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Original Contribution

Increased prognostic accuracy of TBI when a brain electrical activity biomarker is added to loss of consciousness (LOC)

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ABSTRACT

Background: Extremely high accuracy for predicting CT+ traumatic brain injury (TBI) using a quantitative EEG (QEEG) based multivariate classification algorithm was demonstrated in an independent validation trial, in Emergency Department (ED) patients, using an easy to use handheld device. This study compares the predictive power using that algorithm (which includes LOC and amnesia), to the predictive power of LOC alone or LOC plus traumatic amnesia.
Participants: ED patients 18–85 years presenting within 72 h of closed head injury, with GSC 12–15, were study candidates. 680 patients with known absence or presence of LOC were enrolled (145 CT+ and 535 CT− patients).
Methods: 5–10 min of eyes closed EEG was acquired using the Ahead 300 handheld device, from frontal and frontotemporal regions. The same classification algorithm methodology was used for both the EEG based and the LOC based algorithms. Predictive power was evaluated using area under the ROC curve (AUC) and odds ratios.
Results: The QEEG based classification algorithm demonstrated significant improvement in predictive power compared with LOC alone, both in improved AUC (83% improvement) and odds ratio (increase from 4.65 to 16.22). Adding RGA and/or PTA to LOC was not improved over LOC alone.
Conclusions: Rapid triage of TBI relies on strong initial predictors. Addition of an electrophysiological based marker was shown to outperform report of LOC alone or LOC plus amnesia, in determining risk of an intracranial bleed. In addition, ease of use at point-of-care, non-invasive, and rapid result using such technology suggests significant value added to standard clinical prediction.

1. Introduction

It is estimated that approximately 90% of those who sustain a closed head injury who present to the ED with high GCS are referred for CT scans, and yet, the vast majority (estimated to be as high as 90%) are found to be negative for clinically important brain injury [1]. With increased awareness of unnecessary exposure to head CT and the recognition that CT scans are not sensitive to the full spectrum of TBI, the ability to improve prediction of intracranial injury in this population is an outstanding clinical need. Indicators of the risk of intracranial injury following closed head injury have been under discussion and the focus of study for several years. The history of loss of consciousness (LOC) as a diagnostic indicator for traumatic brain injury (TBI) is present in several guidelines and decision rules for CT scanning (VA DoD, CDC, CPGs). However, questions remain regarding the predictive accuracy of using LOC as a diagnostic indicator for TBI, especially in those who present with high function. Several studies have reported that LOC was not a reliable indicator of TBI [2,3]. In a multisite study of >2400 blunt head injured patients the odds ratio (OR) for CT+ findings was comparable between patients with presence or absence of LOC and post traumatic amnesia (PTA) [4]. Another multisite study with over 40 000 pediatric and adolescent patients reported that patients with a history of LOC in isolation with no other predictive factor were at very low risk for CT+ findings [5].

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Advances in signal processing technology and use of sophisticated classification methodology leveraging machine learning has greatly enhanced the clinical utility of EEG beyond that reported from conventional visual inspection of the EEG signal. In addition, these advances have enabled data acquisition devices that are handheld, use a limited montage embedded in a disposable headset (for ease of application) and with real time data quality feedback for ease of use. Studies have demonstrated the high accuracy of using a quantitative EEG (QEEG) based algorithm to predict the likelihood of CT+ findings (traumatic hematomas) in a population of high functioning (GCS 12–15) closed head injured patients [6,7]. A recent independent validation trial demonstrated extremely high accuracy of the Ahead 300 device (FDA 510(k) clearance, K161068) in predicting CT+ brain injury using an expanded QEEG based classification algorithm [8]. The current study compares the performance of the BrainScope Ahead 300 classification algorithm, which includes LOC information, to the predictive and prognostic power of using LOC alone or LOC plus traumatic Amnesia (PTA/RGA).

2. Method

2.1. Study design

This is a retrospective analysis using subjects who were participants in the B-Ahead III prospective validation study reported on in detail elsewhere [8]. The study was conducted at 11 US Emergency Departments (EDs) between February 2015 and December 2015.[1] The trial (Validation of TBI Detection System for Head Injured Patients (B-AHEAD III)) was registered on clinicaltrials.gov #NCT02367300; (June 17, 2016).

