A Retrospective Review on Post Traumatic Agitation Predictors in Hospitalized Patients with Acute Traumatic Brain Injury

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Abstract: *Objectives*: To determine if socio-demographic, medical and radiological variables have an impact on the risk of developing post-traumatic agitation in patients with mild complex to severe Traumatic Brain Injury (TBI). In addition, determine prognosis using the Extended Glasgow Outcome Scale (GOS-E), length of stay (LOS) and orientation at discharge of agitated patients with TBI.

Methods: A retrospective observational study of all 778 patients admitted to the Montreal General Hospital, a tertiary specialized trauma centre, following a TBI that occurred between 2013 and 2015. Data was collected from the national trauma registry and TBI program database. Independent variables collected were socio-demographic, clinical, and neurological information. Dependent variables were LOS in days, non-pharmacological treatment, GOS-E at discharge, and discharge destination.

Results: 55 patients (7.1%) suffered from post-traumatic agitation. The group with agitation had a significantly higher proportion of men, psychiatric history and suffered in a greater proportion a moderate TBI. The median GCS was significantly lower and post traumatic amnesia was longer in subjects with agitation. A higher percentage of patients with agitation were transferred to long-term care (LTC) facilities.

Keywords: Traumatic Brain Injury, Post-Traumatic agitation, Acute Care, Predictors, Outcome.

INTRODUCTION

TBI is a serious medical condition, in industrialized societies such as in North America, 500 cases are noted per 100,000 population each year [1, 2]. Most individuals with TBI are young adults in their twenties and a second peak occurs in the seventies [3].

There are several definitions of post-traumatic agitation in the literature. According to Chew and Zafonte [4] it is a state during the period of post-traumatic amnesia that can manifest itself by continuous or intermittent verbal or physical behavior. Excessive behavior is often found in combination with hostility, disinhibition and emotional lability. The essential factors to consider are the inability to maintain or shift attention, perceptual disorders, disorganized thinking, explosive anger, impulsivity, increased psychomotor activity, and verbal and/or physical aggression [5]. Sometimes it is described as a subtype of delirium unique to TBI [5]. In the presence of post-traumatic agitation, possible concurrent diagnoses need to be addressed such as acute drug intoxication, drug withdrawal, infection/sepsis, pain, seizures and concomitant disorders, such as anxiety and hallucinations [4].

Most studies report agitation in 30 to 70% of patients with TBI but extremes can range from 8 to 96% [1, 6-8]. The absence of a clear consensus on the definition contributes to the significant variations found in the literature in terms of prevalence. Other factors are the differences in the assessment tools used and the recovery periods studied [9, 10].

The purpose of this study is to compare post-traumatic agitated and non-agitated patients with mild complex to severe TBI in terms of the independent socio-demographic, medical, psychosocial and radiological variables. In addition, determine the overall recovery and prognosis of patients with TBI with post-traumatic agitation in acute care using the Extended Glasgow Outcome Scale (GOS-E), length of hospitalization, length of post traumatic amnesia, and orientation at discharge, as well as report hospital human resources applied to control agitation. Our study

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specifically addresses risk factors for post-traumatic agitation. The identification of such factors is a key element in prevention, care and orientation of TBI patients with agitation.

METHOD

Study Design, Setting and Participants

This is a retrospective observational study of all patients admitted to McGill University Health Centre, Montreal General Hospital (MUHC-MGH), a tertiary specialized trauma centre, following TBI that occurred between 2013 and 2015. In that time frame, a total of 778 patients were admitted to the TBI service, having sustained mild complex to severe traumatic brain injury. Out of those patients, 55 had a post-traumatic agitation. The diagnosis of TBI was made based on evidence of an acute clinical history of TBI, including the initial Glasgow Coma Score (GCS), loss of consciousness (LOC) and/or post-traumatic amnesia and a traumatic abnormality on Head CT scan. A psychiatrist, intensivist, physiatrist or neurosurgeon made the diagnosis of post-traumatic agitation. In this retrospective review, agitation was diagnosed as a variation of delirium, occurring during the PTA period after a TBI, in which there may be any combination of 1) cognitive symptoms, such as reduced attention, decreased information processing, and disorientation; 2) behavioral symptoms, such as verbal outbursts, disinhibition, and uncooperativeness; 3) emotional symptoms, such as emotional lability, impulsivity, and explosive anger; and 4) physical symptoms, such as motor hyperactivity, and wandering. All medical charts were reviewed and diagnoses validated by us with the criteria as per the Agitated Behavior Scale (ABS) [11]. ABS criteria relied on a PTA (assessed by the GOAT), short attention span, uncooperativeness, sudden changes of mood or emotional lability, explosive anger, impulsivity, restlessness, increased psychomotor activity such as pulling on tubes and restraints, and verbal and/or physical aggression noted by the nursing personal and or family members in the absence of medical, toxic-metabolic disorders or psychiatric causes [5]. The MUHC-MGH's ethics committee and the hospital director of professional services approved the research protocol.

