TÜBİTAK

Original Article

Turk J Med Sci
2012; 42 (1): 47-54
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E-mail: medsci@tubitak.gov.tr
doi:10.3906/sag-1010-1226

A comparative study of preoperative versus intraoperative meperidine administration in patients receiving general anesthesia: a prospective, randomized double-blind study

Hüseyin SERT[1], Rüveyda İrem DEMİRCİOĞLU[1], Burhanettin USTA[1], Bünyamin MUSLU[1], Ümmügülsüm YAZICI[1], Muhammet GÖZDEMİR[1], Önder SÜRGİT[2]

Aim: To evaluate the effects of preoperative and intraoperative administration of intravenous meperidine as a preemptive analgesic.

Materials and methods: A total of 50 patients were randomly divided into 2 groups; group P received 1 mg/kg of meperidine intravenously immediately before induction of anesthesia, and group I received the same amount of meperidine 20 min before completion of surgery. Consumption of desflurane, recovery parameters, heart rate, mean arterial pressure, sedation scores, visual analog scale (VAS) scores for pain, analgesic needs, and anesthesia-related complications were recorded for both groups.

Results: Time to recovery was significantly shorter in group P than in group I for all parameters except spontaneous respiration. The postoperative sedation scores were mostly similar for the 2 groups, with the exception of the number of patients with postoperative 60-min sedation scores of 2; this score was seen in 1 patient in group P and 7 patients in group I. The VAS scores of group I in the postoperative period were higher than those of group P.

Conclusion: Preoperative meperidine administration shows superiority to intraoperative administration with regard to recovery parameters and early postoperative pain scores, but there were no significant differences between the groups with regard to other intraoperative and postoperative parameters.

Key words: Desflurane consumption, meperidine, postoperative pain, preemptive analgesia, recovery

Meperidinin preoperatif ve intraoperatif kullanımının karşılaştırılması: Prospektif, randomize çift-kör çalışma

Amaç: Preemptif analjezik olarak intravenöz yolla uygulanan meperidinin preoperatif ve intraoperatif etkilerinin incelenmesi.

Yöntem ve gereç: Çalışmada 50 hasta rastgele iki gruba ayrıldı: grup P'ye anestezi indüksiyonundan hemen önce grup I'ya ise cerrahi tamamlanmasından 20 dakika önce intravenöz olarak 1 mg/kg meperidin verildi. Desfluran tüketimi, derlenme parametreleri, kalp hızı kan basıncı, sedasyon skorları, görsel ağrı skoru (VAS), analjezik gereksinimi ve anestezi ile ilgili komplikasyonlar her iki grupta da kaydedildi.

Bulgular: Bütün derlenme parametreleri (spontan solunum dönme zamanı hariç) istatistiksel olarak anlamlı şekilde grup P'de daha erken olarak bulundu. Postoperatif sedasyon skorları iki grup için genelde benzer olmasına rağmen postoperatif 60. dakikada sedasyon skoru 2 olan hasta sayısı grup P'de 1 iken grup I'da 7 olarak saptandı. VAS skorları grup I'da grup P'ye göre yüksek olarak bulundu.

Received: 16.10.2010 – Accepted: 10.12.2010

[1] Department of Anesthesiology, Faculty of Medicine, Fatih University, Ankara - TURKEY
[2] Department of General Surgery, Faculty of Medicine, Fatih University, Ankara - TURKEY

Correspondence: *Hüseyin SERT, Department of Anesthesiology, Faculty of Medicine, Fatih University, Alparslan Türkeş Caddesi No. 57, 06520 Yenimahalle, Ankara - TURKEY*
E-mail: drhuseyinsert@yahoo.com

Sonuç: Derlenme parametreleri ve erken dönem postoperatif ağrı skorları açısından değerlendirildiğinde meperidinin preoperatif dönemde uygulanması intraoperatif dönemde uygulanmasına göre üstünlükleri olmasına rağmen intraoperatif ve postoperatif takip parametreleri açısından gruplar arasında farklılık bulunmamaktadır.

