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Clinical Study

The Effects of Intrathecal Fentanyl on Sedation Depth and Postoperative Recovery Room Delirium

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Background/Aim. Intrathecal anaesthesia has been shown to increase sedation level. This study aimed to evaluate the effects of intrathecal applied fentanyl with levobupivacaine on intraoperative sedation and recovery room delirium. *Materials and Methods*. The study included 68 patients, ASA I–III, 55–85 years. One day preoperatively, the Confusion Assessment Method (CAM) and the Mini Mental Status Test (MMST) were applied and patients were separated into two groups. In Group L 2.5 mL levobupivacaine and in Group LF 2 mL levobupivacaine and 0.5 mL fentanyl were applied intrathecally. In a supine position, following a propofol IV 1 mg kg^{-1} bolus to obtain Bispectral Index (BIS) of 70–85, propofol infusion was started (1 mg kg^{-1} st^{-1}). With observation of SpO_2, BIS, and the Observer Assessment and Alertness/Sedation Scale (OAA/SS) with the haemodynamic values, the total propofol amount was calculated. Evaluations were made of pain severity (VAS), analgesic use, transfusion requirement, and recovery room delirium. *Results*. In the comparison within the groups, a significant decrease was determined in HR and MAP compared to the initial values ($p < 0.05$). A positive correlation was found between the BIS and OAA/SS values. The amounts of propofol used were similar between the groups. *Conclusions*. Intrathecal fentanyl and levobupivacaine had the same effect on sedation or BIS and fentanyl did not cause delirium.

1. Introduction

During regional anaesthesia, there is a reduced requirement for the use of sedative drugs, pain control is achieved, and this reduces the incidence of postoperative delirium [1]. Spinal anaesthesia with local anesthetics alone has been reported to reduce sedative requirements in high sensory block levels [2, 3]. Although the mechanism is not fully understood, it is thought to be due to a reduction in the afferent stimulation in the reticular activating system associated with deep sensory block [1]. Apart from that, the other theories have been proposed to explain sedative effect of spinal anaesthesia including a direct effect of local anesthetic, either by systemic absorption or by rostral spread through the CSF [4]. However, the degree of adequate sedation for spinal anaesthesia has not been fully researched. BIS and electroencephalography (EEG) measurements are the basis for the determination of the degree of sedation [5].

Delirium is an acute organic brain syndrome, characterized by disturbances in orientation, memory, thought, perception, and behavior, of acute onset and fluctuating course [6]. Delirium may be seen in the form of acutely impaired cognition occurring with inattention and waves of consciousness when waking from anaesthesia or in the recovery room [7]. This postoperative delirium can be a reason for the patient harming themselves, removing invasive catheters, or of potential injuries such as a fall [8]. Risk factors are primarily dementia, age, systemic disease, inhalation and intravenous anesthetics, benzodiazepines, and anticholinergic medications [7]. Untreated pain in particular can increase postoperative delirium. Therefore, although known to be a risk factor, the perioperative use of opioids

in some patients undergoing major surgery is unavoidable in some circumstances.

The aim of this study was to compare the effect of intrathecal anaesthesia of levobupivacaine and a levobupivacaine-fentanyl combination on depth of sedation and the effect on recovery room delirium.

2. Materials and Methods

Approval for the study was granted by the Local Ethics Committee and informed consent was obtained from all the study participants. The study comprised 68 patients, aged 50–85 years, who were operated on under spinal anaesthesia for elective hip or femoral fracture. Those with contraindications for spinal anaesthesia (significant narrowing of the aorta, impaired clotting, anticoagulant use, spinal cord disease, and refusal of spinal anaesthesia), allergic to the medications used in the study, not cooperative, using tranquillisers or antidepressants, undergoing reoperation, with severe heart failure, with severe chronic obstructive pulmonary disease (COPD), and with neurological disease were excluded from the study.

One day prior to surgery, together with the preoperative anaesthesia evaluation applied by the anaesthetist, the MMST [9] to determine cognitive impairment and the CAM [10] to determine delirium were applied. Patients with an MMST score of <15 (severe cognitive impairment) were excluded from the study to prevent delirium being confused with dementia. Patients diagnosed with preoperative delirium with a positive CAM were also excluded from the study.

