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Prospective longitudinal study of biochemical changes in critically ill patients with severe traumatic brain injury: Factors associated and outcome at 6 months

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Abstract: Biochemical prognostic markers of severe traumatic brain injury have not been clearly identified. This study was conducted to study biochemical changes in patients with severe traumatic brain injury, with respect to neurological outcome.

Adult patients admitted within 24 hours of traumatic brain injury with Glasgow Coma Score 4-8, were prospectively studied for changes in various biochemical parameters. Outcome was assessed at 6 months. The mean serum albumin levels showed progressive fall till 2 weeks from 3.23 g/dL to nadir value of 2.86 g/dL, followed by mild increase to 2.99 g/dL at 3 weeks (p<0.001). The mean daily urine creatinine values demonstrated significant fall from 1255.4 mg/d to 1010.2 mg/d at 3 weeks (p<0.001). There was significant increase in mortality at 2 months among patients with atleast 15% fall in serum albumin and urine creatinine less than 1000 mg/d at 3 weeks (p < 0.005). Unfavorable outcome was noted in 12 out of 15, with at least 15% fall in serum albumin at 3 weeks, compared to 11 out of 25, with less than 15% fall in serum albumin (p=0.03). Unfavorable outcome was also noted in 16 out of 22, with low urine creatinine (<1000 mg/d) at 3 weeks, compared to 6 out of 17, with normal urine creatinine (p=0.02).

In patients with severe TBI, unfavorable neurological outcome at 6 months was associated with 15% fall of serum albumin or low urinary creatinine at 3 weeks, more so with the former.

Keywords: biochemical changes, factors, outcome, traumatic brain injury

INTRODUCTION

Severe Traumatic Brain Injury (TBI) is a major cause of disability and death in the young[1]. Severe TBI initiates a complex cascade of metabolic perturbations with the primary injury triggering secondary events that evolve over many days, leading to deleterious pathophysiological and biochemical reactions[2]. Numerous studies have consistently demonstrated increased protein catabolism following TBI[3-5]. Surprisingly, only a few biochemical markers have been identified to prognosticate the patients' response to brain injury. These markers also exhibit changes over time in patients of trauma as a component of metabolic response to injury or infection (MRII), independent of the nutritional status[6]. Even though this has also been noted in patients with severe TBI[7], detailed analysis of associated factors and their overall significance with respect to neurological outcome at 6 months are yet to be established. This was a prospective study to evaluate the efficacy of weekly biochemical monitoring in patients of severe TBI and their influence on neurological outcome.

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MATERIALS AND METHODS

Adult TBI patients admitted within 24 hours of injury with Glasgow Coma Score (GCS) 4 to 8, under the Department of Neurosurgery, AIIMS, New Delhi, from June to December 2005, were enrolled for the study. Patients with age more than 60 years, GCS 3, hypotension (admission systolic BP ≤ 90 mm Hg), diabetes mellitus, renal dysfunction (blood urea > 50 mg/dL) or hyperbilirubinemia (total bilirubin > 1 mg/dL) were excluded from the study.

Standard care given to study patients consisted of ventilation, seizure prophylaxis with Phenytoin, antibitiotic prophylaxis with Cefotaxime or Ceftriaxone and Netilmycin, and gastric ulcer prophylaxis with Ranitidine. Mannitol was given to patients with CT having evidence of mass effect. Frusemide was added to patients with midline shift. Fluid and electrolyte homeostasis was maintained. Decision regarding surgical decompression was taken according to the mass effect noted in computed tomography (CT) and was individualized to each patient. Enteral feeding was initiated either through nasogastric tube or orally as early

as possible and the volume of feed increased gradually according to the gastric tolerance. No patient had received parenteral hyperalimentation or albumin supplements. The clinical characteristics and weekly biochemical parameters till 3 weeks were noted in a pre-planned prospective database and were followed up.

Serum albumin and total protein levels were tested by Bromcresol green dye binding method and Biuret method respectively using Beckman Synchron CX5 Delta Clinical System (GMI Inc, Minnesota)[8]. Urine creatinine levels were tested by Jaffe's colorimetric method, using Hitachi 717 auto-analyzer (GMI Inc)[8].

Outcome: The primary outcome was Glasgow outcome scale (GOS)[9], assessed at 6 months following injury, either directly or over telephone. Good recovery or moderate disability was considered as favorable outcome and severe disability, persistent vegetative state or death was considered as unfavorable outcome. The secondary outcome measure assessed was mortality at 2 month.

