Systematic Review and Meta-analysis of the Efficacy of Perineural Local Anaesthetic Catheters after Major Lower Limb Amputation

D.C. Bosanquet a,*, J.C.D. Glasbey b, A. Stimpson a, I.M. Williams b, C.P. Twinea

a South East Wales Regional Vascular Network, Royal Gwent Hospital, Newport, UK
b South East Wales Regional Vascular Network, University Hospital of Wales, Cardiff, UK

WHAT THIS PAPER ADDS
Perineural catheters, placed alongside the transected sciatic nerve (for transfemoral amputations) or tibial nerve (for transtibial amputations), have been used to provide targeted local anaesthetic during the postoperative period. Various studies have suggested this may reduce postoperative pain, opioid use, and long-term phantom limb pain. This systematic review and meta-analysis demonstrated that postoperative opioid consumption is approximately halved, without affecting immediate postoperative pain, mortality, long-term phantom limb or stump pain. However, the quality of included papers is generally low, and further research is required to confirm these findings.

Objective: The aim of this systematic review and meta-analysis was to evaluate the effects of using an intraoperatively placed perineural catheter (PNC) with a postoperative local anaesthetic infusion on immediate and long-term outcomes after lower limb amputation.

Methods: A systematic review of key electronic journal databases was undertaken from inception to January 2015. Studies comparing PNC use with either a control, or no PNC, were included. Meta-analysis was performed for postoperative opioid use, pain scores, mortality, and long-term incidence of stump and phantom limb pain. Sensitivity analysis was performed for opioid use. Quality of evidence was assessed using the GRADE system.

Results: Seven studies reporting on 416 patients undergoing lower limb amputation with PNC usage (n = 199) or not (n = 217) were included. Approximately 60% were transtibial amputations PNC use reduced postoperative opioid consumption (standardised mean difference: −0.59, 95% CI −1.10 to −0.07, p = .03), maintained on sensitivity analysis for large (p = .03) and high-quality (p = .003) studies, but was marginally lost (p = .06) on studies enrolling patients with peripheral arterial disease only. PNC treatment did not affect postoperative pain scores (p = .48), in-hospital mortality (p = .77), phantom limb pain (p = .28) or stump pain (p = .37). GRADE quality of evidence for all outcomes was very low.

Conclusion: There is poor-quality evidence that PNC usage significantly reduces opioid consumption following lower limb amputation, without affecting other short- or long-term outcomes. Well-performed randomised studies are required.

© 2015 European Society for Vascular Surgery. Published by Elsevier Ltd. All rights reserved.
Article history: Received 28 March 2015, Accepted 30 April 2015, Available online 9 June 2015
Keywords: Amputation, Meta analysis, Nerve sheath catheter, Perineural, Phantom limb, Postoperative pain

INTRODUCTION
Major lower limb amputation remains one of the highest mortality procedures performed in the UK. Any intervention to reduce morbidity or mortality is therefore high on the agenda for vascular surgeons. Improving the management of postoperative pain in such a high-risk population would potentially reduce morbidity associated with the stress response to surgery, and minimise opioid use.

Immediate postoperative pain management commonly involves epidural or intravenous patient controlled analgesia...
et al. in 1991, the PNC is inserted adjacent to either the postoperatively. First described for amputees by Malwer catheter (PNC), inserted at the time of surgery to provide a reduce pain. One such adjunct is the use of a perineural acetaminophen), anticonvulsants, and other adjuncts to delay psychosocial adjustment, and reduce the chance of deterioration renal function, and polypharmacy; attributes pharmacokinetics of opioids are altered with increasing age, and female sex. Although many pharmacological agents are available for treatment of phantom limb pain, their efﬁcacy is variable, and better or alternative postoperative analgesia may prevent hyperplastic peripheral changes and central neural sensitisation.

