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'SERUM LACTATE AND CALCIUM AS POSSIBLE OUTCOME PREDICTORS IN SEVERE TRAUMATIC BRAIN INJURY'

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ABSTRACT: Background: Traumatic brain injury has significant morbidity and mortality. Several prognostic markers have been evaluated to predict outcomes. ABG (arterial blood gas) analyzers are routinely available and predict the value of calcium, lactate and other electrolytes. We evaluated serum calcium and lactate as a prognostic markers in severe TBI. **Methods:** We prospectively studied 100 patients with severe TBI. Blood samples for calcium and lactate were taken following admission, day 3 and day 7 after trauma and the relationship with mortality and functional outcome was studied. The Glasgow Outcome Scale (GOS) was used to access functional outcomes. GOS≤3 was considered a poor outcome (Group I). GOS>3 was taken as a good outcome (Group II). **Results:** Mean age was 51 years. Most patients were males, 77% in Group I and 70% in Group II. Patients in the GOS≤3 group were significantly older than patients with a GOS score >3(p=0.007). Lactate levels were significantly higher in the GOS≤3 group on day 3 (p<0.0001) but no association on day 7. GOS and ionized calcium (P<0.0001) had a significant association on day three. There was no statistical association of GOS with non-ionized calcium. **Conclusion:** Raised serum lactate levels and low serum ionized calcium on day 3 correlated with poor outcomes. They can be used as prognostic markers for isolated severe TBI.

INTRODUCTION: Traumatic Brain Injury (TBI) affects about 70 million people annually worldwide [1]. The total number of TBI in India is unknown, but estimates suggest more than a million trauma-related deaths in India each year, of which 50% are TBI related [2]. The prognostic factors for TBI may range from clinical indicators, radiological imaging and biomarkers (in blood or CSF). To predict the outcome of TBI, the biomarker should be readily accessible, predictive, sensitive, and specific. Patients with TBI are at increased risk of developing electrolyte abnormalities [3].

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The use of crystalloids, diuretics, mannitol, cerebral salt wasting, and SIADH are reasons for electrolyte imbalance in TBI patients. TBI patients undergo neuroinflammatory response, which triggers the release of pro-inflammatory proteins/ cytokines, which cause calcium binding [4]. This leads to low calcium levels in the intracellular space with consequent calcium release from the sarcoplasmic reticulum, activating caspases and resulting in cell death [5].

Patients with TBI undergo various metabolic changes in the brain, reflecting brain energy metabolism in response to trauma. Lactate in the brain tends to be elevated in TBI even though there is enough oxygen delivery to the brain [6]. Astrocytes and neurons signal the metabolic pathway shift from aerobic to anaerobic [7]. The traumatic brain also has a dysfunction of mitochondria which shifts pyruvate into the tricarboxylic acid cycle and

increases the amount of lactate produced [6]. Also, LDH5 an isoform of lactate dehydrogenase, is found in astrocytes and promotes the conversion of pyruvate into lactate [8, 9]. ABG analyses are routinely done and easily predict the value of calcium, lactate and other parameters. This study intended to analyse the predictive qualities of calcium and lactate as prognostic markers for short-term outcomes in patients with severe TBI.

MATERIAL AND METHODS: This observational study was conducted in the Department of Anesthesiology & Critical Care, at a tertiary care centre in North India over a period of two years. After obtaining approval from the Institutional Ethical Committee (122/ETH/GMC/ICMR), the patient's family members obtained written informed consent. The study included severe TBI (GCS≤8) patients. All the patients were managed according to the institutional protocol by recent Traumatic brain injury guidelines.

Inclusion Criteria: patients with isolated severe TBI (GCS3-8) admitted within 24 hrs of injury, age more than 18 years, no previous history of inflammatory, metabolic, and neuropsychiatric disorders. Severe brain injury was defined as a closed injury with a post-resuscitation Glasgow Coma Score (GCS≤8) or deterioration to a GCS ≤ 8 with in 24 h of admission. Exclusion Criteria: patients undergoing repeat surgical procedures, those with co-morbid conditions predisposing them to an intraoperative increase in serum lactate e.g liver disease, kidney disease, shock and sepsis. Other exclusions were hemodynamic instability, chronic severe neurological disorders, TBI beyond 24 hrs, medication intake or diseases affecting calcium metabolism, hyperphosphatemia, hypoalbuminemia, hypomagnesemia. All baseline investigations were recorded in every study subject, including CBC, KFT, LFT, blood glucose, serum electrolytes, and baseline lactate levels. Age, gender, and weight was noted. Lactate and calcium levels (ionized and non-ionized) were analyzed on admission, 3rd day and 7th day. Lactate and calcium levels in the patient with TBI were statistically compared between two groups having GOS≤3 and GOS>3. The Glasgow Outcome Scale (GOS) was used to access functional outcomes that rated patient status into one of five categories: 1. Dead, 2. Vegetative State, 3. Severe Disability, 4. Moderate Disability or 5. Good Recovery. GOS≤ 3 was taken marker of morbidity and mortality. Hypocalcemia was defined as serum calcium<2mmol/l and ionized calcium<1.10mmol/l. High serum lactate was taken as >2mmol/l.

