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Local Administration of Morphine for Analgesia after Iliac Bone Graft Harvest

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Background: **Harvesting autogenous bone grafts from the ilium may cause considerable pain and may represent a significant source of postoperative morbidity. The local application of morphine can reduce pain in a rat model of bone damage. We evaluated the analgesic efficacy of administering morphine to the donor bone graft site for spinal fusion surgery.**

Methods: **Sixty patients undergoing cervical spinal fusion surgery using autogenous bone harvested from the ilium were randomly assigned to one of three groups: Group 1 was given saline infiltrated into the harvest site, group 2 was given 5 mg intramuscular morphine; group 3 was given 5 mg morphine infiltrated into the harvest site. After surgery, all patients were given morphine through a patient-controlled analgesia pump. Pain scores both from the harvest and the incision sites, as well as morphine use, were recorded at 2, 4, 6, 8, 12, and 24 h after surgery. At 1 yr after surgery the presence and subjective characteristics of donor site pain were recorded.**

Results: **Total 24-h morphine use (milligrams) was significantly lower ($P < 0.0001$) in group 3 (33.7 ± 8.3 mg, mean ± SD), compared with either group 1 (64.3 ± 6.6 mg) or group 2 (59.6 ± 9.3 mg). Pain from the graft site was scored the same at 2 h but remained significantly lower ($P < 0.0001$) for group 3 at all later time intervals. Pain scores from the incision site were similar among the three study groups. One year after surgery, 25% of patients reported having chronic donor site pain. The association of chronic donor site pain was significantly higher ($P < 0.05$) in groups 1 (33%) and 2 (37%) compared with group 3 (5%).**

Conclusion: **Low-dose morphine applied to the harvest graft site can reduce local pain, morphine use, and chronic donor site pain after cervical spine fusion surgery.**

AUTOGENOUS bone grafts from the ilium are frequently harvested for purposes of bone fusion in patients undergoing spinal stabilization surgery. Often, the pain from the donor site can be more severe than from the laminectomy incision.[1–4] Although this pain usually resolves over a period of several weeks, it may persist and represent a significant source of postoperative morbidity.[1–4] In fact, donor site pain has been reported in up to 39% of patients at 3 months, 38% at 6 months, and 19% at 2 yr after bone graft harvesting from the iliac crest.[3–4]

Recently, research has revealed that opiates can act directly on the peripheral terminals of afferent nerves to mediate antinociception.[5] This has led to a growing number of controlled clinical studies examining the analgesic efficacy of locally applied opioids in the management of acute pain. Houghton *et al.*[6] have shown that the local application of a low dose of morphine can effectively reduce nociception in a rat model of bone damage. This analgesic effect was considered to be mediated through μ-opioid receptor action in the bone.

The goal of the current study was to evaluate the analgesic efficacy of low-dose morphine administered to the site of bone graft harvesting in patients undergoing cervical spinal fusion surgery. In addition to short-term analgesic effects, the incidence of chronic donor site pain was evaluated 1 yr after surgery.

Materials and Methods

The protocol was approved by the Institutional Review Board at Baystate Medical Center (Springfield, MA), and written informed consent was obtained from each patient. Sixty adult patients scheduled to undergo elective decompressive cervical laminectomy with spinal fusion using autogenous bone grafts were enrolled in this prospective, randomized, double-blind study. Patients were eligible for participation if they spoke English, they were greater than 18 yr of age, they weighed more than 40 kg, they were American Society of Anesthesiologists physical status I or II, and they could operate a patient-controlled analgesia (PCA) device and had no allergies to morphine.

All surgical procedures were performed using a partial-thickness posterior iliac crest bone graft harvested through a lateral oblique incision just cephalad to the crest. Anesthesia was induced with 2 mg/kg propofol and 5 μg/kg fentanyl and maintained with isoflurane in 70% N_2O in oxygen. After the graft was harvested and hemostasis was achieved, patients were randomly assigned to one of three treatment groups using a computer-generated random number table. Group 1 (control group) was given 10 ml normal saline (NS) infiltrated into the harvest site, and 1 ml NS was administered intramuscularly. Group 2 (intramuscular morphine) was given 10 ml NS infiltrated into the harvest site and 5 mg morphine (1 ml) intramuscularly. Group 3 (donor site

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Table 1. Patient Demographics and Surgical Data

