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Regional Cerebral Oxygen Saturation Decreases During Primary Hip Arthroplasty: An Analysis of Perioperative Regional Cerebral Oxygenation (rSO_2), S100 Calcium-Binding Protein B (S100B) and Glial Fibrillary Acidic Protein (GFAP) Values. A Pilot Study

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Background: The incidence of postoperative cognitive dysfunction (POCD) after major joint arthroplasty is high. In the etiology of POCD, many factors have been cited, including thromboembolic complications. The incidence of cerebral embolization after lower extremity arthroplasty may be as high as 40–60%. The potential events of cerebral embolization could lead to a decrease in the regional cerebral oxygenation (rSO_2) and increased serum levels of biochemical markers of brain damage. The objective of the study was to test whether there are any changes in the rSO_2 values and serum markers of brain damage in patients who underwent total hip arthroplasty.

Material/Methods: Fifteen patients who underwent primary hip arthroplasty under spinal anesthesia were analyzed. The rSO_2 was monitored using infrared spectroscopy. Biochemical analyses of S100 calcium-binding protein B (S100B) protein and fibrillary acidic protein (GFAP) serum concentrations were performed using immunoassay methods.

Results: The values of rSO_2 decreased during the surgery, but this was not related to mean arterial pressure variations or hemoglobin saturation. The concentration of S100B was increased compared to its preoperative values, and there were no changes in GFAP values. The changes in rSO_2 readings correlated with the biomarkers' levels just after the surgery.

Conclusions: Our results suggest that S100B may be a more specific marker of astroglial damage in patients after primary total hip arthroplasty. The decrease in rSO_2 readings may be due to micro-thromboembolic events that occurred during the surgery. However, the results of this study are preliminary, and further studies are needed to establish its clinical efficacy.

MeSH Keywords: Arthroplasty, Replacement, Hip • Glial Fibrillary Acidic Protein • S100 Calcium Binding Protein beta Subunit • Spectroscopy, Near-Infrared

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Background

The incidence of postoperative cognitive dysfunction (POCD) after major joint arthroplasty varies from 16% to 45% [1], although it has been reported [2] to be as high as 72% at 6 days and 30% at 6 months postoperatively. However, its etiology remains unclear. Thromboembolic complications are some of the many factors that can contribute to the development of POCD [1,3]. With thromboprophylaxis, the incidence of objectively confirmed deep venous thrombosis occurring within 7–14 days after lower extremity orthopedic surgery varies from 40–60%. Of this percentage, 1–14% will progress to venous thromboembolism [4]. Thromboembolic material, including that released from the site of the surgery, can travel within the bloodstream to the brain. Moreover, the decrease in blood flow in the involved cerebral vessels may lead to a decrease in oxygen delivery. As a result, oxygen saturation may also decrease. The objectives of this observational study were to analyze the cerebral oxygen saturation in patients undergoing primary hip arthroplasty and to analyze the concentrations of 2 biochemical markers of brain damage, S100 calcium-binding protein B (S100B) and glial fibrillary acidic protein (GFAP), in the early postoperative period.

Material and Methods

This project was designed as an observational, prospective study, and after commencing the research, the design was not modified. The study was approved by the regional Ethical Committee (ref: 31/WIM/2013) and registered with the Clinical Trials database (ref: NCT02342236). Written informed consent was obtained from all of the study participants. This research was conducted in the Department of Orthopedics and Department of Orthopedics and Traumatology at the Military Institute of Medicine in Warsaw, Poland.

Twenty patients scheduled for elective total hip arthroplasty under spinal anesthesia were enrolled in this study. There was no control group, but the preoperative values of the patients were considered to be controls. After each patient's arrival in the operating room, both standard monitoring including heart rate (HR) and pulse oximetry (SpO_2) monitoring, and regional cerebral oxygen saturation (rSO_2) monitoring were initiated. These measurements were finished at the end of the surgery.

All of the orthopedic procedures were performed under spinal anesthesia with a 0.5% solution of bupivacaine hydrochloride (Marcaine 0.5% Spinal; Astra, Sweden). A proper level of sedation was achieved with intravenously administered midazolam (Midanium®; Polfa Warszawa S.A., Poland). The intravenous volume was maintained with an infusion of a crystalloid (Optilyte®; Fresenius Kabi Polska Sp. z o.o., Warsaw, Poland).

