

# Evaluation of analgesic effect of local administration of morphine after iliac crest bone graft harvesting: A double blind study

Devinder Singh, K K Gombar<sup>1</sup>, Nidhi Bhatia<sup>2</sup>, Satinder Gombar, Sudhir Garg<sup>3</sup>

Department of Anaesthesia and Intensive Care, GMCH, <sup>1</sup>Inscol Hospital, <sup>2</sup>PGIMER, <sup>3</sup>Department of Orthopaedics, GMCH, Chandigarh, India

## Abstract

**Background and Objective:** Pain is a complex process influenced by both physiological and psychological factors. In spite of an armamentarium of analgesic drugs and techniques available to combat post-operative pain, appropriate selection, and effective management for relief of post-operative pain still poses unique challenges. The discovery of peripheral opioid receptors has led to growing interest in the use of locally applied opioids (intra-articular, intra-pleural, intra-peritoneal, and perineural) for managing acute pain. As bone graft harvesting is associated with significant post-operative pain and there is a paucity of literature on the use of peripheral opioids at the iliac crest bone harvesting site, the present study was planned to evaluate the analgesic efficacy of local administration of morphine after iliac crest bone graft harvesting.

**Materials and Methods:** A total of 60 patients, 20-50 years of age scheduled to undergo elective surgery for delayed and non-union fracture both bone leg with bone grafting under general anaesthesia (GA) were randomly assigned to one of the four groups of 15 patients each: group 1: 2.5 ml normal saline (NS) + 2.5 ml NS infiltrated into the harvest site at 2 sites + 1 ml NS intramuscularly (i/m); Group 2: 2.5 ml NS + 2.5 ml NS infiltrated into the harvest site at 2 sites + 5 mg morphine in 1 ml i/m.; Group 3: 2.5 mg (2.5 ml) morphine + 2.5 mg (2.5 ml) morphine infiltrated into the harvest site at 2 sites + 1 ml NS i/m; Group 4: 0.5 mg naloxone (2.5 ml) + 5 mg (2.5 ml) morphine infiltrated into the harvest site at 2 sites + 1 ml NS i/m. Pain from the bone graft site and operative site was assessed for 24 h post-operatively.

**Results:** The patients who had received morphine infiltration (Group 3) had significantly less pain scores at the graft site at 4, 6, and 10 post-operative hours. They also had significantly less morphine consumption and overall better pain relief as compared to the other groups.

**Conclusions:** Morphine administered peripherally provided better analgesia as compared to that given systemically and this effect was noticeable after 4 h post-operatively.

**Key words:** Local morphine, iliac crest bone graft, post-operative analgesia

## Introduction

Pain is a complex process influenced by both physiological and psychological factors.

Bone injury following fractures, bone marrow aspiration, and bone graft harvesting is often accompanied by acute

and chronic pain. Autogenous bone grafts from ilium are routinely harvested for the purpose of bone fusion in patients undergoing craniofacial surgeries, non-united fractures, and spinal stabilization surgeries.<sup>[1]</sup> Often pain from the donor site in such cases maybe more severe than pain at the site of incision, leading to an increase in post-operative morbidity.<sup>[2]</sup> Periosteum has a high concentration of neurosensory fibers, whereas fine myelinated and unmyelinated fibers accompany vessels into bone. These are responsible for pain associated with bone injury.<sup>[3]</sup>

One of the most salient features of donor site pain is its stubborn resistance to treatment. In spite of an armamentarium of analgesic drugs and techniques available to combat post-operative pain, appropriate selection, and effective management for its relief still poses unique challenges. The traditional use of opioids for relief of post-operative pain maybe associated with ventilatory depression, increased sedation, post-operative nausea and vomiting, voiding difficulties,

Address for correspondence: Dr. Nidhi Bhatia,  
Department of Anaesthesia and Intensive Care, PGIMER,  
Chandigarh, India.  
E-mail: nidhi.bhatia75@gmail.com

Access this article online	
Quick Response Code:	Website: www.joacp.org
	DOI: 10.4103/0970-9185.117109

and ileus.<sup>[4]</sup> Earlier reports suggested that non-steroidal anti-inflammatory drugs (NSAIDs) possessed analgesic properties comparable to those of opioids without any related side effects. However, NSAIDs are in fact associated with increased risk of gastrointestinal bleeding, abnormalities of platelet aggregation, and impairment of renal function.<sup>[5]</sup> Though post-operative epidural local anesthetic injection provides adequate analgesia, but requires close surveillance of the patient and maybe associated with motor and autonomic dysfunction.<sup>[6]</sup>

