*Effects of Fentanyl with Levobupivacaine on Cognitive Functions and Cerebral Oxygenation**

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ABSTRACT

Preoperative risk assessment may fail in most patients who may be exposed to postoperative neurological sequelae. The aim of this study was to assess the effects of Fentanyl added to epidural levobupivacaine on cerebral oxygenation and cognitive functions. There was a negative correlation between age and MMT, and a positive correlation between SpO_2 and MMT. MMT scores of Group 2 at postoperative first hour and fifth hours were lower than those of Group 1. It was concluded that while fentanyl added to epidural local anesthetic had no effect on hemodynamic parameters, SpO_2, and right-left cerebral oxygen saturation, and although it may have caused a decrease in MMT scores in the early postoperative period, it did not cause impairment in cognitive functions.

Key words: *Epidural anesthesia, fentanyl, levobupivacaine, cognitive function, cerebral oxygenation*

Türkçe Başlık

ÖZET

Postoperatif nörolojik sekele maruz kalabilen çoğu hastada preoperatif risk değerlendirmesi yetersiz kalabilir. Bu çalışmanın amacı epidural levobupivakaine fentanilin eklenmesinin serebral oksijen ve kognitif fonksiyonlara etkisini araştırmaktır. Yaş ile MMT arasında negatif, SPO_2 ile MMT arasında pozitif korelasyon vardı. Postoperatif 1 ve 5. saatte Grup 2 MMT skorları Grup birinkinden düşüktü. Epidural lokal anesteziye fentanilin eklenmesi hemodinamik parametreleri, oksijenasyonu ve sağ-sol serebral oksijenasyonu etkilemediği, erken postoperatif peryodda MMT skorlarında azalma neden olmasına rağmen kognitif fonksiyonlarda bir bozukluk meydana getirmedi.

Anahtar kelimeler: *Epidural anestezi, fentanil, levobupivakaine, kognitif fonksiyon, serebral oksijenasyon*

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INTRODUCTION

The Mini Mental Test (MMT) was used to assess cognitive functions. This is a shorter assessment than the other tests used to assess cognitive performance quantitatively during the standard neuropsychiatric examination (1). Kramer et al. (2) have recommended the MMT to evaluation of cognitive function. This test was adapted the world's most widely using method as a known short cognitive examination (3–5). Therefore, MMT is widely used, both in clinical practice and in research.

Preoperative risk assessment may fail in most patients who may be exposed to postoperative neurological sequelae. Thus, monitoring the intraoperative brain blood oxygen saturation in patients was brought to agenda. Cerebral oximetry provides direct measurement of oxygen saturation in the cerebral cortex affected by provision and consumption. Knowing the oxygen saturation in this area provides early warning for the potential cerebral ischemia (6).

Although most studies on monitoring the cerebral oxygen saturation have been conducted in cardiovascular surgery, it has also been implemented in non-cardiovascular surgical interventions with success (7). There are no studies in the literature comparing the effect of epidural opioids on cognitive functions and monitorization of cerebral oxygen saturation in anesthesia.

The aim of this study was to assess the effect of epidural Fentanyl plus levobupivacaine on cerebral oxygenation and cognitive functions.

MATERIALS AND METHODS

The study was approved by the Ethics Committee. Written and verbal consents were obtained from the patients. In a double-blind, randomized, controlled study, 20 patients with the age range of 20 to 60 from the ASA (American Society of Anesthesiologist) I–II group who were to undergo elective surgery under epidural anesthesia were included.

The exclusion criteria were hypersensitivity to drugs, gastrointestinal disease such as malabsorption, current or history of renal or liver failure, hypertension, goiter, heart failure, cardiovascular disease, valvular disease, hypotension, CNS disease, history of alcoholism, drug addiction, psychosis, antagonistic personality, poor motivation or intellectual problems, and illiteracy. Patients requiring intraoperative general anesthesia, patients in whom adequate anesthesia could not be provided with 18 ml 0.5% levobupivacaine, and patients with hemorrhage causing hemodynamic instability were excluded from the study.

