The Predictive Role of Biochemical Plasma Factors in Patients with Severe Traumatic Brain Injuries

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Traumatic brain injuries (TBI) represent a high impact public health problem due to a high rate of death , long term disability and occurrence especially in young adults. Despite several promising animal studies, several parameters were proposed as biological markers and were assessed for this aim. Our study proposes the study of the early biochemical changes in association to hematological parameters for severe TBI patients prognosis. 43 patients with acute TBI were included in study based on clinical, laboratory and imagistic findings. The severity of the TBI was established by Glasgow Coma Scale GCS 3-8. In all patients were evaluated hematologic parameters (Red blood cell count - RBC, Hematocrit, blood Hemoglobin, White blood cell - WBC, Platelet count and biochemical parameters (glucose, urea, creatinine, electrolytes). Outcome was expressed as Glasgow Outcome Scale (GOS), between 1-5. Values were compared to control group -15 cases. Significant early differences in body temperature, heart rate, and systolic blood pressure were observed in TBI group versus control ($p<0.05$). After correlation, laboratory findings significantly associated to severe outcome - GOS = 1, 2 - ($p<0.05$) were plasma Na decrease and significant glucose increase. An early increase of temperature and decrease of Na may predict a severe outcome in patients with acute TBI; association with shifts in heart rate and blood pressure, imposes aggressive treatment measures.

Keyords: traumatic brain injury, hyponatremia, glucose

TBI is the cause of approximately two-thirds of post-traumatic deaths and the most common generator of post-traumatic permanent disability; an European meta-analyze presented an overall incidence rate of 262 (CI, 185–339) per 100,000 per year for admitted TBI patients [1].

All patients with severe TBI and 75% of those who have suffered mild trauma remain with physical and mental disabilities [2].

Shortly after brain trauma, the sympathetic adrenal system activation produces a real *storm* due to intense and multilateral pathophysiological cascades [3,4].

In this context, recent results reveal the appearance of systolic dysfunction following TBI; according to authors, early hypertension and tachycardia involve a catecholamines excess leading to systolic dysfunction which may generate secondary brain injuries [5].

Despite promising results in animal studies, no biological markers relevant for the evolution of TBI have been identified to improve outcome in human.

Our study tries to identify an early marker or cluster of markers who may outline clinical outcome and serve as predictor of prognosis in patients with severe TBI.

Experimental part

Methods

The present study was carried out in the Neurosurgery Clinic, Emergency St.Pantelimon Hospital Bucharest, Romania, between 01.01.2017 and 31.12.2018 and consisted of a retrospective analyze performed in accordance to ethical regulations derived from the Declaration of Helsinki and with respect of the personal data management.

Study population

Inclusion criteria: The group with traumatic brain injury was composed of 43 patients, both gender, >18 years old, with Glasgow Coma Scale (GCS) at admission between 3-8, and an estimated time from injury of maximum 12 h. Brain injury was documented by CT or IRM and patients undergone neurosurgical treatment when necessary.

Exclusion criteria: aging <18 years, other brain lesions (stroke, aneurysms, brain tumors), concomitant major thoracic or abdominal trauma, infectious diseases/sepsis; pregnant or lactating mothers; drug administration - corticosteroids, diuretics, antiplatelet drugs.

Data from 15 apparent healthy persons, presented at emergency department for minor orthopedic injuries (ankle sprain) served as control.

Demographic data of the patients, GCS score and physical examination were recorded at admission; outcome at six month was evaluated using Glasgow Outcome Scale - GOS [6].

Laboratory data collection - in the TBI patients, blood samples were drawn at presentation for hematologic parameters (erythrocyte count - RBC, Hematocrit, Hemoglobin, White blood cell count - WBC total and differentiated, Platelet count and biochemical parameters (urea, creatinine, glucose, plasma electrolytes - Na^+, K^+, Ca^{2+}. Analyses were performed on a Pathfast Compact immune Analyzer ver. 2.00 Mitsubishi.

