Continuous Regional Anaesthesia Provides Effective Pain Management and Reduces Opioid Requirement Following Major Lower Limb Amputation

O.G.S. Ayling [a], **J. Montbriand** [b], **J. Jiang** [b], **S. Ladak** [b], **L. Love** [a], **N. Eisenberg** [a], **J. Katz** [b,c], **H. Clarke** [b], **G. Roche-Nagle** [a,*]

[a] Division of Vascular Surgery, Toronto General Hospital, Peter Munk Cardiac Centre, University Health Network, University of Toronto, Toronto, Ontario, Canada
[b] Department of Anesthesia and Pain Management, Pain Research Unit, University Health Network, Toronto General Hospital, University of Toronto, Toronto, Ontario, Canada
[c] Department of Psychology, York University, Toronto, Ontario, Canada

WHAT THIS PAPER ADDS

Postoperative stump pain after major lower limb amputation is a significant impediment to the recovery of amputees. The vast majority of patients require opioid analgesics following surgery, which are associated with opioid-related side-effects. Continuous perineural catheter infusions of local anesthetic are a safe and effective method for reducing opioid analgesic medications following lower limb amputations. This adds to existing literature and is one of the largest studies to date.

Objectives: Postoperative stump pain after major lower limb amputation is a significant impediment to the recovery of amputees. The vast majority of patients require opioid analgesics following surgery, which are associated with opioid-related side-effects. Here, we investigate whether intraoperative placement of a peripheral nerve stump catheter followed by continuous infusion of local anesthetic is as effective at pain control as current analgesic practices. If beneficial, this procedure could potentially reduce post-amputation opioid consumption and opioid-related adverse effects.
Methods: A retrospective chart review was conducted of 198 patients over a 4-year period who had undergone a major lower limb amputation for indications related to peripheral vascular disease. Postoperatively, 102 patients received a perineural catheter were compared to 96 patients who did not. The primary outcomes of this study were the amount of morphine equivalents used in the first 72 hours postoperatively and postoperative pain intensity in the first 24 hours.
Results: A total of 198 lower-limb amputations were selected for analyses. Multiple regression analyses indicated that perineural catheter use was associated with a lower cumulative postoperative opioid consumption over the first 72 hours but not postoperative pain scores at 24 hours. Perineural catheter use led to a 40% reduction in opioid use during the first 72 hours postoperatively. Mixed model repeated measures analysis demonstrated that this opioid reduction was consistent over time. Other variables related to total opioid use included age, pre-surgical chronic pain, pre-surgical opioid use, patient-controlled analgesia.
Conclusions: Continuous perineural infusions of local anesthetic are a safe and effective method for reducing post-amputation opioid analgesic medications after major lower limp amputation.

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INTRODUCTION

Lower limb amputations lead to significant disability and up to ~80% of patients will suffer from phantom limb and stump pains.[1–4] Stump pain is a significant sequela in the initial postoperative phase that impedes rehabilitation of amputees. In addition, the development of chronic pain following amputation is a long-term complication[5] that greatly impairs quality of life.

Opioids are the most common agents used to manage postoperative amputation pain. However, opioids are associated with substantial adverse effects including delirium, nausea, and sedation. These adverse effects are particularly difficult for elderly patients, who make up the largest population of patients undergoing lower limb amputation.[3,6] Regional analgesic techniques[7,8] provide simple and effective methods to reduce acute postoperative pain, opioid use, and their adverse effects.

In this retrospective chart review we evaluate whether continuous infusion of local anesthetic via a perineural catheter is as effective as opioids alone, thus offering potential for reducing post-amputation pain, opioid consumption, and concomitant adverse effects.

* Corresponding author. G. Roche-Nagle, Toronto General Hospital, 200 Elizabeth Street, Toronto, Ontario M5G 2C4, Canada.
E-mail address: graham.roche-nagle@uhn.ca (G. Roche-Nagle).
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METHODS

Approval to conduct the research was obtained from the University Health Network research ethics board. The hospital charts of 162 patients undergoing major lower limb amputation between January 2009 and June 2013 were reviewed. A total of 209 separate amputations were reviewed. Nine participants were excluded as extreme outliers (4 catheter, 5 non-catheter), using standard outlier detection (±6 standard deviations or greater).[9] An additional two patients were excluded due to indications unrelated to peripheral vascular disease manifestations (aged 24 and 37 years, both with congenital abnormalities), leaving 198 amputation cases for analysis (20 were a second primary amputation and 16 were revisions of primary amputations).

