				Analgesics consumption	Effectively reduced analgesics prescription
				McGill pain questionnaire	Effectively reduced affective component
				Neuropathic Pain Symptom Inventory (NPSI)	No significant difference
				Brief Pain Inventory questionnaires	No significant difference
				Quality of sleep	No significant difference
Buchheit 2019	Upper or Lower limb injury with neurologic damage N=132	1. Valproic Acid, Oral + either peripheral nerve or epidural block 2. Placebo + either peripheral nerve or epidural block	Up to 7 days postoperatively	PLP + RLP	RR= 0.92 [0.71 to 1.19]
				The Brief Pain Inventory, short form (BPI)	No significant difference
				Defense and Veterans Pain Rating Scale (DVPRS)	No significant difference
Bosanquet 2019	Lower limb PVD N=50	1. PNC Levobupivacaine 2. No active equivalent	5 days postoperatively	PLP	RR= 1.5 [0.35 to 6.40]
				RLP	RR= 0.67 [0.14 to 3.09]
				The hospital depression score	MD= −1.21 [−4.10 to 1.68]
von Plato 2019	Lower limb PVD N=93	1. PNC Ropivacaine infusion 2. Placebo (Normal saline)	3 days postoperatively	PLP	MD= -0.30 [-1.17 to 0.57]
				RLP	MD= 0.1 [-0.77 to 0.97]
Hunt 2023	Lower limb PVD N=90	1. PNC Levobupivacaine 2. Normal saline	4 days postoperatively	PLP	RR= 0.56 [0.14 to 2.14]
				RLP	MD= 7.01 (-0.23 to 14.24)

Epidural Bupivacaine + Opioids

Seven studies investigated the efficacy of perioperative epidural infusions of bupivacaine and an opioid of choice to keep their patients pain-free. Most studies used a cutoff of <3 on a 0 to 10 numerical rating scale for the definition of "Pain-Free." Four studies compared interventions with conventional analgesia, and their pooled data suggested an odds ratio (OR) of 0.56 [95% CI, 0.37- 0.85], Table 2 and Figure 3 (28-31). In post-hoc sensitivity analysis, we only included low-risk-of-bias studies (30, 31), and the effect was no longer present (OR, 0.80 [95% CI, 0.52-1.23] (Figure 4). Funnel plot of these studies suggests possibility of unpublished smaller studies with less precise negative results (Figure 5). Studies by Karanikolas et al and

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Table 1. Study Characteristics & Effect Estimates in Prevention of Phantom Limb Pain

