 

# *Analgesic Effects of Intravenous Lidocaine and Morphine on Postamputation Pain*

## *A Randomized Double-blind, Active placebo-controlled, Crossover Trial*

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***Background:*** **Phantom and stump pains, common sequelae of limb amputations, are significant impediments to rehabilitation of amputees. The pathophysiology and optimal treatment of postamputation pain states are unclear. While stump pain may result from neuromas in the stump, phantom pain is thought to be related to cortical reorganization. The authors hypothesized that morphine and lidocaine may have differential effectiveness on stump and phantom pains.**

***Methods:*** **The authors conducted a randomized double-blind, active-placebo-controlled, crossover trial to compare the analgesic effects of intravenous morphine and lidocaine on postamputation stump and phantom pains. An intravenous bolus followed by an intravenous infusion of morphine (0.05 mg/kg bolus + 0.2 mg/kg infusion over 40 min), lidocaine (1 mg/kg bolus + 4 mg/kg infusion) and the active placebo, diphenhydramine (10 mg bolus + 40 mg infusion), were performed on three consecutive days. Phantom and stump pain ratings and sedation scores were recorded at 5-min intervals using a 0–100 visual analog scale. Pain measures were initiated 30 min before drug infusion and continued until 30 min after the end of infusion. Subjects' self-reported pain relief and satisfaction were assessed at the end of each infusion.**

***Results:*** **Thirty-one of 32 subjects enrolled completed the study. Eleven subjects had both stump and phantom pains, 11 and 9 subjects had stump and phantom pain alone, respectively. Baseline pain scores were similar in the three drug groups. Compared with placebo, morphine reduced both stump and phantom pains significantly ($P < 0.01$). In contrast, lidocaine decreased stump ($P < 0.01$), but not phantom pain. The changes in sedation scores for morphine and lidocaine were not significantly different from placebo. Compared with placebo, self-reported stump pain relief was significantly greater for lidocaine ($P < 0.05$) and morphine ($P < 0.01$), while phantom pain relief was greater only for morphine ($P < 0.01$). Satisfaction scores were significantly higher for lidocaine (mean ± SD: 39.3 ± 37.8, $P < 0.01$) and morphine (45.9 ± 35.5, $P < 0.01$) when compared with placebo (9.6 ± 21.0).**

***Conclusions:*** **Stump pain was diminished both by morphine and lidocaine, while phantom pain was diminished only by morphine, suggesting that the mechanisms and pharmacological sensitivity of stump and phantom pains are different.**

PHANTOM limb and stump pains are widely recognized sequelae of limb amputation that often result in significant reduction in patients' quality of life.[1–5] The prevalence of both phantom limb and stump pains in amputees has been estimated at approximately 50–80%.[2] Although phantom and stump pains are often discussed as independent entities, recent data indicate that they may be interrelated.[2] The pathophysiology of phantom limb and stump pains is not fully understood; however, both peripheral and central mechanisms have been thought to contribute to the pain states.[4] Peripheral mechanisms include ectopic neural activity originating from afferent fibers in a neuroma and spontaneous activity in dorsal root ganglion neurons resulting from activation of tetrodotoxin-resistant (TTX-R) sodium channel subtypes (*e.g.*, PN3/SNS and NaN/SNS2) that are expressed in injured neurons.[6,7] Central mechanisms that may generate and maintain postamputation pain states include cortical reorganization and spinal cord sensitization.[4,8,9]

Although numerous therapeutic approaches have been used to treat postamputation pain states, the long-term effectiveness of these approaches has been less than satisfactory. Many pharmacologic agents have been used in an uncontrolled fashion in an attempt to control postamputation pain. Opioid analgesics and local anesthetics are two classes of pharmacologic agents that have been commonly used for the treatment of phantom limb and stump pains. The role of opioids in the management of nonmalignant pain states has been intensely debated, but recent controlled trials indicate a beneficial effect of opioids on certain neuropathic states, such as postherpetic neuralgia and nonmalignant neuropathic pain.[10,11] In addition, local anesthetics may diminish postamputation pain by binding to sodium channels and attenuating peripheral ectopic neural activity.[12]

Both opioids and local anesthetics may be used to treat postamputation pain states; however, it is not clear whether one class of agents is preferentially more effective on stump or phantom pains. We performed a randomized double-blind, active-placebo-controlled, crossover trial of intravenous morphine *versus* lidocaine to determine the efficacy of each agent on postamputation stump and phantom pains.

