J Anesth (2009) 23:11–18
DOI 10.1007/s00540-008-0700-9

Journal of
Anesthesia

Perineural morphine in patients with chronic ischemic lower extremity pain: efficacy and long-term results

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Abstract
Purpose. To compare the efficacy, safety, and impact on daily activity of peripherally administered morphine plus a local anesthetic with that of a local anesthetic alone in patients with chronic ischemic lower extremity pain.
Methods. Fifty patients with lower extremity ischemic pain due to peripheral vascular disease who had undergone surgical sympathectomy and who were not responding to systemic analgesics were included. Study treatments were bupivacaine plus morphine or bupivacaine alone administered via popliteal catheter. Each patient received both study treatments consecutively, with a washout period, in a double-blind fashion. The effects of treatments on pain severity (numerical rating scale), duration of analgesia, and daily activity were evaluated. Then, patients were asked to state which one of the treatments they preferred for the long term, during which catheter outcomes were evaluated.
Results. Both treatments provided significant pain control compared to baseline at all time points, both at rest and during activity. However, the combination treatment provided superior pain control at 8 and 12 h, and longer analgesia duration (12 ± 2 h vs 9 ± 1 h; $P < 0.001$). During the long term, treatments were similar in terms of analgesia. The combination treatment had a higher incidence of side effects (30% vs 0%; $P < 0.001$).
Conclusion. A peripherally administered bupivacaine plus morphine combination provided better and longer analgesia for ischemic pain compared to bupivacaine alone for the short term, but not for the long term. On the other hand, our results show that continuous popliteal treatment is an effective, safe, and comfortable modality for long-term use in the home setting for patients with intractable chronic pain.

Key words Perineural morphine · Bupivacaine · Lower extremity pain · Ischemic pain

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Received: June 18, 2008 / Accepted: September 27, 2008

Introduction

Recent interest has focused on the role of opioid receptors in nociception, because their activation can inhibit pain directly at its origin without unwanted central side effects. Peripheral opioid receptors are now known to be synthesized in the dorsal root ganglion (DRG) and transported intraaxonally to the peripheral sensory nerve endings [1–3]. The demonstration of opioid receptors in the peripheral nervous system offers the possibility of providing analgesia not only during the postoperative period but also for chronic pain [4].

Previous studies have shown that perineural opioids on top of local anesthetics prolong postoperative analgesia and that this kind of analgesia is mediated by peripheral opioid receptors [5–9]. These peripheral analgesic effects of opioids are predominant under inflammatory conditions [10–12]. Local inflammatory processes can be a signal for the intraaxonal transport of specific receptors for opioids to the nerve endings in inflamed tissue [13]. Nevertheless, relatively few studies have examined the effects of locally administered opioid agonists in chronic pain [14]. Peripheral vascular disease (PVD) is a good example of chronic pain due to inflammation under ischemic conditions [15]. Therefore, the peripheral administration of opioid agonists may theoretically inhibit ischemic pain in PVD.

A continuous popliteal sciatic nerve bock with a perineural infusion of local anesthetic has been shown to provide multiple benefits after moderately painful orthopedic procedures on the foot, including decreases in pain, opioid use, opioid-related adverse effects, and sleep disturbances [16–20]. The use of adjunctive opioids has not been investigated in the setting of popliteal sciatic nerve bock.

This study in patients with chronic ischemic lower extremity pain aimed to compare the efficacy of morphine plus a local anesthetic with that of a local anesthetic alone, both given peripherally for a long term. In

addition, the safety and impact on daily activity of the long-term treatment selected by the patients were evaluated.

Patients, materials, and methods

The present study was conducted at the Pain Clinic of the Anesthesiology Department, Istanbul University Cerrahpasa Medical Faculty. The study was designed as a single-center, double-blind, randomized controlled trial. The study protocol was in accordance with the Declaration of Helsinki and it was approved by the institutional ethics committee. All patients gave their written informed consent prior to study entry.