Regional cerebral oxygen saturation was recorded with an INVOS 5100C Oximeter (Somanetics, USA) using SomaSensor® (Covidien Inc., USA) electrodes. The INVOS system utilizes the near-infrared spectroscopy method, with wavelengths of 730 nm and 810 nm. Because of the observational design of the study, we did not consider any algorithm or protocol of corrections for predicting changes in the rSO_2 values. The S100B and GFAP serum concentrations were examined before (blood sample A) and immediately after the surgery, when the dressing was put on (blood sample B) and 6, 24, and 72 hours after the procedure. The blood samples were centrifuged for 15 minutes at 3000 rpm, and the obtained serum was frozen to –70°C. The S100B plasma concentration was analyzed with the LIAISON® Sangtec®100 test (DiaSorin S.p.A., Italy), a quantitative automated chemiluminescent immunoassay. The GFAP concentration was analyzed using a GFAP ELISA Kit (EMD Millipore Corp., USA), a high-sensitivity sandwich ELISA assay. Our primary outcome measures were a complete record of the cerebral oxygen saturation of the patient as well as measurements of the S100B and GFAP concentrations at the selected time points. The secondary measures were records of the heart rate, blood pressure and pulse oximetry values of the participants. There were no changes in the trial outcomes after the trial commenced.

Sample size calculation, randomization, and blinding

Because of the insufficient number of published papers in this field, the sample size of the study was not determined. The participants were enrolled by the authors of this study. There was only one study group since the same intervention was applied to all participants. Therefore, the participants were not randomized and allocated. This study was not blinded.

Statistical methods

The data were analyzed using R statistical software. The patients' characteristics (age, gender, height, and body mass), duration of anesthesia and surgery, administered doses of local anesthetic, levels of anesthesia, and concentrations of S100B and GFAP at the time points were analyzed using descriptive statistics. Because the stages of the surgeries were performed in different sequences of stages, each procedure was divided into 10 equal periods. The analyzed data (HR, BP, mean arterial pressure [MAP], SpO_2, and rSO_2) were averaged in each period. Non-parametric tests were used due to the relatively low number of patients in the study. Changes in the concentrations of S100B and GFAP as well as the variations in the HR, noninvasive BP, pulse oximetry, and rSO_2 were analyzed using the Wilcoxon signed rank test. The relationships between the rSO_2, MAP, and pulse oximetry were analyzed using linear regression. Correlations were measured by Spearman's Rho. $P<0.05$ was considered to be statistically significant.

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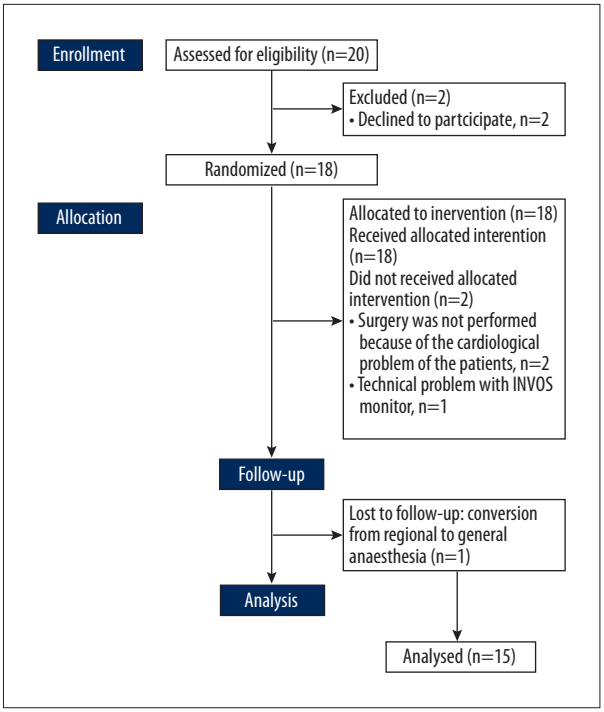

Figure 1. The flow of participants in the study.

Results

The data were collected between June 2014 and December 2015, and the trial ended after completion of the study protocol. Twenty patients were assessed for eligibility. Two declined to participate, so 18 were allocated to the intervention. Three of the allocated patients did not finish the protocol of the study due to severe hypotension observed before the surgery, resulting in the cancellation of the procedure, technical problems with the cerebral saturation monitor; and the need for induction of general anesthesia. The data obtained from the remaining15 participants were analyzed. The flow of the patients in this study is shown in Figure 1.

