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Anish N. Sen, Shankar P. Gopinath, Claudia S. Robertson, "Clinical application of near-infrared spectroscopy in patients with traumatic brain injury: a review of the progress of the field," *Neurophoton.* **3**(3), 031409 (2016), doi: 10.1117/1.NPh.3.3.031409.

Neurophotonics 3(3), 031409 (Jul–Sep 2016)

REVIEW

Clinical application of near-infrared spectroscopy in patients with traumatic brain injury: a review of the progress of the field

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Abstract. Near-infrared spectroscopy (NIRS) is a technique by which the interaction between light in the near-infrared spectrum and matter can be quantitatively measured to provide information about the particular chromophore. Study into the clinical application of NIRS for traumatic brain injury (TBI) began in the 1990s with early reports of the ability to detect intracranial hematomas using NIRS. We highlight the advances in clinical applications of NIRS over the past two decades as they relate to TBI. We discuss recent studies evaluating NIRS techniques for intracranial hematoma detection, followed by the clinical application of NIRS in intracranial pressure and brain oxygenation measurement, and conclude with a summary of potential future uses of NIRS in TBI patient management. [DOI: 10.1117/1.NPh.3.3.031409]

Keywords: near-infrared spectroscopy; traumatic brain injury; intracranial hemorrhage.

Paper 16020SSRR received Mar. 31, 2016; accepted for publication Mar. 31, 2016; published online Apr. 25, 2016.

1 Introduction

Near-infrared spectroscopy (NIRS) has been used in a growing number of clinical applications over the past two decades. The clinical application of NIRS in the study of human cerebral metabolism was first reported by Jöbsis et al.[1] The basic principle of NIRS as it applies to the brain relies on the ability of near-infrared light to penetrate the scalp, skull, and brain for a certain depth, unlike light in the visible spectrum. Near-infrared light is absorbed to different degrees by differing chromophores within the cranial vault. By far, the two chromophores that absorb the majority of the near-infrared spectrum light intracranially are oxyhemoglobin and deoxyhemoglobin at wavelengths near 700 to 900 nm. Using appropriately placed detectors, transcranial NIRS can detect the strength of absorption across different areas of the cranium. The spatial and temporal dynamics of NIRS allow for the measurement and detection of various intracranial physiologic conditions and parameters, which can be utilized to help clinicians in treating patients with traumatic brain injury (TBI). In this review, we highlight the advances in clinical applications of NIRS over the past two decades as they relate to TBI. We begin with a review of the current literature on the applications of NIRS in patients with traumatic intracerebral hemorrhage, followed by a review of the use of NIRS in measuring brain tissue oxygenation, and conclude with a discussion of the potential future applications of NIRS as it relates to TBI.

2 Near-Infrared Spectroscopy and Intracranial Hemorrhage

As briefly described above, NIRS can be used to determine absorption strength in different regions of the brain noninvasively and transcutaneously. As extravascular blood more strongly absorbs near-infrared light than intravascular blood, due to the higher proportion of hemoglobin in a hematoma than in normal brain parenchyma, NIRS can be used for detection and localization of intracranial hematomas.

In 1993, we reported a proof-of-concept series in the use of NIRS to localize intracranial hematomas in the *Journal of Neurosurgery*.[2] Forty patients were admitted to our trauma center with computed tomography (CT) findings of intracranial hematomas (22 subdural, 10 epidural, and 8 intracerebral). NIRS was performed in all 40 patients, confirming greater light absorption at 760 nm on the side of the hematoma. Moreover, in 36 patients, asymmetry in the optical density between hemispheres resolved with improvement in the hematoma via either surgical evacuation or spontaneous resolution. Ten control patients demonstrated, as expected, no asymmetry in the optical density between two hemispheres.