Study ID	Settings	Intervention & Comparison	Duration	Long-term Outcomes (6 months to 1 year)	Effect Estimate [95% Confidence Interval]
Byrne 2023	Lower limb Not specified N=80	1. PNC Bupivacaine sciatic nerve block and a continuous infusion 5 days before and 5 days after surgery. 2. PNC infusion 5 days after surgery	5 days pre-operatively	PLP RLP	RR= 1.07 [0.64 to 1.79] Not measured at 6 months
Makkar 2022	Trauma N=30	1. Bolus block with Ropivacaine 2. Normal saline	Intraoperatively	PLP RLP	RR= 0.2 [0.15 to 0.55] No incidence in either group.
Reuben 2006	Lower limb PVD N=80	1. Bupivacaine + Clonidine bolus block 2. Normal Saline	Intraoperatively	PLP RLP	RR= 1.05 [0.84 to 1.32] RR= 1.21 [0.56 to 2.61]
Bach 1988	Lower limb PVD mostly N=25	1. Epidural Bupivacaine + epidural Morphine hydrochloride until the patient was pain-free 2. PCA	3 days preoperatively	PLP	RR= 0.42 [0.02 to 9.43]
Jahangiri 1994	Lower limb PVD, Diabetic Foot N=24	1. Epidural bupivacaine diamorphine + clonidine 2. PCA – details not mentioned	At least 24 h preoperatively, continued for 72 h postoperatively	PLP RLP	RR= 0.11 [0.02 to 0.72] RR= 0.42 [0.14 to 1.31]
Nikolajsen 1997	Lower limb Not specified N=60	1. Epidural bupivacaine + morphine 2. Placebo + PCA	18 h preoperatively and intraoperatively	PLP incidence RLP intensity PLP intensity Consumption of opioids	RR= 1.48 [0.93 to 2.34] No significant difference No significant difference No significant difference
Karanikolas* 2011	Lower limb PVD N=65	Five arms originally, rearranged to 2 arms*: 1. Epidural bupivacaine + fentanyl infusion 2. PCA	Started 48 h preoperatively and continued for 48 h postoperatively	PLP PLP intensity (measured with the VAS and MPQ scales RLP intensity (measured with the VAS and MPQ scales	RR= 0.37 [0.16 to 0.87] Significantly reduced in those who received epi. intervention pre-, intra- and post-surgery altogether No significant differences
Yousef 2017	Lower limb PVD N=60	1. Epidural bupivacaine + fentanyl + calcitonin 2. Epidural bupivacaine + fentanyl + placebo	Intraoperatively and 2 days postoperatively	PLP Allodynia Hyperalgesia	RR= 0.26 [0.08 to 0.83] Significantly lower in the calcitonin group No significant difference
Lambert 2001	Lower limb Not specified N= 30	1. Epidural bupivacaine + diamorphine - 24h before to 72h after surgery 2. PNC bupivacaine - intraoperatively placed until 72 h after surgery	Intraoperatively and 3 days postoperatively	PLP RLP Consumption of opioids	RR= 0.71 [0.39 to 1.30] RR= 1.33 [0.43 to 4.13] No significant difference
Fekry 2019	Lower limb Not specified N= 90	1. Epidural bupivacaine + fentanyl 2. Epidural bupivacaine + dexmedetomidine 3. Epidural bupivacaine	Intraoperatively	PLP	Groups 1,3: RR= 1.06 [0.67 to 1.68] Groups 2,3: RR= 0.94 [0.57 to 1.53]

PVD: Peripheral vascular disease
Inf.: infusions
PCA: patient-controlled anesthesia
PLP: phantom limb pain
RLP: residual limb pain (stump pain)
*: Data by Karanikolas et al. was rearranged into 2 arms for this review based on receiving perioperative epidural bupivacaine and fentanyl; merging the 3 arms that received it into one and the other 2 on PCA into another.

Nikolajsen et al also provided pain intensity scores using ordinal scales (30, 31). Karanikolas et al divided patients into 5 groups in their trial; we decided to rearrange their data into 2 arms for the benefit of our PICO (Patient or Problem, Intervention, Comparison, and Outcome) based on receiving perioperative epidural bupivacaine and fentanyl; merging the 2 arms that received it perioperatively into one and the other 3 on **patient-controlled analgesia** (PCA) into another. Lambert et al compared the efficacy of PNC bupivacaine with a combination of epidural bupivacaine and diamorphine administered for 3 postoperative days and did not observe any difference in incidence of PLP or RLP between the 2 groups (RR, 0.71 [95% CI, 0.39-1.30]; RR, 1.33 [95% CI, 0.43-4.13]), respectively (27). Fekry et al investigated the addition of epidural fentanyl in one arm and epidural dexmedetomidine in another arm to epidural bupivacaine, compared with epidural bupivacaine alone as the third arm. None of the additives resulted in a significant

Table 2. Epidural Bupivacaine + Opioids Compared to Conventional Analgesia for Prevention of Phantom Pain

Patient or population: Amputation candidates opt for Prevention of Phantom pain / Setting: Perioperative pharmacological interventions / Intervention: Epidural Bupivacaine + Opioids / Comparison: conventional analgesia

Outcomes	Anticipated absolute effects* (95% CI) Risk with conventional analgesia	Risk with Epidural Bupivacaine + Opioids	Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
Phantom Limb Pain (PLP) assessed with: Incidence follow-up: 6 months	481 per 1,000	342 per 1,000 (256 to 350)	OR 0.56 (0.37 to 0.58)	146 (4 RCTs)	⊕◯◯◯ Very low[a,b,c]	Epidural Bupivacaine + Opioids may result in a reduction in Incidence of Phantom Limb Pain at 6 months.
Stump pain (RLP) assessed with: Incidence follow-up: 6 months	The study by Bach et al. reported no incidence of phantom pain in either group. Jahangiri et al. reported an RR of 0.42 [95%CI: 0.14, 1.31].			47 (2 RCTs)	⊕◯◯◯ Very low[d e]	The evidence is very uncertain about the effect of epidural Bupivacaine + Opioids on stump pain.