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Received from the Department of Anesthesiology and Critical Care Medicine, and the Department of Neurology, The Johns Hopkins University School of Medicine, Baltimore, Maryland. Submitted for publication June 25, 2001. Accepted for publication November 12, 2001. Supported by grant No. NIH P01 HD 33990 Bethesda, Maryland; and grant No. NIH/NCRR MO1 RR00052 from the Johns Hopkins University School of Medicine, General Clinical Research Center, Baltimore, Maryland. Presented in part at the American Pain Society National Meeting, Atlanta, Georgia, November 3, 2000.

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## Methods

*Study Population*

The protocol was approved by our institutional human subjects review board. The enrollment period began on October 6, 1997 and lasted until February 28, 2001. Inclusion criteria were: age >18 but < 85 yr; presence of persistent postamputation pain for >6 months after amputation of an extremity or portion thereof. Exclusion criteria included: age <18 or >85 yr; history of allergic reaction to any study drug; cardiac conduction defects (second degree or complete heart block), or myocardial infarction within 3 months of enrollment; severe pulmonary disease; current history of alcohol or substance abuse; presence of seizures, dementia, or encephalopathy; pregnancy or breast feeding; chronic hepatic disease or hepatic failure; hematologic disease associated with leukopenia or thrombocytopenia; and any terminal illness with a life expectancy of <6 months. Baseline assessment included a detailed medical history and physical examination. Stump pain was defined as ongoing or stimulus-evoked pain localized to the region of the stump. Phantom pain was defined as pain experienced in the missing part of the limb subsequent to an amputation.

*Study Design*

We used a randomized, double-blind, active-placebo-controlled, crossover design. Informed consent and baseline laboratory data (electrocardiogram) were obtained, and a physical examination was performed. Before the administration of any test drug, all subjects were gradually titrated off any opioids, benzodiazepines, antiepileptic drugs, mexiletine, baclofen, or neuroleptic drugs prescribed for pain such that there was a 2 week period where none of these medications were taken by the patients. However, they were allowed to take acetaminophen or nonsteroidal antiinflammatory agents as needed during this period.

Subjects were admitted for a series of three intravenous infusions of test drugs administered in a randomized, double-blind fashion. Before the start of the test, a standardized set of directions was read to the patient to minimize the placebo effect. An intravenous catheter was inserted in an unaffected limb. The subject maintained a supine position throughout the infusion period, and hemodynamic parameters (heart rate, oxygen saturation, respiratory rate, blood pressure, and electrocardiography) were continuously monitored. Subjects rated their ongoing stump pain and phantom pain, and sedation level on a visual analog scale (VAS) using a computer program developed in the authors' laboratory. A physician was present throughout the infusion period to assess and treat any adverse effects of the infusion.

Each morning (3 days total), the infusion consisted of an initial bolus dose followed by a continuous infusion. After a 30-min baseline period, one of 3 solutions (1 mg/kg of lidocaine, 0.05 mg/kg of morphine, or 10 mg of diphenhydramine) was administered as an intravenous bolus over 2 min, followed by an infusion (4 mg/kg of lidocaine, 0.2 mg/kg of morphine, or 40 mg of diphenhydramine) over 40 min. The maximum infusion dose was 400 mg of lidocaine and 25 mg of morphine. The rate of infusion was decreased if cardiovascular or respiratory depression, central nervous system excitation, or excessive sedation were observed during the drug administration.

The sequence of these infusions was balanced to minimize order effects. The infusions were administered each morning (3 days total), and the interval between the infusions was at least 24 h to minimize carry-over effects. Blood for drug assay was obtained from the patient at the end of the infusion period to determine if therapeutic lidocaine and morphine levels were achieved.

*Randomization and Blinding*

Subjects were randomized to one of six possible combinations of placebo (P), lidocaine (L), morphine (M): L-M-P; L-P-M; M-L-P; M-P-L; P-M-L; and P-L-M. The subjects were randomized in balanced blocks of 12 so that there would be an equal number of subjects who would receive lidocaine, morphine, or placebo as the first drug treatment.

Drugs were prepared by a pharmacist in a way that allowed for administration of an equal volume for each of the three study medications. All study medications were identical in appearance. During the infusion, the investigator administering the study medication was blinded from the outcome assessment (pain and sedation), and the subject and research coordinators were blinded to the exact timing of study medication administration.

