

# Fast glycorrachia and cerebrospinal fluid protein as predictors of sensory block in anesthesia with subarachnoid Ropivacaine

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## Abstract

**Background.** Identify if glycorrachia and cerebrospinal fluid protein could influence the time of sensory block to T10, the duration and the metameric block's level, after a standard dose of Ropivacaine.

**Methods.** 80 patients, ASA I - III undergoing to transurethral prostate resection with spinal anesthesia in a prospecting open study were recruited. A 0.2 ml liquor's sample was taken; glycorrachia, by glycemic stix and CSF protein, by urinary stix, were got, before Ropivacaine 0.5% 15 mg injection (0.10 - 0.15 mlsec).

After anti-trendelenburg, with 30 ° tilting for 15 min, the onset of sensory block to T10, the maximum metameric level to 15' and the time of sensory block were reported. The data collection were analyzed using the software language R.

**Results.** A significant correlation liquor specific weigh preoperative glycemia (0.749), liquoral specific weigh glycorrachia ( $\rho = 0.751$ ;  $R^2 = 0.564$ ;  $P 0.05$ ) and specific weigh CSF protein ( $\rho = 0.684$ ;  $R^2 = 0.468$ ;  $P 0.05$ ) were reported. Inverse relation CSF weightsensory block level ( $\rho -0.789$ ,  $P 0.05$ ,  $R^2 0.621$ ) was evidenced. Inverse relation onset time to T10 glycorrachia (84%) and cephalic block glycorrachia (76%) were found.

Inverse correlation onset time to T 10 CSF protein and cephalic block proteinorrachia was respectively 84% and 67%. A  $\rho$  of 0.712 with  $R^2$  of 51% BMI onset to T10 and  $\rho$  of 0.681 with  $R^2$  of 51% BMI maximum cephalic block with  $P 0.05$  were reported.

**Conclusions.** The predictability of a iso-hypobaric local anesthetic could reduce the risk of procedure failure and adverse events by further cephalic spread. *Clin Ter 2016; 167(6):e171-179. doi: 10.7417/CT.2016.1964*

**Key words:** spinal, subarachnoid anesthesia, ropivacaine, glycorrachia, cerebrospinal fluid (CSF) protein

## Introduction

Over a century has gone since the first spinal anesthesia on humans was realized, but the difficulty to guarantee a satisfactory subarachnoid block, in extension and in intensity, remains; the dispersion of local anesthetics into the cerebrospinal fluid, as described by August Bier (1), remains "capriciousness".

The effectiveness of a spinal anesthesia, the intensity of the block and the diffusion of the local anesthetic cannot depend on the physiologic composition of the cerebrospinal fluid (CSF) and on the pharmacokinetic and pharmacodynamic properties of the drug selected.

During the 80s and the 90s many studies examined the responsible factors for the interindividual variability when the dispersion of iso-hypobaric anesthetics and intensity of sensory-motor block happen (2) It can depend on their characteristics, but also on the liquor one's (3,4).

CSF and Individuals factors may influence the behavior of iso-hypobaric anesthetics within the subarachnoid space; clinical studies tried to attribute to single factors the variability in intrathecal drug's dispersion. Nowadays, no study proved a multi-factorial close correlation with the CSF composition, to predict the local anesthetic's effect.

The patient's position influences the intrathecal diffusion of the hyperbaric anesthetics (5); the metameric level obtained with the isobaric solutions is unpredictable (6) and little influenced by the position (7,8); however, the considerable interindividual variability of the block still remains controversial.

There are many factors patient dependent like the anesthetic diffusion, the injection's technique and the injected solution (9,10).

The CSF is a clear, transparent, and uncoagulable liquid, with a specific weight between 1002 to 1010 (at 37° C average value is 1003), higher in the spinal cord, because of the high level of proteins. The density of CSF depends on the NaCl content, temperature, protein and carbohydrate concentration; it increases in the elderly, in the lower spine's region, during pathological conditions that alter the qualitative composition as hyperazotaemia, hyperglycemia, hypoproteinemia, hyperbilirubinemia, or hyperthermia.

The higher spinal cord density is an important factor that can interfere with the cranial spread of local anesthetics.

Compared to plasma, liquor contains less protein (15-45 mg / dl) and glucose (45-80 mg / dl), the pH is slightly acid (7.32 to 7.34), because of the greater CO<sub>2</sub> pressure (pCO<sub>2</sub> 48 mmHg) and the lower bicarbonate's level.

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The cerebrospinal fluid's pressure in lateral decubitus varies from 9 to 20 cm H<sub>2</sub>O, between 37.5 to 50 cm H<sub>2</sub>O in a sitting position.

This pressure's variation depends on age (increases with age), intracranial venous pressure (with higher values of 40-50 mm H<sub>2</sub>O compared to the latter), pulmonary ventilation (oscillations of 4-10 mm H<sub>2</sub>O with breaths) and heart rate (ranging from 2-5 mm H<sub>2</sub>O) (11).

The glycorrhachia (n.v. 40 to 80 mg / dL) has plasma-origins and corresponds to 2/3 of glycemia. The glycorrhachia is considered pathological when the glucose level decreases (less than 60%) in comparison with the plasma glucose, typical of the meningeal disease or intracranial neoplasia.

Increased values of glycorrhachia is very common in diabetics and when patients are taking glucose solutions (12).

The CSF protein (n.v. 15 to 45 mg / dl) varies with age and the metameric sample level, higher in elderly and lumbar subarachnoid space, where the proteinorrachia is 25-50 mg / dl.

The brain proteins derived both from the CSF and plasma; the plasma concentration corresponds to 4/5 (70-80%) of total protein with a 55% of albumin, after passive filtration from the plasma. The remaining 1/5 (20-30%) is synthesized in the central nervous system (CNS).

CSF protein increases when meningitis, spinal tumors and serious bleeding are present, when the barrier damage occurs, with increased passage of proteins from plasma to CSF (13).

