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The feasibility of fNIRS as a diagnostic tool for pediatric TBI: A pilot study

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ABSTRACT

Background: Functional near-infrared spectroscopy (fNIRS) enables assessment of prefrontal hemodynamic response. This study explored the feasibility of fNIRS in determining hemodynamic changes related to cognitive task performance in pediatric traumatic brain injury (TBI) in order to assess its potential as a diagnostic tool.

Methods: We measured changes in oxygenated hemoglobin [O₂Hb] during a verbal fluency task (VFT), which activates frontal brain regions involved in working memory, in 15 TBI patients and 21 healthy controls using a 3-channel fNIRS system. Baseline and absolute changes in [O₂Hb] during the VFT were compared to the rest condition to obtain effect-scores. Patients were tested in the acute phase and six weeks after injury. Task-related fNIRS responses were categorized into positive, negative, and no response.

Results: For patients and controls, a positive response was observed in 61% (n = 22), a negative response in 19% (n = 7), and no response in 19% (n = 7). Patients showed a mean [O₂Hb] effect-score of 2.18 compared to 2.52 in the control group (p = 0.743) in the acute phase after injury. Follow-up effect-scores did not differ significantly (p = 0.721). Decreased task performance was associated with a higher effect-score in controls compared to decreased task performance with lower effect-score in the patient group.

Discussion: Our study shows that it is feasible to assess hemodynamic response with fNIRS in pediatric TBI patients. A trend of reduced prefrontal hemodynamic response in patients in the acute phase after injury was found suggesting impairment in cognitive performance that warrants further study.

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1. Introduction

Traumatic brain injury (TBI) is one of the most important causes of morbidity and mortality in children and contributes substantially to the health resource burden [1]. Therefore, it is important to determine in an early phase after injury which children are at risk of incomplete recovery after TBI to provide sufficient and appropriate care and treatment in an early stage.

Functional near-infrared spectroscopy (fNIRS) provides information about hemodynamic response in a non-invasive manner. Decreased hemodynamic response in the frontal lobes directly after injury has been related to worse outcome [2]. fNIRS might be a suitable method for evaluating cerebral hemodynamics in the

pediatric population without the disadvantages of ionizing radiation.

The objectives of this pilot study were to determine the feasibility of fNIRS testing in conjunction with a working memory task in children with TBI. This was achieved by measuring hemodynamic changes during a verbal fluency task (VFT) condition in the first few days after trauma and in healthy controls (HC). The VFT was chosen as task, because it is related to cognitive performance generated in the frontal lobes and can be easily executed by children in a short time frame. Furthermore, it is a sensitive task that generates a response in the frontal areas, which can be picked up by the fNIRS device. Additionally, we aimed to investigate whether hemodynamic changes could be related to cognitive performance in order to provide information on the etiology of cognitive impairment after TBI.

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2. Methods

2.1. Subjects

TBI patients were prospectively identified with the following inclusion criteria: age between 3 and 18, Glasgow Coma Score between 13 and 15 on admission, posttraumatic amnesia ≤ 24 h, and loss of consciousness ≤ 1 h after trauma. Exclusion criteria: no follow-up possible, medical history with neurological or psychiatric disorders, use of medication interfering with brain function, insufficient comprehension of Dutch language, and conditions limiting fNIRS measurements (substantial hypoxia, anemia, hypo-/hypercapnia). HC were recruited at a day care center and from the personal environment of researchers. Informed consent was obtained from all subjects.

2.2. Test procedure

With a 3-channel single-oximeter (PortaLite, Artinis Medical Systems, the Netherlands) oxygenated hemoglobin [O₂Hb] and deoxygenated hemoglobin [HHb] were measured. The device was attached to the right forehead of patients without passing the midline. A complete test consisted of three blocks, each comprising two phases: a rest phase and a VFT phase. In the rest phase patients listened to classical music in supine position during one to 2 min, depending on the duration of the process of normalization of [O₂Hb] to baseline values. The VFT phase lasted for 1 min. Children aged less than ten years performed a semantic VFT during which subjects were instructed to enumerate items corresponding to a given category. For each of the three blocks a different category was given, namely animals, names, and food and drinks. Children aged ten years or older performed a phonemic VFT in which the categories were replaced by letters and subjects were instructed to sum up words starting with the given letter. The letters 'D', 'A', and 'T' were given at baseline and the letters 'P', 'G', and 'R' were used at follow-up. The patients were not allowed to use names (e.g. geographical names, persons, companies), numbers, and words with the same stems but different suffixes (e.g. dark, darker, darkness). For all patients the first measurement (baseline) was performed during hospital admission after injury and when possible a second measurement (follow-up) was done six weeks after injury.

2.3. Data processing

The main outcome value of the fNIRS was the 'effect-score', which is the absolute difference between the mean [O₂Hb] of the rest phase and the mean [O₂Hb] of the VFT phase per block. To ensure maximum values, the mean [O₂Hb] values of the last 10 s of the rest phase were regarded baseline [O₂Hb] values, since [O₂Hb] values slowly normalize during a rest phase. For the VFT phase the mean of all [O₂Hb] values captured 10 s after start of the VFT phase were regarded maximum [O₂Hb] values. Based on visual inspection comparing the task condition to the rest condition, three different response patterns were discerned during the VFT: 1) positive pattern: with increased [O₂Hb] concentration 2) negative or inversed reaction pattern: with decreased [O₂Hb] concentration 3) no difference in [O₂Hb] concentration.

2.4. Statistical analysis

SPSS version 23 was used. Normality of the fNIRS data was tested with a Shapiro-Wilk test. One-sample Wilcoxon signed rank test was used to test if the effect-scores differed significantly from zero. Mann-Whitney *U* test was applied for not normally distributed values to test for differences between HC and patients. With a

Wilcoxon signed rank test the effect-scores of baseline and follow-up measurements were analyzed. Statistical significance was defined as *p*-value < 0.05 .

