Cerebral Oximetry in the Head-injured Patient: Is it Time for Widespread Application?

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Traumatic brain injury (TBI) continues to be a leading cause of morbidity and mortality, not only of the young but affecting all age groups in the United States. Annually, an estimated 1.5 million TBIs occur in the United States, with more than 52,000 deaths. In children, trauma leads to greater mortality than all other causes combined, with TBI the leading factor in morbidity and mortality. This has a particularly significant impact economically to not only the patients and families, but to healthcare cost, with economic expenditures greater than $60 billion a year going to the treatment of patients with TBI.[11]

Most clinical protocols and algorithms that have been developed to date have, for the most part, focused on maintaining homeostasis and *reacting* to intracranial hypertension, secondary injury, and the pathophysiological response of injury, rather than being proactive, responding before the problems and damage occur. At present, other than management directed at intracranial pressure (ICP) and/or cerebral perfusion pressure (CPP), little is understood or established for directing treatment and treatment algorithms of the injured brain with a goal toward earlier intervention. In addition, little is known about the pathophysiological response after injury and the correct parameters to measure and potentially intervene, thus, highlighting the problem. Because it is not understood what measures indicate that the injured brain is doing poorly, it is unknown what parameters are best to treat. As a result, a better understanding of the overall pathophysiological response after injury is needed to help in directing therapeutic care. To do this requires further and more complex monitoring of the patient, continuously in the acute period, to determine and understand what happens in the injured patient throughout their course, to determine outcomes, and to correlate the parameters identified that potentially may require intervention. It is likely that a multimodality approach to cerebral monitoring for TBI and other intracerebral injuries will be required to fully understand the disease processes, identify potential indicators of the need for intervention beyond ICP and CPP, and improve long-term outcome.

Cerebral oximetry has been frequently used in the monitoring of patients after TBI, although it has not generally had widespread application. It is unclear whether the use of cerebral oximetry could assist in the measurement of the cerebral physiological response and aid in the management of these patients in the acute period. To answer this question, it is important to understand: 1) the problems faced by the clinician in dealing with the patient with a TBI; 2) the potential available technologies for cerebral monitoring, including cerebral oximetry; and whether 3) the technology for cerebral oximetry fits the criteria for implementation into clinical practice. The goal of this paper is to provide an overview of the understanding available on cerebral oximetry and the stepwise approach to determine whether cerebral oximetry is ready for widespread application and implementation.

DEFINING "INJURY" MECHANISMS IN TBI

It is important first to understand the definitions and, often, the lack of definitions of the basics of TBI. To begin this basic understanding, it is important to differentiate the terminology that has been used and clarify the particular mechanisms of injury. In TBI, the "primary" injury is the injury that occurs at the time of the impact or trauma and results in the direct damage that occurs. This type of injury is avoided or lessened only through injury prevention and/or safety devices. As a public health service and the most likely to have the greatest impact, all physicians should be active in educating patients and their families regarding safety and injury prevention, whether through personal interaction or through injury prevention education groups (i.e., ThinkFirst), and should encourage the implementation of seatbelts, motorcycle helmets, side-impact airbags, etc.

Interestingly, although there is little disagreement regarding the definition of the primary injury, there is significant confusion in the literature between the terms "secondary injury" and "second insults." It is a misnomer to consider that a second insult is the same as a secondary injury. A second insult, by definition, is an additional insult that follows the

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primary injury, but is not a direct result of that primary injury. This would include such situations as hypotension, hypoxia, and/or hyperthermia that, although they may be a result of the trauma, are not caused by the primary injury to the brain itself but can contribute to the worsening of the secondary response of the primary injury. These second insults may themselves be insufficient to cause any neurological injury, but, in combination with the primary trauma, may markedly worsen the final extent of damage. Second insults are often confused with secondary injury, which is an injury that is a direct result of the primary injury and is a response to the primary injury and other contributing factors. The secondary injury is best defined as the pathophysiological response of the brain that follows the primary injury and that is often described as a cascade of events that is triggered by the primary impact, which lead to further injury and damage. Secondary injury may include conditions such as excitotoxicity, inflammation, and dysautoregulation, to name a few, and result in the brain swelling and intracranial hypertension frequently observed after TBI. If the primary injury is coupled with second insults, the extent of the secondary injury is worsened, leading to a worsened outcome.