Ropivacaine was introduced in clinical practice in 1996; only in February 2004 the intrathecal administration (14, 15) was approved by European Union.

The ropivacaine hydrochloride monohydrate is a long-life local anesthetic (16), pH 6, belonging to the amide type, 99.5% as the S-isomer (17,18).

Kristensen et al (19), first documented the safety of ropivacaine in the subarachnoid space. Rosemberg and Heinonen in 1983 (20), by isolating the vagus and phrenic nerves on mice, show that ropivacaine at low concentrations (25-50 micromol / l), produces a rapid and profound block both of A $\delta$  and C fibers without motor block. At higher concentrations sensory and motor block become equivalent.

According Wildsmith et al (21,) the C fibers block is faster than A ones, while low pKa and high lipid solubility enhances A fibers block. The magnitude of the block, frequency-dependent, depends on the lipid solubility, the local anesthetic's molecular weight and fiber's diameter. The lower lipid solubility of ropivacaine, compared to bupivacaine, could be responsible for the slower diffusion of the anesthetic through the myelin sheath of the large motor fibers, being more selective for the autonomic and sensory nerve fibers, easier and markedly blocked (22,23).

The best block's level with ropivacaine at low concentrations and the possibility of determining a frequency-dependent block, determine clinical advantages, especially in terms of reduced haemodynamic effects, better control of postoperative analgesia and faster recovery times (24).

Ropivacaine 0.5% at 23° C is considered an isobaric local anesthetic, with a density of 1.00380 (3DS) while at 37° C becomes slightly hypobaric with a density of 0.99953 (3DS).

The metameric level of analgesia after subarachnoid anesthesia with Ropivacaine hydrochloride 0.5% is a little bit predictable.

The factors that regulate the CSF dispersion of the local anesthetics is the question that supports a lively scientific discussion.

Among different mechanisms that influence the sensory block extension, we can include: the injection's technique (lumbar interspace, patient position, needle tip direction and infusion rate), the anesthetic solution (volume, density, baricity, concentration and temperature), as well the CSF physico-chemical characteristics (CSF pressure, density, glycorrhachia, CFS protein, CSF volume, pH changes, temperature) and patient's characteristics (age, BMI, metabolic disorders).

The density of CSF, compared to the local anesthetic one, influences its distribution in the subarachnoid space.

## Background

The purpose of the study was to identify if CSF physiochemical characteristics (glycorrhachia and CFS protein) could influence the time of sensory block to T10, the duration and the metameric level of the block, after a intrathecal standard dose of Ropivacaine hydrochloride 0.5% 15 mg. When these two parameters interact subarachnoid block, a quick concentration test might be useful for the quantification of the local anesthetic to be administered.

## Methods

80 patients, ASA I-III, undergoing to transurethral prostate resection (TURP) were recruited for a prospective, open, unicenter study. After obtaining the informed consent, data on sex, age, weight, height, BMI (kg / m<sup>2</sup>) and fasting plasma glucose (FPG) were collected (Table 1).

Blood sugar, one hour before the surgical procedure, was tested in all patients; intraoperative analgesia, through a lumbar spinal anesthesia, was obtained.

Exclusion criteria were related to bleeding disorders, a history of headache, injection site infection, neurodegenerative diseases, known allergy to amide local anesthetics or anesthetic procedure denial.

Vital parameters of each patient (SaO<sub>2</sub>, NIBP, FC, ECG) were monitored; premedication with midazolam 0.02 mg / kg i.v. and i.v. infusion with 500 ml NaCl 0.9% were administered. Body and anesthetic solution's temperatures (°C) were noticed through a thermal sensor; in the case of local anesthetic, the probe was introduced into a vial of the same package, used as a sample. The patient was sitting on the operating table and, after threefold skin disinfection and the

Table 1. Cases - Mean  $\pm$  SD (range).

Age	71,07 $\pm$ 7,45 (46-88)
Weight (Kg)	78,98 $\pm$ 13,66 (46-110)
Height (cm)	171 $\pm$ 7,56 (150-187)
BMI (Kg/m <sup>2</sup> )	26,73 $\pm$ 4,23 (18-41)
ASA I/II/III	6/35/39

local infiltration of subcutaneous tissue with lidocaine 2% 3 mL, spinal anesthesia at L3-L4 with Whitacre needle (25 G) was performed. A 0.2 ml liquor's sample was taken; glycorrachia, by glycemic stix (Bayer-2- **BREEZE**® reaction by the enzyme glucose oxidase) in 5 seconds, while the CSF protein, urinary density stick (Yercon™- **URS-10**), in 60 seconds, were got. Ropivacaine 0.5% 15 mg were injected, without neither barbotage nor aspiration and mixing the local anesthetic with CSF, in an average time between 20 and 30 sec (0,15- 0.10 ml / sec).

Thereafter, all patients were positioned in anti-trendelenburg, with 30 ° tilting for 15 min.

The onset of sensory block to T10, the maximum metameric level to 15' and the period of sensory block were reported.

The data collection were analyzed using the software language R. Relationship between the variables were highlighted by the simple regression model,  $Y = \alpha + \beta x + \epsilon$ , which expresses the linear relationship between the variable X (independent variable) and the variable Y (dependent variable), while  $\alpha$  represents the intercepta,  $\beta$  the angular coefficient and  $\epsilon$  the difference. The Pearson correlation coefficient (rho) was used to express any reports of linearity between the variables analyzed, considering them from -1 (negative correlation) and +1 (positive correlation); A value of 0 indicates no correlation. The determination coefficient R2 (or correctness of model adaptation to the data) was used to evaluate the linear relationship probability, ie, the variability ratio of Y. Its value ranges from 0 (no adaptation) and 1 (perfect fit).

Data were rendered as mean, standard deviation and range (difference between the maximum and minimum). A P-value <0.05 was considered significant.