Patient selection

Fifty patients who were referred to the Pain Clinic from the Cardiovascular Surgery Clinic were included in the study (mean age, 50 ± 14 years). All patients had lower extremity ischemic pain due to Fontaine grade IV PVD, and all had undergone surgical sympathectomy. Following the assessment of pain, patients not responding to systemic analgesic drugs (the third stage on the WHO treatment ladder) were considered to require interventional treatment. For this purpose, popliteal analgesia was administered by a peripheral approach. Patients who were already taking anticoagulants for their peripheral vasculopathy were treated according to the guidelines on anticoagulants and neuraxial block [21]. Exclusion criteria were as follows: uncooperative patients; patients receiving debridement treatment for their ischemic ulcer; and patients with diabetes mellitus, severe bronchopulmonary disease, clotting disorder, hepatic or renal insufficiency, or second- or third-degree cardiac A-V block. In addition, any contraindications for peripheral nerve block, such as patient's refusal, history of recent systemic or local infection at the puncture site, history of central or peripheral neuropathy, or known allergy to local anesthetic and trial drugs were also accepted as reasons for exclusion.

Study design

The primary objective of the present study was to compare the analgesic efficacy of perineural morphine added to local anesthetic with that of perineural local anesthetic alone in the long term in patients with chronic ischemic extremity pain. For this purpose, the study was designed in three phases. The first phase was defined as the time during which the popliteal block procedure and its assessment would be accomplished. The second phase, also called the trial period, was the time interval beginning with the injection of the first study solution and its assessments, continuing with a 24-h washout period, followed by the injection of the second study solution and its assessments. At this point, patients were required to select the most satisfying treatment. The third phase was the long-term phase, beginning with the initiation of the most satisfying treatment which would be continued thereafter. The last phase included a 24-h in-hospital follow-up and a week follow-up after discharge. After the end of the study, the patients were allowed to continue their treatment at home as long as they needed, and weekly follow-ups were scheduled.

In the first study phase, the efficacy of the block and the place of the catheter were assessed while a distal sciatic block procedure was performed. In the trial phase, the efficacy and safety of the study solutions and their effects on daily activities were assessed in a double-blind fashion. In the long-term phase, study outcomes were monitored in a single-blind fashion while the patient was at home.

The secondary study objective was to compare the safety of these treatments and their impact on the daily activities of the patients in the long term.

First phase of the study

Peripheral nerve block procedure

A peripheral intravenous catheter was placed in each patient. Patients were monitored by ECG, pulse oximeter, and blood pressure, and the measurements were recorded at baseline and during peripheral nerve block. Then patients were placed in the prone position for the procedure. An experienced pain physician performed all the blocks. A conventional aseptic procedure was used to insert popliteal block catheters. All popliteal blocks were performed using nerve stimulators (Stimuplex HNS 11; B. Braun Melsungen, Melsungen, Germany) with a posterior approach. After local skin infiltration with 1 ml of 1% lidocaine, insulated short-beveled stimulating needles (Plexolong; Pajunk, Geisingen, Germany) connected to the nerve stimulator were advanced horizontally with a 45° cephalad angle until muscular stimulation was elicited. The intensity of the current, initially set at 2 mA, was gradually decreased to a threshold of 0.4–0.3 mA, while stimulation of the tibial nerve (plantar flexion of either the foot or toes) or common peroneal nerve (dorsal flexion or eversion of either the foot or toes) was maintained and the placement of the needle was considered to be successful. A nonstimulating 20-gauge catheter was then inserted through the needle for 2 to 3 cm. The catheter was secured and covered with a transparent dressing. After negative aspiration for blood, 2 ml of bupivacaine 0.5% was injected initially and after disappearance of muscular twitch, the rest of the local anesthetic solution (total,

30 ml of bupivacaine 0.5%) was injected with gentle aspiration in divided doses.