Clinical, demographic, laboratory features of the TBI patients were centralized in a database. The statistic comparison between groups was done using IBM SPSS 22.0 software. Quantitative variables such as demographic,

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clinical and laboratory parameters was used descriptive statistic to calculate mean and standard deviation; the differences between two groups were analyzed using Student t-tests and considered significant if $p<0.5$. To study the relation between outcome (appreciated through GOS scale) and laboratory /clinic parameters, ANOVA variance analyze was applied; if not normal variance distribution, Kruskal –Wallis nonparametric test was used.

Results and discussions

Demographic and clinical data

26 patients were male (60.46%) and 17 were female (39.53%). The severity of TBI was scored using GCS - severe: GCS < 8; the most common symptoms were coma (67%), stupor (55%), confusion 31%. Other clinical signs were pupillary changes (48%) and clear fluids draining from nose or ear (15%).

Demographic and clinical approached parameters are presented in table 1. Significantly increase of body temperature and systolic blood pressure were recorded in TBI group versus control (37.0 ± 0.52 in TBI versus 36.42 ± 0.39 in control, $p<0.05$, respectively 135.9 ± 21.62 in TBI versus 124 ± 21.46 in control, $p<0.05$).

Laboratory determinations results are presented in fable 2.

Significant changes consisted of increase in WBC and plasma glucose and reduction in platelet count and plasma Na ($p < 0.05$).

At 6 month, patient's outcome was evaluated according to Glasgow Outcome Scale (table 3). The highest percentage of case presented moderate disability and good recovery at 6 month, instead 9.3% were in vegetative status and 6.97% deceased.

From previously mentioned parameters, when correlated to severe GOS at 6 month - in severe TBI patients, only Na and plasma glucose levels were significant.

We identified a significant change in body temperature in TBI group versus control (37.0 ± 0.54°C in TBI group versus 36.42 ± 0.39°C in control, $p<0.0001$).

An early body temperature increase can be associated with severe lesions at admission, resulted of brain edema confirmed by CT scan [7,8].

In patients with TBI, when treated in the intensive care unit, recorded temperatures higher than 38°C were associated with a higher probability of death (10–20%) [9,10].

In our study, heart rate were 97.34 ± 14.1 in TBI group versus 86.33 ± 9.69 ($p= 0.004$) in control. This result sustains another study, which showed a relation between heart rate and mortality in severe TBI patients. Authors found that a HR between 80-89 is related to the lowest mortality in patients with severe TBI. HR lower than 50 or higher than 110 beats per minute was related to a higher mortality. That is why HR could serve as a marker for more intense treatment options [11,12].

No. of patients	Control = 15	TBI =43
Age	37.16 ± 8.12	37.72±_12.4
Male/Female	9/6	26/17
Body temperature (°C)	36.42 ± 0.39	37.0 ± 0.52 (p <0.05)
Heart rate	86.33 ± 9.69	97.34 ± 14.1 (p <0.05)
Systolic BP (SBP) in mm Hg	124 ± 21.46	135.9 ± 21.62 (p <0.05)
Diastolic BP (DBP) in mm Hg	86.46 ± 16.9	84.37 ± 13.28

Table 1
DEMOGRAPHIC AND CLINICAL DATA

No. of patients	Control = 15	TBI =43
Erythrocyte count (x 10^6)/mm^3	4.17 ± 0.65	3.86 ±0.78
Hemoglobin (g/dL)	13.32 ± 0.69	13.43 ± 0.74
WBC (x 10^3) /mm^3	7.16 ± 1.59	9.98 ± 3.49(p <0.05)
Platelet count (x 10^5) /mm^3	231.53 ± 63.7	194.53 ± 58.9 (p <0.05)
Plasma Na^+ (mmol/L)	134.98 ± 3.35	132.41 ± 3.05 (p <0.05)
Plasma glucose (mg/dL)	99.33 ± 10.5	117.51 ± 15.3 (p <0.05)