*Outcome Measures*

Phantom and stump pain ratings and sedation scores were recorded at 5-min intervals using a computerized 0–100 visual analog scale (VAS). These measures were initiated 30 min before drug infusion, continued throughout the drug infusion period, and continued for 30 min after completion of the infusion. Subjective pain relief scores for both stump and phantom pains were also assessed at the end of each infusion by asking the subject to rate the pain relief on a 0–100% numeric scale. Subjects' overall satisfaction with the treatment was rated at the end of each infusion on a 0–100% numeric scale.

*Statistical Analysis*

The sample size was based on pilot data and a standard biostatistical formula[13]: $n = (z)^2/(\Delta)^2$, where $\Delta$ is fixed by using the formula: $|\mu - \mu 0|/\sigma$. $\Delta$ was estimated to be $11/22 = 0.5$, and the sample size was estimated to be:

$(1.96 + 0.84)^2/(0.5)^2 \approx 32$ patients ($\alpha = 0.05$, two-tailed; $\beta = 0.20$, one-tailed). This sample size allowed us to determine a 20% change in pain from baseline values. Pain and sedation scores were analyzed using two-way repeated measures analysis of variance (ANOVA). Between-group comparisons of pain and sedation scores were then performed using paired *t* tests. Pain relief, verbally reported by patients for the three medications, was analyzed using one-way ANOVA. Bonferroni multiple comparisons test was used to conduct *post hoc* analysis.

As a separate measure of drug effects, the number needed to treat (NNT)[14] was obtained for lidocaine and morphine. In recent reviews on drugs used for neuropathic pain, NNT has been used as a clinically relevant measure to quantify treatment effects.[15,16] It is defined as the number of subjects that are required to be treated to obtain one patient with the desired outcome. Analysis was based on the number of subjects in each drug group who obtained at least 30% pain reduction during the infusions. Statistical analysis was performed using Stata 6.0 software (Stata Corporation; College Station, Texas). $P < 0.05$ was considered statistically significant.

## Results

Thirty-two eligible subjects were enrolled in the protocol. Of the subjects who were enrolled, one dropped out from the study because of absence of pain before the initiation of the infusion. Of the remaining 31 subjects, 11 subjects had stump pain alone, 9 had phantom pain alone, and 11 had both stump and phantom pains. Data could not be collected on four infusion days because of technical difficulties with intravenous access (n = 2) and because of the cancellation of the infusion as a result of nausea and vomiting from the previous day's infusion (n = 2). Demographic data obtained at the time of enrollment in the study are shown in table 1.

Stump pain was commonly described by the patients as a burning, throbbing, or stabbing sensation. The most common descriptors for phantom pain were burning or crushing. On the days of infusion, pain was rated as mild, moderate, and severe by 25%, 66%, and 9% of the subjects, respectively. Three fourths of the subjects reported use of prosthesis. Physical stress (55%), changes in weather (52%), stump spasm (52%), excessive use of prosthesis (42%), stump problems (39%), back pain (30%), and psychological stress (23%), were some of the factors that altered the level of pain in the subjects.

The effects of study medications on stump and phantom pain scores are shown in figure 1. Compared with placebo, morphine significantly reduced both stump and phantom pains ($P < 0.01$ and $P < 0.001$, respectively). In contrast, lidocaine significantly reduced stump but not phantom pain ($P < 0.01$ and $P > 0.05$, respectively) when compared with placebo. Placebo infusions did not result in significant reduction in phantom or stump pains.

**Table 1. Demographic Profile of Study Subjects**

| | |
|---|---|
| Age (yr; mean ± SD) | 54 ± 13 |
| Gender (male/female) | 19/12 |
| Ethnicity (Caucasian/African American) | 27/4 |
| Duration of amputation (months; mean ± SD) | 81.0 ± 87.4 |
| Site of amputation (upper/lower limb) | 9/22 |
| Side of amputation (left/right/both) | 14/14/3 |
| Type of pain (phantom only/stump only/both) | 9/11/11 |

(n = 31)

Self-reported stump and phantom pain relief scores and satisfaction scores for the three study medications are shown in table 2. Both lidocaine and morphine infusions provided significantly greater self-reported pain relief when compared with the placebo. There were no differences in self-reported pain relief of stump and phantom pain between the lidocaine and morphine groups. Similarly, satisfaction scores were significantly higher for both lidocaine and morphine when compared with placebo, but were not different between the lidocaine and morphine groups. Significant correlation was observed between pain reduction measures based on VAS and patients' self-reports of pain relief ($P < 0.05$ for lidocaine and $P < 0.01$ for morphine). There were no significant differences between groups with regard to sedation scores (table 3).