The American Society of Anesthesiologists recommends using multimodal analgesic strategies for managing postoperative pain. This includes the use of opioid-sparing agents (such as nonsteroidal anti-inflammatory drugs, or acetaminophen), anticonvulsants, and other adjuncts to reduce pain. One such adjunct is the use of a perineural catheter (PNC), inserted at the time of surgery to provide a continuous infusion of local anaesthetic for up to 7 days postoperatively. First described for amputees by Malwer et al. in 1991, the PNC is inserted adjacent to either the sciatic nerve for above-knee amputations (AKAs) or the tibial nerve for below-knee amputations (BKAs), and has been used as a method of reducing both immediate postoperative and stump/phantom limb pain. However, data are conflicting as to its efﬁcacy for both short- and long-term outcomes, and utilisation of this treatment modality varies.

The aim of this systematic review and meta-analysis was to evaluate the effect of PNCs on immediate postoperative opioid use and pain, postoperative mortality, and long-term phantom limb and stump pain in patients undergoing lower limb amputation.

METHODS

Data sources, search strategy, and selection criteria

The Cochrane collaboration speciﬁed protocol was utilised for this systematic review, which is reported as per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement for the conduct of meta-analyses of interventional studies. The following sources were searched without date restrictions: PubMed, Embase via OVID, the Cochrane Library Database, and the Current Controlled Trials register. The search strategy, including MeSH terms utilised, was drafted and reﬁned by two authors (DCB and CT, online supplement 1). An extensive search was also conducted of articles to be included in the analysis using the “Related Articles” function in PubMed, and reference lists checked for other papers suitable for inclusion. In addition, the European Journal of Vascular and Endovascular Surgery, British Journal of Surgery, and Journal of Vascular Surgery websites were searched individually. There was no search restriction based on language. The last search date was January 14, 2015. Outcomes were captured when given in two or more included papers. When papers were suitable for inclusion, but presented non-abstractable data for included outcomes, the corresponding authors were contacted for further data.

Randomised controlled trials (RCTs), cohort studies, and case series detailing adult patients undergoing major (hindquarter, transfemoral, through-knee, or transtibial) lower limb amputation were suitable for inclusion. All included papers utilised a cohort of patients with an intraoperative placement of a PNC for a postoperative infusion of a local anaesthetic (intervention group), compared with either a placebo control (i.e. containing normal saline), or alternative anaesthetic regimen without a PNC (control group). Studies detailing nerve catheters placed distant to the site of the operation (i.e. transgluteal sciatic nerve catheters placed under ultrasound guidance), and those giving a single intraoperative perineural injection of local anaesthetic without a PNC, were excluded.

Data extraction, outcome measures, and assessment of study quality

A data abstraction proforma was designed by one author (DCB) and piloted before reﬁnement from all data abstractors (DCB, JCDG, CT). Data abstraction (DCB and JCDG) and assessment of methodological quality (DCB, AS) was performed independently by two authors with reference to the senior author (CT) on matters of disagreement. Extracted demographic and baseline data included: ﬁrst author, year of study, study type (RCT, cohort, or quasi-experimental) and design (including whether retrospective or prospective, single or multiple centres, and if consecutive patients were enrolled), number of patients, primary anaesthetic given to both intervention and control groups, local anaesthetic used in the treatment group, and study quality as assessed using the Downs and Black score. This checklist is used to score both RCTs and observational studies for scientiﬁc rigor, and thus permits quality comparisons between these study types. It scores studies on ﬁve methodological criteria: reporting (10 questions, 11 points), external validity (3 questions, 3 points), bias (7 questions, 7 points), confounding (6 questions, 8 points) and power (2 questions, 5 points), with a maximum score of 34.

The outcome measures collected were:

1. Postoperative opioid consumption;
2. Postoperative pain;
3. Postoperative mortality;
4. Phantom limb pain (pain experienced where the limb used to exist) incidence at follow-up; and
5. Stump pain (pain localised to the residual portion of the limb) incidence at follow-up.
Statistical analysis and evidence rating

Review Manager version 5.2.6 was used for meta-analysis (RevMan; Nordic Cochrane Centre, Copenhagen, Denmark). A random-effects (Mantel-Haenszel) model was used for dichotomous data using odds ratio (OR) as the summary statistic, and reported with 95% confidence intervals (CI), and an inverse-variance random-effects model was used for continuous data using standard mean difference (SMD) as the summary statistic, and reported with 95% CIs. Continuous data presented as a median and range were transformed to a mean and standard deviation (SD) using the methodology described by Hozo et al. Missing SDs required for meta-analysis were imputed as per Cochrane recommendations, for which the means were used as SDs. Heterogeneity was assessed using an I² calculation.