Although they may be semantics, these distinctions are important in the development of management protocols to treat patients with TBI. On the basis of these definitions, we can begin to better understand the potential for therapeutic intervention and evaluate our present knowledge base of the management of TBI. We know that the primary injury can best be treated through avoidance, or lessening the impact through safety devices. As has been mentioned, after the acute primary TBI, the extent and magnitude of the secondary injury response is likely worsened by the second insults that follow. Previous studies have shown that morbidity and mortality are increased in patients with TBI who had episodes of hypoxia and/or hypotension.[4] Hypoxia and hypotension are relatively common, and both have been shown to contribute to a worsened secondary injury response. In addition, a mild TBI or insult that ordinarily would have minimal effect individually can be devastating when combined experimentally.[8] In evaluating the algorithms and protocols on the basis of the adult[3] and pediatric[1] TBI guidelines after severe head injury, the focus of neurotrauma management is, for the most part, twofold: 1) to avoid second insults (i.e., maintain oxygenation, temperature, normal perfusion, etc.) and 2) manage intracranial hypertension or treat the secondary injury response (i.e., with mannitol, pentobarbital, etc.) and diffuse brain swelling and edema. Surgical intervention in select cases may be performed either to avoid second insults (i.e., epidural hematoma compression) and/or treat the secondary injury (i.e., decompressive craniectomy for intracranial hypertension). Therefore, our state-of-the-art management schemes for TBI, in both adults and children, attempt to create a milieu for optimal recovery and are based on minimizing second insults and interrupting the secondary injury cascade. However, to achieve this, these insults and injuries have to be detectable. Although, clearly, issues of hypoxia, hypotension, and hyperthermia are presently being managed within the prehospital, emergency department, and intensive care unit (ICU) settings, other potential second insults need to be considered and may not be presently being managed. It is through this avenue that the concept of higher levels of cerebral monitoring and multimodality monitoring needs to be considered.

ICU MONITORING

If one compares the ICA settings of the cardiac care unit to the neurointensive care unit (NICU), in the cardiac care unit, a number of different parameters are being measured on a continuous basis to understand the response of the heart during and after surgical intervention or periods of ischemia. These measured parameters include not only the different systolic and diastolic pressures but also central venous pressure, pulmonary pressure, pulmonary wedge pressure, cardiac output, systemic vascular resistance and O_2 saturation, to name a few. In addition, a number of different serum markers, including creatine kinase fractions, creatine kinase MB subunit, and troponin are collected to determine the hearts that are at risk for further injury. Physiologically, the heart is being monitored with electrocardiography and intermittently with echo cardiography and thallium scans. If one were to look at the pharmacological interventions available for patients with cardiac problems, there are more than 200 drugs and pharmacological therapeutic agents that could potentially be used to assist the heart in its recovery. These include medications for improving preload, after load, cardiac output, etc. to create the optimal environment and recovery potential for the heart after injury. Conversely, in the NICU, the only measures that are presently used to any extent are mean arterial pressure and ICP (and CPP, although CPP is a calculated parameter equal to the mean arterial pressure minus ICP). Although oxygen saturation, blood pressure, and temperature are measured, there is limited neural-specific monitoring and, as a result, limited cerebral specific medications. In the NICU, there are only approximately four medications that are used for patients with TBI; mannitol or hypertonic saline, pentobarbital, paralytics, and sedation with narcotics.

