Original Article

Preemptive analgesia with intra-articular pethidine reduces pain after arthroscopic knee surgery

Sayed Jalal Hashemi, Hasanali Soltani, Sayed Morteza Heidari, Mahmoud Rezakohanfekr

Department of Anesthesiology, Anesthesiology and Critical Care Research Center, Isfahan University of Medical Sciences, Isfahan, Iran

Abstract

Background: Postoperative pain relief is important in procedures of the lower extremity. Several previous studies have evaluated the efficacy of intra-articular (IA) pethidine as a compound, which has local anesthetic and opioid agonist properties, on postoperative pain relief in arthroscopic knee surgery (AKS). This study compared the postoperative analgesic effect of pre- and post-surgical IA pethidine administration in AKS.

Materials and Methods: Seventy-five patients of American Society of Anesthesiologists (ASA) I and II undergoing AKS with general anesthesia were enrolled in this double-blind study. Patients were randomized in three equal groups to receive either 50 mg IA pethidine before surgical incision incision and saline after skin closure (PS), saline before surgical incision and pethedine after skin closure (SP), and only saline at two different times (SS). In each patient with operated knee joint, pain at rest and joint movement was evaluated at 1, 2, 6, 12, and 24 h after surgery completion using Visual Analog Scale (VAS). Data were analyzed using analysis of variance (ANOVA)-repeated measure, *t*-paired, and Chi-square tests.

Results: Postoperative pain score at rest and joint movement in PS group was significantly lower than those in other groups. The time (Mean ± SD) between completion of operation and patient's request for morphine, total morphine consumption (Mean ± SD) in postoperative 24 h, and the numbers of patients requesting analgesic in PS, SP, SS, groups were: 5.2 ± 1.3, 3.3 ± 1.5, and 2 ± 1.3 h ($P < 0.05$); 4.4 ± 2.4, 8.7 ± 2, and 11.6 ± 4.4 mg ($P < 0.05$); 11, 18, and 21 persons ($P < 0.05$), respectively.

Conclusion: The present study shows that preemptive intra-articular pethidine 50 mg injection is more effective than preventive injection for postoperative pain relief at rest and joint movement in arthroscopic knee surgery.

Key Words: Arthroscopy, intra-articular, knee, pain after surgery, pethidine

Address for correspondence:
Dr. Sayed Morteza Heidari, Department of Anesthesiology, Anesthesiology and Critical Care Research Center, Isfahan University of Medical Sciences, Isfahan, Iran. E-mail: m_heidari@med.mui.ac.ir

Received: 02-05-2012, Accepted: 27.06.2012

Access this article online	
Quick Response Code:	Website: www.advbiores.net
	DOI: 10.4103/2277-9175.107971

INTRODUCTION

Treatment of the postoperative pains after surgical operations of lower limbs is of special importance. Inadequate treatment of these pains results in the reduction of patients' activities and related complications.[1] Knee arthroscopy is one of the surgeries of lower limbs which are associated with postoperative pain.[2] Since this operation is one of the most common outpatient surgeries, sufficient

How to cite this article: Hashemi SJ, Soltani H, Heidari SM, Rezakohanfekr M. Preemptive analgesia with intra-articular pethidine reduces pain after arthroscopic knee surgery. Adv Biomed Res 2013;2:9.

analgesia must be applied.[3]

There are various methods for controlling postoperative pain in these patients, including intra-articular injection of local anesthetic drugs or other drugs and oral and intravenous administration of analgesics.[4-7] Oral administration of rofecoxib before knee arthroscopy leads to favorable analgesia after surgery.[8] Application of opioid injections such as intra-articular morphine, preemptively, before knee arthroscopy causes a longer analgesia with lower doses of analgesics compared to its administration after surgery.[9]

Pethidine as an opioid with local anesthetic effect[10] has been effective in reduction of pain after knee arthroscopy. A study showed that preemptive intra-articular pethidine before surgery was more effective in controlling pain than prilocaine.[3] The time for injection of opioids may influence the intensity of postoperative pain. Therefore, different studies have used analgesics at various times in period around the surgical operation and found different effects. So far, no study has been done on the effect of preemptive and preventive application of this drug. The present study examined the preemptive intra-articular pethidine before surgery versus its preventive administration after surgery. To do so, 50 mg of pethidine was used for intra-articular injection before surgery and parameters including pain intensity after knee arthroscopy, dosage of morphine, and the time of administration of the first dose of the analgesic drug within 24 h after surgery were compared to those of administration of pethidine after surgery.