Group No.	Age (yr)	Height (cm)	Gender (M/F)	Weight (kg)	Operative Time (min)
1 (n = 20)	42 ± 8	170 ± 10	12/8	76 ± 15	277 ± 44
2 (n = 20)	44 ± 9	173 ± 10	11/9	74 ± 14	266 ± 45
3 (n = 20)	43 ± 7	170 ± 10	11/9	79 ± 15	272 ± 43

Data are presented as mean ± SD. There were no significant differences between the groups.

morphine) was given 5 mg morphine (10 ml) infiltrated into the harvest site and 1 ml NS intramuscularly. All intramuscular injections were administered in the deltoid muscle at the same time as harvest site infiltration. The study medications were prepared by the pharmacy and administered by the surgeon and anesthesiologist, who were blinded to their contents.

In the recovery room, patients were connected to a PCA pump (Abbott PCA Plus, Abbott Laboratories, North Chicago, IL) containing 1 mg/ml morphine. The initial settings were an incremental dose of 1.5 ml, a lockout interval of 8 min, and a 4-h limit of 30 ml. The incremental dose was increased to 2.0 ml and the 4-h limit was increased to 45 ml if analgesia was inadequate after 1 h. If analgesia was inadequate after an additional hour, the incremental dose was further increased to 2.5 ml. Patients were asked to quantify their pain from both the donor and the laminectomy incision sites on a verbal analog pain scale of 0–10, with 0 representing no pain and 10 the worst imaginable pain. Pain assessments were made by a blinded research nurse observer 2, 4, 6, 8, 12, and 24 h after completion of surgery. In addition, PCA morphine use was recorded at these six time intervals. Analgesic duration was defined as the time from local administration of study drug to the first requirement of PCA morphine.

At 1 yr after surgery, patients were interviewed by telephone by a blinded investigator (Dr. Reuben), and a detailed questionnaire (Appendix) similar to that reported in a previous study on donor site pain[3] was completed. The presence and subjective characteristics of any residual donor site pain, including its quality, severity, and frequency, as well as provoking factors and treatment received, were recorded.

Statistical Analysis

Demographic data, procedure duration, analgesic duration, and doses of morphine required were analyzed by analysis of variance with a Bonferroni–Dunn test for multiple comparisons. Pain scores were analyzed by using the Kruskal–Wallis test. If a significant result was obtained, the Mann–Whitney U test was performed to determine between which groups there was significance; a Bonferroni adjustment was made for multiple comparisons. The presence of chronic pain was compared with the chi-square test. Significance was determined at the level of $P < 0.05$.

Data are presented as mean ± SD. The following assumptions were made for the power analysis performed before the investigation: (1) for 24-h total morphine use, a 33% difference; (2) for pain scores, a 33% difference. With these assumptions, for a power of 90% and an α of 0.05, the pain score comparison required the largest sample size of 18 per group.

Results

There were no significant differences among the three treatment groups with respect to age, gender, height, weight, or duration of surgery (table 1). There were no significant differences in the analgesic duration in groups 1 (44 ± 14 min), 2 (46 ± 15 min), or 3 (42 ± 12 min). There were no significant differences in the interval dose of morphine at 2 h among the three groups (fig. 1). However, patients given morphine at the donor site (group 3) had significantly lower interval dose of morphine use at 4, 6, 8, 12, and 24 h ($P < 0.0001$) (fig. 1). Cumulative 24-h morphine use was significantly lower ($P < 0.0001$) in group 3 (33.7 ± 8.3 mg) compared with either group 1 (64.3 ± 6.6 mg) or group 2 (59.6 ± 9.3 mg). There were no differences in morphine use between groups 1 (control treatment) and 2 (intramuscular morphine) at all time intervals after surgery. Pain scores from the donor site followed a similar pattern (table 2). Patients given local morphine at the donor site had significantly lower verbal analog pain scale scores than groups 1 (control treatment) and 2 (intramuscular morphine) at 4, 6, 8, 12, and 24 h after surgery ($P < 0.001$). Verbal analog pain scale scores at the donor site were similar at 2 h after surgery for all three groups. Pain scores at the laminectomy incision site were similar at all time intervals among the three study groups.

