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Cerebral oxygenation in traumatic
brain injury; Can a non-invasive
frequency domain near-infrared
spectroscopy device detect changes
in brain tissue oxygen tension as well
as the established invasive monitor?

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Abstract

The cost and highly invasive nature of brain monitoring modality in traumatic brain injury patients currently restrict its utility to specialist neurological intensive care settings. We aim to test the abilities of a frequency domain near-infrared spectroscopy (FD-NIRS) device in predicting changes in invasively measured brain tissue oxygen tension. Individuals admitted to a United Kingdom specialist major trauma centre were contemporaneously monitored with an FD-NIRS device and invasively measured brain tissue oxygen tension probe. Area under the curve receiver operating characteristic (AUROC) statistical analysis was utilised to assess the predictive power of FD-NIRS in detecting both moderate and severe hypoxia (20 and 10 mmHg, respectively), as measured invasively. 16 individuals were prospectively recruited to the investigation. Severe hypoxic episodes were detected in 9 of these individuals, with the NIRS demonstrating a broad range of predictive abilities (AUROC 0.68-0.88) from relatively poor to good. Moderate hypoxic episodes were detected in seven individuals with similar predictive performance (AUROC 0.576 – 0.905). A variable performance in the predictive powers of this FD-NIRS device to detect changes in brain tissue oxygen was demonstrated. Consequently, this enhanced NIRS technology has not demonstrated sufficient ability to replace the established invasive measurement.

Keywords

frequency domain near-infrared spectroscopy; traumatic brain injury; brain tissue oxygen tension; critical care; cerebral hypoxia; cerebral non-invasive monitoring.

Introduction

Traumatic brain injury (TBI) is a global health problem constituting a significant and expanding disease burden. Within the United States and other similar western economies it is thought to directly affect up to 2% of the population. ¹ It is a broad spectrum of pathology, encompassing a variety of levels of severity from mild injury where recovery is brisk and complete, to death or devastating injury resulting in the requirement for life-long care.

In the case of moderate or severe TBI (where consciousness is impaired and significant neurological damage has been sustained), invasive monitoring techniques of various brain-based physiological parameters is required. Output parameters from these monitoring modalities can be utilised by clinicians to:

- a) Optimise intra-cranial homeostasis (for brain tissue preservation);
- b) Orchestrate timely surgical or non-surgical intervention;
- c) Forecast prognosis and formulate suitable management plans based on these.

These brain monitoring are used alongside general systemic physiological parameters such as arterial blood pressure, blood gas composition, core temperature and pupillary reflex function. The most frequently employed are intra-cranial pressure (ICP) measurement, brain tissue oxygen tension

measurement (PbtO₂) and cerebral tissue microdialysis.² In the absence of contemporaneous operative intervention (craniotomy), all of the abovementioned brain monitoring techniques require an access hole to be drilled into the skull vault along with a wire or catheter to be passed through cerebral tissue. This is an invasive procedure, with an associated potential morbidity and high equipment cost arising from single-use items.³

This method of ICP monitoring is the most commonly applied invasive monitoring technique in TBI. Despite this, the evidence surrounding the intensive management of these patients, based directly on the absolute values of this parameter, is equivocal and potentially has no discernible benefits over serial axial/CT imaging.⁴ However, this evidence must be considered carefully within the confines of the surgical equipoise on which they were executed.

Cerebral tissue oxygen tension (PbtO₂) is an established adjunct to the measurement of ICP,⁵ and substantial evidence exists to suggest that making clinical decisions and guiding management based on this parameter have a positive effect on clinical outcome.⁶ Beyond its current independent abilities, PbtO₂ also has the advantage of providing more detailed information regarding changes in brain oxygenation and perfusion than pressure measurement alone, this in turn allows for qualification of metabolic data.⁷ Despite these promising findings, PbtO₂ still represents a highly invasive and expensive method of monitoring brain physiology after TBI, and its use (like all similar modalities) is currently limited to critical care centres within tertiary referral (specialist) centres. A non-invasive monitoring technology that can demonstrate an accurate

reflection of this parameter and an acceptable equivalence would be extremely useful in expanding the effective monitoring of brain physiology earlier in the patient journey and beyond this specialist environment. The potential reduction in cost and potential morbidity would also be of significant advantage for such a monitoring device.

