Original Article

Tramadol in traumatic brain injury: Should we continue to use it?

Saeed Mahmood[1], Hassan Al-Thani[1], Ayman El-Menyar[2,3], Mushrek Alani[1], Ammar Al-Hassani[1], Saji Mathrdikkal[1], Ruben Peralta[1], Rifat Latifi[1,4]

[1]Department of Surgery, Section of Trauma Surgery, Hamad General Hospital (HGH), [2]Department of Surgery, Clinical Research, Section of Trauma Surgery, HGH, Doha, Qatar, [3]Clinical Medicine, Weill Cornell Medical School, Doha, Qatar, [4]Department of Surgery, University of Arizona, Tucson, AZ, USA

Abstract

Background and Aims: Tramadol is commonly used to treat moderate to moderately-severe pain in adults. We aimed to analyze the clinical relevance of tramadol use during weaning and extubation in patients with traumatic brain injury (TBI).
Material and Methods: A retrospective observational study was conducted and included all the intubated TBI patients at the level I trauma center between 2011 and 2012. Data included patient's demographics, mechanism of injury (MOI), Glasgow Coma Scale (GCS), injury severity score, length of Intensive Care Unit (ICU) stay length of stay (LOS), agitation scale, analgesics, failure of extubation and tracheostomy. Patients were divided into two groups based on whether they received tramadol (Group 1) or not (Group 2) during ventilatory weaning. Chi-square and Student's *t*-tests were used for categorical and continuous variables; respectively. Logistic regression analysis was performed for predictors of agitation in ICU.
Results: The study included 393 TBI patients; the majority (96%) was males with a mean age of 33.6 ± 14 years. The most common MOI were motor vehicle crash (39%), fall (29%) and pedestrian (17%). The associated injuries were mainly chest (35%) and abdominal (16%) trauma. Tramadol was administered in 51.4% of TBI patients. Tracheostomy was performed in 12.4% cases. Agitation was observed in 34.2% cases. Group 1 patients had significantly lower age (31.6 ± 12.4 vs. 35.7 ± 15.6; $P = 0.005$) and head AIS (3.5 ± 0.8 vs. 3.9 ± 0.9; $P = 0.001$) compared to Group 2. The incidence of agitation, ICU and hospital LOS were higher in Group 1. Failure of extubation and tracheostomy were reported more frequently in Group 1 ($P = 0.001$). On multivariate analysis, tramadol use was an independent predictor for agitation (adjusted odds ratio 21; $P = 0.001$), followed by low GCS.
Conclusion: Patients with TBI who received tramadol are more likely to develop agitation, undergo tracheostomy and to have longer hospital LOS. Therefore, an extensive risk-benefit assessment would help to attain maximum efficacy of the drug in TBI patients.

Key words: Agitation, brain injury, extubation, tramadol, trauma

Introduction

Traumatic brain injury (TBI) is a leading public health concern with an estimated annual incidence of 10 million worldwide.[1] Consistent with the global prevalence, the previous study reported that TBI is associated with a higher rate of morbidity and mortality in Qatar.[2] Management of TBI patients in trauma Intensive Care Unit (TICU) may require concomitant use of multiple medications. Goal of the therapy is to avoid secondary injury, maintenance of cerebral perfusion pressure (CPP), and optimization of cerebral oxygenation.[3]

Poor management of pain is also responsible for neuromuscular excitability causing restlessness and agitation.[4] Development of agitation may lead to prolonged intubation, need for reintubation and tracheostomy. Therefore, analgesia and sedation are essential for pain management in moderate to severe head injuries.[3] Opioid analgesics such as morphine, fentanyl, alfentanil and remifentanil are the key drugs used for pain management in critically ill patients.[5] They are often prescribed in combination with sedatives. Therefore,

Address for correspondence: Dr Saeed Mahmood, Department of Surgery, Section of Trauma Surgery, Hamad General Hospital, Doha, Qatar.
E-mail: traumaresearch@hamad.qa

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generally intubated patients receive analgesia and sedation with morphine and midazolam infusions.[6]

Tramadol is a commonly used opioid like analgesic used to treat moderate to moderately-severe pain in adults. It is as effective as morphine or meperidine and has lower adverse effects and potential for abuse or development of dependency compared with other morphine-like agents.[7] Tramadol is used to reduce the need for sedation and analgesia during weaning of patients who shows recovery and could be potentially extubated.

