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Evidence for the optimal management of acute and chronic phantom pain: a systematic review

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Authors' objectives	To determine the optimal management of phantom limb pain (PLP) in the pre- and post-operative phases of amputation.
Searching	MEDLINE was searched from 1966 to 1999 for publications in the English language. Key search terms were: 'randomised controlled trial', 'controlled clinical trial', 'double-blind method', 'single-blind method', 'placebos', 'research design', 'comparative study', 'evaluation studies', 'follow-up studies', 'prospective studies', 'phantom limb', 'phantom limb pain' and 'human'. Previous review articles and references from relevant studies were examined, and experts in the field were contacted for missing or ongoing trials.
Study selection: study designs	Controlled trials were eligible for inclusion whereas case reports were excluded. The included studies were: randomised controlled trials (RCTs), including parallel group and crossover designs; pseudo-randomised trials; non-randomised controlled trials, including parallel group and crossover designs; and cohort studies with intervention and control cohorts. The final follow-up ranged from immediately post-intervention to 2 years.
Study selection: specific interventions	<p>Studies that examined any intervention for PLP were eligible, including treatments before and during amputation and chronic pain treatments. The interventions in the review were conducted in the pre-operative, intra-operative, early post-operative (less than 2 weeks) and late post-operative (greater than 2 weeks) periods.</p> <p>The active interventions in the pre-operative, intra-operative and early post-operative periods included epidural anaesthesia (starting 18 to 72 hours before surgery), regional nerve blocks (starting during or post-operatively), intravenous calcitonin and transcutaneous electrical nerve stimulation (TENS). The control interventions were placebo saline infusion or epidural anaesthesia with on-demand opioid analgesia, opioid analgesia and sham TENS with and without chlorpromazine. The active interventions in the late post-operative period were TENS, Farabloc (metal threaded sock), vibratory stimulation and infused ketamine. The controls in the late post-operative period were placebo stimulation and intravenous saline infusion.</p>
Study selection: participants	Studies of people with acute or chronic PLP were eligible. The participants were aged from 47 to 75 years. The majority of the included patients were undergoing lower limb amputations, mostly below the knee. Other types of amputation included through knee, above knee, hip, elbow, shoulder disarticulation and undefined upper extremity amputation. The reasons for amputation included peripheral vascular disease, diabetes mellitus, trauma, infection, failed embolectomy, chronic deformity, cancer, renal failure, radiation and polio. In the late post-operative trials, the time since amputation ranged from 36 days to 46 years.
Study selection: outcomes	Studies that measured PLP as either a primary or secondary outcome were eligible. In the included studies, PLP was assessed as a dichotomous outcome or using a visual analogue scale or the McGill pain questionnaire. Other

