Original Article

Predisposing factors, clinical assessment, management and outcomes of agitation in the trauma intensive care unit

Saeed Mahmood¹, Omaira Mahmood², Ayman El-Menyar^{3,4}, Mohammad Asim³, Hassan Al-Thani¹

¹ Trauma Surgery Section, Department of Surgery, Hamad General Hospital (HGH), Doha, Qatar

² College of Pharmacy, Qatar University, Doha, Qatar

³ Clinical Research, Trauma Surgery Section, Department of Surgery, HGH, Doha, Qatar

⁴ Clinical Medicine, Weill Cornell Medical School, Doha, Qatar

Corresponding Author: Ayman El-Menyar, Email: aymanco65@yahoo.com

BACKGROUND: Agitation occurs frequently among critically ill patients admitted to the intensive care unit (ICU). We aimed to evaluate the frequency, predisposing factors and outcomes of agitation in trauma ICU.

METHODS: A retrospective analysis was conducted to include patients who were admitted to the trauma ICU between April 2014 and March 2015. Data included patient's demographics, initial vitals, associated injuries, Ramsey Sedation Scale, Glasgow Coma Scale, head injury lesions, use of sedatives and analgesics, head interventions, ventilator days, and ICU length of stay. Patients were divided into two groups based on the agitation status.

RESULTS: A total of 102 intubated patients were enrolled; of which 46 (45%) experienced agitation. Patients in the agitation group were 7 years younger, had significantly lower GCS and sustained higher frequency of head injuries ($P<0.05$). Patients who developed agitation were more likely to be prescribed propofol alone or in combination with midazolam and to have frequent ICP catheter insertion, longer ventilatory days and higher incidence of pneumonia ($P<0.05$). On multivariate analysis, use of propofol alone ($OR=4.97$; 95% $CI=1.35-18.27$), subarachnoid hemorrhage ($OR=5.11$; 95% $CI=1.38-18.91$) and ICP catheter insertion for severe head injury ($OR=4.23$; 95% $CI=1.16-15.35$) were independent predictors for agitation ($P<0.01$).

CONCLUSION: Agitation is a frequent problem in trauma ICU and is mainly related to the type of sedation and poor outcomes in terms of prolonged mechanical ventilation and development of nosocomial pneumonia. Therefore, understanding the main predictors of agitation facilitates early risk-stratification and development of better therapeutic strategies in trauma patients.

KEY WORDS: Trauma; Intensive care unit; Agitation; Head injury; Propofol; Outcome

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INTRODUCTION

Agitation is an acute cognitive dysfunction commonly observed among critically ill patients admitted to the intensive care unit (ICU).^[1] It is a state of restlessness accompanied with excessive and aimless motor and cognitive activities.^[2] It is characterized by changes or fluctuation in baseline mental status, disorganized thinking or an altered level of consciousness.^[3] Development of agitation in ICU might result in inappropriate diagnosis and management

as it makes the patient unable to cooperate with the recommended therapeutics and monitoring procedures that need the patient to be lying calm and awake.^[3] It is often associated with other neuro-muscular disorders such as anxiety, delirium and pain.^[4] As agitation is a sign of central nervous system disorder, it might be associated with various negative consequences. Investigators suggested poor prognosis of agitated critically ill patients as compared to those without agitation.^[5] Rubio-Valera et al^[6] observed that agitated

patients are more likely to have organ system failure, higher risk for reintubation, prolonged hospital stay and higher cost of treatment. Moreover, agitated patients may require prolonged mechanical ventilation, physical restraints to control agitation and need more sedative and analgesic medications which subsequently extend the length of ICU stay.^[3]

In the current ICU settings with advanced devices, it is possible to effectively manage agitated patients using effective monitoring and titrated care.^[7] Also recent advancement in the understanding of the critical illness leads to the development of various validated clinical tools for pain, agitation, and delirium assessment in the trauma IUC patients.^[8] Since, Agitation has a multifactorial underlying etiology and is associated with higher morbidity and treatment cost, it is imperative to focus on the early diagnosis. However, there is lack of information regarding the potential underlying specific causes of agitation in trauma patients. Therefore, this study aims to evaluate the frequency, predisposing factors, management and outcomes of agitation in trauma ICU.

