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Spinal fluid density in rheumatoid arthritis

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Abstract : *Background:* In previous studies we noticed a greater than expected spread of sensory spinal block in patients with rheumatoid arthritis (RA).
Objective : Our aim was to analyze the density of cerebrospinal fluid (CSF) in RA and non-rheumatoid (non-RA) control patients suspecting a higher density in RA patients.
Methods : CSF was collected prior to spinal anesthesia from 30 patients with seropositive RA and from 30 non-RA control patients. All the patients were undergoing lower limb surgery and the rheumatoid patients were operated as a result of their rheumatoid disease.
Results : The density of the CSF appeared higher in patients with RA (median 1.00080, IQR 0.00035) than in non-rheumatoid patients (median 1.00070, IQR 0.00045) although not statistically significantly (p = 0.19). Although BMI did not correlate significantly with the density or viscosity (r = 0.02, p = 0.89 and r = -0.07, p = 0.58, respectively) of the CSF, the BMI correlated significantly with the glucose levels of the CSF (r = 0.48, p = 0.008) in RA-patients.
Conclusions : The density of the CSF was not statistically significantly higher in RA patients when compared to non-RA-patients.

Key words : *density, glucose, proteins, rheumatoid arthritis, spinal fluid, viscosity*

Seropositive rheumatoid arthritis (RA) is an autoimmune disease affecting the whole body. Typical manifestations of this disease are anatomical changes or diseases in the circulatory system, pulmonary changes, and changes in the mucosa and blood cells. The most visible changes occur in the musculoskeletal system, and these changes may require orthopedic surgery. The most typical operations are joint replacement surgery, especially of the lower extremities, typically carried out under spinal anesthesia.

Spreading of spinal anesthesia is affected by variables such as the patient's age, weight, body mass index (BMI), gender, and height (1-6). All these variables probably affect the volume of cerebrospinal fluid (CSF), which may be the most important factor related to spreading of the anesthetic (7-8). We have previously investigated the maximum spread of spinal block induced with plain bupivacaine (Bicain Spinal 0.5%) in patients with and without RA (9). Our conclusion was that the mean spread of sensory block 30 min after the injection of plain bupivacaine was 1.5 segments higher cephalad in patients with RA than in patients without RA. Inflammatory or degenerative changes (inflammation, synovitis, granulomatosis) which narrow the spinal canal thus cause a smaller volume of CSF, which could explain the wider spreading of spinal anesthesia in patients with RA (10-15).

On the other hand, an increased density of the CSF of RA patients could be another explanation for the wider spread of spinal block, provided that the anesthetic agent would be of lower density. This hypothesis is supported by the multi-organ inflammatory nature of RA, which could raise the protein content and, hence, the density of the CSF. The density of the CSF in healthy subjects varies between 1.0004 and 1.0013 g/cm^3. Thus, we hypothesize that spinal stenoses or increased CSF density, or both, have an impact on the spreading of spinal anesthesia.

This study was designed to test our hypothesis that the density of CSF is higher in patients with RA than in patients without RA. We found no previous reports addressing this.

Patients, Methods and Materials

The study protocol was reviewed and approved by the Ethics Committee of the Turku University

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Hospital (protocol Nr.: 93/180/2009, 11/17/2009) and each patient gave informed consent. Altogether, 60 patients older than 18 years and undergoing lower limb orthopedic surgery under spinal anesthesia were studied. They were of American Society of Anesthesiologists (ASA) class I-IV. Of the patients, 30 had seropositive RA diagnosed at least five years prior to study enrollment for the study group, and the 30 control patients were consecutive patients without RA scheduled for elective surgery or trauma patients with single unilateral lower limb operation. The sample size was calculated (80 percent power ; α = 5 percent) by using PS Power and sample size calculator. The main variable was CSF density.

Exclusion criteria were a diagnosed malignant disease, chronic renal or liver failure, diabetes mellitus, or a chronic inflammatory disease, e.g., Crohn's disease, or acute infection, or a neurological disease affecting the central nervous system. A full medical history was obtained from all patients. If any macroscopic blood was identified in the spinal fluid, the patient was excluded from the study.

The protocol was standardized for all patients. Prior to the spinal block, 2.5-3.0 ml of CSF was collected when free flow of clear CSF was verified. No barbotage (i.e., repeated injection and aspiration of fluid, to break up and remove e.g. calcification) or aspiration was performed.