Beginning with this proof-of-concept study, multiple further studies have been performed in the application of NIRS to localization and detection of intracerebral hemorrhage. In 1995,[3] our group published a larger series of patients in whom the use of NIRS in early detection of delayed traumatic intracranial hematomas was evaluated. One hundred and sixty-seven patients underwent serial NIRS to detect the development of delayed hematomas following admission for TBI. NIRS was able to detect development of delayed intracerebral, extracerebral, and postoperative hematomas in 27 patients (16%), of whom 18 required further surgery. Most interestingly, in 24 of the 27 patients, a significant increase in the difference in absorbance of light between the noninjured and injured sides was detected by NIRS before any increase in other clinically used parameters for monitoring changes, including increases in intracranial pressure (ICP), changes in neurological examination, or changes on computed tomography scans. At that time, we concluded that NIRS could successfully be used to detect intracerebral, subdural, and epidural hematomas in a delayed

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manner following TBI. Limitations in the technology, however, included the inability to precisely localize the hematoma within the brain, and hence the need for subsequent computed tomography scans for surgical decision making. Moreover, patients with bilateral hematomas or chronic subdural hematomas could not be reliably evaluated with NIRS due to no difference in optical density between the two hemispheres as they were covered by the same fluid and had equal signals and differences in absorption characteristics in patients with chronic subdural hematomas.

3 Newer Studies on Near-Infrared Spectroscopy and Intracranial Hemorrhage

These early studies were followed by a number of series at other institutions. In 2007, Kessel et al.[4] reported their series of 110 patients with TBI who underwent NIRS during initial evaluation prior to obtaining CT scans. They found that the spectroscopy was 90.5% sensitive and 95.5% specific for detecting epidural and subdural hematomas. Moreover, the positive predictive value was 82.6%, and the negative predictive value was 97.7%. The authors found similar results to our initial study, concluding the utility of NIRS in rapid hematoma detection. Similarly, a group in Spain published their series of 35 patients with TBI who were evaluated by NIRS technology.[5] They found sensitivities and specificities of 89.5% and 81.2%, respectively, using the Infrascanner (Infrascan Inc., Philadelphia, Pennsylvania). Similar sensitivities were noted when the scan was completed within 12 h or after 12 h from the initial trauma.

However, the largest investigation to date in the evaluation of NIRS for intracerebral hematoma detection was a multi-institution study performed by Robertson et al.[6] In this study, 431 patients were enrolled at five trauma centers upon presentation with suspected TBI. Ninety-six patients were determined by CT scan to have intracranial hematomas. Utilizing the Infrascanner device, NIRS was able to demonstrate an overall sensitivity of 68.7% and specificity of 90.7%. When evaluating only the subset of patients with clinically relevant hematomas and those within 2.5 cm of the brain (i.e., at a depth within the technical constraints of the NIRS scanner), the sensitivity rose to 88%, and the specificity remained unchanged at 90.7%.

More recently, studies have focused on the use of NIRS as a screening tool in intracerebral hematoma detection in locations or situations where computed tomography is not readily available. In 2008, Ghalenoui et al.[7] published a prospective observational study in which they evaluated 148 patients admitted to a hospital in Iran with head injuries with both CT and NIRS. They found that NIRS found 46.6% of the admitted patients to possibly have intracranial hematoma, while CT scan determined that the true number of patients with intracranial hematoma was actually 36.5%. The authors calculated the sensitivity and specificity of NIRS to be 88.9% and 77.7% in hematoma detection. They concluded that NIRS may be a useful tool to screen patients for intracerebral hematoma, particularly in CT-deprived locations such as prehospital situations, rural areas, or after large disasters. Furthermore, a German study published in August 2015 evaluated the utility of NIRS in detecting traumatic intracranial hemorrhage (ITH) in a German army field hospital in Afghanistan.[8] In an evaluation of the feasibility of NIRS technology in a demanding and remote location, the investigators found that NIRS could effectively be used in emergency situations to assist in determining whether trauma patients had intracranial hematomas and warranted medical air evacuation to facilities with neurosurgical services. While the study did not report on the efficacy of the scanner or whether the technology changed clinical management of such patients, the authors did note that the technology worked flawlessly, quickly, and easily, without hindering the flow of their emergency center.