Near Infra-Red Spectroscopy (NIRS) represents a clinically viable method of monitoring brain physiology within a number of important clinical contexts (e.g., cardiac surgery).⁸ This technology relies on the passage of near-infrared light (wavelength 700-1000nm) through a proscribed block of target tissue, the degree of absorbance of this light (as predicted by the Beer-Lambert principle. Fig. 1) is then directly proportional to the quantity of target absorbing molecules (i.e., chromophores) within the volume of tissue passed through by the emitted photons.

To date, attempts of incorporate NIRS into mainstream TBI management has been limited due concerns regarding the reliability of output parameters.^{9,10} The overwhelming majority of clinical investigations into the use of NIRS in TBI have utilised a traditional form of the technology (continuous wave parameter recovery) in which the amount and nature of tissue scatter are assumed homogenous through the observed tissue.⁹ At the present time, this technology has not yet demonstrated sufficient ability to replace invasively measured intracranial parameters including PbtO₂ measurement.⁸⁻¹⁰

Many theoretical explanations regarding why the technology has failed to demonstrate sufficient accuracy have been proposed. For example, signal contamination from superficial (non-brain) tissue, the inability to confidently quantify photon scatter within tissue and the absence of absolute quantitative measurements of chromophores are considered among the most important factors.¹¹ Within the context of TBI, quantitatively accurate parameters and the reduction in inter subject variability of these are of particular importance. In many clinical settings where NIRS has demonstrated useful utility a key factor is prior functional knowledge of the patient specific functional (neurological) status⁹. In such cases the initial NIRS parameters are meaningless and can be normalised to an arbitrary unit baseline, simple knowledge of how these parameters change over a period of observation is sufficiently useful. In TBI management, however, quantification of the injury sustained (in comparison to normal physiology) is essential early in the patient journey.

Many advances in NIRS technology have been implemented to overcome its limitations and facilitate its greater use in key clinical settings; the development of frequency domain (FD-NIRS) parameter recovery is worthy to be mentioned. Continuous wave devices emit light into target tissue at a constant intensity, whereas FD-NIRS continuously modulates this intensity. These changes in intensity are detected, allowing an assessment of phase shift (Fig. 2). From these a specific tissue value for light scatter can be derived and incorporated into the

device output parameters, in turn this will theoretically improve their quantitative accuracy.

A number of important advances in NIRS parameter recovery demonstrating promising improvements in quantitative accuracy have involved complex skin contact arrays,^{11,12} and expensive (often customised) light emitting and detection technology.^{13,14} However, this technology has (as yet) not been tested in the mainstream clinical TBI area as to its ability to replace mainstream invasive monitoring modalities or be utilised independently.

Aim

Our primary aim is to investigate the ability of a commercially available and clinically viable FD-NIRS device to predict clinically significant changes in contemporaneously measured brain tissue oxygen tension within the context of TBI patients.

Methods

National and institutional ethical approval was obtained for this investigation as part of the National Institute for Health Research portfolio study Red Diamond (approval code 14/EE/0165, July 2014). Due to the nature of the investigation, consent at the time of enrolment in all cases was obtained either by a nominated professional or personal consultee.

Setting

The University Hospital Birmingham, Queen Elizabeth represents one of the largest tertiary referral and major trauma centres in the UK. The neurosurgical and traumatic brain injury service serves a population of over 4 million individuals, it also represents the primary role 4 medical facility for the UK armed forces, with the headquarters of the Royal College of Defence medicine situated on site.

Equipment

The Raumedic PbtO₂ invasive brain tissue oxygen measuring system is an established and commercially available monitoring system utilising fluorescence-quenching technology. This detects changes in free oxygen concentration within a given medium via a reduction or 'quenching' of the fluorescence (to a specific wavelength of light) of a given substance (in this specific case ruthium/pyrene di-butyric acid ¹⁵) by the presence of oxygen (Fig. 3). ¹⁵Alternatively available systems utilise a Clarke cell (Catalytic platinum electrode under a permeable membrane) to quantify free oxygen. ¹⁶ Reports

within the literature suggest that these two methods are at least equivalent in terms of their accuracy,¹⁷ however the fluorescence quenching method has certain theoretical advantages including negating the requirement for a metallic catalyst within the tip of the electrode and a theoretical improved resistance to particulate fouling of the detection interface. Placement of the Raumedic PbtO₂ catheter can be either via an intra-cranial bolt or tunnelled free-hand placement, the device is fully MRI compatible and is a combined ICP and brain tissue temperature sensor (removing the requirement for an additional ICP monitor). When introduced via the proprietary bolt system the depth of tissue penetration is fixed, in cases where this was utilised the manufacturers specific drill was utilised. The position and insertion method of each invasive monitor were recorded, in cases of where open surgery was not performed prior to the insertion of the monitor (and without any additional indication) the bolt was placed over Kocker's point (right side, 2cm anterior to coronal suture, mid pupillary line) in line with our ethical approval to follow standard departmental procedure.

