Optimized Perioperative Analgesia Reduces Chronic Phantom Limb Pain Intensity, Prevalence, and Frequency

A Prospective, Randomized, Clinical Trial

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ABSTRACT

Background: Severe preamputation pain is associated with phantom limb pain (PLP) development in limb amputees. We investigated whether optimized perioperative analgesia reduces PLP at 6-month follow-up.

Methods: A total of 65 patients underwent lower-limb amputation and were assigned to five analgesic regimens: (1) Epi/Epi/Epi patients received perioperative epidural analgesia and epidural anesthesia; (2) PCA/Epi/Epi patients received preoperative intravenous patient-controlled analgesia (PCA), postoperative epidural analgesia, and epidural anesthesia; (3) PCA/Epi/PCA patients received perioperative intravenous PCA and epidural anesthesia; (4) PCA/GA/PCA patients received perioperative intravenous PCA and general anesthesia (GA); (5) controls received conventional analgesia and GA. Epidural analgesia or intravenous PCA started 48 h preoperatively and continued 48 h postoperatively. The results of the visual analog scale and the McGill Pain Questionnaire were recorded perioperatively and at 1 and 6 months.

Results: At 6 months, median (minimum–maximum) PLP and P values (intervention groups vs. control group) for the visual analog scale were as follows: 0 (0 –20) for Epi/Epi/Epi (P = 0.001), 0 (0 – 42) for PCA/Epi/Epi (P = 0.014), 20 (0 –40) for PCA/Epi/PCA (P = 0.532), 0 (0 –30) for PCA/GA/PCA (P = 0.008), and 20 (0 –58) for controls. The values for the McGill Pain Questionnaire were as follows: 0 (0 –7) for Epi/Epi/Epi (P = 0.001), 0 (0 –9) for PCA/Epi/Epi (P = 0.003), 6 (0 –11) for PCA/Epi/PCA (P = 0.208), 0 (0 –9) for PCA/GA/PCA (P = 0.003), and 7 (0 –15) for controls. At 6 months, PLP was present in 1 of 13 Epi/Epi/Epi, 4 of 13 PCA/Epi/Epi, and 3 of 13 PCA/GA/PCA patients versus 9 of 12 control patients (P = 0.001, P = 0.027, and P = 0.009, respectively). Residual limb pain at 6 months was insignificant.

Conclusions: Optimized epidural analgesia or intravenous PCA, starting 48 h preoperatively and continuing 48 h postoperatively, decreases PLP at 6 months.

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PHANTOM limb pain (PLP) prevalence varies between 50% and 80%1–3 in limb amputees; when present, this kind of pain is difficult to manage. Both PLP and residual limb pain (RLP) are common sequela of limb amputation and usually have a considerable impact on patients’ quality of life.4,5 Animal and human data suggest that severe preamputation pain is associated with PLP development,6,7 and more severe pain etiologies (e.g., gangrene) have been associated with more severe PLP.8

Several therapeutic interventions have been evaluated for PLP prevention and/or treatment,9–15 including continuous brachial plexus blockade in combination with N-methyl-d-aspartate acid receptor antagonists,16 intravenous17 or epidural18 ketamine administration, postoperative perineural bupivacaine/clonidine infusion,19 and oral gabapentin,20 but their effectiveness remains unclear. Intravenous morphine seems to be effective in PLP treatment, whereas both intravenous lidocaine and morphine diminish RLP.21 Because cortical reorganization plays a major role in phantom limb phenomena,22–23 many therapeutic approaches focus on changes in cortical plasticity for PLP treatment.24–30 Epidural analgesia has also been evaluated, with conflicting results. A study by Bach et al.31 observed significantly lower PLP prevalence in patients with rigorous perioperative epidural analgesia. Subsequent clinical trials32,33 confirmed the findings of Bach et al., but a prospective randomized trial by Nikolajsen et al.15 showed that perioperative epidural analgesia did not reduce PLP or RLP prevalence.

This study was conducted to evaluate the hypothesis that optimized perioperative analgesia using continuous epidural analgesia or intravenous patient-controlled analgesia (PCA) reduces the intensity, prevalence, and frequency of PLP and/or RLP after elective lower-limb amputation.

Materials and Methods

This was a prospective, randomized, double-blind clinical trial. After approval of the Institution Ethics Committee, this trial was conducted at Patras University Hospital, Patras, Greece, between December 12, 2003 and May 26, 2008. Patients older than 18 yr who had severe (i.e., resistant to usual medical treatment), frequent, or continuous pain (visual analog scale [VAS] pain score, ≈ 60 mm [on a scale of 0–100 mm]) one week before scheduled major (above or below the knee) lower-limb amputation for inoperable peripheral vascular disease were invited to participate. Exclusion criteria were older than 85 yr, emergency amputation, ipsilateral reamputation, foot or toe amputation, inability to complete a detailed pain questionnaire, history of substance abuse, active psychiatric disease requiring treatment, other preexisting chronic pain conditions, and any contraindication to epidural catheter placement (e.g., anticoagulation or antiplatelet medications). Written informed consent was obtained from all patients. All amputations were performed by the same team of vascular surgeons (I.T. and S.P.).

