

# The effect of opioid administration by different routes on the psychological functions of elderly patients

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## ÖZET

### Farklı yollarla opioid uygulamalarının yaşlı hastalardaki psikolojik fonksiyonlara etkisi

Epidural ve intravenöz morfin uygulamaları sırasında hastaların psikolojik durumunda oluşan değişiklikler yeterince bilinmemektedir. Epidural ve intravenöz uygulanan morfinin plazma konsantrasyonlarının benzer olduğu ancak serebrospinal sıvıdaki konsantrasyonlarının farklı olduğu gösterilmiştir. Bu randomize tek kör çalışmada major ortopedik girişimler sonrası uygulanan iki farklı yol ile uygulanan analjezik rejimin yaşlı hastaların psikolojik ve mental fonksiyonları üzerine olan etkileri araştırılmıştır. Hasta kontrollü analjezi yöntemi kullanılarak E grubundaki hastalara epidural yoldan, i.v. grubundaki hastalara ise intravenöz yoldan morfin uygulanmıştır. Tüm hastaların psikolojik durumu Kısa Semptom Envanteri kullanılarak operasyondan bir gün önce ve operasyondan iki gün sonra değerlendirilmiştir. Kısa Semptom Envanterinin sonuçları Rahatsızlık Ciddiyet İndeksi (RCİ) kullanılarak yorumlanmıştır. Bu indeks kullanılarak ayrıca depresyon, somatizasyon, obsesif-kompulsif kişilik, anksiyete, kişiler arası duyarlılık, fobik anksiyete, düşmanlık, paranoid düşünce ve psikotizm gibi dokuz farklı (alt grup) psikolojik durum ile ilgili çıkarımlar yapılmıştır. Preoperatif ve postoperatif RCİ sonuçları arasında anlamlı bir farklılık saptanmamıştır ( $p>0.05$ ). Sadece kişiler arası duyarlılık alt skalası i.v. grupta basal değere göre anlamlı olarak düşük bulunmuştur ( $p<0.001$ ). Preoperatif Kısa Semptom Envanteri ve alt grup değerlendirme sonuçları her iki grupta da toplam morfin tüketimi ile ilgili bir korelasyon ortaya koymamıştır ( $p>0.05$ ). Bu çalışma, epidural ve intravenöz morfin kullanımı sonrasında her iki gruptaki hastalarda da postoperatif dönemde psikolojik strese artış olmadığını göstermiştir. Ancak intravenöz morfin alan hastalarda, postoperatif dönemde kişiler arası iletişimi gösteren parametrelerde olumlu sonuçlar elde edilmiştir.

**Anahtar kelimeler:** postoperatif analjezi, psikolojik fonksiyon bozukluğu, ortopedi, yaşlılık, morfin

## SUMMARY

Psychological status of patients during epidural and intravenous (i.v.) morphine administration are not known enough. It's known that after administration of morphine epidurally and intravenously plasma concentrations are similar but the concentrations in cerebrospinal fluids are different. The effects of two postoperative analgesia treatment regimens on the psychological and mental functions of the elderly after major orthopedic surgery were investigated in this randomized, blinded study. Morphine was used epidurally in Group E and intravenously in Group IV with patient controlled analgesia method for postoperative analgesia treatment. All patients were assessed for psychological status the day before surgery and 2 days after surgery using the Brief Symptom Inventory (BSI). The results of the BSI were assessed with the Global Severity Index (GSI). Nine subscales were also derived: depression, somatization, obsessive-compulsive, anxiety, interpersonal sensitivity, hostility, phobic anxiety, paranoid ideation, and psychoticism. There was not significant difference between the groups for preoperative and postoperative GSI results ( $p>0.05$ ). Only interpersonal sensitivity subscale results in Group i.v. were decreased compared to the baseline ( $p<0.001$ ). Preoperative BSI and submeasurement test scores revealed no correlation with total morphine consumption in both groups ( $p>0.05$ ). Mental changes like agitation, time and place disorientation were seen equally in both groups. This study showed that after epidural and intravenous morphine administration, no psychological changes were observed in the postoperative period compared with baseline. Patients who received morphine intravenously were showed less interpersonal sensitivity in the postoperative period.

