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REPORTS OF ORIGINAL INVESTIGATIONS

Preoperative opioid consumption increases morphine requirement after leg amputation

La consommation préopératoire d'opiacés augmente les doses requises de morphine après amputation de la jambe

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Abstract

Purpose *The aim of this observational study was to assess the influence of preoperative opioid consumption on postoperative morphine consumption after leg amputation performed under combined regional and general anesthesia.*

Methods *After Institutional Review Board approval, patients scheduled for leg amputation were included in a prospective observational study. A popliteal sciatic nerve catheter was placed preoperatively and 0.75% ropivacaine 20 mL was injected incrementally. Amputation was performed under general anesthesia. Postoperative analgesia included acetaminophen, a continuous infusion of 0.2% ropivacaine at 7 mL · hr^{-1}, and intravenous morphine if the visual analogue scale (VAS) pain score was >3 on a 0–10 scale. Patients were divided post-hoc into two groups according to their preoperative opioid consumption: yes (Preop opioids) or no (No preop opioid).*

Results *Twenty-two patients were included, 12 in the Preop opioids Group and 10 in the No preop opioid Group. The VAS score after catheter insertion and before induction of general anesthesia was zero in both groups. Total postoperative opioid consumption from day 1 to day 3 and daily consumption at day 7 was greater in the Preop opioids Group than in the No preop opioid Group (52 [13–133] mg morphine equivalents vs 0 [0–26] mg; $P = 0.02$) and (10 [8–25] mg vs 0 [0–0] mg; $P = 0.01$), respectively, (median [25–75 interquartile values]).*

Conclusion *Despite the use of regional anesthesia, chronic opioid consumption before leg amputation is associated with increased postoperative morphine consumption and phantom limb pain.*

Résumé

Objectif *Le but de cette étude observationnelle était d'évaluer l'influence de la consommation chronique préopératoire d'opiacés sur la consommation postopératoire de morphine après amputation de la jambe réalisée sous anesthésie locorégionale et générale combinée.*

Méthode *Après accord du comité d'éthique local, des patients devant bénéficier d'une amputation de jambe ont été inclus prospectivement. Un cathéter sciatique poplité était mis en place en préopératoire et de la ropivacaïne 0,75 % 20 mL était injecté en doses fractionnées. L'amputation était réalisée sous anesthésie générale. L'analgésie postopératoire comportait de l'acétaminophène, une perfusion continue de ropivacaïne 0,2 % à 7 mL·hr^{-1} et de la morphine intraveineuse si le score sur une échelle visuelle analogique de 0 à 10 (EVA) était > 3. Les patients ont été divisés a posteriori en deux groupes selon qu'ils étaient*

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traités (groupe Preop opioids) ou non (groupe No preop opioid) par des opiacés en préopératoire.

Résultats *Vingt-deux patients ont été inclus : 12 dans le groupe Preop opioids et 10 dans le groupe No Preop opioid. Le score EVA après l'insertion du cathéter et avant l'induction de l'anesthésie générale était égal à 0 dans les deux groupes. La consommation totale postopératoire d'opiacés du 1er au 3e jour et la consommation quotidienne au 7e jour étaient significativement plus importantes dans le groupe Preop opioids : 52 [13-133] mg équivalents de morphine vs 0 [0-26] mg (P = 0,02) et 10 [8-25] mg vs 0 [0–0] mg (P = 0,01) respectivement (médiane [interquartile 25–75]).*

Conclusion *La consommation chronique d'opiacés avant amputation de la jambe est associée à une augmentation de la consommation postopératoire de morphine et de la douleur de membre fantôme malgré une technique d'anesthésie locorégionale.*

Leg amputation induces complex postoperative pain and neuropathic symptoms such as phantom limb pain. Morphine remains the preferred analgesic for postoperative pain despite adverse effects, such as nausea, vomiting, drowsiness, respiratory depression, and opioid tolerance. In contrast, regional analgesia decreases morphine consumption and adverse effects. In cases of lower limb amputation, an epidural or peripheral nerve catheter inserted into the nerve sheath by the surgeon may reduce postoperative pain and morphine consumption.[1–3] Furthermore, as continuous popliteal sciatic block is effective for postoperative pain management after leg, ankle, or foot surgery,[4] this technique may be indicated in the perioperative management of amputation pain.