The ISS (IL, USA) Oxiplex TS is a commercially available and clinically viable point of care FD-NIRS device. In standard form (as used) it has 2 functioning channels with a linear 4 source / 1 detector layouts (Fig. 4). Each source emits light at 2 wavelengths of 680 and 830nm, this combined with its intensity modulation provides a (theoretical) quantitative output parameter (micrograms of chromophore within the region of acquisition) for both oxygenated and deoxygenated haemoglobin (Hb). Flexible contact pads incorporate the

source/detector array, with light transmitted to and from the skin via fibre optic bundles with detected light augmented via a photo-multiplication device (PMT).

Both monitoring modalities were set at identical data acquisition frequencies of 1Hz, with synchronisation of data streams undertaken contemporaneously (Fig. 5); higher resolution observation was available but not undertaken. Event triggers on respective devices logged significant events (e.g. patient turning)

Procedure

Eligible patients are identified through the institutional neurosurgical referral service by research staff. Consent was then obtained once it was established that invasive intra-cranial monitoring was mandated.

The ICP/PbtO₂ catheter was placed as dictated by clinical requirement (bolt/tunnelled), including site/side of catheter. Fibre optic integrity was then confirmed along with an oxygenation challenge to confirm functionality of the probe as described by Wilensky et al.¹⁷ Failure to establish a reliable and reactive tissue oxygen tension measurement to this acute challenge excluded that individual data from the primary analysis. Radiological investigation to confirm the anatomical site of the catheter tip was not routinely performed.

Regular calibration prior to use of the ISS NIRS device was undertaken with manufacturer supplied (fixed scatter property) gel blocks to ensure consistent

measurements throughout the investigation. NIRS probes were placed symmetrically on both sides of the forehead, with prior surface preparation and cleaning of the skin. On each individual, the centre of the probe (corresponding approximately to the field of NIRS acquisition) was placed approximately 2 cm superior to the supra-orbital ridge in the mid-pupillary line. After establishing a stable baseline signal, the probes were secured and shielded from ambient light contamination with a 6-cm wide elastic bandage, this also served to stabilise the associated fibre optic lines.

Once stable observations were established for each monitoring modality, data markers were placed simultaneously on both modality loggers allowing accurate synchronisation of the data streams. Recording would then be continued for the duration of clinical monitoring or up to 72 hours after injury (whichever occurred first). No more than 20 hours of continuous observation was undertaken to minimise the risk of skin necrosis due to the presence of the pads, a minimum of 4 hours rest would then be allowed prior to re-commencement.

Specific Inclusion Criteria

Inclusion criteria into this investigation included adult patients admitted with moderate or Severe TBI requiring the insertion of an invasive cerebral monitor.

Specific Exclusion Criteria

- Any significant frontal bone or soft tissue injury causing significant disruption of the normal anatomy
- Existing frontal / bi-frontal craniectomy or bony defect under NIRS probe placement site (pre-monitoring)
- Frontal extra/sub-dural haematoma or contusion within the field of NIRS acquisition **at the commencement of measurement.**
- Any pre-existing chronic or progressive neurodegenerative disease

Data Acquisition and Analysis

Continuous 1Hz data acquisition was acquired and recorded for both NIRS and PbtO₂, for the purpose of analysis only NIRS data acquired from the channel ipsilateral to the inserted invasive monitoring catheter was considered (as this is acknowledged as a local/focal measurement). For both modalities data was recorded via device specific loggers, and exported in excel format after protocol completion for analysis. Output data relating to PbtO₂ was recorded as an absolute partial pressure (mm Hg), and NIRS parameters were recorded (for the purposes of analysis) as Hb saturation (derived from the relative absorptions of oxygenated and deoxygenated Hb). This was felt to be the most appropriate NIRS-based parameter as it incorporates data from both oxygenated and deoxygenated Hb.

