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Predictive value of early near-infrared spectroscopy monitoring of patients with traumatic brain injury

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ABSTRACT

Background and objective: Traumatic brain injury (TBI) is the leading cause of death and disability in young adults. Study aimed to define the predictive value of early near-infrared spectroscopy (NIRS) monitoring of TBI patients in a Lithuanian clinical setting.
Materials and methods: Data of 61 patients was analyzed. Predictive value of early NIRS monitoring, computed tomography data and regular intensive care unit (ICU) parameters was investigated.
Results: Twenty-six patients expressed clinically severe TBI; 14 patients deceased. Patients who survived expressed higher NIRS values at the periods of admission to operative room (75.4% ± 9.8% vs. 71.0% ± 20.5%; $P = 0.013$) and 1 h after admission to ICU (74.7% ± 1.5% vs. 61.9% ± 19.4%; $P = 0.029$). The NIRS values discriminated hospital mortality groups more accurately than admission GCS score, blood sugar or hemoglobin levels. Admission INR value and NIRS value at 1 h after admission to ICU were selected by discriminant analysis into the optimal set of features when classifying hospital mortality groups. Average efficiency of classification using this method was 88.9%. When rsO_2 values at 1 h after admission to ICU did not exceed 68.0% in the left hemisphere and 68.3% in the right hemisphere, the hazard ratio for death increased by 17.7 times ($P < 0.01$) and 5.1 times ($P < 0.05$), respectively.

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Conclusions: NIRS plays an important role in the clinical care of TBI patients. Regional brain saturation monitoring provides accurate predictive data, which can improve the allocation of scarce medical resources, set the treatment goals and alleviate the early communication with patients' relatives.

1. Introduction

Traumatic brain injury (TBI) is a heterogeneous pathological condition including a wide range of clinical disorders. For a long period of time TBI remains the leading cause of death and disability in young people. The socioeconomic damage of TBI is vast: its incidence rates exceed 500 per 100,000 and it is responsible for 200 of 100,000 hospitalizations in Europe [1].

Pathogenesis of TBI is divided into primary and secondary injuries. Primary injury involves functional and structural neuronal damage that results from direct kinetic effect. Secondary injury is best described as a neurochemical pathophysiological cascade that includes inflammation, metabolic imbalance, mitochondrial dysfunction and other intracranial processes. Secondary injury develops as a response to primary damaging factor and leads to cerebral edema and intracranial hypertension, which further aggravate patients' condition [2].

Previously it was thought that primary injury occurs immediately after the impact, but increasing amount of evidence suggests that part of neuronal loss develops over a course of few hours. This implicates that primary injury is also at least partially reversible [3].

Despite promising animal trials, no neuroprotective agents were proved to be effective in human population. Current treatment strategy of TBI thus relies on disrupting the neuropathophysiological cascade of secondary injury, preventing or minimizing the rates of secondary insults (e.g., hypoglycemia, hypoxia, etc.) and establishing an environment which empowers regeneration. In achieving these goals, neuromonitoring becomes an intrinsic part of treatment process of TBI patients. In addition, due to diversity of outcomes, prognosis becomes the integral part of the clinical care of TBI patients. The establishment of accurate prognostic models would not only ease clinicians in distributing scarce medical resources communicating with patients' relatives but also improve the provided care and lay grounds for future medical research.

So far, the method of near-infrared spectroscopy (NIRS) has been well established in neonatal care [4], carotid [5] and cardiac surgery [6]. NIRS can also be used in identifying the formation of intracranial hematoma or cerebral edema [7], but there has been limited investigation in the field which carried the biggest expectations of its usefulness – the clinical care and prediction of outcomes of the injured brain patients [8]. Currently, ischemic thresholds of the injured brain have not been well-defined [9]. Also, there are no data on the outcomes of TBI and their relationship with possible risk factors in a Lithuanian clinical setting. We decided to investigate the prognostic value of early near-infrared spectroscopy monitoring and various other parameters used in monitoring of patients who suffered TBI and underwent surgical treatment.

2. Materials and methods

During the period from September 2011 to March 2013, data of 61 patients treated in the Hospital of Lithuanian University of Health Sciences were collected. Gathering of data concerning the clinical state monitoring (computed tomography (CT) findings, NIRS data, laboratory test results, etc.) was performed prospectively during the course of 72 h since patients' admission to hospital. Outcomes were identified from medical documentation after patients' death or discharge.