METHODS

A retrospective observational study was conducted to evaluate all intubated patients admitted to the trauma ICU at the level I national trauma center, Hamad General Hospital, in Qatar over the period between April 2014 and March 2015. The medical record and trauma registry database were used as the primary source of information for data collection. Agitation was assessed according to Ramsey Sedation Scale (RSS) which is a subjective tool commonly used to evaluate the level of consciousness more precisely for titration of sedative medication in ICU patients.^[9] It is comprised of 6-point scale and the assessment value of 1 corresponds to the agitation response option of “patient anxious or agitated or both”. Documentation of agitation was also identified from the medical record of the daily clinical assessment notes of physicians and nurses (at every two hours for three shifts per day) for every patient admitted to the trauma ICU.

Patient's data included demographics, mechanism of injury (MOI), associated injuries, initial vitals, depth of sedation using Ramsey Sedation Scale, Glasgow Coma Scale (scene & trauma room), Injury Severity Score (ISS), Abbreviated Injury score (AIS), types of traumatic brain injury (TBI) lesions, administration of sedatives (Midazolom, Propofol and tramadol), and analgesics (Fentanyl, Remifentanyl and Dihydrocodeine), ICP

catheter insertion, head interventions (craniectomy & craniotomy), ventilatory days, hospital and ICU length of stay and in-hospital complications. Clinical data included oxygen saturation in trauma room, serum lactate, and blood electrolytes such as sodium, potassium, and magnesium. The choice of sedatives in intubated patients with TBI has no defined institutional protocol and so they were selected depending upon the level of consciousness needed for clinical assessment, severity of lesion, and ICP insertion. Patients on midazolam are deeply sedated and may require more time for extubation and such patients are eventually being shifted to propofol during weaning. Study variables were analyzed and compared in trauma patients who developed agitation (group-1) and patients who did not have it (group-2). The Glasgow Coma Scale (GCS) is a simple objective tool for the assessment of degree of impaired consciousness and coma based on eye opening, verbal and motor response; comprised of a scale ranging from 3–15 in which progressively higher scores indicate higher levels of consciousness.^[10] Injury Severity Score (ISS) is anatomically-based ordinal scale which describes the global severity of injury based on the severity score of lesions established by AIS. It is obtained by summing the square value of the 3 highest AIS scores, identifying severity of patients with greater score correlates with higher injury severity.^[11]

We used the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3).^[12] Pneumonia was defined according to the CURB-65 severity score and the ventilator associate pneumonia (VAP) as the nosocomial pneumonia in patients who are on mechanical ventilation for > 48 hours.^[13]

Ethical approval was obtained from the Institutional Review Board, Medical Research Center (IRB# 15234/15) at Hamad Medical Corporation, Qatar.

Data were presented as proportions, mean±standard deviation or median and range. Analysis was performed to compare agitated and non-agitated groups using the Student's *t*-test for continuous variables and Pearson Chi-square (χ^2) test or Fisher's exact test for categorical variables. For skewed continuous data nonparametric Mann-Whitney *U*-test was done. Multivariate logistic regression analysis for the predictors of agitation in trauma ICU was performed after adjusting for the significantly relevant variables such as age, sex, initial GCS at ED, ISS, subarachnoid hemorrhage (SAH), propofol use and ICP catheter insertion. Data were expressed using odds ratio (OR) and 95% confidence interval (CI). A significant difference was considered

when the two-tailed $P \leq 0.05$. Data analysis was carried out using the Statistical Package for Social Sciences version 18 (SPSS Inc., Chicago, IL, USA).

RESULTS

A total of 102 intubated patients were admitted to the trauma ICU during the study period with a mean age of 34.3 ± 13.9 ; the majority of them were males (89.2%). Motor vehicle crash (58.8%) was the commonest mechanism of injury. Agitation was reported in 45% patients using Ramsey Sedation Scale (RSS) and clinical notes (Figure 1).