Randomization

Randomization was performed using computer-generated blocks, with five treatment groups and 13 patients per group.†† Each patient assigned to participate in the study had a sequentially numbered sealed envelope containing a randomization code. The envelopes were concealed until after consent was obtained.

Treatment Groups

Epi/Epi/Epi Group. Patients received preoperative and postoperative continuous epidural analgesia (bupivacaine, 2 mg/ml, and fentanyl, 2 μg/ml, infusion at 4–8 ml/h), starting 48 h before and continuing until 48 h after amputation. They also received intravenous patient-controlled normal saline (N/S), through a second pump, preoperatively and postoperatively. The amputation was performed under epidural anesthesia, using 10–15 ml of bupivacaine, 5 mg/ml and epidural fentanyl, 100 μg, supplemented by additional epidural bupivacaine, 5 mg/ml, at increments of 3–5 ml as needed.

PCA/Epi/Epi Group. Preoperatively, patients received intravenous fentanyl PCA (dose, 25 μg; lockout, 20 min; and no basal infusion) for 48 h and also received epidural (Epi) N/S at 2 ml/h. The amputation was performed under epidural anesthesia, using exactly the same intraoperative anesthetic regimen as in the Epi/Epi/Epi group. They received postoperative epidural analgesia with bupivacaine, 2 mg/ml, and fentanyl, 2 μg/ml, infused at 4–8 ml/h for 48 h. A second PCA pump administered intravenous N/S in a PCA mode for 48 h postoperatively.

PCA/Epi/PCA Group. Patients received preoperative and postoperative intravenous fentanyl PCA (doses and lockout same as in the PCA/Epi/Epi group), starting at 48 h before and continuing for 48 h after amputation. A second infusion pump administered N/S epidurally at 2 ml/h for 48 h preoperatively and postoperatively. All amputations were performed under epidural anesthesia, using the same anesthetic regimen as in the first two groups.

PCA/GA/PCA Group. Patients received preoperative and postoperative analgesia with intravenous fentanyl PCA (dose, 25 μg; lockout, 20 min; no basal infusion), starting at 48 h before and continuing for 48 h after amputation. A second infusion pump administered N/S epidurally at 2 ml/h for 48 h preoperatively and postoperatively. Amputations were performed under general anesthesia (GA) with a laryngeal mask airway (intravenous midazolam, 1–3 mg, for premedication; propofol, 2 mg/kg, for induction; sevoflurane, 0.7–1.0 end-tidal age-adjusted minimum alveolar concentration; and remifentanil by continuous intravenous infusion, titrated to patient response for maintenance of anesthesia).

Control Group. Preoperatively and postoperatively, patients received intramuscular meperidine, 50 mg, four to six times...
Approximately 48 h before amputation, patients in groups 1–4 had a lumbar epidural catheter placed by one of us (D.A.) using an 8-cm 18-gauge Tuohy needle (Smiths Medical Ltd., London, United Kingdom) that was inserted into the epidural space at the L3–L4 or L4–L5 interspace with the loss-of-resistance technique. A test dose of lidocaine, 2%, with 3 ml epinephrine, 1:200,000, was injected through the catheter, to confirm epidural placement and minimize the likelihood of unintentional intrathecal or intravascular injection. The analgesic protocol started immediately after the epidural catheter was placed and continued for 48 h after amputation. One of us (D.A.) was responsible for pain treatment while the protocol was in effect and adjusted the epidural or PCA dose as needed to keep the VAS score at 40 mm or lower. If a patient experienced severe pain after the end of the analgesic protocol, conventional analgesia was provided. Table 1 summarizes the anesthesia and analgesia protocol by group.

### Pain Assessment

Pain intensity was evaluated with a VAS (on a scale of 0–100, with 100 being the maximum imaginable pain) and the McGill Pain Questionnaire (MPQ). The MPQ provides various quantitative measures of clinical pain. The three major MPQ measures are as follows: (1) the pain rating index (PRIR), based on two types of numeric values that can be assigned to each word descriptor; (2) the number of words chosen (NWC); and (3) the present pain intensity (PPI), measured on an intensity scale of 1–5. For each measurement, higher scores indicate worse pain.

**Pain frequency** (the frequency of pain episodes in the past 24 h) was rated as follows: 0 indicates never (no pain attacks); 1, rarely; 2, frequently; and 3, continuously (the patient felt pain continuously).

One of us (G.M.) examined patients for pain before epidural catheter placement and recorded mean (during the past week) and present VAS, MPQ scales (i.e., PRIR, NWC, and PPI), and pain frequency. This investigator (G.M.) conducted all the postoperative interviews at 4 and 10 days and 1 and 6 months. During the analgesic protocol, one of us (D.A.) examined patients and adjusted the epidural or intravenous PCA regimen at least every 8 h, in an attempt to keep VAS scores at 40 mm or lower; another investigator (M.K.) recorded VAS scores every 8 h. The MPQ pain score and pain frequency were also recorded by this investigator (M.K.) 24 h after the analgesic protocol started. Two of us (G.M. and M.K.), nursing staff, and patients were blinded to treatment assignment.