The goals of increasing the number and complexity of the neurological monitoring would be to 1) detect whether present management, on an individual basis, is contributing to the recovering injured brain; 2) avoid iatrogenic second insults; and 3) measure novel parameters through which manipulation will improve outcomes. Because current neurological monitoring is very limited, the potential for detection of cerebral decline and then therapeutic intervention also remains limited. Ideally, by introducing new technologies

involving neurological monitoring, present day algorithms for treatment can be further evaluated for efficacy, further insults could be avoided, and new algorithms for treatment and care of the injured patient can be developed. These further modalities will not likely supplant ICP monitoring but rather assist in providing a more global and individualized picture of the injured brain in the acute and subacute periods. By adding adjunctive information to the ICP and CPP, an appropriate recovery environment of the brain can be measured and optimized.

A number of technologies are available for neuromonitoring that have not reached widespread application. These technologies include brain oxygen and cerebral oximetry, measurements of cerebral blood flow and perfusion, functional measures such as electroencephalography and somatosensory evoked potentials, biochemical analysis sampling the cerebral microenvironment through microdialysis and cerebrospinal fluid analysis, or globally with serum biomarkers of neural damage and recovery. It is incumbent to determine the impact and value of each technology and determine how best to implement them into the management of the patient with cerebral injury. As the clinician is able to evaluate the different parameters and their change relative to intervention, further therapeutic interventions will be developed to optimize the environment for recovery. Using cerebral oximetry as an example, it is important to evaluate the impact and value of this technology and the steps necessary for implementation and widespread application.

CEREBRAL OXIMETRY TECHNOLOGIES

Currently, three types of cerebral oximetry technologies that have been used in the clinical setting for patients with TBI are available, with variable experiences of usefulness and efficacy. These include jugular bulb oximetry ($SjVO_2$), extracranial/scalp monitors of cerebral oximetry (i.e., near-infrared spectroscopy [NIRS], rSO_2, Somanetics; or tissue index of oxygenation, Hamamatsu), and cerebral parenchymal oximetry monitors (LICOX [$P_{br}O_2$] and Neurotrend). Despite extensive literature in support of these different technologies, the studies have been variable in their recommendations and inadequate to provide definitive evidence for widespread acceptance of any one of these particular technologies. The likely problem with each of these technologies is that there is no specific "number" or parameter to define when the patient is experiencing a clinical decline or level to maintain to treat that have been proven as efficacious. The question is whether the technology is not "useful" or whether clinicians are expecting too much from a new technology or therapeutic intervention (i.e., hypothermia) in relation to significant improvement in outcome. It is, therefore, useful to explore each of the available technologies relative to their usefulness in TBI and examine this future regarding the potential for further widespread application.

Jugular Bulb Oximetry

There is much literature regarding the use of jugular bulb oximetry in conjunction with ICP-directed therapy in TBI. This is not a new technology, and it has been used for longer than 20 years to measure global cerebral oxygenation and can be used in calculation to determine the arterial venous difference to calculate oxygen consumption. With its placement in the jugular bulb, at the proximal portion of the jugular vein, therapy is aimed at keeping the $SjVO_2$ greater than 50 to 55%. A number of studies have shown that poor outcome has increased with values less than 50%, particularly when there are multiple episodes of desaturations below 50%. Although the duration of these episodes is infrequently cited, a desaturation episode is generally defined as $SjVO_2$ below 50% for longer than 5 minutes.[14,16,17] Jugular bulb oximetry provides an early identification and potential therapeutic target to treat the injured brain after trauma,[5] although it remains unclear whether outcome can be improved with treatment of $SjVO_2$. There are a number of disadvantages of the jugular bulb catheter. The first is the sensitivity of the catheter regarding the location and placement of the sensor. The sensor is quite sensitive with value changes if placed against the wall of the jugular bulb or too far distal within the jugular vein itself and not within the bulb. Technically, the catheter is inserted retrogradely within the jugular vein to the jugular bulb and the placement requires x-ray confirmation. In addition, positioning of the head during the course of treatment may alter the position of the catheter within the jugular bulb, providing inconsistent values. Secondly, because there is a mix of extracranial and intracranial venous blood in the jugular vein, there may be false oxygenation values, particularly during periods of cerebral ischemia. It is generally recognized that $SjVO_2$ alone is not efficacious.