One year after surgery, 56 of 60 patients were contacted by telephone and were queried about donor site pain. Four patients (two in group 1 and one in each of groups 2 and 3) were unable to be contacted by telephone and were not included in data analysis. No postoperative complications were noted in any of the three study groups. Overall, 25% of patients (14 of 56) reported having chronic donor site pain. The association of chronic donor site pain was significantly higher ($P < 0.05$) in groups 1 (33% [6 of 18]) and 2 (37% [7 of 19]) compared with group 3 (5% [1 of 19]). The characteristics of the chronic donor site pain are listed in table

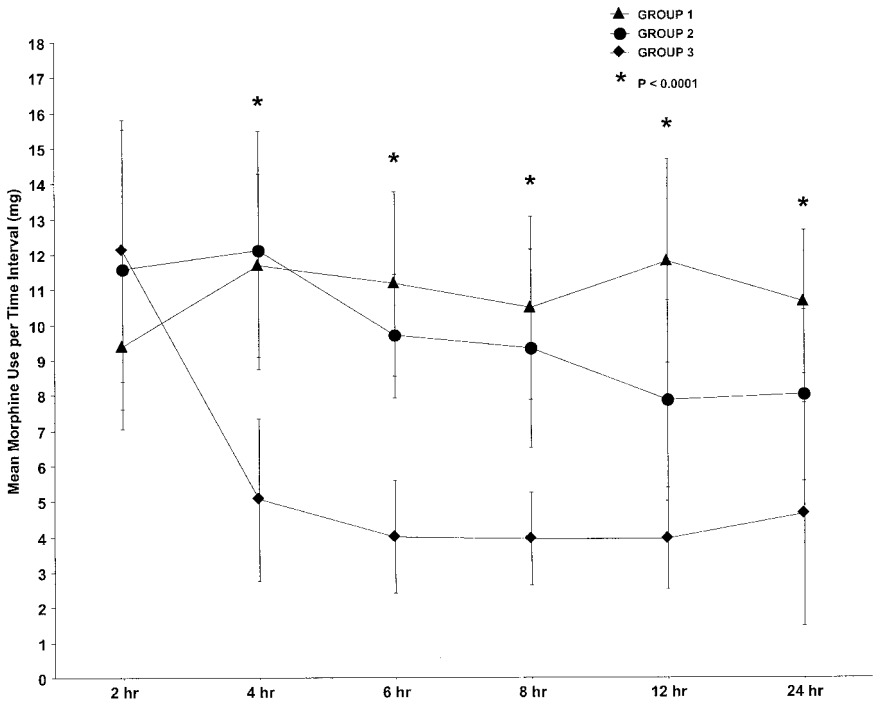

Fig. 1. Interval dose of morphine at each postoperative time interval. There were no significant differences in the interval dose of morphine at 2 h among the three groups. Patients given morphine at the donor site (group 3) had significantly lower interval dose of morphine use at 4, 6, 8, 12, and 24 h. *$P < 0.0001$. There were no differences in morphine use between group 1 (control treatment) and group 2 (intramuscular morphine) at all time intervals after surgery. Values are mean ± SD.

3. Only 5 of the 14 patients with chronic pain were given medical treatment. All five patients were given nonsteroidal antiinflammatory drugs and amitriptyline. Only one patient, who rated his pain as severe, was referred to a pain management center and was treated with nonsteroidal antiinflammatory drugs, amitriptyline, gabapentin, and mexiletine. In addition, he received three local injections of corticosteroids with bupivacaine. At the time of writing, he was still being treated for chronic donor site pain at the Pain Management Center.

Discussion

This study revealed a significant analgesic benefit from the local administration of morphine to the iliac bone graft harvest site in patients undergoing cervical spinal fusion surgery. Patients who were given local administration of morphine at the bone graft harvesting site reported lower pain scores and used less morphine in the 24 h after surgery.

The discovery of peripheral opioid receptors has led to a growing number of controlled clinical studies examining the analgesic efficacy of locally applied opioids in the management of acute pain. These studies have examined the local application of morphine through the intraarticular, interpleural, intraperitoneal, perineural (ankle, axillary, dental), intravenous regional, or intravesical route.[5,7] Although the most consistent results have come from the intraarticular administration of morphine, many of the other alternative routes have revealed equivocal results.