There were 4 (26.67%) males and 11 (73.33%) females in the study group. Of the 15 patients, 9 (60%) underwent cementless total hip arthroplasty and 6 (40%) underwent a cemented procedure. The mean age of the patients was 70 years old (95% confidence interval [CI]: 65–75 years), the mean height was 163 cm (95% CI: 158–169 cm) and the mean weight was 73 kg (95% CI: 65–81 kg). The mean dose (16.6±1.5 mg, 95% CI: 15.8–17.4 mg) of Marcaine 0.5% Spinal produced spinal anesthesia at the 10±1 (95% CI: 9–10) thoracic dermatome. The surgical time varied from 70–130 minutes (95% CI: 83–101 minutes).

The values of both analyzed markers of brain damage (S100B and GFAP) are shown in Table 1 and Figure 2. We found a significant increase in the concentration of S100B after the surgery compared to the preoperative values. However, there were no changes in the postoperative GFAP values. The results of the analyses when the value of the outlier was excluded were similar for both the S100B protein and GFAP.

The rSO_2 values decreased during the procedure. The precise measurements and *P* values are presented in Table 2. Changes in the rSO_2, S100B, and GFAP concentrations from the values observed before the surgery to just after the procedure and 72 hours after the operation are shown in Table 3.

We found significant correlations between absolute and percentage changes in rSO_2 values at the T10 and T1 time points and biomarkers concentration just after the surgery (S100B: Spearman's rho=0.5676 and 0.5576, *P*=0.0273 and 0.0308, respectively; GFAP: Spearman's rho=0.5787 and 0.5596, *P*=0.0238 and 0.0301, respectively). We also found significant correlations between the absolute change in rSO_2 values at the analyzed time points and the change in biomarker serum concentration just after the surgery compared to the preoperative values (S100B: Spearman's rho=0.5676 and 0.5576, *P*=0,0273 and 0,0308, respectively; GFAP: Spearman's rho=0.5189 and 0.5276, *P*=0.0475 and 0.0434, respectively).

The correlations between all other analyzed values were not statistically significant.

The hemodynamic parameter values (HR and MAP) and pulse oximetry during the respective periods of the surgery are shown in Table 4. The linear regression analysis showed no relationships between the rSO_2 and MAP values during the surgery (*P*=0.0899, 0.3425, 0.1857, 0.0802, 0.42, 0.876, 0.3972, 0.848, 0.7181 and 0.9016, respectively). Similarly, no relationships were observed between the rSO_2 and pulse oximetry readings (*P*=0.1679, 0.2825, 0.2816, 0.7335, 0.8507, 0.8885, 0.3733, 0.566, 0.1504 and 0.2317, respectively).

We observed no significant negative outcomes or unintended side effects in any of the patients participating in this study.

Discussion

We found a significant increase in the serum concentration of S100B, but not in GFAP, immediately after the surgery compared to the preoperative values. The measured rSO_2 regional cerebral oxygen saturation decreased during the procedure. A decrease in the rSO_2 can result from a decrease in the oxygen delivery to the brain regions via vessels occluded with embolic material. This explanation may be supported by an increase in the S100B serum concentration. High concentrations of S100B are present inside the brain, mainly in astroglial and Schwann cells and adipocytes, chondrocytes, and melanocytes. Increased S100B levels in serum and cerebrospinal fluid were observed

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Table 1. S100B and GFAP concentration at the analyzed time points.

Sample	Mean	95% CI for mean	P value (compared to sample A)
S100B: sample A	0.12	0.07–0.17	–
	0.12	0.06–0.18	–
S100B: sample B	3.81	2.55–5.07	0.0000
	3.57	2.33–4.80	0.0001*
S100B: sample C	0.65	0.45–0.85	0.0000
	0.64	0.42–0.85	0.0001*
S100B: sample D	0.37	0.27–0.47	0.0007
	0.36	0.25–0.46	0.0011*
S100B: sample E	0.17	0.12–0.22	0.0079
	0.17	0.11–0.22	0.0134*
GFAP: sample A	4.58	–0.26–9.42	–
	2.38	1.23–3.53	–
GFAP: sample B	5.93	1.05–10.82	0.6387
	4.04	1.12–6.95	0.4631*
GFAP: sample C	5.08	1.32–8.84	0.3303
	3.41	2.18–4.64	0.1189*
GFAP: sample D	4.7	0.41–8.99	0.8904
	2.76	1.6–3.93	0.6257*
GFAP: sample E	4.99	0.9–9.07	0.5097
	3.2	1.67–4.73	0.2212*

S100B and GFAP serum concentrations in mcg/L. * Results of the analysis after the removal of the outlier.

