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REGIONAL ANAESTHESIA

Bupivacaine concentrations in the lumbar cerebrospinal fluid of patients during spinal anaesthesia†

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Background. Data on bupivacaine concentrations in the cerebral spinal fluid (CSF) during spinal anaesthesia are scarce. The purpose of this study was to determine the concentration of bupivacaine in the lumbar CSF of patients with an adequate level of spinal anaesthesia after injection of plain bupivacaine 0.5%.

Methods. Sixty patients with an adequate level of spinal block after standardized administration of plain bupivacaine 20 mg in men and of 17.5 mg in women were studied. To measure the CSF bupivacaine concentration, we performed a second lumbar spinal puncture and obtained a CSF sample at a randomized time point 5–45 min after the bupivacaine injection. In addition, we calculated the half-life of bupivacaine in the CSF and tested the hypothesis that the level of spinal block is related to the lumbar CSF bupivacaine concentration.

Results. Men and women had CSF bupivacaine concentrations ranging from 95.4 to 773.0 μg ml^{-1} (median 242.4 μg ml^{-1}) and from 25.9 to 781.0 μg ml^{-1} (median 187.6 μg ml^{-1}), respectively. The large variability of bupivacaine concentrations obtained at similar times after subarachnoid administration made calculation of a meaningful half-life of bupivacaine in CSF impossible. There was no association between CSF bupivacaine concentration and spinal block level, and CSF bupivacaine concentrations for the same spinal block level differed between patients by six-fold.

Conclusions. There is a large variability of CSF bupivacaine concentrations in patients with an adequate level of spinal anaesthesia.

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Spinal anaesthesia is a commonly used regional anaesthesia technique.[1–3] The skills to perform this technique are easy to learn, and the success rates are typically high, ranging from 80% to 90%.[4–6] Although injection of an inadequate dose of local anaesthetic into the intrathecal space, due to technical or dosing errors, is regarded as the most frequent cause for an insufficient or failed spinal anaesthesia,[7] other reported causes include dural ectasia in patients with Marfan's syndrome,[8] a very large intrathecal volume,[9] and resistance to bupivacaine.[10]

Little is known about bupivacaine concentrations in the cerebrospinal fluid (CSF) necessary to achieve an adequate level of spinal block and about the CSF kinetics of bupivacaine in humans. We are aware of only three studies,[11–13] which include a total of 51 patients with reported bupivacaine concentrations in the CSF during successful spinal anaesthesia. There is a large variability in the reported CSF bupivacaine concentrations. This may be due to (i) different dosing; (ii) different physical properties of the bupivacaine solutions used, that is, bupivacaine–HCl *vs* bupivacaine–CO_2 and hyperbaric *vs* hypobaric solutions; and (iii) different CSF sampling, i.e. by a second spinal puncture or by aspiration through a catheter placed in the intrathecal space. The differences between these studies and the small

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overall number of patients studied might explain the large variability in the CSF bupivacaine concentrations reported.

The primary aim of this study was to determine the concentration of bupivacaine in the lumbar CSF of patients with an adequate level of spinal anaesthesia after injection of plain bupivacaine 0.5%. In addition, we calculated the half-life of bupivacaine in the CSF and tested the hypothesis that the level of spinal block is related to the lumbar CSF bupivacaine concentration. Finally, we tested the hypothesis that moving patients after injection of plain bupivacaine increases the level of sensory block.

Methods

The study protocol was approved by the local ethics committee of the University Hospital Basel, Basel, Switzerland, and written informed consent was obtained from each patient. Inclusion criteria were age between 50 and 75 yr, ASA physical status I or II, body height 150–185 cm, and a BMI <30 kg m^{-2}. Patients with a history of post-puncture headache were not eligible for the study. Exclusion criteria that resulted in abandonment of a second spinal puncture in the intervention group were spinal block levels below T11 and a technically difficult initial spinal puncture at the time of bupivacaine administration.

The 120 study patients were randomly assigned to an intervention or a control group using a computer-generated random list. Sixty patients in the intervention group underwent two spinal punctures: the first puncture was performed for injecting plain bupivacaine 0.5% (Carbostesin®, Astra Pharmaceutica AG, Dietikon, Switzerland) and obtaining spinal anaesthesia, the second for obtaining a 1 ml CSF sample for subsequent analysis of CSF bupivacaine concentration. The 60 patients in the control group underwent only one spinal puncture for injecting plain bupivacaine 0.5%. The control group was included to study the effect of turning on block level. No second lateral turning and no second spinal puncture were performed in the control group, and no CSF sample was obtained for measurement of bupivacaine concentration.

