

# Cerebrospinal Fluid Density Influences Extent of Plain Bupivacaine Spinal Anesthesia

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**Background:** The attempts to explain the unpredictability of extent of spinal block provided by plain local anesthetic solutions have resulted in many clinical reports; however, causes of this uncertainty are as yet unknown. Recently, normal values of the human cerebrospinal fluid densities have been studied showing important interindividual variations, especially between females and males. The current study was designed to evaluate as primary endpoint the influence of cerebrospinal fluid density values on the extent of spinal block with plain bupivacaine. The ancillary endpoints were search of factors explaining the interindividual differences in cerebrospinal fluid density values reported and determination of the relation between upper extent and regression of spinal anesthesia.

**Methods:** Sixty-four consecutive patients undergoing peripheral orthopedic surgery with spinal block were enrolled. Spinal anesthesia was performed in the lateral decubitus position with the operated side upward. Two milliliters of cerebrospinal fluid was sampled before injection of 3 ml plain bupivacaine 0.5%. The patient was immediately turned supine and remained in the horizontal position until the end of the study. Maximal sensory block level and time to sensory regression to L4 were determined for each patient enrolled. Cerebrospinal fluid and bupivacaine densities as well as cerebrospinal proteins, glucose, sodium, and chloride concentrations were measured.

**Results:** A highly significant correlation between cerebrospinal fluid density and maximal sensory block level was found ( $P = 0.0004$ ). However, this correlation was poorly predictive ( $R^2 = 0.37$ ). Cerebrospinal fluid density, proteins, and glucose concentrations were significantly higher in men than in women:  $1.000567 \pm 0.000091$  versus  $1.000501 \pm 0.000109$  g/ml ( $P = 0.014$ ),  $0.46 \pm 0.18$  versus  $0.32 \pm 0.13$  g/l ( $P = 0.001$ ), and  $3.27 \pm 0.7$  versus  $2.93 \pm 0.5$  mm ( $P = 0.023$ ), respectively. A highly significant ( $P = 0.0004$ ) and predictive ( $R^2 = 0.73$ ) inverse correlation was found between maximal upper sensory extent and sensory regression to L4.

**Conclusion:** These findings indicate an influence of cerebrospinal fluid density on subarachnoid distribution of 3 ml plain bupivacaine 0.5% and show that with higher cerebrospinal fluid densities, a higher spinal block level can be expected.

ACCORDING to Greene,<sup>1</sup> the extent of spinal anesthesia may be influenced by more than 20 demonstrated or hypothetical factors. Whereas for hyperbaric spinal solutions the patient's position is accepted as the main determinant of subarachnoid spread,<sup>2</sup> the extent of plain spinal anesthetic solutions is considered to be unpredictable<sup>3</sup> and is not<sup>4</sup> or less<sup>5</sup> position dependent. Nevertheless, causes for these wide interindividual variabilities of extent of subarachnoid blocks with plain anesthetic solutions, performed using identical injection techniques and dosage of local anesthetic, remain unknown.

Recently, different studies have reported that normal values of human cerebrospinal fluid (CSF) densities show important interindividual variations and are significantly different between pregnant and nonpregnant women,<sup>6</sup> premenopausal and postmenopausal women,<sup>7</sup> and females and males.<sup>8</sup> This raises the question as to what extent the variations observed in CSF densities contribute in explaining the variability of the subarachnoid distribution of plain local anesthetics.

The current study was designed to evaluate, as a primary endpoint, the relation between CSF density and the extent of spinal anesthesia with plain bupivacaine. The ancillary endpoints were as follows: (1) to measure CSF proteins, glucose, sodium, and chloride to determine the causes of previously reported differences in CSF densities between men and women<sup>8</sup>; and (2) to investigate if the phenomenon (*i.e.*, higher sensory block levels provide shorter duration, lower levels are associated with longer duration of block), which has been reported for hyperbaric spinal solutions,<sup>2</sup> can also be observed for plain spinal solutions.

## Methods

After obtaining approval from the Ethical Committee of the University Hospital Geneva (Geneva, Switzerland) and written informed consent from patients, we enrolled 67 consecutive patients, American Society of Anesthesiologists (ASA) physical status I-II, undergoing peripheral orthopedic surgery with spinal anesthesia with plain bupivacaine. Apart from usual contraindications to spinal anesthesia, patients with a height greater than 190 cm or less than 140 cm, or with obvious spinal postural abnormalities (cyphosis), were excluded. Moreover, inability to comprehend basic aspects of the study or difficulty with language as well as psychiatric disease or dementia were exclusion criteria.

