BIS guided sedation with propofol during spinal anaesthesia: influence of anaesthetic level on sedation requirement

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Background. In this prospective, clinical study we tested the hypothesis whether two different doses of spinal administered bupivacaine and accordingly, two different levels of spinal anaesthesia can affect the dose requirement of propofol during BIS guided sedation.

Methods. Fifty women undergoing vaginal hysterectomy (high spinal group, HS) or transvaginal tape (TVT) procedure for urinary incontinence (low spinal group, LS) under spinal anaesthesia were enrolled to the study. In group HS, 17.5 mg and in group LS, 7.5 mg of hyperbaric bupivacaine were given intrathecally. After 15 min to obtain the appropriate level of spinal anaesthesia, propofol infusion was started at a rate of 100 \( \mu \text{g kg}^{-1} \text{min}^{-1} \) to reach a BIS level of less than 75 (onset time), and titrated to maintain the BIS value between 65 and 75. Propofol infusion was stopped 45 min after placing the spinal to measure the time to reach a BIS level of 90 (recovery time).

Results. Median anaesthetic level was T3 (T1–4) in the HS group and T10 (T9-11) in the LS group. In both the HS and the LS groups, onset time was 226 (47) vs 273 (48) s (P=0.001), recovery time was 234 (47) vs 202 (56) s (P<0.001), total dose of propofol was 2.17 (0.43) vs 3.14 (0.56) mg kg\(^{-1}\) (P<0.001), respectively.

Conclusion. A high spinal block obtained with hyperbaric bupivacaine 17.5 mg was associated with a faster onset, delayed recovery and lower doses of propofol sedation compared with a low spinal block with 7.5 mg of the same drug.

Keywords: anaesthesia, depth; anaesthetic techniques, subarachnoid; anaesthetics i.v., propofol; monitoring, bispectral index; sedation

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During gynaecological operations performed under spinal anaesthesia, sedation of the patients is often required. Continuous infusion of propofol is a useful sedation method because of the easy management by titration and rapid emergence. Previous studies have shown that spinal,1–3 epidural4–5 or i.m.6–8 administration of lidocaine or bupivacaine decreases the sedative/anesthetic dose requirement of general anaesthetics. Therefore, it is possible that after a spinal anaesthesia, even routine doses of sedatives can lead to some unwarranted effects.9

However, there is not enough data about the relationship between the dose requirements of propofol and the administered dose of local anaesthetic or the level of spinal anaesthesia.

The bispectral index (BIS), an EEG derivative, has been shown to be a sensitive and simple monitor to assess the hypnotic component of anaesthesia,10–11 and the level of consciousness during propofol sedation.12

In this prospective, clinical study we tested the hypothesis that two different doses of spinal administered bupivacaine and accordingly, two different levels of spinal anaesthesia can affect the dose requirement of propofol during BIS guided sedation.

Methods
The Institutional Ethics Committee approved this prospective clinical study and a written informed consent was obtained from each patient.
Power analysis (α=0.05 and β=0.1) suggested that a sample size of 18 patients per group was needed to detect a 30% reduction in propofol requirements. Fifty women with the ASA physical status I or II, undergoing vaginal hysterectomy or transvaginal tape (TVT) procedure for urinary incontinence, were enrolled in the study. Exclusion criteria included age >65 yr, known allergy to drugs, contraindications for spinal anaesthesia, obesity (BMI>30), neurological or psychiatric disease or concurrent medications. No patient received premedication.

All patients were given i.v. sefazolin 1 g (Sefazol flacon, Mustafa Nevzat İlaç A.Ş., İstanbul), before operation. For thombophrophylaxis, patients wear elastic stockings up to 8–10 cm above the knee level. Nadroparine 0.6 ml (Fraxiparine® 0.6 ml, Sanofi-Doğu İlaç A.Ş., İstanbul) was given s.c. at 10 pm every day, starting to be administered on the night before surgery.

Routine monitoring of ECG, pulse oximetry and non-invasive blood pressure (Horizon XL, Mennen Medicals Inc., Rehovot, Israel) were established. Electrodes (BIS™ Sensor; Aspect™ Medical Systems, Inc., Newton, MA, USA) were applied to the patient’s forehead to monitor the BIS of the EEG (A-2000 BIS™ monitor, System rev.2.1, Aspect™ Medical Systems, Inc., Natick, MA, USA). BIS smoothing rate was set at 15 s.