**Results**

The following observational study involved 80 pts, 25 females (31.3%) and 55 males (68.7%), matched for age, weight, height, BMI and ASA, undergoing TURP surgery.

Routine glycemia, preoperative FPG and body temperature were reported (Table 2).

Glycorrachia, CSF protein and specific weight were tested in the liquor sample; Onset T10, maximum dermatomal level block and sensitivity normalizing were evaluated after the local anesthetic injection (Table 3).

Table 3. Parameters - mean ± SD (range).

	Glycorrachia	CSF protein	Specific weight	Block level	Onset T10	Sensitivity
Media	69,16	22,31	1,0100	8,56	9,80	183,33
DS	16,30	7,54	0,0041	1,56	4,71	33,99
Min	46,00	15,00	1,0050	6,00	2,06	90,00
Max	105,00	30,00	1,0150	10,00	20,00	250,00

Statistical analysis evidenced a significant correlation (rho) between the liquor specific weight and the preoperative glycemia equal to 0.749, i.e. 75%. Statistically significant correlations resulted between the liquoral specific weight and glycorrachia (rho = 0.751; R2 = 0.564; P-value <0.05); between the specific weight and CSF protein (rho = 0.684; R2 = 0.468 ; P-value <0.05). The correlation between CSF weight and maximum range of sensory block showed an inverse relation with values of rho -0.789 and P-value <0.05, but, simultaneously, with an R2 of 0.621. The correlation between the specific weight and ΔT (the difference between body temperature and anesthetic temperature) was low, with values of 16% Table 4 and Figure 1-4.

Table 4. The parameter specific weight has been correlated respectively with preoperative blood glucose, glycorrachia, CSF protein, dermatomal maximum range of the block and difference in temperature between the body and of the anesthetic. Statistical indices evaluated: rho, R2, p-value.

Specific weight	Preop glycemia	Glycorrachia	CSF Protein	Max range block	ΔT
rho	0,749	0,751	0,684	-0,788	0,156
R-squared	0,538	0,564	0,468	0,621	0,013
P-value	8,41E-53	1,04E-12	2,70E-09	<2,2E-16	1,52E-14

Table 2. Parameters - Mean ± SD (range).

FPG (mg/dl)	99,4 ±31,5 ( 50-180)
Preoperative FPG (mg/dl)	91,2± 20,6 (51-140)
Body Temperature (°C)	36,05 ±0,4 (35-37)