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One hour before arrival in the operating theater, all patients received 7.5 mg midazolam orally as premedication. After placement of standard noninvasive monitoring and intravenous infusion of 10 ml/kg crystalloid, a lumbar puncture was performed using a 25-gauge Whitacre needle, at the L3-L4 level, with the patient in lateral decubitus position with the operated side up. After observing a free CSF reflux, 2 ml CSF was sampled, immediately stored in closed tubes to avoid evaporation, and frozen at  $-30^{\circ}\text{C}$ . Spinal injection of 3 ml (15 mg) plain bupivacaine 0.5% (5-ml vial Carbostesine<sup>®</sup> 0.5%; AstraZeneca, Grafenau, Zug, Switzerland) with the needle aperture directed toward the nondependent (operated) side was then performed over 10 s, and the patient was immediately turned supine and remained in the horizontal position until the end of the study. The remaining 2-ml bupivacaine solution from the 5-ml vial were also sampled and frozen at  $-30^{\circ}\text{C}$ . The extent of sensory block was assessed by loss of cold sensation tested by ether drops application on the skin on the midline from top to bottom of the body up to T12 and on the nonoperated side thereafter. For practical reasons, motor block was only evaluated on the nonoperated side by the previously described modified Bromage scale<sup>9</sup> (0 = able to move hip, knee, ankle, and toes; 1 = unable to move hip, able to move knee, ankle, and toes; 2 = unable to move hip and knee, able to move ankle and toes; 3 = unable to move hip, knee, and ankle, able to move toes; 4 = unable to move hip, knee, ankle, and toes). Hemodynamic data (mean arterial pressure, heart rate) were also recorded. Data sampling was performed every 5 min for the first 30 min after spinal injection and then every 15 min until the end of the observation period, defined as regression of sensory block level to L4 and total motor recovery. These data were recorded by the anesthesiologist in charge during surgery, and after arrival in recovery room by the nurses in charge of the patient, who were instructed to report accurately sensory block level and degree of motor block while being unaware of the purpose of the study.

All surgical procedures were performed with a thigh tourniquet. After spinal injection, crystalloid infusion was standardized, *i.e.*,  $5 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ . Ephedrine (5-10 mg) was administered intravenously when decrease in mean arterial pressure was more than 30% of baseline value. A decrease in heart rate to less than 45 beats/min was treated with 0.5 mg intravenous atropine. Demographic data of each patient and amount of vasopressor drugs administered were also noted.

At the end of data collection, all samples were unfrozen at room temperature for measurement of CSF and bupivacaine density up to six digits at  $37^{\circ}\text{C}$ , using an Anton Paar densitometer (DMA 4500; Anton Paar GmbH, Graz, Austria). These measurements were performed twice for each sample after repeated calibration for atmospheric pressure and under the supervision of a tech-

nician of the densitometer manufacturer (Anton Paar GmbH). All measurements were performed over a limited period of time of 2 days for all samples (CSF samples on the first day and bupivacaine samples on the next). When values differed by more than 0.000005 between two measurements, a mean value was calculated; otherwise, the first value was considered. Baricity of spinal injectate for each patient was calculated by dividing the density value of remaining 2 ml bupivacaine administered by the density of CSF. Determination of CSF protein, glucose, and electrolyte concentrations were performed by the Laboratory of Clinical Chemistry (Nouri Mensi, Ph.D., Central Chemical Laboratory, University Hospital, Geneva, Switzerland). The relation between maximal sensory block level and CSF density, protein, glucose, sodium, and chloride as well as demographic data (weight, height, and age) were calculated. In addition, maximal sensory block level and measured CSF variables were compared between women and men.

The relation between maximal sensory block level and duration of sensory block (regression at level L4), duration of motor block (complete motor recovery), and maximal decrease in mean arterial pressure during first 60 min after spinal injection were calculated.