The NNT with lidocaine for at least 30% reduction in stump pain was 2.5 (95% confidence interval [CI]: 1.5 to 7.4), while NNT with morphine to obtain similar relief was 2.1 (95% CI: 1.4 to 5.2). For a 30% reduction in phantom pain, the NNT with lidocaine was 3.8 (95% CI: 1.9 to 16.6) and the NNT with morphine was 1.9 (95% CI: 1.3 to 3.7).

Eleven subjects had both stump and phantom pains on the days of infusion. In this subset of subjects, no significant correlation (Pearson correlation coefficient, r = 0.13, $P = 0.49$) between phantom and stump pain scores was found at baseline; however, a significant correlation (r = 0.62, $P < 0.01$) was observed after the infusions, as shown in figure 2. Plotting the relationships between change in phantom and stump pains from baseline, at, and 30 min after the end of infusion suggests that lidocaine may have a significant but transient effect in reducing postamputation pain, unlike morphine, which may be associated with a more persistent analgesia (fig. 3). The mean ± SD plasma lidocaine and morphine levels were 2.1 ± 1.5 μg/ml and 36.2 ± 40.7 ng/ml, respectively.

## Discussion

The treatment of phantom and stump pain has been disappointing, in part, because of the uncertain nature of the mechanisms of postamputation pain and the lack of

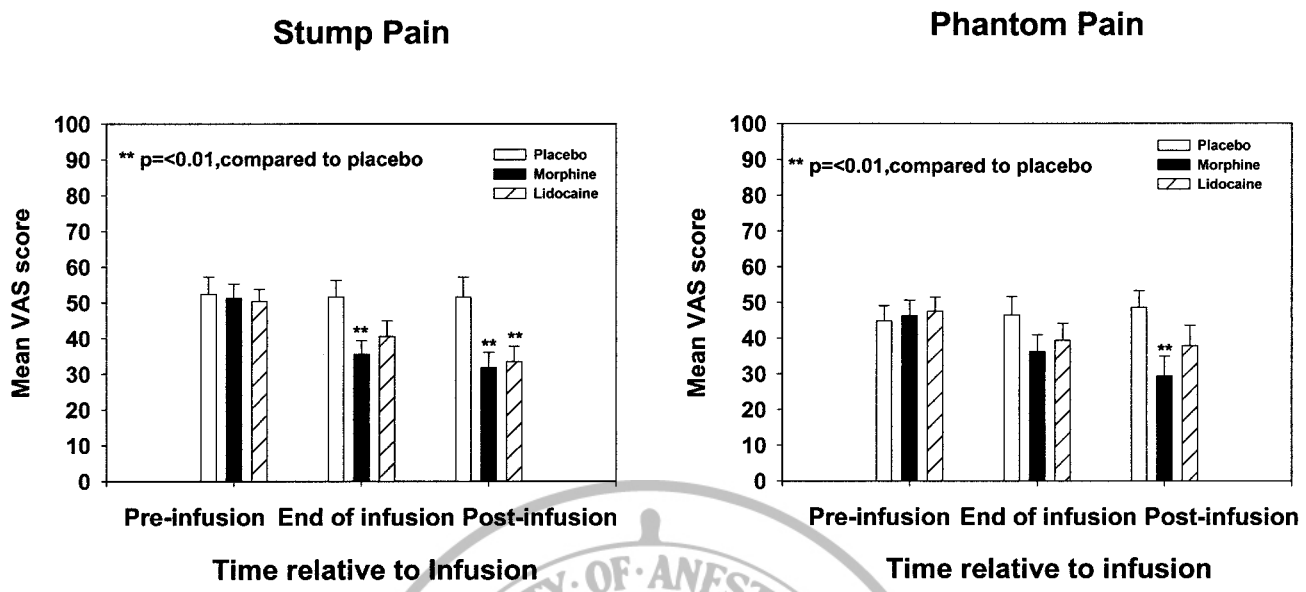


**Fig. 1. Effects of lidocaine, morphine, and placebo on stump and phantom pains. Stump and phantom pains were rated by patients on a visual analog scale (0–100) where 0 = no pain and 100 = worst pain imaginable. Scores were obtained every 5 min beginning 30 min before the infusion and continuing through 30 min after the end of infusion.**

well-controlled clinical studies. We performed a randomized, double-blind, active-placebo-controlled, crossover trial comparing the effect of intravenous morphine and lidocaine on phantom and stump pains. We demonstrated that stump pain was attenuated by both morphine and lidocaine, while phantom pain was attenuated by morphine but not lidocaine. These data suggest that different therapeutic sensitivities of stump and phantom pain to opioids and sodium channel blockers exist, and that the mechanisms of stump and phantom pain may differ.