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: confidence interval; RR: risk ratio

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimated of effect.

Explanations

a. 2 out of 4 studies suggest serious bias in blinding and hence, the outcome assessment. Given that these domains are highly reflected in pain self-reports, we decided to downgrade the evidence.

b. 145 patients participated in total, which does not provide an adequate event rate. The calculated optimal information size is 300.

c. Asymmetry noticed in funnel plot, together with the small number of low-power trials, is suggestive of unpublished data due to possible lack of efficacy.

d. Both studies lack blinding and are prone to bias in outcome assessment.

e. Very small sample sizes with low incidence of desired outcome.

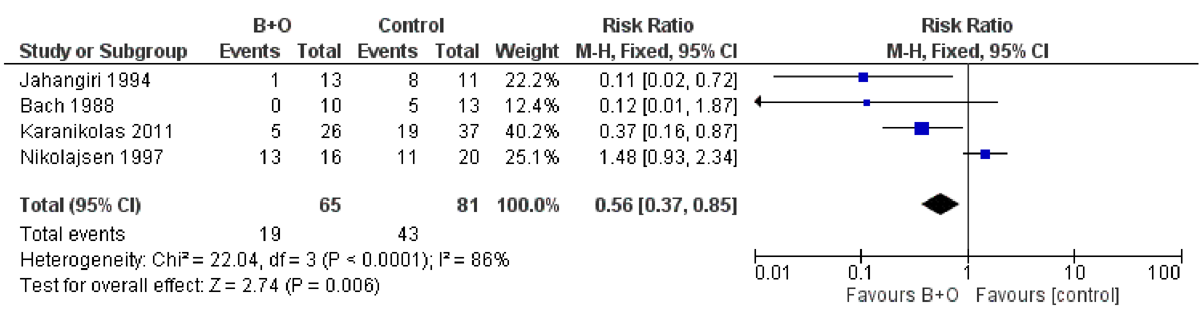

Figure 3. Epidural bupivacaine + Opioid PLP prevention at 6 months

difference in incidence of PLP at the 1-month follow-up (32).

Epidural Calcitonin

Yousef et al assessed the effect of adding calcitonin to the combination of bupivacaine and fentanyl and found it to reduce pain intensity at 6 months (RR, 0.26 [95% CI, 0.08-0.83]). Risk of bias is low for this study; however, the sample size is small and more studies are required to form a consensus on this intervention (33).

Perineural Catheters

Six studies assessed the efficacy of perineural sheath catheters (Table 3). All studies included adults with peripheral vascular diseases, except for Makkar et al, which strictly included trauma patients (26). Makkar et al and Reuben et al used the perineural catheters only for intraoperative bolus administration of amide anesthetics (26, 34). Other studies used them for perioperative infusion of anesthetics for 3 to 5 days (35-38). The study by Bosanquet et al was an open-label feasibility study for the adequacy of different pain questionnaires in PVD patients. Although they found a large effect on the prevention of PLP, hospital

[DOI: 10.47176/mjiri.39.92]