NIRS has also been explored for ITH detection in children and may be of particular benefit in this population. NIRS is thought to be more effective in the pediatric population since children have thinner scalps and skulls so there is less noise in the NIRS signal. Moreover, NIRS monitoring may particularly benefit children by allowing them to forgo serial CT imaging for ITH monitoring, decreasing their overall radiation exposure at a vulnerable age. One prospective case-control study of 28 children aged 0 to 14 years showed a sensitivity of 100%, specificity of 80%, positive predictive value of 80%, and negative predictive value of 100% when NIRS was performed in eight different scalp locations in each subject.[9] The study defined an optical density difference of >0.2 between hemispheres as the cutoff to define abnormal imaging and correctly identified all 21 cases of acute ITH. As in other studies, the authors cautioned about false positives and negatives. They noted that the NIRS was negative in one subject with bilateral chronic subdural hematomas and reported a false positive in the one patient with a subgaleal hematoma. Despite drawbacks, with further study, NIRS has promising potential to reduce the need for serial CT imaging in children.

In summary, the role of NIRS in hematoma detection is yet to be firmly established. NIRS has utility in aiding the clinician in evaluating TBI patients in locations where CT scanners are not readily available; however, the limited sensitivity of the device and inability to provide anatomic localization of hematomas significantly limit its utility in comparison with the gold standard of a CT scan. The clinical application and utility of NIRS may be stronger as it relates to prevention of secondary brain injury following TBI (such as with cerebral autoregulation-guided therapy, as is discussed later in this review).

4 Near-Infrared Spectroscopy Technology and Limitations

The technology used for traumatic-brain-injury-related NIRS has also improved significantly over the past 20 years. In our initial studies in the 1990s, we used a dual-wavelength NIRS unit with a probe consisting of two tungsten filament lamps placed 3.5 cm on either side of a 760- and 850-nm detector (RunMan, NIM, Inc., Philadelphia, Pennsylvania). This allowed our unit to analyze tissue within an estimated volume of 2 cm wide by 2- to 3-cm deep.[3] Newer units include more portable NIRS devices allowing for greater ease of use and larger volumes of detection, including the Crainscan (Odicrain GmbH, Hanover, Germany; single-laser light source and detector, unknown wavelength) used by the aforementioned group in Israel, as well as the Infrascanner (808-nm laser diode source, single detector) used by the German Army group in Afghanistan, as well as by the multicenter study in 2010. These scanners, unlike our initial equipment from the 1990s, are more compact units that can be portably used in more rugged situations. Moreover, advances in technology have allowed more quick and accurate display of results, including simplified presentation of results such that clinicians with minimal training can interpret findings accurately. The equipment used in our initial pilot study required one experienced investigator to perform

the examination and required manual calibration and calculation of the change in optical density. Moreover, newer devices feature fiber-optic lightguides which can be brought in contact with the scalp between hairs, obviating the need for shaving the scalp as hair (particularly when thick and darkly colored) has been implicated as a complicating factor in prior studies using NIRS for hematoma detection.[10]

By far the most serious challenge involved in the clinical application of NIRS to TBI patients relates to the problems of extracerebral contamination of the NIRS signal with the scalp, skull, and CSF. NIRS light attenuation is not just a result of absorption by target chromophores but also of light scattering. Hair, subgaleal hematomas, bone, and differences in areas of subarachnoid space contribute to the inhomogeneity of the underlying tissue being analyzed, resulting in nonlinear relationships between absorption and attenuation changes. Moreover, regional differences in pathophysiology (e.g., differing ages of subdural blood, cerebral contusion, perfusion, vascularity, and edema) following TBI are also confounding factors in analyzing signals to obtain accurate results. Newer NIRS technologies under current investigation may help address these confounders in the future.