Sensitivity analyses were performed for studies enrolling vascular patients alone, larger studies (>50 patients in total) and high-quality studies (D&B scores of greater than 17). It was impossible to perform sensitivity analysis for RCTs comparing PNC using either local anaesthetic or placebo control as only one paper used this methodology, or to compare outcomes at different levels of amputation (AKA versus BKA) as data were not abstractable in this format.

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system was used to rate the quality of evidence and strength of recommendation, as per Cochrane collaboration recommendations. Quality is assessed by evaluating: risk of bias, indirectness of evidence, heterogeneity, imprecision of results and publication bias, and is ranked “high,” “moderate,” “low,” or “very low.” RCTs by definition, have a “high” quality of evidence, while cohort studies have a “low” quality of evidence prior to further quality assessment. Outcomes derived from equal numbers of “high” and “low” grade papers are considered to have a “moderate” level of evidence prior to further quality assessment. The presence of one or more serious limitations results in sequential downgrading of evidence.

RESULTS

Paper search and selection process

The literature search yielded a total of 2196 papers, of which 38 (including four conference proceedings) were retrieved for full evaluation. Seven papers met the inclusion criteria and were included in the review (Fig. 1). Excluded papers of note included four series of PNC use but without a comparator, five series detailing nerve catheters placed distant to the operative site (e.g. to the sciatic nerve under ultrasound guidance), five case reports, two series detailing upper limb amputations alone or where lower limb data were not abstractable separately, three protocols, and one of a perineural injection of local anaesthetic without catheter. A further abstract was suitable for inclusion according to the methodology, but gave no data for abstraction. Repeated attempts to contact the authors for further data for evaluation were met with no response. The remaining ten papers reviewed either did not insert a PNC (n = 6) or placed PNCs postoperatively (n = 4). A total of 416 patients undergoing lower limb amputation with PNC usage (n = 199) or not (n = 217) were therefore included.

Study design and baseline characteristics

Baseline study characteristics are detailed in Table 1. Downs and Black scores ranged from 3 to 23 (median 11) out of a maximum of 34. Two were prospective RCTs and the rest were observational studies. Two included patients with neoplastic pathologies either exclusively, or in combination with patients with PAD. Patients in three papers were well matched with regards to baseline demographics, while significant differences in either co-morbidities or type of amputations performed were noted in two (no data for two). Data on amputation level were given in all but one paper, with approximately 60% being BKAs. Anaesthetic regimens for both the treatment and control groups included GA (62% of cases where reported), epidural (17%), and spinal anaesthetic (21%). Six studies used 0.25–0.5% bupivacaine alone as the local anaesthetic, while one used 0.25% bupivacaine, 0.2% ropivacaine, and 1% lignocaine. All papers used a continuous infusion of local anaesthetic postoperatively for the treatment group, except for two which used a combination of continuous infusion and bolused local anaesthetic. PNCs remained in place for a weighted mean of 3.3 days postoperatively.

Outcomes

Postoperative opioid consumption and pain. All papers gave data on postoperative opioid use, which was given as morphine sulphate equivalents (calculated using opioid conversion tables), except for two where morphine use alone was documented. Seventy-two hour postoperative use was given in all but one paper, which gave overall postoperative morphine use. Meta-analysis showed that PNC use was associated with a significant reduction in postoperative opioid use (SMD −0.59, 95% CI −1.10 to −0.07, p = .03, I² = 79%, Table 2, Fig. 2). This effect was maintained on sensitivity analysis for large studies (p = .03) and high-quality studies (p = .003), but was lost, albeit marginally, for patients with PAD alone (p = .06). GRADE quality of evidence was very low (Table 3).