Preoperative biochemistry values were examined for the patients and then they were randomly separated into 2 groups using the sealed envelope method. Without any premedication, the patients were admitted to the operating theatre and monitorisation of HR, MAP, peripheral oxygen saturation (SpO_2), and BIS was applied (BIS XP model and Quatro sensor electrode system; Aspect Medical System Inc., Norwood, MA). Oxygen was administered with a mask (4 lt min^{-1}). At 30 minutes preoperatively, Ringer lactate was administered at 6–8 mL kg^{-1}. With the patient in the lateral position, the spinal anaesthesia was applied between L4 and L5 with a 26 G Atraucan (B. Braun Melsungen, Germany) atraumatic spinal needle. To the patients in Group L, 2.5 mL (12.5 mg) 0.5% levobupivacaine was administered and to Group LF, 2 mL (10 mg) 0.5% levobupivacaine + 0.5 mL (25 mcg) fentanyl. The study syringe was prepared by an independent anaesthetist and the second anaesthetist in charge was blinded to the group allocation. In the supine position, an intravenous bolus of propofol 1 mg kg^{-1} was administered at 5 minutes, and then a propofol infusion of 1 mg kg^{-1} was started.

The intraoperative infusion rate was adjusted for the BIS to be 70–85. After starting the propofol infusion, the haemodynamic values (MAP, HR) and SpO_2 were recorded and at 1, 5, 10, 20, 30, 40, 50, 60, 75, 90, 105, 120, and 135 minutes. The BIS levels were measured together with the propofol infusion at 5, 10, 20, 30, 40, 50, 60, 75, 90, 105, 120, and 135 minutes. The degree of sedation was evaluated with the OAA/SS at the same measurement times (Table 1). If the intraoperative MAP value reduced by more than 30% of the preoperative value or was below 60 mmHg, it was evaluated as hypotension, treatment was applied with fluids or ephedrine, and the patient number was recorded. If HR fell below 45 beats min^{-1}, it was accepted as bradycardia and planned treatment of atropine was given and the number of patients who developed bradycardia was recorded.

For intraoperative nausea and vomiting, metoclopramide HCl was administered IV. When the skin sutures were finished, the propofol infusion was terminated and a record was made of the total amount of propofol administered, complications (nausea, vomiting, and itching), and recovery time (time taken to reach BIS of 90). Postoperatively, the patients were taken to the recovery room and, at 30 and 60 mins, the CAM was applied by the anaesthetist and VAS scores were evaluated. Those with a VAS score of >4 were treated with 1 mg kg^{-1} tramadol HCl.

For each patient a record was made of VAS scores, whether or not there was any intraoperative nausea and vomiting, hypotension, bradycardia, and any requirement for ephedrine, atropine, antiemetics, postoperative opioids, or transfusion. The amount of bleeding was calculated with the amounts of crystalloid and colloid given throughout the surgery.

2.1. Statistical Analysis. For statistical analysis, the NCSS (Number Cruncher Statistical System) 2007 and PASS (Power Analysis and Sample Size) 2008 Statistical Software (Utah, USA) programs were used. As a result of the power analysis applied, the sample number was determined as 31 in the groups determined for power: 0.80, β: 0.20, and α: 0.05 in the evaluation made according to the mean OAA/SS. Besides the descriptive statistical methods (mean, standard deviation, and frequency) in the evaluation of the study data, Student's t-test was used in the comparison between the groups of parameters showing normal distribution and the Mann-Whitney U test was used for parameters not showing normal distribution. Paired sample t-test was used for intragroup analysis. In the evaluation of the relationship between BIS and OAA/SS measurements, Spearman's correlation analysis was used. The Chi-square test was used in the comparison of qualitative data. Results were evaluated at 95% confidence interval and a value of $p < 0.05$ was accepted as statistically significant.

3. Results

The demographic data and operation times were similar in both groups ($p > 0.05$) (Table 2). No statistically significant difference was determined in terms of HR, MAP, and SpO_2 ($p > 0.05$). However, in the intragroup comparisons of HR, MAP, and BIS in both groups, statistically significant decreases were determined in comparison to the initial values ($p < 0.05$).

Of the BIS measurements between the groups, apart from BIS measurements at 5 minutes, no statistically significant difference was determined ($p > 0.05$) (Figure 1). The BIS value at 5 minutes was measured higher in Group L than in

Table 1: Observer's Assessment of Alertness/Sedation (OAA/S) Scale.

Subscore	Responsiveness	Speech	Facial expression	Eyes
5	Responding readily to name spoken in normal tone	Normal	Normal	Clear, no ptosis
4	Lethargic response to name spoken in normal tone	Mild slowing or thickening	Mild relaxation	Glazed or mild ptosis
3	Responding only after name is spoken loudly and/or repeatedly	Slurring or prominent slowing	Marked relaxation (slack jaw)	Glazed and marked ptosis
2	Responding only after mild prodding or shaking	Few recognized words		
1	Not responding to mild prodding or shaking			

The final score is the sum of the responsiveness, speech, facial expression, and eyes component scores. Thus, a "wide awake" scores 5 and a "deeply sedated" scores 1.

Table 2: Demographic and clinical values (mean ± SD).