To study whether men and women require the same dose of intrathecally administered bupivacaine to achieve similar lumbar CSF concentrations, we analysed men and women separately. As all men received bupivacaine 20 mg and all women bupivacaine 17.5 mg, we calculated the ratios between the CSF bupivacaine concentration and body weight, and the ratios between CSF bupivacaine concentration, body weight, and dose.

Standard clinical monitoring and peripheral venous access was established in all patients. All patients were then placed in the lateral position and a spinal puncture was performed at the L3/L4 level using a median approach and a 25 G pencil-point needle (Polymedic®, Temena SRL, Bondy, France). Men and women were injected with 20 and 17.5 mg of plain bupivacaine 0.5%, respectively. Before and after bupivacaine injection, free aspiration of CSF was tested to make sure that the needle opening was correctly positioned in the intrathecal space. After injection of the bupivacaine, all patients were placed back in the supine position, and spinal block level measurements were performed with cold-warm discrimination using cotton swabs soaked with ether at 5, 15, 30, and 45 min. When spinal block levels were asymmetric, the median level was used for analysis. In the intervention group, a computer-generated randomization chart was used to assign a time interval of 5–45 min between intrathecal bupivacaine administration and aspiration of a 1 ml CSF sample for analysis of the bupivacaine lumbar CSF concentration. For the second spinal puncture, these patients were again placed in the same lateral position, and the puncture was performed in the same manner and at the same level as the first puncture. The CSF samples obtained were frozen at -20°C. The bupivacaine concentration in the CSF was determined by reversed phase high-performance liquid chromatography using UV detection (wavelength 210 nm), which allows for quantification of concentrations as low as 50 ng ml^{-1}. Between-assay and within-assay variability was below 10% (coefficient of variation). All determinations were done in duplicate.[14] Follow-up for possible post-spinal headache was obtained by clinical visits on the first, third, and seventh day after surgery. Post-spinal headache was diagnosed, if the patient described a headache that was aggravated in the upright position and diminished in the supine position.

Concentration data are presented as range and median, and were analysed using the Mann–Whitney *U*-test. Maximum cephalad spread between the control and the intervention groups was analysed using the Mann–Whitney *U*-test. GraphPad Prism Version 4 (GraphPad Software, San Diego, CA, USA) was used for all calculations. $P<0.05$ was considered statistically significant.

Table 1 Characteristics of 60 control group patients and 54 intervention group patients. Values are median (range)

	Control group ($n=60$)	**Intervention group ($n=54$)**
Men	40	33
Women	20	21
Age (yr)	62 (38–75)	64 (47–75)
Height (cm)	172 (152–190)	170 (155–190)
Weight (kg)	77 (50–99)	73 (50–100)
BMI (kg m^{-2})	26 (21–36)	25 (17–33)

Results

Patient characteristics are shown in Table 1. At the first spinal puncture, CSF could be freely aspirated in all patients both before and after bupivacaine administration. No patient had a maximum cephalad spread below T11 or a technically difficult initial spinal puncture; so, no patient was excluded from the study. The level of spinal block in the 120 patients was between T11 and T1. CSF samples of