Because intravenous fentanyl administration raises serious concerns about respiratory depression, one of us (D.A.) assessed the depth of patients’ sedation at 8-h intervals and was informed about all adverse events during the analgesic protocol. Caretakers were instructed to call a physician in case of respiratory depression (defined as a respiratory rate lower than 12/min), nausea, or vomiting. Nursing personnel examined patients for respiratory depression, nausea, vomit-
ing, drowsiness, dizziness, pruritus, motor deficits, and hypotension every 2 h and called a physician (D.A.) if needed.

The pain assessment method was identical in all groups. PLP was used to describe any painful sensation associated with the missing limb, whereas RLP referred to pain in the stump or remaining portion of the limb.

**Study Outcomes**

PLP intensity (measured with the VAS and MPQ-PRIR) 6 months after amputation was the primary outcome. PLP intensity at 10 days and 1 month (measured with the VAS and MPQ-PRIR), PLP intensity at 10 days and 1 and 6 months (measured with the MPQ, NWC, and PPI), and PLP frequency at 10 days and 1 and 6 months after amputation were secondary outcomes. Other outcomes of interest included PLP prevalence at 10 days and 1 and 6 months after amputation, RLP intensity (VAS and MPQ) 6 months after amputation, adverse events, and whether an intravenous opioid PCA is effective for the short-term management of ischemic/neuropathic pain.

**Statistical Analysis**

Our data were initially analyzed with “per-protocol” analysis, which included all subjects who underwent the study intervention and completed the study. Data from withdrawn subjects and from patients excluded because of a protocol violation were not used while conducting per-protocol analysis. Subsequently, we performed data analyses according to the “intention-to-treat” principle, using the last-observation-carried-forward method. During intention-to-treat analysis, all subjects who were excluded after randomization (because of protocol violations or death before the protocol was completed) were analyzed in the group in which they were initially randomized. Results are presented according to intention-to-treat analysis. However, the results do not change, and all significant findings remain statistically and clinically significant, regardless of whether analysis is conducted on a per-protocol or an intention-to-treat basis.

For the study to have adequate power, sample size calculation was conducted before the study started, using sample size estimation methods for one-way ANOVA, as described in the book by Norman and Streiner on biostatistics, using the VAS pain score at 6 months as the primary outcome and a clinically meaningful difference and an SD of more than 0.6, because we considered a 30-mm difference in VAS scores as a clinically meaningful difference and an SD = 30 as a reasonable value. Then, based on table 1 (in the appendix of the book by Norman and Streiner47), we concluded that eight patients per group would give the study adequate power when \( \alpha = 0.05 \) and \( \beta = 0.2 \).

To validate the previous sample-size calculations, we conducted power analysis using a statistical software package (Statistica, release 7; Statsoft, Tulsa, OK). In Statistica, the sample-size calculation, based on similar assumptions (one-way ANOVA, five groups, power = 0.8, \( \alpha = 0.05 \), root mean square standardized effect = 0.6), showed that 10 patients per group should be adequate. Then, we decided to use the more conservative of the two calculations (the one derived using Statistica) and increase the estimated sample size by 30% to 13 patients per group, to allow for possible erroneous assumptions and patient attrition.

A Kolmogorov–Smirnov test was used to check the normality of continuous variables. An ANOVA was used to evaluate differences among groups for normally distributed variables (i.e., age, length of surgery, pain score before randomization, analgesia duration, and fentanyl use), whereas a Kruskal–Wallis test was used to assess differences among groups for nonnormally distributed variables (pain scores and pain frequency).

The Mann–Whitney U test was used for comparisons between two groups for variables not normally distributed. PLP and RLP prevalence rates were analyzed with the \( \chi^2 \) test. Results are presented as mean ± SD for normally distributed variables, as median (minimum–maximum) for nonnormally distributed variables, and as number (percentage) for categorical variables.

Bonferroni correction was used to adjust the level of significance regarding the two primary outcomes (VAS and MPQ-PRIR at 6 months) to 0.05/2 = 0.025. Similarly, the level of significance regarding post hoc pairwise comparisons for the two primary outcomes was adjusted to 0.025/4 = 0.0063. For secondary outcomes (total of 13 secondary outcomes), the level of significance was adjusted to 0.05/13 = 0.0038, whereas the significance level for post hoc pairwise comparisons was adjusted to 0.0038/4 group comparisons = 0.00096, and rounded to 0.001.