The included participants met the following criteria:

- Neurosurgery performed due to diagnosed TBI lesions in the acute period;
- Consent to participate in the study (either by participant himself/herself or the relatives if the patient was unconscious);
- Adulthood (aged more than 18 years).

The exclusion criteria were as follows:

- Technical difficulties of applying NIRS (traumatic lesions in forehead region or other situations when optodes could not be applied);
- Development of clinical death prior to hospitalization;
- Obesity (body mass index over 35 kg/m^2);
- Alcoholic or other type of intoxication;
- Allergy to any drug used during the time of hospitalization;
- Pregnancy and nursing;
- Personal or familial anamnesis of malignant hyperthermia.

Prior to neurosurgery, the data concerning patients' demographics, clinical state, trauma details, concomitant traumatic lesions (Hannover Polytrauma Score [HPS]) and CT findings were collected. An admission Glasgow coma score (GCS) was used to assess the clinical severity of TBI. As typically, a GCS score of 8 or less indicated clinically severe brain injury [10].

Intensive monitoring, which included NIRS and the follow-up of regular clinical parameters, started with patients' arrival to operative room and lasted up 72 h postoperatively (mostly during the stay in intensive care unit). Regional cerebral saturation (rsO_2) was measured using INVOS series SOMANETICS® spectrometers. The periods at which regional cerebral saturation values were recorded were as follows:

- rsO_2L_1/rsO_2R_1 – at patient's arrival to operative room;
- rsO_2L_2/rsO_2R_2 – just after craniotomy or trepanation;
- rsO_2L_3/rsO_2R_3 – after 1 h in ICU;
- rsO_2L_4/rsO_2R_4 – after 24 h in ICU.

Capital letters ''L'' and ''R'' indicate rsO_2 values of the left and the right brain hemispheres, respectively.

Approval of Bioethics Committee, Lithuanian University of Health Sciences, was obtained before performing the study.

2.1. *Statistical data analysis*

Statistical analysis was performed using software package IBM SPPS Statistics 21 for Windows. Data are presented as mean ± standard deviation (SD) or median with range. After testing for normality, the parametric (Student *t* test, ANOVA) and nonparametric (Mann–Whitney *U*, Kruskal–Wallis) criteria, were used to compare means or quantitative samples. Normal approximation *z* test was used to compare probabilities and the Chi-square test was used to test statistical hypothesis about independence of features.

Discriminant analysis was used for selection of optimal set of diagnostic features and determination of classifying rules for prediction of outcomes, evaluation of classification results (sensitivity and specificity of features). Fisher linear discriminant equations were used to determine limiting value of the feature when discriminating groups of survivors and non-survivors. Cox proportional hazard regression model was used for prognosis of hospital mortality. The level of statistical significance for testing statistical hypothesis was 0.05.

3. Results

The study included data from 61 patients. Demographic characteristic are presented in Table 1. The mean age of women in this study was significantly higher than the mean age of men (62.9 ± 15.3 vs. 52.8 ± 16.5; $P < 0.05$). Twenty-six patients (42.6%) expressed clinically severe TBI (as indicated by an admission GCS of 8 or less). The mean age did not differ statistically significantly between the groups of different severity. Thirteen women (68.4%) and 13 men (31.0%) expressed clinically severe TBI, which indicated a statistically significant relationship between gender and the clinical severity of TBI ($\chi^2 = 7.5$; $df = 1$; $P = 0.007$).

Of the patients studied, 47 (77%) scored 1 and 14 (23%) scored 2 in the HPS. None of the patients scored high in the HPS (3 or 4 points).

CT indicated 32 patients (52.5%) with traumatic injuries in the left hemisphere of the brain; 24 (39.3%), in the right; and five patients (8.2%) had bilateral brain lesions.

A total of 49 cases with intracranial hematomas were identified by CT: 8 epidural, 30 acute subdural, 6 chronic subdural and 5 patients were identified to have both, epidural and acute subdural hematomas. 4 patients had subarachnoid hemorrhage and the remaining 8 were operated due to skull bone fractures causing mild bleeding in the surrounding area.

Foci of brain contusion were witnessed in 22 cases (36.1%) and 42 patients (68.9%) presented with brain dislocation on admission (as indicated by brain mid-line dislocation of 5 mm or more in CT).