The density and viscosity of the CSF were analyzed in the department of Chemistry of the University of Turku with an accuracy of 0.0001 g/cm^3. The density was measured with an Anton Paar DMA45 densitometer and the viscosity with an Anton Paar AMVn Microviscometer. The glucose and protein concentrations were also analyzed, as these can affect CSF density.

Statistical analyses

Data is expressed as mean (standard deviation SD), median (interquartile range IQR) or numbers (percentages). The normality of distributions was checked using Kolmogorov-Smirnov test. Age, BMI, and glucose levels were normally distributed. The comparisons between groups for normally distributed variables were done with the two-sample t-test and for non-normally distributed variables with the Mann-Whitney U-test. Categorical variables were analyzed using the χ^2-test or Fisher's exact test. The correlations between variables were calculated with Spearman's rank-order correlation coefficients. P-values <0.05 were considered statistically significant. All statistical analyses were conducted using IBM SPSS Statistics for Windows, version 23.0 (IBM corp., Armonk, NY).

Table 1
Patient characteristics.

	Rheumatoid patients	Non-rheumatoid patients	*P*
Gender, men	7 (23.3%)	12 (40.0%)	0.17
Age (years)	59.8 (9.8)	69.1 (9.7)	0.001*
BMI (kg/m^2)	27.5 (5.6)	27.7 (4.0)	0.839
ASA classification			0.045*
I	0 (0.0 %)	4 (13.3%)	
II	6 (20.0%)	3 (10.0%)	
III	20 (66.7%)	14 (46.7%)	
IV	4 (13.3%)	9 (30.0%)	
CSF Protein level	394.2 (151.7)	471.2 (163.0)	0.063
CSF Glucose level	3.37 (0.27)	3.21 (0.25)	0.020*
CSF Density	1.00080 [0.00035]	1.00070 [0.00045]	0.186
CSF Viscosity	0.708 [0.003]	0.710 [0.004]	0.105
CSF Viscosity error %	0.04 [0.05]	0.06 [0.06]	0.162

Data are given as n (%), mean (standard deviation) or median [interquartile range]. Age of the patients, ASA classification and CSF glucose levels were different between the groups.

Results

Patient characteristics are outlined in Table 1. There was no difference in BMI between the study groups (Table 1). Non-rheumatoid patients had higher ASA-classification than patients with RA ($p = 0.045$). Rheumatoid patients were younger ($p = 0.001$) than the control (non-rheumatoid) patients.

The density of the CSF appeared higher in patients with RA (median 1.00080, IQR 0.00035) than in non-rheumatoid patients (median 1.00070, IQR 0.00045) although not statistically significantly ($p = 0.19$). The CSF glucose levels were higher in the rheumatoid group ($p = 0.020$), although all glucose levels were within normal limits (between 2.2 and 4.2 mmol/l) in both groups. Age, BMI, ASA-classification, gender, CSF proteins or glucose levels were not associated with the density of the CSF, neither among all patients, or within groups.

There was no statistically significant correlation between CSF density or CSF viscosity (for all patients $r = 0.03$, $p = 0.80$, in RA patients $r = -0.02$, $p = 0.92$, and in control patients $r = 0.18$, $p = 0.35$). BMI did not correlate statistically significantly with the CSF density or viscosity ($r = 0.02$, $p = 0.89$ and $r = -0.07$, $p = 0.58$, respectively). BMI correlated positively with the CSF glucose levels ($r = 0.48$, $p = 0.008$) in RA-patients, but correlation was not significant in control patients ($r = -0.03$, $p = 0.88$).

Discussion

There was no statistically significant difference in the density of the CSF between the groups of patients with and without RA ($p = 0.19$). Our hypothesis that a higher density of the CSF could

Table 2

Statistical significance of variables tested for density and viscosity in patients with rheumatoid arthritis (RA) and in control patients (C) separately

	P value			
	Density		Viscosity	
	RA	C	RA	C
Gender	0.804	0.178	0.666	0.28
Age	0.561	0.429	0.354	0.167
Height	0.741	0.024*	0.231	0.108
BMI	0.271	0.866	0.112	0.847
CSF Protein level	0.042*	0.492	0.990	0.139
CSF Glucose level	0.481	0.995	0.188	0.580

Positive correlation (*) was found in non-rheumatoid patients between height and CSF density ($p = 0.024$) as well as with CSF Protein level and CSF density in rheumatoid patients ($p = 0.042$).

explain the wider cephalad spread of the spinal block was thus not supported. However, the patients were significantly younger in the RA group than in the control group. That could also be the reason why the distribution of the ASA-classification was skewed toward higher values in the older, non-RA group.