Statistical analysis was performed with SPSS, version 16.0 (SPSS Inc., Chicago, IL), except for the \( \chi^2 \) test, which was performed using the StatCalc component of the Epi-Info v.3.5.1 statistical package.‡‡

**Results**

Of 107 eligible patients, 42 were excluded before randomization (fig. 1): 12 underwent an emergency amputation, 7 underwent an ipsilateral reamputation, 5 were older than 85 yr, and 8 had contraindications to epidural analgesia because of ongoing use of antplatelet medications (these medications were usually discontinued by the surgeon 1 week before scheduled surgery). Ten patients declined participation and chose to undergo amputation immediately. We randomized 65 patients (13 in each group). As we performed an intention-to-treat analysis, all patients were analyzed in the group in which they were initially randomized, regardless of protocol violations. In total, we analyzed 63 patients and only excluded two patients (one underwent a different operation, and one died before surgery). One

patient had an epidural catheter accidentally pulled before amputation, but his data were included in the group to which he was randomized. Figure 1 shows trial enrollment, the assigned intervention, and the follow-up according to an intention-to-treat protocol.

Baseline patient characteristics are presented in table 2 and did not differ significantly among groups, except for median VAS pain score, which was significantly lower in the control group 1 week before randomization. Differences among groups regarding PLP data are presented in table 3 (for VAS) and table 4 (for MPQ), whereas the significance of pain score differences between all groups versus the control group is presented in figure 2 and table 5.

**Primary Outcomes**

**VAS for PLP Intensity at 6 Months.** The VAS PLP scores differed significantly among groups at the 6-month follow-up (table 3, \( P = 0.001 \)). (By using Bonferroni correction, the significance level was adjusted to \( 0.05/2 = 0.025 \) [two primary outcomes].) Differences between intervention groups and the control group are presented in table 5 and figure 2A. (By using Bonferroni correction, the significance level for these results was adjusted to \( 0.025/4 \) [group comparisons] = 0.0063.) Compared with controls, PLP VAS scores at 6 months were significantly lower only in the Epi/Epi/Epi group. \( P \) values comparing the Epi/Epi/Epi, PCA/Epi/Epi, PCA/GA/PCA, and PCA/Epi/PCA groups with the control group were as follows: \( P = 0.001 \), \( P = 0.014 \), \( P = 0.008 \), and \( P = 0.532 \), respectively.

**MPQ-PRIR for PLP Intensity at 6 Months.** The MPQ-PRIR pain scores differed significantly among groups at the 6-month follow-up (\( P < 0.001 \), table 4). (By using Bonferroni correction, the significance level was adjusted to \( 0.05/2 = 0.025 \) [two primary outcomes].) Based on the PRIR, the Epi/Epi/Epi, PCA/Epi/Epi, and PCA/GA/PCA groups had significantly lower phantom pain scores compared with controls (\( P < 0.001 \), \( P = 0.003 \), and \( P = 0.003 \), respectively), but there was no significant difference for the PCA/Epi/PCA group.
Table 2. Baseline Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Epi/Epi/Epi (n = 13)</th>
<th>PCA/Epi/Epi (n = 13)</th>
<th>PCA/Epi/PCA (n = 12)</th>
<th>PCA/GA/PCA (n = 13)</th>
<th>Control (n = 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>7</td>
<td>9</td>
<td>9</td>
<td>9</td>
<td>7</td>
</tr>
<tr>
<td>Age, yr*</td>
<td>74.3 ± 7.1</td>
<td>70.7 ± 8.5</td>
<td>69.2 ± 8.1</td>
<td>69.6 ± 10.1</td>
<td>71.7 ± 13</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>6</td>
<td>6</td>
<td>5</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>6</td>
<td>7</td>
<td>8</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>End-stage renal disease</td>
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<td>6</td>
<td>6</td>
<td>4</td>
<td>5</td>
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<tr>
<td>Previous stroke</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>4</td>
<td>6</td>
<td>5</td>
<td>4</td>
<td>6</td>
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<tr>
<td>Level of amputation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Below the knee</td>
<td>11</td>
<td>10</td>
<td>10</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>Above the knee</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Length of surgery, min*</td>
<td>64 ± 6.6</td>
<td>60 ± 7.3</td>
<td>58 ± 10.2</td>
<td>68 ± 7.8</td>
<td>62 ± 6.8</td>
</tr>
<tr>
<td>Duration of preexisting pain</td>
<td>17 ± 3.2</td>
<td>18 ± 0.7</td>
<td>21 ± 4.2</td>
<td>17 ± 3.5</td>
<td>18 ± 4.2</td>
</tr>
<tr>
<td>VAS pain score 1 wk before</td>
<td>92 (88–96)</td>
<td>85 (80–90)</td>
<td>90 (80–96)</td>
<td>80 (70–90)</td>
<td>70 (60–90)†</td>
</tr>
<tr>
<td>randomization, mm†</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Epidural or IV patient-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>controlled analgesia duration, h*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before amputation</td>
<td>47.18 ± 6</td>
<td>49.3 ± 6</td>
<td>46.7 ± 5.4</td>
<td>46.27 ± 6.5</td>
<td></td>
</tr>
<tr>
<td>After amputation</td>
<td>48.27 ± 3</td>
<td>46.8 ± 1.6</td>
<td>48.2 ± 1.9</td>
<td>49.18 ± 4</td>
<td></td>
</tr>
<tr>
<td>Fentanyl use during IV</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>patient-controlled analgesia, µg/h</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before amputation</td>
<td>60.8 ± 8.4</td>
<td>60.6 ± 8.5</td>
<td>58.3 ± 8.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>After amputation</td>
<td>52 ± 9.4</td>
<td>54.5 ± 9.5</td>
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</tr>
</tbody>
</table>

Data are given as number in each group unless otherwise indicated.