MATERIALS AND METHODS

Once the present research project was approved by the local research committee, 75 candidates for elective knee arthroscopy under general anesthesia were studied in this double-blind clinical trial after they declared their consent to participate in this study. Inclusion criteria were age of 15–65 years, non-addicted patients, no history of mental illnesses, no history of allergy to pethidine, not having renal and liver diseases, previously experiencing arthroscopy, and American Society of Anesthesiologists (ASA) physical status class I and II.

Exclusion criteria were the need for an open-knee surgery and incidence of any severe hemodynamic disorder during operation. The patients did not receive any other intra-articular injection or premedication on the day of operation. The surgical operations included diagnostic arthroscopy, meniscectomy, and cartilage resection.

All the operations were performed by one surgeon. Both the surgeon and the anesthesiologist responsible for assessing the patients were unaware of the content of syringes for intra-articular injection. An anesthesia technician prepared syringes with identical volume and shape and coded them confidentially. The night before operation, all the patients were visited by the anesthesiologist and were trained the way of using Visual Analog Scale (VAS) system in a range of 0–10 cm. The patients were restricted to Non Per os NPO for 8 h during which fluid therapy was performed based on regulations (law) 4, 2, and 1 by serums 1/3 and 2/3.

The patients were divided into three groups, each with 25 people, using random number table. After induction of anesthesia, 10 min before arthroscopic incision, 50 mg of pethidine diluted in 10 ml of saline was injected into the knee joint of the patients in the first group (PS group) by the surgeon. Then, the same volume of normal saline (placebo) was injected intra-articularly by the surgeon after operation and skin closure. The reverse process was performed in the second group (SP group), as the normal saline was injected before the operation and pethidine after the operation.

The patients in the third group (SS group) were injected normal saline intra-articularly before and after the operation.

Pain intensity of the patients in the three groups was assessed and recorded before the operation, both when they were at rest and when they moved their knee joint on the operating table. The induction of anesthesia for the patients was done using 5 mg/kg sodium thiopental, 0.6 mg/kg atracurium, and 2 μ/kg fentanyl. After tracheal intubation, the patients received mechanical ventilation and the rest of anesthesia was performed using 1–1.2% isoflurane along with a mixture of N_2O and O_2 in equal proportions. Morphine at a dose of 0.1 mg/kg was injected to all the patients intravenously. Once the operation ended, muscle relaxation was reversed by 0.04 mg/kg neostigmine and 0.02 mg/kg atropine intravenously, then extubation was done and the patients were transferred to the recovery room. Parameters including pulse oximetry, electrocardiography, noninvasive blood pressure, and capnography were monitored during anesthesia. The systolic and diastolic blood pressure and heart rate were measured and recorded before intervention and on the 5^{th}, 10^{th}, 15^{th}, and 20^{th} min and then every 10 min up to the end of operation.

Pain value was determined and recorded based on VAS (where 0 = no pain and 10 = worst possible), 1, 2, 6, 12, and 24 h after operation, when the patients were

at rest and when they moved their joints.

After operation, at patients' request, 0.05 mg/kg of morphine was injected to them intramuscularly. Furthermore, the time of the first injection of morphine after operation, total amount of injected morphine within 24 h after operation, and also the incidence of nausea and vomiting in the patients were determined and recorded. When the patients were in recovery room, percentage of peripheral blood oxygen saturation was measured using a pulse oximeter and the saturation less than 90% was recorded as hypoxemia.

The data were analyzed using statistical package for social sciences version 14 (SPSS Inc., Chicago, IL, USA). On the assumption that a 12% difference in mean pain score among the three groups would be of clinical interest, the sample size was calculated in each group to have a power B = 80% and σ = 0.05.

The Mean and standard deviation (SD) of the pain scores for the three groups were analyzed using analysis of variance (ANOVA) for repeated measures. Total morphine consumption, the first time of patients request for morphine administration, heart rate, and blood pressure in each group were compared with *t*-paired test. Chi-square test was used for comparison of some demographic data and postoperative nausea and vomiting. A *P* value of <0.05 was considered as significant.

RESULTS

The 75 patients who were assessed in this study did not differ significantly in terms of the mean age and weight, sex frequency distribution, the mean time for anesthesia and operation, frequency distribution for the type of surgical operation, ASA status, and mean pain value before operation when the patients were at rest and when they moved their joints [Table 1]. However, mean systolic and diastolic blood pressure and heart rate of the patients before and during operation were not significantly different [Table 2].