Post-amputation pain consists of stump pain and phantom limb pain. The pathophysiology of phantom limb pain is complex.[5] Pre-amputation pain may occur in patients with or without morphine treatment.[6–8] After leg amputation, stump pain is associated with phantom limb pain in 50–80% of amputees.[5] Pre-amputation leg pain,[7,8] like preoperative opioid dependence,[9] is an important risk factor for postoperative pain and morphine consumption. However, no study has evaluated the role of chronic preoperative opioid use on post-amputation pain.

We conducted a prospective study in consecutive patients with peripheral arterial disease scheduled for lower limb amputation. Postoperative balanced analgesia, including continuous popliteal sciatic nerve analgesia with ropivacaine, was used in all patients. The patients were allocated into two groups according to their preoperative opioid consumption. Postoperative morphine consumption and the intensities of postoperative stump pain and phantom limb pain were compared.

Methods

This observational study was approved by our Institutional Review Board. Informed consent was obtained from patients older than 18 yr with peripheral arterial disease who were scheduled for below-knee amputation under general anesthesia during the 18-month inclusion period. Exclusion criteria included post-traumatic or post-infectious amputation; pre-existing sciatica; infection at the sciatic catheter insertion point; coagulation disorder; local anesthetic, morphine, or acetaminophen allergy; and inclusion in another research protocol.

On the day before surgery, daily morphine or fentanyl consumption was recorded as an average per day over the last 2 weeks before amputation, regardless of the reason for analgesic consumption. Opioid consumption was expressed as intravenous (*iv*) morphine equivalents according to the following potency conversion: transdermic fentanyl 25 $\mu g \cdot hr^{-1}$ = morphine 60 mg *po* = morphine 20 mg *iv*. Leg pain intensity at rest was evaluated using a visual analogue scale (VAS) ranging from 0 cm for no pain to 10 cm for the worst imaginable pain.

On the day of amputation, an *iv* cannula was inserted, and patients were monitored with a non-invasive blood pressure device, electrocardiogram, and pulse oximeter. A few hours before general anesthesia, a sciatic nerve catheter was placed in the popliteal fossa.[10] A stimulating catheter (Stimulong®, Pajunk©, Geisingen, Germany) was inserted under sterile conditions using a nerve stimulator. A bolus of 0.75% ropivacaine 20 mL was injected and a disposable pump (Infusor LV7®, Baxter S.A.S., Maurepas, France) with 0.2% ropivacaine was connected to the catheter. The saphenous nerve was not blocked. During the procedure, we noted the time for catheter insertion, the number of attempts, and adverse events: paraesthesiae, vascular puncture, tachycardia, cardiac arrhythmia, pain on injection, and seizures. Sciatic nerve block was considered successful when response to pinprick in the sciatic nerve territory was eliminated and when patients were unable to move their foot.

One hour before induction of general anesthesia, patients were premedicated orally with hydroxyzine 1 $mg \cdot kg^{-1}$, and amoxicillin–clavulanic acid 2 g *iv* was administered. In case of penicillin allergy, patients received clindamycin 600 mg and gentamycin 3 $mg \cdot kg^{-1}$. After preoxygenation, general anesthesia was induced with sufentanil 0.5 $\mu g \cdot kg^{-1}$, ketamine 0.15 $mg \cdot kg^{-1}$, and propofol 2.5 $mg \cdot kg^{-1}$ or etomidate 0.3 $mg \cdot kg^{-1}$. Atracurium 0.5 $mg \cdot kg^{-1}$ was administered to facilitate tracheal intubation, and neuromuscular block was monitored. After tracheal intubation, anesthesia was maintained with sevoflurane in oxygen/air without nitrous oxide. Sufentanil 0.1 $\mu g \cdot kg^{-1}$ was administered if the patient's heart rate increased by more than 20% over the

preoperative value (the day before amputation) for more than 60 sec. For patients who had a transdermic patch of fentanyl, the patch was left in place perioperatively.