Data Collection

Data was obtained from the Quebec national trauma registry and the TBI service database. In order to increase data completeness, every chart was manually reviewed.

Socio-demographic information was collected on patients' gender, age, marital status, education, employment status, history of drug and alcohol use, psychiatric history (depression, anxiety, schizophrenia, and antisocial personality traits) medical neurological history and homelessness.

Clinical Characteristics

TBI severity is considered to be mild complex if the GCS upon arrival was between 13 and 15, LOC lasted less than 30 minutes, PTA was less than 24 hours and if the CT scan of the brain was positive. For moderate TBI, the GCS had to be between 9 and 12, LOC between 30 minutes and 24 hours, and the PTA from 24 hours to two weeks. Severe TBI was determined as a GCS between 3 and 8, LOC lasting more than 24 hours and a PTA longer than two weeks. Alcohol level and drug screens were tested on admission when deemed appropriate by the emergency staff [12].

Computed tomography (CT) of the brain was analyzed using the Marshall Classification [13]. Diffuse Injury I refers to all head injuries without any intracranial visible pathology; Diffuse Injury II includes injuries with a midline shift of less than 5 mm, in presence of cisterns and absence of high or mixed density lesions; Diffuse Injury III is determined by swelling with compression or absence of cisterns and a midline shift between 0 and 5 mm, again without any high or mixed density lesions; and Diffuse Injury IV is identical to Diffuse Injury III except for a midline shift exceeding 5 mm [13].

The Injury Severity Score (ISS) was also used to determine overall injury severity [14, 15]. It is a method for describing and assessing the overall severity of injury, whether it is an isolated injury or a polytrauma. To obtain the ISS, each injury is assigned an Abbreviated Injury Scale (AIS) score, and the squares of the three highest AIS scores are then added together. The AIS classifies the injuries according to their severity, which vary from 1 (minor) to 6 (maximal, untreatable) for each of the following anatomical regions: head & neck, face, chest, abdomen (and pelvic contents), extremities (upper, lower and pelvic girdle), and external (burns, lacerations etc.). This results in ISS values ranging from 0 to 75 [16].

Outcomes Measures

The length of stay (LOS) corresponded to the amount of days patients remained in the acute care setting from admission to discharge.

The GOS-E, a validated functional outcomes measure [17, 18], was collected at patients' discharge by the patients' interdisciplinary team. The GOS-E is an extended version of the original Glasgow Outcome Scale (GOS), which are both widely used and accepted as valid functional outcomes measure following TBI. According to Wilson *et al*., the scoring varies from 1 to 8, and is the following: (1) death, (2) vegetative state, (3) lower severe disability, (4) upper severe disability, (5) lower moderate disability, (6) upper moderate disability, (7) lower good recovery and (8) upper good recovery.

The Galveston Orientation Amnesia Test (GOAT) was collected as soon as the patient was assessable, and repeated, to detect the presence of post-traumatic amnesia, and determine its length. This test was performed by the occupational therapists of the TBI program and repeated every 2 days. It consists of a ten-item questionnaire regarding orientation to person, place, and time, as well as memory of events both before and after the injury. PTA is considered to be over if a score ≥75 is obtained on three consecutive administrations [19, 20].

The use of sitters for managing the post-traumatic agitation was collected and their cost calculated. Finally, discharge destination was obtained for all patients, and categorized into the following: home, outpatient or inpatient rehabilitation, long-term care, or death.

Statistical Analysis

Descriptive statistics are used in both groups of patients with TBI with and without agitation. They are presented using means, medians, standard deviations and interquartile gap for continuous variables and proportions for categorical variables. A logistic regression was done to predict post-traumatic agitation in patients with TBI from demographic and medical variables that had a bivariate relation with agitation ($p < 0.10$, gender, education, alcohol consumption, psychiatric history, TBI severity, GCS and length of PTA). A linear regression was done to predict length of stay, GOS-E, use and costs of bed side sitters and discharge destination in patients with TBI from the following independent variables: demographic and medical that had a bivariate relation with agitation ($p < 0.10$, TBI severity, GCS, length of PTA, ISS).