Assessment of popliteal block

Patients were then placed in the supine position for all assessments. A block was considered successful when sensory block (inability to recognize cold temperatures with an ether-soaked cotton swab on the tip of the dorsal and plantar surfaces of the foot) and motor block (plantar and dorsal flexion) was present 45 min after the injection of bupivacaine. Motor block was evaluated with a three-point scale score: 0, no motor block; 1, partial motor block; 2, complete motor block. The onset of analgesia was determined after diagnostic block. The block was considered as failed if sensory and motor blocks were not noted or when analgesia was absent until 45 min after the first injection. Hemodynamic parameters were also measured during the diagnostic peripheral block. A 20% decrease in basal blood pressure and a 20% decrease in heart rate were accepted as hypotension and bradycardia, respectively. An arterial oxygen saturation (Sp_{O_2}) of 85% or less was defined as respiratory depression.

Second phase of the study (trial phase)

Patients who had a successful block were advanced to the second phase (also called trial phase) when the pain intensity increased again to a score of 4 or more on a numerical rating scale (NRS) after the first phase. They randomly received study treatment 1 solution (bupivacaine) and study treatment 2 solution (bupivacaine plus morphine) from a popliteal catheter consecutively, or vice versa, for one time in a double-blind fashion, with a washout period in between. The randomization was done with respect to the order of administration. Only the coordinating staff had the information regarding the medications throughout all study phases; thus, neither the patient nor the investigator was informed on medications at any time point, so that the double-blind design was never infringed. Study treatment 1 solution contained 0.125% bupivacaine in 20 ml of saline and study treatment 2 solution contained 0.125% bupivacaine + 10 mg morphine in 20 ml of saline.

All patients received each study treatment solution as only a single bolus shot throughout the second phase (trial phase). The trial phase was divided into two periods. The period during which the first study solution after randomization was assessed was called trial period 1 (T1), and the period during which the second solution was assessed was called trial period 2 (T2). Patients who received study treatment 1 solution in T1 were given study treatment 2 solution in T2 or vice versa. There was a 24-h washout period between the two trial periods, considering a carry-over effect. At the end of the washout period, the other study treatment was also administered when the score on the NRS was 4 or more. Rescue analgesia with IV lornoxicam vials 8 mg was also available in case it was required to maintain acceptable pain relief (NRS < 4) throughout the washout period. Lornoxicam is a nonsteroidal anti-inflammatory drug (NSAID) of the oxicam class and has a short plasma half-life of 3–5 h [22]; thus, no residual effect of lornoxicam was considered in T2.

Assessments during trial phase

The efficacy of each study treatment was assessed by resting and active state NRS values and the duration of analgesia. The NRS score was recorded at 60 min and at 8 and 12 h. The duration of analgesia was assessed by the time period during which pain was controlled with an NRS score of less than 4 (first analgesic requirement). Sensory and motor blocks were assessed only at 30 and 60 min. Hemodynamic parameters, Sp_{O_2}, side effects related to the study drug (nausea, vomiting, constipation, pruritus, micturition, somnolence, signs and symptoms of local anesthetic toxicity) were assessed at 30 and 60 min and at 12 h in the second phase of the study. Additionally, daily activities were also questioned at the end of the second phase. Daily activity was measured with a standardized seven-point Likert scale [23,24]. The patient was asked to score daily activity according to the questionnaire illustrated in Table 1. Improvement of daily activity was defined as a score of 6 on the Likert scale.