	Group L ($n = 34$)	Group LF ($n = 34$)	p
Age (year)	71.03 ± 8.43	69.68 ± 9.24	0.053
Length (cm)	164.15 ± 9.35	162.91 ± 7.92	0.56
Weight (kg)	73.00 ± 12.70	72.00 ± 13.60	0.755
BMI	27.37 ± 4.85	27.12 ± 4.83	0.824
Operation (min)	127.27 ± 42.96	148.09 ± 60.06	0.109
Gender			
Female	25 (73.5%)	24 (70.6%)	
Male	9 (26.5%)	10 (29.4%)	0.787

BMI: Body Mass Index.

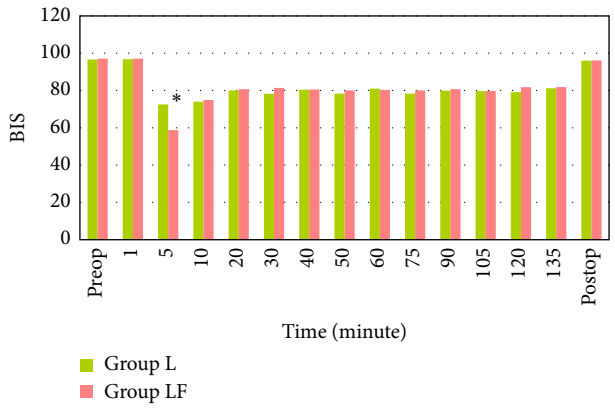

Figure 1: BIS measurement distribution by groups: $^{*}p < 0.01$.

Group LF. In both groups, there was a positive correlation between the BIS and OAA/SS values.

The total amount of propofol used was 368.94±149.64 mg in Group L and 423.53 ± 228.19 in Group LF. No statistically significant difference was determined between the groups in respect of propofol consumption and total propofol amounts ($p > 0.05$). In both groups, the side effects and requirement for ephedrine, atropine, and postoperative analgesia were similar ($p > 0.05$). The amount of bleeding was statistically significantly greater in Group LF ($p < 0.05$). However,

Table 3: Intraoperative amount of crystalloid, colloid, and bleeding by groups (mean ± SD).

	Group L	Group LF	p
Crystalloid (mL)	1151.47 ± 367.32	1388.24 ± 607.91	0.057
Colloid (mL)	631.03 ± 164.97	671.67 ± 156.29	0.335
Bleeding (mL)	294.12 ± 164.58	464.71 ± 451.85	0.045*

$^{*}p < 0.05$.

Table 4: Recovery and MMST times by group (mean ± SD).

	Group L	Group LF	p
Recovery times (min)	8.03 ± 3.56	8.29 ± 2.83	0.738
MMST	27 ± 2	27 ± 2	1
VAS-recovery room 1st min	0.79 ± 1.75	1.53 ± 2.82	0.414
VAS-recovery room 60th min	1.63 ± 2.42	1.53 ± 1.91	0.76

MMST: Mini Mental Status Test; VAS: Visual Analog Scale.

the crystalloid and colloid amounts and need for blood transfusion were found to be similar ($p > 0.05$) (Table 3).

No statistically significant difference was determined between the groups in recovery time and mean MMST ($p > 0.05$) (Table 4). The VAS scores on admission to and leaving the recovery room were similar in both groups ($p > 0.05$) (Table 4). The results of the CAM applied in the recovery room were negative in both groups.

4. Discussion

This study showed that fentanyl (25 mcg) added to intrathecal isobaric levobupivacaine 0.5% (10 mg) had similar effect of levobupivacaine alone on the sedation level of patients. Intrathecally applied fentanyl did not change the total amount of propofol required to reach the target BIS levels. Also the addition of fentanyl to local anesthetic did not create any risk in respect of delirium.

Intrathecal anaesthesia has been shown to increase sedation level by decreasing cerebral stimulation secondary to the decreased afferent input from the spinal cord [11]. Fentanyl is often used in intrathecal anaesthesia to increase the level of sensory block together with local anesthetics [12, 13]. In

recent publications, the sedation structural effect of intrathecal fentanyl has been monitored using BIS [14]. There are various sedation scores to determine the level of sedation in patients in addition to BIS monitorisation. One of these, which was used in this study, is the Observer Assessment and Alertness/Sedation Scale (OAA/SS). This scale is used to measure the degree of consciousness in individuals under sedation [15].

In studies by Kushida et al. [14], fentanyl was added to 0.5% isobaric bupivacaine during spinal anaesthesia as 20 μg intrathecally, 100 μg intravenously, and 100 μg epidurally. The BIS values of the intrathecally applied fentanyl group were found to be significantly lower than those of the other groups. Nakamoto et al. [16] compared the effects of adding intrathecal fentanyl to hyperbaric and isobaric bupivacaine in spinal anaesthesia and the BIS values of the group with fentanyl added to hyperbaric bupivacaine were found to have decreased more than those of the isobaric bupivacaine group.