All patients were monitored for noninvasive blood pressure (mmHg), heart rate (HR) and peripheral O2 saturation (SpO_2) prior to the operation. Infusion was begun with 10 mL/kg 0.9% NaCl solution. The forehead of the patient was cleaned with alcohol in the operating room. Two adhesive SomaSensors were placed on the forehead corresponding to the right and left frontal lobes. They were connected to cerebral oximetry (Invos SOMANETICS® Cerebral Oximetry). A 20 G epidural catheter was placed by inserting an 18 G epidural needle into the midline L3-4 or L4-5 interspinous space while the patient was seated, paying attention to asepsis-antisepsis rules. The cases were divided into two groups according to their order of admission: After confirming the localization of the catheter with 3 ml test dose, 15 ml 0.5% levobupivacaine (without phentanyl) was administered to the individuals in the first group (n:20), and 15 ml 0.5% levobupivacaine (with 75 µg phentanyl) was administered to individuals in the second group (n:20).

Following epidural anesthesia, intraoperative systolic blood pressure (SBP), diastolic blood pressure (DBP), mean blood pressure (MBP) (mmHg), heart rate (HR) and

Table 1. *Ramsay scale*

Observation	*Score*
Anxious, agitated or restless	*1*
Cooperative, orientated and tranquil	*2*
Sedated but responds to commands	*3*
Asleep; brisk response to physical stimulation or loud auditory stimuli	*4*
Asleep; sluggish response to physical stimulation or loud auditory stimulus	*5*
Asleep; no response to painful stimuli	*6*

SpO_2 were recorded every five minutes in all patients. MMT was assessed one day before the operation and at the first hour, fifth hour, and seven days after the operation. The Ramsay Sedation Scale (RSS) (8) (Table 1) was assessed preoperatively and at the first hour and fifth hours after epidural administration of the drug. Right (right rSO_2) and left (left rSO_2) cerebral oxygenation saturations were recorded during the operation. No premedication or oxygen was administered to the patients so as not to affect the results.

Hypotension was defined as a decrease of >20% compared to values before anesthesia in SBP or being <90 mmHg. It was planned to accelerate the I.V. fluid infusion or to add I.V. 5 mg ephedrine bolus. Bradycardia was defined as the HR being <45 beat/min and atropine 0.01 mg/kg was planned to be administered I.V. The first values recorded for the right and left hemisphere by cerebral oximetry were accepted as the preoperative baseline values. A decrease by 20% from the awakening baseline value was accepted as the threshold for intervention (9). Interventions included increasing the oxygen, normalizing hemodynamics and warning the surgeon. Cerebral oxygenation monitorization was followed up during the operation.

Statistical analyses

Statistical analyses were performed using the two-way repeated measurement ANOVA, variance analysis and the Tukey multi comparison test. The Spearman Correlation Coefficient was calculated for each group to define the linear relationship between the parameters. The level of significance was set as $p<0.05$, and the level of extreme significance was set as $p<0.01$.

RESULTS

The cases had similar demographic details (Table 2) ($p>0.05$). There was no significant difference between the two groups for SBP, MBP, DBP, HR, right rSO_2 (Table 3) and left rSO_2 (Table 4), SpO_2, RSS (Table 5) ($p>0.05$). The preoperative measurements for SBP, MBP, DBP, HR, right rSO_2 and left rSO_2, SpO_2, RSS were parallel to those at other times when the two groups were compared within themselves ($p>0.05$). The MMT results of Group 2 at postoperative first hour and fifth hour (Table 6) were normal; however, they were lower than those of Group 1 ($p<0.05$). There was a negative correlation between the age and MMT. While there was no impairment in cognitive functions in the group without Fentanyl at ages 20-40 years, mild POFB was seen in the group with Fentanyl at a rate of 2.5% in patients aged 20-40 years and at a rate of 17.5% in patients aged 40-60 years. There was a positive correlation between SpO2 and MMT.

***Table 2**. Demographic values (mean±SD)*

	Group I	Group II
Age (Year)	*41.70±13.97*	*42.65±14.19*
Gender M/F	*13/7*	*15/5*
ASA I/II	*14/6*	*15/5*