Third phase of the study (long-term phase)

For their long-term use at home, patients were allowed to choose the most satisfying treatment. Treatments were administered as long-term continuous infusion + bolus via a patient-controlled analgesia (PCA) pump (Abbott; North Chicago, IL, USA). Patients who preferred bupivacaine in the trial phase received bupivacaine 0.125%/5 $ml \cdot h^{-1}$, and those who preferred bupivacaine plus morphine received bupivacaine 0.125% + 1 mg morphine/5 $ml^{-1} \cdot h^{-1}$, again in a double-blind manner. In both groups, the bolus dose was 5 ml, with a lockout time of 20 min. All patients were

Table 1. Likert scale seven-point scoring system: daily activity [23,24]

Score	Percent change	Description
7	≥75% Improvement	Very good
6	≥50% Improvement	Good
5	≥25% Improvement	Fairly good
4	0	Same as before
3	≥25% Worse	Fairly bad
2	≥ 50% Worse	Bad
1	≥75% Worse	Very bad

educated on the usage of the PCA pump. Patients were discharged following 24 h of in-hospital observation after the completion of the study phases. During the first week at home, patients were followed up with phone calls by one of the authors. Assessments were also done at the time of discharge and at the end of the first week at home. Regular weekly follow-up visits were done at the hospital after 7 days. Also, popliteal catheter dressing and filter change were done at this time, and the PCA pump set was replaced and drugs for the next week were prepared again.

Assessments during the long-term phase

The worst and best pain scores, daily activity, PCA bolus demand and consumption, drug- and catheter- and equipment-related problems (catheter site infection, occlusion, dislodgement outside the sheath, withdrawal outside the body, kinking, leakage, and filter related problems) were recorded. Furthermore, the patient's satisfaction with the comfort and convenience aspects of this treatment was assessed on a five-point scale (5, very satisfied; 4, satisfied; 3, neutral; 2, not satisfied; 1, very unsatisfied) and sleep quality was also evaluated. The NRS was also used to assess how pain interfered with sleep (0, "pain does not interfere with sleep" to 10, "pain completely interferes with sleep").

In addition, after a patient terminated the treatment the following parameters were evaluated regarding the use of the popliteal catheter in the home setting: duration of the treatment, catheter duration, catheter number per patient, complications related to the drugs (including physical and psychological addiction) and the catheter, and reasons for terminating popliteal pain treatment.

Statistical analysis

SPSS version 15.0 (SPSS, Chicago, IL, USA) was used for the analyses of data. Unless otherwise stated, data values are expressed as means ± SD. For the comparison of continuous variables of paired samples, Student's *t*-test for paired samples or the Wilcoxon sign test were used, where appropriate; and for the comparison of continuous variables of independent samples, an independent sample *t*-test or the Mann-Whitney *U*-test was used. For the comparison of categorical data, the χ^2 test (independent samples) or McNemar test (paired samples) was used. A P value smaller than 0.05 was considered significant.

Results

A total of 50 patients were recruited. Four patients dropped out of the study at the end of the first period because of inaccurate catheter placement. Forty-six patients were included in the study. Patients preferring bupivacaine or bupivacaine plus morphine for long-term treatment were similar in terms of age, weight, sex, and vascular disease distribution. Patient characteristics are shown in Table 2.

Second-phase outcomes (trial phase results)

Pain control

Both treatments provided significant pain control compared to baseline at all time points, both at rest and during activity. However, bupivacaine plus morphine provided superior pain control over bupivacaine alone at 8 h and 12 h (Table 3). Treatments were similar in terms of pain control at 60 min. Duration of analgesia was longer with the combination treatment (12 ± 2 vs 9 ± 1 h; $P < 0.001$). More patients in the bupivacaine group used rescue analgesics compared to those in the bupivacaine plus morphine group (65% vs 13%; $P < 0.001$; Table 4).

Hemodynamic and respiratory parameters

The combination treatment resulted in a significant decrease in heart rate and mean arterial pressure at 8 and 12 h, compared to baseline and bupivacaine alone. The treatments did not have any effect on Sp_{O_2}.

Side effects

The incidence of side effects was higher with the combination treatment compared to bupivacaine alone (30% vs 0%; $P < 0.001$; Table 4). Somnolence and nausea were the side effects seen in patients receiving the combination treatment.