Gelatine solution (Gelofusine®, B.Braun, Melsungen AG, Germany) 500 ml was infused i.v. for prehydration and followed by Ringer’s lactate. Initial values of mean arterial pressure (MAP), heart rate (HR), peripheral oxygen saturation (SpO2) and BIS were recorded (prespinal). Spinal anaesthesia was induced in the lateral decubitus position at L3–4 or L4–5 interspace using a 25 G spinal needle (Pencan®, B.Braun, Melsungen AG, Germany) and hyperbaric bupivacaine 0.5% (Marcaine 0.5% heavy spinal, Astra Zeneca İlaç AŞ, İstanbul, Turkey) was given as local anaesthetic. Bupivacaine 17.5 mg was injected intrathecally for vaginal hysterectomy to establish an anaesthetic level at T4 dermatome (high spinal group, HS). For TVT procedure, bupivacaine 7.5 mg were used to reach an anaesthetic level at T10 dermatome (low spinal group, LS). Anaesthetic level was evaluated by the pin-prick test every 2 min until the block remained the same level at least 3 consecutive times.

MAP was maintained within 20% of baseline values using ephedrine 5 mg bolus and the infusion rate was increased. Bradycardia (HR<60 beats min⁻¹) was treated with atropine 0.5 mg. Oxygen 6 litre h⁻¹ was applied using a face mask.

Fifteen minutes after the spinal bupivacaine injection to obtain the appropriate level of spinal anaesthesia, block height, motor blockade according to modified Bromage scale, MAP, HR, SpO2 and the BIS values were noted, and propofol infusion was started by an anaesthetist, who was blinded to the study, at a rate of 100 µg kg⁻¹ min⁻¹ to reach a BIS level of less than 75 (onset time). Afterwards, the infusion rate was titrated to maintain the BIS value between 65 and 75. When BIS score went out of these limits for more than 10 s, the dose of propofol was changed by 10 µg kg⁻¹ min⁻¹ every 20 s. Surgery was started immediately after the ‘onset time’. Onset time and the propofol dose required for the onset were recorded.

Propofol infusion was stopped at the 45th min after the spinal anaesthesia (i.e. 30 min after the start of propofol infusion) to measure the time to reach a BIS level of 90 (recovery time). Recovery time and the 30 min propofol consumption were recorded. After the measurement, propofol infusion was continued throughout the operation. During this period of 45 min, sedation level according to Observer’s Assessment of Alertness/Sedation scale¹³ (OAA/S), MAP, HR, SpO₂, ventilatory frequency and BIS value were recorded every 5 min. If the patient was clinically uncomfortable (OAA/S=5) despite an appropriate BIS score, she was planned to be sedated further and excluded from the study.

Statistical analysis

Statistical analysis was done using SPSS 11.5 software (SPSS Inc., Chicago, IL, USA). Comparisons between groups for patient characteristic data, onset and recovery time, propofol doses, fluid and ephedrine consumptions, BIS values, haemodynamic variables, SpO₂ and ventilatory frequencies were performed by independent-samples t-test. Anaesthetic levels were compared with Mann–Whitney U-test. Changes in MAP, HR and BIS values within groups were evaluated using repeated measures ANOVA. Post hoc comparisons were made using Tukey HSD and Dunnet’s t-test. Fisher’s exact test was used to compare Bromage scores. OAA/S scores were compared by using Kruskal–Wallis ANOVA. The results are presented as mean (SD), except anaesthetic level and sedation scores, which are given as median (range). Statistical significance was assumed for P<0.05.

