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Early predictive factors on mortality in head injured patients: a retrospective analysis of 112 traumatic brain injured patients

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Aim. **Early hyperglycemia is a feature of traumatic brain injured (TBI) patients. The aim of our study was to analyze the impact of early hyperglycemia on in-ICU mortality in isolated TBI and its correlations with other factors responsible for secondary injury.**
Methods. **We studied admission values (AV) and worse values in the first 48 hours (WV 48 h) of 112 ICU TBI patients (mortality 29.6%) of blood glucose (BG), base excess (BE), mean arterial pressure (MAP), PaO_2/FiO_2 ratio and serum hemoglobin (Hb). Predictive strength as the area under the receiver operating curves (AUROC) and correlation between all variables were calculated.**
Results. **Data are expressed as median, 1st-3rd quartile. Both BG AV (147.5, 126-182 mg/dL; AUROC 0.716, P=0.0002) and WV 48 h (156.5, 132-192 mg/dL; AUROC 0.721, P=0.0001) are predictive of mortality. AV and WV 48 h are respectively: PaO_2/FiO_2 (366.8, 237.2-477.6 *vs.* 320, 214.4-426; P=0.05), MAP (90, 80-100.5 *vs.* 75, 66-83 mmHg; P<0.0001) and Hb (11.4, 9.7-13.1 *vs.* 10.6, 9-12.2 g/dL; P<0.02). BG AV and WV 48 h correlates with: age (r=0.419, P<0.0001 and r=0.489, P<0.0001), PaO_2/FiO_2 AV (r -0.223, P<0.03 and r -0.236, P<0.02), PaO_2/FiO_2 WV 48 h (r -0.215, P<0.03 and r -0.279, P<0.005) and MAP WV 48 h (r -0.216, P<0.03 and r -0.261, P<0.007).**
Conclusion. **Early hyperglycemia is a major predictor of mortality and correlates with other factors responsible for secondary injury. Early hyperglycemia seems to be a marker of inflammatory reaction responsible for early cardiovascular and respiratory impairment.**

KEY WORDS: Brain injuries - Hyperglycemia - Hospital mortality.

Traumatic brain injured (TBI) patients suffer of severe neurological morbidity, poor recovery and high incidence of death.

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Brain injury following head trauma is a consequence of both primary and secondary insult; the first a consequence of trauma, the second a complication of the primary insult and reflects both intracranial and systemic impairment.

The main target of TBI management is to prevent the development of conditions which favor secondary insults.

The predictive role of systemic secondary insults has been already confirmed in many studies, but only a few of them considered more than three factors all together. Hypocapnia is the most studied one followed by hypotension, acidosis, hypoxia and hyperglycemia.[1]

Severe hypocapnia and hypercapnia reflect aggressive early management of breathing and both worsen outcome by impairing cerebral blood flow (CBF) in a significant way.[2]

There is a strong correlation between early hypotension, hypoxia and mortality.[3-5] Also acidosis [6] and hyperglycemia play an important role in predicting the outcome.[7-9]

Hyperglycemia is known as a part of the neuroendocrine response to stress mediated by counter-regulatory hormones, which lead to increased gluconeogenesis, increased peripheral and hepatic

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TABLE I.—*Demographic data and comorbidities of patients.*

	Patients (N.)
Mean Age (yrs)	49.8 (±24.1)
Sex (M:F)	75:37
Associated diseases	
Diabetes	9
Ischemic Heart Disease	6
Essential hypertension	8
Congestive heart failure	1
Myocardial infarction	2
Arrhythmias	1
Hypotyroidism	2
Hypoparatyroidism	1
HCV	3
Chronic Liver Disease	4
GERD/Hiatal hernia	2
Chronic renal failure	2
Acute renal failure	1
Epilepsy	2
Cerebrovascular disease	3
Sepsis	1
Neoplasm	1
Atopic asthma	1

glycogenolysis, decreased hepatic glycogenesis, augmented lipolysis in the fat tissue and exogenous glucose administration.[10, 11]

The primary aim of this study was to analyze early conditions correlated with secondary insults (such as hyperglycemia, acidosis, hypotension, hypoxia and anemia), their development during the first 48 hours of the hospital phase and their predictive role on in-ICU mortality. As secondary end-point we investigate the correlations between the up-cited factors responsible for secondary brain damage.

