



## ARAŞTIRMA/RESEARCH

# Comparison of incidence and risk factors of delirium between general and regional anesthesia in elderly patients after lower extremity surgery

Alt ekstremitte cerrahisi geçiren yaşlı hastalarda genel ve rejyonel anestezi sonrası görülen deliryum sıklığı ve risk faktörlerinin karşılaştırılması

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*Cukurova Medical Journal 2016;41(1):34-40.*

### Abstract

**Purpose:** The aim of this study is to compare the risk factors and the incidence of delirium following orthopedic surgery under the general or regional anesthesia in elderly patients.

**Material and Methods:** One hundred twenty elderly patients aged  $\geq 65$  years scheduled for total hip or knee arthroplasty and femur fracture surgery were enrolled into the study. Patients were allocated into two groups to receive regional anesthesia (group R, n=50) or general anesthesia (group G, n=70). Hemodynamic and blood parameters, potential risk factors of delirium including age, sex, duration of surgery, the type of anesthesia, coexisting disease, smoking and amount of drug used delirium tests (Confusion Assessment Method, Delirium Rating Scale-Revised-98), hospital stay and costs were recorded for all patients.

**Results:** Demographic data, duration of surgery, preoperative and postoperative hemodynamic and laboratory parameters were similar in two groups. Delirium incidence was 12.5% for all patients. We found delirium in six patients (8.6%) of group G and nine patients (18%) of group R. The most important risk factors were advanced age and polypharmacy for all patients. Hospital stay and cost were associated with severity of delirium.

**Conclusion:** We found that the incidence of delirium is 12.5% in elderly patients undergoing total hip or knee arthroplasty and femur fracture surgery. Advanced age and polypharmacy are risk factors of delirium. Delirium increases the hospital stay and cost.

**Key words:** General anesthesia, regional anesthesia, postoperative delirium

### Öz

**Amaç:** Bu çalışmada; ortopedik cerrahi geçiren yaşlı hastalarda genel anestezi veya rejyonel anestezi sonrası görülen deliryum insidanslarının ve risk faktörlerinin karşılaştırılması amaçlanmıştır.

**Gereç ve Yöntem:** Total kalça protezi, total diz protezi, femur kırığı cerrahisi geçiren, 65 yaş üzeri toplam 120 hastada gerçekleştirildi. Genel anestezi (n: 70) veya rejyonel anestezi (n:50) uygulanmasına göre iki gruba ayrıldı. Tüm hastaların, hemodinamik ve kan parametreleri, yaş, cinsiyet, ameliyat süresi, anestezi tipi, eşlik eden hastalıklar, sigara ve kullanılan ilaç miktarı gibi deliryumun potansiyel risk faktörleri, deliryum testleri (Confusion Assessment Method, Delirium Rating Scale-Revised-98), hastanede kalış süreleri ve maliyetleri kaydedildi.

**Bulgular:** demografik veriler, operasyon zamanı, preoperatif ve postoperatif hemodinamik ve laboratuvar değerleri her iki grupta aynıydı. Tüm hastalar için deliryum insidansı %12.5 idi. Grup G'de 6 hastada (%8.6), grup R'de 9 hastada (%18) deliryum görüldü. En önemli risk faktörlerinin ileri yaş ve polifarmasi olduğu saptandı. Ağır deliryum görülen hastalarda hastanede yatış süresi ve maliyet yüksekti.

**Sonuç:** bu çalışma total kalça- diz artroplastisi, femur kırığı cerrahisi geçiren yaşlı hastaların %12.5'unda deliryum geliştiğini göstermiştir. Deliryum insidansı rejyonel veya genel anestezi ile değişiklik göstermedi. İleri yaş ve polifarmasi deliryum için risk faktörleridir. Deliryum hastane maliyeti ve hastanede yatış süresini artırır.

**Anahtar kelimeler:** Genel anestezi, rejyonel anestezi, postoperatif deliryum

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Geliş tarihi/Received: 30.05.2015 Kabul tarihi/Accepted: 27.07.2015

## INTRODUCTION

Delirium is a condition that characterized with an acute onset, and progressed undulated, presented with symptoms such as loss of attention, cognitive and circadian rhythm abnormalities<sup>1</sup>. The prevalence of delirium increases sharply with age, and about 20 percent of older patients have delirium at the time of hospital admission for any reason<sup>2</sup>.