Results

The groups did not differ with respect to age, weight and height (Table 1). Median anaesthetic level was T3 (T1–4) in the HS group and T10 (T9–11) in the LS group. Bromage score was 3 in all patients in the HS group, 2 in 16 patients and 3 in 9 patients in the LS group (P<0.011). The BIS values were not decreased significantly after the spinal bupivacaine administration until the propofol infusion in both groups [from 98.3 (2.1) to 97.2 (2.0) in HS, and from 98.5 (2.2) to 98.1 (1.9) in LS]. There was also no significant difference between the two groups in BIS values in any

| Table 1 Patient characteristic variables of the groups. Values are mean (range or SD) |
|-----------------|-----------------|
| **Age (yr)**    | **49.1 (43-62)**| **52.3 (42-60)** |
| **Weight (kg)** | **69.7 (7.1)**  | **68.2 (8.7)**   |
| **Height (cm)** | **163.4 (8.6)** | **161.7 (7.4)**  |

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measurement time, but all measurements obtained after 15 min are significantly lower than those obtained before ($P<0.001$) (Fig 1). No sudden changes above 75 were observed immediately after surgical stimulation. OAA/S scores were also in accordance with BIS values (Table 2). Haemodynamic variables during sedation period did not differ between the groups. None of the patients demonstrated bradycardia (HR <60 beats min$^{-1}$) or hypotensive episodes (MAP 20% lower than baseline or lower than 60 mm Hg). In this period, a total of 808 (153) and 174 (58) ml of Ringer’s lactate was infused ($P<0.001$) to group HS and LS, respectively. Ten patients in the HS and five in the LS group needed ephedrine (mean dose, 2.6 (3.5) mg and 1.1 (2.3) mg in group HS and LS respectively, not significant). None of the patients showed hypoxia ($\text{S}_\text{pO}_2<96\%$) or hypoventilation (ventilatory frequency $<12$ min$^{-1}$). In all patients, BIS levels were in accordance with the clinical sedative status (OAA/S) (i.e. all patients within the BIS range 65–75 had an OAA/S of 3), so that no patient was excluded from the study because of the change in the sedation strategy.

**Table 2** BIS values and OAA/S scores of the groups during study period. BIS values are mean (SD) and OAA/S scores are median (range). *$P<0.001$ vs prespinal, 5, 10 and 15th minute values of the same group

<table>
<thead>
<tr>
<th></th>
<th>Prespinal</th>
<th>5th min</th>
<th>10th min</th>
<th>15th min</th>
<th>20th min</th>
<th>25th min</th>
<th>30th min</th>
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<tr>
<td>HS</td>
<td>98.3 (1.2)</td>
<td>97.8 (1.6)</td>
<td>96.9 (1.5)</td>
<td>97.2 (1.4)</td>
<td>72.4 (2.1)*</td>
<td>68.3 (2.4)*</td>
<td>68.4 (2.5)*</td>
<td>68.7 (1.7)*</td>
<td>67.5 (2.8)*</td>
<td>69.2 (2.2)*</td>
</tr>
<tr>
<td>LS</td>
<td>98.5 (1.6)</td>
<td>97.4 (1.8)</td>
<td>97.7 (1.9)</td>
<td>98.1 (1.9)</td>
<td>74.2 (2.4)*</td>
<td>71.4 (1.5)*</td>
<td>69.8 (1.9)*</td>
<td>67.2 (3.1)*</td>
<td>68.9 (2.9)*</td>
<td>68.3 (3.2)*</td>
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<td><strong>OAA/S</strong></td>
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<tr>
<td>HS</td>
<td>5 (5–5)</td>
<td>5 (5–5)</td>
<td>5 (5–5)</td>
<td>5 (5–5)</td>
<td>3 (3–4)</td>
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<tr>
<td>LS</td>
<td>5 (5–5)</td>
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<td>3 (3–4)</td>
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**Table 3** Induction, wake-up time and total propofol consumptions in the high and low spinal (HS and LS) groups. Values are presented as mean (SD) and range. Induction and maintenance doses of propofol are expressed in mg kg$^{-1}$. Onset time was defined as time from the beginning of propofol infusion until the moment the BIS level was less than 75. Recovery time was defined as the time from cessation of propofol infusion until the moment the BIS level was higher than 90. Propofol induction equals the required dose of propofol for onset time. Propofol maintenance equals the required dose of propofol to keep the BIS level between 65 and 75