Two papers captured postoperative pain, assessed using a visual analogue scale (VAS) or verbal rating scale (VRS) (both scored 0–10), which have been shown to give comparable scores suitable for pooled analysis. Treatment with a PNC did not alter pain scores compared with control (SMD 0.53, 95% CI −0.93 to 1.98, p = .48, I² = 92%, Table 2). Sensitivity analyses could not be performed because of a lack of studies. GRADE quality of evidence was very low (Table 3).

Postoperative mortality. In-hospital postoperative mortality was evaluated by two papers, and was equivalent between
the treatment and control groups (OR 0.82, 95% CI 0.22 to 3.07, \( p = .77 \), \( I^2 = 38\% \), Table 2). Sensitivity analyses could not be performed because of a lack of studies. GRADE quality of evidence was very low (Table 3).

**DISCUSSION**

This systematic review identified seven studies, comprising 416 patients, comparing the use of a PNC following lower limb amputation with either no treatment or placebo control. Meta-analysis showed that postoperative opioid consumption was reduced by approximately 50% in those receiving PNC treatment, which was maintained on sensitivity analysis of large and high-quality studies, but was marginally lost on studies enrolling patients with PAD only. PNC treatment did not affect postoperative pain scores, in-hospital mortality, phantom limb pain or stump pain. Quality of evidence as assessed by the GRADE score was very low for all outcomes.

**Strengths and weaknesses**

To date, this is the only systematic review and meta-analysis to compare the use of a PNC with a control group. An
Table 1. Demographic data and Downs and Black score for included studies.

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Type of study</th>
<th>Retrospective/prospective</th>
<th>Number of centres</th>
<th>Consecutive patients</th>
<th>Pathology necessitating amputation</th>
<th>Patients (n)</th>
<th>Treatment group (n)</th>
<th>Control group (n)</th>
<th>Treatment group anaesthetic</th>
<th>Control group anaesthetic</th>
<th>Outcomes</th>
<th>D&amp;B score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ayling (2014)</td>
<td>Cohort study</td>
<td>Retrospective</td>
<td>ND</td>
<td>No</td>
<td>PAD</td>
<td>198</td>
<td>102</td>
<td>96</td>
<td>ND</td>
<td>ND</td>
<td>1,2,3,4,5,6,7</td>
<td>23</td>
</tr>
<tr>
<td>Elizaga (1994)</td>
<td>Cohort study</td>
<td>Retrospective</td>
<td>Single</td>
<td>ND</td>
<td>Neoplastic pathologies</td>
<td>59</td>
<td>19</td>
<td>40</td>
<td>1,2,3</td>
<td>1,2,3</td>
<td>1,8,9,10</td>
<td>10</td>
</tr>
<tr>
<td>Fisher (1991)</td>
<td>Quasi-experimental study</td>
<td>Retrospective</td>
<td>ND</td>
<td>ND</td>
<td>PAD</td>
<td>31</td>
<td>11</td>
<td>20</td>
<td>1</td>
<td>1</td>
<td>1,3,9</td>
<td>7</td>
</tr>
<tr>
<td>Grant (2008)</td>
<td>Quasi-experimental study</td>
<td>Retrospective</td>
<td>Single</td>
<td>ND</td>
<td>PAD</td>
<td>64</td>
<td>33</td>
<td>31</td>
<td>ND</td>
<td>ND</td>
<td>1,3,9</td>
<td>7</td>
</tr>
<tr>
<td>Lambert (2001)</td>
<td>RCT</td>
<td>Prospective</td>
<td>ND</td>
<td>ND</td>
<td>PAD</td>
<td>30</td>
<td>16</td>
<td>14</td>
<td>1</td>
<td>2</td>
<td>1,2,3,9,10</td>
<td>12</td>
</tr>
<tr>
<td>Malawer (1991)</td>
<td>Case controlled study</td>
<td>ND</td>
<td>ND</td>
<td>Yes</td>
<td>PAD and neoplastic pathologies</td>
<td>13</td>
<td>7</td>
<td>6</td>
<td>ND</td>
<td>ND</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Pinzur (1996)</td>
<td>RCT</td>
<td>Prospective</td>
<td>Single</td>
<td>No</td>
<td>PAD</td>
<td>21</td>
<td>11</td>
<td>10</td>
<td>1,3</td>
<td>1,3</td>
<td>1</td>
<td>19</td>
</tr>
</tbody>
</table>