While a detailed discussion of some of the newer NIRS technologies is beyond the scope of this review, some of the technologies of interest include functional NIRS (fNIRS) methods [frequency-domain (FD) systems, spatially resolved spectroscopy (SRS), and time-resolved systems (TRS)], ultrasound-tagged NIRS (UT-NIRS), and diffuse optical imaging (DOI). fNIRS is the application of NIRS technology to functional neuroimaging, where brain activity is determined by the coupling of neuronal activity to localized changes in cerebral blood flow (CBF). fNIRS is based on the same principle as functional MRI imaging techniques, where neurovascular coupling allows spatial determination of brain activity in different situations.[11] As it relates to TBI, fNIRS may allow more portable assessment of brain function in critically injured patients who would be unable to undergo fMRI, though the exact role of this technology remains unclear. fNIRS spectroscopy, pioneered by the initial studies by M. Ferrari, has expanded to involve a number of modern spectroscopic techniques including FD systems, TRS, and SRS systems.

UT-NIRS is a new technology allowing for the noninvasive continuous monitoring of cerebral blood flow, potentially avoiding some of the potential optical confounders of traditional NIRS. By locally modulating coherent laser light with a localized, low-power ultrasound wave (i.e., acousto-optic effect), UT-NIRS measures the effect of Doppler shifts in the signal, allowing for blood flow measurement independent of the specific light wavelength and thus the oxygen saturation.[12] Schytz et al. investigated UT-NIRS for detecting cerebral blood flow in healthy volunteers and found promising results, with UT-NIRS results correlating well with cerebral blood flow as measured by ^{133}Xenon single-photon emission computer tomography, a well-established method of CBF measurement. Finally, DOI is a relatively new imaging modality using NIRS to determine the spatial and temporal characteristics of neuronal activity by measuring both the absorption and scattering of light and utilizing this information to perform tomographic reconstruction of a three-dimensional volume of tissue. By inherently taking advantage of scattering, DOI is an improvement on traditional NIRS, but its role in TBI remains to be elucidated.

Finally, another emerging technology in the field of NIRS and TBI is the use of NIRS to measure tissue metabolism. Recent work has been conducted in using NIRS to detect the oxidation state of the enzyme cytochrome-c-oxidase. Cytochrome-c-oxidase is the final enzyme in the mitochondrial electron-transport chain, the basis of cellular oxidative metabolism. The reduction state of the enzyme can be detected by NIRS as its copper A (CuA) component has absorption in the NIR spectrum and changes its absorption spectrum depending on its reduction state. Hence, NIRS can measure oxygen utilization in cerebral tissue via cytochrome-c-oxidase.

5 Near-Infrared Spectroscopy for Monitoring Cerebral Autoregulation in Traumatic Brain Injury

NIRS has also been used to provide clinicians information regarding cerebral autoregulation after TBI. Neuroprotective care for the prevention of secondary cerebral injury after TBI is currently the mainstay of severe TBI management. Secondary injury is a complex, multifactorial process by which the brain is further injured after its initial injury. One major contributor to secondary injury is the loss of cerebral autoregulation that occurs in damaged brain tissue. This loss of autoregulation leads to sub- and superoptimal delivery of oxygen to brain tissue, causing further tissue loss and expansion of the primary injury. ICP, cerebral perfusion pressure, partial brain tissue oxygenation ($PbtO_2$), jugular bulb venous oxygen saturation, and increasingly microdialysis catheter monitoring are all reasonably validated measures that serve as a proxy for loss of autoregulation and allow for directed treatment and prevention of secondary brain injury. These measures also require invasive probes, a skilled clinician for placement, and therefore continuous monitoring in an intensive care setting. Given its noninvasive nature and theoretical ability to monitor changes in cerebral blood flow and oxygenation, NIRS has naturally been studied as an alternative to conventional neuromonitoring devices to determine the degree of autoregulation. While NIRS devices for intracranial hematoma detection exploit the profound difference in infrared absorption of extravascular versus intravascular blood, various groups have attempted to exploit changes in the NIRS signal over time in an attempt to correlate temporal changes in the NIRS signal to current invasive measures routinely monitored for neuroprotective care after TBI.