Introduction

Preemptive analgesia is based on the concept of the early blockade of pain pathways and can prevent the occurrence of strong pain stimulus, hyperexcitation, and hyperalgesia (1). A variety of preemptive analgesic regimens have been used, such as intravenous administration of opioids or nonsteroidal antiinflammatory drugs (NSAIDs), local anesthetic infiltration, peripheral nerve block, and epidural block (2). Preemptive analgesic applications such as opioid administration reduce the volatile anesthetic requirement by decreasing minimum alveolar concentration (MAC) values, increasing intraoperative hemodynamic stability, decreasing analgesic requirements and morbidity, and shortening recovery times (3-5).

The timing for the preemptive analgesic administration in postoperative pain control is still controversial. Woolf et al. (6) suggested that simple changes in the preemptive analgesic administration time can have profound effects on postoperative pain. Many clinical trials suggested that the timing of analgesic treatment for surgical injury is the most important issue. Various studies with clinical preemptive analgesia have been designed to test this hypothesis (6,7). Several trials have questioned the timing of opioid administrations such as preemptive analgesia and their effects on postoperative pain (8). Meperidine is a commonly used opioid analgesic licensed for short-term use in the management of moderate to severe postoperative pain. There are only 2 studies in the literature in which meperidine was given intravenously as a preemptive analgesic (9,10). To the best of our knowledge, there is no study in the literature evaluating the effects of preemptive meperidine use on volatile anesthetic consumption, intraoperative hemodynamic stability, and postoperative early recovery times. Thus, the aim of this study was to examine the effects of intravenous meperidine according to its preoperative or intraoperative administration in patients undergoing thyroid and breast surgeries.

Materials and methods

This prospective, randomized, and double-blind study was approved by the ethics committee of our institution. Informed consent from each patient was obtained before participation in the study. The study group consisted of 50 patients with an American Society of Anesthesiologists (ASA) physical status of I or II, aged between 20 and 60 years, and scheduled for elective subtotal thyroidectomy or breast-conserving surgery. We excluded patients requiring radical neck dissection, because the incision size was larger than that of simple thyroid surgery, and patients requiring axillary lymph node dissection. Patients receiving regular sedative narcotic medications or who had received systemic opioids within 48 h preoperatively; patients with a significant history of cardiovascular, hepatic, or renal disease; and patients with hypersensitivity to anesthetics were also excluded. An anesthesiologist who was not involved in the data collection process prepared the study solutions. Another anesthesiologist, who was blinded to the treatment group allocation, collected the data during the operations. The patients were randomly allocated using a computer-generated randomization scheme to 1 of 2 groups: the preoperative meperidine group (group P, n = 25) and the intraoperative meperidine group (group I, n = 25). Pharmacological premedication was not applied to patients for whom oral intake was cut off 8 h prior to the operation. Standard monitoring was applied upon arrival to the operating room. Monitoring included noninvasive arterial pressure (BP), electrocardiogram (ECG), heart rate (HR), peripheral arterial oxygen saturation (SpO_2), bispectral index (BIS), end-tidal CO_2 ($ETCO_2$), and end-tidal anesthetic drug concentrations. The anesthesia instrument used was a Datex-Ohmeda S/5 Avance anesthesia machine (GE Healthcare, Helsinki, Finland). The BIS was derived from the frontal EEG and calculated with a BIS monitor (GE Healthcare) using a BIS sensor (Aspect Medical Systems, Inc., Newton, MA, USA). The smoothing time of the BIS monitor was set to 15 s.