Postoperative delirium (POD) has a special importance in the elderly patients undergoing surgery. The pathophysiological mechanism of POD is not fully clarified, however some contributing factors are known including previous delirium, age  $\geq 70$ , previous cognitive impairment, narcotic analgesic or benzodiazepine use before surgery, polypharmacy, previous history of POD, and self-reported health impairment from alcohol<sup>3</sup>. Perioperative triggers of delirium are acute pain, use of physical restraints, malnutrition, addition of three or more medications in 24–48 h, urinary bladder catheter, anemia, electrolyte and fluid disturbances, major surgical bleeding and blood transfusion<sup>4</sup>. Delirium is associated with increased the risk of mortality, prolonged hospital stay and higher costs<sup>5</sup>. Currently, the role of type of anesthesia is still unclear although many studies demonstrate that there is no difference between general and regional anesthesia in terms of the incidence of postoperative delirium<sup>6</sup>.

In the present study, we aimed to compare the effect of the general and regional anesthesia on the postoperative delirium incidence and to determine its risk factors in elderly patients undergoing lower extremity surgery.

## MATERIAL AND METHODS

After obtaining approval by the Cukurova University Clinical Research Ethics Committee and written informed consent, with American Society of Anesthesiologists physical status I-III, 120 patients aged  $\geq 65$  years scheduled for total hip or knee arthroplasty and femur fracture surgery were enrolled into the study. Exclusion criteria were patient refusal, abuse of alcohol and/or drugs, hypersensitivity to local anesthetics, vertebral abnormality, previous lumbar vertebra surgery, coagulation disorder, infection (systemic or local), cerebrovascular disease, chronic diabetes mellitus, renal and hepatic insufficiency, neurosurgery,

vascular surgery, frequent use of analgesic drug,  $\geq 5$  drugs per day and psychiatric medication. Two patients were excluded from the study; a patient developed acute kidney failure in the postoperative period and hypoglycemia occurred in one patient in group R. Total of 118 patients were included in the study. Patients were allocated into two groups to receive regional anesthesia (group R,  $n=48$ ) or general anesthesia (group G,  $n=70$ ). Blood pressure, heart rate and peripheral oxygen saturation, American Society of Anesthesiologists physical status (I-III), delirium tests (CAM and DRS-R-98) were recorded for all patients. Hematocrit, red and white blood cell counts, sodium, potassium, creatinine, and glycaemia values in blood samples were also recorded. Patients received iv morphine 0.1 mg/kg 30 minutes before the end of surgery and 5 mL of bupivacaine 0.5% with morphine 1mg via epidural catheter for postoperative analgesia in group G and group R, respectively. Hemodynamic and laboratory parameters and delirium tests were recorded for 24 and 72 hours in postoperative period. We administered haloperidol to patients if severe delirium occurred. We recorded some of the values that could be risk factors of delirium including age, sex, the duration of surgery, the type of anesthesia, coexisting disease, smoking and amount of drug used. We evaluated hospital stay and costs associated with delirium.

We recorded the laboratory test results including hemoglobin, red and white blood cell counts, platelet count, sodium, potassium, alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN), creatinine, total protein, albumin and glucose values in patient's blood samples one day before surgery. Confusion Assessment Method (CAM) and the Delirium Rating Scale revised version-98 (DRS-R-98) tests were performed to assess the presence of preoperative delirium and its severity at the same time. On the day of surgery, after all patients were monitored with electrocardiography, non-invasive blood measuring and peripheral oxygen saturation, patients were randomly allocated into two groups to receive regional anesthesia (group R,  $n=50$ ) or general anesthesia (group G,  $n=70$ ) according to manual randomization list. In group G, anesthesia was induced with iv propofol (2 mg.kg-1) and maintained with 2% sevoflurane in a mixture of 65 % nitrous oxide and 35 % oxygen with a total gas flow rate of 6 L min-1. Neuromuscular relaxation was induced with iv rocuronium (0.5 mg.kg-1).