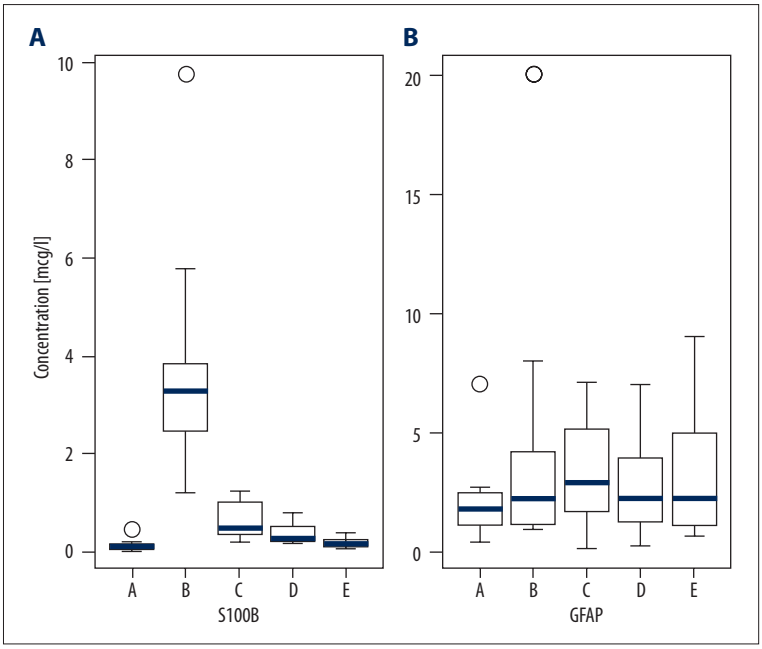

Figure 2. The serum concentrations of SB100B (**A**) and GFAP (**B**) at the analyzed time points. Analyzed time points: A – before the suregry, B – just after the procedure, C – 6 hours, D – 24 hours, E – 72 hours after the operation.

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Table 2. Values of rSO_2 (%) during the respective periods of the surgeries.

Analyzed time point	Median	95% CI	P
T1	67	61–68	–
T2	66	60–67	0.0332
T3	64	58–65	0.0000
T4	61	58–65	0.0083
T5	62	56–64	0.0013
T6	62	55–64	0.0011
T7	63	55–64	0.0007
T8	63	55–64	0.0001
T9	61	55–64	0.0007
T10	57	54–62	0.0007

The *P* values were calculated by comparing them to the rSO_2 in the T1 period.

after brain infarction, trauma, and toxic injury [5]. However, there is some evidence that S100B protein may be released from non-neuronal sources [5–7], as increased concentrations of this protein were found in sports players [8,9]. Also, elevated levels of S100B protein can be caused by increased permeability of the blood-brain barrier [10]. The possibility that the S100B protein could be released from an extra-cerebral location restricts its utility as a marker of brain damage, which, nonetheless, still ranges in efficacy from 70–80% [10]. Increased S100B concentration have also been noted in patients after orthopedic surgery, including major joint arthroplasty [11–13].

The lack of correlation between the changes in the rSO_2 and MAP values and the results of regression analysis excludes the possibility that cerebral desaturation was produced by systemic hypoperfusion. We also found no changes between the rSO_2 and hemoglobin saturation measured via pulse oximetry. Harilall et al. [14] found that, in patients undergoing surgical revascularization of the coronary arteries, hemoglobin oxygen saturation predicted cerebral oxygen desaturation. Moreover, the authors noted that, in patients with a longer period of cerebral desaturation, the concentration of S100B was higher. Because we found

Table 3. Changes in the rSO_2, S100B, and GFAP concentrations from the values observed before the surgery (A sample) to just after the procedure (B sample) and 72 hours after the operation (E sample).

Patient's ID	rSO_2 value at T1 period	rSO_2 value at T10 period	Absolute change in rSO_2 values between T1 and T10 periods	Percentage change in rSO_2 values between T1 and T10 periods	S100B concentration		GFAP concentration	
					Sample B *vs.* sample A	Sample E *vs.* sample A	Sample B *vs.* sample A	Sample E *vs.* sample A
1	74	75	1	+1.4%	3.78	0.00	18	–0.4
2	56	57	1	+1.8%	3.48	0.01	5.3	–1.3
3	62	57	–5	–8.1%	9.74	0.20	–0.5	–0.7
4	68	63	–5	–7.4%	2.91	0.08	1.6	–0.3
5	48	46	–2	–4.2%	2.91	0.06	–1.2	1.6
6	55	54	–1	–1.8%	7.14	0.14	–2.9	–5.4
7	66	63	–3	–4.5%	3.46	0.02	3.2	0.0
8	60	57	–3	–5.0%	1.12	0.00	3.7	1.4
9	67	60	–7	–10.4%	2.78	0.13	–1.1	4.8
10	70	64	–6	–8.6%	3.65	0.11	0.9	5.1
11	70	63	–7	–10.0%	2.47	0.02	–1.4	–1.4
12	69	56	–13	–18.8%	2.06	0.01	1.0	1.5
13	59	52	–7	–11.9%	2.33	0.02	–3.0	2.6
14	68	63	–5	–7.4%	5.37	–0.05	–0.2	0.7
15	55	47	–8	–14.5%	1.2	0.04	–3.1	–2.1

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Table 4. Values of the hemodynamic and oxygenation parameters during the respective periods of the surgeries.

