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Original Research Paper

Pathology

ROLE OF VON WILLEBRAND FACTOR IN HEAD INJURY PATIENTS- A PROSPECTIVE STUDY.

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ABSTRACT

Introduction: - Head injury is an important health issue and its incidence is rapidly increasing. The serum level of vWf increases in response to various stimuli without attendant endothelial injury. An elevated serum level of vWf may suggest endothelial activation in severe head injury.

Aims and Objectives: - The purpose of this study was to find out correlation between plasma von Willebrand factor concentration and Primary outcome of severe traumatic brain injury in men.

Patients & Methods: This is a prospective study on 20 consecutive severe TBI (GCS 3-8 at arrival) male patients, aged 16-65 years arrived at emergency room, without previous history of neurological or psychiatric disease admitted at our institute.

Conclusion:-The result of mean plasma vWf concentration was significantly higher in the Head injury group than in the control group.

KEYWORDS :

INTRODUCTION

Head injury is an important health issue and its incidence is rapidly increasing in the world, especially in developing countries like India. Road traffic accidents contribute to about 60% of head injuries, remaining are due to fall from height and assault injuries. Among the accident deaths, 70% are due to head injury.

There are some well-established clinical (Glasgow Coma Scale (GCS)) and radiological (Marshall computerized tomography (MTCT) classification) parameters to measure severity of head injury.

von Willebrand factor (vWf), a known biomarker, synthesized by endothelial cell, is an endothelial specific glycoprotein. The serum level of vWf increases in response to various stimuli without attendant endothelial injury [8]. An elevated serum level of vWf may suggest endothelial activation in severe head injury. Measuring the vWf may be useful for predicting Delayed Traumatic Intra Cerebral Hemorrhage (DTICH), produced by weakness of the vessel wall in the cerebral parenchyma, occurring as either a direct or indirect effect of head injury.

A significant correlation exists between vWf concentration and score of Acute Physiology and Chronic Health Evaluation score (APACHE II), Injury severity score (ISS) and lung Injury score (LIS), suggesting that increased concentration of vWf in plasma are predictive of poor prognosis of patients following severe trauma.
The present study was thus carried out to correlate plasma von Willebrand factor levels with clinical outcome of severe traumatic brain injury.

AIMS AND OBJECTIVE

This study was conducted on 20 prospective patients to determine whether there is a correlation between plasma von Willebrand factor concentration and:

1. Primary outcome of severe traumatic brain injury in men.
2. Clinical and radiological measures following severe traumatic brain injury in men.

PATIENTS AND METHODS

PATIENTS

This is a prospective study on 20 consecutive severe TBI (GCS 3-8 at arrival) male patients, aged 16-65 years arrived at emergency room, without previous history of neurological or psychiatric disease admitted at our institute. Clinical, hematological, biochemical investigations, like electrolyte were evaluated daily or as the need arises, serum protein were evaluated daily for 4 days, management, and outcome data were recorded for all patients. Group A includes victims of severe TBI and Group B includes control group of 10 healthy male volunteers.

METHODS

Group A

Informed consent was obtained from the patients relatives as the patients were unconscious. Relatives were informed about the purpose of this study. Clinical outcome variables of severe TBI comprised survival, time for discharge from hospital and neurological assessment using the GOS at discharge. At admission and subsequent GCS scores were monitored.

Brain CT scans were performed within 24 h after the TBI and analyzed according to Marshall CT classification. Out of these patients first CT scan was done within 6 hours in 12 patients and within 6-12 hours in 8 patients. CT scans were repeated in all patients. In 5 patients CT was not repeated more than once, due to shorter stay with death in two patients and because of hemodyanamic unstability in 3 patients.

Only males aged 16-65 years were enrolled in the study to avoid interference of possible sex dependent difference in outcome as female are less susceptible to posttraumatic and post ischemic brain in injury as has been observed previously.

Group B

To establish normal values of plasma vWf, a control group was included consisting of 10 healthy male volunteers without history of brain damage (median age, 26.1 years; range, 24–29 years). Blood samples had been taken after obtaining informed consent.

Inclusion Criteria

Patients of severe TBI (GCS 3-8) at the time of admission without previous history of neurological and psychiatric illness.

Exclusion Criteria

We had excluded the following patients from the study:

1. Patients whose head injury suspected to be caused by an underlying disease (syncope, heart disease, malignant tumor, epilepsy).
2. Patients with preexisting disorders of the central nervous system.
3. Those with preexisting systemic disease that might be associated with a coagulation disorder (e.g., anticoagulant

therapy, renal dysfunction).
4. Patients with clinical evidence of brain death.
5. Female patients.