For the purposes of analysis, the PbtO₂ values were categorised in terms of significant change and absolute values as follows:

- Severe hypoxia as a change in PbtO₂ below 10mmHg
- Mild hypoxia as a change in PbtO₂ below 20mmHg

These numbers are based on a number of extensive published investigations quantifying physiological and pathological values for PbtO₂ within the context of TBI, with accompanying outcome data.^{5, 6, 17, 18} The identification of episodes of invasively detected ischemia by our selected NIRS device is a primary aim of this investigation, as the overall objective of this work is to test the suitability of this monitor to be used independently within the context of TBI. Therefore, we feel that NIRS technology should be sufficiently sensitive to detect moderate changes in PbtO₂.

These definitions were then used to conduct logistical regression analyses utilising Area Under Curve Receiver Operating Characteristics (AUROC) to relate changes in NIRS parameters (saturation) to changes in PbtO₂. This method of analysis gives a measure of discrimination, quantifying the ability of any point measurement in NIRS saturation to predict hypoxia. The closer the AUROC value to 1 the better the discriminative ability. An AUROC value of 0.5 is approximately equivalent to the average performance from guessing at random.

Results

A total of 16 patients (13m/3f) were recruited to the investigation between December 2014 and March 2016. In 4 of these individuals, specific equipment issues (inadequately reactive PbtO₂ trace, overly noisy NIRS parameters, evolving forehead haematoma) made useful analysis of the data impossible, they were therefore excluded. 18 patient/patient families were approached in total however 2 declined consent.

Of the 12 remaining recruited patients (9m/3f) the mean age of these individuals was 50.5yrs (median 54, S.D 17.5yrs). The most frequent mechanism of injury sustained was fall (n=6), followed by road traffic collision (n=4), blunt object assault (n=1) and gunshot injury (n=1). The mean initial (best) post-resuscitative Glasgow Coma Scale of these individuals was 8 (range 4-11, median 8, S.D 2.3), with the majority (n=7) sustaining a severe TBI as classified by an initial GCS of 8 or less.

The mean time from injury to commencement of contemporaneous bi-modal monitoring (PbtO₂ and NIRS) was 12.2 hours (median 12, S.D 5). A total of 1,021,590 paired data points were analysed (over 283 hours across all 12 patients), with 160,576 measurements representing severe hypoxia, and 492,988 measurements representing moderate hypoxia. The smallest individual patient data stream was 16,200 (4.4 hours) data points, the largest 111,000

(30.5 hours) and a mean of 86,901 (24 hours) data points across the group. In certain patients, corresponding data plots between NIRS and PBtO₂ demonstrated good agreement on visual inspection (Fig. 6), however in a number of cases this was not the case (Fig. 7).

No fixed regime of post monitoring imaging was instigated; axial imaging requirements were dictated by clinical need. However all individuals recruited underwent imaging during the acute episode after commencement of multi modal monitoring. The timing of this varied from 2 hours to 6 days. No apparent mass lesion directly within the field of NIRS acquisition was observed, however a number of images were acquired after removal of the monitoring apparatus.

After initial inspection by institutional statisticians, and the construction of best-fit regression model (flexible splines), a considerable variability in the change in NIRS parameters for a given change in brain tissue oxygen tension was observed (i.e., a significant change in NIRS parameters predicting hypoxia in one patient was very different from that recorded in another). The relationship was also non-linear, in that the change in NIRS saturation accompanying a change in PbtO₂ varied depending on pre-event parameters (e.g., the magnitude of NIRS parameter change seen corresponding to a change in tissue oxygen tension of 5mmHg would be different at a baseline (NIRS) saturation of 72% as those from a baseline of 78%). It was therefore considered impractical to consider the data set (all patients) as one continuous stream, and therefore the data of each individual patient was considered separately.

Baseline NIRS Saturation varied from 49% to 74% (mean 66.8% S.D 7.9%). This was taken as an average of the first 600 seconds of recording (after setup and the confirmation of a stable reading) on the ipsilateral channel to invasive monitoring. These are similar figures to those recorded in our previous investigations using similar equipment in healthy individuals.¹⁹

Predicting changes representing severe hypoxia

Episodes of severe hypoxia were recorded in 9 of the 12 considered patient PbtO₂ data streams (Table 1). In the majority of patients (7 of 9) the point of

care FD-NIRS device demonstrated a moderate or good discriminatory (predictive) ability. However, the remaining 2 demonstrated relatively poor performance.