* Data are given as mean ± SD. † Data are given as median (minimum–maximum). ‡ P < 0.05 vs. all other groups.

Epi = Epidural; GA = general anesthesia; PCA = patient-controlled analgesia; VAS = visual analog scale (range, 0–100 mm, with 100 mm being the maximum imaginable pain).

Secondary Outcomes

By using Bonferroni correction, the significance level was adjusted to 0.05/13 (secondary outcomes) = 0.0038. Similarly, the significance level for post hoc pairwise comparisons was adjusted to 0.0038/4 (group comparisons) = 0.00096 and rounded to 0.001.

VAS for PLP Intensity at 10 Days and 1 Month. Ten days and 1 month after amputation, VAS PLP scores and differences among groups are presented in table 3 (P = 0.002 and P = 0.008, respectively). Detailed results, comparing intervention groups with the control group, are presented in table 5 and figure 2A. For the Epi/Epi/Epi group, P = 0.004 at 10 days and P = 0.005 at 1 month; for the PCA/Epi/Epi group, P = 0.039 at 10 days and P = 0.026 at 1 month; for the PCA/GA/PCA group, P = 0.017 at 10 days and P = 0.041 at 1 month; and for the Epi/Epi/PCA group, P = 0.349 at 10 days and P = 0.209 at 1 month.

MPQ for PLP Intensity. Differences among groups for all three MPQ scales (i.e., PRIR, NWC, and PPI) are presented in table 4, and differences between the four intervention groups versus the control group are presented in table 5. Based on the PRIR, at 10 days, P = 0.001 for the Epi/Epi/Epi group, P = 0.021 for the PCA/Epi/Epi group, and P = 0.002 for the PCA/GA/PCA group. At 1 month, P = 0.001 for the Epi/Epi/Epi group, P = 0.011 for the PCA/Epi/Epi group, and P = 0.006 for the PCA/GA/PCA group (fig. 2B). Results were generally similar when other MPQ variables (i.e., NWC and PPI) were analyzed. These results are presented in detail in table 5 and graphically in figure 2, C and D.

PLP Frequency. The PLP frequency differed significantly among groups at the 10-day and 6-month follow-up (P = 0.001 and P < 0.001, respectively; table 4). Differences between groups are presented in table 5 and figure 2E. At 10 days, P = 0.001 for the Epi/Epi/Epi group, P = 0.024 for the PCA/Epi/Epi group, P = 0.023 for the PCA/Epi/PCA group, and P = 0.003 for the PCA/GA/PCA group. At 1 month, P = 0.005 for the Epi/Epi/Epi group and P = 0.006 for the PCA/Epi/Epi group. At 6 months, P = 0.001 for the Epi/Epi/Epi and PCA/Epi/Epi groups, P = 0.015 for the PCA/Epi/PCA group, and P = 0.003 for the PCA/GA/PCA group.

Other Outcomes

Perioperative Pain Intensity and Frequency. All patients had severe ischemic pain before analgesia started, but pain

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scores improved markedly and were significantly lower in all intervention groups compared with control at all times while the protocol was in effect (\(P \leq 0.001\) for VAS, PRIR, NWC, and PPI; tables 3 and 4). The VAS and MPQ scores suggest that perioperative epidural analgesia and intravenous fentanyl PCA were both effective in alleviating perioperative ischemic pain, PLP, and RLP (tables 3 and 4). Pain frequency differed significantly among groups 24 h after the protocol started (\(P = 0.004\), table 4).

**PLP Prevalence.** The prevalence of PLP differed significantly between groups 1 and 6 months after amputation (\(P = 0.024\) and \(P = 0.004\), respectively; table 3). The PLP prevalence was highest (75% at 1 and 6 months) in the control group and lowest in the Epi/Epi/Epi group (23% at 1 month and 7.7% at 6 months; \(P = 0.009\) and \(P = 0.001\), respectively, vs. the control group).

**Residual Limb Pain.** While the analgesic protocol was in effect, postoperative VAS and MPQ RLP scores were significantly lower (\(P < 0.05\) at 24 and 48 h) in the intervention groups versus the control group. No significant differences were detected among groups regarding RLP 1 and 6 months after amputation (\(P = 0.22\) and \(P = 0.34\), respectively).

**Adverse Events.** Analgesia-related adverse events included nausea (24%) and vomiting (17.5%), although all patients received antiemetic prophylaxis (intravenous ondansetron, 4 mg, 2–4 times daily). Other adverse events were drowsiness (15.7%), motor deficits (13.8%), dizziness (12%), pruritus (10.6%), constipation (8.7%), and mild hypotension (7.7%). Because most patients had a Foley catheter, urinary retention was not a problem. Motor deficits, whenever present, were temporary and clinically not significant. There were no cases of respiratory depression.