Table 2. Patient characteristics

	Overall (n = 46)	Patients preferring bupivacaine alone (n = 32)	Patients preferring combination (n = 14)
Age (years)	50 ± 14	51 ± 14	48 ± 14
Sex (male; %)	67	59	86
Weight (kg)	71 ± 10	71 ± 11	72 ± 8
Type of vascular disease			
Atherosclerotic peripheral vascular disease: n (%)	21 (46)	17 (53)	4 (29)
Buerger's disease: n (%)	25 (54)	15 (47)	10 (71)

Table 3. NRS scores at rest and during activity in the second phase

	Baseline	60 min	8 h	12 h
Resting NRS scores				
Bupivacaine alone	9 ± 1	1 ± 0.2*	3 ± 1.1*	3 ± 0.6*
Combination	9 ± 0.6	1 ± 0.3*	2 ± 0.7*,**	2 ± 0.8*,**
NRS scores during activity				
Bupivacaine alone	9 ± 0.7	2 ± 0.1*	4 ± 1.2*	3 ± 0.6*
Combination	9 ± 0.7	2 ± 0.2*	2 ± 0.5*,**	3 ± 0.6*,**

* $P < 0.0001$ versus baseline; ** $P < 0.0001$ versus bupivacaine alone
NRS, numerical rating scale

Table 4. Comparison of side effects, rescue analgesic need, and treatment preference during phase 2

	Study treatment solution 1 ($n = 46$) Patients $n = 46$ (%)	Study treatment solution 2 ($n = 46$) Patients $n = 46$ (%)	P value
Side effects (nausea)	0	30	<0.001
Rescue analgesic (IV lornoxicam 8 mg)	65	13	<0.001
Patients' preference	70	30	0.008

Treatment preference
Significantly fewer patients preferred the combination treatment for long-term use (30% vs 70%; P = 0.008; Table 4).

Third-phase outcomes (long-term results)

The groups did not differ in terms of the following factors at either 24 h or 7 days: NRS scores at rest or during activity, PCA bolus demand and drug consumption, daily activity, and sleep quality. The side effects related to drugs, catheter, and equipment also did not differ between groups.

Follow-up results after 7 days
The groups did not differ in terms of the following factors: best and worse NRS scores, sleep quality, daily activity, and patient satisfaction. Three patients from the bupivacaine group and two patients from the bupivacaine plus morphine group received more than ten PCA bolus doses due to newly developed foot infection.

When popliteal treatment was evaluated retrospectively, it lasted for a range of 30 to 368 days (mean, 177.3 days). Mean duration of catheter use was 142 days and the number of catheters per patient was 1.24. A total of 57 catheters were used in the 46 patients. Eleven patients required a second catheter (24 %). The incidence of catheter-related complications was as follows: infection in 4 patients (9%; 3, insertion-site infection; 1, deep infection-myositis), occlusion in 7 patients (15%), accidental withdrawal in 2 patients (4%), leakage in 2 patients (4%), and kinking in 1 patient (2%). The only equipment-related side effect was occlusion due to air in the set ($n = 4$; 9%).

Drug-related side effects in the long term were: nausea in four patients (9%), constipation in one patient (2%), and sedation in one patient (2%). All these side effects were seen in patients receiving combination treatment. None of the patients experienced physical or psychological dependence.

Popliteal pain treatment was terminated for the following reasons: (1) 2 patients died (4%) but neither of the deaths could be attributed to the popliteal pain treatment; (2) treatment was no longer needed ($n = 42$; 91%) because of the resolution of pain. The resolution of pain was attributed to amputation in 13 (28%) patients and spontaneous remission of pain in 29 (63%) patients. (3) Lack of cooperation was seen in 2 patients, due to psychiatric disturbances.

Discussion

Our study result showed that morphine plus a local anesthetic provided superior pain control over that of a local anesthetic alone, both given peripherally in patients with chronic ischemic lower extremity pain. However, fewer patients preferred to select the combination treatment for long-term use. Additionally, both treatments chosen by patients were effective, safe, and compatible with daily life in the long-term period.