The pain value 1, 2, and 6 h after operation at the two statuses of resting and joint moving in PS group was significantly less than that in SP group [Table 3]. However, pain value at all times in PS and SP groups was significantly less than that in SS group ($P < 0.05$). The mean pain value when the patients were at rest, 1, 2, 6, and 12 h after operation in PS group and at all times in SP and SS groups was significantly more than that before operation ($P < 0.05$).

The mean pain value when the patients moved their joints at all times after operation in PS group was less than that before operation; however, the difference was only found 1, 6, and 24 h after operation ($P < 0.05$).

In SP group, mean pain value when the patients moved their joints, 1, 2, and 6 h after operation was significantly more than that before operation ($P < 0.05$), whereas the later hours (after 6th hour) showed less mean pain value than that before operation. In SS group, mean pain value when the patients moved their joints at all hours after operation was significantly more than that before operation ($P < 0.05$).

The mean for total injected morphine and the number of patients asking for an opioid in PS group were significantly less than those in other groups. The time of first request of the patients for an opioid in PS group was significantly more than those in other groups [Table 4].

With respect to postoperative complications, incidence

Table 1: The results by the analysis of demographic and clinical specifications of the three groups (Mean±SD)

Variable	PS group (*n*=25) Pethidine before operation Placebo after operation	SP group (*n*=25) Placebo before operation Pethidine after operation	SS group (*n*=25) Placebo before and after operation
Age (years)	36.9±12.3	44.9±15	41.7±13.1
Weight (kg)	72.9±10.3	71.7±9.8	73.1±9.2
Sex (male to female)	7.18	9.16	6.19
Duration of anesthesia (min)	112±30	118±29	120±25
Duration of operation (min)	85±28	87±27	83±26
Type of surgery (patient)			
Meniscectomy	12	14	11
Diagnostic	10	8	10
Cartilage resection	3	3	4
Physical status class (ASA I/II)	17.8	15.10	14.11
Preoperative pain at rest (score)	1±1.2	0.8±1	1.3±2.4
Preoperative pain when joint moving (score)	3.3±2.6	2.9±1.8	3±1.6

The analysis using Chi-square test and *t*-test showed no significant difference among the three groups

Table 2: Comparative analysis of number of heartbeats, systolic and diastolic blood pressure of the three groups at various times (Mean±SD)

Number of heartbeats (beats/min) Systolic blood pressure (mmHg) Diastolic blood pressure (mmHg)	PS group (*n*=25)	SP group (*n*=25)	SS group (*n*=25)
Before operation	81±6	83±7	80±7
	132±11	135±15	137±12
	97±12	95±11	98±6
5 min after operation	76±10	72±9	78±12
	127±8	125±7	129±5
	99±5	97±8	100±6
10 min after operation	72±7	70±5	71±8
	123±6	121±8	122±6
	85±6	88±6	89±3
15 min after operation	77±5	75±5	75±3
	121±7	122±9	124±6
	87±6	84±7	85±7
20 min after operation	75±5	76±7	78±9
	120±4	121±5	123±3
	85±3	81±4	83±6
30 min after operation	73±7	76±8	72±7
	118±5	122±3	120±6
	80±6	78±5	81±3
50 min after operation	76±6	74±5	77±8
	121±6	122±9	120±6
	79±6	81 ±	82±6
80 min after operation	73±8	71±5	73±5
	121±7	122±5	120±6
	82±6	79±7	79±6

The paired *t*-test did not indicate a significant difference among the groups

Table 3: Comparative analysis of pain values of the three groups after operation (Mean±SD)

At rest When moving joint	PS group (*n*=25)	SP group (*n*=25)	SS group (*n*=25)	*P*
1st hour	2.4±2.0	4.9±2.4	7.6±3.1	0.001
	2.7±1.9	5.8±2.9	7.9±2.4	0.001
2nd hour	2.0±1.5	3.9±1.9	6.8±2.5	0.001
	2.9±1.7	4.7±2.1	7.4±2.7	0.005
6th hour	1.9±1.4	3.4±1.6	6.3±2.1	0.01
	2.7±0.5	3.8±1.5	7.5±2.4	0.02
12th hour	2.0±1.6	2.9±1.4	5.1±1.1	NS
	2.8±1.7	2.9±1.6	4.5±2.1	NS
24th hour	1.3±0.9	1.7±1.1	3±1.6	NS
	2.0±1.0	2.5±1.1	4±2.4	NS

The analysis by ANOVA test showed a significant difference among the three groups; *P* value was calculated for PS and SP groups; NS, nonsignificant