2.2. Patient selection

Patients between the ages of 18 and 85 years who presented to an ED within 72 h of suffering a closed head injury, and who had a Glasgow Coma Scale (GCS) score in the range 12–15, were candidates for study inclusion. Patients were excluded if they had scalp lacerations, skull abnormalities or clinical condition which would preclude placement of the electrodes on the forehead in the prescribed locations. Patients were also excluded if intoxicated to the point where too obtunded to participate in the study or could not give informed consent. Patients with advanced dementias, Parkinson's disease, known chronic drug or alcohol dependence (intoxication alone was not grounds for exclusion), known seizure disorder or other central nervous system disorder, were also excluded. Signed informed written consent, or in a few sites consent by proxy was obtained. Assessment of the capacity of the subject to give informed consent was performed using the Conley criteria [9].

2.3. EEG data acquisition

Five to ten (5–10) minutes of eyes closed resting EEG was acquired in the ED using the Ahead 300 handheld device. The EEG data was collected using a disposable self-adhesive headset which positioned electrodes on the standard frontal locations of the expanded International 10/20 system, and included FP1, FP2, AFz, F7, and F8, referenced to linked ears. This limited montage allows rapid application from specific regions of interest which are maximally susceptible and vulnerable to TBI [10,11]. Electrode impedances were required to be below 10 kΩ for data acquisition. EEG amplifiers had a band pass filter from 0.3 to 250 Hz (3 dB points).

2.4. Clinical data

Report of LOC at the time of injury was obtained by self-report, confirmed when available by witness (22.4%) and source verified in the ED record. In addition, demographic and additional signs and symptoms related to the state of the subject at the time of the EEG evaluation was collected using the Standard Assessment of Concussion (SAC) and Concussion Symptom Inventory (CSI). Information related to the presence of post-traumatic and retrograde amnesia was obtained from these assessments by trained research technicians.

2.5. Determination of clinical truth

In all cases referral for a CT scan was made by the ED physician at the clinical site, according to standard of care. The determination of CT scan results was made by a blinded, independent adjudication panel reading de-identified DICOM images transferred from the site. A positive scan (CT+) was prospectively defined as an adjudicated determination of the presence of intracranial injury visible on CT scan. Adjudication involved sequential evaluation by imaging specialists and physician specialist readers with image-based initial independent determination of CT+ or CT− and then adjudication of discrepant readings and adjudicated unanimity for final determinations.

Patients who were not referred for a CT scan in the judgement of the site evaluated physician were deemed negative if they had GCS = 15, had no loss of consciousness or amnesia, or had a loss of consciousness or amnesia but did not have any clinical findings from the New Orleans Criteria (NOC) (headache, vomiting, drug or alcohol intoxication, short-term memory deficits, physical evidence of trauma above the clavicles, or seizure). Details regarding this procedure are provided elsewhere [12].

2.6. Quantitative analysis of brain electrical activity

Advanced signal processing modules perform a sequence of operations on the acquired EEG. Temporal segments of EEG data suspected of being contaminated by artifact are identified, flagged and removed from the EEG stream using a suite of artifact detection algorithms. The artifact-free EEG epochs are used to compute a broad set of quantitative EEG features from the EEG power spectrum and covariance matrix, and include both linear and non-linear measures [13]. All EEG features are subjected to deterministic mathematical transform (usually log-based) to ensure Gaussianity and compared to age-expected normal values.

2.7. Classification algorithms

The likelihood that a patient was CT positive was predicted by the application of the classification algorithm described in detail elsewhere [12] and validated as part of the Ahead 300 device (FDA 510(k) clearance, K161068). This algorithm was independently developed using a Least Absolute Shrinkage and Selection Operator (LASSO) methodology, which uses a regularized logistic regression model [14]. The classifier consists of a weighted combination of selected linear and nonlinear EEG features, enhanced with selected clinical features. The features which are inputs to the algorithm were selected to optimally reflect traumatic structural brain injury. The details of the process used in classifier development are presented elsewhere [7]. It is important to note that the classification algorithm was finalized a priori and applied in this independent population to classify each subject's likelihood of being CT+. For the purpose of this study, the same methodology was followed to derive an additional classifier function using only LOC and amnesia information and did not include any EEG features.