Postoperatively, intravenous acetaminophen 1 g was given four times daily. A continuous infusion of 0.2% ropivacaine at 7 mL · hr^{-1} was started in the popliteal sciatic nerve catheter at the end of surgery. In the postanesthesia care unit, intravenous morphine 2 mg every 5 min was administered until the VAS score was <3. On the surgical ward, patients used a patient-controlled analgesia (PCA) device for morphine *iv* administration (bolus 1 mg, lock-out time 10 min, no continuous infusion). If they could not use a PCA device, the patients received sub-cutaneous and oral morphine with an appropriate rescue analgesia protocol.

On the surgical ward, an anesthesiologist, who was aware of the protocol, visited each patient on days 1, 2, and 3 and recorded the following: VAS score for stump pain and phantom limb pain, presence of phantom limb sensation, daily morphine consumption, plasma troponin level, electrocardiogram changes, seizures, nausea or vomiting, sedation, respiratory failure, urinary retention, and antiemetic consumption.

Phantom limb pain was defined as any painful sensation in the missing limb. The following sensations were sought: burning, painful cold, electric shocks, painful tingling, sensation of pins and needles, painful numbness, and itching.[11] If a patient reported one or more of these painful sensations in the missing limb, he/she was considered as having phantom limb pain.

Popliteal sciatic catheters were removed on day 3. On day 7, an anesthesiologist visited the patients and the following parameters and events were noted: scores of stump pain and phantom limb pain, daily morphine consumption, troponin levels, new surgical amputation, cardiac events, local or general sepsis, and death. Patients were followed by surgeons and anesthesiologists, and cardiac events and death were recorded during the first year.

Statistical analysis

Patients were divided into two groups according to chronic preoperative opioid consumption during the 7 days prior to surgery. Patients taking morphine or fentanyl preoperatively were allocated to the Preop opioids Group, while patients with no opioid consumption were allocated to the No preop opioid Group. The primary endpoint was to assess the influence of chronic preoperative opioid consumption (>7 days before surgery) on total postoperative morphine consumption until postoperative day 3. The secondary endpoint was to assess the influence of preoperative opioid consumption on morphine consumption at postoperative day 7. Variables in both groups were compared with a Mann–Whitney test for quantitative data and with a Fisher exact test for qualitative data. Statistical analysis was performed with SAS® software (SAS Institute, Cary, NC, USA). Results are expressed as mean ± SD or median (25–75 interquartile range). A P value <0.05 was considered as indicating statistically significant differences.

Results

From July 2005 to November 2006, 30 patients were scheduled for leg amputation. Twenty-two patients agreed to participate and were included in the study: 12 patients in the Preop opioids Group and 10 patients in the No preop opioid Group. One patient from each group did not complete the trial until day 7. Patient characteristics are presented in Table 1. No significant difference was noted except for preoperative opioid consumption. Patients with preoperative opioids had been treated for at least 1 week with opioids before amputation. All patients received acetaminophen as analgesic treatment.

All continuous sciatic nerve blocks were successful. Mean time for catheter insertion was 15 ± 8 min and all catheters were inserted after one attempt. In the No preop opioid Group, there was one vascular puncture and one patient complained about pain during injection without any clinical complication. Before induction of general anesthesia, median VAS score was 0 in both groups.