Blood sampling and biochemical measurements

Three venous blood samples were taken. First sample at admission, second 24 h after the first and third sample 96 hrs after the first sample. These were collected in 3.5 ml blue top tube (3.2% citrate) and filled to the line. Samples were processed (spun and frozen) within 1 hr. Two,1 ml aliquots of double spun plasma were frozen at ≤ -80°C until final estimation of plasma vWf Antigen (vWf:Ag) levels have been done through automated latex immunoassay. The assay correlates well with reference ELISA methods.

To avoid possible differences in hemodilution among the groups studied, total serum protein concentration of each sample had been measured.

OBSERVATION AND RESULTS

The observation and results of 20 male patients of severe TBI admitted in our hospital are as follows:-

TABLE 1. SHOWING GLASGOW COMA SCALE (GCS) AT ADMISSION

	GCS at admission (Mean)	No.	Standard Deviation
Total	6.20	20	1.508
Survivors	6.07	15	1.624
Non-survivors	6.6	05	1.140

Mean GCS at admission was 6.20 (range 4-8). For survivors mean GCS was 6.07 and for non survivors it was 6.60. On Mann Whitney U test these values are not significant (p = 0.476).

Mean hospital stay of all patient was 10.4 (range 4-26).For survivors and non survivors mean values were 11.9 days and 5.8 days respectively.

TABLE 2. SHOWING MARSHAL CT SCALE SCORE

	Mean Value	N	Standard Deviation
Total	4.30	20	0.657
Survivors	4.13	15	0.640
Non-survivors	4.80	05	0.447

Table 2 and 3 shows Marshal CT scale score and correlation of Marshal CT scale score and vWf in survivors and non survivors respectively.

Of all patients means value of Marshal CT Scale was 4.3 ± 0.657. For non survivors (mean 4.8 ± 0.447) values are significantly higher than survivors (mean 4.13 ±0.640) on Mann- Whitney U test (p = 0.042).

In non survivors all patients have features of raised ICP on serial CT scans with one has added post traumatic infarct and other one have IVH.

Correlation between plasma vWf concentration and Marshal CT score was statistically not significant (Table 5).

TABLE 3 SHOWING CORRELATION BETWEEN MARSHAL CT SCORE AND vWf IN SURVIVORS AND NON SURVIVORS.

			vWf at adm	vWf at 24 hr	vWf at 96hr
Non survivors	Marshal CT SCALE	Correlation Coefficient	.354	.707	.354
		P value	.559	.182	.559
		N	5	5	5
Survivors	Marshal CT SCALE	Correlation Coefficient	.055	.296	.087
		P value	.845	.284	.758
		N	15	15	15

TABLE 4: APACHE II SCORE

	Mean Value	N	Standard Deviation
Total	8.50	20	2.32
Survivors	7.733	15	1.71
Non-survivors	10.8	5	2.58

For all patients APACHE II scores mean values were 8.50 ± 2.32. APACHE II score was significantly higher for non-survivors 10.8 ± 2.58 (p = 0.014) than for survivors (7.733 ± 1.71). Thus APACHE II correlates well with severity of head injuries.

TABLE 5: SHOWING CORRELATION BETWEEN vWf LEVEL AND APACHE II AT ADMISSION AND 96 HOURS

Spearman's rho	Apache II score		vWf at adm	vWf at 24 hr	vWf at 96hr
		Correlation Coefficient	.455(*)	.385	.766(**)
		p value	.044*	.094	.000**
		N	20	20	20

There was a significant correlation between plasma von Willebrand factor concentration and Apache II level at admission (Spearman's rho 0.455 p = 0.044) and 96 hrs (Spearman's rho 0.766 p = 0.00)[Table 5]

TABLE 6: PLASMA von WILLEBRAND FACTOR IN SEVERE HEAD INJURY PATIENT AND CONTROL

	CASE			CONTROL
	vWf at admission(U/dL)	vWf at 24 hours (U/dL)	vWf at 96 hours(U/dL	U/dL
Mean	94.64	113.35	139.64	41.67
N	20	20	20	100
Standard Deviation	27.05	24.4	17.5	7.2090

Table 6 show mean values for vWf at admission, 24 hours and 96 hours are 94.64U/dL (± 27.45), 113.35 U/dL (± 29.4) and 139.64U/dL (± 17.56) respectively which are significantly higher than control group 41.67U/dl (± 7.209) and highly significant (p = 0.00) on Mann-Whitney U test.

