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Non-Invasive Techniques for Multimodal Monitoring In Traumatic Brain Injury: Systematic Review And Meta-Analysis

María Roldán, Tomas Ysehak Abay, and Panayiotis A. Kyriacou

Abstract

Monitoring brain oxygenation and intracranial pressure non-invasively and continuously is of paramount importance in traumatic brain injury (TBI). The primary motivation of this study was to identify and provide robust evidence of the most effective techniques for the non-invasive multimodal monitoring for traumatic brain injury. Two reviewers independently searched PubMed, Embase, Scopus, the Cochrane Library, and the Web of Science between January 15, 2010, and January 22, 2020. Cohort studies assessing correlation or accuracy of non-invasive techniques for intracranial pressure (ICP) and/or brain oxygenation monitoring in TBI patients were included. The Newcastle–Ottawa Scale was used to assess the methodological quality of the studies. PROSPERO registration ID is CRD42020164739. Eight out of the 12 studies selected focused on the non-invasive measurement of ICP. Near-Infrared spectroscopy was the main technology for brain oxygenation, whereas ultrasound-based techniques were also used for ICP monitoring. $PbtO_2$ monitoring through near-infrared spectroscopy showed low correlation and limited accuracy in detecting hypoxic events. A meta-analysis on non-invasive ICP monitoring revealed a strong pooled correlation coefficient of 0.725 (95 % confidence interval [CI]: 0.450–0.874; I^2 91.31%) between transcranial Doppler and the gold standard ICP monitoring. The current meta-analysis has shown that the two most prominent and widely used technologies for non-invasive monitoring in TBI are near-infrared spectroscopy and transcranial Doppler. Both techniques could be considered for the future development of a single non-invasive and continuous multimodal monitoring device for TBI.

Keywords: brain oxygenation; intracranial pressure; multimodal monitoring; non-invasive techniques; traumatic brain injury

Introduction

Traumatic brain injury (TBI) is defined as an alteration in brain function pathology caused by an external force.[1] TBI can be categorized as mild, moderate, or severe, and it is often caused by road accidents, falls, or violent acts.[1–3] It is estimated that every year there are 50,000,000 new cases of TBI worldwide, with one person dying every 10 min, and TBI being the most dominant cause of neurological disabilities.[4] The economic burden of the treatment and rehabilitation of TBI patients is significant, and is often related to direct hospital treatment, without considering productivity loss, disability, and reduction of patients and caregivers' quality of life.[5]

TBIs can alter cerebral autoregulation as well as increasing intracranial pressure (ICP) and reducing cerebral perfusion pressure (CPP), thus potentially leading to brain hypoxia if not promptly treated.[6–8] Management of TBI patients aims at lowering mortality and improving neurological outcome by decreasing ICP (i.e., increase in CPP) and by increasing brain oxygenation.[9] These two variables (ICP and brain oxygenation) are considered to be the main biomarkers for guiding treatment of TBI patients and for monitoring disease severity. Continuous and simultaneous monitoring of both biomarkers could significantly contribute to a better monitoring and treatment of TBI, which can result in lower mortality and disability outcomes.[6] In current clinical practice, these biomarkers are mainly measured by invasive methods, thus introducing additional risks for the patient and relying on neurosurgical expertise, which could potentially delay treatment.[10,11]

Monitoring brain oxygenation and ICP non-invasively and continuously could provide significant benefits by providing safe and easily obtainable clinical information in the first hours after trauma.[12] Although yet not adopted in standard clinical practice, several techniques such as near infrared spectroscopy (NIRS), transcranial Doppler (TCD), and optical nerve sheet diameter (ONSD) have been investigated in the last decade in order to

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respond to the current demand for non-invasive monitoring of brain oxygenation and ICP. Previous reviews summarized these efforts, but results on the efficacy of these techniques are scattered and differ among each other.[13–16]

This systematic review and meta-analyses aims to assess how correlated or accuarate are non-invasive and invasive techniques used for ICP and brain oxygenation monitoring in TBI patients. To date, no such systematic review has been published in the literature. By analyzing the reported correlation and accuracy, it is hoped that this systematic review will help in identifying the most promising, optimal. and impactful non-invasive technique(s) for monitoring and assessing TBI.

Methods

Protocol and registration

This review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[17] The study was funded by City University of London and there were no competing interests. The protocol was designed following the Cochrane Handbook for Systematic Reviews of Interventions[18] and it was registered at the International prospective register of systematic reviews in PROSPERO before the data extraction started (ID: CRD42020164739).