Intraoperative consumption of sufentanil was significantly higher in the Preop opioids Group than in the No

Table 1 Patient characteristics

	Preoperative opioids	
	No (n = 10)	Yes (n = 12)
Age (yr)	68 ± 12	70 ± 10
Gender: male/female	9/1	10/2
Amputation level		
Leg (below knee)	7	10
Transmetatarsus	3	2
BMI (kg · m^{-2})	22.2 ± 4.5	23.7 ± 3.4
ASA class 2/3/4	1/7/2	2/10/0
Creatinine clearance (mL · min^{-1})	67 ± 47	66 ± 40
Diabetes mellitus	7	8
Preoperative VAS score (0–10 scale)	2 (0–4)	7 (4–8)
Daily morphine equivalent dose (mg · day^{-1})	0 (0–0)	27 (12–58)

Patients were divided into two groups according to chronic preoperative opioid consumption. Data are expressed as mean ± SD, median (25–75 interquartile range) or number. Creatinine clearance was calculated by the Cockroft and Gault formula

ASA American Society of Anesthesiologists, *BMI* body mass index, *VAS* visual analogue scale

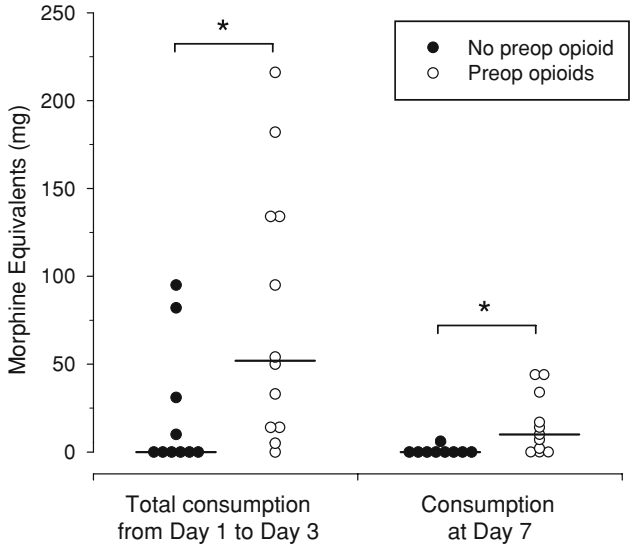

Fig. 1 Total postoperative consumption of morphine equivalents from day 1 to day 3 and daily consumption at day 7. Each point represents a patient. Plain circles = no preoperative opioid; empty circles = preoperative opioids. Horizontal bars represent median values. * $P < 0.05$ between groups

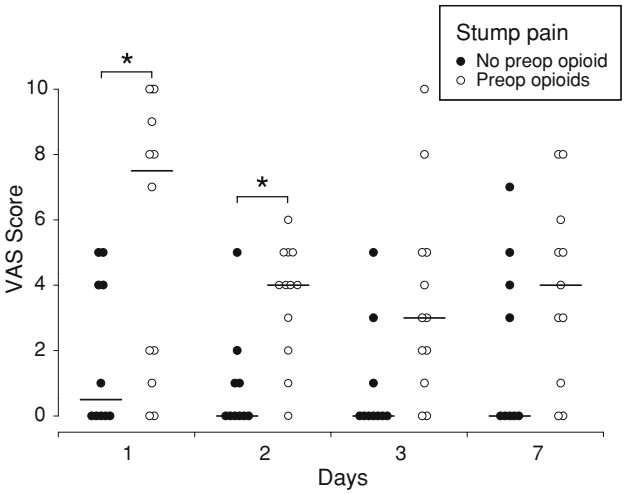

Fig. 2 Visual analogue scale (VAS) score for stump pain at days 1, 2, 3, and 7. Each point represents a patient. Plain circles = no preoperative opioid; empty circles = preoperative opioids. Horizontal bars represent median values. * $P < 0.05$ between groups

