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Lactate and Hypocalcaemia as Possible Prognostic Factors of Mortality and Morbidity in Early Phases of Moderate and Severe Traumatic Brain Injury

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Abstract

Background: Traumatic Brain Injury (TBI) is one of the most common disorders within the vast field of neurology. Recent identification of multiple markers regarding trauma assessment has brought potential tools in outcome prediction.

Objective: The aim of this study was to evaluate whether elevated serum lactate is a prognostic factor for mortality and morbidity and investigate its correlation with hypocalcemia (defined as ionized serum calcium <1.10 mmol/L [4.5 mg/dL]) and non-ionized serum calcium <2.1 mmol/L [8.5 mg/dL] in early phases of moderate and severe isolated TBI.

Methods: We retrospectively (January 2004 to July 2012) compiled data from 99 patients. Prospectively, (December 2013 to December 2015) we recruited 61 patients with moderate and severe isolated TBI. Beside demographic and clinical features, blood samples were taken following admission, day 3 and day 7 after trauma.

Results: Median age at presentation was 47 years (range: 16 to 87). N=88 (55%) were men and 72 (45%) women. N=69 (43%) had a GOS ≤ 3 and n=91 (57%) had a GOS>3. Patients in the GOS ≤ 3-group were significantly older than patients with a GOS>3 (p=0.008). Lactate levels were significantly higher in the GOS ≤ 3-group on day 3 with p=0.002, but not on day 7. Furthermore, there was a significant association between GOS-group and hypocalcemia.

Conclusion: Elevated lactate serum levels and hypocalcaemia correlated with dismal outcome. Furthermore, lactate and calcium are easy assessable serum markers. Both could serve as prognostic markers evaluating the severity of isolated TBI and thus predict mortality and disability following TBI.

Keywords: Lactate; Hypocalcaemia traumatic brain injury; Prognostic factor; Glasgow outcome score

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Background

Traumatic Brain Injury (TBI) is a common disorders occurring all over the world with a high prevalence. With an approximate incidence of 332 per 100,000 people in Germany, its occurrence is significantly higher than strokes [1].

Different serum markers such as magnesium (Mg^{2+}) and calcium (Ca^{2+}) have been studied in context with TBI and calcium in particular seems to play an important role [2-5]. On the cellular level, trans membrane inflow of calcium and outflow of potassium due to traumatic deformation of the cellular membrane have been demonstrated following TBI; these are accompanied by the release of excitatory neurotransmitters such as glutamate [6]. This increase in intracellular calcium (evident in acute ischemia) causes an inhibition of mitochondrial enzymatic processes as well as lipase activation and therefore plays an important role in apoptotic processes [6-10]. Hypocalcemia may be a consequence of calcium chelation by pro-inflammatory molecules/proteins such as Protein S-100 B and Interleukin 6 (IL-6). Hence, an increase of metabolic molecules due to disruption of the aerobic mitochondrial pathway leads to acidosis with lactate being one of the key markers. The relation between hypocalcaemia und high levels of calcium following TBI is poorly understood. We therefore studied the role and correlation of calcium and lactate in TBI.

Objective

Our aim was to evaluate if high serum lactate levels (defined as >1.80 mg/dl) is a prognostic

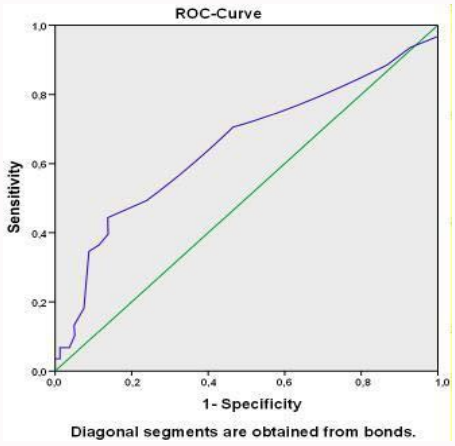

Figure 1: ROC-curve showing a cut-off value of 0.95 mg/dl and a sensitivity of 70.5% and specificity of 53.7% (Youden-Index =0.242). Furthermore, the area under curve was shown to be between 0.6 and 0.7 and therefore indicates its limited clinical relevance.

factor for mortality and morbidity (defined as GOS ≤ 3). In addition, we investigated if there is a potential correlation to hypocalcemia (defined as ionized serum calcium <1.10 mmol/L [4.5 mg/dL] and non-ionized serum calcium <2.1 mmol/L [8.5 mg/dL]) in early phases of moderate and severe TBI.