Materials and methods

Our study is a retrospective analysis based on clinical records from 14th January 2002 to 20th April 2006 of head injured patients admitted to the Intensive Care Unit of Cattinara Hospital in Trieste, Italy. We analyzed clinical data collected in the first 48 hours of ICU stay of 112 TBI patients. Demographic characteristics, comorbidity and prognosis are summarized in Table I.

Inclusion criteria were mild to severe TBI (GCS: minimum=3, maximum=15) requiring intensive care referral and monitoring (alive *vs.* deceased GCS ≤8: 43 *vs.* 23 patients; GCS >8: 36 *vs.* 10 patients); no associated major thoracic or abdominal trauma (considered as AIS thorax and abdomen less than 3 each).

Neurological and general evaluation included Glasgow Coma Scale (GCS), Injury Severity Score (ISS), Revised Trauma Score (RTS) and Trauma and Injury Severity Score (TRISS) on admission for all patients.

The anatomic features following TBI are summarized in Table II.

Endotracheal intubation (ETI) has been achieved whereas airway protection and mechanical ventilation were mandatory (99% patients needed ETI; 78% out-of-hospital). Fluid resuscitation included colloid and/or crystalloid infusion, whereas red blood cell replacement cut-off levels were: serum hemoglobin (Hb) less than 8 g/dL and less than 10 g/dL for non-heart-diseased (HD) and HD patients respectively.

On admission hematological analysis including red and white blood cells counts, platelets count, serum glucose, electrolytes, serum creatinine, BUN,

TABLE II.—*Head injury's' anatomical features of study patients.*

	Tot	Facial fracture	Cranic fracture	SAH	Cerebr. contus.	Comm. trauma	Subdural/ Epidural hematoma	Cerebr. hemorrage
Facial fracture	9		1	0	4	3	1	1
Cranic fracture	23			6	11	0	5	2
SAH	20				9	0	7	2
Cerebr. contusion	44					0	13	2
Commotive trauma	20						1	1
Subdural/Epidural Heamatoma	39							3
Cerebral Hemorrage	11							
Gun Shot	3							

SAH: subarachnoid hemorrage.

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coagulation tests (PT, aPTTr, INR) and arterial blood gas analysis were performed in the emergency room. All patients were submitted to CT-scan evaluation and neurosurgeons were asked for an evaluation. On arrival at the Intensive Care Unit patients were treated following the guidelines of the Advanced Trauma Life Support; fractures were stabilized and intracranial hemorrhage evacuated, medical therapy was started as soon as possible.

The first data recorded in ER were considered as the admission variables.

We analyzed the admission values (AV) and the worse value during the first 48 hours (WV 48 h) of recovery in ICU of serum hemoglobin (Hb, g/dL), serum glucose (BG, mg/dL), mean arterial pressure (MAP, mmHg), PaO_2/FiO_2, base excess (BE).

Worse values were considered the data with more variability from normality range. The variables investigates have been chosen retrospectively, basing on literature, as the major factors responsible of secondary injury. The outcome measure was in-ICU mortality.

Data with a non-normal distribution were presented as median, 1st and 3rd quartile. Non parametric tests have been used for comparing groups with opposite outcomes.

Receiver Operating Curves (ROC) were performed to detect cut-off values of each variable and their predictive value was estimated by the Area Under the Curve (AUROC).

Spearman rank correlation coefficient was calculated to demonstrate significant correlations between the variables collected.

We also performed Multiple Regression in order to compare factors responsible of secondary insult and to find which one was the best predictor of mortality.

A statistical software package for personal computers was used (Microsoft Office Excel 2000 Professional and Medcalc Software for Windows 9.3.1.0). Significance was defined as $P<0.05$.

Results

Our population included 112 patients with TBI: 29.6% deceased during ICU recovery.

Transfusions were performed in five patients (6.4%) who survived and in 13 (39%) who did not (OR 9.49 CI 95% 3.02-29.79, $P<0.001$).

There were nine diabetic patients in our population: we did not obtain different statistical results by excluding those subjects from the general pool.