Table 1 demonstrates the patients' demographic, clinical characteristics and associated injuries based on the agitation status. Patients in the agitation group were

Figure 1. Frequency of Ramsey Sedation Scale in trauma ICU patients.

seven years younger in age, had significantly lower GCS at the scene and in the emergency department and sustained higher frequency of head injuries (84.8% vs. 57.1%; $P=0.003$). Also, there was a higher proportion of patients in the agitation group who had SAH (69.6% vs. 21.4%; $P=0.001$) (Figure 2). However, the frequency of spinal injuries was more frequent among non-agitated patients (41.1% vs. 17.4%; $P=0.01$). The two groups were comparable for gender, mechanism of injury, ISS, other associated injuries, types of TBI lesions (except for SAH) and head AIS.

Fentanyl (70.9%) and remifentanyl (29.1%) were mainly administered as analgesics while, combination of midazolam and propofol (37.0%), midazolam alone (30.0%), propofol alone (26.0%), and dihydrocodeine (7.0%) were primarily used for sedation (Table 2).

Figure 2. Types of TBI lesions by agitation status (* $P=0.001$).

Table 1. Demographics, clinical presentation and associated injuries by agitation status in trauma intensive care unit patients

Variables	Overall (n=102)	Patients without agitation (n=56)	Patients with agitation (n=46)	P value
Age (mean±SD)	34.3±13.9	37.2±14.8	30.2±11.7	0.01
Males	91 (89.2%)	47 (83.9%)	44 (95.7%)	0.05
Mechanism of injury				
Motor vehicle crashes	60 (58.8%)	33 (58.9%)	27 (58.7%)	0.91 for all
Fall from height	21 (20.6%)	13 (23.2%)	8 (17.4%)	
Fall of heavy object	2 (2.0%)	1 (1.8%)	1 (2.2%)	
All-terrain vehicle	3 (2.9%)	1 (1.8%)	2 (4.3%)	
Assault	5 (4.9%)	2 (3.6%)	3 (6.5%)	
Others	11 (10.8%)	6 (10.7%)	5 (10.9%)	
GCS Scene	9.6±4.4	10.5±4.4	8.5±4.1	0.03
GCS at trauma room	7.4±5.3	8.5±5.6	6.1±4.5	0.02
GCS 1-hour post-admission	5.7±4.9	6.5±5.4	4.8±4.2	0.07
Associated injuries				
Head	71 (69.6%)	32 (57.1%)	39 (84.8%)	0.003
Chest	48 (47.1%)	27 (48.2%)	21 (45.7%)	0.79
Spine	31 (30.4%)	23 (41.1%)	8 (17.4%)	0.01
Upper extremity	25 (24.5%)	15 (26.8%)	10 (21.7%)	0.55
Lower extremity	26 (25.5%)	13 (23.2%)	13 (28.3%)	0.56
Abdomen	23 (22.5%)	15 (26.8%)	8 (17.4%)	0.25
Pelvis	19 (18.6%)	12 (21.4%)	7 (15.2%)	0.42
Face	9 (8.8%)	3 (5.4%)	6 (13.0%)	0.17
Injury Severity Score	21.6±11.1	20.6±12.0	22.9±9.7	0.30
Head AIS	3.8±0.9	3.9±0.9	3.7±0.8	0.53
Severe Head Injury (GCS<8)	54 (77%)	22 (71.0%)	32 (82.1%)	0.27

GCS: Glasgow Coma Score; TRU: trauma resuscitation unit.

Tramadol was used in 13% of the trauma patients in order to reduce the general anesthesia and sedation doses. Patients who developed agitation were more likely to be prescribed either propofol alone (39.1% vs. 14.8%) or in combination with midazolam (43.5% vs. 31.5%) whereas, midazolam alone (42.6% vs. 15.2%) and dihydrocodeine (11.1% vs. 2.2%) were used more among non-agitated patients ($P<0.001$ for all). Also, patients developed agitation were more likely to have ICP catheter insertion (61% vs. 18%; $P=0.001$), had significantly longer ventilator days and higher incidence of pneumonia (17.4% vs. 3.6%; $P=0.04$) than those without agitation. The mean head AIS was comparable in patients with and without ICP catheter insertion (3.9 ± 0.9 vs. 3.7 ± 0.8 , $P=0.59$). The electrolyte profile except for magnesium, use of analgesics, head interventions, development of sepsis, hospital and ICU length of stay were comparable in patients with and without agitation.