Patients and Methods

We performed an ambispective comparative case-control study. Retrospectively, clinical profiles from patients treated from January 2004 to December 2012 were assessed. Prospectively, patients admitted to our hospital from December 2013 to December 2015 were evaluated. Patients between the age of 16 and 87 years and a Glasgow Coma Scale [GCS] of 3-13 points following TBI with demonstrable intracranial lesions in cranial Computed Tomography [CT] were included. A total of n=191 patients were initially enrolled, but only n=31 patients were excluded due to the following exclusion criteria:

- TBI older than 24 h.
- Intake of medication, conditions or diseases affecting calcium metabolism (such as hyperparathyroidism, acute pancreatitis, massive blood transfusion and treatment with hydrochlorothiazide).
- Multi-system trauma, open fracture, lacerated spleen, liver, great vessels or hypovolemic shock III-IV.
- Lesions in the brainstem as an isolated finding.
- Previous treatment in another clinic.
- Pregnancy.
- Alcoholism.
- Hypoalbuminemia at admission.
- Prior disability to TBI.

Management and intervention

The patients were admitted to our emergency room and treated according to the guidelines of Advanced Trauma Life Support (ATLS). Once the patients were stabilized, blood samples for hematic biometry and serum electrolytes (sodium, potassium, calcium, and ionized calcium), arterial blood gases and serum lactate were taken. All patients were treated according to the Brain Trauma Guidelines.

Table 1: Characteristics of the study population and results of the inter-group differences between patients with a score of the Glascow Outcome Scale (GOS) ≤ 3 and >3. Data are presented as mean ± standard deviation and as frequency (n) and valid percent (%).

Variable	GOS ≤ 3 (n=69)	GOS>3 (n=91)	p-Value
Age (years)	53.5 ± 22.25	44.1 ± 21.44	**0.008**
Age by Group			**0.036**
<30 years	13 (18.8)	33 (36.3)	
30-59 years	25 (36.2)	31 (34.1)	
≥ 60 years	31 (44.9)	27 (29.7)	
Sex			0.233
Male	51 (73.9)	59 (64.8)	
Female	18 (26.1)	32 (35.2)	
Dayson ICU	42.9 ± 41.99	31.3 ± 27.88	0.061‡
Mean arterial pressure (mmHg)	105.7 ± 16.47	114.2 ± 13.44	**0.005**‡
pH-Level			
Day 0	7.4 ± 0.09	7.4 ± 0.10	0.507
Day 3	7.4 ± 0.05	7.4 ± 0.05	**0.046**
Pupils†			0.057
Isocoria	51 (75.0)	79 (87.8)	
Anisocoria	17 (25.0)	11 (12.2)	
Pupil reaction††			**0.007**
Reactive	42 (60.9)	73 (81.1)	
Non-reactive	27 (39.1)	17 (18.9)	
Lactate levels (mg/dl)			
Day 0 (admission)	2.0 ± 1.22	1.8 ± 1.23	0.497
Day 3	1.5 ± 1.13	1.0 ± 0.59	**0.002**‡
Day 7	4.0 ± 5.46	4.5 ± 3.91	0.136‡
Calcium Day 3 (mmol/l)			
Ionized calcium	1.1 ± 0.12	1.2 ± 0.05	**<0.0001**‡
Non-ionized calcium	2.0 ± 0.17	2.1 ± 0.17	**0.002**‡
Hypocalcemia (Ionizedcalcium <1.10 mmol/l)	31 (60.8%)		**<0.0001**

†1 missing value in each group
††1 missing value for the group GOS>3
‡Mann-Whitney-U test for unpaired variables

Treatment regimens included a crystalloid solution, proton pump inhibitors, analgesic and tranquillizers in case of agitation. A combination of propofol and rocuronium was used for endotracheal intubation. At admission, clinical variables were age, sex, seizures and pupillary reaction assessment. We further measured respiratory and cardiac frequency as well as arterial systolic, diastolic and mean arterial pressures.

Statistical analysis

Statistical analysis was performed using SPSS software (SPSS 23, IBM, Armonk/USA). Metric data are shown as means and standard deviation, nominal data as frequency and valid percent. Variables were tested for normal distribution using the Kolmogorov-Smirnov test in addition to Q-Q plots and histograms. If the assumption of normality was violated, Mann-Whitney U test was performed to test for differences between groups, instead of student's t-test for unpaired variables. Nominal data was analyzed by Pearson's Chi-square test. Also, for correlation analysis Pearson's correlation coefficient (r) was

used. For the determination of cut-off levels for lactate regarding outcome (GOS-score) ROC-analyses was conducted. A p-value of <0.05 was considered as significant.