NIRS

NIRS is a noninvasive monitor of cerebral oxygenation and has been used to determine the underlying regional cerebral parenchymal oxygen saturation (rSO_2). It has been used primarily in the intraoperative setting as well as in the NICU, with the goal in clinical management to keep regional oxygen saturation greater than 55%. Other available devices using NIRS technology measure a tissue oxygen index that is, by definition, equal to the oxyhemoglobin divided by the total hemoglobin. Once an individual's baseline number is obtained, the goal of management is to treat any "significant" change, which is defined as a reduction of 20% from this defined baseline. As a result, there is no specific number value to measure but, rather, a trend. In the healthy patient, such as an elective operative patient, this may be adequate, but, in the injured patient, in whom the "baseline" may be a measure of already compromised brain, this is likely not useful. NIRS has, for the most part, been used to guide the anesthetic planning and treatment during cardiac surgery, in

which, theoretically, the patient has intact cerebral oxygenation, and baseline and continuous monitoring using NIRS during cardiac procedures has been able to reduce morbidity and mortality.[13] For the head-injured patient, NIRS has been used for measurement of cerebral oxygenation and as an early detection monitor of hematoma formation.[14] Unfortunately, NIRS has numerous problems that have limited its usefulness in the NICU setting. NIRS measurements of cerebral oxygenation tend to be unstable and at times do not reliably reflect episodes of cerebral oxygen desaturation. In addition, although the optodes are positioned frontally to avoid hair-bearing areas, it is thought that the whole brain probably contributes to signal changes. However, the percentage distribution of venous, capillary, and arterial blood representing the NIRS signal is undefined. Lastly, NIRS cerebral oxygen parameters have not been shown to have good correlation with other monitored values either of cerebral oxygenation or other physiological variables (i.e., $SjVO_2$, ICP, CPP, cerebral blood flow) or with outcome in TBI patients.

Brain Tissue Oxygenation

A newer technology with increasing experience is the measurement of the brain tissue oxygenation ($P_{br}O_2$). The brain oxygen monitor is a probe inserted (usually through a bolt that is anchored within the cranium) to a set depth in the white matter of the frontal lobe. The probe provides regional oxygen saturation measurements and there have been studies that have determined not only prognostic information but early attempts for treatment by maintaining adequate "oxygenation" for the brain during the acute phases. The disadvantage of this monitoring modality is that it measures a small regional area of brain, does not provide a global measure, and to date, optimal location (i.e., proximate to contusions or hematomas versus injured though salvageable tissue) and need for multiple probes have not been defined. The potential for the $P_{br}O_2$ monitor may be as an early alert for iatrogenic or preventable second insults and the need for the clinician to focus on ventilatory and perfusion parameters, including relative hypoxia, hypocarbia, and hypotension.

In an attempt to correlate $P_{br}O_2$ with outcome, it has been suggested that mortality is increased with increasing duration of time of $P_{br}O_2$ less than 15 mmHg,[20,21] less than 10 mmHg for longer than 30 minutes,[2,21] or at most 6 mmHg, regardless of duration. Only limited studies have attempted to improve outcome with treatment of low $P_{br}O_2$ values with therapy directed at the low values to "normalize" both metabolic and clinical parameters. Using oxygen-directed therapy after severe TBI ($F_iO_2 = 1.0$) within 6 hours of admission compared with historical controls, there was a suggestion of improved metabolic patterns but a nonsignificant improvement in outcome in the treatment group. More recently, there has been a study of ICP-directed therapy versus ICP combined with $P_{br}O_2$ monitoring, with a goal of maintaining both low ICP and high $P_{br}O_2$. The parameters used included ICP less than 20 mmHg, CPP greater than 60 mmHg, and $P_{br}O_2$ greater than 25%. Outcomes for mortality were compared with historical controls of only ICP- and CPP-directed management. The mortality in the controls was 44%, whereas the combination therapy with $P_{br}O_2$ monitoring reduced mortality to 25%.[18] The limitations of this paper are the historical controls and a mortality of the controls higher than present standards. However, these studies warrant further investigation to determine the potential for this addition to a multimodal approach.