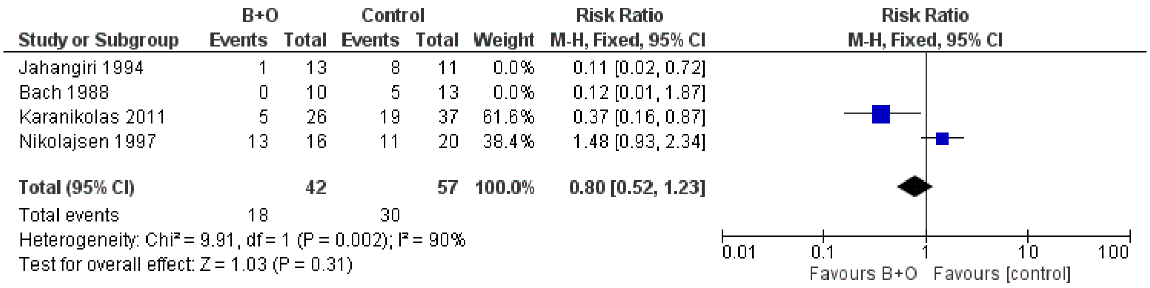

Figure 3. Epidural bupivacaine + Opioid PLP prevention at 6 months - sensitivity analysis for bias

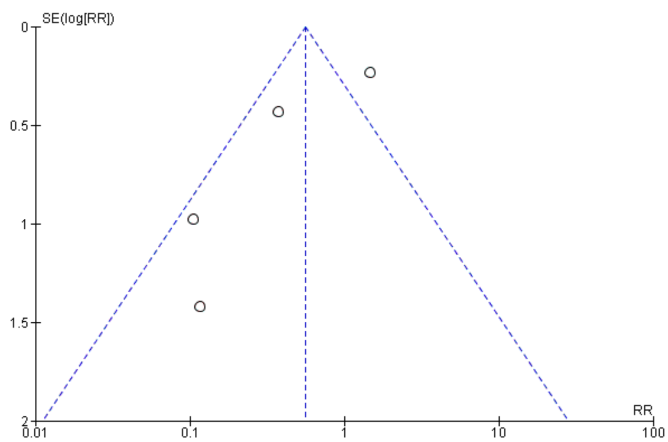

Figure 5. Funnel plot of Epidural bupivacaine + Opioid PLP prevention at 6 months

Table 3. Peripheral Nerve Catheters Compared to Conventional Analgesia for Prevention of Phantom Pain

Patient or population: Amputation candidates opt for Prevention of Phantom pain / Setting: Perioperative pharmacological interventions / Intervention: Peripheral Nerve Catheters / Comparison: conventional analgesia			
Outcome № of participants (studies)	Relative effect (95% CI)	Certainty	What happens
Phantom Limb Pain score (PLP) assessed with: Inverse Variances follow-up: 6 months № of participants: 125 (3 RCTs)	OR 0.72 (0.30 to 1.73)	⊕⊕⊕◯ Moderate[a]	The evidence suggests that Peripheral Nerve Catheters result in little to no difference in reduction of Phantom Limb Pain score at 6 months time.
Stump pain score (RLP) assessed with: Inverse Variances follow-up: 6 months № of participants: 129 (3 RCTs)	OR 1.30 (0.65 to 2.60)	⊕⊕⊕◯ Moderate[a]	The evidence suggests that peripheral Nerve Catheters results in little to no difference in 6 months stump pain score.

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: confidence interval; OR: odds ratio
GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect. Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

a. Study populations are too small.

depression scores were not significantly different between arms (38). The 3 other studies giving infusions could not establish a difference in PLP or RLP between study groups. The meta-analysis for the PNC infusion method did not establish efficacy in prevention of PLP or RLP (OR, 0.86 [95% CI, 0.41-1.81]; OR, 1.30 [95% CI, 0.72-2.35]), respectively (Figures 6 and 7). Funnel plots in this scenario do not point towards censorship of negative results (Figures

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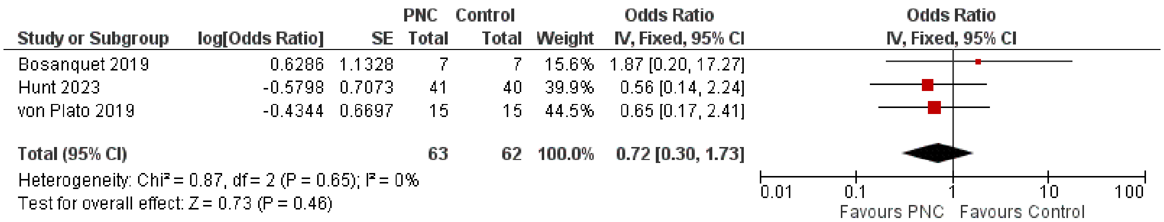