Age showed an important divergence between survivors and deceased group (39.5, 25.2-67.7 years *vs.* 67, 43.2-76 years; $P=0.005$).

The calculated ISS, RTS and TRISS expressed as median, 1st-3rd quartile were respectively: 24, 17-29; 5.967, 5.03-6.904 and 61.3%, 22.9-88.9%.

No statistical difference was found in ISS and RTS between survivors and non-survivors (22, 17-28.5 *vs.* 29, 27-33 and 5.967, 5.724-7.841 *vs.* 5, 4.094-5.967) whereas there was a difference in TRISS (79.5%, 20.6-92.1% *vs.* 39.3%, 24.8-58.9%, $P=0.01$) due to the different distribution of age in the subgroups.

In Table III we report median, 1st and 3rd quartile value of the variables considered on admission and their worse values in the first 48 hours of recovery.

ROC analysis resulted in areas under the curves (AUROC) and their relative p values both on admission and the worst record in the first 48 hours of recovery (Table IV). GCSs AUROC on admission was 0.652 with a P significance level of 0.0048.

We have collected statistical significant correlations coefficients among the variables analyzed. Blood glucose on admission correlates with age

TABLE III.—*Admission and worse values of the first 48 h (median, 1°-3° quart).*

	AV			WV 48h			P*
	1st quart.	Median	3rd quart.	1st quart.	Median	3rd quart.	
Serum Glucose (mg/dL)	126	147.5	182	132	156.5	192	0.106
PaO2/FiO2	237.2	366.8	477.6	214.4	320	426.3	0.0503
MAP (mmHg)	80	90	100.5	66	75	83	< 0.0001
Hb (g/dL)	9.7	11.4	13.1	9	10.6	12.2	0.0231
BE	-0.4	-2.4	-0.7	-0.4	-2.4	-0.7	0.8728

*P value calculated with Mann-Whitney test.
AV: admission value; WV 48 h: Worse Value up to 48 hours; BG: blood glucose; MAP: mean arterial pressure; Hb: serum hemoglobin; BB base excess.

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TABLE IV.—*Areas under the receiver operating curves (AUROC).*

Variables	AV		WV 48h	
	AUC	P	AUC	P
GCS	0.652	0.0048		
BE	0.549	0.4174	0.540	0.5074
Hb	0.693	0.0002	0.598	0.0849
MAP	0.654	0.0050	0.666	0.0021
PaO2/FiO2	0.660	0.0041	0.693	0.0003
BG	0.716	0.0002	0.721	0.0001

GCS: Glasgow Coma Scale; AV: admission value; WV 48 h: worse value up to 48 hours; BG: blood glucose; MAP: mean arterial pressure; Hb: serum hemoglobin; BB: base excess.

TABLE V.—*Multiple regression.*

Variable	Admission	48 hours
	r	r
Age	-0.288	/
GCS	-0.186	/
BE	-0.0546	0.0289
Hb	-0.234 (p 0.0229)	-0.0797
MAP	-0.217	-0.240
PaO2/FiO2	-0.140	-0.292 (P=0.0192)
BG	0.355 (P=0.0003)	0.390 (P=0.0003)

GCS: Glasgow Coma Scale; BG: blood glucose; MAP: mean arterial pressure; Hb: serum hemoglobin; BB: base excess; r: regression coefficient.

(r 0.419, P<0.001), PaO_2/FiO_2 both on admission and in the first 48 h (r -0.223, P=0.023 and r -0.215, P=0.028), MAP in the first 48 h (r -0.216, P=0.025). The worst value of blood glucose in the first 48 h correlates also with age (r 0.489, P<0.001), PaO_2/FiO_2 both on admission and in the first 48h (r -0.256, P=0.015 and r -0.276, P<0.005), MAP in the first 48h (r -0.261, P=0.006).

Multiple regression results are summarized in Table V: the dependent variable considered is in-ICU mortality (survivors 0; non survivors 1).

Discussion

In this retrospective analysis on TBI patients mortality has been shown as 29.6% during the hospitalization period in ICU.