Results

A total of n=160 patients were included in our study (n=99 retrospectively/n=61 prospectively) from 2004 to December 2015. Median age was 47 years (range: 16 to 87). N=88 (55%) were male and n=72 (45%) female. N=69 (43%) patients had a GOS ≤ 3 (group 1) and n=91 (57%) had a GOS>3 (group 2). After evaluation of demographics and clinical variables (Table 1), following parameters showed a statistically significant difference between the two groups. Patients in the GOS ≤ 3-group were significantly older than patients with a GOS>3 (p=0.008). Also, there was a significant association between age stratified by age-groups and GOS with χ^2=6.72, df=2, p=0.036 and Cramer's V of 0.205 (weak association). Also, a significant difference in mean arterial pressure was seen between the groups, with patients of the GOS>3 group having a higher mean arterial pressure of 114.2 ± 13.44 mmHg *vs.* 105.7 ± 16.47 mmHg, p=0.005. Furthermore, the pH-level on day 3 was higher in the GOS ≤ 3-group than in the GOS>3 with p=0.046 (7.4286 ± 0.05595 *vs.* 7.4103 ± 0.05508) and a significant association between GOS-group and pupil reaction with χ^2=8.0, df=1, p=0.007 and Phi of 0.224 (weak association) was seen. Additionally, a significant association between GOS-group and pupil reaction existed with χ^2=8.0, df=1, p=0.007 and Phi of 0.224 (weak association). Evaluating lactate levels we found a significant difference between patients with a GOS ≤ 3 and the lactate level on day 3 with p=0.002 and a correlation coefficient of r=0.243 (weak correlation) and R^2=0.059.

Therefore, patients with a GOS ≤ 3 account for only 5.9% of the variability in the lactate level on day 3. Lactate levels were significantly higher in the GOS ≤ 3-group on day 3 with p=0.002, but not on day 7. There was a significant correlation between the lactate level on admission and the lactate level on day 3 with p<0.0001 and a correlation coefficient of r=0.333 (weak correlation) and R^2=0.111. Therefore, lactate level on admission accounted for 11.1% of the variability in the lactate level on day 3. ROC-analysis showed a lactate cut-off value of 0.95 mg/dl on day 3 with a sensitivity 70.5% of and a specificity of 53.7% (Youden-Index =0.242), though further investigation showed its relatively poor clinical relevance (Figure 1). Also, a significant difference between having hypocalcemia or not and lactate levels on day 3 with p<0.0001 was seen. Both, ionized calcium and non-ionized calcium levels were lower in the GOS ≤ 3-group (p<0.05) and a significant association between GOS-group and hypocalcemia with χ^2=42.50, df=1, p<0.0001 and Phi of 0.574 (mean association) was present. A significant correlation between hypocalcemia and the lactate level on day 3 with p<0.0001 and a correlation coefficient of r=0.467 (weak correlation) and R^2=0.218 was calculated. Therefore, hypocalcemia accounts for 21.8% of the variability in the lactate level on day 3.

Discussion

Our data indicate an association of hypocalcemia and lactate elevation in isolated TBI. Several pathomechanisms for hypocalcemia have been discussed among which are a sudden intracellular Ca++ - influx and apoptosis [1-5]. Furthermore, a disruption of the aerobic mitochondrial pathway may lead to Lactate accumulation. This enhances calcium chelation with further hypocalcemia. Cell death through calcium sensible caspases [6-15] may be induced. A key factor for impairment of the aerobic mitochondrial pathway is a lower MAP value with poor tissue oxygenation enhancing lactate accumulation [16]. Moreover, an increased intracranial pressure due to brain edema and swelling causes malperfusion and inadequate delivery of oxygen to already insulted neuronal cells [16,17]. Within our cohort, the presence of acidosis and lactate elevation on day 3 occurred significantly more frequently in patients with GOS ≤ 3. At this point, a switching from aerobic to anaerobical mitochondrial pathway may occur causing a neuro inflammatory response. Considering the host defense reaction, treatment approaches may include the maintaining of adequate cerebral blood perfusion, avoidance of acidosis. This may prevent inflammation and disturbances in the aerobic mitochondrial metabolism and therefore improve the patient`s outcome [18].

Present changes in the demography of TBI show an increase of the median age of individuals who experience TBI. Age is a well-known factor predisposing unfavorable outcomes in patients with TBI. In general, elderly patients with TBI tend to who have more severe pre-existing medical conditions before experiencing TBI compared to younger adults. Furthermore, other aging-related changes such as cerebrovascular atherosclerosis and decreased free radical clearance should be considered. They may increase the risk of brain injury or secondary insult and activating neuronal programmed death. This assumption was confirmed by the studies from Vinas and Manuel their cohorts mainly consisted of patients >65 years of age at time of TBI. Age was a significant factor for dismal outcome. Our results show that increased levels of serum lactate combined with decreased ionized serum calcium levels may be a valuable marker for the depth of brain damage three days after trauma. This may reflect the result of a cascade of various pathologic mechanisms such as direct mechanical trauma, neuro-inflammation, altered vessel-autoregulation and hypoxia. It could be useful as a marker for severity of trauma and may help to predict the clinical course and patient's outcome.

Conclusion

Serum levels of lactate and calcium are markers which are easy to assess. According to our study, they can be useful to assess the severity of TBI. Further studies should be performed to clarify the role of lactate in TBI regarding the on-going pathophysiological process involving intracellular calcium.

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