However, some reports found adverse consequences, especially for concomitant use of tramadol with other drugs. Tramadol administration with other drugs that lowers seizure threshold will eventually increase the risk of seizures.[8] It has been speculated that concomitant use of tramadol with some drugs might induce adverse events in TBI patients. Therefore, use of tramadol should be cautiously monitored in TBI patients with increased intracranial pressure (ICP). Moreover, it remains unclear that whether tramadol should be used or avoided in patients of head injury. We aimed to evaluate the clinical needs versus complications of tramadol use among intubated TBI patients in order to suggest the need for its continuation or cessation during the weaning and extubation process.

Material and Methods

A retrospective observational study was conducted to include all intubated head injury patients admitted to TICU at level I trauma center between December 2011 and December 2012. Patients with incomplete data or who died on the scene were excluded. Data included patients' demographics, mechanism of injury (MOI), associated injuries, Glasgow Coma Scale (GCS), injury severity score (ISS), ICU and hospital length of stay (LOS), development of agitation and failure of extubation.

Agitation was described as "motor restlessness that accompanies anxiety."[9] Extubation failure was defined as the inability to sustain spontaneous breathing after removal of the artificial airway; an endotracheal tube or tracheostomy tube; and need for reintubation within a specified time period: Either within 24-72 h or up to 7 days.[10] Weaning is routinely assessed by the attending anesthesiologist in the ICU according to the extubation protocol of the institution that mainly considers the GCS score and ventilatory settings guided by the spontaneous breathing trial. Since, the present study focused on the TBI patients, there was no fixed weaning period as some patients might take longer time than others depending on the severity of injury. Usually weaning is done on an individual basis according to the clinical status of the patient. Tramadol was administered with a dose of 50 mg intravenously every 6 h during weaning. Patients were categorized into two groups (tramadol) versus (nontramadol) users and were analyzed accordingly. As this was a retrospective study, we used waiver of consent signed by the lead principle investigator and approved by the medical research center. The study was approved by the Local Review Board (IRB# 11354/11).

Data were presented as proportions, mean ± standard deviation or median and range. Analysis was performed to compare tramadol and nontramadol users groups using the Student's *t*-test for continuous variables and Pearson Chi-square (χ^2) 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 ICU was performed after adjusting for the important relevant variables as age, severity of head injury, initial GCS and sedations used. Data were expressed using odds ratio (OR) and 95% confidence interval (CI). A significant difference was considered when the two-tailed $P < 0.05$. Data analysis was carried out using the Statistical Package for Social Sciences version 18 (SPSS Inc., Chicago, IL, USA).

Results

The study included 393 TBI patients, of them the majority (96%) were males with a mean age of 32.7 ± 13.2 years. The most common MOI was motor vehicle crashes (MVCs) in 40% of cases, followed by fall (30.4%) and pedestrian injury (15.7%) [Table 1]. Injuries of chest (32.7%) and abdomen (15.3%) were the most frequently associated injuries. The mean ISS was 21.2 ± 7.6, GCS was 10.6 ± 3.6, head AIS was 3.5 ± 0.9, and the median ICU LOS was 4 (range: 1-155) days [Table 1]. Tramadol was administered in 51% of head injury patients during weaning in order to reduce the general anesthesia and sedation doses to allow patient to be awake faster. Midazolam (33.4%) and propofol (26.2%) were used for sedation, whereas fentanyl and remifentanyl were used as analgesics. Signs of agitation were observed in 21% of patients [Table 1]. Tracheostomy due to extubation failure was needed in 7.5% of cases. Table 2 shows the clinical profiles and outcomes of TBI patients with and without tramadol use. Patients with and without tramadol were comparable for age, gender and MOI. Tramadol group had significantly higher incidence of chest injuries (40% vs. 21.4%; $P = 0.001$), increased ISS (22.6 ± 7.6 vs. 19.1 ± 7.2; $P = 0.001$), ICU LOS (6 [1-155] vs. 3 [1-126]; $P = 0.001$) and hospital LOS (19 [1-192] vs. 8 [1-164]; $P = 0.001$) and lower GCS ([9.1 ± 3.4] vs. [12.6 ± 2.7]; $P = 0.001$) in comparison to nontramadol group. Moreover, the use of sedatives and analgesics was also observed more frequently in tramadol group [Table 2]. Similarly, in the tramadol group,