Table 4: Comparative analysis of total injected morphine, the time of first request of the patient for an opioid, and the number of patients receiving opioid among the three groups

Groups	PS group (*n*=25)	SP group (*n*=25)	SS group (*n*=25)
Total injected morphine during the first 24 h	4.4 ± 2.4*	8.7 ± 2.0	11.6 ± 4.4
The time of first request for opioid (h)	5.2 ± 1.3*	3.3 ± 1.5	2.0 ± 1.3
Number of patients asking for opioid	11*	18	21

*The analysis by paired *t*-test showed a significant difference among the three groups

of nausea and vomiting in PS, SP, and SS was 2, 3, and 2, respectively, with no significant difference. Oxygen saturation of hemoglobin in all groups showed no reduction less than 90%.

DISCUSSION

This study showed that intra-articular injection of 50 mg of pethidine before intervention of operation in patients undergoing knee arthroscopy was significantly effective in postoperative pain reduction.

This study, in fact, proved the superiority of preemptive administration over preventive administration.

The reduction of total injected morphine after operation, the increase in the time of receiving the first morphine dose, and reduction of patients receiving morphine in the group receiving pethidine before operation – all revealed better effect of preemptive administration than preventive administration.

In Soderlund *et al.*'s study, the use of 50–200 mg doses of pethidine intra-articularly before operation resulted in analgesia, as the increase in plasma level of pethidine expressed its central analgesic effect besides the peripheral effect.[3] Therefore, in the present study, the analgesic effect induced by intra-articular injection of pethidine might be due to the following three mechanisms:[1] the effect of the drug as a local anesthetic,[2] the effect of drug on peripheral opioid receptors, and (3) the effect of drug on central opioid receptors.

Preemptive analgesia refers to a pharmacological intervention which leads to reduction of pain through inhibition of nociceptive mechanism before any painful surgical stimulation.[11]

In fact, opioids, in preemptive administration, affect local pain receptors and prevent the stimulation of receptors in central nervous system; consequently, the process of pain relief is enhanced after operation.[12]

A study by Lasscelles *et al.* showed the effectiveness of intra-articular injection of pethidine, before hysterectomy of dogs, on controlling pain after operation compared to its injection after operation. They considered it as the result of inhibition of central

sensitization development subsequent to the surgical stimulations.[13]

In the present study, the increased effectiveness of preemptive administration of pethidine versus preventive administration might be due to its effect on existing peripheral receptors in knee joint and the reduction of central sensitization, and thus analgesia following surgical stimulations.

The preemptive effect of analgesics and local anesthetics has been assessed by several studies. In these studies, intra-articular injection of tramadol, morphine, fentanyl, bupivacaine, and prilocaine before operation has been remarkably effective in pain reduction after knee arthroscopy.[3,4,14,15] Both the results of the present study and the results of the above studies indicated the increased effectiveness of preemptive method in controlling postoperative pain.

In this study, after injection of pethidine into the knee joint and its binding to the receptors in the joint space, the remaining drug was washed out following the arthroscopic cut and joint opening and it did not contact any longer with the knee. Therefore, the effectiveness of preemptive method might be due to vascular absorption of drug, systemic effects, and also initial effect of the drug on intra-articular opioid receptors.[3] However, in preventive administration, the drug was injected after skin closure, so it remains a longer time in knee. This also proves the analgesic power of preemptive administration that despite the probable presence of the drug in postoperative injection, preoperative injection and then washing out the drug from the joint space provided more analgesic effect after operation. This effect is evident especially during early hours after operation. The reason for the lack of significant difference 12 and 24 h after operation might be the subsidence of edema and acute inflammation in the joint, which resulted in pain reduction in all groups.

Moreover, in this study, complete blocking of the areas which were the source of pain could be the cause of this obvious effect of preemptive administration. The special feature of pethidine in affecting simultaneously peripheral opioid receptors and sodium channels in peripheral nerves and causing local anesthesia[10] may play an important role in this regard. More inhibition of central sensitization, which happens by complete blocking of peripheral structures in surgical field, leads to a more complete analgesia[16,17] and this was achieved through the method selected in the present study. The analgesic effect of preemptive administration was evident in the present study even after the end of drug effect, which was an analgesic feature of preemptive method.[18]

In this study, the effect of preoperative injection of pethidine resulted in pain reduction when the patients moved their joint, while the postoperative injection could not do so. Lack of hemodynamic variations during operation and reduction of postoperative complications such as nausea, vomiting, and drop of oxygen saturation show the systemic absorption of drug from the joint tissues, especially synovium, into the blood circulation to the extent that prevents side effects.[3] Limitations of this study include not measuring the plasma level of pethidine, not assessing the pain intensity over a longer time after the operation due to the outpatient surgery, and discharge of patients from the hospital.

