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To Bleed or Not to Bleed: INR As A Prognostic Factor in Traumatic Brain Injured Patients

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Abstract

Background: Traumatic brain injury (TBI) is one of the leading cause of morbidity and mortality in the working class community in various part of the world including India. It is a common cause of coagulopathy, primarily due to blood loss and hemodilution secondary to fluid resuscitation. Traumatic injury-associated coagulopathy often follows a course of transition from hyper to hypocoagulable state exemplified in disseminated intravascular coagulation. The present study aims to ratify the cut-off value of INR to conform a prognostic value in isolated Traumatic Brain Injured patients.

Patients and Methods: This was a pilot prospective observational study done at a tertiary care centre in coastal Karnataka. The study design was presented and prior approval was obtained from the Scientific Review Board and Ethics Committee of Kasturba Hospital, Manipal. Written informed consent was obtained from patients or their next-of-kin in accordance to the ethical committee pre-requisites. INR from the patients were tabulated and analysed using commercial software SPSS version 16.0

Results: 105 patients were enrolled for the study with an age range between 18 to 60 years. The patients who were dichotomised based on GCS and GOS. Based on GOS, 89.5% (94) of the patients fell into good prognosis group and 11 (10.5%) into the poor prognosis category. The GCS assessment saw 82 patients (78.1%) to be in the non-high risk category and 23 patients (21.9%) in high risk group. Using the ROC curve (Graph 1), the cut-off value of INR was found to be 1.06. This suggested that INR values lesser than 1.06 were likely to be associated with a better prognosis than those with an INR value which was higher than the cut-off. This was found to have a sensitivity of 59.6% and a specificity of 72.7%. The positive predictive value was at a staggering 94.9% and a negative predictive value of 17.4% with a 61.0% accuracy.

Discussion: TBI is also known as acquired brain injury and can be classified in several ways[2]. Major mechanisms which are pivotal in primary injury are contact and acceleration-deceleration. These in turn cause anatomical and physiological impairment such as intracranial hematoma. There are several mechanisms proposed to explain acute traumatic coagulopathy in Traumatic Brain Injury. One of it is the tissue factor hypothesis. The other proposed hypothesis is explained via over-activation of the protein C pathway[6]. Trauma causes hypoperfusion and damages the endothelium, thus activating the protein C pathway. Protein C in-turn inhibits coagulation factors; Va and VIIa by cleaving them. Based on the results from this study, one could predict that patients with INR values lesser than or equal to 1.06 would improve significantly as compared to those with a higher INR value. However, at the same time it neither substantiates the need for prophylactic antifibrinolytic agents nor recommends the delay in any neurosurgical intervention[8].

Conclusion: INR is a good tool in predicting the prognosis in isolated TBI. Nonetheless clinical correlation should be considered before initiation of antifibrinolytic therapy and delaying neurosurgical intervention.

Keywords: Traumatic brain injury (TBI); Prognostic Factor; INR.

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Introduction

Traumatic brain injury (TBI) is one of the leading cause of morbidity and mortality in the working class community in various part of the world including India. It is a common cause of coagulopathy, primarily due to blood loss and hemodilution secondary to fluid resuscitation. Traumatic injury-associated coagulopathy often follows a course of transition from hyper to hypocoagulable state exemplified in disseminated intravascular coagulation. An epidemiological study in 2002 reported that nearly 1.5 to 2 million people is injured and 1 million succumb to TBI every year in India.[1] Majority of the TBI can be attributed to road traffic accident (RTA) and is closely followed by falls from height and assault.

International Normalized Ratio (INR) is a measure of the extrinsic pathway of coagulation, hence helpful in determining the clotting tendency of blood. Based on previous studies, INR cut off value has been kept at 1.5. Patients with INR more than 1.5 are associated with higher mortality. The present study aims to ratify the cut-off value of INR to conform a prognostic value in isolated Traumatic Brain Injured patients.

Materials and Methods

This was a pilot prospective observational study done at a tertiary care centre in coastal Karnataka. The study design was presented and prior approval was obtained from the Scientific Review Board and Ethics Committee of Kasturba Hospital, Manipal. Written informed consent was obtained from patients or their next-of-kin in accordance to the ethical committee pre-requisites. The study was conducted over 7 months from April 2015 to October 2015 including all consecutive patients diagnosed with TBI from the trauma triage of the hospital. The first three months were spent in recruiting the patient population for the study and they were followed up for the next 3-4 months after discharge. INR from the patients were tabulated and analysed using commercial software SPSS version 16.0.