The probabilities (predicted) of severe hypoxia based on changes from baseline values were heterogeneous throughout the group. For example, in the case of patient 4 an increase in NIRS saturation of 1% from 58.2% to 59.2% corresponded to a reduction in the odds of being severely hypoxic of only 5% [Odds Ratio (OR) 0.95 (0.94, 0.97)]. However, an increase in NIRS saturation of 5% from 58 to 63% resulted in a reduction in the odds of being severely hypoxic of 74% [OR 0.26 (0.24, 0.29)]. Alternatively, a decrease in NIRS saturation from 63 to 58% increased the relative likelihood of hypoxia by 383%. In the case of patient 5 an increase of 1% from 69.2% to 70.2% corresponded to a reduction in the odds of being severely hypoxic of 53% [OR 0.47 (0.44, 0.49)], and an increase in NIRS saturation of 5% from baseline resulted in a reduction in the odds of being severely hypoxic of 98.7% [OR 0.013 (0.009, 0.018)]. Alternatively, a 5% decrease in saturation represented an increase in the relative probability of hypoxia of 769%.

Predicting Changes representing moderate hypoxia

Episodes of moderate hypoxia were recorded in 7 of the 12 considered patient data streams (Table 2). In a similar pattern to that observed in the prediction of episodes of severe hypoxia the majority (5 out of 7) demonstrated moderate to good abilities in the discrimination and prediction of episodes of moderate

hypoxia. Again, the remaining 2 patient data streams demonstrated poor predictive performance with 1 recording an AUROC of 0.576.

The probability of predicting moderate hypoxia throughout the group was varied, and non-linear in a similar fashion to that demonstrated in episodes of severe hypoxia. In Patient 9 an increase in NIRS saturation of 1% (from 61.4% to 62.4%) corresponded to a decrease in the odds of being mildly hypoxic of 40% [OR 0.60 (0.50, 0.72)]. However, an increase of 5% in NIRS saturation (from 61.4% to 66.4%) resulted in a decrease in the odds of being moderately hypoxic of 94% [OR 0.06 (0.04, 0.08)]. This represents an increase in the relative likelihood of hypoxia following a 5% reduction in saturation of approximately 1660%.

In contrast to this, an increase of 1% from 57.2% to 58.2% in patient 4 corresponded to an increase in the odds of being mildly hypoxic of 0.009% [OR 1.00 (0.99, 1.01)], with an increase in NIRS saturation of 5% (from 57% to 62%) resulting in an increase in the odds of being mildly hypoxic of 2% [OR 1.02 (0.97, 1.06)]. Conversely, a reduction in NIRS saturation of 5% increased the relative likelihood of mild hypoxia by approximately 98%.

Discussion

Invasive intra-cranial monitoring is the current cornerstone of TBI management, and undertaken exclusively within the confines of specialist critical/intensive care units. Alongside the avoidance of the significant cost and morbidity

associated with an invasive intra-cranial monitor, a non-invasive equivalent has the potential to allow the brain tissue specific direction of therapy to be undertaken in a much wider range of environments.^{20,21} Studies utilising commercially available NIRS devices similar in portability to the system utilised in our investigation have demonstrated that the use of this technology is entirely possible in a wide range of pre-hospital environments.^{22,23} This also has the potential to move brain tissue directed resuscitation measures closer to the time of injury (e.g., roadside).

For a new monitoring device (or modality) to potentially be utilised independently for the process of clinical decision making in any medical discipline it should usually demonstrate excellent agreement with an established clinical gold standard (measuring parameter/predicting an event/predicting outcome). Intuitively, the proposed novel method of measuring a given physiological parameter should detect every clinically significant change in parameters that the previous gold standard reports.

Alternatively, if the performance differs, the discrepancy in reports should be justifiable by the avoidance of certain inherent limitations or complicating factors (I.e. invasive vs non-invasive – the risk of missing a significant physiological change is offset by the reduction in risk associated with the invasive application). The measurement of cerebral haemodynamic activity in resuscitation is by no means isolated in the quest for a non-invasive device to demonstrate equivalence to (and displace) an existing expensive or invasive

clinical gold standard. In cases where non-invasive measurement of blood pressure (a conceivably simpler prospect to cerebral vascular activity) in the critically ill has been compared to novel non-invasive alternatives, the invasive method of monitoring is still recommended as irreplaceable with respects to critical care. ^{24, 25}

Within the recent literature, the reported risk of morbidity with conventional invasive intra-cranial monitoring with intra-parenchymal pressure transducers is approximately 1% and 0.5% for haematoma and infection respectively. ^{26, 27}

This risk has been demonstrated as significantly higher when an intra ventricular catheter is utilised. ^{28, 29} These risks must therefore be considered against the possibility of a 'missed' critical physiological episode that 'should' be actively managed. No trial has yet assessed the difference in outcome between invasively guided TBI management and NIRS, ⁸⁻¹⁰ therefore quantification of this risk/benefit with currently utilised NIRS technology is imprecise.

