The role of biochemical markers following minor head injury: A systematic review and meta-analysis

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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 synthesize 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 minimum 20 patients and at least half had GCS13-15 at presentation, b) they evaluated a biochemical marker as a triage or screening tool for the identification of intracranial injury on CT scan following head injury c) provided data that allowed true positive (TP), true negative (TN), false positive (FP) and false negative (FN) numbers to be extracted or calculated, and e) written in English (full text papers were excluded for pragmatic reasons - cost of translation).

The QUality Assessment of Diagnostic Accuracy Studies (QUADAS) 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 bi-variate 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], norepinephrine, epinephrine, dopamine, amylase and total catecholamines) and one study provided diagnostic data on both protein S100B and NSE levels. Data could only be extracted and synthesized from the S100B 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(18) to 1,309(11), with the single paediatric study recruiting only 109 subjects.(15) 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.

Summary table of protein S100B studies

Author, year	Sample	Cut-off value	Time to sample (Average)	Analyser	Positive CT (%)	TP	FP	FN	TN	Sensitivity	Specificity
Poli de Figueiredo 2006	S100B serum	> 0.10 µg/L	82 minutes	Elecsys	6/50 (12%)	6	35	0	9	100	20.5
Biberthaler 2006 (D & V)	S100B serum	> 0.10 µg/L	60 minutes	Elecsys	93/1309 (7.1%)	92	855	1	361	98.9	29.7
Morochovic 2009	S100B serum	>0.10 µg/L	<6 hours	Elecsys	18/102 (17.6%)	15	59	3	25	83.3	29.8
Muller 2007 (D)	S100B serum	≥0.10 µg/L	<3 hours	Liaison	21/226 (9%)	20	141	1	64	95.2	31.2
Biberthaler 2002 (D)	S100B serum	>0.12 ng/ml	<2 hours	Liaison	24/104 (23.1%)	24	43	0	37	100	46.3
	S100B plasma	> 0.18 ng/ml	<2 hours	Liaison	24/104 (23.1%)	24	43	0	37	100	46.3
Mussack 2002 (D)	S100B plasma	>0.21 ng/ml	<40 minutes	Liaison	19/139 (13.7%)	19	60	0	60	100	50.0
Biberthaler 2001	S100B serum	>0.12 ng/ml	75 minutes	Liamat	15/52 (28.8%)	15	22	0	15	100	40.5
Romner 2000	S-100B serum	>0.2 µg/L	<24 hours	Sangtec	25/278 (9%)	23	85	2	168	92	66.4
Ingebrigtsen 2000	S-100B serum	>0.2 µg/L	<12 hours	Sangtec	10/182 (5.5%)	9	60	1	112	90	65.1
Castellani 2009	S100B serum	>0.16 µg/L	<6 hours	Elecsys	36/109 (30.3%)	36	42	0	31	100	42.5

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 (17) also used the ROC curve to generate a threshold as a best fit for both sensitivity and specificity which was 0.15µg/L but dropped the sensitivity to 81% (specificity increased to 58%). The remaining studies used a predefined threshold calculated from normal population data(10;11) (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 that have been used were from a limited number of studies and may explain the lack of heterogeneity for sensitivity.

Results *contiuned*

Bayesian meta-analysis of these pooled data for 2,442 adult subjects gave a sensitivity of 96.8% (95% High Density Region (HDR) = 93.8-98.6%) and specificity of 42.5% (95% HDR = 31.0-54.2%) with a negative likelihood ratio of 0.076 (95% HDR = 0.031-0.156)

Neuron-Specific Enolase

The two studies (not amenable to meta-analysis) that investigated the role of NSE in triage for CT look at different age groups. Mussack analysed samples in 139 adults alongside their study on S100B, identified a cut-off value (using ROC curve data) of 12.28ng/ml, giving a sensitivity of 100% but a specificity of only 6.9%. The AUC was 0.589 demonstrating an almost complete lack of differentiation. Fridriksson studied 49 children from 0-18 years of age, selecting patients by the need for CT scan following blunt head trauma (severity not defined). Using a different radioimmunoassay technique they identified a cut-off value of 15.3ng/ml from their ROC curve analysis. This resulted in a sensitivity of 77% with a specificity of 52%. These two studies have not been validated elsewhere but suggest that NSE is a poor marker for predicting intracranial injury, or the lack of, on cranial CT.

Other markers

In 1995 Levitt studied 107 intoxicated patients following minor head injury, all of whom received a CT scan and had a sample of blood taken within three hours. Of the potential biochemical markers under investigation (CK-BB, norepinephrine, epinephrine, dopamine, amylase and total catecholamines) only epinephrine and dopamine were associated with positive CT findings. From these data the authors generated ROC curves calculating a cut-off value of 116 pg/ml for epinephrine and 104 pg/ml for dopamine that gave a sensitivity for intracranial injury of 100% (95% CI 66-100%) with an acceptable specificity of 57% (95% CI 47-67%) and 58% (95% CI 48-68%) respectively. These findings do not appear to have been validated elsewhere in the literature.

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.

Conclusion

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.