Preoxygenation was performed for 3 min in all patients before induction. The patients in group P received 1 mg/kg of meperidine HCl (Meperidine Injection BP® 50 mg/mL, Antigen Pharmaceuticals, Tipperary, Ireland) intravenously immediately before induction of anesthesia, and group I received 1 mg/kg of meperidine HCl intravenously 20 min before the end of the surgery. All patients had general anesthesia induction with thiopental (5-7 mg/kg), fentanyl (1 μg/kg, administered for 30-40 s), and vecuronium (0.6 mg/kg) to facilitate endotracheal intubation. Tracheal intubation was performed when neuromuscular block was obtained. During the maintenance of anesthesia, all patients were mechanically ventilated with 40% oxygen (O_2) and 60% nitrous oxide (N_2O) with 4% desflurane (gas flow rate of 2.0 L/min). Ventilation was controlled with a tidal volume of 8-10 mL/kg, and the ventilatory rate was adjusted to maintain an end-tidal CO_2 pressure of 30-40 mmHg. The desflurane concentration was adjusted to keep the BIS between 45 and 55 during surgery. In the case of an increase or decrease of BIS values for more than 30 s, the desflurane concentration was increased or decreased by 0.5%. During the last 15 min of the procedure, BIS values were allowed to increase up to 65. Hypotension (a decrease of >20% in mean arterial pressure (MAP) baseline values), if any, was initially treated with intravenous fluid replacement (Ringer's lactated, 5 mL/kg), and desflurane concentration was then reduced in steps of 0.5 vol%. If the response was inadequate, an intravenous vasopressor (5 mg of ephedrine) was used according to usual clinical practice. If hypertension and tachycardia (an increase of 20% above baseline values) occurred, the desflurane concentration was increased in steps of 0.5 vol%. If the response was inadequate, nitroprusside was given according to usual clinical practice. Bradycardia (HR < 40 beats/min) was treated with 0.5 mg of atropine intravenously. Ondansetron (4 mg) was routinely administered 15 min before the end of surgery for the prophylaxis of opioid-induced emesis. During the last surgical suture, desflurane was discontinued, and the lungs were ventilated with 100% oxygen at a fresh gas flow of 6 L/min. Patients received supplementary nasal oxygen after tracheal extubation. Intraoperative MAP, HR, SpO_2, and BIS values were recorded before and after induction of anesthesia; after tracheal intubation; immediately after skin incision; at 15, 30, 45, 60, and 75 min; and after the extubation period. The age-adjusted (11) MAC-hours of desflurane administered between intubation and extubation were calculated for every patient in both groups from the recorded end-tidal desflurane concentrations. Emergence from anesthesia was recorded as the time to resumption of spontaneous respiration, extubation, the time taken to eye-opening on command, the finger-squeeze time, and orientation to correctly stating name and date of birth (assessed at intervals of 30-60 s). All patients were discharged from the operating room when they showed stable hemodynamic status and an Aldrete score greater than or equal to 9. Anesthesia time and duration of surgery were also noted in both groups.

The day before surgery, all patients were instructed on the use of a 10-cm visual analog scale (VAS) for pain assessment (0 = no pain, 10 = worst imaginable pain) and use of a patient-controlled analgesia (PCA) device (Abbott Laboratories, North Chicago, IL, USA). In the recovery room, all patients had access to intravenous analgesia by means of a PCA device containing tramadol (Contramal® ampoules, Abdi İbrahim, İstanbul, Turkey). The settings of the PCA device were as follows: loading dose of 1 mg/kg, bolus dose 20 mg, no continuous background infusion; lockout time of 15 min; and no 4-h maximum. A pain score of ≤3 was considered satisfactory pain relief. If a patient reported a pain score of >3, he or she was encouraged to trigger the next bolus until achieving satisfactory pain relief. The VAS scores of the patients were recorded at 30 min and 1, 2, 6, 12, and 24 h after the operation. The total tramadol consumption during the same period and over 24 h was recorded. The time of first analgesic use was also recorded.

Side effects such as bradycardia, hypotension, respiration depression, itching, and allergic reaction were recorded. The sedation score was recorded in the same period. The degree of sedation was rated on a 4-point scale (0 = awake, 1 = drowsy, 2 = asleep but can be roused, 3 = asleep and unable to be roused) (12).

Statistical analysis

All statistical procedures were performed using SPSS 13.0 for Windows (SPSS Inc., Chicago, IL, USA). A sample size of 25 subjects was determined based on a previous study (13), in which statistical

significance of the changes over time to an Aldrete score of ≥9 were ensured at a level of α error of 0.05 and β error of 0.8. The normal distribution of the collected data was tested with the Shapiro-Wilk test. Patient demographic data, the duration of anesthesia and surgery, MAP, and HR were analyzed using Student's t-test. Recovery times, VAS scores of pain, consumption of desflurane and tramadol, and the time to first analgesia request were compared using the Mann-Whitney U-test. Scores of sedation were compared using the chi-square test. The results are given as means (SD), medians (25th/75th percentiles), exact numbers, or proportions expressed as a percentage. $P < 0.05$ was considered statistically significant.