The results of this investigation indicate that (in its current state) the point of care FD enhance NIRS device tested does not demonstrate sufficient reproducibility in its ability to predict changes in PbtO₂ to replace the current invasive gold standard. A consistently very good predictive power would be required in all cases for this to be plausible, and even in our modest number of patients it is demonstrable that the margin of disagreement is too great. Within the NIRS parameter recovery apparatus there are a number of factors that may

account for inconsistency, including site and placement technique of probes, ambient noise and movement artefact, together with evolving oedematous changes within the extra cranial tissues due to diffuse injury of the upper extremity. However, this was a pragmatic investigation into the use of this technology, and a certain degree in the heterogeneity of application of the skin probes, movement and ambient artefact together with changes in the skin tissue (including sweating) themselves would be inevitable and expected in clinical practice. We therefore maintain that these findings are directly translatable to the technology within the intensive management of TBI.

A previous investigation into the abilities of point of care NIRS to predict changes in invasively measured brain tissue oxygen concluded that in its current state NIRS is not sufficiently sensitive to replace intra-cranial measurement. It utilised a continuous wave device, and the invasive measurements were made with a Clarke cell based probe.³⁰ Other significant differences exist in the relative methodologies of this earlier study and our own; with Leal-Novel et al taking shorter 1 hour observations in a larger number of injured patients (22 vs 16), a different definition of severe and moderate hypoxia, and a significantly different number of paired measurements (42,000, vs 1,02,1000). Despite this the results in both investigations are comparable despite the potential advantages of the FD-NIRS device utilised in our trial. Specifically, Leal-Novel et al observed that the NIRS device could detect severe hypoxic changes (defined as a PbtO₂ of <12mm Hg) with an AUROC of 0.82 and moderate hypoxic changes (defined as a PbtO₂ of

15mmHg) with an AUROC of 0.62, which are within the range that we observed across our patient cohort.

While the FD-NIRS device provides the advantage of quantifying a global tissue value for light scatter, it is not able to topographically isolate values for scatter within individual layers of tissue. As such, it does not represent a definitive solution to excluding the influence of superficial extra-cranial tissue or the definitive quantification of chromophores.³¹ Consequently, this may account for the apparent inability of this device to improve the predictive power seen in the previous similar investigation utilising continuous wave technology.³⁰

It should be acknowledged that our measurement of PbtO₂ from the invasive probe will be local to that part of the brain and thus not absolutely uniform in terms of its proximity to the field of NIRS acquisition (although always from the ipsilateral cerebral hemisphere). Therefore, a degree of variability in the measurement could certainly be attributed to our invasive gold standard. This potentially represents a limitation in our investigation; as the comparison of two largely focal measurements that are not in all cases measuring at identical locations is sub-optimal. This is an important factor in drawing conclusions from this investigation (and previous similar investigations), as it could certainly account for a degree of inconsistency in the agreement between modalities.

Conclusions

A clear predicative relationship between NIRS parameters measured by this point of care device utilising FD technology and invasively measured PbtO₂ has been established. However, currently this has not demonstrated to be sufficiently robust for the non-invasive cerebral oxygenation measurements to replace the existing invasive gold standard in clinical practice.

