Triage of Mild Head-Injured Intoxicated Patients Could Be Aided by Use of an Electroencephalogram-Based Biomarker

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ABSTRACT

Objective: Drug and alcohol (DA)–related emergency department (ED) visits represent an increasing fraction the head-injured population seen in the ED. Such patients present a challenge to the evaluation of head injury and determination of need for computed tomographic (CT) scan and further clinical path. This effort examined whether an electroencephalogram (EEG)-based biomarker could aid in reducing unnecessary CT scans in the intoxicated ED population. **Method:** This is a retrospective secondary study of an independent prospective US Food and Drug Administration validation trial that demonstrated the efficacy of (1) an automatic Structural Injury Classifier for the likelihood of injury visible on a CT (CT+) and (2) an EEG-based Brain Function Index to assess functional impairment in minimally impaired, head-injured adults presenting within 3 days of injury. Impact on the biomarker performance in patients who presented with or without DA was studied. **Results:** Structural Injury Classifier sensitivity was not significantly impacted by the presence of DA. Although specificity decreased, it remained several times higher than obtained using standard CT decision rules. Furthermore, the potential to reduce the number of unnecessary scans by approximately 30% was demonstrated when the Structural Injury Classifier was integrated into CT clinical triage. The Brain Function Index was demonstrated to be independent of the presence of DA. **Conclusion:** This EEG-based assessment technology used to identify the likelihood of structural or functional brain injury in mildly head-injured patients represents an objective way to aid in triage patients with DA on presentation, with the potential to decrease overscanning while not sacrificing sensitivity to injuries visible on CT.

Keywords: brain electrical activity, brain function index, drug and alcohol intoxication, EEG, quantitative electrophysiological measures, structural brain injury, structural injury classifier, traumatic brain injury, TBI

The ability to achieve rapid, objective, and accurate identification of traumatic brain injury (TBI) is key to enabling rapid triage of head-injured patients in an emergency department (ED) or urgent care environment. Drug and/or alcohol (DA)–related ED visits are increasing at a greater rate than overall ED visits.[1] At the same time, ED visits for TBI are also increasing,[2] with between 35% and 80% of alcohol-intoxicated patients reported in the adult population with TBI.[3–6] In addition, a significant positive association between alcohol consumption and head injury severity has been reported in the ED.[6,7] The presence of DA adds difficulty to both patient assessment and management. Complications associated with head-injured

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patients include the confounding effects of intoxication on the ability to assess mental status and other symptoms that may be the result of either the intoxicant or head injury and render the use of imaging guidelines such as the New Orleans Criteria or Canadian CT Head Rule problematic, often leading to scanning a number of patients who are found to be computed tomography (CT) negative. On the other side of the problem, Cheever and Barbosa-Leiker[8] reported systematic gender and age bias for underscreening for alcohol, leading to misinterpretation of screening tools and inappropriate referrals to the intensive care unit for head trauma cases. The need for more objective triage of head trauma in those patients under the influence of drug and alcohol could assist in more appropriate scanning decisions and patient transfers.

Currently, CT scan remains the accepted "standard" for evaluating TBI in the ED, although the vast majority of these patients (approximately 91%) are found to be negative.[2,9] Patients with alcohol-related head injuries are reported to be at a higher risk for brain injury, with studies showing that they are approximately twice as likely to have an abnormality on CT than sober head-injured patients.[10] However, the potential patient risk associated with overscanning remains a concern.[11,12] An objective predictor of the likelihood of CT-positive TBI could greatly facilitate a triage nurses' workup of head-injured DA patient including avoidance of unnecessary head CT scans.

The electroencephalogram (EEG)-based Structural Injury Classifier (SIC) and EEG-only Brain Function Index (BFI) are outputs from classifier algorithms that indicate the likelihood of a structural or functional injury. In a multisite prospective US Food and Drug Administration (FDA) validation trial, SIC was demonstrated to have high accuracy in predicting the likelihood of TBI visible on CT (CT+), with a high negative predictive value, and the BFI was demonstrated to scale significantly with functional impairment.[13] Details of the trial are reported elsewhere following STARD guidelines.[14,15] In light of an abundant research literature demonstrating that many features of the resting state EEG are influenced by the presence of drugs and alcohol,[16–19] the present retrospective study investigates the influence of intoxication on the accuracy of an EEG-based SIC and BFI.