#### Statistical Analysis

Continuous data are expressed as mean  $\pm$  SD, and discrete data are expressed as medians with ranges. Comparisons between groups were performed using the Kruskal-Wallis multiple regression, Mann-Whitney, or unpaired student *t* tests when indicated. Correlation coefficient and correlation statistics were performed using CSF density, duration of sensory and motor block, and decrease in mean arterial pressure compared with baseline as independent variables, and maximal sensory block level as a dependent variable, considering for multiple regression tests an  $R^2$  value greater than 0.5 as predictive. Significance level was accepted at  $P < 0.05$ . Prospective power tests defined the sample size according to SD estimates derived from SDs of the mean in CSF density ( $1.00054 \pm 0.00017 \text{ g/ml}$ ) reported previously.<sup>8</sup> Sample size was computed to detect a difference in number of dermatomes involved in the spinal block (minimum 20%, *i.e.*, a four-segment difference) at 30 min after injection with a power 80% or greater and 5% or less chance of type I error ( $\beta = 0.2$ ; two-tailed  $\alpha = 0.05$ ). A minimal sample of 60 patients met these criteria.

#### Results

Among 67 consecutive patients included in the study, three were not considered for further analysis because sampling volume of CSF was insufficient. For analysis of CSF variables, patients mean age was  $54 \pm 15$  yr, mean weight was  $72 \pm 13$  kg, and mean height was  $167 \pm$

**Table 1. Maximal Sensory Block Level, Cerebrospinal Fluid (CSF) Measurements, and Bupivacaine Density and Baricity**

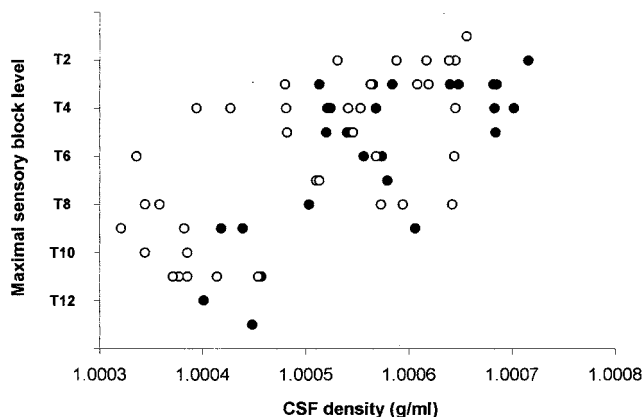
Maximal sensory block level	T5 (T1-L1)
Time to maximal sensory block level (min)	25 (5-60)
CSF density at 37°C (g/ml)	1.000529 ± 0.000107
CSF proteins (g/ml)	0.38 ± 0.17
CSF glucose (mM)	3.08 ± 0.6
CSF sodium (mM)	136 ± 18
CSF chloride (mM)	116 ± 15
Bupivacaine density at 37°C (g/ml)	0.999343 ± 0.000004
Bupivacaine baricity	0.998815 ± 0.000106

Median with ranges in parenthesis, or mean ± SD, n = 64.

8 cm. There were 37 women and 27 men; 33 patients were ASA physical status I and 31 were ASA II.

Maximal sensory block level, CSF measurements, and bupivacaine density and baricity are presented in table 1. As expected, the upper sensory block level in the overall study population showed important interindividual variation between T1 and L1 spinal block levels (13 spinal segments). Bupivacaine density showed minimal variations between samples when measured at 37°C. The relation between maximal sensory block level and CSF density is represented in figure 1. This correlation is highly significant ( $P = 0.0004$ ) but poorly predictive ( $R^2 = 0.37$ ). Relations between maximal sensory block level and other CSF parameters (proteins, glucose, sodium, and chloride) or demographic data (age, weight, and height) were not significant.

For women and men considered separately, demographic data are presented in table 2 and anesthetic and CSF data in table 3. In addition to morphologic differences shown in table 2 (weight and height), men showed significantly higher values of CSF densities, protein, and glucose concentrations compared with women. Correlation between maximal upper sensory block levels and CSF densities was also highly significant but poorly predictive for both women ( $P = 0.0008$ ,  $R^2 = 0.31$ ) and men ( $P = 0.0015$ ,  $R^2 = 0.28$ ) subgroups.