Author disclosure statement

None to disclose

References

1. Manley, G.T. and Maas, A.I. (2013). Traumatic brain injury: an international knowledge-based approach. *Jama* 310, 473-474.
2. Tisdall, M.M. and Smith, M. (2007). Multimodal monitoring in traumatic brain injury: current status and future directions. *Br J Anaesth* 99, 61-67.
3. Munch, E., Weigel, R., Schmiedek, P. and Schurer, L. (1998). The Camino intracranial pressure device in clinical practice: reliability, handling characteristics and complications. *Acta Neurochir (Wien)* 140, 1113-1119; discussion 1119-1120.
4. Chesnut, R.M., Temkin, N., Carney, N., Dikmen, S., Rondina, C., Videtta, W., Petroni, G., Lujan, S., Pridgeon, J., Barber, J., Machamer, J., Chaddock, K., Celix, J.M., Cherner, M., Hendrix, T. and Global Neurotrauma Research, G. (2012). A trial of intracranial-pressure monitoring in traumatic brain injury. *N Engl J Med* 367, 2471-2481.
5. Pascual, J.L., Georgoff, P., Maloney-Wilensky, E., Sims, C., Sarani, B., Stiefel, M.F., LeRoux, P.D. and Schwab, C.W. (2011). Reduced brain tissue oxygen in traumatic brain injury: are most commonly used interventions successful? *The Journal of trauma* 70, 535-546.
6. Stiefel, M.F., Spiotta, A., Gracias, V.H., Garuffe, A.M., Guillaumondegui, O., Maloney-Wilensky, E., Bloom, S., Grady, M.S. and LeRoux, P.D. (2005). Reduced mortality rate in patients with severe traumatic brain injury treated with brain tissue oxygen monitoring. *J Neurosurg* 103, 805-811.
7. Valadka, A.B., Goodman, J.C., Gopinath, S.P., Uzura, M. and Robertson, C.S. (1998). Comparison of brain tissue oxygen tension to microdialysis-based measures of cerebral ischemia in fatally head-injured humans. *Journal of neurotrauma* 15, 509-519.
8. Ghosh, A., Elwell, C. and Smith, M. (2012). Review article: cerebral near-infrared spectroscopy in adults: a work in progress. *Anesthesia and analgesia* 115, 1373-1383.
9. Davies, D.J., Su, Z., Clancy, M.T., Lucas, S.J., Dehghani, H., Logan, A. and Belli, A. (2015). Near-Infrared Spectroscopy in the Monitoring of Adult Traumatic Brain Injury: A Review. *Journal of neurotrauma* 32, 933-941.
10. Sen, A.N., Gopinath, S.P. and Robertson, C.S. (2016). Clinical application of near-infrared spectroscopy in patients with traumatic brain injury: a review of the progress of the field. *Neurophotonics* 3, 031409.
11. White, B.R. and Culver, J.P. (2010). Quantitative evaluation of high-density diffuse optical tomography: in vivo resolution and mapping performance. *Journal of biomedical optics* 15, 026006.
12. Boas, D.A., Dale, A.M. and Franceschini, M.A. (2004). Diffuse optical imaging of brain activation: approaches to optimizing image sensitivity, resolution, and accuracy. *NeuroImage* 23 Suppl 1, S275-288.
13. Torricelli, A., Contini, D., Pifferi, A., Caffini, M., Re, R., Zucchelli, L. and Spinelli, L. (2014). Time domain functional NIRS imaging for human brain mapping. *NeuroImage* 85 Pt 1, 28-50.