At last, it can be concluded that intra-articular injection of 50 mg of pethidine before knee arthroscopy, compared to the postoperative injection, may significantly result in postoperative pain reduction when the patients are at rest and when they move their joint, reduction of morphine dose, and increase of analgesia duration in patients.

ACKNOWLEDGMENTS

We would like to thank the vice chancellor research, the physician, and staff of operative room at Alzahra Hospital for assistance with this study.

REFERENCES

1. Simanski CJ. Pain therapy for the lower extremities. Orthopade 2008;37:959-60, 962-9.
2. Drosos GI, Stavropoulos NI, Katsis A, Kesidis K, Kazakos K, Verettas DA. Post-operative pain after knee arthroscopy and related factors. Open Orthop J 2008;13;2:110-4.
3. Söderlund A, Boreus LO, Westman L, Engström B, Valentin A, Ekblom A. A comparison of 50, 100 and 200 mg of intra-articular pethidine during knee joint surgery, a controlled study with evidence for local demethylation to norpethidine. Pain 1999;80:229-38.
4. Samoladas EP, Chalidis B, Fotiadis H, Terzidis I, Ntobas T, Koimtzis M. The intra-articular use of ropivacaine for the control of post knee arthroscopy pain. J Orthop Surg Res 2006;23:1-17.
5. Batra YK, Mahajan R, Kumar S, Rajeev S, Singh Dhillon M. A dose-ranging study of intraarticular midazolam for pain relief after knee arthroscopy. Anesth Analg 2008;107:669-72.
6. Grabowska-GaweşA, GaweşK, Hagner W, Biliş̧ki PJ. Morphine or bupivacaine in controlling postoperative pain in patients subjected to knee joint arthroscopy. Ortop Traumatol Rehabil 2003;30;5:758-62.
7. Cagla OzbakisAkkurt B, Inanoglu K, Kalaci A, Turhanoglu S, Asfuroglu Z, Tumkaya F. Effects of intravenous small dose ketamine and midazolam on postoperative pain following knee arthroscopy. Pain Pract 2009;9:289-95.
8. Karamanlioş̧u B, Alagöl A, Turan FN. Preemptive oral rofecoxib plus postoperative intraarticular bupivacaine for pain relief after arthroscopic knee surgery. Agri 2005;17:29-33.
9. Reuben SS, Sklar J, El-Mansouri M. The preemptive analgesic effect of intraarticular bupivacaine and morphine after ambulatory

arthroscopic knee surgery. Anesth Analg 2001;92:923-6.
10. Oldroyd GJ, Tham EJ, Power I. An investigation of the local anaesthetic effects of pethidine in volunteers. Anaesthesia 1994;49:503-6.
11. Campiglia L, Consales G, De Gaudio AR. Pre-emptive analgesia for postoperative pain control: A review. Clin Drug Investig 2010;30:15-26.
12. Woolf CJ, Chong MS. Preemptive analgesia–treating postoperative pain by preventing the establishment of central sensitization. Anesth Analg 1993;77:362-79.
13. Lascelles BD, Cripps PJ, Jones A, Waterman AE. Post-operative central hypersensitivity and pain: The pre-emptive value of pethidine for ovariohysterectomy. Pain 1997;73:461-71.
14. Tuncer B, Babacan A, Arslan M. Preemptive intraarticular tramadol for pain control after arthroscopic knee surgery. Agri 2007;19:42-9.
15. Hube R, Tröger M, Rickerl F, Muench EO, von Eisenhart-Rothe R, Hein W, *et al*. Pre-emptive intra-articular administration of local anaesthetics/opiates versus postoperative local anaesthetics/opiates or local anaesthetics in arthroscopic surgery of the knee joint: A prospective randomized trial. Arch Orthop Trauma Surg 2009;129:343-8.
16. Dahl JB, Møiniche S. Pre-emptive analgesia. Br Med Bull 2004;71:13-27.
17. Hurley RW, Wu CL. Acute Postoperative Pain. In: Miller R, editor. Miller's Anesthesia. 7th ed. Philadelphia: Churchill Livingstone Elsevier; 2010. p. 2757-87.
18. Kissin I. Preemptive analgesia. Anesthesiology 2000;93:1138.

Source of Support: Nil, **Conflict of Interest:** None declared.