Influence of the baricity of a local anaesthetic agent on sedation with propofol during spinal anaesthesia


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Background. This study examined the effect of different levels of spinal anaesthesia, induced by solutions of different baricity but containing the same amount of local anaesthetic agent, on the requirement for sedation with propofol.

Methods. Thirty-six patients undergoing varicose vein surgery under spinal anaesthesia were randomly allocated to receive tetracaine 15 mg in 3 ml of either glucose 5% (hyperbaric) or CSF (isobaric). I.V. propofol was started 5 min after the intrathecal injection and was titrated to maintain a bispectral index (BIS) score of 65–75. The propofol requirements to maintain this range in the two groups were compared every 5 min.

Results. The propofol requirement was always lower in the hyperbaric group, with the differences becoming statistically significant 20 min after the intrathecal injection. Total consumption of propofol over the 55 min of the study was also less in the hyperbaric group.

Conclusion. The known difference in level of spinal anaesthetic block induced by solutions of different baricity, but the same dose of local anaesthetic, was associated with different requirements for propofol sedation as determined by BIS assessment.

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Previous studies have shown that regional block exerts some degree of sedative effect, and that the requirements for sedative drugs are inversely proportional to the level of spinal anaesthesia. However, most studies have used different doses of local anaesthetic to induce different levels of spinal anaesthesia, so it is unclear whether the reduced requirements for sedative drugs were an effect of the larger dose, the higher level of block, or a combination of the two. Thus, this study was designed to evaluate prospectively the effect of spinal anaesthetic blocks induced by solutions of different baricity, but containing the same dose of local anaesthetic, on the requirements for propofol sedation as assessed by the bispectral index (BIS). It has been shown that this index, derived from cortical EEG activity, can adequately reflect the sedative effects of drugs which act through the gamma-aminobutyric acid–A (GABA_A) receptor.

Methods

The institutional review board of our hospital approved the study and 36 ASA class I or II patients, aged 18–60 and undergoing elective varicose vein surgery under spinal anaesthesia gave informed written consent before taking part. Subjects treated for neurological disease or alcohol abuse, receiving psychotropic or analgesic medication or that known to be active on the cardiovascular system, or with a body weight 130% above ideal were excluded.

No premedication was given and the patients were monitored with ECG, non-invasive blood pressure, pulse oximetry, and BIS (A-2000 ver 2.1, Aspect Medical Systems, Natick, MA, USA). Colloid solution 500 ml was infused initially for prehydration, and followed by Ringer’s lactate given according to the assessment of the supervising clinician.
With patients in the lateral decubitus position, an intrathecal injection (L3–4 or L4–5 interspace) of tetracaine HCL, naphionoid crystals (Pantocainsterile®, Daehan Med Co., Seoul, Korea) dissolved in 3 ml of either 5% glucose solution (hyperbaric group) or CSF (isobaric group) was performed. Group allocation was made using a sealed envelope technique. Immediately after injection, the patient was turned to the supine position and the level of anaesthetic block was evaluated after 5 min. Anaesthetic level was evaluated by the pin-prick test using sharp tip of a sterile 25G Whitacre needle.

The sedation technique (discussed later) was then started, but no further assessment of block level was performed because this might interfere with the sedation or result in unreliable responses. Instead, to verify that different block levels would have occurred in the two groups, we identified a ‘control’ for each patient. Such control patients were identified from the same surgeon’s varicose vein patients and were included in the study if they had the same sex, body weight and height within 10%, and a similar age (±2 yr). These patients also gave consent to the study and were happy to undergo surgery without any sedative cover. Block levels were checked every 5 min after intrathecal drug injection until the end of operation using the same method.

In the study, sedation consisted of bolus injections of i.v. midazolam 0.02 mg kg\(^{-1}\) and lidocaine 40 mg, and a target controlled infusion (Master TCI, Fresenius Vial, Brezins, France: TCI) of propofol set to achieve a blood concentration of 1.0 μg ml\(^{-1}\). If the BIS score was out of the target range (65–75) for more than 10 s, the target concentration of propofol was changed by 0.1 μg ml\(^{-1}\) every 20 s. The patients’ ears were packed with cotton wool to block ambient noise and a headset (HA-G11, Victor Company of Japan Ltd, Japan) was applied. During the first 45 min period, blood pressure, heart rate, and propofol consumption were recorded every 5 min, and then every 10 min until the operation ended. Sedation level, using the Observer’s Assessment of Alertness/Sedation score (OAA/S, range 1–4),\(^{11}\) was checked every 10 min.