Figure 6. Forest plot for efficacy of PNC infusions in Prevention of PLP

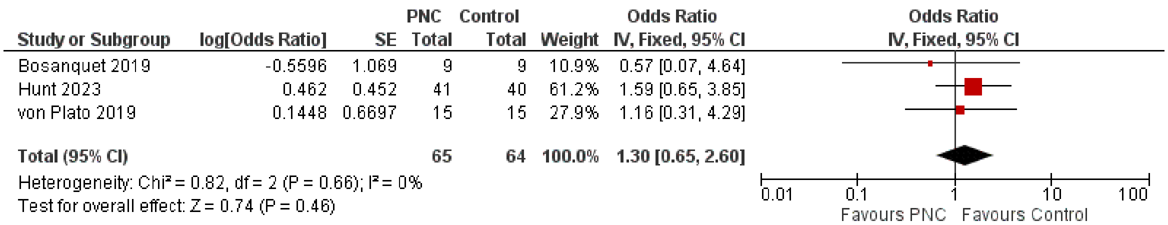

Figure 7. Forest plot for efficacy of PNC infusions in Prevention of RLP

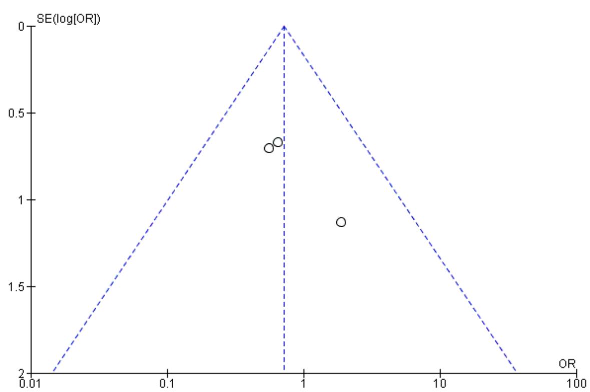

Figure 8. Funnel plot for efficacy of PNC infusions in Prevention of PLP

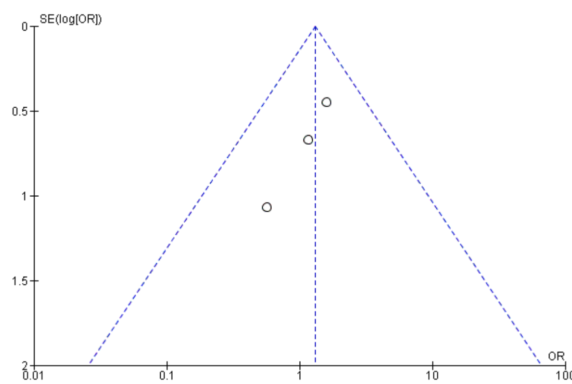

Figure 9. Funnel plot for efficacy of PNC infusions in Prevention of RLP

8 and 9).

Gabapentin

Two studies evaluated the efficacy of gabapentin: Nikolajsen et al prescribed gabapentin for 30 days to 41 adults with lower limb PVD. They did not find any significant difference in the incidence or intensity of PLP or RLP, or McGill pain questionnaires, and opioid consumption (39). Wang et al found that PLP incidence was reduced in children with malignant bone tumors at 2 months (RR, 0.56 [95% CI, 0.34-0.94]) (25).

Memantine

Two studies investigated oral memantine compared with conventional analgesia (Table 4). Morel et al studied women who underwent mastectomy for the incidence of PLP and neurotic pain. They also investigated other outcomes: Memantine effectively reduced analgesics prescription and the affective component of McGill pain questionnaire, but did not affect QoL and sleep (40). Schley et al included patients with traumatic upper extremity amputations. Both the 6-day and 6-month PLP intensity were lower in the memantine group without significant differences in adverse events (41). Pooled data showed a mean reduction of 0.63 (95% CI, 0.10-1.15) in the 6-month intensity of PLP by memantine (Figures 10 and 11).