The 198 amputations were classified into one of two groups. The treatment/catheter group consisted of patients who received a continuous perineural stump catheter following either a below-knee amputation (BKA) or an above-knee amputation (AKA). The second group, the comparison group, also underwent BKA or AKA but did not receive a perineural stump catheter. As of July 2009, the division of vascular surgery gradually began introducing the practice of using stump catheters for limb amputation, which was driven by a new staff appointment. Patients were allocated to group (catheter vs. no catheter) based on the attending surgeon availability. Each surgeon was trained in the procedure but uptake was variable. The rates of perineural catheters were variable over the time period studied (2009: 66%; 2010: 34%; 2011: 72%; 2012: 47%; 2013: 43% of patients receiving catheters in the listed year). Patients in both groups received postoperative analgesia with opioids that were delivered parenterally by intravenous (IV) patient-controlled analgesia (IV-PCA), non-PCA (e.g., oral, transdermal, or nurse-administered IV analgesia), or a combination of both. Patients were advised by the acute pain service (APS) when given IV-PCA devices to maintain their pain less than 4/10 (i.e., in the mild rage). At our institution, the APS includes an attending anesthesiologist and several nurse practitioners (NPs) who have specialized training in pain management. The APS is involved in the care of all patients requiring a PCA device, an epidural, or a peripheral nerve/stump catheter following surgery. Patients are visited and care issues discussed daily to optimize pain control.

The patient records were reviewed for age, gender, level of amputation, indication for the operation, placement of a perineural catheter, preoperative pain intensity, duration of preoperative pain, preoperative pain medication use in the 24 hours prior to the amputation, and comorbidities, specifically diabetes, smoking, and chronic pain (greater than 6 months in duration). Postoperative analgesic use during the first 72 hours postoperatively was documented and converted to morphine equivalents (University of Alberta, Faculty of Medicine and Dentistry, Multidisciplinary Pain Centre; http://www.uofapain.med.ualberta.ca/en/ForHealthProfessionals/OpioidConversionGuide.aspx). Postoperative patient-reported pain intensity scores during the first 24 hours were recorded on an 11-point numeric rating scale (NRS) (0 is "no pain", 10 being the "worst pain imaginable"). Finally, duration of the perineural catheter placement, duration of hospital stay postoperatively, time to mobilization, and delirium (delirium was assessed by the Confusion Assessment Method.[10] RNs assess the patients each shift and as required), sedation, and nausea were also measured.

Placement of the perineural stump catheter

Five different surgeons placed perineural stump catheters that supplied a continuous infusion of ropivacaine (0.2%, 2–6 mL/hour), bupivicaine (0.25%, 2–5 mL/hour), or lidocaine (1%, 5–8 mL/hour); 90.20% of catheters delivered ropivacaine (0.2%).

Using the described technique of Malawer, et al.,[11] at the time of amputation, a 20-gauge polyamide catheter (Portex 4910-16/17) was inserted under direct vision several centimeters above the level of transection of either the exposed sciatic (AKA) or posterior tibial nerve (BKA), depending on the level of amputation. The catheter was then advanced cephalad 5–10 cm. The catheter was externalized and secured. Typically, a 10-mL bolus was injected into the catheter before wound closure to confirm patency of catheter. Continuous infusion of local anesthetic was commenced in the recovery room. We limited the infusion volume to 2 mL/hour in the BKAs due to the small compartment space.

Statistical analysis

Standard methods were used to assess the appropriateness of statistical techniques and to investigate outliers including standardized scores, probability of Mahalanobis distance and/or Cooks's distance as appropriate.[9] Of the 165 participants, nine were excluded as extreme outliers (4 catheter, 5 non-catheter). Two participants were excluded due to indications unrelated to peripheral vascular disease, leaving a total of 198 amputations for analysis. Participant demographics were compared between catheter and non-catheter groups using *t* tests, Fisher exact tests, and chi-square analyses as appropriate. A Bonferroni correction was applied to the Type I error rate when comparing pre-surgical variables, setting alpha at 0.01.