Opioids have long been known to act exclusively within the central nervous system. However, an increasing number of studies has recently reported the existence of opioid receptors outside the central nervous system, therefore suggesting that opioids may also be able to produce analgesic effects in the periphery [3]. Such effects are particularly prominent under painful

inflammatory conditions, both in animals and in humans [12,13]. Immune cells containing endogenous opioid peptides accumulate within the inflamed tissue. Environmental stimuli (e.g., stress), as well as releasing agents (e.g., corticotropin-releasing factor, cytokines) can liberate these opioid peptides from leukocytes (leukocyte-derived opioids). At the same time, the inflammation of peripheral tissues leads to increased synthesis in the DRG and to the axonal transport of opioid receptors toward the peripheral sensory nerve endings, resulting in opioid receptor upregulation and enhanced G-protein coupling at peripheral sensory nerve terminals. On the other hand, disruption of the perineural barrier due to inflammation facilitates the access of opioid agonists to their receptors [25]. All these events lead to the enhanced analgesic efficacy of opioids at their peripheral receptors during inflammation [3,26].

In peripheral vascular disease (PVD), decreased tissue oxygen levels due to insufficient circulation result in the modification of the Ca^{+2} signal in smooth muscles, leading to the production of proinflammatory cytokines [15]. Therefore, the peripheral administration of opioid agonists may, theoretically, inhibit the chronic pain of inflammation under ischemic conditions in PVD. Locally administered opioids have been shown to elicit effective analgesic effects in various acute and chronic clinical pain syndromes, including burn pain [27], inflammatory pain [28], osteoarthritis [7], and rheumatoid arthritis [29], as well as after dental [11], urinary bladder [30], and knee surgery [31], too. In the present study we used morphine as an adjunct to bupivacaine through a popliteal catheter in chronic pain due to PVD, based on the interaction between opioids and inflammatory conditions and also based on clinical trials as mentioned above. Accordingly, we preferred to give morphine peripherally as an adjunct to bupivacaine, not systemically. Our primary aim was to compare the long-term effects of peripheral nerve block with bupivacaine with and without morphine. Thus, we did not need to have a study arm receiving the same dose of systemic morphine. This is also a limitation of the present study. According to our results, the morphine and bupivacaine combination treatment provided superior pain control over treatment with bupivacaine alone at 8 h and 12 h ($P < 0.0001$) and also prolonged the duration of analgesia ($P < 0.001$), but with central side effects (nausea 30% vs 0%). Interestingly, relatively fewer patients preferred the combination treatment for long-term use (30% vs 70%; $P = 0.008$). Although the addition of morphine to bupivacaine perineurally may offer an advantage in terms of quality and duration of analgesia, inability to avoid central side effects may be considered as a disadvantage in the short term. The morphine dose used in the present study (10 mg) may be held responsible for the opioid-related central side effects This central effect of morphine may be attributed to its analgesic effects too. Nevertheless, side effects were not so frequent during the long-term treatments in patients who preferred the combination (nausea, 9 %). This may be attributed to both the continuous administration of opioid and the development of tolerance to the side effects. On the other hand, considering the similar NRS results, daily activity scores (Likert scale >6), and patient satisfaction observed during the long term, together with more side effects in the combination group, it seems that the addition of opioid may not offer an advantage in the long term.