Results

105 patients were enrolled for the study with an age range between 18 to 60 years. Only patients with isolated traumatic brain injury were included so as to avoid the bias of polytrauma which in itself

Table 1: Demographics based on GCS

GCS	Category	Number of patients	Percentage (%)
9–15	Group 1 (Non-high risk)	82	78.1
3–8	Group 2 (High risk)	23	21.9
Total		**105**	**100**

Table 2: Demographics based on GOS

GOS	Groups	Number of patients	Percentage %
4–5	1 (Good prognosis)	94	89.5
1–3	2 (Poor prognosis)	11	10.5
	Total	105	100

Table 3: Spearman's rank correlation coefficient test, non-parametric test to assess the relationship between GCS and INR

Parameters	GCS	INR Value
Correlation Coefficient	1.00	–0.304
p-value	0	0.002

Table 4: Spearman's rank correlation coefficient test, non-parametric test to assess the relationship between GOS and INR

Parameters	GOS	INR Value
Correlation Coefficient	1.00	–0.191
p-value	0	0.052

Table 5: Mann-Whitney U test, non-parametric test for calculation of median INR in both groups

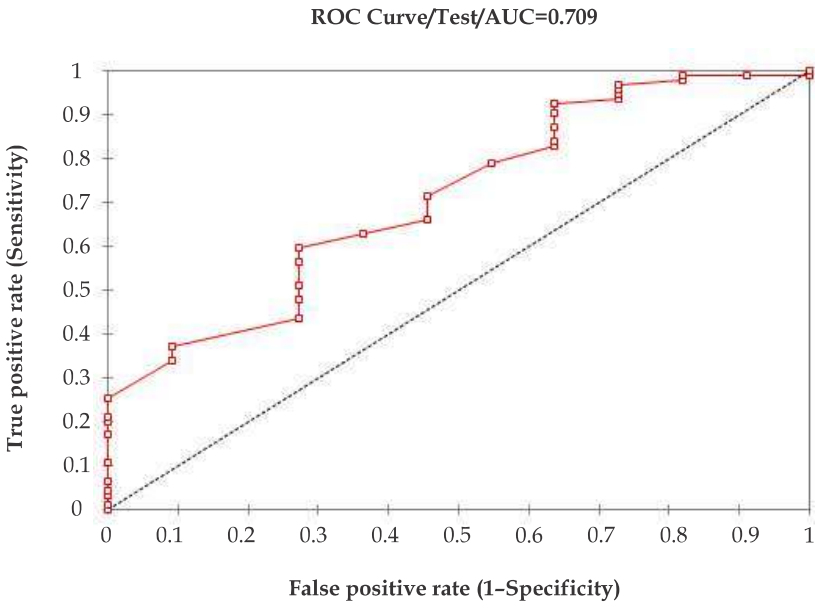
Parameter	Median (Inter-Quartile Range)		*p*-value
	Group 1 (Low-moderate risk)	Group 2 (High risk)	
INR value	1.03 (0.99, 1.10)	1.1 (1.03, 1.13)	0.016

Table 6: Mann-Whitney U test, non-parametric test for calculation of median INR in both groups

Parameter	Groups		*p*-value
	1 (Good prognosis)	2 (Bad prognosis)	
INR value	1.04 (0.99, 1.10)	1.09 (1.02, 1.32)	0.023

is a hypercoagulable state. These patients had non-head Abbreviated Injury Score of less than 3. All those with history of vitamin K deficiency, on anti-coagulation therapy, with a history of liver disease were excluded from the study, since these conditions affect the coagulation pathway.

Prothrombin time (PT) and International Normalized Ratio (INR) investigation are an integral part of the routine haematological investigation for all trauma patients in accordance with the department protocol. The justification behind the consideration of INR as a parameter for TBI prognostication can easily be attributed to the fact that this is a routine and easily available test which could help prognosticate this fragile subgroup of moribund patients. Thus, INR has the potential to be a cost-effective routine test with an added advantage in predicting the outcome. This is even more essential in isolated traumatic brain injury in which prognosis is often variable and difficult to predict. INR values at admission were routinely recorded in all the patients with isolated TBI.



Graph 1: ROC curve to find the cut-off value of INR for predicting good prognosis

Glasgow Outcome Scale (GOS) was used to assess the progress in the patients. It was classified as; GOS score 1 (death), 2 (severe disability) and 3 (moderate disability requiring an assistant to do daily activity). These were clubbed together as "poor prognosis" considering its innate mortality and morbidity aspects. GOS score of 4 (mild disability, being able to do daily activity alone) and 5 (complete recovery) were considered as good prognosis.

Glasgow Coma Scale (GCS) of the patients was also recorded to investigate its relationship with INR. Based on GCS, patients were divided into high risk and low risk groups. High risk group included patients with a GCS of 8 and below, while the low risk group included patients with GCS 9–15.

In the 105 patients with isolated Traumatic Brain Injury: The outcome is as below

The present study included 105 patients who were dichotomised based on GCS and GOS. Based on GOS, 89.5% (94) of the patients fell into good prognosis group and 11 (10.5%) into the poor prognosis category. The GCS assessment saw 82 patients (78.1%) to be in the non-high risk category and 23 patients (21.9%) in high risk group.

The correlation between INR, GCS and GOS (Tables 1–6) was analysed using the Spearman's rank correlation coefficient test, which is a non-parametric test. GCS and INR showed a negative relationship; –0.304 with a *p*-value of 0.002. This was statistically significant.

Higher values of INR was often associated with the "high risk group" of patients. GOS and INR also showed a negative relationship; –0.191 with a significant *p*-value of 0.052. This could be interpreted as a better outcome in patients with a normal to lower INR.