Results

The study was conducted over a 9-month period from June 2009 to February 2010. No patient was excluded from the study for any reason, and the drugs were well tolerated. There were no statistically significant differences between the 2 groups regarding sex, age, weight, height, ASA physical status, duration of anesthesia and surgery, or types of surgery (Table 1). All recovery parameters, except for spontaneous respiration time, were significantly shorter in group P than in group I (Table 2).

MAP and HR, recorded at various time points during anesthesia, were comparable for both groups. There were no statistically significant differences in hemodynamic measurements between the groups in the intraoperative periods (Figures 1 and 2). As a hemodynamic side effect, hypotension was observed in 1 patient in group I, and it was managed by ephedrine administration. Hypertension and tachycardia were observed in 1 patient in group P. Bradycardia was not observed in either group. There were no statistically significant differences regarding hemodynamic side effects between the groups.

There were no statistically significant differences in consumption of desflurane between the 2 groups ($P = 0.107$) (Table 3).

VAS scores for pain in group I at 30 and 60 min and 2 h in the postoperative period were significantly higher than those of group P ($P < 0.05$) (Figure 3). However, the time of first use of analgesic was not statistically significant ($P = 0.800$) (Table 3). Similarly, there was no significant difference between the groups regarding the cumulative tramadol consumption during the first postoperative day ($P = 0.946$) (Table 3). The postoperative sedation scores in both groups were mostly similar (Table 4); however the number of patients with a postoperative 60-min sedation score of 2 in group P was 1, while in group I it was 7 ($P = 0.021$).

Table 1. Demographic data and surgical characteristics (mean ± SD).

	Group P (n = 25)	Group I (n = 25)	P-value
Age (years)	43 ± 9.82	47 ± 11.35	0.132
Weight (kg)	71 ± 6.65	74 ± 14.37	0.422
Height (cm)	161 ± 6.65	162 ± 7.51	0.418
ASA physical status (I/II)	16/9	14/11	0.564
Sex (female/male)	18/7	19/6	0.747
Duration of surgery (min)	128 ± 52.83	124 ± 43.73	0.752
Duration of anesthesia (min)	140 ± 51.93	135 ± 43.38	0.742
Type of surgery (breast/thyroid)	14/11	13/12	0.777

Table 2. Emergence and clinical recovery (median (25th/75th percentiles)).

Recovery variable (min)	Group P (n = 25)	Group I (n = 25)	P value
Spontaneous respiration	3 (3/5)	5 (3/7)	0.057
Extubation	5 (3/6)	7 (5/10)	**0.004**
Eye opening	5 (4/7)	8 (6/11)	**0.016**
Squeeze fingers	7 (6/10)	10 (8/13)	**0.012**
State name	7 (5/10)	10 (8/12)	**0.021**
State birth date	7 (6/11)	11 (9/14)	**0.014**
Aldrete score ≥ 9	7 (5/10)	10 (7/13)	**0.016**

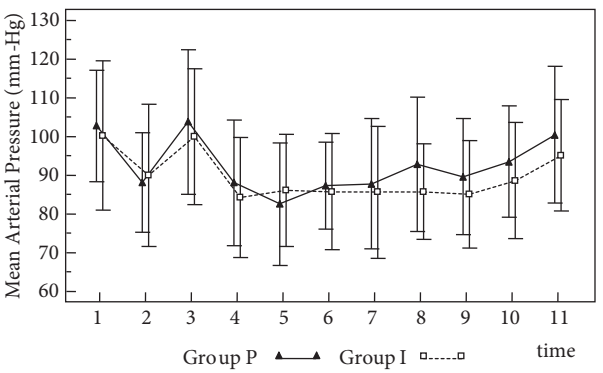

Figure 1. Mean arterial pressure (MAP) in intraoperative period (mean ± SD). 1: Preoperative, 2: after induction, 3: after intubation, 4: after surgery incision, 5: 15 min, 6: 30 min, 7: 45 min, 8: 60 min, 9: 75 min, 10: before extubation, 11: after extubation.