Table 2
LABORATORY DATA RESULTS

Outcome	Score	No. of patients	%
Deceased	1	3	6.97
Vegetative state	2	4	9.3
Severe disability	3	6	13.95
Moderate disability	4	13	30.23
Good recovery	5	17	39.53

Table 3
GLASGOW OUTCOME SCALE

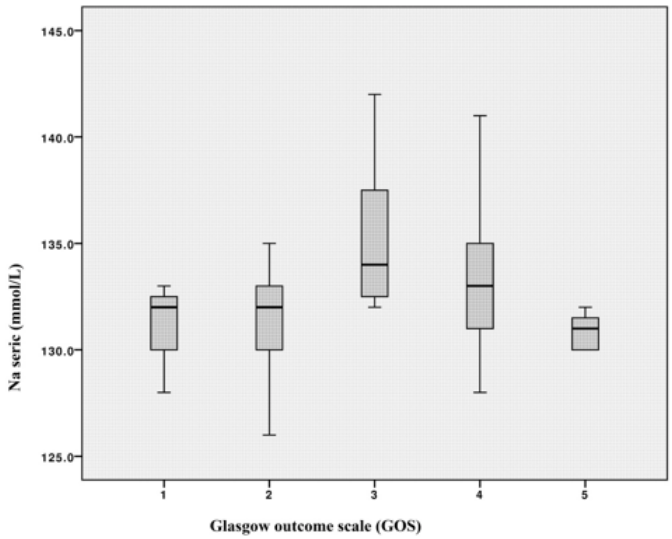

Fig. 1 Relation between outcome (expressed as GOS) and plasma Na in patients with severe TBI

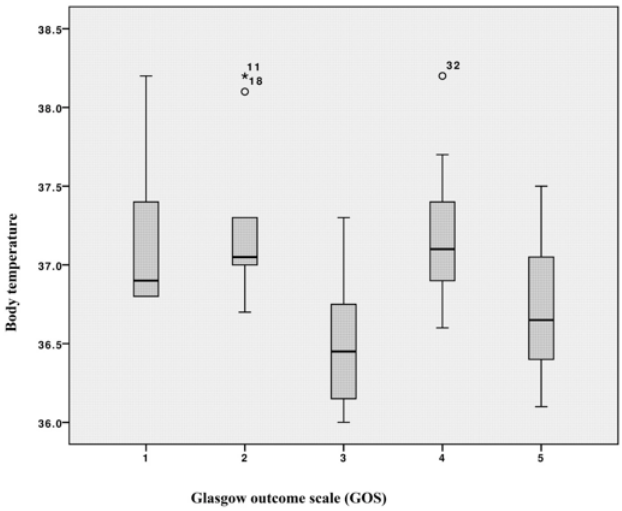

Fig. 2 Relation between outcome (expressed as GOS) and body temperature in patients with severe TBI

In present study, systolic blood pressure (SBP) was found significantly increased in TBI group: 135.9 ± 21.62 mm Hg versus 124 ± 21.46 mm Hg, p = 0.03 in control; DBP was reduced but not significant: 84.37 ± 13.28 mm Hg in TBI group versus 86.46 ± 16.9 mm Hg, p = 0.316 in control. If older studies showed that related with time evolution, patients with early hypotension did worse more than patients with delayed hypotension, recent studies found a linear association between lowest pre-hospital systolic blood pressure and probability of mortality, but not an identifiable threshold or inflection point between 40 and 119 mm Hg [13-15]. Taken together, these results sustain the theory of systolic dysfunction after severe TBI; this is why common cardiovascular measurements become valuable parameters in brain trauma [16].

Regarding laboratory findings, no differences were registered for erythrocyte count, hemoglobin and hematocrit.

Our results showed a significant increase in the total number of WBC in TBI group versus control (9.98 ± 3.49) x 10^3 /mm^3 versus 7.16 ± 1.59) x 10^3/mm^3, p= 0.0022. TBI initiates an inflammatory reaction encompassing several interrelated components [17,18].