Statistical Analysis: SPSS software (ver 10, SPSS Inc, Chicago) was used for the statistical analyses. The changes in biochemical parameters over time were analyzed by using General Linear Model (GLM) repeated measures analysis. Proportions were compared by using chi-square tests or Fisher's exact test, wherever appropriate. Subgroup analyses were carried out using Breslow-Day test of homogeneity of odds ratios. Multivariate analysis was conducted with logistic regression adjusting for admission GCS, surgical intervention, timing of full enteral feeding and changes in biochemical parameters. Two sided significance tests were used throughout, and the significance level was kept at $P \leq 0.05$.

RESULTS

From June through December 2005, 114 patients that fulfilled the eligibility criteria were enrolled for the study. Out of these 114 patients, 67 were prospectively assessed weekly till 21 days for changes in biochemical parameters during the hospital stay, the rest 19 were discharged and 28 patients expired before 21 days. The mean age of study sample was 35.4 years. There were 62 males and 5 females. Associated systemic injury was present in 16 patients. Surgical intervention was required in 39 patients, tailored according to the mass effect noted in CT.

Biochemical changes (Fig 1-3): As shown (Fig 1), the mean serum total protein levels showed insignificant increase in the first week from 6.25(SD±0.9) g/dL to a peak value of 6.49(SD±1.2) g/dL, followed by stabilization (p=0.54). The mean serum albumin levels showed significant fall till 2 weeks from 3.23(SD±0.5) g/dL to a nadir value of 2.86(SD±0.4) g/dL, followed by a mild increase to 2.99(SD±0.5) g/dL at 3 weeks (p<0.001) (Fig 2). The mean daily urine creatinine values demonstrated significant progressive fall from 1255.4 (SD±369) mg/d to 1010.2 (SD±246) mg/d at 3 weeks, as shown (Fig 3) with p value < 0.001.

Age, gender, GCS, systemic injury and surgical intervention had no significant association with degree

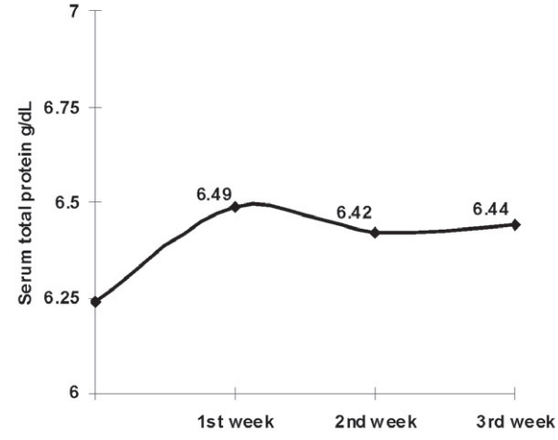

Fig 1: Changes in serum total protein

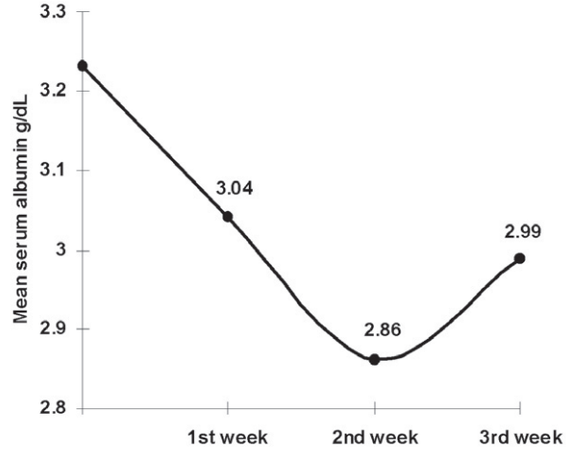

Fig 2: Changes in serum albumin

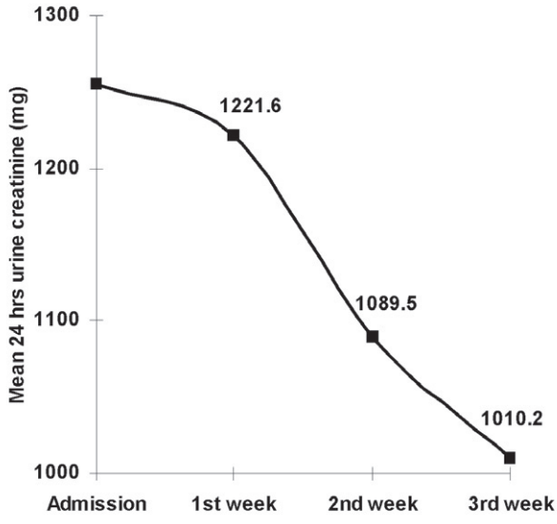

Fig 3: Changes in urine creatinine

of changes in any of these biochemical parameters (Table 1).