extensive review was performed for this analysis and authors were contacted for further information when articles otherwise suitable for inclusion gave either no, or non-abstractable data. The only previous review of the use of PNCs evaluated pre-emptive analgesia for chronic limb pain after surgery. Within the review Ypsilantis et al. identified three studies utilising a “perineural block,” but did not attempt meta-analysis and included a study comparing a single intraoperative perineural injection of local anaesthetic and clonidine versus control. However, there were a lack of rigorous randomised trials available for analysis, with the remaining papers being generally of low quality. Studies were heterogeneous by design (RCT versus cohort), control group employed (patients without PNC versus those with PNC with placebo), and outcomes measured. Most studies were small (<50 patients),

Table 2. Summary table of outcomes for treatment and control groups.

<table>
<thead>
<tr>
<th>Sensitivity analysis</th>
<th>N studies (patients)</th>
<th>Treatment group (n)</th>
<th>Control group (n)</th>
<th>HG I² (per cent)</th>
<th>HG p value</th>
<th>SMD/OR (95% CI)</th>
<th>Overall effect Z</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postoperative opioid use</td>
<td>All studies</td>
<td>7 (416)</td>
<td>199</td>
<td>217</td>
<td>79</td>
<td>.0001</td>
<td>−0.59 (−1.10 to −0.07)</td>
<td>2.22</td>
</tr>
<tr>
<td>PAD patients only</td>
<td>5 (344)</td>
<td>173</td>
<td>171</td>
<td>85</td>
<td>.0001</td>
<td>−0.66 (−1.35 to 0.04)</td>
<td>1.85</td>
<td>.06</td>
</tr>
<tr>
<td>Larger studies</td>
<td>3 (321)</td>
<td>154</td>
<td>167</td>
<td>76</td>
<td>.01</td>
<td>−0.59 (−1.13 to −0.06)</td>
<td>2.18</td>
<td>.03</td>
</tr>
<tr>
<td>High quality studies</td>
<td>2 (219)</td>
<td>113</td>
<td>106</td>
<td>0</td>
<td>.45</td>
<td>−0.41 (−0.67 to −0.14)</td>
<td>2.97</td>
<td>.003</td>
</tr>
<tr>
<td>Postoperative pain</td>
<td>All studies</td>
<td>2 (228)</td>
<td>118</td>
<td>110</td>
<td>92</td>
<td>.0006</td>
<td>0.53 (−0.93−1.98)</td>
<td>0.71</td>
</tr>
<tr>
<td>In-hospital mortality</td>
<td>All studies</td>
<td>2 (262)</td>
<td>135</td>
<td>127</td>
<td>38</td>
<td>.21</td>
<td>0.82 (0.22−3.07)</td>
<td>0.29</td>
</tr>
<tr>
<td>Phantom limb pain</td>
<td>All studies</td>
<td>3 (101)</td>
<td>50</td>
<td>51</td>
<td>18</td>
<td>.29</td>
<td>0.49 (0.14−1.76)</td>
<td>1.09</td>
</tr>
<tr>
<td>Stump pain</td>
<td>All studies</td>
<td>2 (37)</td>
<td>17</td>
<td>20</td>
<td>0</td>
<td>.73</td>
<td>0.50 (0.11−2.33)</td>
<td>0.89</td>
</tr>
</tbody>
</table>

PNC = perineural catheter; HG = heterogeneity; SMD = standardised mean difference; OR = odds ratio; PAD = peripheral arterial disease.

Figure 2. Forest plot of treatment versus control group and postoperative opioid use; all papers and sensitivity analysis.
and two had significant baseline differences between the cohorts examined. Quality of included studies, as assessed by the Downs and Black score, was low. As a result, GRADE quality of evidence was very low for all outcomes.