CHART 1: PLASMA vWf LEVELS IN CASES AND CONTROL

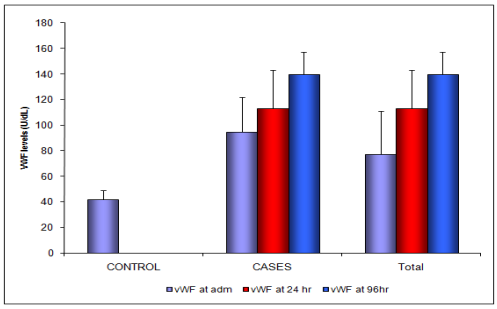


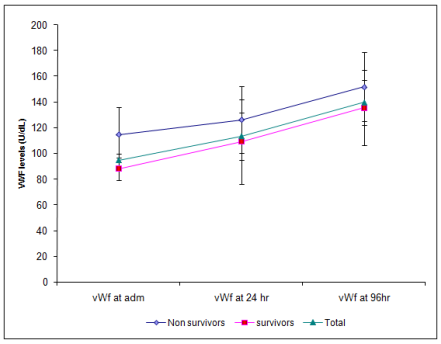
TABLE 7: COMPARISON OF vWF VALUES IN SURVIVORS AND NON SURVIVORS.

		vWf at adm U/dL	vWf at 24 hours U/dL	vWf at 96 hours U/dL
Survivors	Mean	88.013	109.087	135.540
	No	15	15	15
	Standard Deviation	25.93	32.7697	15.4178

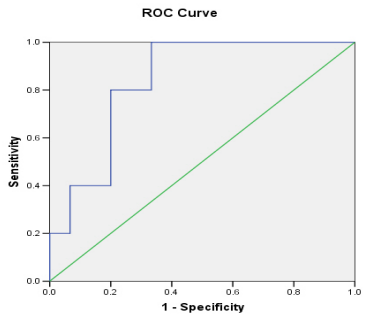
Non Survivors	Mean	114.520	126.160	151.960
	No	5	5	5
	Standard Deviation	21.5674	8.7891	5.0998

Mean values of plasma vWf level in non survivors are 114.52 U/dL , 126.16 U/dL and 151.96U/dL at adm, 24hrs and 96hrs respectively. In survivors these are 88.013U/dL,109.087U/dL and 135.54U/dL respectively. In non survivors values are significantly higher at admission and at 96 hrs (p = 0.026 and p = 0.013 respectively) (Table 7).

CHART 2: COMPARISON OF PLASMA vWf LEVELS IN SURVIVORS AND NONSURVIVORS.



We plotted a Reciever Operated Characteristic (ROC) curve and searched for a cut off point that would ensure detection of the highest proportion of individuals with potentially fatal outcome and the least compromise of specificity. Therefore a cutoff point of 92.6u/dL initial plasma vWf concentration was chosen. The sensitivity of plasma vWf concentration in predicting mortality according to the cut off is 1000, and specificity of 0.667(p= 0.026).ie sensitivity of 100% and specificity of 66.7%.



The area under the curve for initial plasma concentration is 0.840, p=0.026 (true area=0.5 or higher considered as significant).

DISCUSSION

In this study, we evaluated the potential role of plasma vWf as an early predictor of unfavorable outcome following severe TBI. Moreover, we tried to correlate plasma vWf with clinical and radiological parameters in adult male patients with severe TBI.

Biochemical markers of cellular stress/injury have been proposed to indicate outcome in the early phase after head injury. Early selection of patients at risk for deterioration after acute brain injury is crucial to improve current treatment strategies. Once deterioration becomes clinically evident, the patient may be out of the window of potential benefit.

We found an increased plasma vWf level in all severe TBI victims when compared to the control group. Our data are in concordance with previous studies suggesting that vWf could indicate evolving cerebral injury and endothelial activation in severe TBI and other brain injuries.

We found that the mean plasma level remained elevated in subsequent determinations among TBI patients, with the highest concentration being detected at the last measure (fourth day). Becker et al studied the post-trauma haemostatic disturbances in children with severe TBI, and also found vWf significantly increased 24 h after admission, with a peak of level within the second week. Similar results are observed by Olievera de Olievera et al[5] and Yokota et al[8] in adults. Thus results are in agreement with Oliviera at al[5] & Yokota et al[8].

Lai et al, in 1998, after studying 48 patients of SHI reported of mortality of 35 percent. In our study mortality is 25%, the incidence is high in both these studies but our figures are marginally low. The reason for this difference could be the small sample size of present study. Masson et al reported that death usually occurs within 5 days as consequence of cerebral injury. Ghajar also reported that most deaths from severe TBI occurring in the first week are caused by raised intracranial pressure. In our study also it is found that most of the deaths occur in the first week, mean is 5.8 days, range 3 to 9 days. We did not compare postmortem findings thus cannot comment of cause of death but the death occurs in first week so, our findings are in agreement with that of previous studies.

Of all deaths CT scans were repeated in all patients, but in two patients CT scans were not repeated more than once because of short hospital stay (3 days).

In the present study six patients (30%) had associated injuries. Three patients had associated long bone injury, 10% had chest injuries (multiple rib fractures). Both long bone injury and chest injuries did not positively correlate with poor outcome. Leone et al reported chest injury with pulmonary contusion does not appear to increase morbidity and mortality of multiple trauma patients with head injury. Our patients with chest injury did not warrant CT Chest and did not correlate with poor outcome. Thus our findings are in agreement with Leone et al.