On multivariate logistic regression analysis, after adjusting for potential covariates such as age, sex, GCS at emergency department, ICP catheter insertion, propofol use, ISS and SAH, we found that use of

propofol alone ($OR=4.97$; 95% $CI=1.35-18.27$; $P=0.01$), SAH ($OR=5.11$; 95% $CI=1.38-18.91$; $P=0.01$) and ICP catheter insertion for severe head injury ($OR=4.23$; 95% $CI=1.16-15.35$; $P=0.03$) were the independent predictors of agitation in patients admitted to trauma ICU (Table 3).

DISCUSSION

This is a unique study from our institution to measure the frequency, predisposing factors, management, and outcomes of agitation in critically ill trauma patients. The prevalence and clinical importance of agitation are not well explored in certain settings.^[14] Our results showed that less than half (45%) of patients who were admitted to the trauma ICU experienced agitation. Moreover, patients experienced agitation were younger in age, had lower initial GCS, higher frequency of head injuries (particularly SAH), and ICP insertion; more likely to be sedated by propofol alone or in combination with midazolam, required prolonged mechanical ventilation and had higher rate of pneumonia.

To date, various scoring systems have been utilized

Table 2. Laboratory findings, management and outcomes by agitation status in patients admitted to trauma intensive care unit

Variables	Overall (n=102)	Patients without agitation (n=56)	Patients with agitation (n=46)	P value
Oxygen saturation in trauma room	99.6±0.8	99.6±0.6	99.5±0.9	0.62
Lactate (mmol/L)	0.5 (0.1–3.2)	0.5 (0.1–2.8)	0.55 (0.1–3.2)	0.49
Sodium (mmol/L)	139.3±13.7	138.0±18.3	140.8±2.9	0.32
Potassium (mmol/L)	4.0±0.3	4.1±0.3	4.0±0.2	0.13
Magnesium (mmol/L)	0.67±0.05	0.7±0.05	0.6±0.05	0.02
Tramadol	13 (12.7%)	8 (14.3%)	5 (10.9%)	0.60
Analgesics				
Fentanyl	56 (70.9%)	25 (71.4%)	31 (70.5%)	0.92 for all
Remifentanyl	23 (29.1%)	10 (28.6%)	13 (29.5%)	
Sedatives				
Midazolom alone	30 (30.0%)	23 (42.6%)	7 (15.2%)	0.001 for all
Propofol alone	26 (26.0%)	8 (14.8%)	18 (39.1%)	
Midazolom + Propofol	37 (37.0%)	17 (31.5%)	20 (43.5%)	
Dihydrocodeine	7 (7.0%)	6 (11.1%)	1 (2.2%)	
Head intervention				
Craniectomy	10 (9.8%)	1 (1.8%)	9 (19.6%)	0.003
Craniotomy	15 (14.7%)	6 (10.7%)	9 (19.6%)	0.21
ICP catheter insertion	38 (37.3%)	10 (17.9%)	28 (60.9%)	0.001
ICP (median, range)	19 (11–28)	19.5 (12–22)	19 (11–28)	0.38
Ventilator days	8 (2–25)	7 (2–13)	9 (2–25)	0.001
Hospital length of stay (days)	25.5 (2–147)	21 (2–88)	29 (2–147)	0.34
ICU length of stay (days)	13 (1–96)	11.5 (1–78)	17 (1–96)	0.15
Sepsis	5 (4.9%)	1 (1.8%)	4 (8.7%)	0.10
Pneumonia	10 (9.8%)	2 (3.6%)	8 (17.4%)	0.04

ICP: intracranial pressure; ICU: intensive care unit.

Table 3. Multivariate analysis for the predictors of agitation in trauma ICU

Variables	OR	95% CI	P value
Age	0.95	0.91–1.00	0.05
Males	8.55	0.98–74.66	0.05
Initial GCS at trauma room	1.005	0.89–1.12	0.92
ICP catheter insertion	4.23	1.16–15.35	0.03
Injury Severity Score	1.001	0.95–1.05	0.98
Subarachnoid hemorrhage	5.11	1.38–18.91	0.01
Propofol alone	4.97	1.35–18.27	0.01

GCS: Glasgow coma score; ICP: intracranial pressure.

to assess the level of sedation/agitation in ICUs. The Richmond Agitation-Sedation Scale, Ramsay sedation score and Sedation-Agitation Scale are the frequently used sedation scales for assessment of the consciousness level.^[15,16] However, these assessment tools are subjective in nature and might be associated with a limited accuracy and underestimation of sedation/agitation level.^[17] In the present study, we utilized medical records and Ramsay sedation score to identify agitation (45%) as our intensive care unit nursing staff are trained to assess sedation level using this tool.