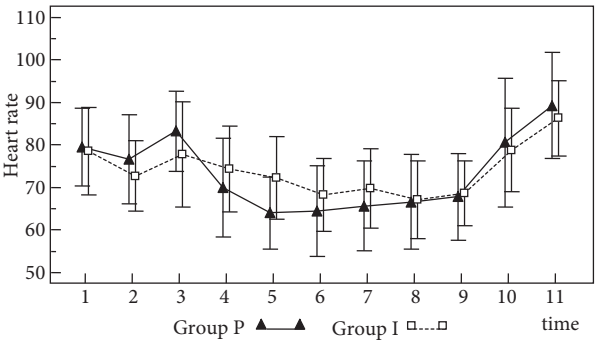

Figure 2. Heart rate (HR) in intraoperative period (mean ± SD). 1: Preoperative, 2: after induction, 3: after intubation, 4: after surgery incision, 5: 15 min, 6: 30 min, 7: 45 min, 8: 60 min, 9: 75 min, 10: before extubation, 11: after extubation.

None of the patients suffered from any adverse events such as respiratory depression, itching, bronchospasm, or allergic reaction.

Discussion

In the present study, we demonstrated that intravenous administration of meperidine at 1 mg/kg preoperatively resulted in better VAS scores than were seen in the intraoperative meperidine group in the early postoperative period, and there was no significant difference regarding the first analgesic requirement time or consumption of tramadol. Secondly, those receiving preoperative administration of intravenous meperidine at 1 mg/kg recovered more quickly than those receiving intraoperative administration. Thirdly, the consumption of desflurane and hemodynamic changes were comparable between the groups.

The provision of preemptive analgesia is defined as the administration of various analgesic agents (systemic and regional opioids, local anesthetics,

Table 3. Consumption of anesthetics and first analgesic requirement.

	Group P (n = 25)	Group I (n = 25)	P-value
Consumption of desflurane (mL)	50 (33-68)	60 (49-67)	0.107
Consumption of tramadol (mg)	95 (68-120)	86 (75-125)	0.946
First analgesic requirement (min)	45 (29-70)	45 (28-82)	0.800

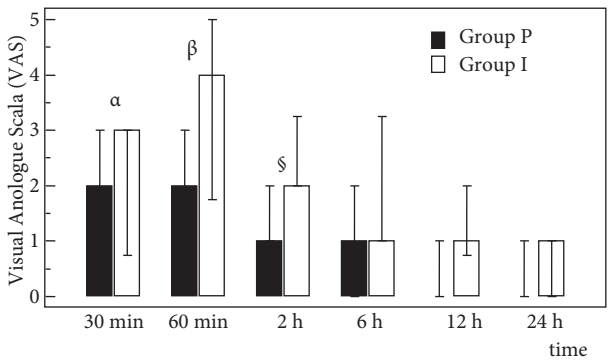

Figure 3. VAS pain score in the postoperative period.
α: P = 0.014, group P versus group I; β: P = 0.004, group P versus group I; §: P = 0.002, group P versus group I.

Table 4. Sedation score (0/1/2/3).

	Group P (n = 25)	Group I (n = 25)	P-value
30 min	1/11/12/1	-/9/15/1	0.675
60 min	15/9/1/-	7/16/7/-	0.074
2 h	18/6/1/-	18/7/-/-	0.584
6 h	22/3/-/-	24/1/-/-	0.297
12 h	25/-/-/-	24/1/-/-	0.312
24 h	25/-/-/-	25/-/-/-	1

NSAIDs) (14) before the onset of surgical stimulus in order to prevent development of central nervous system (CNS) hyperexcitability or sensitization (14,15). It is believed that central sensitization results from increased excitability of the dorsal horn neurons in the spinal cord. After such sensitization, an exaggerated responsiveness to further noxious stimuli may ensue, and this may be associated with a decrease in the pain threshold (8,16). The primary goals of preemptive analgesia are to decrease acute pain following tissue injury, to prevent pathological modulation of the CNS due to this pain, and to prevent development of chronic pain; clinical studies have been unable to clearly show evidence of the achievement of these goals (17). The secondary goals of preemptive analgesia such as opioid administration are to reduce volatile anesthetic requirements by decreasing MAC values, increase intraoperative hemodynamic stability, and shorten recovery times (3,4).