The foundation for using NIRS to monitor cerebral autoregulation lies in the assumption that brain tissue oxygen concentration is positively correlated with arterial oxygen concentration, cerebral blood flow, and tissue oxygen diffusivity while the rate of cerebral oxygen metabolism remains static. Generally, tissue oxygen concentration is assumed to be a surrogate of CBF in the setting of stable arterial oxygenation and stable cerebral metabolic rate of oxygen. Healthy adults generally exhibit "slow-wave" oscillations (0.1 to 0.003 Hz) in cerebral blood volume (CBV), blood flow, and tissue oxygenation secondary to normal physiologic functions ranging from breathing to variations in neuronal activity and cerebrovascular tone. The variations in these slow waves are being increasingly used to compare conventional invasive measures of cerebral autoregulation with newer noninvasive NIRS measures.

There are several methods for employing NIRS to monitor changes in cerebral tissue oxygenation over time. One method is through monitoring the regional cerebral tissue hemoglobin oxygen saturation (rSO_2), a measure of local oxyhemoglobin

concentration. While the specific calculations involved in determining rSO_2 are beyond the scope of this review, SRS uses localized gradients in light attenuation to determine ratios of oxyhemoglobin (HbO_2) and deoxyhemoglobin (HHb) in the tissue. The regional oxygen saturation is calculated by the equation $rSO_2 = [HbO_2]/([HbO_2] + [HHb])$.[13] A baseline rSO_2 is measured with a NIRS device, with the subsequent goal of preventing decreases in tissue hemoglobin oxygenation. This strategy is employed in cardiac and carotid vessel surgeries to prevent complications related to cerebral ischemia, and the prevention of decreases in cerebral tissue oxygenation from baseline rSO_2 has been shown to decrease mortality compared with patients who are not monitored with NIRS.[14,15] Initial studies comparing ICP and NIRS monitoring also used rSO_2, illustrating that rSO_2 was significantly lower in patients with elevated ICP.[16]

More recent techniques focus on measuring changes in the aforementioned slow-wave oscillations to create proxy markers of cerebral autoregulation. NIRS measures and conventional measures are then compared via these surrogate markers. Pressure reactivity index (PRx) is a measure derived from the moving correlation coefficient between arterial blood pressure (ABP) and ICP obtained through invasive monitoring and serves as an index reflecting the reactivity of cerebral arteries to changes in blood pressure and carbon dioxide concentration.[17] Normally, the CBV and ICP vary inversely with ABP. Therefore, negative or zero PRx is suggestive of intact autoregulation. Conversely, positive PRx suggests impaired autoregulation, where the ICP varies passively along with changes in ABP. PRx has been shown to correlate with rate of intact autoregulation as well as outcome in TBI patients.[18] Mean velocity index (Mx) is similarly the moving correlation coefficient of transcranial Doppler flow velocity and ABP and is therefore a surrogate measure of cerebral blood flow.

Total hemoglobin (HbT), defined as the sum of deoxyhemoglobin and oxyhemoglobin, in addition to the relative concentrations of oxy- and deoxyhemoglobin detected by the NIRS device, is used along with ABP to define blood volume and flow surrogates roughly matching PRx and Mx, respectively. HbT reactivity index (THx) is defined to be the NIRS blood volume equivalent to PRx and is a moving correlation between HbT and ABP. Likewise, tissue oxygen reactivity index (TOx) is the NIRS blood flow equivalent and is a moving correlation of rSO_2 and ABP.

Since ICP management currently serves as the foundation of severe TBI care, the majority of studies to date have been comparing fluctuations of ICP with NIRS parameters. Multiple studies comparing PRx with THx[19–22] and Mx with TOx[22,23] have been conducted in TBI and non-TBI patients with varying degrees of success. While there are differing opinions on optimal analytical methods, as well as significant differences in the sophistication of NIRS monitoring devices, most groups have shown reasonable temporal correlation between PRx and THx, as well as Mx and TOx. As an illustration, recently 27 TBI patients were monitored for PRx and Mx for comparison with ipsilateral THx and TOx using advanced analytical techniques.[22] Promising correlations between PRx and THx ($r = 0.63$) and Mx and TOx ($r = 0.61$) were reported. However, it was noted that there was often wide variation between invasive and noninvasive variables both in time and with changes in frequency, with nonsignificant correlations at frequencies below 0.008 Hz.