RESULTS

Demographic and Medical Differences in Patients with TBI with or without Post Traumatic Agitation

The descriptive statistics for demographic variables can be found in Table **1**. In our study, 55 of the 778

Table 1: Demographic and Medical Characteristics

Variable	No agitation	Agitation	Test	Statistical Significance
Age (average ± standard deviation)	61.4 ±21	57.4 ±23	$t_{776df} = 1.347$	p = 0.178
Sex (n, % female)	229 (31.7%)	9 (16.4%)	$\chi^2_{1df} = 5.642$	p = 0.018*
Marital status (n, %)				
Single	197 (29.6%)	18 (36.0%)	$\chi^2_{3df} = 2.198$	p = 0.532
Couples	306 (45.6%)	19 (38.0%)		
Divorced /Separated	74 (11.0%)	4 (8.0%)		
Widow	94 (14.0%)	9 (18.0%)		
Education (n, %)				
No formal education	4 (0.7%)	2 (4.4%)	$\chi^2_{5df} = 9.440$	p = 0.093
Primary	73 (12.5%)	4 (8.9%)		
High school	297 (50.8%)	28 (62.2%)		
College	71 (12.1%)	4 (8.9%)		
University	137 (23.4%)	7 (15.6%)		
Post grad	3 (0.5%)	0 (0.0%)		
Drugs or alcohol misuse (n, %)	176 (23.1%)	19 (34.6%)	$\chi^2_{1df} = 3.682$	p = 0.055
Psychiatric History (n, %)	112 (15.5%)	23 (41.8%)	$\chi^2_{1df} = 24.703$	p < 0.001*
History of previous TBI (n, %)	67 (9.3%)	5 (9.1%)	$\chi^2_{1df} = 0.002$	p = 0.965
Neurological History (n, %)	158 (21.9%)	10 (18.2%)	$\chi^2_{1df} = 0.407$	p = 0.524
Homelessness (n, %)	15 (2.1%)	3 (5.5%)	$\chi^2_{1df} = 2.583$	p = 0.108
Legal History (n, %)	11 (1.5%)	2 (3.6%)	$\chi^2_{1df} = 1.391$	p = 0.238

Patients with agitation suffered in a greater proportion a moderate TBI and less of a mild complex TBI (p = 0.042).

Table 2: Agitation and Severity of TBI

Severity	Agitation		Total
	No	Yes	
Mild n, %	3 (0.41%)	1 (1.82%)	4
Mild Complex n, %	364 (50.35%)	19 (34.55%)	383
Moderate n, %	231 (31.95%)	26 (47.27%)	257
Severe n, %	125 (17.29%)	9 (16.36%)	134
Total n, %	723 (100 %)	55 (100%)	778

Table 3: Agitation in TBI and GCS

Agitation	n	mean	sd	p50	p25	p75
No	721	11.83	4.146286	14	9	15
Yes	55	10.58	4.569184	12	7	15
Total	776	11.74	4.186923	14	9	15

subjects with TBI (7.1%) suffered from post-traumatic agitation. The group with agitation had significantly higher proportion of men ($p = 0.018$), agitation in men was twice as common as women. A significantly greater proportion of subjects with a previously diagnosed psychiatric condition were agitated ($p < 0.001$).

Subjects with agitation had proportionally longer post-traumatic amnesia (PTA): 65% of subjects with agitation have a PTA of 7-14 days and up as compared to 39% of subjects without.

There were similarities between patients with or without agitation on the Marshall score, the Abbreviated Injury Scale **(**AIS) median score, the Injury Severity Score (ISS) and none showed any statistical significance ($p > 0.05$).

Comparison of Global Recovery in TBI Patients with and without Agitation

There is a statistical difference in discharge destination from acute care between the groups ($p = 0.008$). A smaller proportion of patients with agitation 11% were discharged home compared to 25% of subjects without agitation. In addition, a higher percentage of patients with agitation 27% were transferred to long-term care (LTC) facilities compared to 14% of the non-agitated group. No statistical difference is noticeable on the median GOS-E ($p = 0.148$).

The length of stay was significantly much longer in patients with agitation 11 days compared to only 3 days in non-agitated patients ($p = 0.009$). Use of supervision through bedside sitters was significantly much higher in patients with agitation ($p < 0.001$). The median duration of sitters' use was 0 hours for the non-agitated patients and 24 hours for the agitated patients. Furthermore, the cost of sitters was significantly much more expensive in the agitated group 374$ CDN vs. 0$ ($p < 0.001$)

Global Recovery and Progress of Patients with TBI and Post-Traumatic Agitation

Due to the low number of agitated patients ($n = 55$), statistical significance was more difficult to reach.