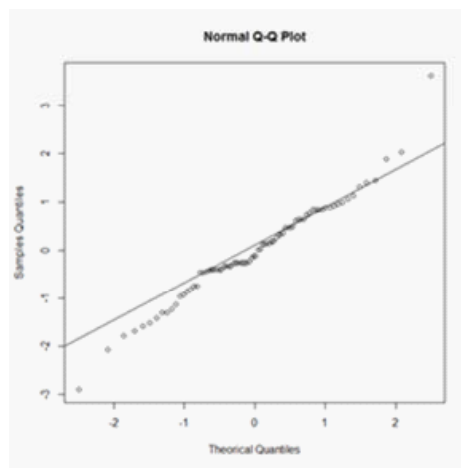


Fig 1. Report PS-glycorrachia

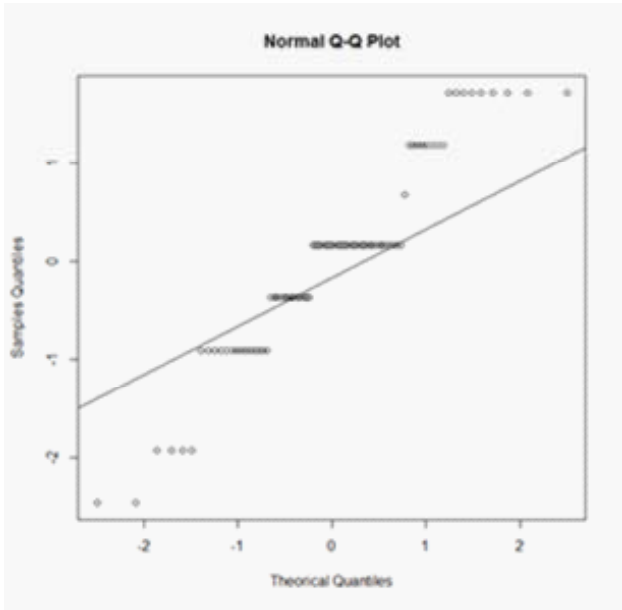


Fig.2. Report PS-maximum extension block

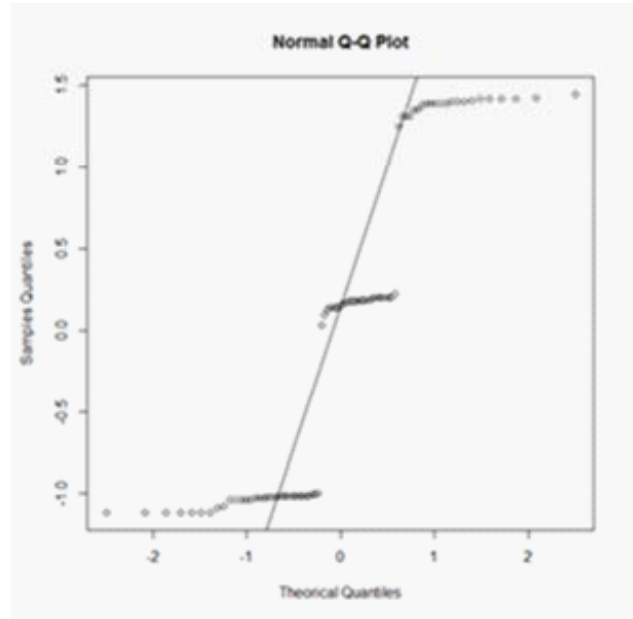


Fig. 4. Report PS -ΔT

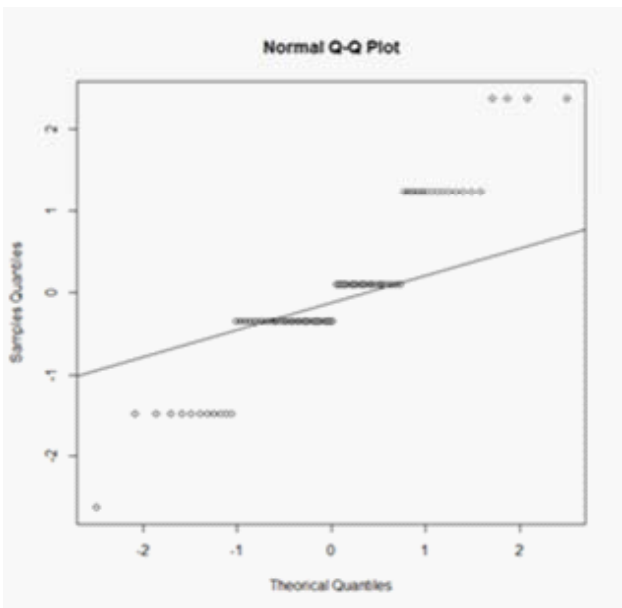


Fig. 3. Report PS-proteinorrachia

The study further investigated the correlation between the onset time to T10 of Ropivacaine 0.5% and glycorrachia, the cephalic block's level and glycorrachia. We got an inverse relation, corresponding to 84% in the first case and 76% in the latter (Table 5). The correlation glycorrachia - cephalic level of the block, was also evaluated in (29) (36,25%) diabetic case patients, resulting weakly positive with a value of 33%.

The onset time to T10 and the cephalad block with CSF protein were compared, with an inversely correlation in both cases, respectively 84% and 67% (Table 5).

Correlations BMI - onset at T10 evidenced a rho of -0.712 with an R2 of 51%; relationship BMI - maximum cephalic block showed a rho of 0.681 with an R2 of 46%. The perfect adaptation is considered good, 51% in the first case and 46% in the second. Both correlations were statistically significant with values of P-value <0.05 (Table 6).

Table 5. Correlation between onset to T10- glycorrachia; cephalic level of the block (in diabetic and not) -gyicorrachia; onset time to T10-CSF protein; cephalic level-CSF protein.

<b>Rho</b>	<b>GLYCORRACHIA</b>
ONSET to T10	-0,836
MAX CEPHALIC BLOCK	
MAX CEPHALIC BLOCK DIABETIC PT.	-0,756
0,328	
<b>Rho</b>	<b>CSF PROTEIN</b>
ONSET to T10	-0,81
MAX CEPHALIC BLOCK	-0,661

Table 6. Correlation between BMI-onset time to T10 and cephalic extension of the block.

	ONSET to T10	MAX CEPHALIC BLOCK
BMI		
Rho	-0,712	-0,681
R-Squared	0,506	0,46
P-value	1,36E-10	3,57E-09

Similarly, a correlation between body mass index and cephalic block in 18 (22.5%) obese patients (BMI > 30) was considered. Inversely relationship of 38%, with a low value of R2 (15%) and a P-value statistically significant resulted (Table 7).

The time of sensibility recovery can decrease with increasing of glycorrhachia, with a correlation coefficient of 71%, 51% of capacity adaptation and increases with the (CSF protein). The time to reversal of sensibility get longer, even when a major cephalic block was obtained (Table 8).

**Discussion**

Spinal anesthesia remains a reference technique, while the pharmacokinetics of local anesthetics, whether isohypobaric or hyperbaric, administered intrathecally, is still a matter of intense discussion (25-28).

Malinovsky et al (29) evaluated an intrathecal injection of isobaric ropivacaine (15 mg) for urologic endoscopic surgery and found that inadequate spinal anesthesia occurred in 16% of patients.

The difficulty to predict the maximum level of sensory block would depend from different inter-individual parameters, that influences the intrathecal dispersion, unpredictable

Table 7. Statistical correlation between obese patients and cephalic block.

	MAX CEPHALIC BLOCK
BMI (>30 Kg/m2)	
Rho	-0,382
R-squared	0,145
P-value	6,65E-05

Table 8. Statistical correlation between time to reversal of sensibility - glycorrhachia - CSF protein - cephalic block.

	GLYCORRACHIA	CSF PROTEIN	CEPHALIC BLOCK
TIME TO SENSIBILITY			
Rho	-0,713	0,588	0,768
R-squared	0,508	0,346	0,589
P-value	1,21E-10	9,54E-06	<2,2E-16

both in extent (30) and duration (31).

Baricity, defined as the ratio between density local anesthetic and cerebrospinal fluid, is considered the factor limiting the distribution of anesthetic in terms of diffusion and metameric level (32,33).

Decubitus, determines the local anesthetics spread in the CSF: the hyperbaric solutions spread caudally, while hypobaric cranially. Moreover, gravity should not have important effects on the isobaric anesthetic spread.

A few studies (34) evaluated the CSF density in relation to the patient’s characteristics (low number of individuals enrolled, neurological abnormalities, and diseases such as diabetes) (35). The temperature influences the CSF density, introducing an additional element of variability (36): the density of all anesthetic solutions “glucose-free” decreases to 0.0003 mg / ml for each temperature increase of 1° C of between 23 and 37° C. Differences of 0.0006 mg / ml can influence the anesthetic spread (37). According to Young Chang (38), warming up reduces the viscosity of the anesthetic not the anesthetic’s density. The high affinity of carbohydrates for water molecules, reduces the physiological movements (39) within the CSF; this effect could explain the failure to density changing in the temperature range tested. The lower the viscosity of the injected solution, the higher is the level of analgesic block achieved (40); no correlation between temperature variation and onset time was evidenced.