All spinal anaesthetics were performed by the same person, and all measurements were recorded by another single clinician. Atropine was administered if the heart rate decreased below 50 beats min\(^{-1}\), and ephedrine if mean arterial pressure decreased by more than 25% of the preoperative value. However, these subjects were excluded from further study because of the use of cardiovascular drugs.

Eighteen patients per group were needed (α=0.05 and β=0.1) to detect a 30% difference in the amount of propofol administered to the two groups. Statistical analysis was performed using SAS version 8.1 software (SAS Institute, Cary, USA). The data are presented as mean (SD) or median (25–75th percentile) where appropriate. Comparison between the groups was performed by t-test or Mann–Whitney U-test. A P-value of <0.05 was considered significant.

### Results

The groups were similar with respect to age, weight, height, and sex ratio, but the hyperbaric group received more i.v. fluid (Table 1) (P=0.002), and two of them required ephedrine. Median OAA/S scores were maintained at 3 in both groups and there was no statistically significant difference between them (P=0.76) (Table 1). The maximum levels of block in the control hyperbaric and isobaric groups were T4 (T3–T9) and T10 (T8–T11), respectively (P<0.05) (Fig. 1).

A significant difference in propofol requirement was first observed 20 min after intrathecal injection, and was maintained throughout the study period (55 min) (Table 2). Cumulative consumption of propofol to maintain the BIS value was also less in the hyperbaric than in the isobaric group.

### Discussion

The main finding of this study was that the requirement for propofol for sedation was dependent on the height of block, even though the same dose of local anaesthetic was administered. Second, the difference between the two

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**Table 1** Patient data. The values are reported as mean (range), mean (SD) or number. The OAA/S is expressed as median (range). There were no differences between the groups except in the amounts of crystalloid infused (P=0.002). Colloid 500 ml was infused in both groups.

<table>
<thead>
<tr>
<th>Hyperbaric group (n=18)</th>
<th>Isobaric group (n=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr) 46.2 (28–57)</td>
<td>46.6 (32–56)</td>
</tr>
<tr>
<td>Male/female 10/8</td>
<td>11/7</td>
</tr>
<tr>
<td>Weight (kg) 66.0 (8.1)</td>
<td>70.5 (7.7)</td>
</tr>
<tr>
<td>Height (cm) 168.1 (9.8)</td>
<td>163.3 (10.1)</td>
</tr>
<tr>
<td>ASA (I/II) 11/7</td>
<td>10/8</td>
</tr>
<tr>
<td>OAA/S 3 (1–4)</td>
<td>3 (2–4)</td>
</tr>
<tr>
<td>Crystalloid infused (ml kg(^{-1}) h(^{-1})) 7.5 (2.3)</td>
<td>4.5 (1.2)</td>
</tr>
</tbody>
</table>

**Fig 1** Block heights after intrathecal drug injection in control patients. The values are the median (25–75th percentiles). ‘Time’ is the interval after intrathecal drug injection.
groups in the propofol requirement for sedation was first observed 20 min after intrathecal drug injection. In this study, we did not establish the definite height of block in the patients under study because of concerns that sedated patients might produce unreliable responses, and because a pilot study showed that assessment of block level under light sedation has a significant influence on BIS. We could have waited until block spread was maximum before administering sedation, but we wanted to try and identify the time course of any difference in sedative requirement, and any absolute difference. Thus, sedation was started (at 5 min) as soon as there was evidence of successful spinal injection. It is well recognized that local anaesthetic solutions which are hyperbaric or isobaric relative to CSF produce markedly different levels of spinal anaesthesia, but we felt that it was important to demonstrate that this applied to the patient population under investigation. To do this, we identified patients whose characteristics were closely matched to the study patients and used the same spinal anaesthetic technique, but no sedation, to demonstrate the differences in onset time and total spread of the local anaesthetic block.

This study showed that the dose-sparing effect on sedation of the higher block level was not observed during the first 15 min. Median anaesthetic levels were T5 (T4-9) and T10 (T9-11) in the hyperbaric and isobaric groups, respectively, at 20 min after intrathecal injection, whereas the figures were T7 (T6-9) and T10 (T8-11) at 15 min in the ‘control’ patients. This shows that the decrease in propofol requirement for sedation during spinal anaesthesia was influenced by the block height, not the dose of local anaesthetic used. However, this study did not demonstrate a correlation between block level and propofol requirement, because the block levels were not so diverse.