Twenty-eight patients (46.0%) had cranial bone fractures, 5 of those were impressed and five were basal fractures.

Death occurred in 14 patients (23%), and 47 (77%) survived during hospitalization. Comparative characteristics of mortality groups are presented in Table 2. Gender had a statistically significant relationship with mortality from TBI ($\chi^2 = 5.7$; $df = 1$; $P = 0.02$). We could not identify statistically significant differences of age between hospital mortality groups ($P = 0.24$).

3.1. *Regional cerebral saturation monitoring*

Data depicting mean rsO_2 at different time intervals is presented in Figure. When analyzing rsO_2 data between groups with different side of injury, a tendency that patients with TBI lesions in the right hemisphere generally expressed lower rsO_2 values was observed, but no statistically significant differences between the groups could be identified.

Patients, who survived hospitalization, expressed higher rsO_2 values at the periods of rsO_2L_1 (75.4% ± 9.8% vs. 71.0% ± 20.5%; $P = 0.013$) and rsO_2R_3 (74.7% ± 1.5% vs. 61.9% ± 19.4%; $P = 0.029$). Other rsO_2 values did not differ significantly between the hospital mortality groups.

Discriminant analysis was used to assess the availability of NIRS values and clinical variables to discriminate hospital mortality groups. First, each variable under investigation was analyzed separately to estimate their sensitivity and specificity. Using Fisher's linear discriminant functions we identified

Table 1 – Demographic characteristics of study population.

Characteristic	Value
Gender *n*, %	
Male	42 (68.9)
Female	19 (31.1)
Age, mean ± SD, years	55.9 ± 16.7
Length of hospitalization, median (range), days	13 (1–66)
Stay length in ICU, median (range), days	2 (0–34)

ICU, intensive care unit.

Table 2 – Comparative characteristics of hospital mortality subgroups.

Characteristic	Deceased *n* = 14, 23.0%	Dismissed *n* = 47, 77.0%
Gender *n*, %		
Male	6 (14.3)	36 (85.7)
Female	8 (42.1)	11 (57.9)
Age, mean ± SD, years	61.8 ± 18.1	54.5 ± 16.8
Length of hospitalization, median (range), days	4 (1–26)	17 (7–66)
Stay length in ICU, median (range), days	4 (1–7)	1 (0–34)

ICU, intensive care unit.

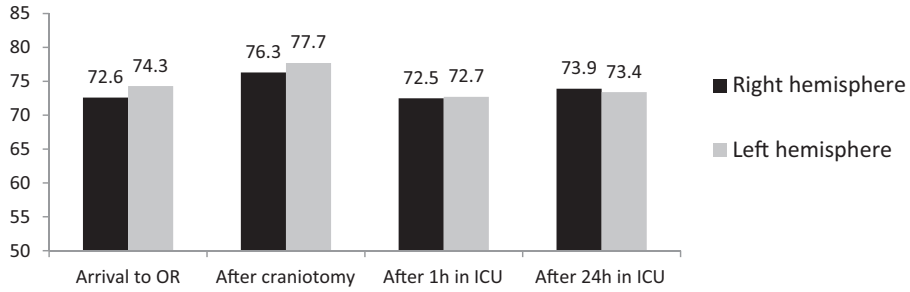

Figure – Mean regional brain saturation values at different time intervals.

the limiting value (barrier) – a value of certain variable, which optimally discriminates hospital mortality groups. Table 3 shows the identified limiting values, their sensitivity and specificity and the *P* values of group discrimination. As one may notice, the earliest rsO_2 values (on patients' admission to the operative room) did not discriminate well between the hospital mortality groups. Also, the later regional brain saturation values discriminated the hospital mortality groups better than an admission GCS.

Next, discriminant analysis was used to select the optimal set of features – a decision rule to classify patients and to evaluate the efficiency of classification. The significance of discriminating variables was estimated using one-factor ANOVA F statistics. The set of optimal features was constructed using stepwise selection of variables minimizing overall Wilk's lambda statistic. The procedure ended after two steps, selecting two features: rsO_2L_3 and admission INR.