The study underlines an higher median of age in the non-survivors group confirming the literature.[12]

Age is both an important confounding and negative predictive factor of mortality and morbidity.[13]

Causes are still unclear: different mechanism of injury, therapeutics treatments, medical complications and pre existing co-morbidities may play a role.[14]

It has been suggested that age *per se* could influence mortality: age may be a negative predictive factor because of ageing intrinsic properties of the central nervous system that could impair its recovery from injury.[15]

This analysis confirms an higher incidence of subdural hematomas in the older patients with a great gap between severe anatomic injury and high values of GCS.[15]

In our study the severity of trauma and GCS influenced mortality. However, the ROC of GCS alone is not a good predictor of mortality, as already demonstrated in literature.[16-18]

Moreover admission evaluation with GCS considers the neurological impairment alone and doesn't count for systemic inflammatory response and cardiopulmonary alterations of TBI patients.

Hyperglycemia is already known to represent an early biological response to traumatic injury. It is both a marker of systemic inflammatory response and influences morbidity and mortality.

Between the six variables included admission hyperglycemia and its worse value during the first 48h were the more accurate mortality predictive criteria.

The authors' opinion is that early hyperglycemia represents a stress response proportional to severity of head injury but also a factor contributing to injury worsening.

Now the synergistic properties of stress metabolic response and hyperglycemia influencing outcome in head trauma are well rendered.[10]

During the first 48h a significant decrease in the MAP was observed because of hemodynamic impairment caused by hemorrhagic episodes, secondary injuries, iatrogenic effects (such as aggressive diuretic therapy).[19, 20]

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This factor has an important role in the development of secondary damage: cerebral autoregulation fails early after TBI leading to increased sensitivity to MAP's alterations.[21, 22] Even so its correlation with mortality derived from the ROC analysis is <0.7.

Admission serum hemoglobin is another significative predictive factor. Worse hemoglobin value of the first 48 h does not share this property: early transfusions to those patients admitted with severe anemia could have biased this variable.

More patients needed blood replacement in the deceased group than in the survivor group. This could be an indirect sign of severity and could represent an indicator of aggressive treatment.

Recent literature reviews current Hb limits for transfusions in trauma patients, without significant alterations in morbidity and mortality.[23-25]

Preventing hypoxemia and hypercapnia is a priority in the management of head trauma patients.

We observed a significant worsening of ventilation during the early phase of hospitalization. Acute lung injury developing during the first 48 h could have a negative predictive role. It is suggested by a decrease of the PaO_2/FiO_2 medians and the increase in the ROC value through the first 48 h.

Respiratory failure has often a neurogenic origin, but inhalation of gastric content can contribute.

Neurogenic injury is caused both by an increased hydrostatic pressure in pulmonary vessels and by endothelial permeability alterations. This leads to endothelial injury, alveolo-capillary barrier disruption and infiltration by proteins of lung tissue.[26, 27]

An animal model with isolated head trauma showed an increase in the following 24 hours of inflammatory cells in the airways and in the alveolar spaces. These cells amplify inflammatory response and modulate secondary injury in the lungs.[26]

Our study demonstrated significant correlation between admission and worse value of the first 48 h of hyperglycemia and PaO_2/FiO_2 both on admission and during the first 48 h.

In traumatized hyperglycemic animals an increase in lung edematous tissue, which was absent in the control group, was found. Glycemic control with insulin was shown to decrease lung leukocyte capture and tissue edema.[28]

Moreover this inflammatory activation in endothelial cells [29] could concur in early hemodynamic impairment in isolated brain injury, as suggested by correlation between admission and 48h hyperglycemia and admission and 48 h MAP.

Conclusions

Our data confirmed the strong predictive value of early hyperglycemia on head trauma patients' prognosis and its significant correlation with acute lung injury and cardiovascular impairment.

The higher median of age in the TBI population and in the non survivors subgroup demonstrated the important role of comorbidities and ageing on outcome, thus being an additional limit for evaluation with GCS alone.

The number of patients included and the retrospective characteristics of the study may have limited the strength of the correlation between the variables considered.

Although we analyzed for the first time in literature the correlations between all parameters considered, testing pro-inflammatory and tissue mediators is still needed to investigate thoroughly correlation between hyperglycemia, hemodynamic impairment and acute lung injury.

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