Biochemical changes Vs Mortality: As shown (Table 2), there was significant increase in mortality at 2 months among patients with at least 15% fall in serum albumin levels and urine creatinine less than 1000 mg/d at 3 weeks with OR 5.1, 11.8 and *p* values 0.005, < 0.001 respectively.

Biochemical changes Vs Neurological outcome: The Glasgow outcome score at 6 months was available for 40 patients. Unfavorable outcome was noted in 12 out of 15 patients with at least 15% fall in serum albumin

Table 1: Baseline characteristics Vs Biochemical changes

Baseline characteristics		≥ 15% fall in s.albumin at 3 wk	*p* value	U creat at 3wk* <1000 mg/d	*p* value
Age	< 40	11/42 (26%)	0.24	23/42 (55%)	0.49
	≥ 40	10/25 (40%)		11/24 (46%)	
Sex	Males	19/ 62 (31%)	0.65	31/ 61 (51%)	1.00
	Females	2/5 (40%)		3/5 (60%)	
GCS	4, 5	9/29 (31%)	0.96	18/28 (64%)	0.08
	6, 7, 8	12/38 (32%)		16/ 38 (42%)	
Systemic injury	Absent	16/51 (31%)	0.99	24/ 50 (48%)	0.31
	Present	5/16 (31%)		10/16 (63%)	
Therapy	Non-surgical	7/28 (25%)	0.34	14/28 (50%)	0.83
	Surgical	14/39 (36%)		20/38 (53%)	

* 1 patient could not undergo urine creatinine estimation at 3 weeks

Table 2: Biochemical changes Vs Mortality

Biochemical monitoring		Mortality at 2 months	OR (95% CI)	*p* value
Fall in serum albumin at 3wk	< 15%	7/ 46 (15%)	5.1(1.6-16.4)	0.005
	≥15%	10/ 21 (48%)		
U creatinine at 3 wk*	<1000mg/d	15/ 34 (44%)	11.8(2.4-57.7)	<0.001
	≥1000mg/d	2/ 32 (6%)		

levels at 3 weeks, as compared to 11 out of 25 patients with less than 15% fall in serum albumin (Fig 4). The difference was statistically significant with odds ratio (OR) of 5.1 (95% CI 1.1-22.7) and *p* value 0.03.

Unfavorable outcome was noted in 16 out of 22 patients with low urine creatinine levels (< 1000 mg/d) at 3 weeks, as compared to 6 out of 17 patients with normal urine creatinine (Fig 5). The difference was statistically significant with OR 4.9 (95% CI 1.2-19.2) and *p* value 0.02.

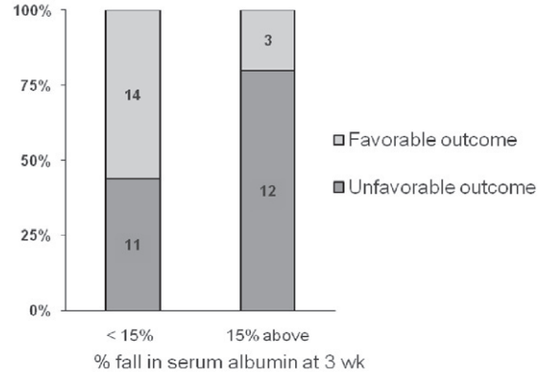

Fig 4: Albumin fall Vs Outcome (*p*=0.03)

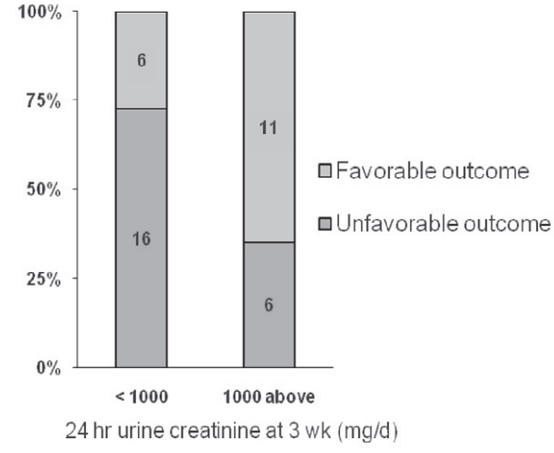

Fig 5: Urine creatinine Vs Outcome (*p*=0.02)

Multivariate analysis: In binary logistic regression model, after adjusting for GCS, surgical intervention, timing of full enteral feeding and biochemical changes, 15% fall in serum albumin level emerged as the only independent risk factor for unfavorable outcome at 6 months with adjusted odds ratio of 8.8 (95% CI 1.4-54) and *p* value 0.02.