SD: Standard deviation, **M:** male, **F:** female

***Table 3**. Right cerebral oxygen saturation values (mean±SD)*

	Group 1	Group 2
Preoperative right rSO_2	*69.40±7.24*	*66.00±7.56*
5 minutes right rSO_2	*69.25±7.58*	*65.20±7.76*
10 minutes right rSO_2	*69.25±7.52*	*65.10±7.17*
20 minutes right rSO_2	*69.90±7.05*	*64.35±8.20*
30 minutes right rSO_2	*69.75±7.30*	*64.60±8.62*
40 minutes right rSO_2	*69.40±7.18*	*64.25±8.78*
50 minutes right rSO_2	*70.10±7.29*	*63.95±9.24*
60 minutes right rSO_2	*71.87±6.70*	*65.64±6.37*
70 minutes right rSO_2	*72.20±5.61*	*65.25±7.21*
80 minutes right rSO_2	*75.67±4.73*	*66.00±9.85*
Postoperative right rSO_2	*70.30±6.78*	*64.40±8.26*

Right rSO_2: Right cerebral oxygen saturation

DISCUSSION

Regional anesthesia is defined as diminishing nerve conduction and sense of pain in a large part of the body without causing loss of consciousness (10). Opioids added to local anesthetics in epidural anesthesia increase

***Table 4**. Left cerebral oxygen saturation values (mean±SD)*

	Group 1	Group 2
Preoperative left rSO_2	*74.30±6.70*	*70.30±7.53*
5 minutes left rSO_2	*73.60±6.85*	*69.50±7.21*
10 minutes left rSO_2	*74.50±6.46*	*68.75±8.06*
20 minutes left rSO_2	*74.30±6.71*	*68.25±7.77*
30 minutes left rSO_2	*74.25±6.69*	*69.10±8.63*
40 minutes left rSO_2	*74.25±6.66*	*68.30±8.23*
50 minutes left rSO_2	*74.65±6.38*	*68.55±8.19*
60 minutes left rSO_2	*76.00±6.50*	*70.21±5.86*
70 minutes left rSO_2	*76.50±6.45*	*71.13±5.99*
80 minutes left rSO_2	*80.00±5.57*	*71.67±10.21*
Postoperative left rSO_2	*74.65±6.23*	*69.35±7.65*

Left rSO_2: Left cerebral oxygen saturation

***Table 5**. Ramsay Sedation Scale values (mean±SD)*

	Group 1	Group 2
Preoperative RSS	2.00±0.00	2.00±0.00
1 hour RSS	2.05±0.22	2.15±0.36
5 hour RSS	2.05±0.22	2.00±0.00

RSS: Ramsay Sedation Scale values

the quality of anesthesia, reduce the adverse effects and are advantageous for postoperative analgesia (11). In this study, we wanted to make use of the advantages of an opioid agent, Fentanyl when added to levobupivacaine.

All anesthesia practices have impacts on peroperative cognitive functions. Postoperative cognitive dysfunctions can be assessed in two main groups: "postoperative delirium" and "mild neurocognitive disorder" which is called "postoperative cognitive dysfunction (POCD)" in the literature. MMT is widely used to assess this disorder as it is short and easily applicable (12). It was first designed by Folstein et al. (1) Scores between 0 and 17 mean severe cognitive disorder; 18–23: mild cognitive disorder; and 24–30: normal (13). We used MMT to assess cognitive functions in this study.

The etiology of POCD is likely to be multifactorial including age, educational status, preoperative cognitive dysfunction, genetic factors, operations such as heart surgery, the duration of surgery, secondary operations, method of anesthesia, hypotension (one or two attacks of mean arterial pressure <60 mmHg for >30 minutes), hypoxia (one or two attacks of an oxygen saturation of <80% for >2 minutes), hormone levels, preoperative medication with benzodiazepines, postoperative infection and respiratory complications, thrombosis or embolism, and postoperative pain (12). It has been reported that differences in prevalence rates of cognitive impairment by age are striking (12,13). In a study, 25.8% of 1218 patients older than 60 years of age had POFB at one week after the operation and 9.9% had POFB at three months after the operation. The prevalence of POFB at one week after the operation was 19.2% even in middle-aged surgery patients (14). In another study comparing the effects of general and regional anesthesia on POFB, although there was no significant difference in cognitive functions MMT scores between the groups on day seven, it was found that POFB prevalence was higher in patients undergoing general anesthesia compared to patients undergoing regional anesthesia (15). We showed in our study that there was a negative correlation between age and cognitive functions. While there was no cognitive disorder in the group without Fentanyl aged 20-40, the prevalence of POFB was 2.5% in the group with Fentanyl aged 20-40. The prevalence of POFB was 17.5% in both groups aged 40-60 years. Sedation and mental status changes are the side effects of intrathecal or epidural opioids (16). The significant decrease in MMT scores at first and fifth hours in the group with Fentanyl compared to the group without Fentanyl was thought to be related to the sedative effect of epidural Fentanyl. Although there was no significant difference between the groups in terms of RSS, RSS at first hour in the group with Fentanyl was higher than that of the group without Fentanyl. This was a supporting result for the sedative effect of epidural opioids.