Intravenous infusion of 0.9% saline was administered at a volume of 5 mL/kg/h. Patients received morphine (0.1mg/kg) for postoperative analgesia 30 minutes before the end of the operation. Anesthesia was terminated and neuromuscular blockade was antagonized with neostigmine (0.05 mg.kg-1) and atropine sulphate (0.01 mg.kg-1). In group R, we performed combined spinal-epidural anesthesia to the patients in the sitting position. We inserted a 18-G Tuohy needle at the L3/L4 or L2/L3 intervertebral epidural space using an epidural loss of resistance technique and thus performed needle-through-needle technique for subarachnoid injection of 2 mL bupivacaine (0.5%) and fentanyl (25 mcg) by 27-G spinal needle. After subarachnoid injection, epidural catheter was advanced and fixed. Following the epidural catheter placement, patients were positioned to supine. Successful surgical anesthesia was defined as achieving a sensory blockade to T4 level with pinprick test. The level of motor block was determined according to Bromage scale. Intravenous infusion of 0.9% saline was administered at a volume of 5 mL/kg/h. Oxygen 2 L/min was given by nasal cannula during the surgery.

We did not perform sedation to any patients. If the patients complained of pain, 5mL of bupivacaine 0.5% could be administered. At the end of the surgery 5 mL of bupivacaine 0.5% plus morphine (1 mg), adding to 4 mL saline was injected via epidural catheter for postoperative analgesia. Side effects such as nausea and vomiting, chilling, hypertension, hypotension were noted. Epidural catheter was removed at 24th hours. Patients were assessed negative neurologic outcomes such as motor or sensory loss.

### Postoperative care

All patients were evaluated at postoperative 24th and 72th hours with laboratory tests including hemoglobin, sodium, potassium, BUN, creatinine, total protein, albumin and glucose values in blood samples and delirium tests (CAM and DRS-R-98). CAM measures the presence or absence of delirium according to four diagnostic criteria as following; acute onset and fluctuating course, inattention, disorganized thinking and altered level of consciousness. Diagnosis of delirium requires the presence of both the first and the second criteria

and of either the third or the fourth criterion. DRS-R-98 rates the severity of delirium as 0-11 "no delirium", 12-16 "mild delirium" and  $\geq 17$  "severe delirium". Hypoactive and hyperactive delirium distinction was made according to clinical findings. If patients had positive values according to the CAM and DRS-R-98 value  $\geq 17$ , they were consulted to the psychiatry.

The primary outcome measure was the presence of postoperative delirium as defined by CAM criteria. Secondary outcome measures were severity of delirium rated with the DRS-R-98, length of hospital stay and costs. The patients who are diagnosed postoperative delirium received 1-5 mg haloperidol depending on the severity of delirium.

### Statistical analysis

All statistical analysis was performed with SPSS for Windows, version 17.0 (SPSS, Inc., Chicago, IL). Characteristics of patients according to the presence of delirium were compared using chi-square analysis or Fisher test. Categorical measurements were valued as means and proportions, continuous measurements were summarized as mean and standard deviation (median and minimum-maximum, if necessary). Potential independent factors of delirium were evaluated using logistic regression analysis. A p value  $< 0.05$  was considered as the level of statistical significance.

## RESULTS

Mean age was  $71.8 \pm 6.7$  and  $72.7 \pm 6.1$  in group G and group R, respectively. There was no statistical difference between the groups ( $p=0.486$ ). The percentage of female patient was 69.1% and that of male was 30.9%. Total hip arthroplasty to 46 patients, total knee arthroplasty to 65 patients and other procedures (extremity amputation, fracture and tumor surgery) to nine patients were performed. There was no statistical difference between the groups according to the coexisting disease. There was no difference between two groups according to the smoking, alcohol or drug use. Laboratory and hemodynamic results were similar in both groups at 24th and 72th hours. ( $p \geq 0.05$ ) Seven patients required to perioperative blood transfusion in both groups. Postoperative delirium incidence was 12.5% at both 24 and 72 hours for all patients (Table 1).