Opioids are widely used to provide analgesia in the induction and maintenance of anesthesia in the postoperative period. Various studies demonstrate that opioid administration reduces the volatile anesthetic requirement by decreasing MAC values (18,19). However, to the best of our knowledge, there is no study in the literature concerning the effects of preoperative or intraoperative meperidine on volatile anesthetic consumption. The present study showed that there was no significant difference regarding consumption of desflurane between the groups. Numerous clinical studies have already shown that preemptive analgesia is very effective in perioperative pain (20-22). Many clinical trials have suggested that the timing of analgesic treatment in relation to the surgical injury is the most important issue (6,7). The sole difference between the study groups in this present work was the timing of meperidine administration. Chew et al. (23) studied the preemptive analgesic effects of meperidine by comparing its analgesic effects when given before or immediately after an operation in a randomized, double-blind study of 40 patients undergoing removal of bilateral impacted third molars under

general anesthesia. They concluded that preoperative administration of meperidine intramuscularly did not confer additional analgesic effects compared with a similar dose given after surgery. Pjević et al. (9) demonstrated that there was no significant difference in pain scores or in the analgesic requirements of patients who received systemic meperidine at 1 mg/kg before the painful stimulus, compared with the patients treated with the opioid intraoperatively. We found that VAS scores for pain values in the intraoperative group in the early postoperative period were significantly higher than those of the preoperative meperidine group. As pain assessment and analgesic requirements were recorded during the first 24 h postoperatively, our results show that the time of first analgesic use was not significantly different between the groups. The mean VAS score in the preoperative meperidine group was reduced during the early postoperative period, but total tramadol consumption was not different between the groups.

Prevention or reduction of pain during the perioperative period is an important component of recovery in the postoperative period (24). Rapid early recovery may also be associated with a greater appreciation of pain in the early postoperative period, which increases postoperative analgesic requirements and thus delays recovery (25). Our study showed that early recovery scores were delayed in the intraoperative meperidine group as compared with the preoperative meperidine group. It may be speculated that the peak hypnotic effect of intraoperative meperidine may occur at the end of the surgery. In a study by Van den Berg et al. (26), use of intravenous meperidine (1.5 mg/kg) before the induction period prolonged recovery of spontaneous respiration by 1-2 min. The high dose of meperidine and the short operation time might be a cause of prolonged recovery in this study. Another study demonstrated that the incidence of drowsiness and sedation with meperidine use was between 13% and 20% (27). In our study postoperative 60-min drowsiness and sedation was found to be 4% in the preoperative meperidine group and 28% in the intraoperative meperidine group. Other postoperative sedation score times were found to be similar in the preoperative and intraoperative meperidine groups.

Opioids also maintain hemodynamic stability by preventing or reducing perioperative pain. Meperidine is known to cause histamine release and myocardial depression more frequently than other opioids. In addition, meperidine has atropine-like effects on heart rate (28). We did not see any differences between the study groups regarding hemodynamic stability and side effects.

Current therapeutic strategies for the management of acute pain are largely dependent on opioid analgesics and NSAIDs (16). Depending on the dosage of opioids delivered by PCA, complications such as respiration depression, sedation, nausea, vomiting, urine retention, and itch may develop. The respiratory depression induced by opioids given during anesthesia has clinical significance in that it may slow the turnover of patients on operating lists (26). Sedation is the earliest indicator of respiratory depression. In the present study, we did not find an increase in sedation scale values resulting in the occurrence of respiratory depression. In this study, the frequency of side effects did not significantly differ between the groups.

We conclude that the preoperative administration of meperidine at 1 mg/kg allows for early recovery and better postoperative VAS scores for pain, when compared with intraoperative administration, in patients undergoing elective subtotal thyroidectomy and elective breast-conserving surgery. The results suggest that preoperatively administered meperidine has a better preemptive analgesic effect on postoperative pain.

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