In diabetic patients, the body temperature rises due to autonomic disorders (41), determined an higher level block for every increasing of 0.15 °C (42).

The sample analyzed of 80 patients contained 29 (36.25%) diabetics; no significant changes in body temperature compared with 51 not diabetics (76.8%) were evidenced, nor increase of sensory block .

The correlation between the CSF weight and the temperature (ΔT) in diabetic patients was only 15%.

Ann et al (43,44), found negative correlation between the glucose concentration and density while they found positive correlation between CSF protein and density.

Otherwise, Harold Davis (45) reported that water, sodium, chlorine, CO2 less than 1/4 and protein less than 1/5 influence CSF density. In abnormal conditions urea, glucose and temperature interfere with density. Davis believes that temperature, more than proteins, interacts with density (46).

However, glycorrhachia and CSF protein are likely the factors determining the density of CSF; both show a positive correlation respectively by 75% and 68%. A similar correlation (rho = 75%) between preoperative density and CSF glucose was observed, confirming the direct relationship between blood glucose level and glycorrhachia.

The study conducted by Schiffer (47), showed that the correlation between the maximum level of sensory block and CSF density appeared highly significant (p = 0.0004), but little predictive (R2 = 0.37), because of the inter-individual variables; CSF density is only one of the factors influencing the block’s level.

Our study shows an opposite correlation between CSF density and maximum cephalic block extension, with a predictivity index of 0.621 and P-value <0.05; similar results were found by correlating glycorrhachia and maximum

extension cephalic block.

Between 2004 and 2006 Hideyuki (48) and Sanchez et al (49), identified a positive correlation between the maximum extension of sensory block and the level of CSF glucose concentration ( $r = 0.50$ ,  $p < 0.01$ ). In our study, the limited block over T10, was related both to the volume of local anesthetic used ((Ropivacaine 0.5% 3 ml) ) and the patient's position.

Intrathecal Ropivacaine 0.5% 15 mg, is the average dosage for lower abdomen, pelvis and lower limbs surgery. This volume secures an adequate sensory block, limits the extension cephalic block over T10, a potential safety factor for reduced cardiovascular adverse events.

The maintenance after spinal anesthesia of anti-Trendelenburg 30° for 15 min, evidenced limited anesthetic spread for all patients.

However, a weak positive correlation between glycorrachia and maximum block extension in 29 diabetic patients, 18 (62%) of them obese, like the correlation between glycorrachia and CSF density were reported (Table 8). It could be hypothesized that ropivacaine takes the characteristics of hypobaric anesthetic or that dural sac compression, typical of obese patients, could determine the rising of anesthetic in 18 patients with BMI > 30 m<sup>2</sup> / Kg. The increased CSF glucose influences onset time to T10 ( $\rho = -0.836$ ), reducing it (Table 5).

In 2008 Echevarria et al (50), thought that CSF glucose in diabetics could influence the outcome of spinal anesthesia; for this reason they divided two groups of 88 patients. No differences were reported in the maximum extension of sensory block, while the onset time was faster. Moreover, the time to sensibility was protracted in diabetic patients. Richardson (51) and Schiffer (52), observed a reduced volume in the lumbar CSF in diabetics. Differently, Nassel (53) thought that CSF glucose increases CSF water volume. The CSF volume controls the level and duration of sensory block but not the onset (54).

The anesthesia level is related to glycorrachia (55); the greater the concentration of glucose in CSF, the greater is the cephalad spread of local anesthetic, regardless of ropivacaine dosage and patient's position.

Tao Xu et al (56) investigated the ED (50) of intrathecal isobaric and hyperbaric ropivacaine, by up-down sequential analysis in the patients undergoing knee arthroscopy and concluded that the ED50 values of hyperbaric ropivacaine and isobaric ropivacaine were 6.55 mg (95% CI 6.07-7.04) and 9.71 mg (95% CI 8.11-11.32), respectively. The presence of higher levels of liquor's glucose could change the density of ropivacaine, changing the onset time and the cephalad spread.

Several clinical trials (57,58) investigated for some possible correlation between BMI and maximum anesthetic's cephalic extension.

The body mass index (BMI), showed a low predictive value ( $R^2 = 0.5$ ) (59), evidencing only partial clinical significance for the local anesthetic spread. The great obese patient, highlights a cephalic anesthetic spread, a rapid onset time to T10 and a faster recovery of sensitivity, when compared with normal-weight patients (60). In our study, 18 (22.5%) obese patients showed a faster onset time to T10 than 62 (77.5%) normal-weight patients ( $5.44 \pm 2.28$  min

vs  $11.63 \pm 4.2$  min).

Nuria (61), identified the glycorrachia as an important factor that predicts the time to sensitivity; the glucose kinetic is the same for bupivacaine and lidocaine (62,63). Schiffer et al (64) found an inverse correlation between maximum extension of the block and duration; the higher the block level, the shorter its lifetime will be. Our results show that higher concentration of CSF glucose, corresponds to a shorter sensory-motor duration block ( $\rho = -0.713$ ;  $R^2 = 0.51$ ;  $P < 0.05$ ).

CSF is the "solvent" of local anesthetics, its physical-chemical characteristics influence the distribution and the block's duration.

Nuria (47) and Nassel (54) believe than an increased volume of CSF water determines a dilution of anesthetic solution, reducing the duration of the block, but increasing the level. Our study confirmed the correlation between the extension of the block and duration in 77% of patients, with a predictivity index of 59% and a P-value <0.05.

Denson et al (65) correlated the increased cephalic block extension with the concentration of CSF protein in diabetic, because of the closer protein link with anesthetics.

The concentration of CSF albumin influences the block's outcome; although the protein binding reduces free anesthetic, it represents a reserve, which can be disposable afterwards.