Two common types of postamputation pain states have been recognized: phantom pain (reported in the missing limb) and stump pain (reported in the residual part of the extremity).[17,18] Although the mechanisms of phantom and stump pains are uncertain, they are considered to be interconnected. Studies have reported a high incidence of concomitant occurrence of both stump and phantom pains.[2,19]

The mechanism of stump pain appears to be primarily peripheral and may include nerve injury and neuroma formation. Animal studies have demonstrated that peripheral nerve injury may lead to spontaneous ectopic discharges from injured axons in the nerve, neuromas, or dorsal root ganglia.[20–22] In addition, more recent evidence suggests that there are several tetrodotoxin-resistant (TTX-R) sodium channels (subtypes; PN3/SNS and NaN/SNS2) that are expressed in injured peripheral neurons and may be involved in the peripheral mechanism of chronic neurogenic pain.[6,7] Sodium channel blockers, such as lidocaine, may attenuate the ectopic activity from these neuromas and hence diminish stump pain.[12] Although the mechanism of ectopic discharge following peripheral nerve injury is currently believed to primarily involve abnormal activation of sodium channels, other mechanisms (*e.g.*, increased sensitivity of $\alpha$-adrenergic receptors) may also exist.[23]

The mechanism of phantom pain is considered to be primarily central, although some studies suggest an important role for input from the periphery in maintaining the altered central state.[24] The central mechanism of phantom pain is most likely the cortical reorganization that occurs as a result of amputation, reflecting the plasticity of the somatosensory cortex.[24,25] Although it is not clear whether cortical reorganization is the result or

**Table 2. Self-reported Outcomes**

| Drug | Stump Pain Relief | Phantom Pain Relief | Satisfaction |
|---|---|---|---|
| Lidocaine | 32.8 ± 33.6† | 25.8 ± 31.2 | 39.3 ± 37.8* |
| Morphine | 44.8 ± 35.4* | 47.9 ± 38.2* | 45.9 ± 35.5* |
| Placebo | 8.2 ± 15.9 | 3.2 ± 10.1 | 9.6 ± 21.0 |

Data expressed as mean ± SD. There were no significant differences between the lidocaine and morphine groups. Subjective self-reported percent pain relief and treatment satisfaction scores were rated on a 0–100% numeric scale. Twenty-two subjects had stump pain and 20 had phantom pain on the day of infusion.

† $P = 0.02$ when compared with placebo; * $P < 0.01$ when compared with placebo.

**Table 3. Visual Analog Scale Sedation Scores**

| Drug | Preinfusion | End of Infusion | 30 min after End of Infusion |
|---|---|---|---|
| Lidocaine | 23.5 ± 27.3 | 25.1 ± 30.3 | 29.5 ± 31.8 |
| Morphine | 16.1 ± 24.4 | 18.3 ± 25.0 | 22.7 ± 29.0 |
| Placebo | 20.4 ± 29.0 | 28.5 ± 34.6 | 30.1 ± 36.3 |

Data are expressed as mean ± SD. Sedation was assessed using a computed 0–100 visual analog scale. No significant differences were observed between the groups.