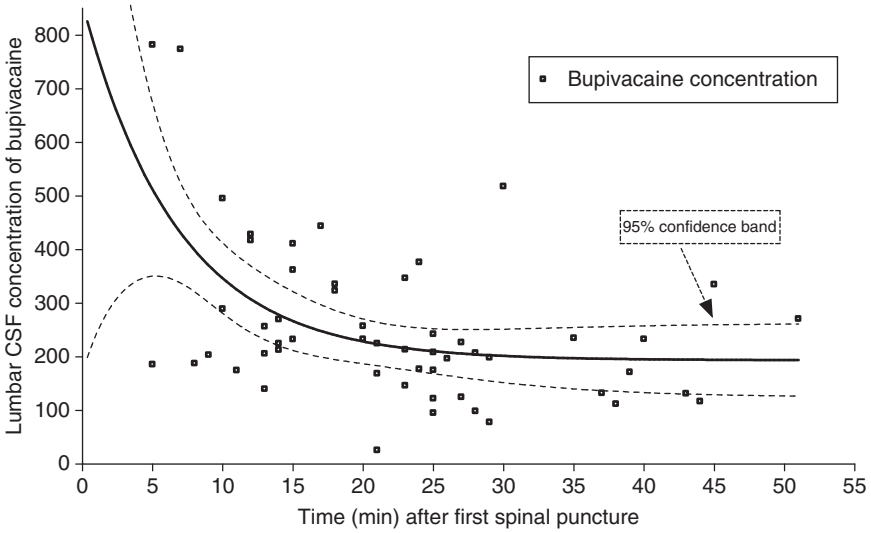

Fig 1 Kinetics of bupivacaine in CSF during spinal anaesthesia in 54 study patients. Bupivacaine concentration is given in $\mu g\ ml^{-1}$.

54 patients (33 men and 21 women) from the intervention group were available for analysis of bupivacaine concentration; six samples were lost. The exact time of aspiration of the CSF sample was between 5 and 51 min after intrathecal administration of bupivacaine.

Men had lumbar CSF bupivacaine concentrations ranging from 95.4 to 773.0 $\mu g\ ml^{-1}$ (median 242.4 $\mu g\ ml^{-1}$) and women 25.9 to 781.0 $\mu g\ ml^{-1}$ (median 187.6 $\mu g\ ml^{-1}$) (Fig. 1). The ratios between the CSF bupivacaine concentration and the intrathecally administered bupivacaine dose were similar in men and women (Fig. 2A). Also similar in men and women were the ratios between the CSF bupivacaine concentration and body weight, and the ratios between the CSF bupivacaine concentration, body weight, and dose (Fig. 2B). Using non-linear regression analysis and assuming a mono-exponential decay, the estimated half-life of bupivacaine in the CSF was 50.8 min (95% CI 2.4–128.2 min). The goodness of fit (r^2) of the non-linear curve was 0.26 (Fig. 1).

The results show a large range of bupivacaine concentrations in the lumbar CSF at every time point measured (Fig. 1). No relationship was detected between bupivacaine concentrations in the CSF and spinal block levels. CSF bupivacaine levels for the same spinal block level were similar in men and women (Fig. 3). In both men and women, the CSF bupivacaine concentrations obtained at similar time points after bupivacaine administration differed up to six-fold (Fig. 3).

Forty-four patients from the intervention group that were repositioned laterally for the second CSF puncture within 30 min of injection of the bupivacaine had significantly more blocked segments after 45 min than the 60 control group patients who were not repositioned (median 18, range 13–22 *vs* 17, range 11–21; P=0.015), and as a consequence had significantly higher spinal block levels (Fig. 4). Initial left to right side differences in the extension of the spinal block were observed in eight patients 5 min after bupivacaine administration but were undetectable by the time of the 45 min control.

One patient from the control group and no patients from the intervention group developed a post-spinal headache. Nine patients (16%) of the intervention group and 10 patients (16%) of the control group reported a non-specific headache.

Discussion

Our results show that bupivacaine concentrations in the lumbar CSF of patients with an adequate spinal anaesthetic block are highly variable (Fig. 1). The variability of samples obtained at similar times after bupivacaine administration was up to six-fold. The variability in CSF bupivacaine concentrations was similar in men and women (Figs 1 and 2), as were the measured concentrations with respect to body weight, height, and dose. This finding is in agreement with the conclusion of Hocking and Wildsmith[15] that men and women develop a similar cephalad spread of intrathecally administered bupivacaine.

There was no correlation between bupivacaine concentrations at corresponding times and the spinal block level 45 min after bupivacaine administration (Fig. 3). For example, the bupivacaine concentrations were 782 and 186 $\mu g\ ml^{-1}$ 5 min after bupivacaine administration in two women whose sensory block levels after 45 min were at T6 and T4, respectively. This variability was not restricted to the early period after intrathecal bupivacaine administration but persisted throughout the study period. For example, the bupivacaine concentrations were 335 and 117 $\mu g\ ml^{-1}$ 45 and 44 min after bupivacaine administration in two men whose sensory block levels at this time were at T8 and T6, respectively (Fig. 2A).