The reason to introduce cerebral oximetry is that it attempts to measure regions or global areas at risk for secondary injury by optimizing the oxygenation and perfusion for recovery of the injured brain and in the acute and subacute periods. Although brain oxygenation has classically been monitored using jugular bulb oximetry, it does not reflect regional changes in oxygenation. Both NIRS and $P_{br}O_2$ provide regional measures of brain tissue oxygenation and likely reflect regional brain oxygenation better than jugular bulb oximetry. This potential for either of these types of monitoring or in combination presents an opportunity for further understanding of the injured brain and its postinjury response as well as the development of algorithms for treatment.

USE OF A NEW TECHNOLOGY

A number of questions should be answered before the implementation of a new technology into clinical practice. As one begins to contemplate the introduction of a technology such as cerebral oximetry, the first question(s) should be whether there are adequate studies supporting the new technology or strategy and whether those studies support the validity of that technology or treatment strategy. The second question is whether this valid technology or strategy is potentially useful or important. Although the technology can provide adequate information that may be accurate, it is important to determine whether indeed this information is useful and has some impact in clinical practice. The third question that arises is whether the technology or strategy is applicable in ones own particular clinical practice. For example, if one is trained on a particular spinal instrumentation system that, in ones practice, has provided excellent outcomes for that patient population, the introduction of a new technology using transthoracic or retroperitoneal approaches may not be applicable for this physician and these patients. In contrast, if more complex spine procedures were being referred elsewhere or had higher morbidity, then the introduction of new technologies that improved outcomes may useful and important adjunct to this particular practice. Lastly, it needs to be determined how easily can the new technology or strategy be implemented or, as is classically termed, how steep the learning curve is. If the new technology builds on

previous and familiar technology, then it may be easily implemented and more likely to be used. In contrast, if there is a significant learning curve for implementation, then one needs to consider again the investment and time necessary to incorporate that technology in ones practice.

We need to apply these questions to cerebral oximetry before implementation. In evaluating brain oxygenation after acute brain injury as well as TBI, these technologies have been shown to be valid in the measurement of brain oxygenation, although there is little information of direct correlates of cerebral oximetry and brain oxygenation to other physiological parameters, such as PaO_2, $PaCO_2$, etc. In addition, there is also little information regarding direct correlates of pathophysiological factors, including intracranial hypertension or high ICP, low perfusion as measured by CPP, cerebral blood flow, etc. Lastly, there has not been much information regarding the relationship of cerebral oximetry and patient outcome. There has been much information regarding indirect correlates of these parameters and trends, but it is clear that cerebral oximetry does not provide a single number that is "good" or a specific indicator that the brain is in stress or a "danger" situation.

When one considers cerebral oximetry as potentially being useful or important, brain oxygenation levels would need to provide early detection of second insults or the physiology of secondary responses or injures after TBI. Because the direct usefulness or importance of cerebral oximetry remains unclear, at least at this time, it is difficult to be definitive. However, if one were to postulate that, indeed, brain oxygenation levels do provide some insight into the pathophysiological responses and having this information lends one to improve care through meticulous adherence to details and avoidance of second insults, then cerebral oximetry would potentially be useful and important. The avoidance or correction of potential iatrogenic insults or aggressive management of second insults may preserve cerebral tissue from further damage. Although there is no direct proof of this at this time, cerebral oximetry has been shown to measure desaturation events and the duration of these episodes, and these have been correlated to outcome in the extreme. Similarly, episodes of decreased PaO_2 or mean arterial pressure are physiological parameters that have been directly correlated to worsened outcome but do not directly lead to changes in ICP. ICP tends to increase later on as a result of worsened secondary injury in response to the second insults. Cerebral oximetry has been shown to identify decrements in these physiological parameters and could potentially improve care with the monitoring of these pulmonary and/or iatrogenic insults. As a result, cerebral oximetry may serve as an early detection system for us to monitor clinically important physiological parameters. Further clinical applicability will come with defining whether cerebral oximetry can measure the autoregulation of the brain and its ability to respond to changes in mean arterial pressure, oxygenation, and $PaCO_2$. However, further answers to the clinical applicability need to be defined, and include the role of cerebral oximetry to measure brain oxygen desaturation or excessive saturation and impact on prognosis and outcome. In addition, again not clearly defined, is the question of how to determine the specific numbers for cerebral oximetry, whether globally, in patients with TBI, or in the individual patient for intervention.