**Key words:** Postoperative analgesia, psychological dysfunction, orthopedics, elderly, morphine

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## Introduction

It is known that cognitive function and mood differences may develop in elderly patients after neurosurgical, cardiac and orthopedic surgery. Microemboli, drugs and the surgical techniques used are the probable causes of these changes. Very old age, low educational level, marked preoperative depressive symptoms, hospitalization, recent history of cognitive dysfunction and duration of surgery are the factors that are mostly associated with the development of postoperative cognitive dysfunction (Canet et al. 2003, Ancelin et al. 2001). It is also known that opioid analgesics used in the postoperative period also have central nervous system (CNS) side effects. Opiate receptors have been found in various areas of the CNS. The plasma levels of morphine after epidural administration seemed comparable to those seen after intravenous or intramuscular administration (Norberg et al. 1984). The cerebrospinal fluid (CSF) concentration of morphine injected in the epidural space far exceeds, that in plasma. The concentrations of morphine in CSF after epidural administration are 100-200 times the corresponding plasma levels. With similar elimination half-lives for morphine in CSF and plasma, the long analgesic duration probably depends on the locally high morphine concentrations achieved. Poor correlation was found between plasma concentrations and analgesic duration after epidural morphine administration. Changes in plasma morphine concentrations would not necessarily be proportional to changes in concentrations in the central nervous system which contains the sites of morphine's analgesic and side effect actions (Nordberg G. et al. 1983). Morphine and fentanyl have been shown to have different effects on mood and these opioids have been used epidurally (Tsueda et al. 1998). We have not come across any studies on whether morphine administered by the epidural or intravenous route has an effect on psychological or cognitive functions. If any unwanted effects of opioids dependant on their administration route were known beforehand, especially in elderly patients, the differential diagnosis of postoperative cognitive dysfunction and psychological changes could be more easily made and successfully treated.

The aim of this study was to investigate the effects of i.v. PCA morphine and epidural PCA morphine on the psychological and mental functions of elderly patients following hip and knee arthroplasty. In this setting side effects, total morphine

consumptions and pain scores in both groups were also evaluated and correlation test was made.

## Materials and Methods

Fifty patients, aged 60-75 years, classified as ASA I-III and scheduled for elective hip or knee replacement surgery using general anesthesia were recruited for this randomized, blinded, two-group parallel study. Neither the patient nor the psychologist knew about the analgesia method preoperatively while the person administering the test was unaware of the analgesia method postoperatively. After Ethic Committee approval was secured, written informed consent was obtained from all patients. A known allergy to morphine, abnormal coagulation profile, psychiatric disease, mental confusion, alcohol or drug abuse, psychotropic medication usage, the presence of chronic pain and morbid obesity were exclusion criteria for the study.

Patients were randomized into two groups. Computer assisted randomized treatment assignments were enclosed in sequentially ordered, sealed envelopes, which were opened just before anesthesia. Group E consisted of patients receiving patient controlled epidural analgesia (PCEA group, n=25) while group i.v. consisted of patients receiving patient controlled intravenous analgesia (i.v. PCA group, n=25), both using a PCA pump. Morphine was used for postoperative analgesia in both groups.

## Measures and Study Procedures

All patients were assessed using the BSI (Brief Symptom Inventory) derived from the symptom check list-90 (SCL-90) (Derogatis et al. 1994, Derogatis 1992). Intended as a screening tool for detecting clinical symptoms as indicators of emotional distress, the BSI is a self-rated questionnaire with 53 items to be answered on a 5-point Likert-type scale (0-4), ranging from "not at all" to "extremely". It is a reliable and valid scale that assesses psychiatric symptoms experienced in the past week. The results of the BSI test were assessed with the Global Severity Index (GSI). GSI is obtained by dividing the total score by 53 for each patient. It reflects the overall level of psychological distress, with higher scores indicating increased severity of symptoms. Nine subscales are evaluated with the following items: Somatization: 2, 7, 23, 30, 33 and 37, Obsessive-

compulsive disorder: 5, 15, 26, 27, 32 and 36, Interpersonal sensitivity: 20, 21, 22 and 42, Depression: 9, 16, 17, 18, 35 and 50, Anxiety: 1, 12, 19, 38, 45, 49, Hostility: 6, 13, 40, 41, and 46, Phobic anxiety: 8, 28, 31, 43, 47, Paranoid ideation; 4, 10, 24, 48 and 51, Psychoticism; 3, 14, 34, 44 and 53.