In other studies, the propofol dose in groups where fentanyl was added to hyperbaric bupivacaine was found to be lower than in groups where fentanyl was not added [17, 18]. In these studies equivalent volume of intrathecal saline which has not sedative effect was used in control group. In the current study, in Group L an equivalent volume of local anesthetic was used rather than saline. Also contrary to other studies, we used isobaric levobupivacaine as a local anesthetic. To our knowledge the sedative effect of intrathecal levobupivacaine followed by BIS and OAA/SS was not investigated previously. We found similar BIS and OAA/SS scores and propofol consumption between the groups. This situation may be due to the sedative effects of both intrathecal fentanyl and levobupivacaine. However, in study by Kushida et al., the BIS values of isobaric bupivacaine-fentanyl were found lower than an equivalent volume of isobaric bupivacaine [14].

In a previous study, the sedation belonging to intrathecal fentanyl or local anesthetic has been reported to develop at earliest 15th minute [3]. Even the peak sedative effect was seen 30 minutes after intrathecal injection [4, 19]. In present study minimum BIS value occurred at 5 minutes in both groups. Depending on previous knowledge we believe that our results occurred because of the influence of propofol sedation rather than the sedative effects of local anesthetic or fentanyl.

Delirium is a common postoperative complication in the elderly. Apart from surgery, other risk factors have been defined as previously impaired cognitive state, psychotropic medications, impaired functional status and sensory failure, opioids uses, high amount of intraoperative blood loss, high amount of postoperative blood transfusion [20, 21], inadequate postoperative pain control and high pain scores (VAS > 4) [20, 21], and abnormal levels of serum electrolytes [22]. Preoperative fluid deficiency and dehydration have been shown to be risk factors for postoperative delirium [23, 24].

Although varying incidence rates have been reported, it has been stated to occur in 37% of hospitalised patients [25–27]. In a study by Sharma et al. [28] of elderly patients (mean age, 77 ± 1 years) who underwent surgery for a hip fracture under general anaesthesia, recovery room delirium was determined at a prevalence of 45% and the extent of the high risk group (ASA III) with preoperative dementia was reported to be related to postoperative delirium. Sieber et al. [29] applied propofol for sedation together with spinal anaesthesia in elderly patients without preoperative dementia or delirium who were to undergo hip prosthesis surgery. In the examination of sedation depth with titred BIS, deep sedation (BIS = 50) was applied to one group and mild sedation (BIS = 80) to the other. The incidence of postoperative delirium was found to be 50% lower in the mild sedation group compared to the deep sedation group. Limiting the depth of sedation under spinal anaesthesia was said to be a simple, reliable, and inexpensive method of preventing postoperative delirium in elderly patients.

In the current study, spinal anaesthesia was applied under mild sedation (BIS, 70–85) to all the patients. Any patients with severe preoperative dementia were excluded from the study, as that could have been a risk factor in recovery room delirium. The CAM score was used in the current study for the determination of delirium. Preoperatively and at postoperative 30 and 60 minutes, all the patients of both groups were found to be negative and no delirium was determined to have developed in the recovery room in any patient of the current study.

In this study, the preoperative electrolytes' levels of all the patients were within normal limits. Sufficient fluids were administered throughout the operation with crystalloid and colloid infusion. In addition, the pain scores on entering and leaving the recovery room were determined as VAS < 4. For all these reasons, postoperative delirium was not observed in any of the patients in the current study.

Although fewer patients received blood transfusion in Group L compared to Group LF, the amount of bleeding in Group LF was found to be significantly higher than that of Group L but delirium was not observed in any patient who had bleeding or transfusion. Therefore, it can be considered that bleeding or blood transfusions alone do not have any effect on the development of recovery room delirium.

Limitations of this study were that as patients with MMST 15–25 were not included (although we did not select a particular) in the study, there was no evaluation of patients with moderate dementia. Thus, it could not be investigated whether preoperative moderate dementia was a factor in the development of recovery room delirium, as has been claimed in previous studies.

In conclusion, with the intrathecal application of equivalent volume of levobupivacaine and a levobupivacaine-fentanyl combination added to propofol infusion in patients, similar sedative effects were observed. The amounts of propofol consumption were found to be similar in both the levobupivacaine and the levobupivacaine-fentanyl groups. The addition of fentanyl did not create any risk in respect of delirium in the recovery room.

Disclosure

There is no financial relationship with the organization that sponsored the research.

Conflict of Interests

There is no conflict of interests between the authors.

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