Subgroup analysis: The prognostic effect of 15% fall in serum albumin level with respect to neurological outcome at 6 months, in various subgroups categorized on the basis of age, GCS, surgical intervention, systemic injury, timing of full enteral feeding and urine creatinine at 3 weeks did not reveal any significant subgroup difference (Table 3).

Table 3: Subgroup analysis

Factor		Unfavorable outcome at 6mth		OR (95%CI)	*P* value
		Alb<15%fall	Alb≥15%fall		
Age	< 40	5/17(29.4%)	5/7(71.4%)	6(0.9-42)	0.57
	≥ 40	6/8(75%)	7/8(87.5%)	2.3(0.2-32)	
GCS	4, 5	7/11(63.6%)	6/7(85.7%)	3.4(0.3-40)	0.62
	6, 7, 8	4/14(28.6%)	6/8(75%)	7.5(1-56)	
Therapy	Non-surgical	6/13(46.2%)	6/7(85.7%)	7(0.6-77)	0.75
	Surgical	5/12(41.7%)	6/8(75%)	4.2(0.6-30)	
Systemic injury	Absent	7/17(41.2%)	10/13(76.9%)	4.8(1-24)	0.53
	Present	4/8(50%)	2/2(100%)	NA	
Full enteral feeding	≤ 7 days	4/14(28.6%)	6/9(66.7%)	5(0.8-30)	0.42
	> 7 days	7/11(63.6%)	6/6(100%)	NA	
24hr U_{Cr} at 3wk	<1000mg/d	7/12(58.3%)	9/10(90%)	6.4(0.6-67)	0.83
	≥1000mg/d	3/12(25%)	3/5(60%)	4.5(0.5-42)	

DISCUSSION

Clinical and laboratory research on TBI in the past two decades had shown that all neurological damage does not occur at the moment of impact, but evolves over the ensuing hours and days, with the primary injury initiating a secondary injury cascade, consisting of several metabolic sequelae[2]. Surprisingly, only a few markers have been identified to prognosticate the biochemical response to trauma at the tissue level.

Increased protein catabolism following TBI has been consistently demonstrated in various studies[3-5]. Daily urinary creatinine excretion is a reliable estimate of somatic protein catabolism[6,8,10]. We noted low urinary creatinine to be a valuable prognostic indicator of unfavorable outcome at 6 months, possibly indicating the critical limit of somatic protein reserve.

Albumin, constituting 60% of protein in human plasma, is a biochemical marker of visceral protein status[6,10,11]. It is also one of the negative acute phase reactants reported to fall as a component of metabolic response to injury or infection (MRII), independent of the nutritional status[6,11]. Young et al noted hypoalbuminemia to last for at least 3 weeks following TBI[7]. This is likely to be due to increased vascular permeability as propounded by Fleck et al[12]. Acute post-injury elevation of cytokines such as interleukin-1 (IL-1), Tumor necrosis factor (TNF-á) and interleukin-6 (IL-6) was observed by McClain et al[13,14], leading to endothelial dysfunction resulting in hypoalbuminemia, following severe TBI. Other mechanisms proposed include hemodilution, decreased synthesis and also increased protein catabolism[6,11].

Various studies had suggested serum albumin to be a valuable prognostic indicator in critically ill patients[15-17]. McClain et al demonstrated hypoalbuminemia to be associated with unfavorable outcome at 18 days, but not 3 months following TBI[13]. We found 15% fall from baseline to be significantly associated with unfavorable outcome at 6 months independent of the effects of GCS, necessity for surgical intervention, timing of full nutritional supplementation and other biochemical changes.

Serum total protein levels did not show significant difference, possibly due to conflicting effect of increased positive acute phase reactants[6] such as C reactive protein (CRP), á-1 acid glycoprotein & á-1 antitrypsin and decreased serum albumin levels. Associated systemic injury did not show significant difference in the biochemical response, probably due to the universal nature of acute phase reaction[18]. Also it was uniform throughout the selected range of GCS. Though both low urine creatinine and 15% albumin fall were associated with unfavorable outcome, only the latter was found to be significant in multivariate logistic regression, probably signaling the combined effect of metabolic response and protein catabolism on recovery after TBI.

The nadir of serum albumin levels was noted at second week followed by partial but significant restitution similar to the findings of Young et al.[7] This may suggest a possible window period which could be of therapeutic relevance with respect to nutritional supplementation with

extraneous albumin. Even though few studies have indicated benefit of albumin in experimental TBI, the exact role of albumin in recovery after human TBI is far from clear.[19, 20]

In conclusion, there is fall in serum albumin levels and daily urinary creatinine excretion every week following severe TBI. Also unfavorable neurological outcome at 6 months was associated with either 15% fall of serum albumin levels or low urinary creatinine at 3 weeks, more so with the former.

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