		Time point									
		1	2	3	4	5	6	7	8	9	10
HR	Median	72	79	78	72	70	70	68	68	67	64
	95% CI	68–84	68–85	67–82	65–77	62–76	62–77	61–78	62–78	61–77	61–75
	P*		1.0000	0.706	0.0423	0.0091	0.0134	0.0097	0.0028	0.0058	0.0083
MAP	Median	118	99	94	93	90	88	90	88	88	91
	95% CI	108–121	92–106	89–100	85–97	83–94	81–95	82–95	82–98	82–97	85–98
	P*		0.0007	0.002	0.0011	0.0001	0.0013	0.0006	0.003	0.002	0.0021
SAT	Median	96	99	99	99	99	99	100	99	100	100
	95% CI	96–98	97–99	98–100	99–100	98–100	98–100	99–100	98–100	99–100	99–100
	P*		0.0438	0.0017	0.002	0.0034	0.0018	0.0023	0.003	0.0021	0.0023

HR – heart rate (1/minute); MAP – mean arterial pressure (mmHg); SAT – blood saturation measured by pulse oximetry (%).
* Compared to the values in the T1 time point.

no correlations between rSO_2 and SpO_2, the possible influence of intraoperative sedation with benzodiazepine on the patients' ventilation and respiratory mechanisms may also be excluded.

We observed no changes in the postoperative GFAP serum concentration but, considering the changes in the rSO_2 and S100B serum concentration, this could be expected. It is remarkable, however, that both the S100B and GFAP concentrations were correlated with the changes in the rSO_2 values between the T1 and T10 time points. This may be the result of the relatively low number of analyzed patients. Moreover, GFAP may be a less sensitive biochemical marker of brain damage in this group of patients compared to the S100B. Kumpaitiene et al. analyzed the relations among decreased rSO_2 brain injury biomarkers after cardiac surgery with cardiopulmonary bypass and found no significant changes in the GFAP concentration in any patient [15]. However, the observations of Papa et al. [16] concerning trauma patients with mild traumatic brain injuries were different. One of the analyzed patients had a significantly higher serum concentration of GFAP than the others, and it is possible that this patient suffered from an astroglial pathology that resulted in an increased concentration of GFAP. The potential influence of the increased GFAP on the final results of this case were considered in the statistical analysis.

One important limitation of our study was the relatively low number of analyzed patients. The authors found no previous studies concerning changes in the rSO_2 of patients who underwent major joint arthroplasty or the relationship between rSO_2 and the biochemical markers of brain damage. Therefore, a proper estimation of the sample size was quite difficult. Moreover, orthopedic surgery was carried out with and without the use of bone cement. The impact of bone cement on the biochemical markers of brain damage [11] and systemic reactions after its implementation [17] have been described before. However, because of the relatively low number of patients, the results were analyzed together.

Despite some limitations, our study might extend the knowledge of the changes in rSO_2 and the serum concentrations of biochemical markers of brain damage in patients after major joint arthroplasty. The decrease in rSO_2 values might be one of the factors increasing the frequency of postoperative cognitive dysfunction in this group of patients. Unfortunately, the threshold values for tissue desaturation-related brain injury remain unknown [18]. However, perioperative analysis of rSO_2 and biochemical markers of brain damage might facilitate the identification of the patients that are at risk for cognitive disorders and thus should begin neuropsychological rehabilitation earlier. Further studies are needed to establish whether this is only a theoretical problem or could truly help improve the quality of life of patients undergoing major joint arthroplasty, who are at risk of postoperative cognitive disorders.

Conclusions

The significant increase in the serum concentration of S100B, but not GFAP, compared to the preoperative values suggests that S100B might be a more specific marker of astroglial damage in patients who underwent primary total hip arthroplasty. The decrease in the rSO_2 measurement might result from the micro-thromboembolic events during the surgery. However, because of the relatively low number of analyzed patients, the results of this study are preliminary and further studies are needed to establish its clinical efficacy.

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Conflicts of interest

None.

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