Regression analyses

Independent exposure variables were classified into five categories: (a) demographic variables (gender, age), (b) preoperative comorbidities (diabetes, chronic pain and smoking status), (c) pre-surgery measures (pre-surgery pain level, pre-surgery opioids), (d) PCA status, and (e) perineural catheter status. The analysis performed in this study is a three-step series of multiple linear regressions, which are built up to the final linear regression model. The first linear regression involved running each variable (age, sex, etc.) as its own linear regression in relation to the dependent variable of total opioid use (unadjusted beta). The unadjusted beta represents the ability of each individual variable to predict total morphine use. Positive values are associated with increased opioid use and negative values are associated with decreased opioid use after amputation. Second, a subsequent multivariate linear regression was conducted for each group (demographics, comorbidities, etc.) using significant variables from within its group that were obtained from the first linear regression (group adjusted beta), postoperative opioid use was the dependent variable. The group-adjusted beta score represents the score of each individual predictor adjusted for the other predictors within its group in relation to postoperative opioid use (demographic, pre-surgery scores, PCA, comorbidity). Finally, a third multivariate linear regression was conducted. The final model took all variables that were significant predictors of total opioid use in their respective groups from the second/group-adjusted linear regression and were used to build the final multivariate linear regression (fully adjusted beta). For each category of exposure variable listed above, separate multivariate regression analyses were conducted to ascertain the variables that showed a significant relationship with the dependent variable (postoperative opioid consumption). A complete multivariable model was then created using all variables found to have a significant relationship with the dependent variable in the previous models, as well as the main variable of interest (perineural catheter status). All analyses were conducted with SPSS (IBM, New York, USA) version 10.05, using a significance level of 0.05.

Mixed-model repeated measures ANOVA. A mixed-model repeated measures ANOVA was conducted on morphine consumption using time as the within-subjects factor, catheter status as the between-subjects factor and the time by catheter status interaction term to assess whether the effect of catheter use on morphine consumption varied by time. Repeated measures analysis is especially susceptible to the effects of outliers. Accordingly analyses were run on the original post-surgical measures of morphine use excluding the extreme outliers ($n = 198$), and also on a (log+1) transformation of the morphine variables on all participants used, to acquire a more normal distribution ($n = 205$).

RESULTS

Descriptive statistics

A total of 162 individual patients underwent 198 lower limb amputations (20 were second primary contralateral amputations and 16 were revisions of previous ipsilateral amputations) for peripheral vascular disease (67% male, 33% female), with an average age of 68 years. Demographics, comorbidities, and perioperative variables are presented in Table 1. There were no significant differences between the catheter and non-catheter groups in gender, age, previous chronic pain, smoking status, diabetes status, preoperative pain scores, preoperative 24-hour opioid, or above knee vs. below knee assignment in surgery (all $p > .05$).

Postoperative opioid use

The use of analgesic medications was converted to morphine equivalents. Multivariable regression analysis was used to determine which variables were related to postoperative opioid use. Stump catheter use was associated with a significantly lower total postoperative opioid use (catheter 81.23 ± 90.77 vs. non-catheter 134.51 ± 145.49, $p = .03$).

In the initial multivariable regression models (see Methods), age, and perineural catheter use were associated with significantly less total opioid use in the first 72 hours postoperatively. While chronic pain, preoperative opioid use, and PCA status were significantly associated with increased total opioid use after amputation (Table 2). In the full multivariable model, all these variables remained significant. With the above-listed variables held constant, perineural catheter use remained a significant predictor of lower total post-surgical opioid use ($p = .004$). There was a decrease in total opioid with increased age, while preoperative opioid use, PCA use, and preoperative chronic pain were all associated with an increase in total opioid use.

Table 1. Demographic and preoperative medical variables.

	Catheter ($n = 102$)	Non catheter ($n = 96$)
Mean age in years (SD)	69.9 (11.78)	66.29 (11.85)
Gender		
Male *n* (%)	65 (48.9)	68 (51.1)
Mean preop 24 hour opioid in mg (SD)	20.01 (29.99)	15.40 (17.56)
Patient-controlled analgesia, *n* (%)	75 (73.5)	74 (77.1)
Diabetes status, *n* (%)	67 (65.7)	75 (78.1)
Smoking status *n* (%)	49 (48)	57 (59.4)
History of chronic pain *n* (%)	32 (31.4)	34 (35.4)
Mean preoperative pain score (SD)	5.14 (3.44)	4.83 (3.24)

Note. There was no significant difference between the groups on these variables (Bonferroni correction applied for multiple comparisons).

Mixed-model repeated measures ANOVA

Table 3 summarizes the average opioid use at each interval by catheter status ($n = 198$). As seen in the average total 72-hour opioid use, patients given a perineural catheter used, on average, 40% less opioid than those not receiving a perineural catheter ($T = 3.11$, $p = .03$). Total opioid use was also examined during three post-surgery time frames: 0—24 hours, 24—48 hours, and 48—72 hours. The time by catheter status interaction was non-significant ($p > .22$), indicating that the opioid sparing effect seen with perineural catheter use does not differ significantly as a function of the time frame sampled, while the overall between-subject effect of perineural catheter use was significant ($p = .03$).