Information sources and search

The reviewers (M.R., T.Y.A.) performed a systematic search of PubMed, Embase, Scopus, The Cochrane Library, and Web of Science between January 15, 2010, and January 22, 2020, for studies that reported ICP and/or brain oxygenation monitoring in TBI patients. In consultation with the Institutional librarian with experience in conducting systematic review searches, the search strategy was designed, and it was focused on the intersection of keywords traumatic brain injury, intracranial pressure, brain tissue oxygen, non-invasive, monitoring, correlation, and accuracy with numerous variations and MeSH/Emtree indexing terms to include all potentially eligible studies.

Eligibility criteria and study selection

After the removal of duplicates, the two independent reviewers (M.R., T.Y.A.) reviewed the titles and abstracts of potentially eligible articles. Studies that satisfied the inclusion criteria were retrieved for full-text assessment. The inclusion criteria were as follows: (1) studies on patients diagnosed with TBI; (2) comparison of non-invasive ICP and/or brain oxygenation monitoring with invasive ICP and/or brain oxygenation monitoring, respectively; (3) studies reporting correlation and/or accuracy; (4) articles with accessible full text; and (5) cohort studies. The exclusion criteria were as follows: (1) reviews, conference proceedings, case reports, letters, editorials, animal and *in vitro* studies, case-control studies, summaries, expert opinions, and comments; (2) studies on patients with open fontanelle; (3) medical imaging studies; (4) insufficient data; (5) duplicate publications of the same data set or non-independent data; (5) studies misreporting data; and (6) articles published in a language other than English.

Data collection process and data items

Any disagreement between the two reviewers (M.R., T.Y.A.) during the full-text review was resolved by an independent arbitrator (P.A.K.). The main reviewers (M.R., T.Y.A.) independently completed data extraction and quality assessment using a data extraction MS Excel® sheet and quality assessment form. The following variables were extracted: bibliometric characteristics, variable monitored, non-invasive and invasive monitoring tool, number of patients, inclusion and exclusion criteria, mean age, sex proportion, cause of TBI, TBI severity according to the Glasgow Coma Scale (GCS), monitoring time, correlation and/or accuracy between non-invasive and invasive techniques, and thresholds relating to the biomarker used.

Risk of bias in individual studies

Quality assessment was completed using the Newcastle–Ottawa Scale, which evaluates the quality of cohort studies.[19] With this quality assessment tool, three domains were assessed: selection, comparability, and outcome. Each domain was scored with one to two stars, which classifies studies quality as good, fair, or poor; following the Agency for Healthcare Research and Quality Standards.[19] Only low-risk-bias studies were included in the synthesis.

Summary measures, synthesis of results, and risk of bias across studies

Aggregate data were used and both narrative and quantitative syntheses were performed. Even if the included studies were not sufficiently homogenous, a quantitative synthesis was conducted to identify the reasons for heterogeneity.

The level of consistency required for the narrative synthesis was based on the quality assessment results. The data that were synthesised include the different non-invasive techniques used for ICP or brain oxygenation monitoring in TBI patients. The outcomes reported in this review include correlation and accuracy of non-invasive techniques compared with invasive monitoring tools for ICP and/or brain oxygenation.

Statistical analysis

Statistical aspects of the exploratory meta-analyses were performed using MedCalc software. The correlations between non-invasive and invasive techniques for each variable were measured by r values after converting the Fisher's z values back into correlation coefficients.[20,21] The pooled correlation for ICP monitoring was estimated using a random-effects model. In terms of statistical heterogeneity, a quantitative analysis was performed using the I^2 test[18]; with an $I^2 > 40\%$ indicating heterogeneity.[18] A funnel plot was also used to analyze and detect systematic heterogeneity among the studies.

Results

Study selection

The flow diagram in Figure 1 illustrates the process of identification, screening, eligibility, and inclusion of publications in this systematic review. The search identified 228 potentially relevant citations, and 20 (8.77%) publications out of these, which met the selection criteria after assessing titles and abstracts, were selected for full-text review. Upon reviewing the full text of the 20 selected studies, only 12 (60%) fulfilled the inclusion criteria for assessing the correlation or accuracy between non-invasive and invasive methods for ICP or brain oxygenation monitoring in TBI patients. None of the selected articles reported a multimodal non-invasive monitoring technique to evaluate both variables simultaneously.