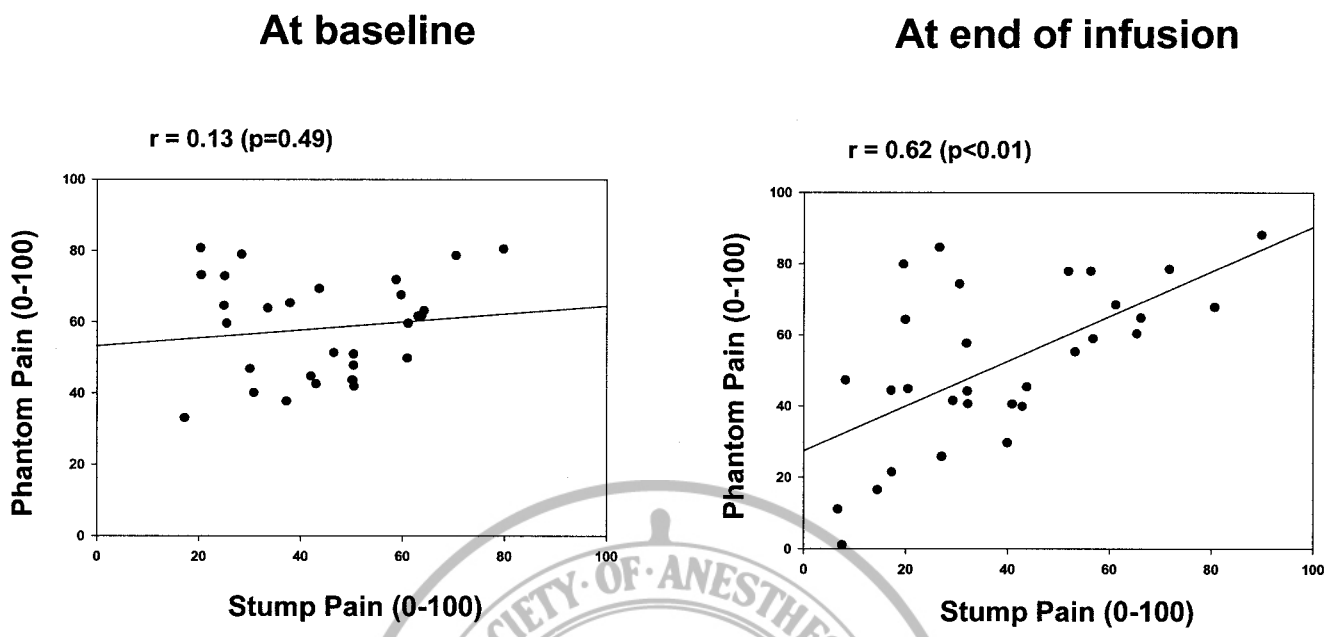


**Fig. 2. Correlation of visual analog scale scores of phantom and stump pains at baseline and at the end of infusion. A subset of eleven patients had concomitant stump and phantom pains. In these patients, stump and phantom pain scores rated on the visual analog scale (0–100) correlated well at the end of infusion but not at baseline.**

the cause of phantom pain, the topographic representation of the lost extremity may be taken over by sensory input from other areas of the body, resulting in perceptual remapping.[8,26] The extent of cortical reorganization may correlate with the intensity of phantom limb pain.[25] Although the mechanisms of cortical reorganization are not clear, long-term potentiation of synapses mediated by *N*-methyl-D-aspartate (NMDA) receptors or reduction of inhibitory neurotransmitters (*e.g.*, GABA) may be implicated.[8] Another possible central mechanism of phantom pain is the NMDA receptor-mediated sensitization of dorsal horn neurons in the spinal cord which results in spontaneous neuronal activity, increased response to afferent input and expansion of peripheral receptive fields.[4] Peripheral input from stump pain (neuroma and nerve injury) may potentially contribute to the maintenance of centrally-mediated pain.[4,9] Hence, despite the fact that stump and phantom pains may have different underlying mechanisms, the two entities may be interdependent. It is possible that continued peripheral activity of stump pain may maintain the central hyperexcitable state of phantom pain.

The therapeutic modalities currently being used clinically for the treatment of postamputation pain syndromes are far from being satisfactory, with success rates rarely exceeding placebo response rates.[26,27] Many therapies have been used empirically, and there are methodological concerns (*e.g.*, small sample sizes, heterogeneous populations, lack of blinding, lack of controls, and short follow-up periods) with published studies that currently make it difficult to determine whether opioids or local anesthetics would be effective for neuropathic pain states such as postamputation pain.

Neuropathic pain has been traditionally viewed as being resistant to the analgesic effects of opioids, although the route of opioid delivery may affect efficacy.[28] Although the exact mechanisms for such apparent ineffectiveness have not been clearly delineated, some cellular phenomena involved in neuropathic pain are implicated in the development of tolerance to morphine.[29] Peripheral axotomy has been shown to result in a reorganization and temporary down-regulation of opioid receptors in the dorsal horn of the spinal cord, which may lead to a decreased effectiveness of opioids in relieving postamputation pain.[30–32] Certainly, there are various reasons (*e.g.*, use of multiple definitions of neuropathic pain, different animal and human models of neuropathic pain, methodological issues in available studies, different methods of pain assessment, and inconsistent duration of follow-up) that have contributed to this controversy.[20]