Use of non-opioid analgesics

There was no difference between the catheter and non-catheter group in the relative use of gabapentin (catheter 40 of 102, 39.22% vs. non-catheter 35 of 96, 36.46%, $p = .77$).

Table 2. Multivariate linear regressions with adjusted and unadjusted beta for the association between demographic variables and total post-surgical opioid use.

	Cases ($n = 102$)	Comparison group ($n = 96$)	Single variable unadjusted beta (95% CI)	Within group adjusted beta (95% CI)[a]	Fully adjusted beta (95% CI)[b]	*p*-values for fully adjusted beta results
Mean age (SD)	69.9 (11.78)	66.29 (11.85)	−4.59 (−5.89 to −3.28)	−4.62 (−5.92 to −3.33)	−3.46 (−4.70 to −2.22)	<.0001
Sex *n* (%)						
Male	65 (48.9)	68 (51.1)				
Female	37 (56.9)	28 (43.1)	25.48 (−11.16 to 62.13)	29.30 (−3.52 to 62.14)		
Catheter status *n* (%)						
Catheter	102 (100)	—	−53.28 (−87.05 to −19.50)	—	−42.88 (−71.76 to −14.01)	.004
No catheter	—	96 (100)				
History of chronic pain *n* (%)						
Yes	32 (31.4)	34 (35.4)	75.67 (40.58 to 110.77)	72.75 (36.94 to 108.57)	50.16 (18.45 to 81.86)	.002
No	70 (68.6)	62 (64.6)				
Mean preop 24-hour opioid (SD)	20.01 (29.99)	15.40 (17.56)	1.90 (1.25 to 2.55)	1.51 (0.70 to 2.23)	1.17 (0.54 to 1.80)	<.0001
Patient-controlled analgesia *n* (%)						
Yes	75 (73.5)	74 (77.1)	45.40 (5.84 to 84.95)	—	35.68 (2.34 to 69.03)	.036
No	27 (26.5)	22 (22.9)				
Diabetes status *n* (%)						
Yes	67 (65.7)	75 (78.1)	−24.73 (−63 to 13.5)	−26.69 (−63.39 to 10.02)		
No	35 (28.3)	21 (21.9)				
Smoking status *n* (%)						
Yes	49 (48)	57 (59.4)	28.31 (−6.13 to 62.75)	15.11 (−18.78 to 48.99)		
No	53 (52)	39 (40.6)				
Mean preoperative pain score (SD)	5.14 (3.44)	4.83 (3.24)	7.83 (1.59 to 14.06)	5.06 (−0.98 to 11.10)		

[a] Adjusted for group variables only. While unadjusted beta represents each individual measures ability to predict total opioid use, this score represents the score of each individual predictor adjusted for the other predictors in its group (demographic, pre-surgery scores, PCA, comorbidity).

[b] Adjusted for all variables that were significant predictors of total morphine use in their respective groups (demographics, pre-surgery scores, PCA and comorbidity). Variable(s) significant in the final model are age, catheter status, pre-surgical opioid use, PCA status, and pre-surgical chronic pain.

Table 3. Mean (SD) opioid use in milligrams during 0—24, 24—48, and 48—72 hour post-surgery time frames by treatment group.

Time frame	Perineural catheter	Non-catheter
0—24 hours	30.28 (33.17)	50.53 (55.88)
24—48 hours	26.92 (34.84)	46.42 (60.30)
48—72 hours	24.85 (36.30)	36.95 (44.44)
72-hour total	81.23 (90.77)	134.51 (145.49)*

*$p = .03$.

Postoperative pain

Postoperatively, multiple regression analysis revealed no difference between the catheter and non-catheter groups in total pain after amputation. In both groups the average 24-hour postoperative pain intensity was low (catheter 3.02 $\pm$ 2.12 vs. non-catheter 3.38 $\pm$ 2.12).

Above-knee versus below-knee amputations

Surgeries in this study were a roughly equal mix of AKA and BKA cases (109 AKA vs. 89 BKA). There was no significant difference in the amount of opioid used between AKA and BKA groupings postoperatively (AKA 104.92 $\pm$ 110.86 vs. BKA 109.68 $\pm$ 137.14; $p = .79$). Pain levels were significantly lower for AKAs than BKAs (AKA 2.81 $\pm$ 2.13 vs. BKA 3.66 $\pm$ 2.03 $p = .046$, CI -6.0 to -0.14).

Mobilization after amputation

The number of days to sit up in bed (catheter 1.86 $\pm$ 1.21 days vs. non-catheter 1.61 $\pm$ 0.85 days, $p = .21$) or to mobilize out of bed within 3 days after amputation (catheter 27.28% [18 of 66] vs. non-catheter 20.00% [9 of 45], $p = .51$) were not different between the catheter and non-catheter groups.