[1] The 11 ED sites included: Washington University Barnes Jewish Medical Center, St. Louis, MI, Detroit Receiving Hospital, Detroit, MI, University of Virginia Health System, Charlottesville, VA, R. Adams Cowley Shock Trauma Center, Baltimore, MD, Baylor University Medical Center, Dallas, TX, Emory University Grady Hospital, Atlanta, GA, Wayne State University Sinai-Grace Hospital Detroit, MI, University of Rochester Medical Center, Rochester, NY, Allegheny General Hospital, Pittsburgh, PA, University of Texas Memorial Hermann Hospital, Houston, TX, and Hartford Hospital, Hartford, CT.

2.8. Statistical analysis

The ROC curve is a graphical representation of the performance of the classifier or the predictor as the classification threshold is varied. The area under the ROC curve (AUC) for the two classifiers (described in this section) and the AUC for LOC alone were compared to obtain the corresponding improvement in class separation. The percentage improvement in class separation was computed for two AUCs as:

$$\frac{(AUC_2-0.5)-(AUC_1-0.5)}{AUC_1-0.5}\times 100$$

The subscript in the equation differentiates between the AUCs of the two classifiers being compared. The subtraction of 0.5 from the AUC prior to the comparison adjusts for the fact that an AUC of 0.5 indicates no separation and an AUC of $0.5 - x$, where x is a real number from 0 to 0.5, is equivalent to an AUC of $0.5 + x$ in terms if class separation.

The odds ratio (OR) was also used for evaluating the class separation for LOC alone and the two classification algorithms. The OR was computed as the ratio of the odds that the response was positive when the predictor was positive to the odds that the response was positive when the predictor was negative. In this case, the response is the CT condition and the predictor is the LOC (or classification algorithm results). Fisher's Exact Test was used (Matlab) to compute the 95% confidence intervals and the p-value.

3. Results

3.1. Patient characteristics

Seven-hundred-twenty (720) closed head-injured subjects were enrolled. For 40 of these subjects, LOC information was unknown and therefore these subjects were excluded from these analyses. 680 patients with known absence or presence of LOC were enrolled in this retrospective study (145 CT+ and 535 patients CT−). CT− subjects had a mean age of 41.16 (18.05–85.11, sd = 17.56), were 57.2% male, and had a mean GCS of 14.98 (sd = 0.17). CT+ patients had a mean age of 53.13 (18.00–85.62, sd = 19.97), were 73.1% male, and had a mean GCS of 14.92 (sd = 0.34). The presence of anticoagulants in the population was 9.2%, with no significant differences between the CT+ and CT− patients (13.1% and 8.0%, respectively). Focal neurological signs were rare in this population (1.6%) with no significant differences between the CT+ and CT− patients (3.5% and 1.1%, respectively). Positive findings on the neurological exam related to orientation were also rare in this high GCS population (2.6%), with no significant differences between the CT+ and CT− patients (5.0%, 1.9% respectively). Table 1 shows the mechanism of injury for the population, with the highest percentage in both the CT+ and CT− patients being either MVA or falls.

3.2. Accuracy of prediction of positive CT finding

Table 2 below shows the AUC value for each of the prediction methods. In addition, the percentage improvement in class separation is computed as a percentage increase compared with LOC alone. It can be seen that LOC alone has the lowest AUC. Class separation is only slightly improved (6%) with the inclusion of traumatic amnesia information, and highly improved with the addition of EEG features (83%).

Table 3 shows the odds ratios for the three different methods of prediction, the 95% confidence intervals associated with each and the significance of the odds ratios obtained. Although all three predictors have significant ORs, the one with EEG added is approximately 4 times greater.

Table 1
Mechanism of injury for CT+, CT− and total population.