The use and efficacy of opioids in treating neuropathic pain syndromes, including postamputation pain, remain controversial, although it appears that opioids may be beneficial in treating some types of neuropathic pain.[33] Our data indicate that opioids would be effective in diminishing both stump and phantom pain. Despite the fact that some animal and clinical studies suggest that opioids may have a poor analgesic effect on neuropathic pain,[30,34] there are other data that corroborate our findings and show that neuropathic pain can be successfully treated with opioid therapy.[32,35,36] A randomized, double-blind, active-placebo-controlled, crossover trial demonstrated that intravenous fentanyl was effective in re-

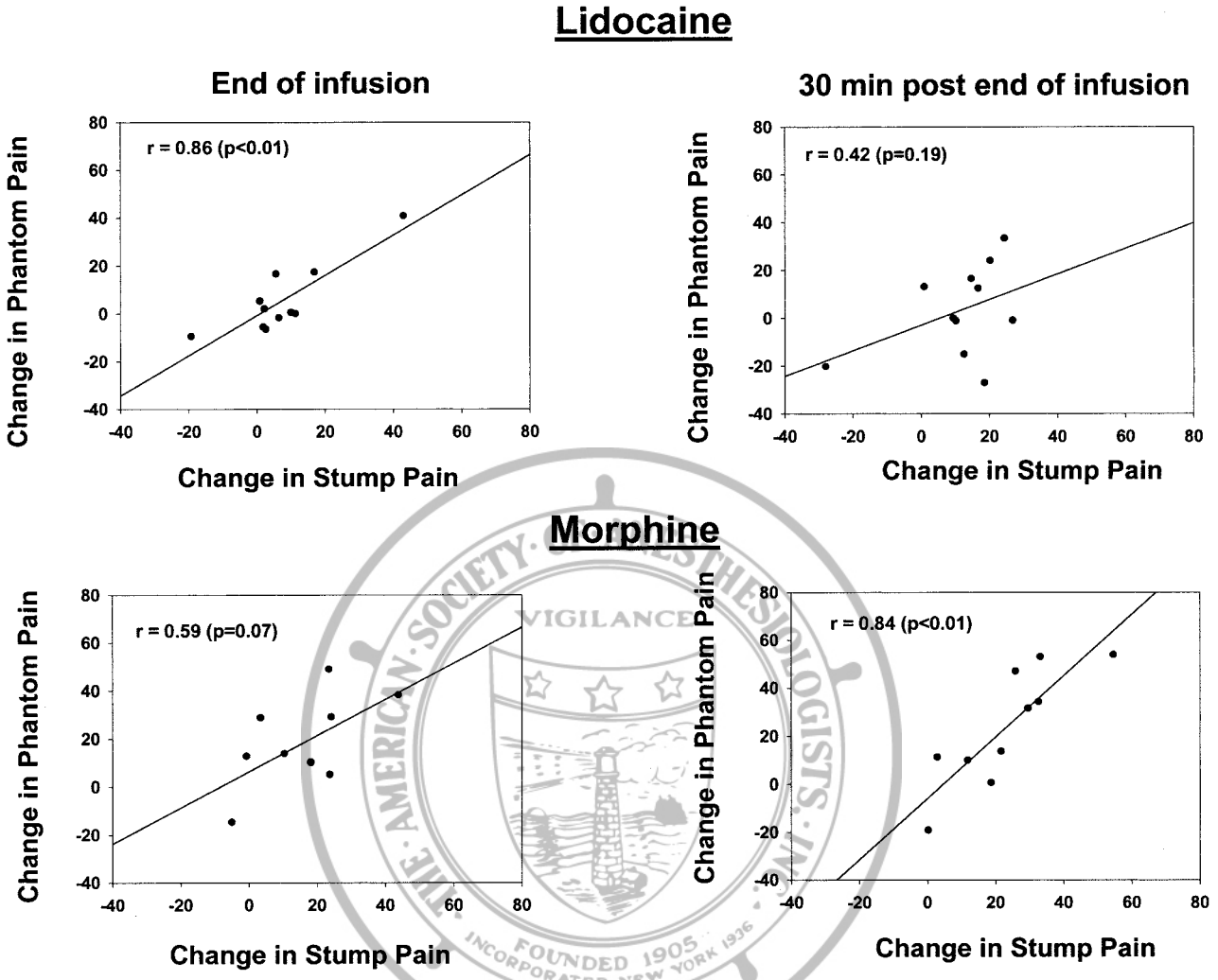


**Fig. 3. Correlation of change in phantom and stump pains at the end of infusion and 30 min later with lidocaine and morphine. In the subset of patients with both stump and phantom pains, correlation was observed between the change in visual analog scale scores of stump and phantom pains. The correlation was short-lived with lidocaine but sustained until 30 min postinfusion with morphine.**