**Explanation of findings and implications for practice**

Despite the quality of evidence analysed, this review suggests that PNC use can reduce postoperative opioid consumption by a factor of around 50%. This is comparable with other large meta-analyses examining the use of PNCs for analgesia for many different types of surgery. Liu et al. pooled data from 44 RCTs (2141 patients) undergoing general, orthopaedic, gynaecological, or cardiothoracic surgical procedures either with or without a PNC. Overall, PNC use was associated with a significant reduction in postoperative pain scores at rest and movement, opioid usage, nausea and vomiting, length of hospital stay, and patient satisfaction.

The recent UK-wide NCEPOD review into lower limb amputations found that strong opioids were the most frequently used class of analgesia postoperatively. Opioid analgesia has a well documented adverse event profile, which is particularly pronounced in the elderly. Non-narcotic analgesia reduces postoperative nausea and vomiting, constipation, sedation and pruritis compared with opioid analgesia. The incidence of delirium may also be reduced, which is an independent variable in predicting poor outcomes and increased mortality in the elderly. Opioid-related side effects increase in-hospital costs by approximately 7–16% and overall length of stay by approximately 10%. Opioid-sparing agents have been shown to reduce overall inpatient cost compared with opioid analgesia. By contrast, complications from PNCs are rare, and infective complications occur in no more than 3.2% of patients.

This analysis found that although PNC reduced opioid use it had no apparent effect on postoperative pain scores. This may simply be a reflection of the excellent pain relief provided by the control group analgesic regimen, or a type II error as a result of the low number of patients evaluated. The RCT proposed by Borghi et al. comparing postoperative PNC and opioids, to opioids alone, terminated after the first four patients were randomised, as all controls requested a PNC because of the apparent improvement in postoperative pain outcomes. A number of case series and reports have also highlighted the impressive analgesic effect of PNCs, with some patients requiring no postoperative opioid analgesia.

PNC use demonstrated no appreciable effect on either phantom limb pain or stump pain. This is not surprising given the complex and poorly understood pathophysiology of phantom limb pain, of which both peripheral and central mechanisms may play an important part. Amputations cause massive tissue and neuronal injury, disrupting the afferent nerve input to the spinal canal compounded by central upregulation of norioceptor receptors in the spinal cord, and cortical reorganisation of the amputated region. Although short-term PNC usage may not help, prolonged (>30 days) PNC treatment has been described with a relatively low incidence of chronic pain.

Although impossible to formally measure in meta-analysis, PNCs are quick and easy to place at the time of the operation. An elastomeric sphere (the On Demand and ON-Q PainBuster Post-Op Pain Relief System (I-Flow LLC/ Kimberly Clark)) or automated syringe driver containing a local anaesthetic of choice can be attached to the end of the PNC, which delivers a constant rate infusion, with the option of boluses as required. The cost of the elastomeric spheres is minimal, at around £25 per patient.

Two RCTs evaluating PNCs are currently recruiting. The FinAPain-1 study is a multicentre RCT conducted in Finland of 180 patients comparing 72 h of ropivacaine versus blinded normal saline control in patients undergoing AKA for PAD, examining postoperative pain, phantom limb pain, opioid consumption, and adverse events. The AMP-study is a Swedish trial comparing bolused chirocaine via a PNC following lower limb amputation with a standardised postoperative epidural regimen in 60 patients. Primary outcome measures are phantom limb pain and sensation, and secondary outcomes are quality of life, subject well-being, and depression scores. Although both of these studies will give further data on which to base clinical decision-making, neither are expected to complete follow-up until 2017 and 2016, respectively.

**CONCLUSIONS**

PNCs appear to reduce postoperative opioid requirements following lower limb amputation by approximately 50%, which can reduce the incidence of opioid-related side effects, without affecting postoperative pain scores, mortality, phantom limb or long-term stump pain. Although two RCTs are currently recruiting to further evaluate their efficacy, neither will report before 2016.

**CONFLICT OF INTEREST**

None.
Perineural catheters after lower limb amputations


46 Continuous administration of local anesthetic for pain after amputation above knee. http://www.isrctn.com/ISRCTN45530042 [accessed 15.01.15].

47 Could treatment with prolonged peripheral nerve block reduce phantom limb pain on lower extremity amputation? http://www.isrctn.com/ISRCTN23704397 [accessed 15.01.15].