**Table 1. The incidence of delirium according to time**

	Group G n (%)	Group R n (%)	Total n (%)	P value
<b>DRS-preop</b>				
No delirium	68(97.1%)	48(96%)	0(0%)	1.000
Mild	2(2.9%)	2(4%)	4(3.3%)	
<b>DRS –postop 24h</b>				
No delirium	64(91.4%)	41(82%)	0(0%)	0.313
Mild delirium	3(4.3%)	4(8%)	7(5.8%)	
Severe delirium	3(4.3%)	5(10%)	8(6.6%)	
<b>DRS- postop 72h</b>				
No delirium	63(91.3%)	41(82%)	7(5.8%)	0.392
Mild delirium	3(4.3%)	4(8%)	8(6.6%)	
Severe delirium	3(4.3%)	5(10%)		

Eight patients with severe delirium were administered haloperidol (severe delirium; CAM positive and DRS-R-98  $\geq 17$ ). One patient had a confusion depend on hypoglycemia and one patient had a delirium depend on acute kidney failure in

group R. DRS-R-98 scores were similar in both groups, however DRS-R-98 scores at 24th and 72th hours were statistically higher than preoperative scores ( $p=0.046-0.0001$ , respectively) (Table 2).

**Table 2. The distribution of DRS-R-98 scores of the groups according to time.**

DRS-R-98 score	Group G Mean $\pm$ SD Med(Min-Max)	Group R Mean $\pm$ SD Med(Min-Max)	Total Mean $\pm$ SD Med(Min-Max)	P value
Preop	2.6 $\pm$ 3.3 2(0-14)	2.3 $\pm$ 3.7 0(0-14)	2.5 $\pm$ 3.5 1(0-14)	0.191
Postop 24h	4.3 $\pm$ 5.3 3(0-28)	5.8 $\pm$ 6.7 3(0-23)	4.9 $\pm$ 5.9 3(0-28)	0.420
Postop72h	4.2 $\pm$ 5.5 2(0-26)	4.8 $\pm$ 6.5 3(0-23)	4.5 $\pm$ 5.9 3(0-26)	0.898
p*		0.046	0.0001	

p: Mann Whitney U test; p\*: as a result of Repeated measures analysis of groups change over time and the total of all patients in the groups without group variables change over time is to test; preop: delirium rating scale for preoperative period; postop 24h: delirium rating scale for postoperative 24th hour; postop 72h: delirium rating scale for postoperative 72th hour

Four of patients (3.3%) with delirium were hyperactive type and eleven of them (9.1%) were hypoactive type. We found that the most important preoperative risk factor that was assessed with DRS-R-98 was older age (95% confidence interval (CI) 0.12-0.29) ( $p=0.0001$ ).

On the other hand, the most important independent risk factors were older age and drug use for postoperative 24 (R=0.44) (95% CI 0.16-0.47 and 95% CI 0.12-4.96, respectively) and 72 hours (R=0.45) (95% CI 0.19-0.5 and 95% CI 0.38-5.15). Delirium incidence of patients who had three or more drug use history was 46.6%. The hospital stay was longer and cost of treatment was higher in patient with delirium than those without delirium ( $p=0.0001$ ) (Table 3). However, there was no

statistical difference between hyperactive and hypoactive types.

## DISCUSSION

In the present study, we investigated the difference between the regional and general anesthesia in terms of postoperative delirium incidence and its risk factors. We found that the overall incidence of delirium was 12.5%; it was 8.6% and 18% for general and regional anesthetic techniques, respectively. We also determined that the most important risk factors for postoperative delirium were the older age and multiple drug use history and postoperative delirium increased the hospital stay and costs. The incidence of delirium was reported as 12–51% for orthopedic surgery<sup>7</sup>. However,

postoperative delirium incidence may not be precisely estimated because of the many factors can mask to describe it, especially in cases with a poor prognosis. The risk factors of delirium include dementia, depression, >70 age, male sex, preoperative opioid or benzodiazepine use, alcohol

use, immobility, previous history of delirium, dehydration, malnutrition, vision impairment, coexisting severe disease such as chronic renal or hepatic disease, stroke, metabolic derangements, BUN/creatinine ratio >18, tobacco use, previous vascular surgery<sup>4,8,9</sup>.