The use of continuous peripheral nerve block for outpatient ambulatory surgery is a growing trend worldwide [32] and has also been reported to have good results in the inpatient setting after surgery [33,34]. Additionally, the use of continuous infusion for pain control after discharge is quite new [18,35] and raises questions about patient acceptance and safety [36]. Sciatic nerve block in the popliteal fossa has been shown to be an effective analgesic technique of limited duration after foot and ankle surgery after the patient is discharged from hospital [16,18,35,37,38]. Although these studies included at-home administration of catheter treatments, they covered relatively short postoperative periods. In our study, long-term treatments were administered to patients with distal lower extremity chronic ischemic pain due to PVD, through a popliteal catheter, using a patient-controlled regional analgesia (PCRA) method with a mean treatment duration of 177 days. During the long-term treatment at home, the results with the selected study solutions—selected as the most satisfying treatment by the patient—did not differ in terms of NRS scores at rest or during activity, patient satisfaction, sleep quality, and daily activity, as compared to the initial 24 h of the long-term treatment. This result was associated with the treatment modality, i.e., treatments were given as continuous infusion + bolus by a PCA pump method during the long term, including the first 24 h. In other studies, PCRA was shown to be effective and safe in the home setting after surgery [35]. Similarly, the present study also found that PCRA was effective, safe, and comfortable for months in patients with chronic ischemic lower extremity pain, representing a quite long-term period for such a technique. Maintenance of daily activities in both groups in our study was particularly notable. Popliteal fossa block enables walking because of its preservation of hamstring function and sensation to the posterior thigh, facilitating ambulation [39,40].

In the present study, external electronic programmable pumps were used, rather than the elastomeric pumps that have been used frequently during recent years, as elastomeric pumps are not available with a

bolus dose option in our country. In addition, electronic pumps are refillable and less expensive than disposable elastometric pumps. Electronic pumps are also found to be better in terms of accuracy, consistency, and reliability [41,42]. We did not observe any electronic programmable pump-related problems when the pumps were used at home. Although electronic programmable pumps are larger and less easy to carry, none of our patients complained about this problem.

Long-term observations in our study revealed that problems were usually related to the catheter rather than the PCA device or medication. The most common catheter-related complication was occlusion (15% per catheter). In the present study, the renewal rate for catheters, for varying causes, was 23%. Although this can be considered a high rate, the mean 142 days' duration of externalized catheter is remarkable. Nitescu et al. [43] used continuous infusion of opioid and bupivacaine via externalized intrathecal catheters in refractory nonmalignant pain for a long-term period. In their trial, the median duration of intrathecal treatment was 60 days (range, 3–1706 days), with a cumulative total of 14 686 days, of which 7460 days (50%) were spent at home.

Infection and colonization from an indwelling foreign body (catheter) is another potential but serious complication. The relatively few reports of this complication suggest that the incidence is low [44]. Capdevila et al. [45] conducted a large prospective multicenter trial examining continuous peripheral nerve blocks after orthopedic surgery, with a focus on neurological and infectious adverse events. Using a nonrandomized design, they followed 1416 patients in the postanesthesia care unit for up to 5 days; and they found that catheters routinely become colonized (29%), but only 3% had local inflammatory signs (focal pain, redness, and induration). Due to the regular wound care carried out in our study, we did not observe a high rate of infection (7% per catheter; 9% per patient), infection being the most unwanted complication of an external system. Brief hospital visits for wound care or for replenishing treatment solutions are a disadvantage of an external system.

A high rate of amputation has been reported in patients with PVD (20%) [46]. In our series, 28% of patients underwent a below-knee or metatarsal amputation for nonhealing foot wounds. Data on the contribution of popliteal local anesthesia to the spontaneous remission of pain due to the reduction of ischemia, and data on its contribution to the rate of postamputation pain are lacking in our study; and this issue should be further studied.

On of the concerns regarding the use of opioids in chronic pain is the possibility of addiction and tolerance [47]. Our patients receiving long-term combination treatment did not develop psychological addiction; interestingly, no tolerance or physical addiction (a pharmacological effect of opioids) was seen. The additional opioid requirement of two patients in the combination group using PCA bolus may be attributed to an increase in pain due to infection.

In conclusion, in PVD, a peripherally administered bupivacaine and morphine combination provided better and longer analgesia compared to bupivacaine alone. However, the addition of morphine did not result in any benefit during the long term. On the other hand, our results have demonstrated that continuous popliteal treatment is an effective, safe, and comfortable modality for long-term use in the home setting for patients with intractable chronic ischemic extremity pain, and this treatment may be considered as a potentially convenient modality for such patients.

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