Risk of bias within studies

From the 20 studies selected after the title and abstract screening,[8–11,22–37] 3 were excluded after full-text reading as they did not fit the selection criteria.[8,33,37] Both reviewers (M.R., T.Y.A.) agreed on the quality assessment results presented in Figure 2. Twelve articles were classified as ''good quality'' and five were

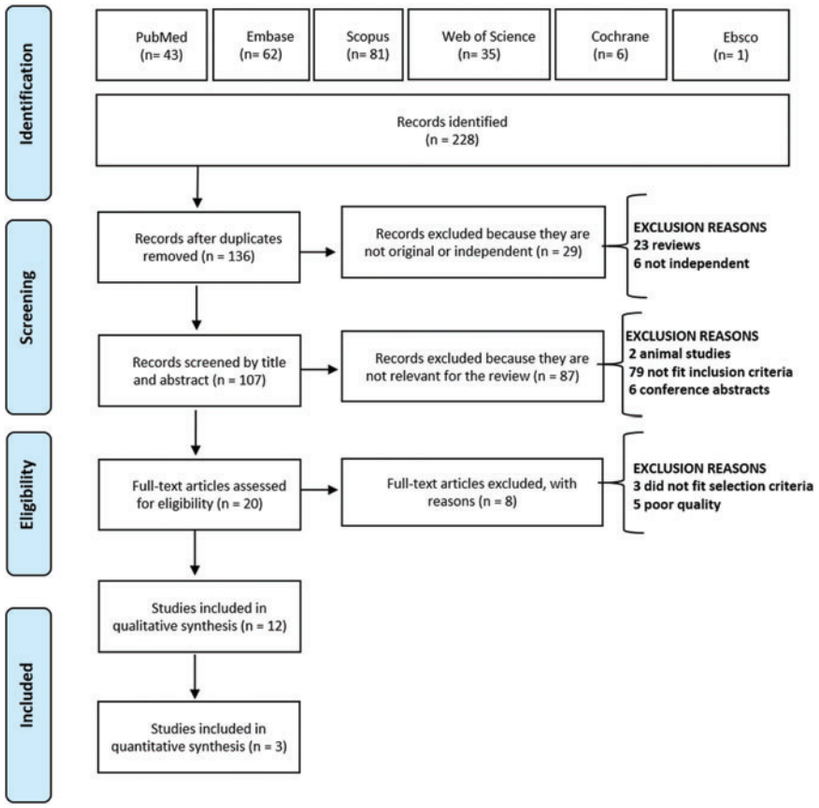

FIG. 1. Studies selection flow diagram describing the identification, screening, eligibility, and inclusion of the systematic review. Color image is available online.

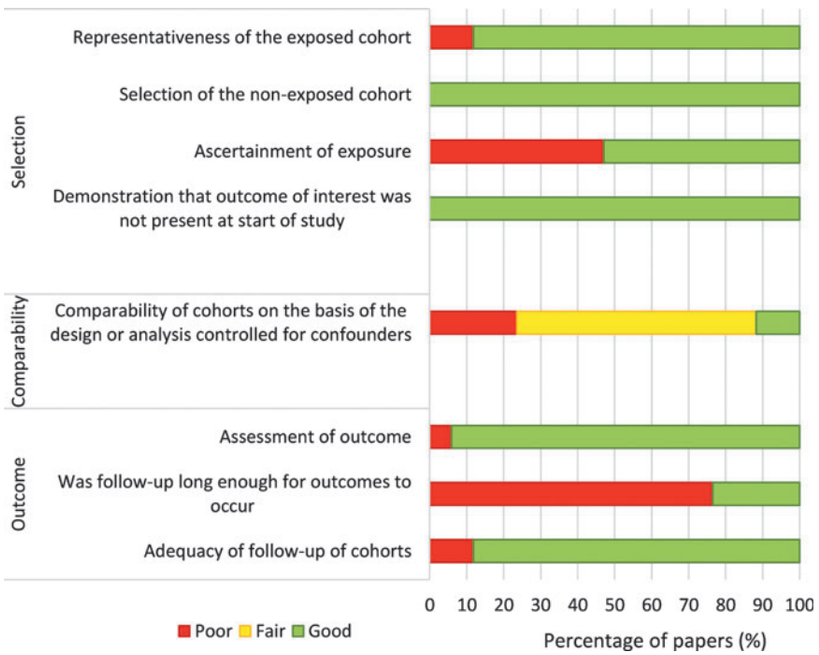

FIG. 2. Quality assessment results. Color image is available online.

classified as ''poor quality.'' The main reasons the quality was poor were: (1) user-dependent data in TCD measurements affecting the ascertainment of exposure; (2) the design or analysis of the study did not control the confounders; (3) the monitoring window expected by the reviewers (M.R., T.Y.A.) was <48 h, or it was not reported.