As the Authors believe that CSF protein increasing have no effect on the block level but can explain its prolonged duration (66,68), we found a negative correlation between maximum extension of the block and protein concentration in cerebrospinal fluid ( $\rho = -0.66$ ), as well as between CSF protein and onset to T10 ( $\rho = -0.81$ ). The correlation between recovery of sensitivity and CSF protein is 58%.

The obvious differences between the results of our study and the other Authors one's could be related to the local anesthetic used: ropivacaine in the present study and bupivacaine in all the others. So far, our study is the only one who has correlated glycorrachia and CSF protein with subarachnoid ropivacaine. The influence of the parameters on block's level and duration confirmed the hypothesis and can be the starting point for further studies on the use of intrathecal ropivacaine.

## Conclusion

Hyperbaric anesthetics evidenced a better learning curve, determining a higher motor blockade and a quick onset; the iso-hypobaric one's show a low cardiac and neurological toxicity, a high sensitive-motor dissociation, a suitable duration and an acceptably onset.

We observed the erratic behavior of intrathecal Ropivacaine 0.5%, in patients undergoing surgery of TURP, although standardized position, level of injection, dose and concentration of local anesthetic.

While it has been written a lot about the characteristics of an ideal local anesthetic (69,70), much less was described about the ideal subarachnoid anesthesia. The predictability of a iso-hypobaric local anesthetic, could reduce the risk of procedure failure and adverse events by further cephalad

spread.

In literature the factors related to the technique (patient's position - level block - needle tip direction - turbulence - barbotage - injection rate), the patient factors (age - weight - height - BMI - spine's anatomy), those related to the CSF characteristics (pressure, volume, density) and those related to the anesthetic's characteristics (volume, density, concentration, temperature) were evaluated.

These factors, were evaluated separately, thinking that each parameter, by itself, could condition the outcome of the procedure.

Few studies that considered these factors identified predictive criteria for adequate spinal anesthesia.

Surgery and personal practice particularly, influence spinal anesthesia technique, anesthetic's choice and dose; the predictive result remains vague. After all, we considered ropivacaine a good choice for spinal anesthesia, overcoming the doubts of other Authors (71). With this study, we tried to identify a protocol for a subarachnoid block that could be simple, rapid and reproducible.

Still remaining the difficulties in obtaining the quality of sensory block, some criteria in predicting the intensity, extension and duration of the spinal anesthesia, by using Ropivacaine 0.5%, an iso-hypobaric local anesthetic, can be identified.

These factors can be listed as follows:

#### 1. Injection level

The vertebral interspace cannot be too low, to avoid an insufficient spread of anesthetic. The block to L4 -L5 interspace, may be insufficient for TURP surgery;

#### 2. Administration rate of the local anesthetic

The administration rate should be moderately high, because of the influence on the cephalad block's; interventions of TURP includes metameric level analgesia between T8 and T10.

#### 3. Decubitus

The patient's position and its duration represent an important parameter for iso-hypobaric anesthetics, affecting the onset time to the cephalic spread, conditioning the success or the procedure's failure.

#### 4. Temperature of the anesthetic

The local iso-hypobaric anesthetic cannot be stored in the refrigerator; temperatures below 24 ° C modifies the density, increasing it. A reduction of the cephalad anesthetic's spread, when injected into a liquor to physiological temperature and density (37 ° C - 1003) occurs.

#### 5. Dextrostix and stix urine.

Glycorrachia test by dextrostix, gives a quickly and reproducible CSF glucose concentration. With a similar test, we used the urine stick for density and CSF protein. The acquisition of these parameters, although not incontestable in absolute, can be considered a suggestion, to decide rapidly any reduction or increase in the anesthetic's dose, the patient's position and duration, etc, with reduction of undue or inadequate cephalad anesthetic's spread.

In our opinion, glycorrachia is a significant and fast index (5 seconds) and, with reasonable accuracy, can help to predict the onset time to T10 of ropivacaine, the maximum cephalad extension and the duration of the block, especially in diabetic patients.

In conclusion, we can say that the use of a iso-hypobaric

local anesthetic is a valid and advantageous alternative. Though the spinal block's extension is influenced by multiple factors, we believe that further parameters are ignored or underestimated in the daily clinical practice.

Ropivacaine 0.5% subarachnoid activity can be reasonably anticipated, through easy and immediate evaluation of glycorrachia and CSF protein.

The time to test the result is acceptable (5 seconds for glycorrachia, 60 seconds for CSF protein), the "real time" dose optimization can help to predict spread and duration of sensory block, reducing unsatisfactory or adverse consequences.