Similar to our findings of the higher rate of agitation in TICU (45%), Kadyan et al^[18] reported agitation in almost 50% of the TBI patients which lasted up to 10 days. Also, Jaber et al^[19] observed a similar frequency of agitation (52%) in patients treated in the medical-surgical ICU. In a study performed by Burk et al^[20] a higher rate of agitation (59%) was reported in patients admitted to medical and surgical-trauma ICU. Contrarily, a lower rate of agitation (16%) has been reported in the mechanically ventilated medical ICU patients.^[21] Agitation is a common medical problem in critically ill patients in the ICU settings especially among the elderly.^[4] However, Fraser et al^[22] observed no age-related variation in the frequency, severity, and management of agitation in patients admitted to ICU. In our cohort the overall trauma ICU admissions comprised of young adults and in particular, those who developed agitation were more likely to be younger in age which is attributed to the unique population distribution in Qatar. There are several factors that could be associated with the development of agitation in ICU which vary depending upon the severity of illness, oxygenation status, metabolic disorders, medications and sepsis-associated encephalopathy.^[4,19]

Saoût et al^[23] suggested agitation or aggressive behavior to be observed in 11% to 34% of patients who sustained TBI. In our study, two-third of patients who sustained TBI developed agitations with lower GCS on the initial presentation to the emergency department. This could be explained by the fact that patients with severe TBI might have different lesions which may influence the behavioral or cognitive function.^[23] In contrast, a prospective study reported agitation and restlessness in only 11% of the closed severe head injury patients (GCS < 8).^[24] In our study, the lesions (except SAH) and severity of head injuries did not differ significantly in cases with or without agitation. A prospective study reported independent association of CT scan findings, severity and duration of agitation with the outcomes in patients with TBI.^[25]

In our study, patients who developed agitation were more likely to have ICP monitoring which was indicated in severe TBI patients. Of note, in patients with ICP catheter insertion, the intracranial pressure did not differ significantly among patients with and without agitation. This could be explained in part by the fact that adequate sedation might limit the elevations of intracranial pressure. It has been suggested that opioids and sedatives are often used to manage agitation in patients with elevated ICP that improves cerebral oxygenation.^[26]

Robert et al^[27] conducted a systematic review to study the effect of sedative agents on the neurologic outcome in patients with severe TBI. The authors identified similar efficacy of propofol and midazolam to improve the intracranial and cerebral perfusion pressures. In our series, patients received propofol alone or in combination with midazolam had higher frequency of agitation whereas; midazolam alone was used more in non-agitated group. It has been suggested that benzodiazepines including midazolam are useful to decrease agitation in acute brain injury patients due to longer action, but it may cause difficulty in neurological examination and delayed weaning from mechanical ventilation.^[28]

We do believe that trauma patients who were sedated for longer duration (>5 days) with dosage of propofol (>50 mg/hour intravenous infusion) had a higher rate of agitation. Therefore, the depth of sedation with propofol is dose-dependent with early weaning from mechanical ventilation to facilitate extubation and these patients become more conscious to be agitated as compared to those who are sedated by midazolam. Moreover, patients on midazolam are deeply sedated and may require more time for extubation and such patients will eventually be shifted to propofol during weaning.

Prolonged mechanical ventilation and ICU stay have been observed in over-sedated patients, which increases the risk of ventilator-associated pneumonia, deep vein thrombosis, and gastrointestinal bleeding.^[29] Consistent with these findings, agitated patients in our series were found to have prolonged mechanical ventilation which might explain the higher rate of ventilator-associated pneumonia than those who did not have agitation. The other explanation is that patients with longer ventilatory support often develop agitation during weaning secondary to tube intolerance, physical stress, and anxiety. Such circumstances might harm the lungs and compromise the respiratory rate which eventually leads to potential complications such as pneumothorax and pneumonia.^[30]