**Discussion.** Our results suggest that rigorous perioperative analgesia reduces PLP prevalence, intensity, and frequency after elective lower-limb amputation. Our findings differ from those of Nikolajsen et al., who conducted a well-designed, randomized, controlled trial of 60 patients, in that the prevalence and severity of phantom pain are markedly lower in our study. At the 6-month follow-up, the median prevalence of PLP in patients with perioperative epidural analgesia was 82% in the study of Nikolajsen et al. compared with 29.4% in patients who received rigorous perioperative analgesia in our study (all groups except the control group). Similarly, the median intensity of PLP (VAS pain score) at 6 months was 19 mm in the study of Nikolajsen et al. compared with 0 mm in our intervention groups. However, the duration of preoperative analgesia was significantly shorter in the study of Nikolajsen et al., and this difference may explain the reported lack of benefit. In contrast, the randomized controlled trial by Bach et al.31 used epidural analgesia for 3 days before...
Table 4. PLP Evaluated with the McGill Pain Questionnaire (PRIR–NWC–PPI) and PLP Frequency

<table>
<thead>
<tr>
<th>Variable</th>
<th>Time*</th>
<th>Epi/Epi/ Epi</th>
<th>PCA/Epi/ Epi</th>
<th>PCA/Epi/ PCA</th>
<th>PCA/GA/ PCA</th>
<th>Control</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRIR</td>
<td>0 h</td>
<td>24 (9–55)</td>
<td>27 (7–55)</td>
<td>30 (18–52)</td>
<td>20 (10–32)</td>
<td>20 (3–45)</td>
<td>0.067</td>
</tr>
<tr>
<td></td>
<td>24 h</td>
<td>0 (0–9)</td>
<td>5 (0–9)</td>
<td>6 (0–24)</td>
<td>3 (0–8)</td>
<td>15 (0–44)</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>10 d‡</td>
<td>0 (0–19)</td>
<td>8.5 (0–13)</td>
<td>12 (0–20)</td>
<td>0 (0–12)</td>
<td>18 (0–38)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>1 mo‡</td>
<td>0 (0–12)</td>
<td>4 (0–12)</td>
<td>9 (0–12)</td>
<td>5.5 (0–11)</td>
<td>10 (0–18)</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>6 mo§</td>
<td>0 (0–7)</td>
<td>0 (0–9)</td>
<td>6 (0–11)</td>
<td>0 (0–9)</td>
<td>7 (0–15)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>NWC</td>
<td>0 h</td>
<td>9 (6–11)</td>
<td>9.5 (2–12)</td>
<td>10.5 (6–13)</td>
<td>7 (5–11)</td>
<td>8 (6–14)</td>
<td>0.097</td>
</tr>
<tr>
<td></td>
<td>24 h</td>
<td>0 (0–4)</td>
<td>3 (0–5)</td>
<td>2.5 (0–10)</td>
<td>2 (0–4)</td>
<td>6 (1–4)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>10 d‡</td>
<td>0 (0–7)</td>
<td>3 (0–12)</td>
<td>4 (0–10)</td>
<td>0 (0–5)</td>
<td>4 (0–15)</td>
<td>NS (0.005)</td>
</tr>
<tr>
<td></td>
<td>1 mo‡</td>
<td>0 (0–6)</td>
<td>2 (0–6)</td>
<td>4 (0–10)</td>
<td>2 (0–6)</td>
<td>5 (0–7)</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>6 mo‡</td>
<td>0 (0–5)</td>
<td>0 (0–4)</td>
<td>3 (0–5)</td>
<td>0 (0–3)</td>
<td>3 (0–7)</td>
<td>0.001</td>
</tr>
<tr>
<td>PPI</td>
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<td>5 (4–5)</td>
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<td>4 (3–5)</td>
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<tr>
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<td>1.5 (0–2)</td>
<td>1 (0–2)</td>
<td>3 (0–5)</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>10 d‡</td>
<td>0 (0–3)</td>
<td>1 (0–3)</td>
<td>2 (0–3)</td>
<td>0 (0–3)</td>
<td>2 (0–4)</td>
<td>NS (0.005)</td>
</tr>
<tr>
<td></td>
<td>1 mo‡</td>
<td>0 (0–2)</td>
<td>1 (0–3)</td>
<td>1 (0–2)</td>
<td>1 (0–2)</td>
<td>2 (0–4)</td>
<td>NS (0.012)</td>
</tr>
<tr>
<td></td>
<td>6 mo‡</td>
<td>0 (0–2)</td>
<td>0 (0–2)</td>
<td>1 (0–2)</td>
<td>0 (0–1)</td>
<td>1 (0–3)</td>
<td>NS (0.004)</td>
</tr>
<tr>
<td>Frequency</td>
<td>0 h</td>
<td>3 (2–3)</td>
<td>2 (2–3)</td>
<td>2 (2–3)</td>
<td>2 (1–3)</td>
<td>2 (2–3)</td>
<td>0.21</td>
</tr>
<tr>
<td></td>
<td>24 h</td>
<td>0 (0–3)</td>
<td>1 (0–2)</td>
<td>2 (0–2)</td>
<td>2 (0–3)</td>
<td>2 (2–3)</td>
<td>0.004</td>
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<tr>
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<td>10 d‡</td>
<td>0 (0–2)</td>
<td>2 (0–2)</td>
<td>2 (0–2)</td>
<td>1 (0–2)</td>
<td>2 (0–3)</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>1 mo‡</td>
<td>0 (0–2)</td>
<td>0 (0–2)</td>
<td>1 (0–2)</td>
<td>1 (0–2)</td>
<td>2 (0–2)</td>
<td>NS (0.018)</td>
</tr>
<tr>
<td></td>
<td>6 mo‡</td>
<td>0 (0–2)</td>
<td>0 (0–1)</td>
<td>1 (0–1)</td>
<td>0 (0–1)</td>
<td>1 (0–2)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Data are given as median (minimum–maximum) unless otherwise indicated.
* 0 h indicates just before the analgesic protocol started; and 24 h, 24 h after the beginning of the analgesic protocol. † Subgroup pain score analysis was conducted with the Kruskal–Wallis test. After Bonferroni correction, P < 0.025 was considered significant for primary study outcomes, whereas P < 0.0038 was considered significant for secondary study outcomes. P values that are no longer significant after Bonferroni correction are indicated by NS. ‡ Time after amputation. Also, secondary study outcome: using Bonferroni correction, α level for significance was adjusted to 0.05/3 primary outcomes = 0.0167. § Primary study outcome: using Bonferroni correction, the α level for significance was adjusted to 0.05/2 primary outcomes = 0.025.