In the recent past research has revealed that opioids can act directly on peripheral terminals of afferent nerves to mediate anti-nociception and have enhanced efficacy in inflammation. Since, they are effective in low doses without any significant systemic absorption, their central effects are avoided.<sup>[7]</sup> Discovery of peripheral opioid receptors has led to growing interest in the use of locally applied opioids (intra-articular, intrapleural, intraperitoneal, perineural) for managing acute pain.<sup>[8-10]</sup> The use of peripheral morphine analgesia after bone damage in rats showed that local administration of morphine could block the development of hyperalgesia and allodynia in a rat model of osteotomy through mu opioid receptor agonism.<sup>[11]</sup>

As bone graft harvesting is associated with significant post-operative pain and there is a paucity of literature on the use of peripheral opioids at the iliac crest bone harvesting site; hence, the present study was planned to evaluate the analgesic efficacy of low dose morphine administration at the iliac crest bone graft harvesting site and to assess the side-effects associated with local morphine administration.

## Materials and Methods

After approval by Hospital Ethics Committee, 60 ASA I and II patients of either sex, 20-50 years of age, scheduled to undergo elective surgery for delayed/non-union fracture both bones leg with bone grafting under general anesthesia were included in this prospective, randomized, double-blind, placebo-controlled study. Patients with a history of chronic pain, long-term opioid intake, history of allergy to morphine, lack of compliance with the study protocol, inability to understand visual analog scale (VAS), drug/alcohol abuse, and any cardiovascular or neurological disease were excluded from the study. After obtaining written, informed consent and using coded, sealed envelopes, patients were randomly assigned to one of the four groups, with Group 1 ( $N = 15$ ) patients receiving 2.5 ml normal saline (NS) + 2.5 ml NS infiltrated into the harvest site at 2 sites + 1 ml NS intramuscularly (i/m). Group 2 ( $N = 15$ ) patients received 2.5 ml NS + 2.5 ml NS infiltrated into the harvest site at 2 sites + 5 mg morphine in 1 ml NS i/m. Patients allocated

to Group 3 ( $N = 15$ ) received 2.5 mg (2.5 ml) morphine + 2.5 mg (2.5 ml) morphine infiltrated into the harvest site at 2 sites + 1 ml NS i/m, whereas Group 4 ( $N = 15$ ) patients received 0.5 mg naloxone (2.5 ml) + 5 mg (2.5 ml) morphine infiltrated into the harvest site at 2 sites + 1 ml NS i/m.

After complete pre-operative evaluation including routine laboratory investigations, all patients were pre-medicated with tablet alprazolam 0.25 mg and tablet ranitidine 150 mg a night before and 2 h prior to surgery. In the operation theatre, non-invasive blood pressure, pulse rate, oxygen saturation, electrocardiogram, end-tidal  $CO_2$ , and temperature monitoring was carried out. General anesthesia was induced with intravenous (i/v) propofol 2 mg/kg and i/v fentanyl 2  $\mu$ g/kg followed by i/v vecuronium bromide 0.1 mg/kg to facilitate tracheal intubation. Anesthesia was maintained with 66% nitrous oxide in oxygen and 0.5-1% halothane. After completion of surgical procedure, residual paralysis was reversed with i/v neostigmine 0.05 mg/kg and i/v atropine 0.02 mg/kg. Intra-operatively, bone graft was taken by the surgeon from the anterior part of iliac crest. Study drug (prepared in 3 syringes by staff nurse who was not involved in the study) was infiltrated into 2 holes drilled 1 cm anterior and posterior to graft site (including infiltration close to the medial branch of the superior gluteal nerve, which passes over the superior rim of iliac crest) by an investigator who was not aware of their contents. Drug in third syringe was given intramuscularly.

Post-operative pain (using VAS) from both the graft site and operative site and hemodynamic parameters (heart rate, non invasive blood pressure, respiratory rate, oxygen saturation) were assessed by the blinded observer at 0, 2, 4, 6, 10, and 24 h after completion of surgery. Post-operatively morphine infusion was given at a rate of 1 mg/h with incremental doses of 1.5 mg (in patients with VAS scores more than 4) and lockout interval of 8 min. Upper limit of morphine for 4 h was 30 mg. Total morphine consumption in 24 h and overall pain relief was calculated.

## Statistical analysis

Demographic data, procedure duration and doses of morphine were analyzed by analysis of variance followed by *post-hoc* test for multiple comparisons. Pain scores were analyzed by using the Kruskal Wallis test, and Mann Whitney U-Test was used to determine the difference between two groups.