lieving neuropathic pain and that this was not the result of any sedative or mood-altering effect of the fentanyl.[11] Other randomized, double-blind, controlled trials have also suggested that intravenous opioids may diminish neuropathic pain.[37,38] In addition, oral administration of opioids has been shown to be effective in diminishing neuropathic pain (*e.g.*, postherpetic neuralgia).[10]

Although our study was not designed to distinguish between central and peripheral mechanisms, our observations that lidocaine may be more effective in relieving stump than phantom pain suggests that phantom pain may have a predominant central mechanism. If there were a significant peripheral contribution into maintenance of phantom pain, we would have expected that there would be a reduction in both stump and phantom pains with lidocaine infusion; however, this was not the case. Presumably, the sodium channel binding property of lidocaine is an important mechanism of action in decreasing ectopic neural activity peripherally and hence reducing stump pain.[12] Intravenous lidocaine infusion has been used to treat various types of neuropathic pain, and prolonged relief of neuropathic pain after systemic local anesthetic administration has been reported.[35,39,40] Despite the fact that our data do not suggest and that of others do not demonstrate a benefit of local anesthetics in relieving central pain,[38,41] there are some data to suggest that local anesthetics may reduce spontaneous and evoked spinal (central) neuronal activity.[42–44]

Under physiologic circumstances, activity in central pain signaling neurons is influenced by input from peripheral nociceptors. The lack of correlation at baseline between stump pain, considered to be predominantly peripherally mediated, and phantom pain in the subset of patients who had both types of pain suggests alterations in central pain modulatory mechanisms after amputations. A reduction in pain by lidocaine and morphine is associated with a change in the relationship

between stump and phantom pains so that the two pain states are positively correlated. In keeping with the pharmacokinetics of lidocaine and morphine, the change in the relation between stump and phantom pains is short-lived with lidocaine, but longer lasting with morphine. These observations need to be verified with additional studies with larger sample sizes.

There are possible limitations of our study. With the crossover design of our study, patients may have had carry-over effects of study medications from one infusion to the next. Although carry-over effects are possible, baseline scores for pain and sedation did not differ significantly between the 3 days of infusion, and with the relatively short duration of action of study medications, it is unlikely that the carry-over effect was significant. Use of an active placebo has been recommended to prevent unmasking of the double-blind design, and diphenhydramine is a good active placebo as it has no analgesic properties and mimics the side effects of the other test drugs.[32,45] Despite the fact that intravenous lidocaine therapy has been used to treat neuropathic pain (such as postamputation pain), there are a number of controversial issues regarding the systemic use of lidocaine for neuropathic pain, including the effective dose range, predictive value, identification of the specific symptoms relieved, and dosage, duration, and endpoint of a positive lidocaine test.[11] Resolution of these problems is important, since successful treatment of neuropathic pain with intravenous lidocaine infusion may predict subsequent efficacy of oral congeners such as mexiletine.[12,46] The results of our intravenous infusions do not allow for conclusions regarding long-term opioid or local anesthetic therapy for the treatment of postamputation pain; however, we are currently undertaking such a study.

In conclusion, this randomized, double blind, active-placebo-controlled, crossover trial demonstrates that stump pain was diminished both by morphine and lidocaine, while phantom pain was diminished only by morphine. Our observations suggest that the mechanisms and pharmacological sensitivity of phantom and stump pains differ. Stump pain may be predominantly peripherally mediated *via* a mechanism involving sodium channels, while phantom pain may involve both peripheral and central mechanisms. Despite the observed efficacy, the drugs tested did not eliminate pain completely, suggesting that these patients may require multimodal therapy. Future analgesic studies in this area might include comparing other treatments (*e.g.*, neuraxial opioids, anticonvulsant, and antidepressants) to the currently tested drugs.

The authors thank The Perioperative Clinical Investigation Unit (Department of Anesthesiology and Critical Care Medicine, The Johns Hopkins University, Baltimore, Maryland) for their assistance in statistical analysis.

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