We estimated the following Fisher linear discriminant functions for classes of survivors (f_0) and nonsurvivors (f_1):

$$f_0 = -20.22 + 0.46 \times x_1 + 3.95 \times x_2;$$

$$f_1 = -16.03 + 0.36 \times x_1 + 5.96 \times x_2.$$

Table 3 – Sensitivity and specificity of NIRS and other variables when classifying hospital mortality subgroups.

Variable	Limiting value	Sensitivity (%)	Specificity (%)	*P*
rsO_2L_1 (%)	73.2	35.7	60.0	0.267
rsO_2L_2 (%)	74.9	69.2	74.5	0.010
rsO_2L_3 (%)	68.0	72.7	78.7	0.003
rsO_2L_4 (%)	69.9	71.4	72.7	0.014
rsO_2R_1 (%)	72.5	28.6	48.9	0.937
rsO_2R_2 (%)	74.7	50.0	52.2	0.156
rsO_2R_3 (%)	68.3	63.3	82.6	0.003
rsO_2R_4 (%)	73.5	57.1	54.5	0.784
Admission hemoglobin (g/L)	121.81	64.3	76.1	0.007
Admission glycemia (mmol/L)	7.8	66.7	73.8	0.031
Admission INR	1.2	30.8	95.5	0.020
Admission GCS	8.5	71.4	66.0	0.030

rsO_2, regional cerebral saturation values of the right (R) and left (L) brain hemispheres at different periods; GCS, Glasgow Coma Score; INR, international normalized ratio.

where x_1 stands for rsO_2L_3 value and x_2 for admission INR value.

Classifying rule: if $f_1 > f_0$, nonsurvivor; if opposite, survivor. Correct classification was reached in 80.0% of nonsurvivor cases (sensitivity) and in 90.9% of survivor cases (specificity). Average efficiency of classification was 88.9%.

For survival analysis and prognosis of hazard function the Cox proportional hazards model was used. Estimated values of Cox model coefficients, *P* values and isolated hazard ratio with 95% confidence interval are presented in Table 4. The highest statistically significant isolated hazard ratio was observed by features of $rsO_2L\_3 \le 68\%$, $rsO_2R\_3 \le 68.3\%$ and admission hemoglobin concentration ≤ 121.8 g/L.

Selection of the optimal set of features and estimation of the standard hazard ratio was done using multivariate Cox regression model. Stepwise forward LR method was used with Entry = 0.05 and Removal = 0.10 probabilities. The procedure converged after two steps, selecting two features rSO_2L_3 and rsO_2R_3 (Table 5). When rsO_2L_3 did not exceed 68.0% and rsO_2R_3 did not exceed 68.3%, the hazard ratio for death increased by 17.7 times ($P < 0.01$) and 5.1 times ($P < 0.05$), respectively. After inclusion of these features into regression equation, other features were considered as nonsignificant ($P > 0.05$).

4. Discussion

Previous studies have well established the prognostic value of such standard clinical parameters as lowest GCS score [11], motor component of GCS [12], pupil reactivity [13] and computerized tomography findings [14,15]. Studies such as CRASH (Corticosteroid Randomization After Significant head injury) and IMPACT (International Mission for Prognosis and Clinical Trial design in TBI) have already presented reliable prognostic models that incorporate the initial clinical parameters of TBI patients [16,17]. On the other hand, there is still much these models cannot explain.

Results of our study indicate that NIRS data can be an efficient tool when predicting patients' outcomes. As one would notice, the rsO_2 values were determined as a stronger discriminator and predictor of hospital mortality than the traditional parameters such as admission GCS and glycaemia. It has to be noted though that due to the inclusion and exclusion criteria, our study could not compare the predictive value or

Table 4 – Isolated hazard ratios for hospital mortality from TBI.