	outcomes assessed in the individual studies were stump pain, phantom sensation and opioid use.
Study selection: how were decisions on the relevance of primary studies made?	The authors do not state how the papers were selected for the review, or how many of the reviewers performed the selection.
Validity assessment	Validity was assessed and scored using the criteria of Jadad et al. (see Other Publications of Related Interest), which assess randomisation method, double-blinding and withdrawals or drop-outs. The validity scores ranged from 0 to the maximum possible score of 5 points. The adequacy of the sample size in detecting a difference between the treatment groups was also assessed. The authors do not state how the papers were assessed for validity, or how many of the reviewers performed the validity assessment.
Data extraction	The following data were extracted by one author and checked by a second author: the number of patients and their characteristics (age, gender, site of amputation); inclusion criteria for trial; methodology; intervention and control treatment details, including timing of the intervention; the length of follow-up; the number of drop-outs and deaths; outcome measures; and results.
Methods of synthesis: how were the studies combined?	The studies were categorised as pre-operative and early pre-operative interventions (less than 2 weeks) or late post-operative interventions (greater than 2 weeks), and a narrative synthesis was undertaken.
Methods of synthesis: how were differences between studies investigated?	Differences between the studies with respect to validity and follow-up periods were discussed in the text of the review.
Results of the review	<p>Twelve studies (375 patients) were included: 6 RCTs (194 patients), one pseudo-randomised trial (25 patients), 4 non-randomised controlled trials (97 patients), and one trial with cohorts of intervention and control patients (59 patients).</p> <p>Only 3 studies scored the maximum 5 points on the validity scale. Of the remaining studies, one trial scored 4 points, one trial 3 points, 4 trials one point, and 3 trials zero points. Three of the 6 trials reported as randomised included an adequate description of randomisation. Four trials were reported as double-blind and 7 trials reported drop-outs and withdrawals. Only 2 studies included a sample size calculation. There were no trials examining membrane stabilisers or tricyclic antidepressants.</p> <p>Pre-operative and early pre-operative interventions (8 trials with 278 patients, including 4 RCTs with 149 patients). Epidural anaesthesia (3 trials, including 1 RCT with a quality score of 5): the trials found different results. The RCT (60 patients entered; drop-outs included 4 patients before amputation, 5 patients with re-amputations and 20 deaths by 12 months) found no significant difference in PLP between epidural bupivacaine plus morphine versus epidural saline plus morphine at one year.</p> <p>Regional nerve block (3 trials, including 1 RCT with a quality score of 5): the small RCT (21 patients) found no significant difference in PLP between an infusion of bupivacaine versus saline at 3 or 6 months.</p> <p>TENS (1 RCT with a quality score of 2): the RCT (51 patients) found no significant difference in PLP between TENS versus sham TENS versus sham TENS plus chlorpromazine at 12 months.</p> <p>Intravenous salmon calcitonin (1 RCT with crossover after 2 hours, with a quality score of 3): the small RCT (21 patients) found that salmon calcitonin versus saline control reduced PLP regardless of the order of infusions. The effect on longer-term follow-up was not controlled.</p>

	<p>Late post-operative interventions (4 trials with 97 patients, including 2 RCTs with 45 patients).</p> <p>TENS (2 non-randomised controlled trials with quality scores of 1 and 0; 52 patients): the 2 trials found different results; one found decreased pain with TENS versus placebo stimulation, while the other had a large drop-out rate and found no difference between the treatments. Farabloc (1 RCT with a quality score of 5): more patients in the small crossover RCT (34 patients) found a short-term reduction of PLP during the Farabloc intervention than with the control intervention. Ketamine (1 RCT with a quality score of 4): the small crossover RCT (11 patients) with follow-up of 80 minutes found that ketamine decreased pain compared with saline.</p>
Authors' conclusions	Although up to 70% of patients have PLP after amputation, there was little evidence from RCTs to guide clinicians with treatment. Evidence on pre-emptive epidurals, early regional nerve blocks and mechanical vibratory stimulation provides inconsistent support for these treatments. There is currently a gap between research and practice in the area of PLP.
CRD commentary	<p>The aims of the review were stated and the inclusion criteria were defined in terms of the study design, intervention, participants and outcome. While experts in the field were contacted for additional trials, restricting the search to English-language publications identified in one database may have resulted in the omission of other relevant studies. It was not reported how many of the reviewers selected the studies for inclusion in the review. Validity was formally assessed and scored using validated criteria. Relevant data were extracted and tabulated, and the methods used to extract the data were described. In addition, the characteristics of the studies were summarised in the text. A narrative review was appropriate given the heterogeneity among the studies.</p> <p>The evidence presented supports the authors' conclusions.</p>
Implications of the review for practice and research	<p>Practice: The authors state that in early PLP, no treatments are clearly more effective than opioid analgesia, and that for late PLP, there is some evidence suggesting consideration of Farabloc.</p> <p>Research: The authors state that further adequately designed studies of therapeutic regimens for PLP are required. They also state that investigation into intravenous ketamine is warranted.</p>
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Other publications of related interest	Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? <i>Control Clin Trials</i> 1996;17:1-12.
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