Table 1: Patients characteristics (*n* = 393)

variable	
Males %	96
Age (mean±SD)	32.7±13.2
Mechanism of injury %	
MVC	39.5
Fall	30.4
Pedestrian	15.7
Fall of heavy object	3.0
Associated injuries	
Abdominal %	15.3
Chest %	32.7
Head AIS (mean±SD)	3.5±0.9
ISS (mean±SD)	21.2±7.6
GCS (mean±SD)	10.6±3.6
ICU LOS (median; range)	4 (1-155)
Hospital LOS (median; range)	16 (1-192)
Tramadol use %	51
Sedation %	
Medazolam	33.4
Propofol	26
Analgesia %	
Fentanyl	49.2
Remifentanyl	10.2
Tracheostomy %	7.5
Agitation %	18

MVC = Motor vehicle crash, ISS = Injury severity score, GCS = Glasgow Coma scale, AIS = Abbreviated injury scale, SD = Standard deviation, LOS = Length of stay, ICU = Intensive Care Unit

Table 2: Comparative analysis of head injury patients with and without Tramadol

variable	Patient without Tramadol (*n* = 191)	Patient with Tramadol (*n* = 202)	*P* value
Males (%)	95.4	96.5	0.405
Age (mean±SD)	34.2±14.2	31.6±12.4	0.097
Mechanism of injury %			
MVC	32.1	44.3	0.102 for all
Fall	34.4	27.9	
Pedestrian	17.6	14.4	
Fall of heavy object	4.6	2.0	
Associated injuries %			
Abdominal	15.3	15.3	0.984
Chest	21.4	40.1	0.001
Head AIS (mean±SD)	3.5±0.9	3.5±0.8	0.955
ISS (mean±SD)	19.1±7.2	22.6±7.6	0.001
GCS (mean±SD)	12.6±2.7	9.1±3.4	0.001
ICU LOS (median; range)	3 (1-126)	6 (1-155)	0.001
Hospital LOS (median; range)	8 (1-164)	19 (1-192)	0.001
Sedation %			
Medazolam	14.5	45.8	0.001 for all
Propofol	14.5	33.8	
Analgesia %			
Fentanyl	18.3	69.3	0.001 for all
Remifentanyl	10.7	9.9	
None	71	20.8	
Tracheostomy (%)	0.0	12.4	0.001
Agitation (%)	0.8	34.2	0.001

MVC = Motor vehicle crash, ISS = Injury severity score, GCS = Glasgow coma scale, AIS = Abbreviated injury scale, LOS = Length of stay, ICU = Intensive Care Unit, SD = Standard deviation

greater proportion of patients showed increased agitation rate (34.2% vs. 0.8%; $P = 0.001$) and tracheostomy rate due to extubation failure (12.4% vs. 0%; $P = 0.001$). Patients who developed agitation had significantly prolonged hospital LOS in comparison to those who were agitation-free (27 [1-192] vs. 11 [1-185]).On multivariate logistic regression analysis, after adjusting for age, head AIS, and sedatives, we found that tramadol use [OR = 21; 95% confidence interval (CI): 2.8-161; $P = 0.003$] and low GCS (OR = 1.43 95% CI: 1.2-1.69; $P = 0.001$) were the significant predictors of agitation [Table 3].