Characteristic	B	P	Exp(B)	95% CI for Exp(B)	
				Lower	Upper
rsO_2L_1, ≤73.2%	−0.151	0.792	0.86	0.281	2.631
rsO_2L_1, >73.2%	0		1		
rsO_2L_2, ≤74.9%	1.713	0.010	5.544	1.499	20.503
rsO_2L_2, >74.9%	0		1		
rsO_2L_3, ≤68%	2.351	0.003	10.492	2.219	49.603
rsO_2L_3, >68%	0		1		
rsO_2L_4, ≤69.9%	4.801	0.100	6.056	0.706	51.923
rsO_2L_4, >69.9%	0		1		
rsO_2R_1, ≤72.5%	−0.8	0.183	0.449	0.138	1.46
rsO_2R_1, >72.5%	0		1		
rsO_2R_2, ≤74.9%	0.233	0.677	1.262	0.423	3.761
rsO_2R_2, >74.9%	0		1		
rsO_2R_3, ≤68.3%	2.001	0.004	7.397	1.909	28.665
rsO_2R_3, >68.3%	0		1		
rsO_2R_4, ≤73.5%	0.841	0.335	2.318	0.419	12.827
sO_2R_4, >73.5%	0		1		
Admission hemoglobin, ≤121.8 g/L	1.622	0.007	5.063	1.558	16.456
Admission hemoglobin, >121.8 g/L	0		1		
Admission glycemia, >7.8 mmol/L	1.355	0.031	3.878	1.131	13.294
Admission glycemia, ≤7.8 mol/L	0		1		
Admission INR, ≤1.2	1.199	0.056	3.316	0.969	11.346
Admission INR, >1.2	0		1		
Admission GCS, ≤8.5	1.569	0.018	4.802	1.31	17.599
Admission GCS, >8.5	0		1		

rsO_2, regional cerebral saturation values of the right (R) and left (L) brain hemispheres at different periods; GCS, Glasgow Coma Score; INR, international normalized ratio.

NIRS with traditional variables in cases of extremely severe TBI (followed by clinical death, etc.).

We could not identify any statistically significant rsO_2 differences between groups with different side of brain lesions. This finding indicates, that NIRS values of the ipsi- or contralateral hemisphere are not distorted by the side of the injury.

Even though NIRS is sensitive and specific method, data of the patients who later deceased did not differ on admission, thus indicating continuous and prolonged rsO_2 monitoring is required to extract the maximum predictive value of this monitoring technique.

Many authors state that individual trends of regional cerebral saturation are more important when predicting patients' outcomes [18]. This study, on the other hand, shows that borderline NIRS values can play an important role too.

Table 5 – B values of the optimal Cox model coefficients, their P values and standard hazard ratio Exp(B) with 95% CI.

Characteristic	B	P	Exp(B)	95% CI for Exp(B)	
				Lower	Upper
rsO_2L_3, ≤68.0%	2.872	0.007	17.666	2.201	141.765
rsO_2L_3, >68.0%	0		1		
rsO_2R_3, ≤68.3%	1.632	0.019	5.113	1.308	19.982
rsO_2R_3, >68.3%	0		1		

rsO_2, regional cerebral saturation values of the right (R) and left (L) brain hemispheres at different periods.

What is also important that some of the most essential information can be obtained relatively early, i.e., within a few hours after surgical treatment.

This study also indicates that several significant differences between genders exist in Lithuanian clinical setting of TBI. Female gender had significant relationships with both, severity and mortality from TBI. This finding is consecutive with others [19], which state that women generally fare worse after suffering TBI. In our case, this might be explained by an older women subpopulation, which would indicate a worse general clinical state. Although, no statistically significant associations between age and hospital mortality have been established in our study.

Our findings support the statements of other authors that hyperglycemia, anemia and coagulation disorders are independent risk factors of negative patient outcomes [20–22]. It was unexpected though, that admission blood glucose levels over 7.8 mmol/L proved to have such an impact on patients' outcomes.

Literature marks the importance of ''locally designed prognostic models of TBI'', since some aspects of certain clinical settings cannot always be tailored to others. We came up with a model that only included two variables, both of which were derived from NIRS. During the literature analysis, we found a statement saying that defining a prognostic model, requires the group of interest to exceed the amount of variables willing to be included by 10 times [9]. This leaves a path for future studies to define a more comprehensive prognostic model of TBI in Lithuanian clinical setting.

5. Conclusions

This study shows that NIRS plays an important role in the clinical care of TBI patients. Monitoring of regional cerebral saturation provides valuable predictive data that has various applications in the clinical setting, such as improving the allocation of scarce medical resources, setting the treatment goals and alleviating the early communication with patients' relatives.

Study indicated that rsO_2 values can help discriminate and predict hospital mortality better than the traditional clinical parameters.

The future research should focus on identifying the impact of different variables on the neurological state and functional outcomes of patients who survive TBI.

Conflict of interest

No conflicts of interest were reported.

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