Several theories have been proposed to explain the sedative effects of spinal anaesthesia, including a direct effect of the local anaesthetic, either by systemic absorption or rostral spread through the CSF, attenuating stimulation of the reticular activating system in a situation where there is also decreased afferent input. Pollock and colleagues reported that the greatest variations from baseline BIS values in nonsedated patients occurred at 30 and 70 min after induction of spinal anaesthesia, and suggested that delayed rostral spread of local anaesthetics might be responsible. Direct application of local anaesthetics to the brainstem of animals does cause loss of consciousness, but there is no evidence to indicate whether or not significant amounts of drug reach that level during routine spinal anaesthesia.

A previous study, in which ‘high’ and ‘low’ blocks (medians T3 vs T10) were produced by the injection of different doses of hyperbaric bupivacaine (17.5 vs 7.5 mg), reported that the BIS values did not change until 20 min after induction of spinal anaesthesia, the propofol infusion having been started, after 15 min in both groups. The authors suggested that 15–20 min was not long enough for local anaesthetics to spread rostrally in concentrations sufficient to influence the electrical activity of higher neuronal centres. Although the possibility of rostral spread of the intrathecal local anaesthetics cannot be excluded, there is a low probability of this occurring, particularly in the ‘low’ block groups. The results of the present study support these conclusions.

The most commonly accepted explanation for sedation during regional anaesthesia is the decrease in afferent input induced by blockade of nerve conduction. Doufas and colleagues having reported good correlations between the extent of epidural block and decreases in the BIS, and brain auditory evoked potential (BAEP). High spinal anaesthesia, particularly, will reduce significantly the level of cerebral ‘awareness’ and perhaps the brain’s sensitivity to sedatives through a pronounced decrease in activity arising in both muscles and other sources of afferent input. There is obviously a complex relationship, which obviously requires further electrophysiological study, between cerebral cortical activity and that at spinal or more peripheral levels. For example, active muscle movement produced by cerebral stimulation in lightly anaesthetized dogs was associated with increased EEG activation, yet the latter was abolished by paralysis with pancuronium, and another study reported the abolition of the suppression of spinal motor neurone excitability by propofol through mild physical stimulation even at a constant plasma propofol concentration. Such observations also support the need to avoid repeated checks of block level and inputs from the operating theatre environment which might influence BIS, particularly in unsedated patients.

Such studies require an objective indicator of relatively minor degrees of central nervous depression and it has been reported that BIS may not be sensitive enough to demonstrate the effects of N2O sedation. However, N2O does not act through the GABA_A receptor and BIS may only be appropriate for use with drugs which act through it. In this study, OAA/S was well correlated with BIS value throughout the study.

There are two limitations to our study. First, the plasma concentrations of local anaesthetics were not measured.

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### Table 2 Cumulative doses of propofol (mg kg⁻¹) during BIS guided monitoring. The values are reported as mean (SD). Propofol was infused to maintain a BIS value between 65 and 75. Propofol infusion was started 5 min after intrathecal injection. ‘Time’ is the interval after intrathecal drug injection.

<table>
<thead>
<tr>
<th>Time</th>
<th>10 min</th>
<th>15 min</th>
<th>20 min</th>
<th>25 min</th>
<th>30 min</th>
<th>35 min</th>
<th>40 min</th>
<th>45 min</th>
<th>55 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperbaic group (n=18)</td>
<td>0.62 (0.39)</td>
<td>0.99 (0.40)</td>
<td>1.25 (0.44)</td>
<td>1.47 (0.53)</td>
<td>1.70 (0.67)</td>
<td>1.85 (0.71)</td>
<td>2.11 (0.79)</td>
<td>2.34 (0.88)</td>
<td>2.65 (0.90)</td>
</tr>
<tr>
<td>Isobaric group (n=18)</td>
<td>0.75 (0.26)</td>
<td>1.22 (0.35)</td>
<td>1.60 (0.36)</td>
<td>1.84 (0.35)</td>
<td>2.13 (0.34)</td>
<td>2.45 (0.39)</td>
<td>2.75 (0.43)</td>
<td>3.00 (0.42)</td>
<td>3.42 (0.46)</td>
</tr>
<tr>
<td>P-value</td>
<td>0.31</td>
<td>0.09</td>
<td>0.02</td>
<td>0.03</td>
<td>0.03</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
</tr>
</tbody>
</table>
Second, there was no control group, where intrathecal local anaesthetic was not given. However, we have confirmed that level of block is the definitive factor in the increased sensitivity to sedation during spinal anaesthesia. This has obvious implications for the use of sedative drugs during extensive central neural blockade.

References