Greene *et al*. presented that the extent of spinal anesthesia could be influenced by more than 20 factors (16). Thus, other reasons like age, BMI, and gender must explain the wider spread of spinal block in RA patients (1-6). All these variables probably influence the CSF volume, especially the CSF volume of the lumbosacral region, which may be the most important factor in the spreading (7-8). Pitkänen (1) examined patients undergoing spinal anesthesia with isobaric bupivacaine and found that persons with higher than normal BMI or short persons had somewhat higher cephalad spread of anesthesia. There was, however, considerable inter-individual variability, which limits the findings. McCullough *et al*. had presented similar results a year earlier and speculated that vena cava compression or an increased volume of fat in the extradural space in more obese persons could reduce the volume of CSF (2). Taivainen *et al*. suggested the use of a lower L4-5 interspace injection of plain 0.5 % bupivacaine in obese patients to avoid too cephalad anesthesia (3). Leino *et al*. reported that adjustment of plain bupivacaine dose according to BMI could be used to achieve a more predictable spread of spinal block, but even further reduction of dose is needed in patients with high BMI (5).

Schiffer *et al*. presented a significant, although poorly predictive positive correlation between cerebrospinal fluid density and the level of spinal block spreading (17). In a previous study we found that patients with RA have a higher cephalad mean spread of sensory block than in patients without RA (9). Pitkänen *et al*. reported that the maximum spread of analgesia increases with age, although the interindividual individual variation is large (4). Our results of similar density between the patients with RA and those without this disease might be biased, since patients in the RA group were significantly younger. Further studies with study groups of similar age are needed.

Schiffer *et al*. (6) reported a significantly higher CSF density in men than women (1.00058, SD 0.00011, and 1.00049, SD 0.00011, respectively, $p = 0.024$), which could not be documented in our study. Although they reported significant differences in body size between men and women in their study, they found no evidence that age, weight or height influenced CSF density. We found that BMI correlated positively with the CSF glucose levels in RA-patients, but this correlation was not significant in control patients. Schiffer *et al*. had excluded patients with diabetes mellitus, as did we in our study. However, in their report, other diseases such as RA were not specified.

Previous reports (11-15) imply that inflammatory or degenerative changes (inflammation, synovitis, granulomatosis) narrow the spinal canal thus reducing the spinal CSF volume and that this could explain the wider spreading of spinal anesthesia in patients with RA, are interesting.

According to our findings, the hypothesis that a higher density of the CSF could explain the wider spread of spinal block is less likely. The wider block is probably due to multifactorial reasons other than density of the CSF.

In our study, the CSF glucose levels were higher among patients with RA ($p = 0.020$), although all values were within normal limits (between 2.2 and 4.2 mmol/l) in both groups. Patients with RA have a high prevalence of metabolic syndrome and associated factors such as obesity, dyslipidemia, and impaired glucose metabolism (18, 19).

It was interesting that the CSF protein levels were, in fact, nearly significantly lower in the group of patients with RA ($p = 0.063$). The reason for this is not obvious, but the patients in the RA group were younger than in the non-RA group and CSF protein levels tend to increase with age, probably due to both a decreased CSF volume and a subtle decline of blood-brain-barrier integrity (20). In our study, age standardization did not, however, change this CSF protein result. CSF protein levels are usually higher in RA patients with more severe disease rather than patients with a long duration of the disease. However, in a study by Polley, the total protein content was slightly raised in only five of the

24 examined CSFs and in two of these other reasons than spondylitis was the cause for the increased CSF protein content (lumbar disk protrusion and hypertrophy of the ligamentum flavum) (21).

BMI correlated positively with the CSF glucose levels ($r = 0.48$, $p = 0.008$) in RA-patients, but not in control patients ($r = -0.03$, $p = 0.88$). Metabolic syndrome is common in RA patients (18, 19), as is the risk of insulin resistance (18, 22).

According to our study, there seems to be no difference in CSF density between RA and non-RA patients. The wider spread of the spinal block in RA patients compared to non-RA patients (5), is thus probably caused by other, probably multifactorial reasons. Higher CSF glucose levels in the RA group could partly explain the wider spread of spinal block (23). The CSF volume is probably lower in the RA patients, especially in obese RA patients, which should be considered prior anesthesia (11-15). A lower L4-5 interspace injection of plain 0.5 % bupivacaine for obese (BMI > 28) RA patients might avoid the anesthesia from spreading too much cephalad (3). However, since the CSF volume was not directly investigated in our study, this assertion has to be considered carefully and further prospective studies are recommended.

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