Statistical Analysis: Using Graph Pad Prism (Version 9), statistical analysis was performed. Mean values with standard deviations were calculated (Mean ± SD). The students-test and one-way analysis of variance (ANOVA), wherever applicable, were used to test the significance of the differences between different experimental variables, and values of P≤0.05 were considered statistically significant. Pearson's correlation coefficient was calculated to estimate the strength of the relationship between different variables using R software, version 4.2.2.

RESULTS: The enrolled patients were divided into two groups based on their outcome, group I (GOS ≤3) and group II (GOS>3). Group I had 45 patients, and group II had 55 patients. The enrolled patients were stratified into age groups (18-29, 30-59, and > 60 years). There was a statistically significant difference in age between the two groups **Table 1.**

TABLE 1: AGE DISTRIBUTION OF PATIENTS

Variable	GOS≤3 (n=45)	GOS≥3 (n=55)	p-value
Age (Years)	51.57±11.22	36.16±12.42	0.0076**
Age by Group			
18-29	3 (6.66%)	25 (45.45%)	
30-59	34 (75.56%)	22 (40%)	0.0406*
≥ 60	8 (17.78%)	8 (14.55%)	

In Group I, out of 45 patients, 35(77.7%) were male, and 12(22.3%) were female. In Group II, out of 55 patients, 39(70.9%) were males, and 16(29.09%) were females. In group I 20 patients died (GOS=1), 15 patients were vegetative (GOS=2), 10 patients had severe disability (GOS=3) on discharge.

In group II 33 patients had moderate disability (GOS=4) and 22 had good recovery (GOS=5) on discharge. The results showed a significantly positive correlation(r =0.34, p< 0.0001) in lactate levels between day 0 and day 3. However, on day 0 and day 7 a positively weak and insignificant

correlation was observed(r=0.03, p > 0.05). On the other hand, a negative correlation was observed between day 3 and day 7(r = -0.02, p>0.05) **Table 2.**

TABLE 2: LACTATE ON DAY 0, DAY 3 AND DAY 7 OF ICU ADMISSION

Lactate levels (m mol/l)	Group I	Group II	P value
Day 0	2.31±0.31	2.29±0.32	0.7049
Day 3	2.90±0.42	1.79±0.18	<0.0001****
Day 7	2.04 ±0.19	2.02±0.18	0.5910

On comparison of ionized and non-ionized calcium between the groups, significant difference and positive correlation was observed only in ionized calcium on day 3 (r=0.302, p<0.0001). On other days no difference was found between the groups' in **Table 3.**

TABLE 3: IONIZED AND NON-IONIZED CALCIUM LEVELS ON DAY 0, DAY 3, DAY 7 OF ICU ADMISSION

Ionized Ca (mmol/l)	Group I	Group II	P value
Day 0	1.04 ± 0.11	1.08±0.13	0.1045
Day 3	0.97± 0.10	1.23± 0.16	<0.0001****
Day 7	1.2± 0.09	1.23± 0.12	0.1685
Non-ionized Ca (m mol/l)			
Day 0	2.08± 0.13	2.13± 0.14	0.0846
Day 3	2.01±0.08	2.18±0.100	0.06777
Day 7	2.24±0.14	2.30±0.17	0.0955

DISCUSSION: TBI is of epidemic proportion in our part of the world with significant morbidity and mortality and mainly involving younger age groups. Although many markers, including calcium and lactate, have been studied in TBI but there are still unanswered questions and controversies like raised lactate levels in patients with TBI were found to have good outcomes. Also there is variability in studies regarding time course and calcium and lactate change patterns. Further calcium and lactate levels in TBI have not been studied in our population subset. As markers' expression depends on genetic factors, findings in population may not be necessarily valid in another population. We studied calcium and lactate as possible prognostic predictors compared to many studies involving either calcium or lactate levels.

During the study period, we examined a total 100 TBI patients. Group I (poor outcome) had patients with higher age than Group II with the level of significance of p value<0.0076. We observed that age influenced the outcome of severe Traumatic brain injury. As the age advanced, the poorer was the outcome. This study's findings were consistent with those of SS Dhandapani *et al.* who conducted a study on TBI patients and found age as a strong prognostic factor [10]. The association of poor outcomes in TBI with increasing age may be attributed to several factors. As the patient ages, the dura becomes more fixed to the skull bone, and with advancing age, the maintenance of adequate cerebrovascular reaction after trauma is decreased [11]. Other age-related changes include inadequate clearance of free radicals, which further enhances oxidative damage after TBI [12]. Patients with TBI were predominantly males in group I or group II, with 77% males in group I and 70% males in group II. The relationship between TBI and gender was statistically significant (p=0.0265), with males being more susceptible to TBI than females. Worldwide there is a higher prevalence of TBI among males with male, female ratio 2:1 [13].