**Fig. 1. Maximal sensory block level correlated to cerebrospinal fluid (CSF) density.  $P$  value for correlation is 0.0004.  $R^2 = 0.37$ . Filled circles = men; open circles = women. Each point represents one patient.**

**Table 2. Demographic Characteristics of Women and Men**

	Women (n = 37)	Men (n = 27)	$P$ Value
Age (yr)	58 ± 15	52 ± 15	0.118
Weight (kg)	67 ± 12	78 ± 11	0.028
Height (cm)	163 ± 5	174 ± 8	0.033
ASA physical status (I/II)	18/19	15/12	0.161

Mean ± SD.

ASA = American Society of Anesthesiologists.

When calculating the correlation between maximal sensory block level and time to sensory regression to L4 to total motor recovery and maximal decrease in mean arterial pressure, three of the 67 patients were excluded: two because of pain at the surgical site requiring general anesthesia, and one because of anxiety despite evident optimal spinal block. These three surgical procedures were conducted until the end with general anesthesia, without problems. However, the three previous patients who were excluded from the CSF analyses because of insufficient sampling volumes were taken into account. Thus, for these 64 remaining patients, the demographic data differed slightly from those considered for CSF analysis and were as follows: mean age, 56 ± 15 yr; mean weight, 72 ± 12 kg; mean height, 168 ± 8 cm. There were 37 women and 27 men; 31 patients were ASA physical status I and 33 were ASA II. The maximal sensory block level achieved, time to sensory regression to L4, time to complete motor recovery, and maximal decrease in mean arterial pressure during first 60 min after spinal injection expressed in percent of baseline values are presented in table 4. A significant and predictive correlation between maximal sensory block level and time to sensory regression to L4 (fig. 2), as well as maximal decrease in mean arterial pressure (fig. 3), were documented. In addition, the relation between maximal sensory block level and time to complete motor recovery was also significant ( $P = 0.0004$ ) and predictive ( $R^2 = 0.67$ ).

**Discussion**

The most striking finding of the current study was the significant relation between maximal sensory block level achieved after spinal injection of 3 ml plain bupivacaine 0.5% and measured CSF densities. This indicates that the higher the CSF density, the higher the maximal level of block observed for plain bupivacaine solutions. Although highly significant ( $P = 0.0004$ ), this relation remains poorly predictive ( $R^2 = 0.37$ ), suggesting that CSF density is only one of the main factors influencing the extent of plain bupivacaine spinal anesthesia. In addition, the results of the current study show that different components of CSF, such as proteins, dextrose, sodium, and chloride concentrations, may influence the density of CSF and thus indirectly the extent of spinal



**Table 3. Maximal Sensory Block Level, Cerebrospinal Fluid (CSF) Measurements, and Bupivacaine Baricity in Women and Men**

	Women (n = 37)	Men (n = 27)	P Value
Maximal sensory block level	T6 (T1–T11)	T5 (T2–L1)	0.057
Time to maximal sensory block level (min)	25 (5–60)	25 (5–60)	0.325
CSF density (g/ml) at 37°C	1.000501 ± 0.000109	1.000567 ± 0.000091	0.014
CSF proteins (g/l)	0.32 ± 0.13	0.46 ± 0.18	0.001
CSF glucose (mm)	2.93 ± 0.5	3.27 ± 0.7	0.023
CSF sodium (mm)	134 ± 15	140 ± 20	0.128
CSF chloride (mm)	114 ± 13	118 ± 8	0.205
Bupivacaine baricity	0.998841 ± 0.000109	0.998777 ± 0.000114	0.075

Median with ranges in parenthesis, or mean ± SD, n = 64.

block. Nevertheless, relations between these CSF component concentrations and upper extent are not significant.

Inability to predict maximal upper sensory level of spinal anesthesia with plain anesthetic solutions prompted many investigators to examine and challenge factors that may influence the distribution of plain local anesthetics into the subarachnoid space. These studies reported that dose of local anesthetics,<sup>10,11</sup> spinal level of injection,<sup>12</sup> or orientation of Whitacre needle aperture<sup>13</sup> did, whereas speed of injection<sup>14</sup> or patient demographic data<sup>15</sup> did not influence extent of spinal anesthesia with plain local anesthetic solutions. In the current study we used in all patients an identical dose of bupivacaine injected with a needle aperture directed toward the nondependent (operated) side, and we believe that the variations observed in maximal upper extent cannot be attributed to these two factors (*i.e.*, dose and technique).