3. Results

3.1. Subjects

The patient group comprised 15 patients (8 male and 7 female, mean age: 11.4 ± 3.5 , range: 3–16 years) and 21 HC participated (8 male and 13 female, mean age: 10.6 ± 2.4 , range: 7–17 years). In the HC group eight subjects performed the semantic VFT and 13 subjects performed the phonemic VFT. In the patient group three subjects performed the semantic VFT and 13 subjects performed the phonemic VFT. Follow-up measurements were obtained in 12 patients.

3.2. fNIRS measurements at baseline

All [O₂Hb] effect-scores were significantly different from zero ($p < 0.05$) for both patients and HC. Changes in [O₂Hb] were faster and more pronounced than changes in [HHb]. In the HC group a positive fNIRS response was seen in 11 (52%) subjects, an inverse or negative fNIRS response in five (24%) subjects, and no response in five (24%) subjects. In the patient group at baseline 11 (73%) subjects showed a positive fNIRS response, two (13%) subjects an inverse or negative fNIRS response, and two (13%) subjects no response. Effect-scores of blocks 1, 2, and 3 in the patient group at baseline were smaller compared to HC, although not significant (respectively $p = 0.743$, $p = 0.837$, and $p = 0.914$) (Fig. 1B).

3.3. Follow-up measurements

In total 12 out of 15 patients had a follow-up measurement. No significant differences were found between baseline and follow-up measurements. Eight patients showed a similar fNIRS response at follow-up compared to baseline, while four patients showed a varying response pattern at follow-up compared to baseline.

3.4. VFT performance

On average HC generated 10.6 ± 4.4 words per task compared to 6.2 ± 4.2 words at baseline by patients and 6.9 ± 3.7 words at follow-up. A significant difference was present between HC and patients at baseline during all task conditions ($p < 0.01$). When age-adjusted norm scores were taken into account, ten subjects (48%) of the HC scored above average on the VFT, whereas only one out of 15 (7%) patients scored above average at baseline and one out of 12 (8%) at follow-up. On visual inspection HC scoring below average on the VFT had higher effect-scores, whereas exactly the opposite is true for the patient group at baseline (Fig. 1B). No differences were present in the patient group regarding the semantic and phonemic VFT.

4. Discussion

In this pilot study we were able to generate consistent responses during a working memory task using fNIRS in children with TBI, which illustrates that fNIRS testing in combination with a working memory task is indeed feasible. As far as we know, we are the first to test the diagnostic value of the fNIRS in combination with a cognitive task in children with a TBI. A non-significant trend towards lower [O₂Hb] effect-scores was found in TBI patients compared to HC at baseline, suggesting changes in mental performance during this cognitive task directly after injury. The lack of

Fig. 1. A. Positive fNIRS response pattern. The grey broken line indicates the different phases of the measurement starting with the first resting phase at timestamp zero and finishing with the third VFT phase at the end of the measurement.

Fig. 1B. Difference in mean O2Hb effect-scores between below average scoring children (VFT performance) and above average scoring children in the control group (N = 21) and the patient group at baseline (N = 15).

statistical significance could be explained by the limited sample size. Therefore, research with a larger sample size is of interest in future studies.

Furthermore, hemodynamic response was defined as a change in [O2Hb], which is in accordance with the majority of previous fNIRS studies, in which only [O2Hb] and not [HHb] was utilized as an indicator of cerebral hemodynamic response [3,4]. It was found that HC scoring below average on the VFT had higher effect-scores compared to patients suggesting that mental performance increases when task demands are high resulting in increase of frontal hemodynamic response. This finding is in line with an earlier study in which a decreased hemodynamic response in the frontal lobes directly after injury was found [2]. On the other hand, the finding that patients with low VFT scores at baseline showed low effect-scores might be interpreted as hampering of cognitive effort for increased task demand in the acute phase after injury, for example by impaired executive functions which appear after TBI or alternatively by pain or discomfort.

In this study we found different types of fNIRS response patterns, namely positive, negative, and no response. The majority of subjects showed a positive response pattern (61%) and the rest of the study population either showed a negative response pattern (19%) or no response pattern (19%). Only a few fNIRS studies have reported similar results [5]. Comparable phenomena with negative responses have been described in fMRI with blood-oxygen-level dependent (BOLD) responses, the so-called negative BOLD responses [6]. We hypothesize that changes in local hemodynamic response might occur in other task-relevant areas of the brain resulting in a negative fNIRS response. TBI patients in particular show activation of different brain regions compared to HC during working memory tasks [7]. This might be related to inter-subject variability, which could manifest itself as a difference in task solving strategy.

Of interest is that at follow-up six weeks after injury, effect-scores and VFT scores were more or less the same compared to the acute phase after injury. A reason for this finding might be that recovery after trauma takes longer than six weeks. On the other hand, it is noteworthy that three out of 12 patients with baseline and follow-up measurements changed from non-responders at baseline to either negative responders or positive responders at follow-up. This biphasic fNIRS response might also be an indication of recovery after trauma. Unfortunately, the sample size was too small to compare results with cognitive complaints of patients.

From this pilot study, it can be concluded that with the fNIRS it is

feasible to detect responses of the [O2Hb] effect-scores in pediatric TBI patients with various response patterns in the acute phase after injury. Participants were able to perform a working memory task with a trend of a reduced prefrontal hemodynamic response in patients compared to HC. Future studies are needed to confirm clinical applicability and to gain insight into the relation between fNIRS responses and recovery of cognitive complaints over time.

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Declaration of competing interest

The authors declare that they have no conflict of interest.

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