Lactate is a commonly used biomarker in resuscitation manoeuvres. High lactate levels are associated with increased mortality in critically ill patients in ICU 1 and predict mortality after severe trauma [2, 14]. Lactate is an end product of metabolism, and elevated levels reflect a disruption of cellular metabolism [15]. Lactate is released from the traumatic brain due to ischemia, hypoxia, or anaerobic metabolism. Following traumatic brain injury, the level of lactate in the blood and cerebrospinal fluid increases [9]. Further, there is mitochondrial dysfunction causing mitochondrial enzymes to fail even though traumatic brain has sufficient oxygen delivery [6]. In this study, we measured blood lactate levels on three days of admission to the Intensive care unit and the outcome of these patients was analyzed using a GOS scale. On day zero, there was no statistical

difference in lactate levels between Group I (GOS≤3) and Group II(GOS>3). On day 3 the lactate values in group I of GOS score≤3 were found on higher side more than 2mmol/l and the data was found to be statistically significant with p value<0.0001, again on day 7 no statistical significance was found. The results of this study co relate with the studies of Kuhna V *et al* [16] where authors reported that in patients with GOS ≤3 elevated lactate levels are commonly seen on day 3 with statistically significant data. Vnas-rios JM *et al* [17] concluded that following TBI there is change over from aerobic to anaerobic mitochondrial pathway causing a neuro-inflammatory response and accumulation of lactate. Laode RA *et al* [18,] who studied lactate levels in TBI, found a statistical significance between lactate levels and GOS score on day zero and day one. In contrast, no statistical significance was found on day seven. However our study did not show any association of lactate with outcome on day zero. Our study could not explain the reason of normal lactate levels on admission and significantly elevated lactate on third day.

Paradoxically research has shown benefit of lactate therapy in animals and recently human studies have also shown benefit of lactate therapy. Duhaut *et al* [19] observed that lactate therapy had beneficial cerebral metabolic effects and also was associated with a significant reduction in intracranial pressure. Cureton *et al* [9] studied 555 TBI patients and found lactate higher in patients with a more severe TBI and they also hypothesized that elevated lactate levels may be neuroprotective. They found that the mean lactate levels in the mild, moderate, and severe head injury patients increased with the severity of trauma.

Cureton *et al* [9] concluded that neurons could use lactate and ischemic brain can enhance the lactate release by the glial cells, which in turn can protect the injured neurons to maintain cognitive development. Thus elevate lactate levels may be neuroprotective and may be an indirectly marker of severity of TBI. Hypocalcemia on admission has been associated with increased mortality and decreased time to death in trauma patients [20]. Calcium has been studied in context to traumatic brain injury and is reported to play a key role in TBI. Calcium has been linked to delayed cell death and damage after TBI. Hypocalcemia results from increased chelation to pro-inflammatory proteins released by injured neurons after TBI, leading to a decrease in calcium levels in the intracellular space with subsequent calcium release from the sarcoplasmic reticulum, activating enzymes caspases and resulting cell death [5]. Balbino M *et al.* [21] explained the correlation of hypocalcaemia with poor prognosis after TBI due to mitochondria enzyme inhibition and activation of lipases. In our study, ionized and non-ionized calcium levels were observed for three days on day zero, day 3, and day 7 of ICU admission. We found a statistically significant difference in the ionized calcium on the day 3rd of admission between the groups. In our study, ionized calcium levels on day three were prognostic markers of severe TBI. Our study did not show any association of non-ionized calcium with outcome. Similar results were reported in previous studies by Manuel VJ et al 22 wherein author reported a significant association between ionized calcium levels and mortality (p<0.008) on the third day of ICU admission.

The results of our study were also consistent with study done by Sanchez-Rodriguez *et al* who carried out a study in 122 patients with moderate and severe TBI and concluded that there is an association of serum ionized calcium (<1.10mmol/l) on third day after head trauma with mortality with significance value of (p<0.0009). No significant relation of non-ionized calcium with outcome was seen in their study [23]. This was contrary to findings of Kuhna *et al* [16] who found both ionized and non-ionized calcium levels as predictors of morbidity and mortality. Reason of ionized calcium being a prognostic marker of TBI in our study could be because ionized calcium reflects true calcium status as non-ionized calcium may be altered by serum protein levels [24].

CONCLUSION: The result of our study showed hyperlactemia and hypocalcaemia (ionized serum calcium<1.10mmol/l) may be significant and easily available markers in assessing the severity of brain damage three days after isolated severe TBI. The ability to stratify a severe TBI patient cohort in the post-traumatic phase with easily available biomarkers like calcium and lactate will help in the focused management of such patients. These results reflect various pathological mechanisms such as

neuroinflammation, altered vessel auto-regulation, and hypoxia.

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