**Table 3. The hospital stay and costs**

	No delirium (n=105)	Hyperactive Type (n=4)	Hypoactive Type (n=11)
Hospital stay (day)	6.4±1.6 (2-9)	10.0±4.7 (4-15)	11.5±5.9 (6-27)
Costs of treatment (TL)	3276.8±1452.7 (570-6800)	6027.5±977.8 (5200-7430)	4640.4±2008.9 (1280-6800)

TL: Turkish Liras

Delirium is associated with various negative outcomes including increased functional inability, institutionalization, dementia and risk of death as independent of age, gender, coexisting disease, disease severity and the presence of dementia<sup>10</sup>. One question that needs to be asked is whether the type of anesthesia has an effect on the rate of postoperative delirium. Several studies comparing general anesthesia with regional anesthesia suggests both anesthetic techniques are similar in terms of incidence of POD<sup>1,8,11-14</sup>. However, the trials had heterogeneous groups of patients and various intraoperative anesthetic agents and also various surgical procedures were used in these studies. Sieber et al<sup>15</sup>. studied the effect of depth of sedation on the development of POD in elderly patients undergoing hip fracture surgery. The authors stated that the light sedation with propofol during regional anesthesia reduced the incidence of POD by 50% compared with deep sedation.

Marcantonio et al. investigated the severity and psychomotor variants of POD and their relationship with outcomes in patients underwent hip fracture repair. This study revealed that severe delirium is usually associated with poor outcomes compared to mild delirium. Hypoactive type of delirium is more frequent than hyperactive type and is associated with improved outcomes<sup>16</sup>. In a study by Ansaloni et al. including 351 elderly patients undergoing general surgery, the overall incidence of POD was 13.2%, and there were hyperactive type in 55%, hypoactive type in 26% and mixed in 19% of patients<sup>17</sup>. The overall incidence of POD of this study is similar to that of our study; however, subtype incidences of POD are considerably higher than our results. Robinson et al. found the overall incidence of delirium was 44% in elderly patients underwent major abdominal, thoracic or vascular surgery. Furthermore, the incidence of hypoactive, mixed

and hyperactive type of delirium were 66%, 33% and 2%, respectively<sup>18</sup>. These results are significantly higher compared to our study. The reason for these higher incidences can be that all the patients required a postoperative intensive care unit admission after major surgery. In another study, Slor et al. found that the incidence of hypoactive type was 16.7%, hyperactive type was 23.3%, mixed type was 20%, no motor subtype 3.3% and variable profile was 36.7%<sup>19</sup>. Several studies reported that multiple drug use could be responsible for the increased incidence of POD<sup>20-22</sup>. Conversely, a study by Nie et al. did not found relation between more than three medications and delirium<sup>23</sup>.

There are conflicting results on relation between opioid administration and the incidence of POD. Radtke et al studied the effect of the choice of opioid analgesic drug on POD and the authors found the increased incidence of POD associated with opioid analgesic use<sup>24</sup>.

Similarly, a prospective cohort study investigating the effect of opioids on the development of delirium after hip fracture revealed that the patients who received <10 mg of parenteral morphine per day had more likely delirium than those who were given more analgesics. Additionally, meperidine was associated with increased risk of delirium compared with other opioid drugs<sup>25</sup>. On the other hand, a prospective observational study evaluating the effect of postoperative pain on the development of POD revealed that there was no relation between type of opioids or their cumulative doses and an increased risk of delirium<sup>26</sup>. It should be considered that postoperative pain can lead to increased incidence of POD or POD can limit the patient's analgesic demand. For postoperative pain control, we administered morphine 0.1 mg/kg iv and 1 mg mixed bupivacaine via epidural catheter to the

patients receiving general and regional anesthesia, respectively.

The deterioration of some blood parameters such as abnormal albumin, hematocrit, abnormal glucose, blood urea nitrogen/creatinine ratio and sodium or potassium abnormalities was reported as associated with increased risk of delirium<sup>17,18,27,28</sup>. In our study, we found no significant differences according to the preoperative, 24th hours and 72th hours blood parameters for POD incidence and no abnormal values. We determined POD in one patient who had high BUN/Cr ratio (27.6) and one patient who had hypoglycemia. Limitations of this study are the exclusion of patients who have the predisposing factors of delirium including dementia or cognitive impairment, depression, visual and hearing impairment, use of physical restraints, use of urinary catheters, emotional stress. Additionally, lack of intraoperative blood transfusion and fluid administration assessments restrict this study. Our study is consistent with previous results including longer hospital stay and increased costs, risk factors such as the older age and multiple drug use in patients with postoperative delirium. Increasing the number of patients and prolongation of postoperative follow-up period will be helpful for future studies.

In the current study, we concluded that there is no difference between regional and general anesthesia in terms of the incidence of POD, older age and >3 or more drug use are associated with increased incidence of POD. POD increases the hospital stay and costs.

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