BSI was applied to both groups by psychologist the day before surgery and 48 hours after the surgery. The patients' mental status was assessed with physical and neurological mental status examination before the BSI test and the patient was excluded from the study if a mental disorder was detected.

Sedation was evaluated in the postoperative period by using the Sedation Scale: 1: awake, 2: reacting to spoken stimuli, 3: reacting to painful stimuli, 4: no reaction.

### **Management of Anesthesia and Postoperative Pain**

Induction was with 3-5 mg/kg thiopental and 1 mg/kg fentanyl in both groups. Tracheal intubation was facilitated by 0.1 mg/kg vecuronium. Anesthesia was maintained by inhalation of nitrous oxide/oxygen (50%) in 1.5-2.0 MAC sevoflurane. Vecuronium was used as needed during the operation and fentanyl was used when the blood pressure increased by 15% according to initial baseline. In group E, an epidural catheter was inserted either at the L3- L4 level or at L4- L5 level preoperatively. After ensuring motor blockade did not develop by using 3 ml of 2% prilocaine as a test dose, general anesthesia was administered to each patient as described above. Two mg of morphine in 10 ml saline was administered epidurally thirty minutes before the end of the operation. In group i.v., 3 mg of morphine was administered intravenously thirty minutes before the end of the operation. The trachea was extubated at the end of the operation after the reversal of neuromuscular block. Analgesic treatment was initiated in the recovery room and maintained for 48 hours in the postoperative period. One mg morphine bolus was given as a loading dose every 10 minutes until VAS 3 was achieved. Intravenous and epidural PCA was applied using a pump (Abbott Pain Manager; Abbott Laboratories, North Chicago, IL, USA) postoperatively. The PCA regimen was 1 mg morphine in 5 ml saline bolus, 30-minute lockout period, 20 ml per four hours limit for group E and

1 mg bolus, 15-minute lockout period with 0.3 mg/ml morphine concentration for group i.v. Demographic data such as gender and age were recorded. The intensity of pain was evaluated in the resting position at hour 0, 1/2, 1, 2, 4, 8, 10, 12, 18, 24, 36 and 48 using the Visual Analog Scale (VAS). A VAS score of 3 was accepted to be an adequate analgesia level. The amount of morphine consumed at the a fore mentioned times was recorded together with the blood pressure, pulse, pain score and any side effects. The patients were followed for side effects that may be caused by morphine such as nausea, vomiting, itching, dryness of mouth, sweating, urinary retention, sedation, respiratory depression and hypotension. A respiratory rate below 10/min was defined as respiratory depression. A heart rate below 50/ minute was accepted as bradycardia and a decrease in the average arterial pressure by 30% compared to the baseline was accepted as hypotension. Metoclopramide 10 mg i.v. was used for vomiting, nausea and the retching reflex while phenylamine 5 mg i.v. was used for itching. Respiratory depression was to be treated with 0.1 mg of i.v. naloxan every 2- 3 minutes until the patient reacted, bradycardia was to be treated with 0.5 mg i.v. atropine, and hypotension was to be treated with the infusion of 1000 ml of crystalloid solution followed by 2.5 mg i.v. ephedrine if there was no improvement.

### **Statistical Analysis**

Assuming an alpha error of 0.05 and power of 0.80, at least 11 cases were required in each group to be able to accept a difference of 0.4 units in GSI units from the baseline between the epidural group and i.v. group as significant. The number of cases was set at 50 taking into account studies where the BSI test had been used (Pietrzak et al. 2006, Endermann 2005) Student's t test was used for comparing group E and group i.v. in terms of their age, blood pressure, heart rate. Chi-square test was used to compare gender difference between groups. The statistical comparison of the VAS scores during the following hours and GSI results were carried out with the Mann-Whitney U test,  $p < 0.05$  was significant. The Wilcoxon Sign Rank test was used for evaluating preoperative and postoperative BSI scores separately for each group. The values were expressed as median and interquartile range (IQR). These results were corrected by using Bonferroni correction and  $p < 0.025$  was accepted as significant

**Table 1:** Demographic data of the groups. Results were expressed mean±s.d.

	<b>Epidural PCA: Group E , n (number of patient) = 21</b>	<b>i.v. PCA : Group i.v., n (number of patient) = 21</b>
<b>Gender (Male/Female)</b>	8/13	3/18
<b>Age (years)</b>	68 ±4	69± 4
<b>Type of surgery:</b>		
<b>Total hip replacement</b>	7	5
<b>Total knee replacement</b>	14	16

*p*>0.05

value. The Spearman correlation coefficient was used for investigating correlations between morphine consumption and preoperative BSI and submeasurement test scores. *P*<0.05 was accepted as a significant value.