Ketamine

Ketamine was used in 2 studies via different routes: Hayes et al used Ketamine with a preinduction IV bolus, followed by IV infusion for 3 days in 45 lower limb amputation candidates due to different causes (42). Wilson et al investigated epidural infusion of ketamine in 47 PVD patients. In addition to pain, they assessed hospital anxiety and depression scores, which also did not differ between the arms (43). Both studies lost around 30% of their study

Table 4. Oral Memantine Compared to Conventional Analgesics for Prevention of Phantom Pain

Patient or population: Amputation candidates opt for Prevention of Phantom pain / Setting: Perioperative pharmacological interventions / Intervention: Oral Memantine / Comparison: Conventional analgesics

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with conventional analgesics	Risk with Oral Memantine				
Phantom limb pain score (PLP score) assessed with: Numerical Rating Scale follow-up: 6 months	The mean phantom limb pain score was 0	MD 0.70 lower (0.18 lower to 1.23 lower)	-	59 (2 RCTs)	⊕⊕◯◯ Low[a,b]	Oral Memantine may result in a slight reduction in phantom limb pain score.
Stump pain (RLP) assessed with: Incidence follow-up: 6 months	450 per 1,000	351 per 1,000 (162 to 756)	RR 0.78 (0.36 to 1.68)	40 (1 RCT)	⊕⊕◯◯ Low[b,c]	Oral Memantine may result in little to no difference in stump pain.

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: confidence interval; MD: mean difference; RR: risk ratio
GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations
a. Study by Schley et al. does not provide a consort diagram nor an explanation for probable missing outcome data.
b. Inadequate number of participants for an optimal information size.
c. CI covers both large effect and no effect.

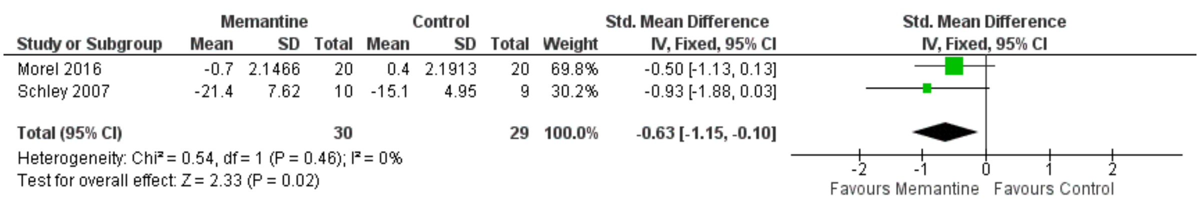

Figure 10. Forest plot for efficacy of Memantine in Prevention of PLP

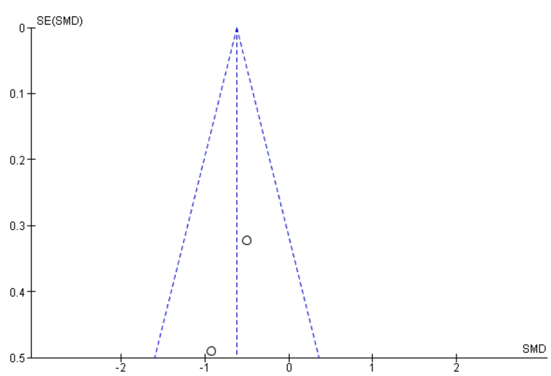

Figure 11. Funnel plot for efficacy of Memantine in Prevention of PLP

populations, mostly due to death and withdrawal of consent.

Valproic Acid

One study by Buchheit et al prescribed patients with valproic acid, which did not find any difference in the incidence or intensity of a mixed outcome of phantom pain and stump pain. Interestingly, they reported that revision surgeries could significantly change the PLP and RLP pain phenotypes (44).