<table>
<thead>
<tr>
<th></th>
<th>HS</th>
<th>LS</th>
<th>$P$-value</th>
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<tbody>
<tr>
<td>Onset time (s)</td>
<td>226 (47) (140–325)</td>
<td>273 (48) (210–385)</td>
<td>0.001</td>
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<tr>
<td>Recovery time (s)</td>
<td>234 (47) (175–330)</td>
<td>202 (56) (125–320)</td>
<td>0.03</td>
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<td>Propofol induction</td>
<td>0.38 (0.07) (0.23–0.54)</td>
<td>0.45 (0.08) (0.35–0.64)</td>
<td>0.002</td>
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<td>Propofol maintenance</td>
<td>2.17 (0.43) (1.56–2.95)</td>
<td>3.14 (0.56) (2.18–3.78)</td>
<td>&lt;0.001</td>
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**Fig 1** BIS values of the groups during the study period. Values are mean (SD). x-Axis refers to the time starting before intrathecal local anaesthetic administration (prespinal). Propofol infusion was initiated immediately after the 15th minute recordings. There are no differences in two groups in any measurement time; all measurements after the 15th minute are significantly lower than the ones before the 15th minute.

Sedation depends on spinal anaesthesia level
Discussion

This study showed that high spinal anaesthesia with hyperbaric bupivacaine 17.5 mg was related to a lower consumption of propofol used for sedation, when compared with low spinal anaesthesia with 7.5 mg of the same drug. Spinal anaesthesia without propofol did not cause measurable sedation in terms of decreased BIS values. However, higher dose bupivacaine was associated with a faster sedation onset and delayed recovery in spite of lower propofol doses.

Previous studies have shown that spinal anaesthesia per se may have sedative properties. Pollock and colleagues reported that in volunteers, spinal anaesthesia leads to a significant decrease in BIS levels. In contrast with their results we did not observe any sedation before the start of propofol infusion. This can be explained by the fact that in Pollock’s study, volunteers were investigated in a darkened room with soft music in contrast with the unpremedicated patients with preoperative anxiety in an operating-theatre in our study.

According to several studies, the interaction between spinal local anaesthetics and sedatives leads to an augmentation of the sedation causing a decrease in the required dose of propofol, thiopental or midazolam to obtain a defined level of sedation. There are some suggestions to explain this interaction: systemic general anaesthetic effects of absorbed local anaesthetics, rostral spread of the local anaesthetic with a direct action on the brain and deafferentation. Most speculated mechanism for sedation during spinal anaesthesia is a deafferentation phenomenon. The loss of facilitatory input to the reticular activating system renders it more susceptible to actions of sedative drugs. Regarding the afferentation theory, active muscle movement has a stimulatory effect on the central nervous system mediated in part by muscle afferent receptors. The blockade of these effects by spinal anaesthesia appears to be the most possible explanation of our findings. Certainly, pronounced reduction of muscle afferent activity and direct neuroaxial sensory blockade of the noxious stimulus by high spinal anaesthesia may be the reason for its significant effect on the brain’s sensitivity to sedative drugs. However, this explanation is in contrast with our findings. We found that in the first 15 min of the spinal anaesthesia, before the application of propofol, none of the two groups showed significant change in BIS values. Besides the stimulatory effects of anxiety, another explanation might be that the first 15 min were not long enough for the cephalad spread of the local anaesthetic to reach the appropriate concentrations to produce perceptible sensory block to influence the electrical activity of higher neural centres. This could have resulted in a decrease of measured BIS value. Morley and colleagues have also shown that in unsedated patients neither epidural nor spinal anaesthesia produce clinically detectable sedation, whereby they found an increase in β frequencies similar to that seen in patients with low plasma concentrations of midazolam. As such, this might represent subclinical sedation.

The recovery time of the high dose/high spinal group was longer than the low spinal group despite the lower consumption of propofol. This finding implies that the level of spinal anaesthesia by a higher dose of the local anaesthetic may play a more important role in sedation than the dose of the sedative drug.

Hypoxia attributed to extended motor blockade of the abdominal and intercostal muscles may be the cause of sedation. However, all of our patients received oxygen and none of them exhibited S_{pO2} levels lower than 96%. Another explanation of sedation seen during spinal anaesthesia is hypotension, which leads to a decrease in cerebral blood flow with resultant somnolence. This possibility was also excluded because of our strict regimens to prevent hypotension with fluids and ephedrine. Systemic administration of ephedrine to protect the haemodynamic stability may also influence sedation and BIS. However, neither the number of patients, who required ephedrine, nor the mean ephedrine consumption differed between the groups.