## Results

One patient from group E and one patient from group i.v. were excluded because of cooperation problems. The analysis of gender, age, type of surgery were performed and no statistically significant difference was found between the groups (*p*>0.05) (Table 1). Blood pressure and heart rate were comparable in both groups in all follow up periods. Agitation and time and place disorientation were observed in six patients (three in group E and three in group i.v.). These symptoms were observed at the end of the first postoperative day. Morphine used for analgesia was stopped and another postoperative analgesia method was initiated. The patients were followed up by the Neurology Unit and their symptoms resolved within a day or two. Intraoperative mean fentanyl consumption was not statistically significantly different between groups (*p*>0.05). The mean VAS score results in both groups during the follow-up period are shown in Figure 1. There wasn't statistically significant difference between the groups in all follow up periods (*p*>0.05). The mean morphine consumption was 18.57±6.63 mg in group E and 61.66±16.92 mg in group i.v. at the end of 48th postoperative hour (Figure 2).

When group E and group i.v. were compared according to preoperative and postoperative BSI and submeasurement test points, although there was a statistically significant difference between the paranoid ideation and somatization test results of group E (*p*<0.05), Bonferroni correction

revealed no significance in these tests results of group E (*p*>0.025). All test results can also be seen from Table 2. When the preoperative and postoperative test results of group i.v. were evaluated, a statistically significant difference was observed only for the interpersonal sensitivity test (*p*<0.001) (Table 3). There was a significant decrease in mean test scores postoperatively. When each group was compared according to their GSI with the Mann-Whitney U test, a statistically significant difference was not found between the test scores of the two groups for the preoperative and postoperative period (*p*>0.05) (Table 4) The Spearman correlation coefficient did not show a statistically significant correlation in either group for preoperative BSI and submeasurement test scores and changes in total morphine consumption (*p*>0.05).

While 8 patients had nausea, 6 had vomiting, 2 had hypotension and 2 patients had itching in group i.v., 6 patients had nausea, 4 had vomiting, 3 had hypotension in group E during the follow up period.

## Discussion

We compared the effect of intravenous and epidural morphine administered by the PCA method for postoperative analgesia on mental functions and mood in 60-75 age patients undergoing lower extremity surgery. We screened for symptoms using the BSI test, which has the same reliability as the SCL-90. It has been recommended as highly sensitive for psychiatric disorder and psychological distress. Although there was no difference in GSI points between groups, we found difference in submeasurement test points as these tests were calculated by summation of some items

of BSI questionnaire. The score of interpersonal sensitivity test was different in both groups.

In the present study both epidural and i.v. patient controlled analgesia regimens were effective in pain relief with similar side effects. In i.v. patient controlled analgesia group side effects were slightly more than other group. It has been reported that epidural analgesia was superior to i.v. analgesia with respect to pain relief after abdominal and major spine surgery (Schenk 2006, Mann 2000) After unilateral total hip arthroplasty, i.v. PCA with morphine and continuous epidural analgesia with 0.125 % bupivacaine provided similar pain relief but hypotension and catheter placement difficulties were observed in epidural analgesia group (Singelyn 2005). In the present study epidural analgesia was provided with morphine because of the study design. The limitation of this study is the pain scores was evaluated only in the rest position. The VAS scores during the movement may be changed.

In elderly patients who have a latent attenuated physiological reserve, special attention should therefore be paid in perioperative hypotension. Number of patients with hypotension episodes during postoperative period were comparable in this study in both groups.