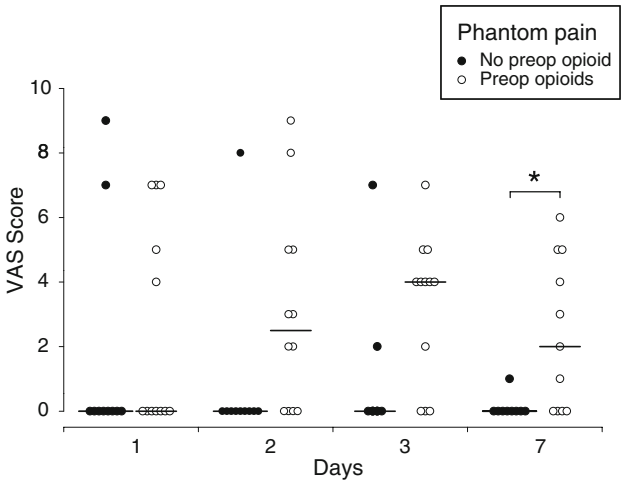

Fig. 3 Visual analogue scale (VAS) score for phantom limb pain at days 1, 2, 3, and 7. Each point represents a patient. Plain circles = no preoperative opioid; empty circles = preoperative opioids. Horizontal bars represent median values. * $P < 0.05$ between groups

preop opioid Group (0.71 ± 0.61 *vs* 0.37 ± 0.27 μg · $kg^{-1} \cdot hr^{-1}$; $P = 0.03$). The Preop opioids Group required more morphine equivalents from postoperative day 1 to day 3 (52 [13–133] mg) than the No preop opioid Group (0 [0–26] mg) ($P = 0.02$). Also, morphine equivalent consumption on day 7 was significantly greater in the Preop opioids Group than in the No preop opioid Group (10 [8–25] mg *vs* 0 [0–0] mg; $P = 0.01$). Individual data are shown in Fig. 1.

Incidence of phantom limb pain from day 1 to day 3 was not significantly different between groups: Preop opioids Group, 67%, 71%, and 88% on day 1, 2, and 3, respectively; No preop opioid Group, 33, 60, and 56%, on day 1, 2, and 3, respectively (NS). The VAS score for stump pain was significantly greater in the Preop opioids Group on days 1 and 2 (Fig. 2). The VAS score for phantom limb pain was significantly greater in Preop opioids Group on day 7 (Fig. 3).

Popliteal sciatic nerve catheters were maintained 62 ± 20 hr in the No preop opioid Group and 56 ± 23 hr in the Preop opioids Group (NS). No local or systemic signs of clinical infection were noted.

On day 1, one patient in the No preop opioid Group presented a respiratory depression with oxygen saturation <92% treated by oxygen; another patient had acute urinary retention and another experienced vomiting. On days 2 and 3, no complications were noted. On day 1, one patient in each group presented an increase in troponin level without any electrocardiographic modification. Troponin levels were normal on days 2 and 3. No coronary cardiac event occurred during the 1-year survey period, even though one patient presented a myocardial infarction less than 1 month before amputation. On day 7, one patient in the Preop opioids Group died because of cerebral ischemia. Three patients in the No preop opioid Group and one in the Preop opioids Group had a local infection at the stump wound. No patient needed a new surgical procedure.

Discussion

This study shows that postoperative morphine consumption is greater in patients with chronic preoperative opioid consumption despite effective analgesia with a continuous popliteal sciatic nerve block placed before limb amputation.

Patients with peripheral vascular disease experience pain before surgery and consume analgesics chronically. Daily morphine consumption is often high, with a median of 27 mg per day in our study, and 40 mg per day in another study.[7] In such patients, preoperative pain has been described as a risk factor for postoperative pain and phantom limb pain after leg amputation.[6,12] Epidural analgesia performed the day before surgery has been suggested to decrease pain before amputation. Nikolajsen *et al.* randomized patients into two groups: epidural bupivacaine and morphine group, or epidural saline and oral or intramuscular morphine group.[7] The study started 18 hr before surgery and treatment was continued for 6-day postoperatively. On day 7, median daily morphine consumption was not significantly different between the groups, but all patients in that study took opioids chronically before the operation.