Houghton *et al.*[6] were the first investigators to report the analgesic efficacy of locally administered morphine in the rat model of bone damage. In their study, low

Table 2. Pain Scores for the Six Time Periods*

Group No.	Evaluation No. 1	2†	3†	4†	5†	6†
Pain scores from graft site						
1 (n = 20)	4.7 ± 0.8	4.3 ± 0.9	4.4 ± 0.7	4.4 ± 0.9	4.1 ± 1.1	4.2 ± 0.9
2 (n = 20)	4.8 ± 0.6	4.2 ± 0.6	4.2 ± 0.8	4.1 ± 0.7	4.0 ± 0.7	3.9 ± 0.9
3 (n = 20)	4.5 ± 0.8	2.5 ± 0.5	2.4 ± 0.6	2.3 ± 0.7	2.4 ± 0.8	2.5 ± 1.1
Pain scores from laminectomy site						
1 (n = 20)	3.0 ± 0.7	3.5 ± 0.5	3.6 ± 0.9	3.7 ± 0.9	3.1 ± 0.9	3.0 ± 0.9
2 (n = 20)	3.0 ± 1.0	3.7 ± 0.7	3.4 ± 0.9	3.7 ± 0.8	3.5 ± 0.9	2.9 ± 0.9
3 (n = 20)	3.4 ± 0.5	3.3 ± 0.6	3.3 ± 0.8	3.5 ± 0.9	3.3 ± 0.8	3.0 ± 0.9

Data are presented as mean ± SD. There were no significant differences in laminectomy-site pain scores between the groups.

* The first evaluation period was 2 h after surgery; the subsequent periods were at 4, 6, 8, 12, and 24 h. † $P < 0.001$ for group 3 compared with either group 1 or 2.

Table 3. Chronic Donor-site Pain Characteristics (n = 14)

	N (%)
Quality	
Burning	6 (43)
Aching	5 (36)
Decreased sensation	3 (21)
Hypersensitive	2 (14)
Tingling	1 (7)
Shooting	0
Severity	
Mild	2 (14)
Moderate	11 (79)
Severe	1 (7)
Average pain score (mean ± SD)	4.4 ± 2.4
Frequency	
Sometimes	9 (64)
Often	4 (29)
Constantly	1 (7)
Provoking factors	
Lying on affected side	9 (64)
Local pressure	8 (57)
Activity	6 (43)
Weather	5 (36)
Light touch	1 (7)

doses of morphine were demonstrated to effectively block the development of hyperalgesia and allodynia. This analgesic effect was thought to be mediated by μ-opioid receptors located in the bone because the effect of morphine was blocked by a μ-opioid receptor antagonist injected into the marrow cavity. Further, animals given the same dose of morphine into the systemic circulation (intramuscular or intraperitoneal) failed to demonstrate a reduction in mechanical hyperalgesia and allodynia.

Our study also revealed a significant benefit to the local administration of morphine to bone after surgery. This was evident by a significant reduction in morphine use and pain scores at the harvest site in patients in group 3 (donor site morphine). Furthermore, this analgesic effect appears to be mediated through local opiate receptors because patients given the same dose of morphine parenterally (group 2) failed to demonstrate any significant analgesic effect compared with saline treatment (group 1). The analgesic effect of morphine was not noticeable in the immediate evaluation period (first 2 h) after surgery. This was evident by a similar time to first request for morphine (analgesic duration), as well as similar opioid use and pain scores in the first 2 h after surgery. These characteristics agree with previous studies involving the intraarticular administration of morphine, in which the peripheral analgesic effects were significantly prolonged but delayed in onset between 2 and 4 h.[8,9] To improve analgesia in the immediate postoperative period, investigators have combined bupivacaine along with intraarticular morphine.[9,10] Similarly, we may have provided improved analgesia with the infiltration of bupivacaine along with morphine at the iliac graft site. Previous studies have revealed an early reduction in pain scores with the infiltration of bupivacaine at iliac crest bone graft sites.[11–13] Currently, we are evaluating the analgesic efficacy of infiltrating both bupivacaine and morphine into bone graft sites.