Concerning the possible influence of site of injection, in our study we assumed that the spinal puncture was performed at the L3–L4 level. It has been previously shown that the clinical determination of spinal level puncture was wrong in more than 50% of cases and generally higher than assumed.<sup>16,17</sup> Accordingly, we can only speculate that in the current study some spinal bupivacaine injections were performed higher at the L2–L3 level, but we believe that this fact cannot influence our results for two main reasons: (1) it seems difficult to imagine that a difference by one segment in site of lumbar puncture can be responsible for the wide variation in upper spread of spinal block observed (13 segments); and (2) the effect of site of injection on cephalad spread of spinal anesthesia with plain local anesthetics seems controversial since another study reported no influence of this factor on maximal sensory

**Table 4. Main Anesthetic and Hemodynamic Data**

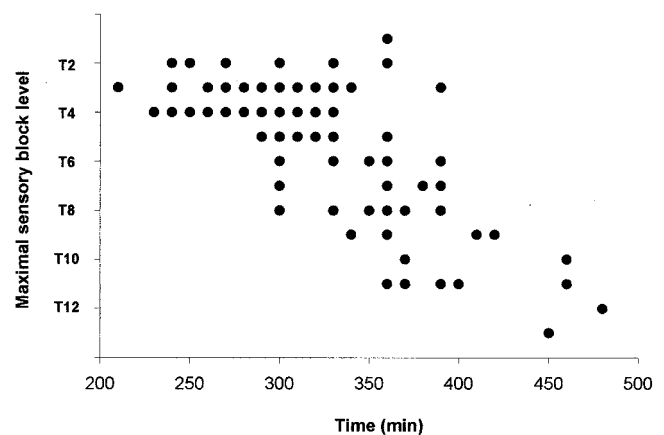
Maximal sensory block level	T5 (T1–L1)
Regression to L4 (min)	323 ± 61
Complete motor recovery (min)	251 ± 65
Maximal decrease in mean arterial pressure (% of baseline value)	20 ± 12

Median with ranges in parenthesis, or mean ± SD, n = 64.

block level achieved.<sup>18</sup> In addition, the uncertainty of injection level, representing an uncontrollable and additional source of variability, should lead, in our study, to an underestimation of the correlation between maximal sensory block level and CSF density.

Five but not 3 ml CSF removed before spinal injection has been shown to have an impact on spread of spinal anesthesia with plain bupivacaine.<sup>19</sup> In the current study only 2 ml CSF was sampled in all patients, excluding any influence of CSF removal on the course of sensory and motor block. Lumbar lordosis has also been evoked as a factor modifying the subarachnoid distribution of local anesthetics.<sup>1</sup> Results of studies reporting the effects of lumbar lordosis on spread of hyperbaric solutions are controversial,<sup>20,21</sup> and there are no data for plain solutions of local anesthetics. The variation in lordotic curve is, in our opinion, a minor factor influencing subarachnoid spread of plain bupivacaine. Once again, however, lumbar lordosis could be an additional source of variability leading to further underestimation of the observed relation between maximal sensory block level and CSF density.

A significant relation between lumbosacral CSF volume and maximal sensory block level achieved has been reported for hyperbaric lidocaine.<sup>22</sup> Whether this phenomenon is valid for plain bupivacaine remains to be demonstrated but could be another important factor



**Fig. 2. Maximal sensory block level correlated to time of regression to L4. Each filled circle represents one patient. Inverse correlation is significant and predictive ( $P = 0.0004$ ,  $R^2 = 0.73$ ).**

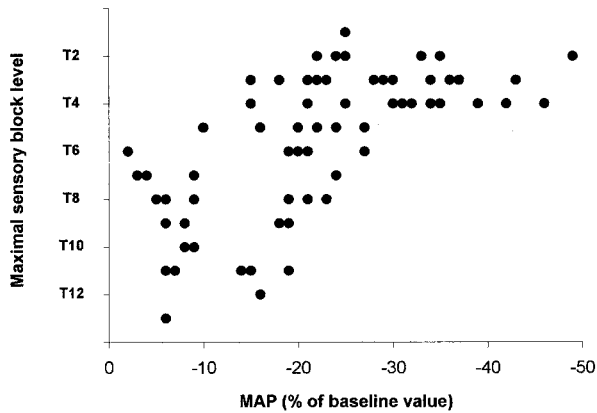


Fig. 3. Maximal sensory block level correlated to maximal decrease in mean arterial pressure (MAP) during the first 60 min after spinal injection expressed as percent from baseline value. Each filled circle represents one patient. Correlation is significant and predictive ( $P = 0.0004$ ,  $R^2 = 0.69$ ).