Study characteristics

A total of 78 TBI patients, with a weighted average age of 33.2 years, received non-invasive and invasive brain oxygenation monitoring.[9,11,23,24] Most of these patients had moderate to severe TBI. In the group of ICP monitoring, a total of 701 patients with severe TBI with a weighted average age of 31 years received non-invasive and invasive ICP monitoring.[10,25–31] Table 1 depicts the bibliometric, demographic, and technological characteristics of each study, while the synthesis presented in the next section mainly describes the outcomes found in the assessment of non-invasive techniques.

Results of individual studies

Four of the publications included were studies related to brain oxygen monitoring.[9,11,23,24] Leal-Noval and coworkers,[24] used the NIRS monitor INVOS 5100 (Medtronic, MN, USA) for non-invasive ipsilateral oxygen measurements and compared the measures with the Licox (Integra NeuroSciences, England) $PbtO_2$ catheter in 27 patients with TBI. The INVOS 5100 NIRS uses light at two different wavelengths (730 and 810 nm) to maximize the absorption contribution of oxygenated and deoxygenated hemoglobin while minimizing the absorption contribution of other compounds.[38] The continuous-wave of near-infrared light can penetrate several millimeters into cerebral tissue, travelling from the sensor's light-emitting diode to either a proximal or a distal photodetector. The light detected by the distal photodetector travels deeper into the tissue, while the light collected by the proximal photodetector detects signals that only pass through the scalp. The signals from the distal and proximal photodetectors are then analyzed in order to estimate the brain tissue oxygenation index (rSO_2).[24,39]

Normal $PbtO_2$ is in the range of 35–50 mmHg, whereas ischemic thresholds have been suggested between 5 and 20 mm Hg, with values <20 mm Hg being associated with worse outcome after TBI.[6] The implementation of NIRS had no significant results with a $PbtO_2 \leq 15$ mm Hg threshold based on the study by Leal-Noval and coworkers. But the rSO_2 accuracy improved when the $PbtO_2$ threshold was reduced to 12 mm Hg, resulting in an area under the curve (AUC) of 0.82 with a sensitivity and specificity of 73% and 86%, respectively.[24] These results suggest that rSO_2 is not capable of predicting the early stages of hypoxia.

Likewise, Davies and coworkers,[9] compared the OxiplexTS (ISS, Illinois, USA) with the Neurovent-PTO (Raumedic, Germany and Mills River, USA) in 16 patients diagnosed with TBI. The OxiplexTS is a non-invasive diagnostic tool using frequency-domain NIRS (FD-NIRS).[9] Continuous-wave NIRS devices emit light into the target tissue at a constant intensity, whereas FD-NIRS continuously modulates this intensity.[9] Oxygenated and deoxygenated hemoglobin concentrations are determined from the measured intensity and phase shift, allowing the calculation of StO_2 or rSO_2.[38] The results by Davies and coworkers indicate that FD-NIRS does not provide enough reproducibility in its ability to predict changes in $PbtO_2$ in order to replace the current invasive gold standard (fluorescence-quenching sensor or Clark electrodes placed in the cerebral cortex). Also, the OxiplexTS has almost the same predictive power seen in similar investigations utilizing continuous-wave NIRS instruments.[9]

Meanwhile, Rosenthal and coworkers compared the CerOx 3110 (Ornim Medical Ltd, Dedham, USA) with the Licox in 18 patients.[23] The CerOx 3110 uses Ultrasound Targeted NIRS principles (UT-NIRS), in which near-infrared light illuminates the tissue while brief pulses of ultrasound waves induce a local and artificial modulation in the detected light intensity. By adopting this method, the device can localize and select the signal originating from a specific volume of brain tissue.[23] The researchers found a significant and strong correlation between the UT-NIRS and the ipsilateral $SjVO_2$, even when the former was adjusted by multiple measurements, but $PbtO_2$ measurements were not significantly related.[23]

The last article included in the current review assessing brain oxygenation is from Sokoloff and coworkers, who also used the Licox, but, in this case, the comparison was made with the mean ipsilateral flow velocity (Vmean) of the middle cerebral arteries (MCA) assessed with a two-dimensional (2D) color-coded TCD in 17 patients.[11] The authors found a limit of 40 cm/sec to correlate low cerebral blood flow (CBF) velocity in the MCA with brain hypoxia ($PbtO_2 < 20$ mm Hg), which could be predicted during the first 7 h after TBI. TCD's sensitivity and specificity diminished as the time after the trauma increased. Despite a statistically significant correlation between $PbtO_2$ and Vmean, this association does not seem to be clinically relevant according to Sokoloff and coworkers.[11]