The median value of INR was also analysed between the dichotomised groups using the Mann Whitney U test. The median value of INR in low-moderate and high risk groups was 1.03 and 1.10 respectively with a statistical difference of 0.016. There was a stark difference in the median value of INR in the good and poor outcome group, which was 1.04 and 1.09 respectively with a *p*-value of 0.016.

Using the ROC curve (Graph 1), the cut-off value of INR was found to be 1.06. This suggested that INR values lesser than 1.06 were likely to be associated with a better prognosis than those with an INR value which was higher than the cut-off. This was found to have a sensitivity of 59.6% and a specificity of 72.7%. The positive predictive value was at a staggering 94.9% and a negative predictive value of 17.4% with 61% accuracy.

Discussion

TBI is also known as acquired brain injury and can be classified in several ways.[2] One such way is as primary and secondary injuries. A primary injury is due to the mechanical brunt force that is applied directly onto the skull and occurs instantly at the time of injury whereas secondary injury is delayed and happens as a sequelae to the primary injury. Major mechanisms which are pivotal in primary injury are contact and acceleration-deceleration. These in turn cause anatomical and physiological impairment such as intracranial hematoma. Secondary injury on the other hand is due to the decrease in cerebral blood flow after TBI igniting a vicious cascade that ultimately leads to neuronal death.

Many changes occur following a TBI. The one that concerns our study is traumatic injury-associated coagulopathy.[3] It is also known as acute traumatic coagulopathy (ATC). This is a condition that has been significantly reported in higher incidence in patients with TBI. This abnormal clotting occurs in 10-20% of brain-injured patients[4] and often is catastrophic and fatalities occur as a result of exacerbation of secondary brain injury. Thus ATC may also be a possible precursor-marker and a predictor of the degree of the primary brain injury.

There are several mechanisms proposed to explain acute traumatic coagulopathy in Traumatic Brain Injury. One of it is the tissue factor hypothesis. Brain tissue is rich in thromboplastin, and Traumatic Brain Injury activates the extrinsic pathway and leading to an initial transient hypercoagulable state. This in turn leads to secondary consumptive coagulopathy resulting in hypocoagulable state[5,6] The other proposed hypothesis is explained via over-activation of the protein C pathway.[6] Trauma causes hypoperfusion and damages the endothelium, thus activating the protein C pathway. Protein C in-turn inhibits coagulation factors; Va and VIIa by cleaving them. Another hypothesis states brain-derived microparticles (BDMP) released from an injured brain are responsible in inducing a hypercoagulable state that rapidly turns into consumptive coagulopathy.[7]

It is a known fact GCS and GOS are positively correlated. A higher GCS score is mostly like to have a higher GOS and vice versa. Patients with less impaired conscious state are more likely to

have a better prognosis.

The relationship between INR and GCS was studied to learn association hypocoagulability with the conscious level of patients. The statistically significant negative correlation of INR and GCS showed that patients with lower consciousness level may be affected with hypocoaguability. This is further proven as the median INR value of high risk group is higher than low-moderate risk groups (Tables 5–6).

The relationship between INR and GOS was studied to note the association of hypocoagulability with the outcomes, hence to assess is prognostic predictability. The statistically significant negative correlation of INR and GOS showed that patients with hypocoaguability due to Traumatic Brain Injury are most likely to have a poorer prognosis. These results are in tandem with our proposed hypothesis.

It is of great interest to note that the cut-off value of INR was 1.06 in the present study. This was much lower than the expected value of 1.50 from other studies reported in literature.[5,8] Various published literature have used INR as a tool to predict mortality in severely brain injured patients. The present study is unique in its methodology to use INR as an assessment tool for both mortality and morbidity in patients with TBI. The lower level cut-off of INR did also help in removing the bias of hypocoagulability secondary to DIC as a possible player in affecting the prognosis of TBI.

Patients with low-moderate risk GCS tended to have a lower INR than the median cut-off and in turn were more likely to be associated with a better prognosis. However, the negative predictability of this cut-off is low. This is due to the small data size of patients with poor outcome. Hence the converse, whereby INR more than 1.06 is associated with poor prognosis is yet to be established. Further studies with larger data size is needed to justify the same.

Based on the results from this study, one could predict that patients with INR values lesser than or equal to 1.06 would improve significantly as compared to those with a higher INR value. However, at the same time it neither substantiates the need for prophylactic antifibrinolytic agents nor recommends the delay in any neurosurgical intervention.[8] This is because, the mean INR in our study still lies within the normal range of INR (0.8–1.2). Interestingly, coagulopathy in TBI is usually transient and is variable over its course within the spectrum of TBI. Hence, clinical correlation plays a more significant role and further studies are needed to validate these findings so as to extrapolate these interpretations to a larger group of patients. The jury is yet to arrive at a consensus.

Conclusion

INR is a good tool in predicting the prognosis in isolated TBI. Nonetheless clinical correlation should be considered before initiation of antifibrinolytic therapy and delaying neurosurgical intervention.

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