Bogner et al^[31] conducted a longitudinal study of 340 consecutive TBI patients during rehabilitation to evaluate the role of agitation in predicting the patients' outcome. The authors found that agitation may lead to more complicated situation which might end-up in prolonged hospitalization as compared to non-agitated patients. Another study by McNett et al^[32] on 219 TBI patients admitted to acute care settings observed a significantly longer hospital stay in patients who experienced agitation. In contrast, the length of ICU and hospital stay in our series was comparable among agitated and non-agitated patients. Consistent with our findings, Burk et al^[20] suggested no association of agitation with longer ICU or hospital stay. The inconsistency in such findings could be explained by the involvement of different intensive care unit settings (medical, surgical, and trauma), protocols, medications, and agitation assessment tools.

In our cohort, ICP monitoring was found to be an independent predictor of agitation. The possible association of agitation with frequent ICP monitoring could be attributed to the fact that severe TBI patients are more likely to be agitated, if under sedated by propofol which might poses a risk of intracranial pressure elevation.^[33] Moreover, our study found no significant association with respect to severity of head injury and ICP catheter insertion. It has been suggested that patients with severe head injury should be adequately sedated to prevent the possible agitation regardless of the need for ICP catheter insertion.^[34] Moreover, Propofol is used often for sedation in patients with TBI which facilitate frequent neurological assessment due to quick onset and offset of action.^[35] It is considered as the sedative of choice due to its short duration of action but at the same time it is associated with a higher rate of agitation.. In line with these findings, we observed that the use of propofol alone is a significant predictor of agitation in trauma patients. This may be attributed to the lower level of sedation attain by quick offset of action using lesser dose of propofol (dose-dependent) to facilitate extubation. However, agitation could be merely related to discontinuation of midazolam, prolonged weaning process of ventilator and requirement of frequent assessment of GCS in more severely ill patients. Another, predictor of agitation identified in our series is SAH. Consistent with our findings, a recent study found an association of agitation on the long-term outcomes, particularly among non-comatosed SAH patients with severe clinical grades.^[36] Therefore, in patients who sustained SAH, the dose of sedatives should be carefully

adjusted during the process of weaning.

Agitation potentially harms patients as it disturbs the planned treatment, necessitates chemical and physical restraints, delays rehabilitation and compromises functional independence.^[34] Furthermore, it increases risk of self-extubation, re-intubation, unintended catheter removal, over-sedation, and treatment cost.^[19,21] The higher frequency of agitation in TBI patients could be related with the impairment of autonomic nervous system.^[34] Therefore, pharmacological interventions such as beta-blockers and anti-adrenergic agents could be considered to counteract the hyperadrenergic activity that might safely minimize agitation in the TBI population.^[37,38]

Moreover, recent recommendation for the management strategy should consider the identification and treatment of the underlying causes of agitation such as pain and development of acute sepsis in patients with TBI.^[39]

There are several limitations of this study which warrant mention. This is a retrospective chart review of patients experienced agitation in trauma ICU, so there is a possibility of missing information which might influence the quality of data. Moreover, small sample size is another limitation which can affect the power of the study. We also lack information of the patterns and onset of agitation, frequency of episodes per day, self-extubation and re-intubation. Development of agitation based on daily use of propofol/midazolam cannot be ascertained. Richmond Agitation-Sedation Scale (RASS) is considered as a good scoring tool for agitation which is validated in various critical care settings.^[40] In our series, Ramsay score was used to assess agitation as our nursing staff is familiar with this score, which is another limitation. This score would be less useful for identification of level of agitation as it is primarily meant to assess the level of sedation in critically ill patients in ICU. In our study, documentation of the severity classification scale such as APACHE II, SOFA and delirium was lacking which could be considered as a limitation of this report.

CONCLUSION

Agitation is a common problem experienced by trauma patients. The onset of agitation is found to be linked to the type of sedation used, and unfavorable outcomes in terms of prolonged mechanical ventilation and development of nosocomial pneumonia. Better understanding of the main predictors of agitation allows early identification of high-risk trauma patients and also helps in developing prophylactic and therapeutic strategies; therefore, further large prospective studies are needed.

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Contributors: SM proposed the study, analyzed the data and wrote the first drafts. All authors contributed to the design and interpretation of the study and to further drafts.

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