The variability in lumbar CSF bupivacaine concentrations in our sample correlates well with the findings of

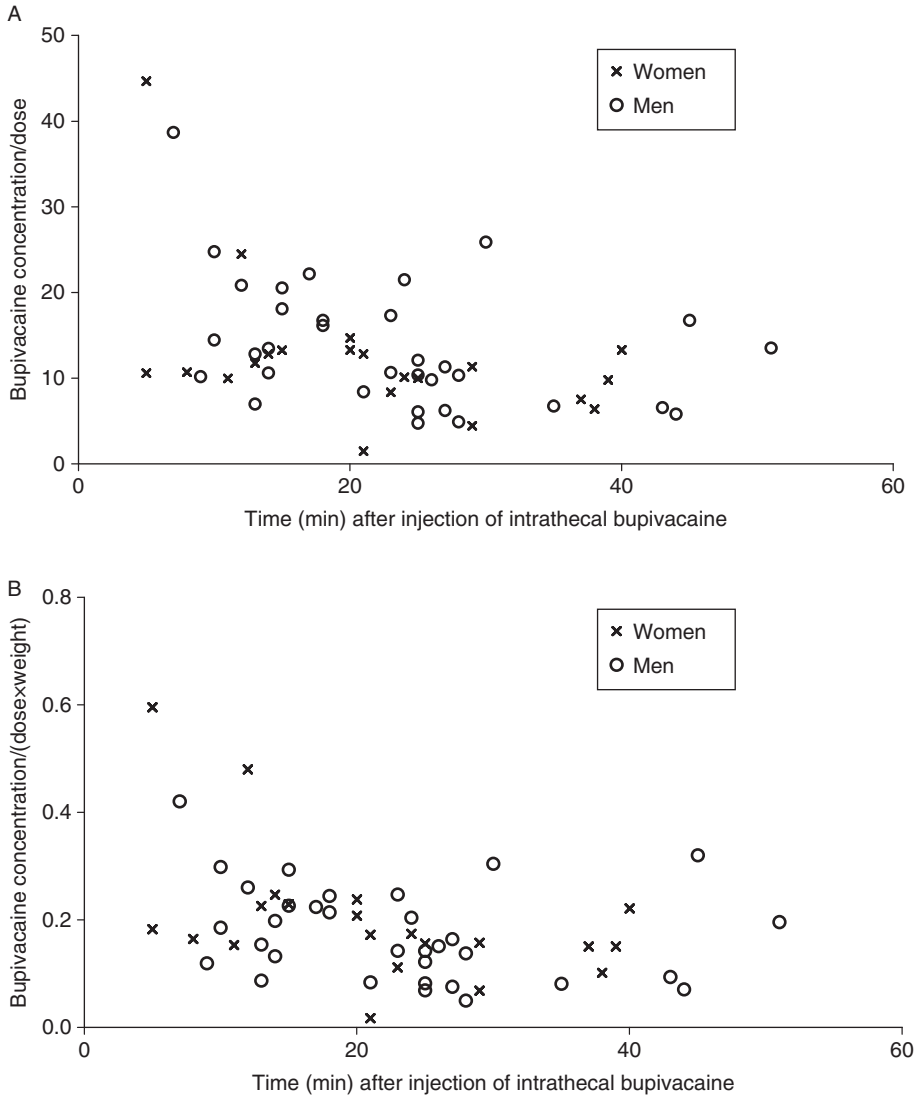

Fig 2 CSF bupivacaine concentration measured at different time points. (A) Bupivacaine concentration ($\mu g\ ml^{-1}$) divided by the intrathecally administered bupivacaine dose (mg) *vs* time in 54 study patients. (B) Ratio of CSF bupivacaine concentration ($\mu g\ ml^{-1}$) divided by the intrathecally administered bupivacaine dose (mg) and weight (kg) *vs* time in 54 study patients.

previous studies.[11–13] We had postulated that the largely differing CSF bupivacaine concentrations in the previous studies were due to methodological differences in conjunction with the small sample sizes. The findings of our larger study show that the variability is also present if the above-mentioned factors are controlled, suggesting that individual anatomical factors have a major influence. In the absence of systematic human studies in this field, we can only speculate about these potential factors. Possible factors might be the non-uniform distribution of the local anaesthetic in the subarachnoid space and the limited utility in using a single point lumbar sample for drawing conclusions regarding the more global movement and intrathecal distribution of bupivacaine. Although there will be a concentration gradient away from the point of injection, it will probably not be constant at any particular level, not even well below the upper level of the block. Both the time needed for complete mixture of bupivacaine and CSF and the time that bupivacaine is capable of moving independently cannot be defined by our data. However, the observation of a higher maximum cephalad spread in patients with a change in body position within 30 min of injection (but not after that time) suggests that the bupivacaine has not mixed completely with CSF within 30 min.