Eight of the 12 articles compared invasive and non-invasive techniques for ICP monitoring in TBI patients. The intraparenchymal catheter and ultrasound were the invasive and non-invasive techniques, respectively, used to measure the ICP in all the articles selected. Six articles used TCD and two articles utilized the ONSD. TCD was used to measure relative changes in flow velocity in the basal arteries of the brain. Spectral analysis was then used to obtain the following parameters: peak systolic velocity (Vs), end-diastolic velocity (Vd), pulsatility index (PI), and time-averaged mean maximum velocity (Vmean).[40]

Four of the eight ICP-related articles included in this review utilized a DWL TCD transducer (Compumedics, Australia) for monitoring the blood flow in the MCA.[26–28,31] Non-invasive ICP was estimated by Huang and coworkers and Rasulo and coworkers, based on mean arterial pressure (MAP) and assessing the proportion of the end-diastolic velocity and the mean flow velocity of both MCAs.[26,31] Both articles concluded that non-invasive monitoring of cerebral hemodynamics may be used as an effective real-time ICP monitoring tool for TBI patients.[26,31] Budohoski and coworkers also input MCA blood flow and MAP into a black-box plug-in of ICM + software to estimate ICP non-invasively. This mathematical model showed an overall good correlation with the invasive measurements of ICP, with an optimal non-prediction cut-off in 17 mm Hg.[28] Likewise, Gura and coworkers used their own non-invasive ICP regression model from the TCD-derived pulsatile index (PI), finding a significant and strong correlation between PI and ICP in the first 5 days after trauma.[27]

Three studies used different TCD probes than those previously mentioned. Martin and coworkers used a 7.5 MHz Vivid I ultrasound probe (GE Healthcare, Boston, MA, USA), and Brandi and coworkers 2010 used the Sonoline G40 (Siemens, San Jose, CA, USA), whereas Melo and coworkers used the Waki 1-TC (Atys medical, France). In these three studies, the authors calculated the PI multiple times (PI = sV−dV/mV) and compared those measurements with intraparenchymal ICP values.[10,29,30] Martin and coworkers reported a PI that did not correlate with ICP (coefficient not reported), and an AUC of 0.67 defining a threshold for hypertension

Table 1. Description of the 12 Included Studies Comparing Non-Invasive and Invasive Techniques for ICP or Brain Oxygenation Monitoring in Traumatic Brain Injury

Author	*Year*	*Country*	*Variable*	n	*Non-invasive commercial device*	*Non-invasive technique*	*Invasive technique*	*Mean age*	*Sex M/F*	*GCS*	*Follow time*	*Losses*	*Outcome*	*Value*
Leal-Noval et al.[24]	2010	Spain	Brain O_2	27	INVOS 5100	NIRS	$PbtO_2$ (Brain)	33.0	NR	6.0	16 h	5	AUC SE-SP (%)	0.82 73–86
Davies et al. [9]	2019	UK	Brain O_2	16	Oxiplex TS	FD-NIRS	$PbtO_2$ (Brain)	50.5	NR	8.0	<30.5 h	4	AUC	Per patient
Rosenthal et al. [23]	2014	Israel	Brain O_2	18	CerOx 3110	UT-NIRS	$SjvO_2$ (Jugular)	45.3	2.6	5.0	2 h/d	0	Correlation	0.6
Sokoloff et al.[11]	2019	Canada	Brain O_2	17	NR	MCA TCD	$PbtO_2$ (Brain)	44.0	4.7	NR	5 d	0	Correlation SE-SP (%)	0.41 38–58
Soliman et al.[25]	2018	Saudi Arabia	ICP	40	HD11XE	ONSD	Intraparenchymal catheter	37.0	2.6	4.5	48 h	0	Correlation	0.74
Martin et al. [10]	2019	France	ICP	58	Vivid I	ONSD MCA TCD	Intraparenchymal catheter	36.5	5.8	6.0	24 h	4	AUC AUC	0. 73 0. 67
Rasulo et al. [31]	2017	Italy	ICP	38	DWL	MCA TCD	Intraparenchymal or ventricular catheter	57.8	NR	NR	3h	0	AUC	0.96
Huang et al.[26]	**2012**	**China**	**ICP**	**52**	**DWL**	**MCA TCD**	**Intraparenchymal catheter**	**37.0**	**4.8**	**7.0**	**5–7 d**	**0**	**Correlation**	**0.881**
Gura et al.[27]	**2011**	**Turkey**	**ICP**	**52**	**DWL**	**MCA TCD**	**Intraparenchymal catheter**	**33.5**	**4.2**	**7.3**	**5 d**	**0**	**Correlation**	**0.779**
Budohoski et al.[28]	**2012**	**UK**	**ICP**	**292**	**DWL**	**MCA TCD**	**Intraparenchymal catheter**	**33.0**	**NR**	**6.0**	**74.8 m**	**0**	**Correlation**	**0.510**
Brandi et al.[30]	2010	Switzerland	ICP	45	Sonoline G40	MCA TCD	ICP probe	37.0	4.6	NR	14 d	8	Δ $\bar{x}\pm$SD	3.2 ± 12.6
Melo et al.[29]	2011	France	ICP	124	Waki 1-TC	MCA TCD	Intraparenchymal catheter	07.6	2.4	6.0	20 m	7	SE-SP (%)	94-41

The studies in bold text have been included in the meta-analysis. The correlation values were not adjusted by confounders, because each study adjusted the coefficient by different variables.