We used BIS to monitor the sedation level. In many studies the sensitivity of BIS in monitoring the sedation have been shown, however there are also some controversies. To eliminate a possible wrong evaluation, we have also used the OAA/S, a clinical observation method for sedation. In all patients, OAA/S was also well correlated to the BIS levels. Actually, it has also been shown that BIS can predict sedation levels more accurately when using propofol than sevoflurane or midazolam.

Only data collected the first 45 min after the spinal anaesthesia were used (the first 30 min after the propofol infusion) because of the short duration of TVT procedure. To compare the two groups, we did not include the records of longer operations.

Propofol was administered via an infusion without a bolus initial dose to obtain a precise determination of the onset time and the dose of propofol needed for the defined level of sedation during a slight induction. This was a BIS-related modification of a previously described propofol administration.

To our knowledge, there are two previous studies investigating the effects of the level of the spinal anaesthesia (or the dose of the intrathecal administered local anaesthetic) on the level of the sedation. Gentili and colleagues have shown in a pair of series of patients (with and without midazolam) that higher spinal block was associated with an increased sedation. In a recent study, Toprak and colleagues have reported controversial results: spinal anaesthesia caused a reduction in the requirement of midazolam, but this dose reduction was not correlated with the level of the sensory block. They used hyperbaric bupivacaine 10 and 17.5 mg and obtained very close anaesthetic levels (at T9 and T7 in group I and II respectively). Our results support the findings of Gentili and colleagues. However, there are some important differences between our study and the two previous studies. First, we used propofol instead of midazolam.
More importantly, we used an objective monitor of sedation (BIS) instead of sedation scores in the other studies.

There are two limitations to our study. First, there was no control group, where any systemic sedative was not given. However, we assume that it would not be ethical to keep the patients unsedated. Second, regarding the findings of our study we cannot conclude whether the level of the spinal block or the dose of the intrathecally administered local anaesthetic was decisive in the reduction of the propofol dose. A further study with a different protocol would be necessary to investigate this question. We concluded that a high spinal block obtained with hyperbaric bupivacaine 17.5 mg was associated with a faster onset, delayed recovery and lower doses of propofol sedation compared with a low spinal block with 7.5 mg of the same drug.

References
4 Hodgson PS, Liu SS, Gras TW. Does epidural anaesthesia have general anaesthetic effects? Anesthesiology 1999; 91: 1687–92
6 Tverskoy M, Ben Shlomo I, Vainshtein M, Zohar S, Fleyshman. Hypnotic effect of i.v. thiopentone is enhanced by i.m. administration of either lignocaine or bupivacaine. Br J Anaesth 1997; 79: 798–800
7 Ben Shlomo I, Tverskoy M, Fleyshman G, Cherniavsky G. Hypnotic effect of i.v. propofol is enhanced by i.m. administration of either lignocaine or bupivacaine. Br J Anaesth 1997; 78: 375–7
11 Lui J, Singh H, White PF. Electroencephalogram bispectral analysis predicts the depth of midazolam-induced sedation. Anesthesiology 1996; 84: 64–9
17 Eappen S, Kissin I. Effect of subarachnoid bupivacaine block on anesthetic requirements for thiopental in rats. Anesthesiology 1998; 88: 1036–42
18 Lanier WL, Milde JH, Michenfelder JD. Cerebral stimulation following succinylcholine in dogs. Anesthesiology 1986; 64: 551–9
19 Lanier WL, laizzo PA, Milde JH. Cerebral function and muscle afferent activity following intravenous succinylcholine in dogs anesthetized with halothane: the effects of pretreatment with a defasciculating dose of pancuronium. Anesthesiology 1989; 71: 87–95
20 Lanier WL, laizzo PA, Milde JH, Sharbrough FW. The cerebral and systemic effects of movement in response to a noxious stimulus in lightly anesthetized dogs. Possible modulation of cerebral function by muscle afferents. Anesthesiology 1994; 80: 392–401
21 Morley AP, Chung DC, Wong ASY, Short TG. The sedative and electroencephalographic effects of regional anaesthesia. Anesthesiology 2000; 85: 864–9