Another factor that might have contributed to the large variability in lumbar CSF bupivacaine concentrations is the variability of CSF volume in the intrathecal space. A large variability in the CSF volume in the intrathecal space was reported by Hogan and colleagues,[16] who found that the volume of lumbosacral CSF varied from 28 to 81 ml in humans. This variability may at least partially explain a variable dilution and spread of bupivacaine in the CSF of patients during spinal anaesthesia, and therefore, a variable level of neural block. This potential factor

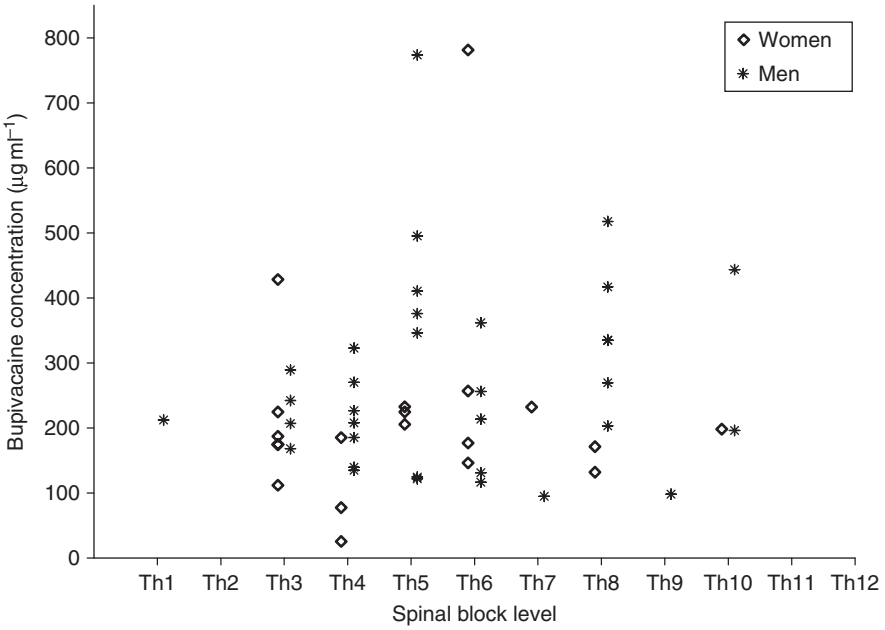

Fig 3 Spinal block level and lumbar CSF bupivacaine concentration in women and men determined at the time of the second spinal tap.

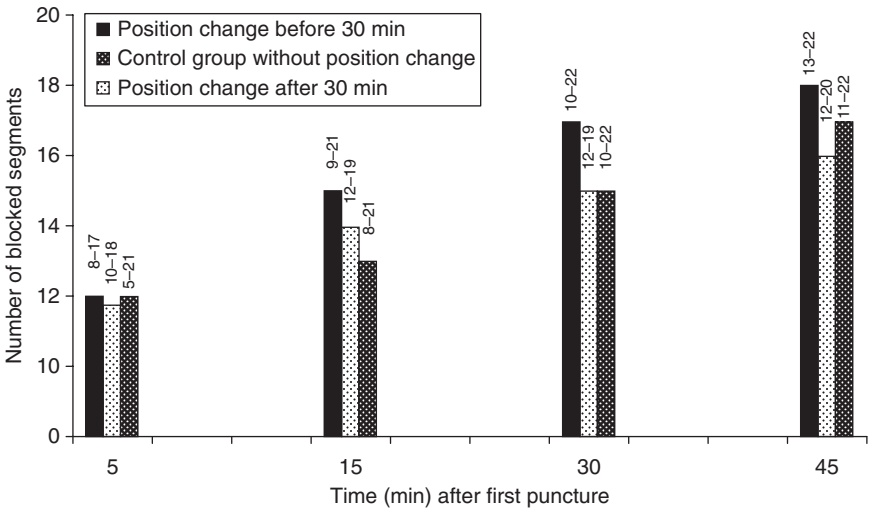

Fig 4 Effect of change in body position within and after the first 30 min after intrathecal bupivacaine administration on spinal block level in 44 patients with position change in the intervention group *vs* 60 patients without position change in the control group. The number of blocked segments is indicated as medians; numbers above the columns indicate the range.