Early after brain injury, neutrophils represent first cell which migrate to injury site; their number increase in the subarachnoid space. When used, immunohistochemistry showed that inflammatory infiltrate contains mainly monocytes, and lesser lymphocytes [19].

Platelet count showed significantly decreased in the patient with severe TBI (194.53 ± 58.9) x 10^3/mm^3 versus (231.53 ± 63.7) x 10^3/mm^3 in control, p = 0.0244.

In other studies, platelet count showed abnormal results in 59% patients reflecting that thrombocytes are affected in patients with TBI [20, 21].

This is a clinically relevant target intended to help monitoring and improve management especially in patients on antiplatelet therapy [22].

In severe TBI group, we identified a significant reduced plasma Na (132.41 ± 3.05 mmol/L versus 134.98 ± 3.35 mmol/L in control versus, p = 0.0047); our results are sustained by literature data which consider that serum Na^+ imbalance are very frequent in brain injuries. These imbalances include hypernatremia or hyponatremia [23].

Hyponatremia appears very often in patients with TBI and its management is extremely important as long as the two main causes, the inappropriate secretion of antidiuretic hormone (SIADH) and cerebral salt wasting syndrome (CSWS) have complete opposite therapeutic approaches [24].

Regarding plasma glucose, we identified a significant increase of plasma glucose in TBI group 117.51 ± 15.3 mg/dL versus 99.33 ± 10.5mg/dL in control, (p <0.05).

Although hyperglycemia in TBI was reported as related with a severe outcome, glucose metabolism changes in the injured brain were not completely understood [25, 26].

However, when related to outcome (expressed as GOS), only plasma Na decrease (p=0.002004) figure 1 and temperature (p=0.0088) figure 2 presented significance.

Conclusions

Our results suggested that the increase in body temperature increase, systolic blood pressure and HR are critical parameters associated with long term negative outcome in patients with severe TBI. In such cases, plasma Na decrease along with temperature increase may represent supplementary early markers for intensive care in patients with major head trauma. However, future studies are necessary to confirm the link between mentioned parameters and major head trauma.

Limitation of the study

Our study included a limited number of cases so we can only present a conclusion. Despite this limitation, our study sustains the early approach of correlated parameters in order to adopt an aggressive treatment for the limitation of the long term disabilities.

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References

1.PEETERS, W., VAN DEN BRANDE, R., POLINDER, S., BRAZINOVA, A., STEYERBERG, E.W., LINQSMA, H.F. Acta Neurochir (Wien). **157**, no.10, 2015 p.1683-1696.

2.ROOZENBEEK, B., MAAS, A.I.R., DAVID, K., MENON, D.K., Nat. Rev. Neurol. **9**, no.4, 2013 p.231-236.

3.RAFTU, G., DEBITA, M., DINU, C., PANGAL, A., HODOROG, D., CUCIUREANU, I. Rev. Chim. (Bucharest), **70,** no.1, 2019, p.228–232.

4.HEFFERNAN, D.S., INABA, K., ARBABI, S., COTTON, B.A. J Trauma. **69**, no.6, 2010, p.1602-1609.

5.KRISHNAMOORTHY, V., ROWHANI-RAHBAR, A., CHAIKITTISILPA, N., GIBBONS, E.F., RIVARA, F.P., TEMKIN, N.R., VAVILALA, M. S. Neurocrit Care **26** no.3, 2017, p.379-387.