Epi = epidural; GA = general anesthesia; NS = nonsignificant; NWC = number of words chosen (with more words indicating worse pain); PCA = patient-controlled analgesia; PPI = Pain Rating Index (based on two types of numeric values that can be assigned to each word descriptor, with higher scores indicating worse pain).

amputation but included fewer patients compared with our study; the studies by Jahangiri et al.32 and Shug et al.33 were neither randomized nor blinded.

Both perioperative epidural analgesia and intravenous opioid PCA were effective in alleviating ischemic pain, PLP, and RLP in the immediate perioperative period. Although neuropathic pain is generally considered resistant to opioids, other data suggest that opioids may be effective in neuropathic pain (including PLP).21,38,39 Our results are in agreement with these data.

Our data indicate that all interventions affect the primary outcomes (VAS and PRIR pain scores at 6 months) similarly compared with the control group, except for the PCA/Epi/PCA group. The Epi/Epi/Epi analgesic regimen was effective for the prevention of PLP at 6 months regarding both VAS and PRIR phantom pain scores, whereas all intervention groups (except the PCA/Epi/PCA group) were effective for the prevention of PLP at 6 months regarding PRIR pain score. The patients in the Epi/Epi/Epi group had lower pain scores for both primary outcomes compared with all other groups, but the differences between the Epi/Epi/Epi group and the other three intervention groups were not statistically significant. Therefore, based on these results, we conclude that epidural analgesia and intravenous PCA similarly affect phantom pain at 6 months.

A limitation of our trial could be the fewer patients per group compared with the study of Nikolajsen et al.13 We had a similar (somewhat greater) overall number of patients, but our patients were allocated to more groups. Placement of an epidural catheter is an invasive procedure, and its use can be problematic in our study population because of frequent use of antiplatelet or anticoagulation medications. Therefore, we decided to allocate study participants to more groups to investigate the effect of other, less invasive, analgesic methods on PLP prevention.

A second possible limitation could be the fact that control group patients did not have an epidural catheter. However, in an attempt to avoid bias, control group patients had an identical catheter placed subcutaneously in the lumbar area, which delivered NS/S. Furthermore, to reduce the likelihood of bias, each amputation was conducted on a different day and patients were placed in different wards, so that contact between patients (which could allow them to identify different treatments) was minimized.

One week before randomization, patients in the Epi/Epi/Epi and PCA/Epi/PCA groups had significantly higher VAS pain scores compared with those in the PCA/Epi/Epi, PCA/GA/
PCA, and control groups. Furthermore, 1 week before randomization, patients in the control group had significantly lower VAS pain scores compared with all other groups (table 2). Despite these baseline differences, patients in the Epi/Epi/Epi group had significantly lower MPQ-PRIR PLP scores at all times, compared with control group patients (table 5). The facts that control group patients had lower baseline pain scores and Epi/Epi/Epi group patients had higher baseline pain scores could actually underestimate the true effectiveness of the analgesic protocol in the Epi/Epi/Epi group compared with the control group. More important, because severe preamputation pain is associated with PLP development, lower baseline pain scores in the control group could reduce the impact of the analgesic protocol on long-term phantom pain development. Therefore, we believe that these baseline differences could reduce the observed effectiveness of perioperative epidural analgesia by introducing a type II error but could not introduce a type I error in our results.