14. Minagawa-Kawai, Y., Mori, K., Hebden, J.C. and Dupoux, E. (2008). Optical imaging of infants' neurocognitive development: recent advances and perspectives. *Dev Neurobiol* 68, 712-728.
15. Knopp, J.A. and Longmuir, I.S. (1972). Intracellular measurement of oxygen by quenching of fluorescence of pyrenebutyric acid. *Biochim Biophys Acta* 279, 393-397.
16. Helliwell, R. (2009). Advances in brain tissue oxygen monitoring: Using the Licox system in neurointensive care. *British Journal of Neuroscience Nursing* 5, 22-24.
17. Wilensky, E.M., Bloom, S., Leichter, D., Verdiramo, A.M., Ledwith, M., Stiefel, M., LeRoux, P. and Grady, M.S. (2005). Brain tissue oxygen practice guidelines using the LICOX CMP monitoring system. *The Journal of neuroscience nursing : journal of the American Association of Neuroscience Nurses* 37, 278-288.
18. Narotam, P.K., Morrison, J.F. and Nathoo, N. (2009). Brain tissue oxygen monitoring in traumatic brain injury and major trauma: outcome analysis of a brain tissue oxygen-directed therapy. *J Neurosurg* 111, 672-682.
19. Clancy, M., Belli, A., Davies, D., Lucas, S.J.E., Su, Z.J. and Dehghani, H. (2015). Comparison of Neurological NIRS signals during standing Valsalva maneuvers, pre and post vasopressor injection. In: *Diffuse Optical Imaging V*. Dehghani, H., Taroni, P. (eds). Spie-Int Soc Optical Engineering: Bellingham.
20. Gopinath, S.P., Robertson, C.S., Grossman, R.G. and Chance, B. (1993). Near-infrared spectroscopic localization of intracranial hematomas. *J Neurosurg* 79, 43-47.
21. Kahraman, S., Kayali, H., Atabey, C., Acar, F. and Gocmen, S. (2006). The accuracy of near-infrared spectroscopy in detection of subdural and epidural hematomas. *The Journal of trauma* 61, 1480-1483.
22. Weatherall, A., Skowno, J., Lansdown, A., Lupton, T. and Garner, A. (2012). Feasibility of cerebral near-infrared spectroscopy monitoring in the pre-hospital environment. *Acta Anaesthesiol Scand* 56, 172-177.
23. Genbrugge, C., Meex, I., Boer, W., Jans, F., Heylen, R., Ferdinande, B., Dens, J. and De Deyne, C. (2015). Increase in cerebral oxygenation during advanced life support in out-of-hospital patients is associated with return of spontaneous circulation. *Critical care (London, England)* 19, 112.
24. McMahan, N., Hogg, L.A., Corfield, A.R. and Exton, A.D. (2012). Comparison of non-invasive and invasive blood pressure in aeromedical care. *Anaesthesia* 67, 1343-1347.
25. Vos, J.J., Poterman, M., Mooyaart, E.A., Weening, M., Struys, M.M., Scheeren, T.W. and Kalmar, A.F. (2014). Comparison of continuous non-invasive finger arterial pressure monitoring with conventional intermittent automated arm arterial pressure measurement in patients under general anaesthesia. *Br J Anaesth* 113, 67-74.
26. Bekar, A., Dogan, S., Abas, F., Caner, B., Korfali, G., Kocaeli, H., Yilmazlar, S. and Korfali, E. (2009). Risk factors and complications of intracranial pressure monitoring with a fiberoptic device. *J Clin Neurosci* 16, 236-240.
27. Guyot, L.L., Dowling, C., Diaz, F.G. and Michael, D.B. (1998). Cerebral monitoring devices: analysis of complications. *Acta Neurochir Suppl* 71, 47-49.
28. Kasotakis, G., Michailidou, M., Bramos, A., Chang, Y., Velmahos, G., Alam, H., King, D. and de Moya, M.A. (2012). Intraparenchymal vs extracranial ventricular

drain intracranial pressure monitors in traumatic brain injury: less is more?

Journal of the American College of Surgeons 214, 950-957.

29. Sussman, E.S., Kellner, C.P., Nelson, E., McDowell, M.M., Bruce, S.S., Bruce, R.A., Zhuang, Z. and Connolly, E.S., Jr. (2014). Hemorrhagic complications of ventriculostomy: incidence and predictors in patients with intracerebral hemorrhage. J Neurosurg 120, 931-936.

30. Leal-Noval, S.R., Cayuela, A., Arellano-Orden, V., Marin-Caballo, A., Padilla, V., Ferrandiz-Millon, C., Corcia, Y., Garcia-Alfaro, C., Amaya-Villar, R. and Murillo-Cabezas, F. (2010). Invasive and noninvasive assessment of cerebral oxygenation in patients with severe traumatic brain injury. Intensive Care Med 36, 1309-1317.

31. Clancy, M., Belli, A., Davies, D., Lucas, S.J.E., Su, Z.J. and Dehghani, H. (2015). Monitoring the Injured Brain - Registered, patient specific atlas models to improve accuracy of recovered brain saturation values. In: *Diffuse Optical Imaging V*. Dehghani, H., Taroni, P. (eds). Spie-Int Soc Optical Engineering: Bellingham.

Patient	Surgery prior to monitoring? (Y/N)	AUROC	Discriminatory performance (severe hypoxia)
3	Y	0.68	Relatively poor
5	N	0.7	Moderate
6	N	0.81	Moderate to Good
7	Y	0.71	Moderate
9	N	0.88	Moderate to Good
10	N	0.841	Moderate to Good
11	Y	0.74	Moderate
12	N	0.748	Moderate
14	N	0.685	Relatively poor

Patient	Surgery prior to monitoring? (Y/N)	AUROC	Discriminatory performance (moderate hypoxia)
3	Y	0.731	Moderate
5	N	0.576	Poor
6	N	0.68	Moderate
7	Y	0.774	Moderate
9	N	0.905	Good
10	N	0.771	Moderate
13	N	0.591	Poor