## Results

All the groups were comparable with regards to age, gender, weight, and duration of surgery [Table 1]. Evaluation of post-operative pain scores at the graft site [Table 2] revealed

**Table 1: Comparison of demographic data**

Demographics	Group 1	Group 2	Group 3	Group 4
Age (years) (mean±SD)	30.46±8.93	35.73±9.05	36.80±11.74	30.86±11.16
Sex (M/F)	13/2	13/2	12/3	13/2
Weight (kg) (mean±SD)	60.80±9.90	56.46±4.37	56.46±3.46	56.86±4.51
Duration of surgery (min) (mean±SD)	93.06±8.03	92.73±7.89	93.06±6.29	93.46±6.50

that at 0 and 2 post-operative hours the patients in Group 2, who received morphine systemically, had significantly lower pain scores as compared to the other groups ( $P < 0.01$ ). At 4 h, the mean pain scores in Groups 2 and 3 were significantly lower than in Groups 1 and 4 ( $P < 0.01$ ). However, the difference in mean pain scores between Groups 2 and 3 was not statistically significant ( $P > 0.05$ ). At 6 and 10 h Group 3 patients had significantly lower pain scores as compared to the other groups ( $P < 0.01$ ), whereas after 24 post-operative hours, the mean pain scores were comparable in all the 4 groups. On assessing pain at the operative site [Table 3], it was found that during the initial 4 h after surgery patients who had received systemic morphine that is Group 2 had significantly lower pain scores as compared to the other groups ( $P < 0.01$ ). However, beyond 4 h all the groups had insignificant difference in pain scores ( $P > 0.05$ ). Total dose of morphine required was significantly less and overall pain relief was better in Group 3 patients as compared to the other groups [Tables 4 and 5]. There was no statistically significant difference in the incidence of post-operative nausea between the various groups [Table 6] and none of the patients had any other complication.

## Discussion

For over 2 decades, anesthesiologists have been trying to improve efficacy of post-operative analgesia by injecting opioids close to the nerve trunks or nerve endings. The biological basis of this is the presence of opioid receptors and their endogenous ligands in the peripheral nervous system and their effect in modulation of inflammatory pain.<sup>[7,11]</sup> Autogenous bone grafts are routinely harvested from the ilium for the purpose of bone fusion in orthopedic surgeries and various modalities such as oral and parenteral analgesics, local anesthetic injections, cryotherapy have been tried in the past for relief of post-operative pain from this donor site.<sup>[12]</sup> The understanding of opioid action on peripheral nerves in animal studies has led to local application of low dose morphine for anti-nociception due to its hydrophilic property and long lasting effect.<sup>[11]</sup> With the non-availability of any controlled study comparing the efficacy of peripherally administered morphine at iliac crest harvest site and its reversal with naloxone, the present study was planned in patients of delayed/non-union fracture both bones lower limb undergoing intraoperative iliac crest bone

**Table 2: Comparison of post-operative pain scores at the graft site in all the groups (mean±SD)**

Hours	Group 1	Group 2	Group 3	Group 4
0	51.00±1.69	38.46±3.11	50.40±2.94	51.80±2.90
2	47.06±2.01	41.93±2.01	47.06±1.66	48.53±2.26
4	47.40±2.38	43.33±2.81	44.73±3.34	48.06±2.25
6	41.46±4.25	39.60±3.08	35.53±1.55	40.20±3.52
10	42.73±3.59	41.66±3.61	37.33±1.83	43.33±1.44
24	35.66±3.33	35.40±1.76	36.20±0.94	36.60±2.28

**Table 3: Comparison of post-operative pain scores at operative site in all the groups (mean±SD)**

Hours	Group 1	Group 2	Group 3	Group 4
0	32.80±1.47	31.20±1.93	33.66±1.23	32.34±1.12
2	32.46±1.80	28.13±1.35	32.00±0.92	32.26±2.15
4	32.06±1.70	28.26±1.53	32.46±1.40	32.33±1.95
6	31.53±1.80	30.20±1.65	30.80±1.01	30.33±1.95
10	31.73±2.96	29.93±1.16	29.86±1.64	30.46±1.80
24	28.33±1.71	28.60±1.24	28.46±1.40	28.73±1.38

