The role of biochemical markers in the identification of intracranial pathology following minor head injury: a systematic review and meta-analysis

INTRODUCTION

Biochemical markers may have a role to play as objective tools for ruling out significant complications following minor head injury, whilst reducing the rate of “unnecessary” Computed Tomography (CT) scans. This study aimed to systematically identify and synthesise data estimating the diagnostic accuracy of biochemical markers for intracranial injury on CT in patients with minor head injury (MHI).

METHODS

Potentially relevant studies were identified by an electronic search of key databases including MEDLINE, EMBASE & CINAHL. Studies were included if they met the following criteria: a) a cohort study with at least 20 patients, or a case control study with at least 10 patients; b) used biochemical markers as a test or screening tool for the identification of intracranial injury on CT scan; c) performed a diagnostic test before CT; d) provided data that allowed true positive (TP), false positive (FP), false negative (FN) numbers to be extracted; e) written in English (full text papers were excluded for pragmatic reasons - cost of translation). The QUADAS (Quality Assessment of Diagnostic Accuracy Studies) checklist was used to assess study quality. Two questions were omitted; the disease progression bias item was addressed through definition of an adequate reference standard (CT within 24 hours), and the incorporation bias item was omitted, as the reference standard was always independent of the index test. As this data was from multiple studies a full Bayesian meta-analysis was conducted using a bivariate random effect method. The Bayesian approach was chosen because the between-studies uncertainty can be modelled directly, which is important in any random effects meta-analysis where there are small numbers of studies and potential heterogeneity.

RESULTS

A total of 12 papers were selected from 8003 citations screened. Nine studies provided diagnostic data on protein S100B only, one on Neuron-Specific Enolase (NSE) only, one on other markers (creatine kinase isoenzyme (CK-BB), neuronenphrine, epinephrine, dopamine, amylase and total catecholamines) and one study provided diagnostic data on both protein S100B and NSE levels. Data could only be synthesized from the 1100B studies. All recruited patients received the reference standard of CT scan, mostly within 6 hours of injury, along with the index test for which sample analysis techniques varied.

Protein S100B: Patient numbers vary greatly between studies, ranging from 50 to 1,300, with the single study using marrow recruiting only 24 subjects. These small numbers lead to the increased influence of individual cases on the final statistical analysis potentially explaining some of the different outcomes between published work in this field. Thresholds for positive results varied between studies with four using a ROC curve analysis and generating the cut-off value from the data, primarily to optimise sensitivity. Muller also used the ROC curve to generate a threshold as a best fit for both sensitivity and specificity which was 0.5 pg/ml, this dropped the sensitivity to 81%, whilst the specificity increased to 98%. The remaining studies used a predefined threshold calculated from normal population data (consistent with a Type 1 error of 5%), with the primary objective of optimising sensitivity and thus reducing the possibility of missing patients with intracranial injury. These calculated thresholds were from a limited number of studies and may explain the lack of heterogeneity for sensitivity. Bayesian meta-analysis of these pooled data for 2,442 adult subjects gave a sensitivity of 98.1% (95% High Density Region (HDR) = 93.9 to 98.6%) and specificity of 42.5% (95% HDR = 31.0 to 54.2%) with a negative likelihood ratio of 0.016 (95% HDR = 0.031 to 0.156).

Neuron-Specific Enolase: The two studies (not amenable to meta-analysis) that investigated the role of NSE in the identification of intracranial injury on CT scan performed, one study identified a cut-off value of 10.2 μg/ml yielding a sensitivity of 99% and a specificity of 80%. The other study used a cut-off value of 10 μg/ml with sensitivity of 100% and a specificity of 97%.

DISCUSSION

Two studies were identified that specifically used this tool in conjunction with current clinical decision rules. The first selected symptomatic patients for cranial CT based on two previously reported North American guidelines and the second used the European Federation of Neurological Sciences (EFNS) guidelines for CT. The results were very different and more prospective research is needed, however use of the marker in conjunction with the decision rules from North America produced clinically significant results yielding a possible reduction of CT use by 30% whilst maintaining patient safety with a 99% sensitivity and negative predictive value. The small number of studies in this area, with only three of these recruiting more than 200 patients, and the heterogeneity in positive CT rates suggest that universal application of this tool, based on the data generated may still be premature. The range of positive CT rates (5.5-28.8%) is significantly wider than that generally reported in the mild head injury population and may well indicate a degree of selection bias despite well-described inclusion criteria.

S100B has high sensitivity and modest specificity for intracranial injury and therefore has potential to rule out significant intracranial injury and reduce the number of CT scans performed. Further testing is required to assess its use alongside existing clinical decision rules in the management of minor head injury patients.

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Figure 1. Summary table of S100B studies

A Pickering1, P Fitzgerald2, S Harnan2, A Pandor2, S W Goodacre2

1. Health Services Research, School of Health and Related Research (ScHARR), University of Sheffield, UK
2. Health Economics and Decision Science (HEDS), School of Health and Related Research (ScHARR), University of Sheffield, UK