## Bibliography

1. Bier A. Versuche uber Cocainisierung des Ruckenmarkes. Dtsch. Zeitschrift. Chir 1899; 51:361-9
2. Pacella E, Collini S, Pacella F, et al. De Blasi RA. Levobupivacaine vs. racemic bupivacaine in peribulbar anaesthesia: a randomized double blind study in ophthalmic surgery. Eur Rev Med Pharmacol Sci. 2010;14(6):539-44
3. Budiman M, Izaham A, Abdul Manap N, et al. The patients' understanding on the status and role of anaesthesiologists. Clin Ter 2015;166(6):227-35
4. Hidayah MN, Liu CY, Joanna OS. Ketamine and tramadol for the prevention of shivering during spinal anaesthesia. Clin Ter. 2014; 165(4):193-8
5. Kooger Infante N, Van Gessel E, Forster A. Extent of hyperbaric spinal anesthesia influences the duration of spinal block. Anesthesiology, 2000; 92; 1319-23
6. Logan MR, McClure JH, Wildsmith JA. Plain bupivacaine: An unpredictable spinal anaesthetic agent. Br J Anaesth. 1986; 58:292-6
7. Wildsmith JA, Brown DT, Scott DB. Effects of posture on the spread of isobaric and hyperbaric amethocaine. Br.J Anaesth 1981;53: 273-8
8. Tuominen M, Kalso E. Effects of posture on the spread of spinal anaesthesia with isobaric 0,75% or 0,5% bupivacaine. Br. J. Anaesth. 1982; 54:313-8
9. G. Hocking, JAW. Wildsmith. Intrathecal drug spread. Br. J. Anaesth, 2004
10. Spinal Anaesthesia. The New York School of Regional Anaesthesia. Accessed 6/10/2010
11. A.Seitun, A. Leonardi. Sindromi da alterata pressione endocranica. Le grandi sindromi neuroloche cap 16; 595-632
12. G.Bernardi, E.Corsini. L'interpretazione quantitativa dei dati liquorali IRCCS Istituto nazionale neurologico. Riv Med Lab-JLM, Vol 3 N.2-S1,2002
13. Hansen TG. Ropivacaine: A pharmacological review. Expert. Rev. Neurother 2004; 4: 781-91
14. McCrae AF, Jozwiak H. McClure JH. Comparison of ropivacaine and bupivacaine in extradural analgesia for the relief of pain in labour. Br. J. Anaesth 1995; 74:261-5
15. VanKleef J, Veering B. Spinal anesthesia with ropivacaine: a double blind study on the efficacy and safety of 0,5% and 0,75% solutions in patients undergoing minor lower limb surgery. Anesth. Analg 1994; 78:1125-1130
16. Pacella F, Collini S, Turchetti P, et al. Ropivacaine vs tetracaine in topical anesthesia for intravitreal injection Senses Sci 2015; 2 (4):106-110 doi: 10.14616/sands-2015-4-106110
17. Hansen TG. Ropivacaine: A pharmacological review. Expert.

- Rev. Neurother. 2004; 4:781-91
18. Fattorini F, Pascarella MA, Benvenuti SG, et al. Use of ropivacaine in axillary brachial plexus block. *Clin Ter* 1997
  19. Kristensen JD, Karlsten R. Spinal cord blood flow after intrathecal injection of ropivacaine: a screening for neurotoxic effects. *Anest. Analg* 1996; 82:636-40
  20. Rosemberg PH, Heinonen E. Differential sensitivity of A and C nerve fibres to long-acting amide local anesthetics. *Br J Anesth* 1983;55:163-7
  21. Wildsmith JAW, Brown DT, Paul D, et al. Structure-activity relationships in differential nerve block at high and low frequency stimulation. *Br. J. Anaesth.* 1989; 63:444-52
  22. Rosemberg PH, Heinonen E. Differential sensitivity of A and C nerve fibres to long-acting amide local anaesthetics. *Br. J. Anaesth.* 1983; 55:163-7
  23. Morrison et al. Differential sensitivity of A and C nerve fibres to long-acting amide local anesthetics. *Br J Anesth* 1983; 55:163-7
  24. Van Kleef JW. Spinal anesthesia with ropivacaine: A double-blind study on the efficacy and safety of 0,5% and 0,75% solutions in patients undergoing minor lower limb surgery. *Anesth. Analg* 1994; 78:1125-30
  25. Sheskey MC, Rocco AG. A dose response study of bupivacaine for spinal anaesthesia. *Anaesth Analg* 1983; 62:931-5
  26. Taivainen T, Tuominen M. Spread of spinal anaesthesia using various doses of plain 0,5% bupivacaine injected at LIV-V interspace. *Acta. Anaesthesiol. Scand* 1989; 33:652-5
  27. Urmey WF, Stanton J. The direction of the Whitacre needle aperture affects the extend and duration of isobaric spinal anaesthesia. *Anaesth. Analg.* 1997; 84:337-41
  28. Van Gessel EF, Praptan J. Influence of injection speed on the subarachnoid distribution of isobaric bupivacaine 0,5%. *Anaesth. Analg* 1993; 77:483-7
  29. Malinovsky JM, Charles F, Kick O, et al. Intrathecal anaesthesia: ropivacaine versus bupivacaine. *Anesth Analg.* 2000 Dec; 91(6):1457-60
  30. Mc Clure JH. Plain bupivacaine: an unpredictable spinal anesthetic agent. *Br J Anaesth* 1956; 58:292-6
  31. Chambers WA. Effect of baricity on spinal anesthesia with bupivacaine. *Br J Anesth* 1981; 53:279-82
  32. Greene NM. Distribution of local anesthetic solutions within the subarachnoid space. *Anesth Analg* 1985; 64:715-30
  33. Lui ACP, Munhall RJ. Baricity and the distribution of lidocaine in a spinal canal model. *Can J Anaesth* 1991; 38:522-6
  34. Davis H, King WR. Densities of cerebrospinal fluid of human beings. *Anesthesiology* 1954; 15:666-72
  35. Becker J, Theiss D. Density of cerebrospinal fluid and extent of isobaric spinal anesthesia influenced by elevated glucose concentrations in blood and cerebrospinal fluid or other factors? *Reg Anaesth* 1990;13:101-7
  36. McLeod. Density of spinal anaesthesia solutions of bupivacaine, levobupivacaine, and ropivacaine with and without dextrose. *Br J Anaesth* 2004; 92(4):547-51
  37. Stientra R. the influence of temperature and speed of injection on the distribution of a solution containing bupivacaine and methylene blue in a spinal canal model. *Reg Anesth* 1990; 15:6-11
  38. Young Chang P, Arai, Wasa. The influence of hyperbaric bupivacaine temperature on the spread of spinal anaesthesia. *Anesth Analg* 2006; 102:272-5
  39. Englelsen SB, Monteiro C. The diluted aqueous solvation of carbohydrates as inferred from molecular dynamics simulations and NMR spectroscopy. *Biophys Chem* 2001; 28:103-27
  40. Uedaira H, Ikura M. Natural-abundance oxygen-17 magnetic relaxation in aqueous solutions of carbohydrates. *Bull. Chem. Soc Jpn* 1989; 62:1-4
  41. Takashi S. Effects of spinal anesthesia on the peripheral and deep temperature in elderly diabetic patients undergoing urological surgery. *J Anesth* 2007; 21:336-9
  42. Frank SM. Predictors of hypothermia during spinal anesthesia. *Anesthesiology* 2000; 92:1330-34
  43. Ann CP, Lui, Tomass Z. Reports of investigation: densities of cerebrospinal fluid and spinal anaesthetic solutions in surgical patients at body temperature. *Can J Anaesth* 1998; 45:5:297-303
  44. Lui Ac, Polis T. Densities of cerebrospinal fluid and spinal anaesthetic solution in surgical patients at body temperature. *Can J Anaesth* 1998; 45:297-303
  45. Harold Davis, Wilbert R. Densities of cerebrospinal fluid of human beings. October 9, 1953
  46. Stanford RV Vergleichende studien ueber cerebrospinalfluesigkeit. *Chem* 1913; 86:43-50
  47. Schiffer MD. Cerebrospinal fluid density influences extent of plain bupivacaine spinal anesthesia. *Anesthesiology* 2002; 96:1325-30
  48. Hideyuki H, Jyun-ichi H. Influence of cerebrospinal fluid density, velocity, and volume on extent and duration of plain bupivacaine spinal anesthesia. *Anesthesiology* 2004;100:106-114
  49. Sanchez Morillo et al. Relacion de los niveles de la glucorraquia con el bloqueo sensitivo y motor durante la anestesia raquidea con bupivacaina hiperbara. *Rev Esp Anesthesiol Reanim* 2006; 53:11-17
  50. M.Echevarria, A. Hachero. Spinal anaesthesia with 0,5% isobaric bupivacaine in patients with diabetes mellitus: the influence of CSF composition on sensory and motor block. *Eur J Anaesth* 2008; 25:1014-9
  51. Richardson MG. Density of lumbar cerebrospinal fluid in pregnant and non pregnant humans. *Anesthesiology* 1996; 85:326-30
  52. Schiffer E. Van Gessel. Influence of sex on cerebrospinal fluid density in adults. *Br J Anesth* 1999; 83:943-4
  53. A.Nasser B. Toxic effects of epidural analgesia with ropivacaine 0,2% in a diabetic patient. *J Clin Anesth* 2004; 16:222-3
  54. Randall Lumbosacral cerebrospinal fluid volume is the primary determinant of sensory block extent and duration during spinal anesthesia. *Anesthesiology* 1998; 89:24-9
  55. Sanchez Ferrari A. Relationship between glucose concentration in cerebrospinal fluid and sensory and motor block during spinal anesthesia with hyperbaric bupivacaine. *Rev Esp Anest Reanim* 2006; 53:11-7
  56. Xu T, Wang J, Wang G, Yang QG. Relative potency ratio between hyperbaric and isobaric solutions of ropivacaine in subarachnoid block for knee arthroscopy. *Int J Clin Exp Med.* 2015 Jun 15; 8(6):9603-6
  57. Keys A, Fidanza F. Indices of relative weight and obesity. *J Chron Dis* 1972; 25:329-43
  58. Moore DC. Factors influencing spinal anesthesia. *Reg Anesth* 1982; 7:20-5
  59. Logan MR. Plain bupivacaine: an unpredictable spinal anaesthetic agent. *Br J Anaesth* 1986; 58:292-6
  60. Mikko T. Pitkanen, MD. Body mass and spread of spinal anesthesia with bupivacaine. *Anesth Analg* 1987; 66:127-31
  61. Nuria Estan Capell. Correlation between glucose and bupivacaine levels in cerebrospinal fluid after spinal anesthesia:



- glycorrachia as predictor for duration of sensory block. *Clin. Chem Lab Med* 2010; 48(4):523-30
62. Clement R, Malinovsky JM. Cerebrospinal fluid bioavailability and pharmacokinetics of bupivacaine and lidocaine after intrathecal and epidural administrations in rabbits using microdialysis. *J Pharmacol Exp Ther* 1999; 289(2):1015-21
  63. Pacella E, Pacella F, Troisi F, et al. Efficacy and safety of 0.5% levobupivacaine versus 0.5% bupivacaine for peribulbar anesthesia. *Clin Ophthalmol.* 2013;7:927-32. doi: 10.2147/OPHTH.S43553. Epub 2013 May 21
  64. Schiffer et al. Cerebrospinal fluid density influences extent of plain bupivacaine spinal anesthesia. *Anesthesiology* 2002; 96(6):1325-30
  65. Denson DD. Bupivacaine protein binding in the term parturient: effect of lactic acidosis. *Clin Pharmacol Ther* 1984; 35:702-9
  66. Dobler K, Nolte H. Are the density of cerebrospinal fluid and the extent of isobaric spinal anesthesia influenced by elevated glucose concentrations in blood and cerebrospinal fluid or other factor? *Reg Anaesth* 1990; 13:101-7
  67. Hideyuki H, Jyun-ichi H. Influence of cerebrospinal fluid density, velocity, and volume on extent and duration of plain bupivacaine spinal anesthesia. *Anesthesiology* 2004;100:106-14
  68. Kitahara T, Kuri S. The spread of drugs used for spinal anesthesia. *Anesthesiology* 1956; 17:205-8
  69. Pacella E, Abdolrahimzadeh B, Brauneis S, et al. Efficacy of preoperative systemic clonidine for intraocular pressure reduction in ophthalmic surgery". *Annals of Ophthalmol* 2001; 33(2):116-8
  70. Pacella E, Collini S, Abdolrahimzadeh B, et al. The prophylaxis of emesis in emergency ophthalmic surgery: the use of ondansetron versus droperidol or metoclopramide: *Invest. Ophthalmol Vis Sci* 2001; 165 – B132: 299
  71. Motha M. Ropivacaine: Is it a good choice for spinal anesthesia? *J Anaesthesiol Clin Pharmacol.* 2015 Oct-Dec;31(4):457-8