6.MCMILLAN, T., WILSON, L., PONSFORD, J., LEVIN, H., TEASDALE, G., BOND, M. Nat Rev Neurol. **12**, no.8,2016, p.477–85
7.YOKOBORI, S., YOKOTA, H. J. Intensive Care. **4**, no.28, 2016
8.MIYATA, K., OHNISHI, H., MAEKAWA, K., MIKAMI, T., AKIYAMA, Y., IIHOSHI, S., NARIMATSU, E. J. Neurosurg., **124,** no.2, 2016, p.527-537.
9.PAPACOCEA, A., PAPACOCEA, T., DANAILA, L., ION, D., BADARAU, A., PAPACOCEA, R. Chirurgia, **105**, no.6, 2010, p.805-807.
10.LEY, E.J., BERRY, C., MIROCHA, J., SALIM, A. J. Surg. Res. **163**, no.1, 2010 p.142-145.
11.SYKORA, M., CZOSNYKA, M., LIU, X., DONNELLY, J., NASR, N., DIEDLER, J., SMIELEWSKI, P. Crit. Care Med. **44**, no.6, 2016, p.1173-1181.
12.NUSSBAUM, L.A., HOGEA, L.M., FOLESCU, R., GRIGORAS, M.,L., ZAMFIR, C., L., BOANCA, M., ERDELEAN, D., ROSCA, E.C.I., NUSSBAUM, L., SIMU, M., A., LUPU, V., Rev.Chim. (Bucharest), **69**, no.4, 2018, p.965-970.
13. CHESNUT, R.M., MARSHALL, S.B., PIEK, J., BLUNT, B.A., KLAUBER, M.R., MARSHALL, L.F. Acta Neurochir Suppl (Wien)., **59**, 1993,p.121-125.
14.PAPACOCEA, T., POPA, E., TURLIUC, D., PAPACOCEA, R. Farmacia, **67**, no. 1, 2019, p. 140-145.
15. VRINCEANU, D., BANICA, B., CIRSTOIU, C. F., PAPACOCEA, R., PAPACOCEA, T. Rom. J. Mat., **48**, no.4, 2018, p.407-411.
16. PAPACOCEA, T., BURAGA, I., PAPACOCEA, R., BADARAU, A.I., BURAGA, M., CIORNEI, C., MIHAI, G, STOIAN, I., ADAM, D. Farmacia, **62**, no.6, 2014, p.1118-1125.
17.ZIEBELL JM, MORGANTI-KOSSMANN MC. Neurotherapeutics, **7**, no.1, 2010, p. 22–30.
18.MIHAI, L.G, MITREA, N., PAPACOCEA, R., CIORNEI, C., BADARAU, A.I. Farmacia, **60**, no. 3, 2012, p.358-366.
19. KELLEY, B.J., LIFSHITZ, J., POVLISHOCK, J.T. J. Neuropathol. Exp. Neurol. **66**, no.11, 2007, p.989–1001.
20.PAPACOCEA, T., ROSCA, A., BADARAU, A.I., PAPACOCEA, R., C. CIORNEI, C., ION, A.D. Chirurgia, **104**, no.1, 2009**,** p. 99-103.
21.CHANG, R., CARDENAS, J.C., WADE, C.E., HOLCOMB, J.B. Blood,**128**, no.8, 2016, p.1043-1049.
22.VRINCEANU, D., BANICA, B., PAPACOCEA, R., PAPACOCEA, T. Rom. J. Leg. Med., **26**, no.1., 2018, p.16-20.
23. STURDIK, I., ADAMCOVA, M., KOLLEROVA, J., KOLLER, T., ZELINKOVA, Z., PAYER, J. Eur. J. Intern. Med. **25**, no.4, 2014, p.379–382
24. KURAMATSU JB, BOBINGER T, VOLBERS B, STAYKOV D, LUCKING H, KLOSKA SP, HUTTNER, H. B. Stroke, **45**, no.5, 2014, p.1285-1291.
25. SELWYN, R., HOKENBURY, N., JAISWAL, S., MATHUR, S., ARMSTRONG, R.C., BYRNES, K.R. J. Neurotrauma, **30**, no.23, 2013, p.1943-1953.
26.AGEU, L., TALPOS, C., KANALAS, G., CRISAN, S., ZAMFIR, C., L., POROCH, V., ANGHEL, M. Rev.Chim.(Bucharest), **69**, no. 3, 2018, p.621-626.

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