The effect of anaesthetic procedure and oxygenation during total hip replacement have been reported. They found that when compared with the preoperative level, the degree of cognitive dysfunction was similar in the regional and general anesthesia groups, and returned to the preoperative level on the third postoperative day (Dahn et al. 2003). Studies indicate that cognitive function impairment does not depend on the anesthetic technique (Rasmussen et al. 2003). Investigators couldn't find the study in literature discussing the effect of epidural or i.v. morphine used in postoperative period on cognitive or psychological dysfunctions. Delirium is a more advanced form of cognitive dysfunction or psychiatric dysfunction and can be seen following 15-25% of elective and 25-65% of emergency orthopedic procedures on elderly patients. Delirium begins in the postoperative period and becomes apparent on the 3rd postoperative day (Marcantonio et al. 2000). Chonchubhair et al. (1995) observed delirium on the 3rd postoperative day in 10 of 43 orthopedic patients. We observed agitation, time and place disorientation in 6 of our patients. These symptoms developed on the first postoperative day in one patient and

the second postoperative day in the others. These patients were equally distributed to the two groups. Our study group consisted of patients undergoing elective surgery observed postoperatively for 48 hours. The route of morphine administration didn't have any effect on the development of cognitive and psychological disorders mentioned above.

Opioids have some positive and negative effects on mood according to the type of opioid used (Tsueda et al. 1998). Unfortunately, there are few studies on opioid usage and their psychological effects following major orthopedic surgery. Tsueda et al. (1998) compared the mood differences of patients receiving epidural fentanyl PCA and epidural morphine PCA. The results showed that epidural fentanyl had negative and depressed effects on mood states and epidural morphine had more positive effects in all follow up times in the postoperative period. While there was an inverse correlation between mood state scores and plasma concentrations of fentanyl, there was no correlation between mood state scores and plasma concentrations of morphine. In present study, similar with the results above, there was no correlation between test results and morphine dose. Only i.v. morphine made a change in interpersonal sensitivity test results. Despite the lack of correlation between psychological test results and morphine dose, group i.v. patients were more confident than others in the postoperative period. For more explanation morphine levels in cerebrospinal fluid in i.v. and epidural group may be measured in future studies.

This study was done with patients between 60-75 years old undergoing knee and hip replacement surgery and the mean age and gender results are comparable between groups. Similar with results of this study Endermann (2005) used BSI as a screening tool for psychological disorders in patients with epilepsy and mild intellectual disabilities and he didn't find meaningful relationship between age, gender and GSI.

The association between postoperative confusion and preoperative psychiatric symptoms (depression, anxiety) and cognitive dysfunction is known (Kudoh et al. 2004, Akerlund et al. 1994). The postoperative confusion rate was increased in patients who used benzodiazepine in the preoperative period (Kudoh et al. 2004). Taking these reports into account, patients who needed treatment because of a psychiatric problem were not included in present study.

Some studies have demonstrated that high anxiety levels increase the sensation of pain (Feeney 2004). Egbert et al. (1993) did not observe any effects of the i.v. PCA technique on the postoperative state anxiety in elderly male patients and they postulated that postoperative state anxiety was related most closely to preoperative anxiety and postoperative complications, rather than the method of analgesia or severity of pain. In this study, similar to the study mentioned above, anxiety scores were not increased in the postoperative period in neither group. We also did not find a correlation between the morphine consumption and anxiety scores in either group. The importance of anxiety and stress management as a component of the treatment of acute pain in older adults was reported (Feeney 2004). For this purpose we explained the analgesic management to the patients the day before surgery and prior to performing the BSI test and this approach may be the reason for the lower anxiety levels of our patients.

## Conclusion

The results of this study show that postoperative morphine used for epidural and i.v. analgesia is an effective postoperative analgesia method in elderly patients after major orthopedic surgery. We observed that the administration route of morphine made no difference in the GSI. The reason for no change in GSI compared to baseline may be that morphine was administered by the PCA method. The patient therefore would receive the minimal dose that would alleviate the pain and made the relevant decision himself/herself. Bolus doses administered by PCA were kept at the lowest possible levels in this study and basal infusion was not preferred. The findings that group i.v. patients who scored lower interpersonal sensitivity points in the postoperative period, suggested that they were more self confident and showed less behavior and feelings of inferiority. This study was performed on patients with no previous psychological disease and treatment. Different results may be obtained in patients who had psychological disorders. The results of the present study suggest that administration route of morphine has neither positive nor negative effect on psychological distress and cognitive impairment in elderly patient undergoing major orthopedic surgery.

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