ICP, intracranial pressure; FD-NIRS, frequency domain near infrared spectroscopy; MCA, middle cerebral artery; TCD, transcranial Doppler; AUC, area under the curve; SE-SP, sensibility and specificity; $\Delta\bar{x}$, ean difference; SD, standard deviation; NR, not reported.

(>20 mm Hg) on PI >1.4.[10,41] Brandi and coworkers used the Bellner equation[42] to calculate a non-invasive ICP value based on the PI, establishing a not significant difference of means between invasive and non-invasive measurements,[30] whereas Melo and coworkers also looked for the accuracy of the PI to identify ICP levels >20 mm Hg. Melo's article considered an altered TCD when the end-diastolic velocity was less than 25 cm/sec or when the PI was >1.31. The thresholds above had an excellent sensitivity but low specificity in identifying intracranial hypertension.[29]

Two of the articles included in this review utilized the ONSD as a non-invasive measurement of ICP. As the dura matter contains cerebrospinal fluid and is contiguous to the optic nerve sheath, Soliman and coworkers used a HD11XE transducer (Philips, Amsterdam) to assess whether the ONSD was correlated with increases in invasive ICP values. Soliman and coworkers found that ONSD was strongly correlated with invasive ICP monitoring, even when the prediction model was adjusted for sex and weight.[25] Likewise, Soliman and coworkers' article defined elevated ICP as occurring when the diameter was >6.4 mm, resulting in good accuracy results for the cutoff value.[25] Similarly, Martin and coworkers measured ONSD using a 7.5 M Hz Vivid I probe and defined an intracranial hypertension parameter of 5.6 mm. Martin and coworkers' article also reports good accuracy results in predicting elevated ICP in the first 48 h after TBI, with an AUC of 0.73.[10]

Synthesis of results

The current review analyzed the use of NIRS to non-invasively and continuously monitor of cerebral oxygenation in TBI patients. Although NIRS appears to be the most promising technique to measure cerebral oxygenation non-invasively and continuously, the correlation and accuracy comparison with the invasive techniques highlighted the greater variability of NIRS measurements.[9,11,23,24] Likewise, this review analyzed the use of TCD to non-invasively and continuously monitor ICP in TBI patients. The correlation and accuracy comparison against the standardized use of intraparenchymal ICP sensors show promising results for the prediction of ICP.[26–29,31]

A meta-analyses for the brain oxygenation monitoring group was not completed because of significant methodological heterogeneity among the included studies. The four articles in this subgroup used four different non-invasive techniques, which does not allow for a quantitative synthesis and comparison among their results.[9,11,23,24] In contrast, mostly all of the ICP articles were methodologically homogenous. However, a quantitative comparison among all of them was not feasible because of the different types of outcomes reported. in In the current review, Melo and coworkers presented the only evidence that assessed pediatric patients (mean age = 7.6 ± 4.4 years).[29] Only three out of the eight articles that made comparisons among techniques for ICP monitoring had comparable outcomes. The quantitative synthesis in the next section put together this evidence through an exploratory meta-analysis to find a pool correlation coefficient. Huang and coworkers, Gura and coworkers, and Budohoski and coworkers reported the correlation between DWL and the intraparenchymal probe for ICP monitoring in TBI patients.[26–28]

According to these three authors, blood pressure and flow velocities are the indirect non-invasive measurements required for ICP calculation. A total of 396 severe TBI patients within a mean age range of 33–37 years and with a median GCS of 7 were followed up for a maximum time period of 7 days. The meta-analyses results presented in Figure 3a show a pooled correlation coefficient