***Table 6**. Mini Mental Test scores of the groups (mean±SD)*

	Group 1	Group 2
Preoperative MMT	26.95±3.99	26.70±3.36
1st hour MMT	25.85±5.01$^{\Delta}$	23.85±3.86*,□,•
5th hour MMT	26.45±4.01	25.25±3.55*,□
24th hour MMT	26.70±4.13	26.65±3.45
7th day MMT	26.90±3.71	27.15±3.18

**: significant inter-group difference (p<0.05), Δ: significant difference compared to all other scores of Group 1 (p<0.05), □: significant difference compared to all other scores of Group 2 (p<0.05), •; significant difference compared to the 5th hour score in Group 2 (p<0.05), MMT: Mini Mental Test*

In one study, cerebral oxygen saturation and cognitive functions were compared and it was found that cognitive functions were impaired when SpO_2 was <80%. The impairment is reversible if SpO_2 is >90% again (17). We found that there was a positive correlation between SpO2 and MMT scores at all hours in the two groups. There were patients with SpO_2 <90%.

Today, the aim is to keep the blood pressure at a safe pre-determined range, both during and after the operation, in order to provide adequate cerebral perfusion and oxygenation. However, even if blood pressure is maintained at an adequate level, brain oxygenation may be impaired (18). Low systolic pressure is associated with cognitive impairment. Two mechanisms have been proposed for this association: Low blood pressure is a consequence of the dementia process and low blood pressure accelerates or predisposes to cognitive decline (19). In our study, blood pressures were generally stable; there were no cases with hypotension or hyperten-

sion and no correlation with MMT was detected.

Neurophysiological monitoring required an intimidating array of complex devices and positive outcome data were lacking (18). The main etiological factors for the decrease in cerebral oxygen saturation are hemodilution, use of blood transfusions with lower capacity of oxygen transport, hypoxia, hypotension, hypercapnia due to bleeding, increase in the cerebral metabolic oxygen consumption due to inadequate depth of anesthesia, impaired blood flow due to neck position and failure in replacement of central venous catheter. In our study, none of these predisposing factors were found. It is possible to monitor the changes in global brain hemoglobin oxygen saturation using cerebral oximetry. As 70-80% of the measured blood is venous, cerebral oximetry generally shows a venous saturation. Inadequate brain oxygen support can be prevented by monitoring the cerebral oxygen saturation during the planning of anesthesia (20). We used continuous monitorization of cerebral oxygen saturation in our study.

In their study where they compared the effects of spinal and general anesthesia on cerebral oxygen saturation in patients undergoing emergency operations for femur neck fracture, Hoppenstein et al. (21) found that cerebral oxygen saturation was lower in patients undergoing spinal anesthesia. They reported that this may be due to patient-related factors rather and independent from the anesthesia technique. They stated that the reason for cerebral oxygen saturation being higher in patients undergoing general anesthesia than those undergoing spinal anesthesia was the suppression of cerebral metabolism by the general anesthesia. In a study, in focal cerebral ischemia produced by distal middle cerebral artery occlusion in mice, it was shown that mild induced hypertension produced by phenylephrine rapidly increased cerebral blood flow and cerebral oxygen saturation and it was also shown that hypotension had a negative effect on the cerebral oxygen saturation (22). In our study, blood pressures in the two groups were normal. There were no changes in the right and left cerebral oxygen saturations and thus no impairment in cerebral oxygenation. This was thought to be due to the fact that the operative procedure was not a hard procedure.

It was found that Fentanyl plus levobupivacaine 0.5% in epidural anesthesia did not have a negative impact on SBP, DBP, MBP, HR, SpO_2, and right-left rSO_2.

It was concluded that while Fentanyl added to epidural local anesthetic had no effect on hemodynamic parameters, SpO_2, and right-left cerebral oxygen saturation, despite possibly causing a decrease in MMT scores in the early postoperative period, it did not cause impairment in cognitive functions.

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