Discussion

Overview of the Literature

We summarized the findings for 7 proposed additional pharmacological interventions, aiming to prevent chronic PLP. Initially, the meta-analysis of mixed epidural infusion of bupivacaine and an opioid suggested a 46% reduced chance of PLP incidence with a very low certainty of evidence, due to high risk of bias in associated studies, small information size, and possible publication bias. In the post-hoc sensitivity analysis accounting for high risk of bias, the preventative effect was no longer observed. Moreover, meta-analysis for PNC local anesthetics did not show any change in incidence of PLP or RLP, even with a moderate certainty of evidence. Memantine was studied in patients subject to brachial plexus block and seemed to be able to decrease the 10-point NRS chronic pain scores by 0.63 (95% CI, 0.10- 1.15). It reduced the pain score to just below the cutoff of significant pain, which was 3/10, compared with conventional scheduled or per-demand NSAIDs, oral and intramuscular opioids, or acetaminophen. The certainty of evidence for Memantine, however, is low due to small sample size and risk of bias. Data for Valproic acid, Ketamine, Dexmedetomidine, and Calcitonin are gathered from single studies; none of which could establish a reduction in PLP incidence. As for the other outcomes of interest, such as quality of life, depression, and anxiety, studies were scarce in general and heterogeneous in measurement tools.

Our review suggests that, except for Memantine, additional pharmacological interventions do not reduce the incidence of chronic PLP or RLP later at 6 months and 1 year compared with conventional analgesia. However, these interventions may be quite effective at controlling the perioperative pain, which suggests either a noncausal or nonlinear association between the immediate perioperative pain and PLP.

Phantom pain is presumed to have a prevalence of 45% to 80% among amputees regardless of the underlying cause. As a neuropathic pain, phantom pain tends to present itself as early as the postsurgical analgesia wears off, with a peak in the first week and then in the first year (4, 7, 45). Although preamputation pain may be worse with trauma etiology compared with medical conditions (due to the preceding neuropathies), several studies suggest that the prevalence of phantom pain does not differ among various causes (5, 6). Based on this, most studies have not stratified their population by etiology.

As for the stump pain, several studies, including a recent prevalence meta-analysis, have described the pain to present in half of the patients within a week of amputation and to decrease gradually to 22% to 27% at 1 year (5, 45).

Several studies have tried to explain the incidence of chronic phantom pain (6 months and longer) through several predictors. Larbirg et al found that a proposed "Chronic Pain Index" (CPI) correlated with PLP incidence at 12 months. The CPI included the intensity, frequency, and duration of a chronic pain condition combined in equal weights before amputation (46). Hanley et al in 2007 reported that preamputation pain intensity and acute postoperative PLP could predict the risk of developing chronic phantom pain and stump pain in amputees (47). Nikolajsen et al, however, suggested that intensity of preamputation pain is a predictor of short-term (1 week and 3 months) PLP incidence, but not at 6 months (8).

Larbirg et al also suggest that preamputation anxiety and depression scores—although well below the threshold for establishing diagnosis—correlated with the incidence of PLP (but not RLP or sensation of phantom limb) at 1 year (46). Two studies that were included in our systematic review suggested that perioperative interventions did not significantly reduce depression scores at 6 months and 1 year compared with conventional postoperation pain control. However, hospital anxiety scores decreased significantly at 1 year after amputations (38, 43). Therefore, it is important to address mood disorders preoperatively irrespective of the pain management approach. Early use of IV ketamine in trauma patients could simultaneously address both concerns (48).

Memantine—as the only intervention which exerted effectiveness, with low certainty of evidence—affects the CNS through inhibition of extrasynaptic NMDA receptors. Although further robust studies are required, this finding is potentially in line with the neuroprotective properties of memantine in neurodegenerative diseases. Moreover, memantine intervention had a longer treatment period of 30 days. On the other hand, ketamine inhibits mostly the synaptic NMDA receptors, and the interventions were as short as 72 hours (49, 50). These differences may potentially explain why one NMDA receptor inhibitor exerts an effect and the other one does not.

This meta-analysis could be considered complementary to previous systematic review by Ypsilantis et al and meta-analysis by Bosanquet et al, as our study is the first meta-analysis to thoroughly investigate different routes of administration and drug combinations quantitatively (14, 51).