Table 4: Agitation in TBI and Length of PTA

Length of PTA	Agitation		Total
	No	Yes	
< 24 hours n, %	309 (42.80%)	13 (23.64%)	322 (41.44%)
1-7 days n, %	134 (18.56%)	6 (10.91%)	140 (18.02%)
7-14 days + n, %	279 (38.64%)	36 (65.45%)	315 (40.54%)
Total n, %	722 (100%)	55(100%)	777(100%)

Table 5: Agitation in TBI and Orientation at Discharge

Discharge destination	Agitation		Total
	No	Yes	
Home n, %	178 (24.76%)	6 (10.91%)	184 (23.77%)
Inpatient Rehabilitation n, %	240 (33.38%)	20 (36.36%)	260 (33.59%)
Outpatient Rehabilitation n, %	80 (11.13%)	8 (14.55%)	88 (11.37%)
LTC n, %	101 (14.05%)	15 (27.27%)	116 (14.99%)
Death n,%	118 (16.41%)	5 (9.09%)	123(15.89%)
Unassigned n, %	2 (0.28%)	1 (1.82%)	3(0.39%)
Total n, %	719 (100%)	55 (100%)	774 (100%)

Discharge Destination

Patients who returned home had proportionately shorter PTAs (50% had a PTA < 24 hours) compared to 80 % of patients discharged to LTC with a PTA of 7-14 days and more, ($p = 0.041$).

Otherwise, there were no statistical differences ($p > 0.05$) in patients with TBI with or without agitation with regards to their discharge destination in terms of age, gender, marital status, alcohol or drugs consumption, psychiatric history, homelessness, education, previous TBI, neurological history, legal history, TBI severity, GCS, Marshall score, AIS score and ISS score.

GOS-E

The greater the TBI severity, the lower the GOS-E score ($p = 0.005$). Length of PTA was negatively associated with the GOS-E ($p < 0.001$).

Otherwise, age, marital status, education, alcohol misuse, psychiatric history, homelessness, legal history, history of TBI, history of neurological disorder, ISS score, Marshall score and AIS score were not significantly associated with the GOS-E score ($p > 0.05$).

Length of Stay

Due to the small number in the agitation group, the length of stay had an asymmetric distribution. To ensure a better distribution we did a logarithmic transformation of the length of stay. TBI severity ($p = 0.026$), GCS ($p = 0.022$) ISS ($p = 0.008$) and length of PTA are ($p < 0.001$) significantly associated with length of stay in patients with agitation.

Age, gender, marital status, education, psychiatric history, history of substance misuse, homelessness, legal history, previous TBI, neurological history, Marshall score and AIS score were not associated with length of stay in patients with agitation ($p > 0.05$).

Post-Traumatic Agitation Predictive Factors

A logistic regression was done to predict post-traumatic agitation from demographic and medical variables that had a bivariate relation with agitation ($p < 0.10$, gender, education, alcohol consumption, psychiatric history, TBI severity, GCS and length of PTA). From this logistic regression, it is shown that men have twice as much probability of developing agitation. A psychiatric history also shows 4 times more chances of agitation. Patients with a long PTA (7-14 days +) are twice as more agitated than those with less than 24 hours of PTA. Furthermore, severe TBI has a higher risk of agitation as compared to Mild complex TBI.

Predictive Variables for Length of Stay, GOS-E and Discharge Destination for Patients with TBI Agitation

A linear regression was done to predict length of stay in patients with TBI from the following independent

Table 6: Length of Stay

LOS	Coef.	Std. Err.	t	P > | t |	[95% Conf. Interval]
Length of PTA					
< 7days	0.45	0.40	1.11	0.27	-0.36 1.25
> 7 days	1.38	0.27	5.13	0.00	0.84 1.92
ISS	0.011	0.01	1.07	0.29	-0.01 0.031

Table 7: GOS-E

GOS-E	Odds Ratio	Std. Err.	z	P > | z |	[95% Conf. Interval]
Length of PTA					
< 7days	11.41	8.37	3.32	0.001	2.71 48.09
> 7 days	18.55	17.18	3.15	0.002	3.02 113.96

variables: demographic, medical, that had a bivariate relation with agitation ($p < 0.10$, TBI severity, GCS, length of PTA, ISS). The variables that had an impact on LOS and agitation are directly related to the length of PTA and the ISS score. These 2 variables explain 42% of the total variation of LOS.