**Table 4: Comparison of total dose of morphine required in 24 h in all the groups**

Groups	Morphine (mg) (mean±SD)
Group 1	31.3±1.11
Group 2	30.4±1.04
Group 3	29.4±0.94
Group 4	31.3±1.31

graft harvesting. As we needed to infiltrate morphine locally at the harvest site, 2 holes were drilled 1 cm anterior and 1 cm posterior to the iliac crest graft site for infiltrating the opioid. We selected a dose of 5 mg of morphine for infiltration at graft site based on a study carried out by Reuben *et al.* who used the same dose in patients undergoing cervical spine fusion with iliac crest bone graft harvesting.<sup>[13]</sup> In our study, pain at the graft site was significantly less at 2 h post-operatively in patients who received morphine systemically in comparison to others who had insignificant difference amongst themselves. These patients continued to have better pain relief even at 4 h. This analgesia could be attributed to central effects of systemic morphine, which has a peak effect in 45-90 min and duration of action of about 4 h after intramuscular administration.<sup>[14]</sup> Reuben *et al.*<sup>[13]</sup> compared 5 mg of morphine infiltrated at iliac crest graft site with 5 mg morphine given intramuscularly in patients undergoing cervical spine fusion surgery. Their results

**Table 5: Comparison of overall pain relief in all the groups**

Groups	No. of patients (%)	Excellent	Very good	Good	Fair	Poor
Group 1	N	8 (53.33)	4 (26.66)	2 (13.33)	1 (6.66)	Nil
Group 2	N	9 (60)	5 (33.33)	1 (6.66)	Nil	Nil
Group 3	N	11 (73.33)	2 (13.33)	2 (13.33)	Nil	Nil
Group 4	N	8 (53.33)	5 (33.33)	1 (6.66)	1 (6.66)	Nil

**Table 6: Comparison of incidence of nausea in all the groups**

Groups	N (%)
Group 1	2 (13.33)
Group 2	4 (26.67)
Group 3	2 (13.33)
Group 4	2 (13.33)

were however, inconsistent with those of our study as they did not find any difference in pain scores amongst the groups at 2 h. This could be attributed to the long surgical duration in their study and evaluation of patients 2 h post-operatively, leading to the wearing off of analgesic effect of systemic morphine. Patients receiving morphine infiltration into the iliac crest harvest site experienced less pain as compared to the other groups at 4 h post-operatively. Peripheral opioid effects are not detectable in normal tissues, but after initiation of inflammatory reaction. Opioid agonists have easier access to neuronal opioid receptors during inflammation because inflammation disrupts the perineurium and number of peripheral sensory nerve terminals is increased in inflamed tissue. Moreover, previously inactive neuronal opioid receptors may become active in the inflammatory milieu.<sup>[1,15,16]</sup> As the infiltration of inflammatory cells into the site of injury and disruption of perineural barrier are time dependent, this possibly explains the onset of analgesia after local morphine infiltration at 4 h. This analgesic effect of local morphine infiltration continued for up to 10 h post-operatively. This may be due to opioid anti-inflammatory effects and variable blood supply at peripheral sites, which determines the rate of opioid removal.<sup>[17]</sup> Pain relief was better in patients who received morphine infiltration in comparison to those receiving morphine and naloxone infiltration, thereby indicating a mechanism of action of peripherally administered morphine specific to opioid receptors. As the effect of peripherally administered morphine got blocked by  $\mu$ -opioid receptor antagonist, naloxone, which was injected in the marrow cavity, the analgesic effect of morphine infiltration could be mediated by  $\mu$ -opioid receptors located in the bone. Post-operative pain at the operative site was less in patients who received systemic morphine and this pain relief continued for 4 h post-operatively. This could be attributed to the continued analgesic effect of systemic morphine. However, after 4 h there was no difference in pain relief at the operative site in all the groups.

Total morphine consumption was significantly less and overall pain relief was also the best in patients who received morphine infiltration at iliac crest harvest site. This could be due to longer duration of pain relief and less incidence of morphine related side-effects in this group. The incidence of post-operative side-effects like nausea was maximum in patients who received morphine systemically, though the difference was statistically insignificant. Post-operative side-effects are expected to be less with peripherally administered morphine because of low doses used and lack of systemic effects.

Our study however, had certain limitations. The pain scores were not recorded between 10 and 24 h post-operatively so as to enable us to know the exact duration of analgesic effect of peripherally administered morphine. It was not possible to measure and prevent losses of drug infiltrated into iliac crest harvest site in spite of all the precautions. Moreover, we did not measure serum levels of morphine to rule out if the analgesic effect of morphine infiltration is by systemic absorption.

In conclusion, post-operative pain at the iliac crest bone graft harvest site was significantly better in patients receiving morphine infiltration at the graft site. This analgesic effect of local morphine infiltration was noticeable at 4 h post-operatively and continued for up to 10 h. In future, larger controlled studies may be directed at confirming the findings of the present study and clarifying the cellular basis of delayed onset of peripheral action of opioids.