Mechanism of injury	CT+ n (%)	CT− n (%)	Overall n (%)
Assault	24 (16.55)	59 (11.03)	83 (12.21)
Sports	1 (0.69)	14 (2.62)	15 (2.21)
Fall	69 (47.59)	152 (28.41)	221 (32.50)
MVA	29 (20.00)	212 (39.63)	241 (35.44)
Motorcycle/bike	9 (6.21)	47 (8.79)	56 (8.24)
Struck by vehicle	4 (2.76)	24 (4.49)	28 (4.12)
Other	9 (6.21)	27 (5.05)	36 (5.29)
Total	145	535	680

Table 2
AUCs for each prediction method, and the percentage improvement obtained relative to LOC alone.

Prediction method	AUC	% improvement over LOC only
LOC only	0.68	–
LOC + RGA/PTA classifier	0.69	6%
BrainScope structural injury classifier	0.83	83%

4. Discussion

Rapid, accurate triage of head injured patients leading to early identification of TBI has been associated with reduced morbidity and improved outcomes [15]. Clinical predictors of the likelihood a closed head injured patient has suffered an intracranial bleed, have long been sought. Prior to the availability of CT scanning, LOC was often considered the main determinant of whether in-patient observation was indicated in a patient presenting to the ED after a closed head injury. In this study LOC was found be show be only a very modest predictor of the presence of a cranial bleed with an AUC of 0.68 (where 0.5 is random) and not a sensitive enough measure on which to base the need for close observation of a potentially developing intracranial bleed. Studies have suggested that adding symptoms of "any alteration in brain function" to LOC, most often using PTA, improves prediction. However, in the current study no change in AUC was obtained with the addition of amnesia to the LOC prediction algorithm. Extremely high sensitivity has been demonstrated in prediction of TBI visible on CT scan using a QEEG based classifier function which includes information on LOC and amnesia. Applying this classifier to the population in this study the AUC was found to be 0.83, demonstrating an 83% improvement in AUC, relative to that obtained with LOC and amnesia alone.

Odds ratios were used to estimate the likelihood of being CT+ in the presence of specific features being positive, compared with the "odds" when those features are negative. That is, what are the odds that a patient who suffered a closed head injury has sustained a TBI, using LOC alone or LOC with amnesia, and how are those odds improved when EEG biomarkers are added to the prediction? The results of this study demonstrated a significant improvement in odds ratios when EEG is used in the prediction model, going from 4.65 to 16.2.

This data demonstrates that the addition of electrophysiological marker to prediction outperforms clinical observation of LOC and amnesia alone in determining whether a head injured patient is likely to have an intracranial bleed. Advances in technology have enabled the feasibility of EEG evaluation into the ED, with a handheld, easy to use, device. Using such a device, the ability to rapidly assess the likelihood of being CT+ in high functioning closed head injured patients at the point of initial triage, using a marker which based on brain electrical

Table 3
Odds ratios for the three different methods of prediction are shown with 95% confidence intervals for each (all p-values <0.001).

Prediction method	Odds ratio	95% C.I.
LOC only	4.65	(3.10–6.97)
LOC + amnesia classifier	4.51	(3.01–6.78)
BrainScope TBI classifier	16.22	(8.09–32.53)

activity, significantly improves the ability predict a CT positive brain injury.

Conflict of interest

Dr. Hack is a consultant to BrainScope Co., Inc., who at the time the study was conducted was Coordinator of the Brain Health/Fitness Research Program at the U.S. Army Medical Research and Materiel Command. Drs. Huff and Naunheim, were Principal Investigators at clinical data acquisition sites. Dr. Prichep is employed by BrainScope as the Chief Scientific Officer, and is a Professor at NYU School of Medicine. Dr. Prichep holds potential financial interest through patented technology licensed by BrainScope from NYU School of Medicine. Dr. Curley is a consultant to BrainScope Co., Inc., who at the time the study was conducted was the Neurotrauma Research Portfolio Manager for Combat Casualty Care Research Program and Defense Health Program at the US Army Medical Research and Materiel Command. Dr. Samanwoy Ghosh Dastidar is employed by BrainScope as manager of the Algorithm Development division. BrainScope Company, Inc. had no role other than indicated above, in the conduct of these studies. This data used in this study was collected under support in part by a research contract from the U.S. Army, contract # W81XWH-14-C-1405, entitled, "Validation of Point-of-Care TBI Detection System for Head Injured Patients," and by research grants from BrainScope Company, Inc. to the clinical sites.[2]

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