Methodological Considerations

First, we assessed the risk of bias the Cochrane's ROB2 tool. ROB2 proved most suitable for the evaluation of pain in a perioperative setting, as it addresses the following:

1. Subjective nature of pain, which places patients as outcome assessors and possible variations in reporting.
2. Details of drug delivery that hinders blinding and protocol adherence.

This meticulous risk stratification enabled us to perform a sensitivity analysis, accounting for risk of bias (17).

Second, we noticed that all interventions were administered for a short duration and at the beginning of the studies; thus, time did not affect the integrity of interventions. These assumptions are proposed by Hernan et al, allowing systematic reviews to safely pool per-protocol and intention-to-treat data, resulting in improvement of information size and reduction in imprecision of evidence (23).

Third, although included studies reported a mix of dichotomous and continuous data, we noticed that all of the studies used a numerical rating scale with a certain cutoff for counting patients. Through this observation, Cochrane's handbook suggests that both dichotomous and continuous effect estimates could be transformed into the natural log of the ORs or standardized MDs using the proposed

[DOI: 10.47176/mjiri.39.92]

coefficient of 1.81 by Chinn (20) and subsequently pooled in the meta-analysis to obtain a larger sample size (21).

Fourth, studies that used ordinal scales to assess and report pain could not be used for quantitative synthesis and had to be reported narratively.

Study Limitations & Certainty of Recommendations

We found that most RCTs investigating PLP suffer from small sample sizes and high attrition rates, which have led to imprecision in their results. A 2019 feasibility trial for PLP by Bosanquet et al reported that at 6 months, the attrition rate was about 30%. In that trial, amputation candidates were recruited from vascular surgery centers, and loss to follow-up was due to mortality, hospitalization for other comorbidities, and prolonged rehabilitation (38). Multicenter trials, shared databases, and international collaborations could help with procurement of adequate information size.

We also found incomplete blinding to cause a high risk of bias among studies, which seriously impacted the main effect estimate. Blinding is particularly important in subjective outcomes like pain, and when accounted for, in sensitivity analyses, the effectiveness of additional pharmacotherapy did not differ from conventional analgesics as a preventative measure.

Another general limitation of PLP studies is the potential selection bias. In the process of recruitment, most studies took their samples from patients with chronic medical conditions such as PVD, diabetes mellitus, or malignancies. Amputations due to trauma often require urgent care, and therefore, it is highly difficult to involve them in clinical trials. Although the literature suggests that the rate of PLP development is universally high among different causes of amputation, it remains to be studied whether immediate analgesia in those without a memory of pain helps prevent future PLP.

Future Direction

Memantine, as the only intervention suggesting effectiveness, requires further studies with adequate sample size and methodology to gain higher certainty of evidence.

We also noticed that patients in PLP trials are mostly recruited from chronic medical conditions (PVD) who suffered from chronic limb pain long before their surgery. Therefore, it may be useful to stratify participants according to chronic pain indices, distinguishing the presence of chronic pain and correlating it with later frequency and intensity of phantom pain. We also noticed that although mood disorders are strongly correlated with the occurrence of PLP, these patients are often excluded from the trials. These stratifications may help understand the underlying mechanism of developing chronic phantom limb pain.

Conclusion

We summarized the findings for 7 proposed additional pharmacological interventions, aiming to prevent chronic PLP. The evidence for Memantine shows some effectiveness with low certainty of evidence, but other interventions do not seem to change the incidence of PLP or RLP compared with conventional analgesics. Further well-designed, multicenter trials that are stratified for the cause of amputation and previous chronic pain may help untangle the complex pathophysiology behind phantom pain. Moreover, immediate perioperative pain scores may not be predictors for the incidence of chronic phantom pain.

Authors' Contributions

N.A. and R.A. developed the PICO and search strategy. All authors participated in screening and data extraction. N.A. and R.A. analyzed results and prepared the manuscript.

Ethical Considerations

The protocol for this systematic review has been recorded in the PROSPERO database under the code CRD42023385291, with a detailed description of the search strategy.

Acknowledgment

None.

Conflict of Interests

The authors declare that they have no competing interests.

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