Methods

Population

In this retrospective study, subjects were a subset selected from a prospective FDA clinical validation trial population,[14,15] used to validate a novel EEG-based algorithm for likelihood of TBI and included

CT positive findings in those with only alcohol present were 3 times that of those without drugs or alcohol present.

all subjects with a Glasgow Coma Scale (GCS) of 15 at the time of evaluation (described in detail elsewhere).[14] As in the parent study, all subjects were between the ages of 18 and 85 years, presenting within 72 hours of a closed head injury. Subjects with GCS of 13 or 14 (~2%) were excluded to avoid any confounds to the clinical assessment of GCS status due to the presence of DA. Exclusion criteria included history of neurological disease or stroke and skull defects or injuries that prevented proper placement of electrode headset (full details are described elsewhere[14]). Electronic Data Capture records were completed on all participants, specifying results of blood alcohol levels as well as results of drug screens, recorded at the time of initial ED evaluation. Institutional review board approvals and informed consent were obtained at each site.

Procedures

Alcohol presence was defined as a detected blood alcohol level of 10 mg/dL or greater (minimum detectable alcohol level[19]), and drugs that triggered inclusion of a patient in the drugs subgroup included cocaine, amphetamines, opiates, fentanyl, cannabinoids, tetrahydrocannabinol, and benzodiazepines. In all cases, the determination to order a head CT scan was made under current standard clinical practice at each site by the ED physician. Computed tomographic scans were deidentified and transferred for independent adjudication as DICOM images, blinded for EEG and clinical findings.[14,15]

Five to ten minutes of eyes-closed resting EEG data was acquired on a handheld device from frontal and frontotemporal electrodes using a self-adhesive headset on the forehead and referenced to linked ears. Automatic artifact rejection algorithms were used to identify and remove any biologic and nonbiologic contamination,[20] and the artifact-free data were then subjected to quantitative analyses to derive the set of univariate and multivariate, linear and nonlinear quantitative EEG features[21] required as input to the algorithms.

Measures

The EEG SIC applied to the patients in this study was based on the a priori algorithm described in detail elsewhere.[14] The SIC was computed using a linear discriminant function, the output of which was binary reporting the likelihood of having a structural brain injury visible on CT (CT+ or CT−). The EEG BFI used in this analysis was derived from the same independent database as the SIC.[15] The BFI, computed as a weighted linear combination of a selected subset of the QEEG feature *z* scores, was shown to scale with severity of clinical impairment in the prospective independent validation study and is described in detail elsewhere.[15]

Data Analysis

In relation to the binary test result of the SIC (likely CT+ or likely CT−), sensitivity is defined as the ratio of true positives over the total number of CT+ subjects, and specificity is defined as the ratio of true negatives over the total number of CT− subjects. Comparisons of these performance measures in subjects with DA and without DA were performed using a test of significance of the difference of 2 proportions.[22] Group comparisons of SIC discriminant scores were also performed using a *t* test (2 samples with unequal variances) to test for significance of the differences between the SIC scores in those with DA and those without DA, separately within the CT+ subjects and within the CT− subjects. Similar comparisons were performed to test for the significance of differences in the BFI percentile scores between the DA and without-DA subgroups, within both the CT+ and CT− populations.

To estimate the potential reduction in overscanning of subjects with DA when integrating the SIC in making a CT referral determination, the performance of 2 clinical triage methods was compared against an independently adjudicated CT finding, similarly to what was reported by Huff et al,[23] but was restricted to subjects with DA. The first triage method follows the clinical judgment of the local site ED physician for CT scan referrals. The second follows the use of SIC determination as the input to CT scan referral. The potential reduction in overscanning was computed as the relative reduction in the number of false positives if the EEG-based biomarker assessment had been used in CT referral determination compared with that resulting from the judgment of the site physician as per local standard of care.

Results

Seven hundred one subjects were included in this analysis, with a mean (SD) age of 43.7 (18.7) years (range, 18–85.6 years); 60.6% were male; and GCS was 15. 131 subjects (19%) had documented DA present (DA group), 51 with alcohol alone, 56 with drugs alone, and 24 with both drugs and alcohol present. This DA group was 74% male. 146 of the 701 subjects were adjudicated as CT+, with 37% of the DA group CT+ and 17% of the no-DA group CT+. The difference between the incidence of CT+ findings in the 2 groups was statistically significant, $P < .0001$. Furthermore, CT+ findings in those with only alcohol present (no drugs) were approximately 3 times that of those with no DA present (55% vs 17%, respectively). These results suggest that head-injured subjects who test positive for DA in the ED are at a high risk of being CT+.