From a bivariate fashion, TBI severity and length of PTA were associated with GOS-E in post-traumatic agitation. Only PTA turned out to be a significant predictor of GOS-E with longer PTAs associated with lower GOS-E at discharge.

Discharge Destination

From a bivariate fashion, the length of PTA was associated with discharge destination in patients with post-traumatic agitation.

DISCUSSION

From the 2-year period reviewed, 7.1% patients with TBI hospitalized with a positive CT scan suffered a post-traumatic agitation. This figure is on the low end of what is typically reported [1, 6-8]. This is probably due to the large spectrum of TBI severity studied, from mild complex to severe TBI: Patients with milder TBI's do not suffer a long posttraumatic amnesia and by de facto are less agitated. Also, only patients in the acute phase of recovery are studied. As well, patients with TBI may be hospitalized on different hospital wards, including the neurosurgical, but also the trauma and orthopedic wards where the personnel are less accustomed in identifying and recognizing the TBI agitation leading to a bias in diagnosis. Finally, the agitation diagnosis made by physicians was done without the specific use of the Agitated Behavior Scale [9]. Being a retrospective study, information in medical charts was used without the ability to lock the diagnosis by the ABS score. However, this figure remains an indicator of the significance of the problem in hospitalized patients with TBI of all severities.

In keeping with other studies, male gender and psychiatric past history was strongly associated with post-traumatic agitation. Male gender is correlated with more impulsive behavior and aggression. Psychiatric history can also cause behavioral and mood changes. In addition, antisocial personality traits are more present in men [2, 21, 22]. Low GCS and longer PTA point to the significance of the brain injury and cognitive deficits that can predispose to the post-traumatic agitation.

Median length of stay for patients with agitation was 3 times longer with use of supervision through bedside sitters and increased cost of hospitalization. In addition, a higher percentage of patients with agitation were transferred to LTC facilities (27%). Agitation is noted to be associated with injury severity, more use of medical resources and a grimmer outcome at discharge [8].

No significant difference was seen between those with and without agitation on the Marshall score. The correlation is possibly related to the severity of the TBI and not the radiological image; however, a research study on agitation and CT head findings can help ascertain this claim.

The length of PTA and the ISS score are 2 variables that explain 42% of the total variation of LOS. As reported by previous authors [7, 8], this study shows that TBI severity and length of PTA were significantly associated with GOS-E. The length of PTA was associated with discharge destination in patients with post-traumatic agitation, which is in keeping with existing results. A study by McNett and colleagues [8] demonstrated that the majority of agitated patients were discharged to acute brain rehabilitation units instead of returning home. This indicates more severe cognitive, behavioral and physical deficits, requiring more time and resources in order for a patient to achieve independence in daily living activities.

Limitations of this study should be noted. First, this study is retrospective, which led to a few missing data. Secondly, 55 patients had post-traumatic agitation, this is a small number, and as a result low power analyses effects were obtained. This figure is comparable to the lower end values found in the literature (8 to 96%) [1, 6-8]. This important range is partly due to the absence

of a clear consensus on the definition of post-traumatic agitation as well as the variability in TBI severity used in studies. Another point is the lack of scoring of the ABS, which could have possibly had an impact on the number of patients with agitation. We tried to minimize this limitation by reviewing all charts and corroborating nursing, medical and clinical findings and physicians' diagnoses with the ABS. Many authors have mentioned an association between agitation and pre-morbid characteristics such as alcohol or substance abuse and legal issues [2]. However, these relationships were not demonstrated in this study. This could partly be explained by missing data and the low percentage of patients with agitation making it more difficult to achieve significance.

One of the strengths of our study is that it specifically addresses risk factors for post-traumatic agitation and demonstrates that acute prognosis of agitated patients is less favorable. The findings of our study support previous results demonstrating a relationship between post-traumatic agitation and increased PTA duration; longer hospital stays and reduced functional independence at discharge. Hence, the identification of such factors is a key element in prevention, care and orientation. By identifying early on the risk factors, we can not only try to prevent but also put in place appropriate treatment plans and positively alter the course of patient's hospital stay. This could also lead to less medical expenses. Finally, with the results of this study, prospective studies can be built.

DECLARATION OF INTEREST

The authors report no conflicts of interests. The authors alone are responsible for the content and writing of the paper.

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