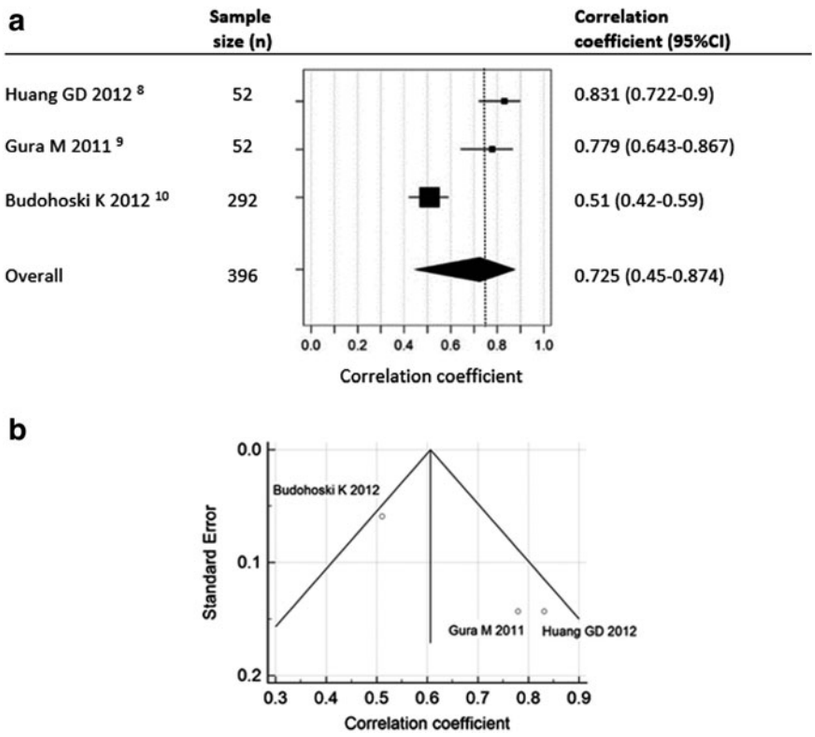

FIG. 3. Forest plot **(a)** and funnel plot **(b)** for the correlation coefficients between non-invasive and invasive intracranial pressure (ICP) monitoring in studies by Huang and coworkers, Gura and coworkers, and Budohoski and coworkers.[26–28]

of 0.725 (95% confidence interval [CI]: 0.450–0.874; I^2 91.31%) corresponding to a random effects analysis. A random effects analysis was used because of the high statistical heterogeneity among studies (Fig. 3a). According to this, a non-invasive ICP value based on blood pressure and the MCA's flow velocities measured by TCD significantly correlated with invasive ICP measurements ($p < 0.001$).

Risk of bias across studies

Finally, the asymmetry in the funnel plot in Figure 3b indicates the heterogeneity induced by the study sizes and the outcomes. In the study by Budohoski and coworkers, the sample size was larger than those in the other two studies by Huang and coworkers and Gura and coworkers ($n = 292$ vs. $n = 52$ for both Huang and coworkers and Gura and coworkers respectively).[26–28] In addition, the monitoring lasted for a shorter time, compared with the monitoring time of the other two studies, resulting in smaller effect estimates and a higher standard error. As all studies fell within the triangular region, no subgroup analysis was required.

Discussion

Summary of evidence

This systematic review identified TCD and NIRS as the main non-invasive techniques used currently to assess changes in ICP and brain oxygenation in TBI patients. Eight out of the 12 studies included in this review focused on the non-invasive measurement of ICP, indicating that this biomarker has attracted most of the interest in the last decade.

When compared with $PbtO_2$, NIRS showed low correlation and limited accuracy in detecting hypoxic events.[9,23,24] As suggested by Davies and coworkers, these results may be caused by limitations of the technique in distinguishing the oxygenation of the different layers of tissue that are interrogated when shining near-infrared light transcutaneously.[9] Interestingly, it appears that ipsilateral measurement by ultrasound-targeted NIRS can provide promising correlation with $SjVO_2$.[23] However, there is still a need for more clarity as to whether these results are caused by the benefits of combining ultrasound and NIRS or by the reference measurements (i.e., $SjVO_2$ vs. $PbtO_2$).

TCD was the technique most used to assess ICP non-invasively, where different algorithms have been developed to estimate ICP from TCD signals. The methods based on MAP changes[26,28,31] or on the features of the pulse signals[27] seem to be the most robust in predicting ICP. Compared with brain oxygenation, the analysis of the results for non-invasive ICP, either qualitative or quantitative, are simplified by the more standardized use of intraparenchymal ICP sensors as a reference measure. Although TCD has shown promising results, further efforts are needed to reduce risks of bias, as the technique is heavily operator dependent and mostly based on intermittent measurements.