Adverse events

Delirium. The one-sided Fisher exact test was used to examine the hypothesis that lower opioid use in the catheter group would be associated with lower levels of post-surgical delirium. The results revealed a trend for delirium levels to be lower in the catheter group ($n = 207$; $p = .054$).

Sedation and nausea. The occurrence of sedation (catheter 3 patients vs. non-catheter 5 patients) and nausea (catheter 1 vs. non-catheter 1) were very low and precluded statistical analyses.

Catheter failure. Perineural catheters remained in place for an average of 3.89 $\pm$ 1.34 days (range 1—7). Nine catheters failed, five became blocked, two were disconnected by the patient, one line became kinked, and one was incompletely inserted in the operating room. Although failure occurred in 8.8% (9 of 102) of the catheters there was no difference in the average time to discharge from the hospital following amputation (catheter 17.00 $\pm$ 13.26 days vs. non-catheter 17.88 $\pm$ 14.06 days; $p = .670$). The yearly failure rate of catheters was low and the rates decreased from year to year (2009: 18.75% [3 of 16]; 2010: 12.5% [2 of 16]; 2011: 9.1% [3 of 33]; 2012: 4.0% [1 of 25]; 2013: 0% (0 of 12).

Deaths. There were eight in-hospital deaths in this sample (catheter 5; non-catheter 3). Chi-square analysis revealed no significant differences in the number of deaths based on catheter status ($p = .33$).

DISCUSSION

This retrospective chart review of 198 consecutive amputations showed that continuous infusion of local anesthetic via perineural catheters is an effective tool to reduce opioid analgesic consumption following lower limb amputation. In the present study, although postoperative pain was well managed in both groups a significant between-group difference in pain scores did not emerge. The use of perineural catheters provided equivalent postoperative pain control relative to the comparison group with significantly less opioid usage.

Previously, it has been reported that perineural analgesia at the surgical site is a safe and effective method that leads to a significant reduction in postoperative opioid consumption for patients undergoing various surgeries.[3,12—17] Several previous studies have examined the use of perineural catheters to control postoperative amputation pain but have produced varied results with small sample sizes.[3,14,16,18—21]

This current study is the largest evaluation of perineural infusion catheters following lower limb amputations. Our results indicate that the use of perineural infusion catheters effectively reduces post-amputation consumption of opioid analgesics with comparable pain scores up to 24 hours. The ability to reduce opioid consumption after amputation but to still maintain adequate pain control is particularly important for patients of advanced age who may be more susceptible to the side-effects of opioids.[3] Although we investigated whether there was a decrease in delirium following lower limb amputation with perineural catheter use, this study was underpowered to have found it. Perineural catheter use was found to be safe and failure rates were low without an increase in adverse events, which is in line with previous studies.[3,14,16,18—20]

In addition to the side effects of opioid analgesics, post-amputation pains are a significant problem for patients recovering from lower limb amputations. We were unable to find any differences in the patient-reported pain scores between the comparison group and the catheter group. Patients in both groups had their pain very well controlled while in hospital.[20] The low levels of postoperative pain in each group support this conclusion. In studies where pain is well controlled, the level of pain medications required by patients may be a better means to assess the efficacy of analgesic regimens such as perineural catheters. Importantly, we noted no differences between AKA and BKA groups in their levels of postoperative opioid use.

There are several limitations to this study. First, given the retrospective nature of the data collected, adequate standardization of postoperative care cannot be assured. Second, there may be a surgeon bias to provide patients with higher morbidity a perineural catheter. Third, due to the variability in the data and small-to-moderate sample size, confidence intervals in the analyses were large. Finally, pain data were not available beyond 24 hours after patients were discharged from the APS.

In this report we did not address whether perineural stump catheters are able to reduce phantom limb pains after amputation. Previous reports after lower limb amputation have suggested that perineural catheters may be effective in reducing phantom limb pains.[3,14,19] However, phantom limb pain is a complex phenomenon that likely develops due to a combination of pre-amputation pain[1,22–24] as well as the transection of nerves at the time of surgery, and ectopic activity from the transected fibers after surgery.[25] Based on the results presented here a large randomized, double-blinded study with clear endpoints should be implemented. A prospective study would enable investigation into the possibility of effectively lowering rates of stump and phantom limb pains.[3,14,25–27]

In conclusion, continuous perineural catheter infusions of local anesthetic are a safe and effective method for reducing opioid analgesic medications following lower limb amputations.

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CONFLICT OF INTEREST

None.

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