Lastly, although easily implementable, that is, it is not difficult to insert the monitors or apply the optodes, there is a learning curve to determine the particular usefulness in particular patients. It has been this author's experience that there may be patients in whom ICP and CPP measures seem to be more important and more unstable and require more intervention than the cerebral oximetry values. In others, ICP and CPP may be stable, however, there is some indication that cerebral oximetry is inadequate, or unstable. These are instances in which experience through day-to-day management of a number of patients allows for the implementation and learning of the clinical applicability of this technology to ones' clinical practice.

On the basis of the above discussion, the question arises whether indeed cerebral oximetry is ready for widespread application. There are a number of reasons why cerebral oximetry may not be useful and ready for use at this time. Cerebral oximetry unfortunately monitors either only a regional area of potential cerebral function or globally despite regional differences in patients with TBI. Cerebral oximetry has not be validated or correlated to particular individual differences in the TBI patient and, as a result, does not measure different areas that may potentially be impacted or at higher risk for further secondary injury. As mentioned, cerebral oximetry does not provide a parameter or specific set of numbers to define patients in a stable state versus those at risk for further or worsening secondary injury. To date, there is still a limited understanding of the relationship to other parameters that are measured in the NICU, including the basic pulmonary function parameters, such as PaO_2 and $PaCO_2$, blood pressure, ICP, CPP, etc. At this time, the use of cerebral oximetry, at least in the clinical setting, does depend on a fair amount of experience and a long learning curve, at least regarding to the relationship of patients in the critical setting, as well as its specific applicability. Lastly, it is indeed necessary that more studies be performed to develop correlative data with these physiological processes and parameters and data that this intensive approach toward management will alter and improve outcome in this patient population.

Despite the above-described shortcomings, cerebral oximetry remains a safe, valid, and proven technology. It remains for us as clinicians to determine the usefulness and application in the clinical setting. Cerebral oximetry provides new information in the monitoring of cerebral physiology and pathophysiological processes and potentially may assist in the

complex management of TBI and/or other cerebral injuries. There is clearly strong preliminary data that indeed it is a useful and clinical applicable technology to monitor the cerebral functional state. Through its further and continued use, there will be improved understanding of the relationship between cerebral oximetry and other physiological and pathophysiological parameters, and it is through this experience and learning that we will better be able to define patients at risk versus those who are in a more stable situation. Although cerebral oximetry alone will not supplant any of the present day monitoring, it is a promising technology that will clearly add and assist in the management of this complex group of patients. In addition, with this whole concept of multimodality monitoring, further information can only assist in ongoing improvements in the management of these patients and potentially improve long-term outcomes. Although cerebral oximetry is not the answer alone, it continues to contribute to our understanding of the optimal management for this patient population.

CONCLUSIONS

Cerebral oximetry is a safe and valid technology that has reached the threshold for widespread use, as part of a multimodality approach to evaluation cerebral function. It is a useful technology for determining cerebral oxygen physiology in both the healthy and pathophysiological states. The literature suggests that episodes of desaturation ($SjVO_2$ 50–55% for 5 min) are associated with worse outcomes, and low values of $P_{br}O_2$ (<10–15 mmHg) and the extent of their duration (30 min) are associated with poor outcome. Although cerebral oximetry is limited until further rigorous and controlled studies are defined to better understand the optimal approach for its application, it is clear that further widespread use will continue to increase the knowledge base and experience necessary to enhance the efficacy of this particular technology.

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