Influence of DA on Derived Biomarkers

Structural Injury Classifier

The sensitivity of the SIC for the full group (n = 701) was 91.8%, and specificity was 52.3%. No significant difference ($P = .256$) in sensitivity was found comparing the subgroups with and without DA. However, significant differences in specificity were found ($P < .0001$) comparing these 2 subgroups (29.3% with DA vs 56.2% without DA).

Although the SIC is EEG based, it includes select clinical features (eg, loss of consciousness (LOC), altered mental status (AMS)) that covary with the presence of structural brain injury.[14] It was found that subjects with DA have significantly higher prevalence of LOC and AMS than those without (55% with LOC in DA vs 30% in no DA; 27% with AMS in DA vs 11% in no DA), suggesting that the presence of such symptoms might be "TBI mimics" in the presence of DA, potentially contributing to the lower specificity found in this group.

Brain Function Index

The BFI, a measure of the likely presence of functional brain impairment (such as seen in concussion), is an EEG-only algorithm. No significant differences in BFI were found when comparing asymptomatic controls with DA to those without DA ($P = .313$). Similarly, no significant differences in BFI were found comparing (mild TBI/concussed CT− subjects) with and without DA ($P = .06$). Thus, the BFI seems to be unaffected by the presence of DA.

Comparison of Impact on CT Scan Referrals of 2 Different Clinical Triage Practices

Local clinical site physician practice resulted in the referral for CT of 127 patients (97%) of the DA group of 131 subjects. In this group, 49 were later adjudicated to be CT+ and 82 were later adjudicated to be to be CT− (number of unnecessary scans). Therefore, the clinical site triage pathway resulted in 82 patients being referred for a CT scan and later found to be CT negative. On the other hand, the integration of EEG-based Biomarkers as an aid in triage referral for CT scanning would have resulted in 58 patients being referred for CT scans who were later found to be CT negative. This represents a potential 29.3% reduction (82 − 58) / 82) in the number of unnecessary CT scans compared with clinical site practice.

Discussion

One of the triage challenges in the ED for patients with TBI is that many such patients present under the influence of DA, confounding the clinical presentation. When uncertain whether DA are responsible for a patient presenting with altered mental status, often a head CT is ordered from triage. In many EDs, clinical protocols allow the triage nurse to either order the CT or contact a physician for a verbal order. This study demonstrates the potential use of integrating an EEG-based biomarker into the triage process.

Drugs and alcohol have an influence on the resting state EEG and on the presence of characteristic TBI symptoms (which may or may not be "TBI mimics"); therefore, it was important to evaluate the possible influence on EEG-based biomarkers. The SIC classifier/biomarker identifies a unique, distinctive multivariate pattern of EEG changes, which are associated with TBI and cannot be determined by any one feature change alone. To minimize the influence of such comorbid or state factors in general, it is important to note that, in the derivation of the algorithm, potentially confounding factors exist in both the CT+ and CT- populations, thus minimizing the potential influence of such factors on significant differences between the 2 groups. This was demonstrated in this study where no significant differences were found in sensitivity between those head-injured subjects with and without DA, confirming the ability of the SIC to accurately identify those likely CT+ regardless of the presence of DA.

Significant differences in specificity were found between the with- and without-DA groups, likely because of the presence of symptoms mimicking those seen in TBI in the DA group. However, specificity remains several times higher than that of standard clinical practice decision rules used in the ED, which was only 3% for the DA group. Importantly, the BFI, an EEG-only measure of brain function impairment (such as seen in concussion) in the head-injured population, showed no significant differences between the with- and without-DA groups, for either the asymptomatic controls or the CT− groups.

Furthermore, the use of the SIC for the potential reduction of CT referrals in the DA subjects found to be CT− was demonstrated to result in approximately 30% reduction when compared with referrals based on standard site practice, supporting the potential clinical utility of the use of the SIC to reduce unnecessary CT scans in this difficult population. A limitation of this study, however, is that it is not known what the results would indicate in a more severely intoxicated patient population.

Conclusion

This retrospective study supports the clinical use of EEG-based biomarkers in the rapid, objective evaluation of head-injured patients with or without DA at presentation, to aid in determining the likelihood of having sustained a structural brain injury (CT+), as well as the likelihood that the patient sustained a functional injury when likely CT−. Furthermore, the use of such a device to aid in determining which head-injured patients under the influence of DA should have a CT scan was demonstrated to have the potential to reduce overscanning by almost 30%, although not decreasing sensitivity to CT+ injuries.

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