In our hospital, patients were transferred to the surgical ward the day before amputation, thus we could scarcely influence their preoperative analgesic treatment. Opioid treatment was not initiated systematically before surgery despite preoperative pain in many patients. We thus defined No preop opioid and Preop opioids groups according to preoperative opioids (morphine or fentanyl) consumption or not. Patients in the Preop opioids Group were on opioids for at least 1 week. We expressed opioid consumption as equivalent *iv* morphine doses; however, equivalent potency conversion of opioids remains empirical and applies to patients on stable doses of opioids.

Patients with preoperative opioid treatment suffered from phantom limb pain at postoperative day 7. Phantom limb pain is a neuropathic pain with a central element probably not fully prevented by regional analgesia in the preoperative period,[7,13,14] whereas thoracic epidural analgesia decreases neuropathic pain until 6 months after thoracotomy.[15–17] For leg amputation, regional anesthesia techniques, such as epidural anesthesia or peripheral nerve catheters, were not found efficacious in entirely preventing phantom limb pain or in decreasing postoperative morphine consumption on day 7, or at 1 and 6 months.[1,2,7,18–23] In these studies, patients experienced pain for days or months before amputation, and central sensitization and cortical plasticity, which had developed over a long period before amputation, were probably also involved.[24,25] For these reasons, prolonged analgesia with ropivacaine in the vicinity of the sciatic nerve could not prevent chronic postoperative pain or phantom limb pain in the case of amputation.[26] A major concern for medical staff is to treat preoperative pain adequately and to block central sensitization as much as possible. There could be an indication to perform regional analgesia several days before surgery. Unfortunately, for patients with peripheral vascular disease, the decision to amputate is not made in most cases until the day before or even the same day as the amputation. Therefore, a true pre-emptive treatment is difficult to initiate.[27] According to the theory of central sensitization and cortical plasticity, phantom limb pain is associated with chronic pre-amputation pain.[24] Prevention of phantom limb pain would require effective preoperative analgesia to counteract central sensitization. Opioid treatment could itself lead to sensitization,[28] and multimodal analgesia, including regional anesthesia, deserves to be investigated further. In our study, we used ketamine during general anesthesia in all patients. Ketamine at low dose acts as an antagonist of *N*-methyl-D-aspartate (NMDA) receptors with anti-hyperalgesic properties.[29] We did not use nitrous oxide, which also could have counteracted central sensitization. For elderly vascular patients scheduled for painful surgery, a regional analgesia technique with popliteal sciatic nerve catheter was performed systematically. After orthopedic surgery, continuous infusions of local anesthetics to block the sciatic nerve offer the benefits of prolonged analgesia with fewer side effects, greater patient satisfaction, and faster recovery than morphine.[30–32]

In our study, patients were elderly (>65 yr old), 15 had diabetes mellitus, and 3 needed hemodialysis. They were at risk of postoperative coronary events[27,33] or local complications after regional analgesia (nervous, muscular, septic). The cardiovascular complications noted in our study are similar to those reported by Subramaniam *et al.*, who classified leg amputation as a surgical procedure with intermediate cardiovascular risk.[33]

There are some biases and limits in our study, for example, the lack of blinding. Most of the patients knew the amount of morphine they were taking before surgery, and the investigators were aware of this information. Some patients were deemed unfit for PCA, which probably influenced the postoperative morphine administered. This is one of the difficulties of studies that include elderly patients. In further studies, it would be an important point to define a single means of administering morphine for all patients.

In conclusion, after leg amputation in patients with sciatic nerve catheter, total postoperative morphine consumption until day 3 and daily morphine consumption on day 7 were significantly higher in patients with chronic preoperative opioid consumption. For patients with a history of morphine consumption, the analgesic protocol could probably be improved by initiating regional analgesia for a longer period before surgery, but further studies are warranted to confirm this hypothesis.

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Conflicts of interest None declared.

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