In addition to a significant short-term analgesic benefit, patients who were given local morphine also demonstrated a significant reduction in the incidence of chronic donor site pain. The precise mechanism of donor site pain remains obscure. It has been postulated to be muscular or periosteal in nature secondary to stripping of the abductors from the ilium.[1] In addition, the pain may be neurogenic in origin secondary to sensory nerve injury. One nerve frequently injured while obtaining bone graft from the anterior ilium is the lateral femoral cutaneous nerve, which has been reported in up to 10% of cases.[2] Injury to the ilioinguinal nerve has also been reported, especially when the bone graft is harvested from the anterior ilium.[2] This injury is thought to be neuropraxic in origin as a result of retraction of the iliacus and abdominal wall muscles when exposing the anterior ilium. Injury to the superior cluneal nerves is more common after obtaining bone graft from the posterior ilium.[2] The superior cluneal nerves pierce the lumbodorsal fascia and cross the posterior iliac crest 8 cm lateral to the posterior superior iliac spine.[14] Injury to these nerves may result in transient or permanent numbness, in addition to pain over the buttock area.

The majority of patients in the current study did not develop donor site pain until several months after the operation. This would suggest that the pain was neurogenic in origin secondary to neuroma formation. However, only 5 of 14 patients (21%) with chronic donor site pain reported decreased sensation or numbness. In addition, the pain was frequently aggravated by walking and well localized to the donor site, indicating it to be more muscular or periosteal in origin. It is possible that the chronic donor site pain is multifactorial, resulting from myofascial, periosteal, or nerve injury.

The reason for the observed lower incidence of chronic donor site pain in patients receiving local administration of morphine into the graft site remains unclear. It has been suggested that effective treatment of acute pain, particularly when accompanied by a neuropathic element, prevents the development of chronic pain syndromes.[15,16] This reduction in chronic pain may be attributed to a preemptive analgesic effect in which a reduction in spinal cord hyperexcitability is attained by a prompt reduction in noxious afferent input.[17] Hoard *et al.*[12] revealed a delayed onset of postoperative pain and earlier time to ambulation and return to normal daily activities by infiltrating bupivacaine at the site of iliac crest bone harvesting. The authors attributed this reduction in postoperative morbidity to a preemptive analgesic effect of the local anesthetic. Brull *et al.*[13] demonstrated a significant reduction in the incidence of immediate and residual postoperative pain by perfusing

the iliac crest donor site with bupivacaine for 48 h after spinal fusion surgery. Their study revealed a lower incidence of chronic donor site pain at 6 months after surgery, which was attributed to the early reduction in acute postoperative pain. Although several studies have documented a preemptive analgesic with local anesthetics,[17] few studies have examined a preemptive role of peripheral opioids. Peripheral morphine administration can inhibit the release of proinflammatory neuropeptides in peripheral tissues[5] and has been shown to block the development of hyperalgesia and allodynia after bone damage.[6] The exact duration of this analgesic effect was not reported in this clinical study (Houghton *et al.*[6]). Our study demonstrated a sustained analgesic benefit that lasted throughout the 24-h study period. Perhaps the peripheral administration of morphine in our present study was effective in reducing acute pain for an extended period. It has been shown that the intensity of acute postoperative pain is a significant predictor of chronic pain.[16] If there is a continuum of pain after surgery ranging from acute to chronic,[15] perhaps the enhanced analgesic efficacy of administering peripheral morphine in the immediate postoperative period reduced the incidence of acute postoperative pain, leading to a reduction in the incidence of chronic donor site pain.

The current study provides evidence that the peripheral administration of morphine to the iliac bone graft harvest site can reduce the incidence of both immediate and chronic donor site pain after spinal fusion surgery. This was associated with lower pain scores, decreased 24-h morphine use, and a lower incidence of donor site pain at 1 yr after surgery.

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Appendix: Donor Site Pain Questionnaire

Patient: _____

1. Donor Site Pain?
   Yes _____ No _____
2. When did you first develop your current pain symptoms? _____
3. Complications post-op?
   Infection _____ Dehiscence _____ Other _____
   Treatment _____
4. Describe quality of pain:
   Burning _____ Tingling _____ Aching _____ Shooting _____
   Hypersensitive _____ Decreased sensation _____ Other _____
5. Severity of pain:
   Mild _____ Moderate _____ Severe _____
   Average daily pain score (0–10): _____
   (0 = no pain, 10 = worst imaginable pain)
6. Frequency of pain:
   Sometimes _____ Often _____ Constant _____
7. What brings on the pain?
   Weather _____ Activity _____ Local pressure _____
   Lying on affected side _____ Light touch _____ Other _____
8. Treatment received:
   Yes _____ No _____
   Medications _____ Injections _____ Other _____