influencing subarachnoid distribution of plain local anesthetics. In addition, repeated spinal anesthesia with plain bupivacaine in the same patient produces spinal block that is less variable in extent and duration than when the same dose of local anesthetic is administered to different patients.<sup>23</sup> Because the volume of lumbosacral CSF varies by a factor three in humans,<sup>24</sup> variable dilution of local anesthetic solutions injected into the lumbosacral CSF can be achieved and therefore expected to have an important effect on characteristics of neural blockade.

In our report, we investigated CSF kinetics of 3 ml plain bupivacaine 0.5%, which is a local anesthetic solution frequently administered for spinal block. Bupivacaine densities of injected samples measured at 37°C were near identical (table 1) and are in agreement with previous reports.<sup>7,25</sup> There are some controversies about the notion of baricity of this bupivacaine solution.<sup>26</sup> Greene<sup>1</sup> reported that plain bupivacaine 0.5% is slightly hypobaric in most patients, but in clinical practice it is considered as isobaric. In addition, the same investigator stated that local anesthetic solutions with baricities less than 0.9990 are predictably hypobaric.<sup>1</sup> In the current study more precise density measurements up to six digits were performed; the mean value of calculated baricity was found to be less than 0.9990 in a majority of patients (table 1), supporting the statement established in 1985 by Greene.<sup>1</sup>

Other important findings of the current study were the significant differences between women and men in CSF density, protein, and glucose contents. The higher CSF density values measured in men confirm our previous report,<sup>8</sup> but the significantly higher CSF protein and glucose concentrations have, to our knowledge, never been reported. The impact of mass represented by higher levels of glucose and proteins in men's CSF samples can explain the higher values of CSF density mea-

sured in men. This higher glucose and protein content, which results in higher values of CSF density, is associated with a greater rostral extent of spinal block. Although several theories can be evoked to explain this relation, such as the difference in densities between CSF and plain bupivacaine resulting in a greater "hypobaricity" of plain bupivacaine relative to CSF, or the higher protein content measured in men resulting in a higher rostral distribution of bupivacaine because it is highly bound to proteins,<sup>27</sup> the exact mechanism for this relation remains to be elucidated. Furthermore, the question still remains as to whether the reported differences in CSF components can affect subarachnoid kinetics of other drugs used in anesthesia, such as opioids.

The relation between a high CSF density and a high upper sensory block level allows a better understanding of the unpredictability of extent of plain bupivacaine spinal anesthesia. However, this finding is not very useful clinically because, in everyday practice, we cannot measure CSF density in all patients. Another finding of the current study that could be clinically relevant is the fact that upper sensory block extent varied by 13 segments (T1 -L1), as reported in table 4, with unnecessary high median values (T5) for lower limb surgery. Figures 2 and 3 indicate that higher sensory block levels are associated with shorter duration of sensory block and greater hemodynamic consequences. Because the spread of plain bupivacaine spinal anesthesia remains difficult to predict, we feel that for lower limb surgery in supine position, plain local anesthetic solutions should be avoided in favor of hyperbaric ones associated with a 30° elevated-torso position of patients during surgery. Indeed, we previously demonstrated that, during hyperbaric bupivacaine spinal anesthesia, maximal sensory level is lower, duration of sensory block is longer, and hemodynamics much better preserved in patients maintained in a 30° torso-elevated position compared with those maintained in a horizontal position.<sup>2</sup>

In conclusion, the results of the current study show that CSF density is one of the main factors influencing maximal upper level of plain bupivacaine spinal anesthesia. Higher densities are significantly but not predictably associated with higher cephalad levels. Because it is documented that CSF density is significantly different between some subgroup populations (higher in men than in women, higher in postmenopausal than premenopausal women, higher in nonpregnant than in pregnant women), maximal upper sensory block levels achieved during plain bupivacaine spinal anesthesia can be expected to vary between these groups of patients.

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