The exploratory meta-analyses included with this systematic review allowed the synthesis of correlation results between invasive and non-invasive measurements of ICP. However, only three studies fit the inclusion criteria for a meta-analysis, and it was difficult to infer an exhaustive conclusion from this limited number of studies. All three articles investigated the measurement of ICP through TCD,[26–28] whereas a meta-analysis on brain oxygenation techniques could not be performed because of methodological heterogeneity. Although a relatively small number of studies were included, the results from the meta-analysis are in line with correlation values reported previously in similar reviews.[13–16] Even if sharing similarities, these reviews cannot be fully compared with the current systematic review, because of methodological differences.

The studies included in this systematic review presented a significant degree of heterogeneity, which decreased the overall comparability among the results. Understandably, this resulted in the inclusion of a very limited number of studies in the meta-analyses and in the analysis of only one of the two biomarkers investigated (i.e., ICP). Therefore, it is vital to homogenize the research methods, with attention to the reported outcomes. Correlation and/or accuracy should be reported methodically, confounders controlled, reference measurements standardized, and length of monitoring defined.

The literature has indicated that there may be additional techniques that may be used to measure ICP non-invasively. Techniques such as tympanic membrane displacement or pulse phase lock loop may be adopted to measure ICP, but there is little or no evidence on their use in TBI patients. Only two studies included in this review used optical nerve sheet diameter measurements to assess ICP, but the results could not be quantitatively compared between them or with any other similar study. Also, imaging techniques were not included in this systematic review because of their intrinsic non-continuous nature.

All the studies in this review investigated populations of severe TBI patients only. Considering that brain oxygenation and ICP are often measured in this group of patients, this result is not surprising. However, most TBIs are categorized as mild to moderate, and future research on non-invasive techniques for brain oxygenation or ICP would greatly benefit these patients who often do not receive brain oxygenation or ICP monitoring.[43]

Limitations

No attempts were made to identify or translate non-English-language publications, and this may have limited the inclusion of some relevant studies in this systematic review. Also, publication bias may have occurred, because only peer-reviewed literature was included and public health reports on non-invasive monitoring in TBI may be available in the gray literature. Moreover, including only studies published since 2010 considerably restricted the number of studies analyzed in this review. However, this criterion provided the added ability to focus on the results in the literature in line with the recent technological advancements of the last decade. A minimum monitoring window of 48 h was set as one of the quality assessments in the screening of the studies. Although a length of monitoring in such studies may be limited because of technological, logistical, clinical, or ethical restrictions, a long monitoring window allows the capture of variations in the parameters measured that would be likely missed by shorter monitoring windows. This will also play an important role in the range of changes measured, if any, and will therefore provide a wider representation of correlation or accuracy in the population investigated.

A critical limitation of using correlation coefficients as the main outcome reported in the included studies is the assumption of a linear relationship between the non-invasive and invasive measurements, which may not necessarily imply agreement or accuracy between the techniques.[44] Accuracy and agreement assessments such as AUC (ROC), analysis of error, or Bland–Altman plots would have been more appropriate for the clinical parameters assessed in this review (i.e., ICP and cerebral oxygenation). However, AUC (ROC) analysis requires the selection of internal thresholds,

which may reduce the scope of technology evaluation.[44] Alternatively, Bland–Altman analysis is a simple and accurate way to assess the agreement between two clinical variables and may help clinicians to compare a new measurement method against a standard reference.[45] Regrettably, none of the articles included in this review used the Bland–Altman analysis to assess agreement between invasive and non-invasive techniques for ICP and cerebral oxygenation. Finally, the variability in the sample size and the number of studies included could have also contributed to the outcome of this systematic review.

The literature has shown the importance of multimodal monitoring in the diagnosis, prognosis, and treatment of patients with TBI.[15] However, no cohort study in the last decade has compared the correlation or accuracy of a non-invasive multimodal monitoring technique with the respective (invasive) reference measurements in TBI patients. This systematic review also identified non-invasive techniques that may be used for the multimodal, non-invasive, and continuous monitoring of brain oxygenation and ICP. Although this review identified NIRS and TCD as the current prominent non-invasive techniques for monitoring brain oxygenation and ICP, significant research is still required to collect sufficient evidence for the implementation of non-invasive multimodal monitoring technologies for TBI patients.

Conclusion

This review and meta-analysis revealed a good correlation between the non-invasive measurement of the pulsatile index by TCD and the standard invasive techniques to measure ICP. With regard to the non-invasive monitoring of brain oxygenation, NIRS showed low correlation and limited accuracy in detecting hypoxic events when compared with standard invasive $PbtO_2$ measurements. However, the variability in the methods and reported outcomes of the cohort studies assessed in this review did not offer robust conclusions on their monitoring capability. This systematic review confirms that there is noticeable work to be done in the quest for non-invasive, continuous, portable, and multimodal monitoring of brain oxygenation and ICP in TBI patients.

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