In an attempt to determine if NIRS measures along with conventional invasive measures detect similar versus distinct stages of cerebral oxygenation, Budohoski et al.[24] examined the relationship between ABP and ICP changes with $PbtO_2$, cerebral blood flow velocity, THx, and TOx. They recorded these modalities in 41 TBI patients, analyzing the change in PbO_2, THx, and TOx to a sustained change in ICP of >5 mm Hg or change in ABP of >15 mm Hg. Temporal changes in ABP were followed first by changes in ICP, then subsequently THx/TOx, and finally $PbtO_2$, suggesting that the different monitoring modalities record different stages of cerebral oxygenation. Unfortunately, the degree to which changes in ICP or $PbtO_2$ were matched by changes in THx and TOx, or vice versa, was not studied.

Budohoski et al. also showed that TOx and $PbtO_2$ varied in the same direction in 77% of cases, suggesting that TOx may serve as a proxy measure for $PbtO_2$. In this vein, Leal-Noval et al.[25] illustrated that $PbtO_2$ and rSO_2 are significantly related, but concluded that NIRS diagnostic accuracy is too limited and not sensitive enough regarding small changes in cerebral oxygenation to replace invasive PbO_2 monitoring. Studies examining the correlation of NIRS measures to jugular bulb venous oxygen saturation,[26–28] as well as microdialysis,[29] show a similar degree of uncertainty, largely due to technological limitations of the NIRS monitoring devices as well as difficulties in computational methodology.

There remain many challenges to using NIRS measures in the prevention of secondary injury in TBI. Defining optimal autoregulatory indices remains difficult. THx and TOx, two of the most studied surrogate measures, still significantly differ from more established invasive measures such as PRx and Mx. Analysis of continuous NIRS data also remains a challenge, with several competing methodologies confounding results of the slow-wave analysis needed to compare NIRS-derived and ICP-derived surrogates of cerebral autoregulation. Technological limitations and variations also confound the literature, with more recent studies using multiple spatially distinct detectors to minimize confounding NIRS signal from sources like scalp blood flow and extracranial hematomas.

As astutely discussed in a recent NIRS review,[30] despite a promising degree of agreement between cerebral autoregulation measures and NIRS measures, studies to date have yet to show independent outcome prediction from NIRS measures. Rather outcome prediction is implied from illustrating a high degree of correlation between NIRS measures and known outcome predictors obtained from invasive monitors. Thus, there is a large opportunity for future studies to correlate NIRS measures independently with outcome after severe TBI. For instance, as it relates to hematoma detection, future studies may investigate differences in outcomes including mortality, Glasgow Outcome Scale, or modified Rankin scales in patients in remote areas without CT availability who underwent initial evaluation with an NIRS device compared with a group who did not. Moreover, with regards to cerebral blood flow and cerebral oxygen concentration, future studies may investigate differences in the same aforementioned outcome measures in TBI patients who underwent continuous NIRS-based CBF and PbO_2 monitoring with those who did not.

6 Conclusion

In summary, since the preliminary studies in the 1990s, the applications of NIRS in patients with TBI has expanded significantly. Advances in both technology and the understanding of

the pathophysiology of TBI have resulted in significantly more research using NIRS devices. As it relates to detection of intracranial hematomas, NIRS's current utility relies on its expeditious, simple, and accurate ability to detect intracranial hematomas, particularly in particularly austere locations. With regards to cerebral autoregulation and oxygenation, NIRS is currently in a preliminary stage for application, with early studies demonstrating limited utility when compared with more invasive cerebral monitoring devices. Significant further research is indicated to better define the role of NIRS in assisting clinicians in preventing secondary neurologic injury in TBI patients.

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