is supported by two case reports of failed spinal anaesthesias: one in a healthy young woman who was subsequently found to have an unusually large intrathecal volume by magnetic resonance imaging;[9] and the second in two parturients with Marfan's syndrome with documented ectatic thecal sacs.[8] A randomized study that found a higher cephalad spread of the spinal block when 5 ml of CSF was removed before intrathecal injection of bupivacaine further supports the importance of CSF volume.[17] Unfortunately, the volume of CSF does not correlate with external physical examination,[18–20] and thus, cannot be considered when estimating the dose of local anaesthetic for spinal anaesthesia in individual patients.

Other factors that might have contributed to the variability in lumbar bupivacaine concentrations in our study patients are non-standardized technical factors during bupivacaine injection including orientation of the port of the pencil-point needle and speed of injection, or the use of barbotage. We did not use barbotage and did not control the orientation of the needle port and the speed of bupivacaine injection. However, based on the observation that a 10-fold difference in speed of subarachnoid bupivacaine injection did not affect spread or onset of sensory and motor block, Stienstra and Van Poorten[21] have concluded that the speed of injection does not affect subarachnoid distribution of plain bupivacaine 0.5%. In summary,

the reasons for the large variability in lumbar bupivacaine concentrations in our study patients remain unclear. It is interesting to note that all study patients had an adequate spinal block, independent of the presence of very low (or high) lumbar CSF bupivacaine concentrations.

We attempted to calculate the estimated half-life of intrathecal bupivacaine using our data, but the described large range of bupivacaine concentrations (Fig. 2A) resulted in a very low goodness of fit (r^2=0.26), indicating that the calculated value is not clinically meaningful.

An analysis of maximum cephalad spread after 45 min revealed that patients who had an additional position change within 30 min of injection had a significantly higher spinal block level than those remaining in the supine position (Fig. 4). This finding may be explained by the fact that spread of spinal anaesthesia is most dynamic during the first 30 min after administration.[15 22] Our findings are in agreement with those of Russell[23] who found an increase of two to three segments in the block level, when patients were turned from a lateral to the supine position, and from the supine to prone positions within 35 min of plain bupivacaine 0.5% administration. An effect of CSF aspiration on block extension in our patients with an additional position change cannot be ruled out, but the small amount of CSF withdrawn (1 ml) questions the relevance of this aspiration.

One limitation of our study is that only one bupivacaine concentration was available from each patient of the intervention group. Therefore, the description of the kinetics of bupivacaine in the CSF is based on the assumption that the medically healthy study patients had a similar clearance of intrathecal bupivacaine. Deciding on the timing of the CSF sampling was a difficult issue with no definitively 'correct' answer. We had decided to obtain samples at randomized intervals after the initial bupivacaine injection, but the large variability in lumbar CSF concentrations in our patients raises the question if choosing a constant time interval would have been a more useful study design. Another limitation is that the initial bupivacaine concentration in the CSF immediately after injection was unknown. This made it more difficult to find reasonable fits of the non-linear regression curve. Introducing a catheter into the intrathecal space would have allowed for repeated sampling but might have introduced other problems such as placement of the tip in a small compartment in the intrathecal space.[14] Another limitation is that we administered different doses of bupivacaine to men and women. Although differences in height and in density of the CSF[24] between men and women might influence drug requirement, there are few data to support the belief that men generally develop less cephalad spread than women.[15] A final limitation of the study is that the speed of bupivacaine injection into the intrathecal space and the orientation of the port during the injection were not standardized.

In summary, we found that lumbar bupivacaine concentrations in the CSF of patients with an adequate spinal anaesthetic block are highly variable, and that there is no correlation between bupivacaine concentrations at corresponding times and the spinal block level 45 min after bupivacaine administration. The large variability of bupivacaine concentrations obtained at similar times after subarachnoid administration made calculation of a meaningful half-life of bupivacaine in CSF impossible. The ratios between the CSF bupivacaine concentration and the intrathecally administered bupivacaine dose were similar in men and women, as were CSF bupivacaine concentrations for the same spinal block level. This finding supports the use of the same dose of intrathecally administered bupivacaine in men and women to achieve similar lumbar CSF concentrations. Finally, we found that a position change within 30 min after spinal anaesthesia increases the spinal block level after administration of plain bupivacaine 0.5%.

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