## References

1. Wai EK, Sathiaseelan S, O'Neil J, Simchison BL. Local administration of morphine for analgesia after autogenous anterior or posterior iliac crest bone graft harvest for spinal fusion: A prospective, randomized, double-blind, placebo-controlled study. *Anesth Analg* 2010;110:928-33.
2. Goulet JA, Senunas LE, DeSilva GL, Greenfield ML. Autogenous iliac crest bone graft. Complications and functional assessment. *Clin Orthop Relat Res* 1997;339:76-81.
3. Williams PI. The skeletal connective tissues. In: Williams PI, Warwick R, Dyson M. editors. *Gray's Anatomy*. 37<sup>th</sup> ed. Edinburgh, Scotland: Churchill Livingstone; 1989. p. 283-315.
4. Walder B, Schafer M, Henzi I, Tramèr MR. Efficacy and safety of patient-controlled opioid analgesia for acute postoperative pain. A quantitative systematic review. *Acta Anaesthesiol Scand* 2001;45:795-804.
5. Ritchey RM. Optimizing postoperative pain management. *Cleve Clin J Med* 2006;73 Suppl 1:S72-6.

6. Richman JM, Wu CL. Epidural analgesia for postoperative pain. *Anesthesiol Clin North Am* 2005;23:125-40.
7. Schäfer M, Imai Y, Uhl GR, Stein C. Inflammation enhances peripheral mu-opioid receptor-mediated analgesia, but not mu-opioid receptor transcription in dorsal root ganglia. *Eur J Pharmacol* 1995;279:165-9.
8. Kalso E, Tramèr MR, Carroll D, McQuay HJ, Moore RA. Pain relief from intra-articular morphine after knee surgery: A qualitative systematic review. *Pain* 1997;71:127-34.
9. Schulte-Steinberg H, Weninger E, Jokisch D, Hofstetter B, Misera A, Lange V, *et al.* Intraperitoneal versus interpleural morphine or bupivacaine for pain after laparoscopic cholecystectomy. *Anesthesiology* 1995;82:634-40.
10. Bullingham R, O'Sullivan G, McQuay H, Poppleton P, Rolfe M, Evans P, *et al.* Perineural injection of morphine fails to relieve postoperative pain in humans. *Anesth Analg* 1983;62:164-7.
11. Houghton AK, Valdez JG, Westlund KN. Peripheral morphine administration blocks the development of hyperalgesia and allodynia after bone damage in the rat. *Anesthesiology* 1998;89:190-201.
12. Wilson PA. Pain relief following iliac crest bone harvesting. *Br J Oral Maxillofac Surg* 1995;33:242-3.
13. Reuben SS, Vieira P, Faruqi S, Verghis A, Kilaru PA, Maciolek H. Local administration of morphine for analgesia after iliac bone graft harvest. *Anesthesiology* 2001;95:390-4.
14. Stoelting RK. Opioid agonist and antagonist. In: *Pharmacology and Physiology in Anaesthetic Practice*. 3<sup>rd</sup> ed. Philadelphia, New York: Lippincott Raven; 1999. p. 83-4.
15. Antonijevic I, Mousa SA, Schäfer M, Stein C. Perineurial defect and peripheral opioid analgesia in inflammation. *J Neurosci* 1995;15:165-72.
16. Singh K, Phillips FM, Kuo E, Campbell M. A prospective, randomized, double-blind study of the efficacy of postoperative continuous local anesthetic infusion at the iliac crest bone graft site after posterior spinal arthrodesis: A minimum of 4-year follow-up. *Spine (Phila Pa 1976)* 2007;32:2790-6.
17. Stein C. The control of pain in peripheral tissue by opioids. *N Engl J Med* 1995;332:1685-90.

**How to cite this article:** Singh D, Gombar KK, Bhatia N, Gombar S, Garg S. Evaluation of analgesic effect of local administration of morphine after iliac crest bone graft harvesting: A double blind study. *J Anaesthesiol Clin Pharmacol* 2013;29:356-60.  
**Source of Support:** Nil, **Conflict of Interest:** None declared.

#### Announcement

#### iPhone App



Download  
iPhone, iPad  
application

FREE

A free application to browse and search the journal's content is now available for iPhone/iPad. The application provides "Table of Contents" of the latest issues, which are stored on the device for future offline browsing. Internet connection is required to access the back issues and search facility. The application is Compatible with iPhone, iPod touch, and iPad and Requires iOS 3.1 or later. The application can be downloaded from <http://itunes.apple.com/us/app/medknow-journals/id458064375?ls=1&mt=8>. For suggestions and comments do write back to us.