A challenging question is whether the observed reductions in pain scores at 6-month follow-up are clinically meaningful. At 6-month follow-up, the median VAS pain score was 0 for patients in the Epi/Epi/Epi group and 20 for patients in the control group, whereas the maximum VAS pain score was 20 for patients in the Epi/Epi/Epi group and 58 for patients in the control group. VAS 0, PRIR 0, NWC 0, PPI 0, and Freq 0 = pain scores and frequency just before the analgesic protocol started; 24 and 48 h = 24 and 48 h after the analgesic protocol started; 72 h = 72 h after the analgesic protocol started (and 24 h after amputation); 10 D = 10 days after amputation; 1 and 6 Mo = 1 and 6 months after amputation.

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**Fig. 2.** (A) Visual analog scale (VAS; range, 0–100, with 100 being the maximum imaginable pain) for ischemic pain and phantom limb pain (PLP). (B) McGill Pain Questionnaire (MPQ)—Pain Rating Index (PRIR; based on two types of numeric values that can be assigned to each word descriptor, with higher scores indicating worse pain) for ischemic pain and PLP. (C) MPQ: number of words chosen (NWC), with more words indicating worse pain, for ischemic pain and PLP. (D) MPQ: present pain intensity (PPI), based on an intensity scale of 1–5, with 5 indicating the worst pain, for ischemic pain and PLP. (E) Frequency of ischemic pain and PLP. Epi = epidural; Freq = frequency of PLP on a scale of 0–3 (0 indicates never; 3, continuous pain); GA = general anesthesia; PCA = patient-controlled analgesia; VAS 0, PRIR 0, NWC 0, PPI 0, and Freq 0 = pain scores and frequency just before the analgesic protocol started; 24 and 48 h = 24 and 48 h after the analgesic protocol started; 72 h = 72 h after the analgesic protocol started (and 24 h after amputation); 10 D = 10 days after amputation; 1 and 6 Mo = 1 and 6 months after amputation.
control group. A median VAS pain score of 20 may not be clinically significant, but the differences in maximum pain score between the two groups (Epi/Epi/Epi vs. control) are much greater and are likely clinically significant. At 6-month follow-up, we have a 20-point difference (on a scale of 0–100 mm) in median pain score between the Epi/Epi/Epi and control groups, whereas the maximum pain score in control group patients is almost three times higher (58 vs. 20 mm) compared with Epi/Epi/Epi group patients. Because baseline differences between groups may have introduced type II error in our study, our data suggest that the differences between groups (mainly the Epi/Epi/Epi group vs. the control group) at 6-month follow-up are both statistically and clinically significant.

The observed lack of benefit in the PCA/Epi/PCA group was puzzling, particularly when considering the benefit observed in the PCA/GA/PCA group. Regression analysis, which was conducted in an attempt to evaluate the significance of different components of the analgesic protocol, suggested that postoperative epidural analgesia and GA are independent factors significantly associated with reduced PLP intensity at 6 months. Therefore, the use of GA in the PCA/GA/PCA group may explain the observed benefit regarding PLP at 6 months in this group. However, because this is a small study, and regression analysis was only secondary, further investigation is needed to better assess the impact, if any, of intraoperative anesthetic technique on phantom pain.

The possibility of epidural catheter misplacement could be a flaw. During the analgesic protocol, only one epidural catheter was accidentally pulled (7 h after the analgesic protocol started) and the patient remained in the study and was treated like patients in the control group. All measurements of PLP and RLP intensity and PLP frequency and prevalence were added to the group in which the patient was initially randomized, and data analysis was conducted according to the intention-to-treat protocol.

Control group patients experienced severe perioperative pain. An analgesic regimen to reduce severe pain to at least a mild or moderate level was clearly needed and was demonstrated in the other groups. However, because only patients with severe pain, resistant to usual medical treatment, were recruited for the study, severe pain persisted in control group patients, despite our attempt to control pain as best as possible with conventional medical therapies. The fact that severe ischemic pain and PLP can be difficult to treat with conventional analgesic medications is really the basis of our study. The high perioperative pain scores in the control group raise the concern that analgesic doses and/or frequency was inadequate. However, unfortunately, analgesia, as provided in the control group, was the norm in our hospital and probably in many other hospitals. Furthermore, outside of research protocols, many amputations are performed on “same-day admission” basis, with patients coming directly to surgery without the benefit of any rigorous preoperative analgesia. Our study indicates the important role of perioperative analgesia in decreasing the prevalence and severity of PLP.

In conclusion, our data suggest that optimized perioperative analgesia, using epidural analgesia and/or intravenous PCA, starting 48 h before and continuing for 48 h after lower-limb amputation is associated with reduced PLP intensity, prevalence, and frequency 6 months after amputation. Epidural an-
algesia and intravenous fentanyl PCA are both effective in controlling severe ischemic and/or neuropathic pain in the immediate perioperative period. RLP was not significant in our study population 1 and 6 months after amputation.

References