In this study, initial APACHE II scores and Marshall CT classification (MTCT) scores were significantly higher for non survivor as compared to survivors. Marshall et al[3], Zagara et al, Lai et al also reported initial high Apache II score and MTCT score.

We have shown that there was a positive correlation between plasma vWf concentrations and APACHE II scores. Siemiatkowski et al measured plasma vWf in posttraumatic acute lung injury and observed increased concentrations, with significant correlations between initial vWf concentration and APACHE II and injury severity score (ISS).

Ghajar[17] has shown that neurological damage after severe TBI does not entirely occur immediately at the moment of impact (primary injury), but evolves afterwards (secondary injury). Most secondary brain injuries are caused by brain edema, with an increase in intracranial pressure and a subsequent decrease in cerebral perfusion leading to ischemia. Patients with severe head injury (SHI) have a significant risk of brain edema, and if this sequel is not prevented or treated properly, it can exacerbate brain damage and increase the risk of death. In the present study, increased plasma vWf was correlated with mortality and higher APACHEII scores following severe TBI. Thus, increases of plasma vWf may indicate sustained cell damage and evolving secondary brain injury, which is the leading cause of death in hospital after TBI as shown in previous study by Ghajar et al and Finfer et al.

Reliable outcome prediction of TBI remains difficult despite major progress in cerebral monitoring and imaging techniques. Early selection of patients at risk of deterioration after acute brain injury is necessary to improve current treatment strategies. In the present study, cut off was at 92.6 U/dL with a sensitivity of 100%, and specificity of 66.67% to predict mortality. In study by Olievera de Olievera et al[5] this value was 234.6 U/dL with a sensitivity of 64%, and specificity of 68%. This variation may be due to racial variation or

type of kit used.

In the scenario of TBI, the cut-off value to determine abnormal plasma vWf concentration was not predefined, thus, the value that would detect the highest proportion of individuals with potentially fatal outcome and the least compromise of specificity was chosen. ROC curve plotted in our study have area under the curve for initial plasma concentration is 0.840(p=0.026). In study by Olievera de Olievera et al[5] the area under the curve for initial plasma concentration was 0.634 ($p = 0.074$).

Although the observed sensitivity and specificity present limitations for clinical use, plasma vWf may predict secondary brain injury progression allowing prognostic evaluation and initiation of treatment strategies.

In our study we did not find any significant correlation of mean arterial pressure and serum protiens values at admission and vWf levels in concordance with study by Olievera de Olievera et al.[5]

The most promising markers in the literature are NSE and protein S100B. Evidence has shown the clinical value of early increases of serum S100B in predicting mortality following acute brain injuries.

Reported predictive values for protein S100B were 70–90% of sensitivity and 80–98% of specificity, within 48 h of severe TBI. Additionally, Hsp70 serum level after severe TBI, and a sensitivity of 70% and specificity of 80% were found, suggesting that increased serum level of Hsp70 is a predictor of unfavorable outcome.

Nevertheless, it is important to mention that vWf is a marker of endothelial injury and hence, the higher prevalence of extra cerebral injuries in survivors increased plasma vWf in these patients.

CONCLUSIONS

- Of the total 20 patients who were included in this study 18 (90%) were victims of RTA and 2(10%) suffered head injury due to fall from height.
- Mean GCS score for all patients was 6.20, it was 6.07 for survivors and 6.60 for non survivors (p=0.476).
- Nonsurvivors presented higher scores in Marshall CT classification score (nonsurvivors mean, 4.80; survivors mean, 4.13). Marshall CT classification score had significant correlation with severity of head injury ($p = 0.042$).
- The result of mean plasma vWf concentration was significantly higher in the TBI group (96.64 U/dL) than in the control group (41.67 U/dL; $p = 0.000$).
- Non survivors presented significantly higher APACHE II scores than survivors (mean for non survivors being, 10.8;and that for survivors being, 7.73; $p = 0.014$), and there was also significant correlation between plasma levels of vWf at first and third plasma samples and APACHE II scores (p -0.044).
- Serum vWf values for non survivors were significantly higher than survivors at admission and at 96 hrs (114.52U/dl;88.01U/dl, p = 0.026 and 151.96U/dl;135.54U/dl p = 0.013 respectively).
- The sensitivity of plasma vWf concentration in predicting mortality according to the cut-off of 92.6 U/dL was 100%, with a specificity of 66.7%. Therefore, vWf increases following severe TBI may be a marker of unfavorable outcome.
- Total serum protein for all patients, survivors and no survivors are 6.035mg/100ml, 6.056, 5.976 respectively (p=0.827)
- ROC curve plotted in our study have area under the curve for initial plasma concentration is 0.840(p=0.026).

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