Discussion

Data of the use of tramadol during weaning and extubation from the mechanical ventilator in patients who sustained TBI are lacking. In this study, we analyze the effect of tramadol on the patients outcomes such as development of agitation, rate of failure of extubation, need for tracheostomy and hospital LOS. To the best of our knowledge, this is a unique study that addresses this critical issue in terms of the utility of tramadol among intubated TBI patients. The majority of TBI patients were young males who were involved mainly in MVCs. Our earlier study on TBI patients also demonstrated that MVC is the leading cause of TBI in Qatar, particularly in the young adults and adolescents groups.[2] Management of TBI patients in Trauma ICU may require concomitant use of different sedatives and analgesia. Table 4 summarizes the indications and side-effects of different medications used in the management of patients with TBI.

Inappropriate pain management may cause adverse effects on the blood and ICPs which might lead to secondary brain damage. Therefore, adequate pain control in trauma ICU will improve the tolerance of the endotracheal tube, mechanical ventilation and other distressing maneuvers. Furthermore, agitation in TBI patients might result in increased blood and ICP as well.[6] Proper sedation and analgesia are crucial in treating elevated ICP to avoid secondary insults to the brain.[11]

In our study, failure of extubation that led to increased rate of tracheostomy was reported in 12.4% of patients who received tramadol while, no cases were reported in nontramadol group.

The underlying causes of agitation could be related to the disease itself (metabolic disorders, medications, sepsis, and encephalopathy) or due to discomfort, pain, or even noise.[5,12] Agitation due to elevated ICP is often managed with intravenous (I.V) opioids and sedatives. It is evident from the European survey in 2001 that morphine, fentanyl, and sufentanil are the most commonly used drugs for analgesia and sedation in the ICU.[13] Caution is advised on the use of morphine in the patients with renal insufficiency. Fentanyl has some advantages over morphine and can be used in patients with morphine allergy and renal insufficiency.[14] Wilhelm and Kreuer[5] showed that the remifentanil could be used for analgesia and sedation in adult ICU patients, leading to a significant reduction in the weaning and extubation times.

Adequate sedation potentiates analgesic action and provides anxiolysis. It also helps in controlling elevated ICP related to agitation and optimizes cerebral oxygenation. Moreover, it improves patient comfort, facilitates mechanical ventilation and nursing care.[11] Propofol is the drug of choice for sedation because of its rapid onset and short duration of action. However, its adverse effect like hypotension may cause a negative impact on the CPP. Midazolam is usually used in patients who have no contraindication to the use of propofol. Midazolam is an effective sedative with less adverse effects, but it does not effectively control ICP.[6]

Table 3: Multivariate analysis for the predictors of agitation in ICU

Variable	OR	95% CI	*P* value
Age	0.98	0.96-1.01	0.42
Head AIS	1.09	0.74-1.62	0.64
Tramadol use	21.15	2.78-161	0.003
Low GCS	1.43	1.20-1.69	0.001
Sedation use	4.27	0.47-38.96	0.19

AIS=Abbreviated Injury Scale, GCS=Glasgow Coma Scale, CI=Confidence interval, OR=Odds ratio, ICU=Intensive Care Unit

Adverse consequences, such as ICU LOS and extubation failure that lead to tracheostomy associated with tramadol use were the important outcomes in the present study. In our study, I.V tramadol was given as analgesia to reduce the requirement for general anesthesia and sedation during the weaning from the mechanical ventilators. Patients in the tramadol group were presented with significantly higher ISS and showed greater ICU and hospital LOS in comparison to nontramadol group. Similarly, in the tramadol group, the greater proportion of patients showed poor outcome as evidenced by higher rate of agitation and extubation failure, which required tracheostomy.

An earlier prospective multicenter study demonstrated that the seizure, tachycardia, hypertension and agitation were associated with low tramadol dose (≤500 mg); whereas severe complication such as coma and respiratory depression were observed with the use of higher doses (≥800 mg).[15] It is known that acute or early posttraumatic seizures usually occur within the 1st week of TBI. Moreover, seizures are one of the known complications of overdose of tramadol use. However, in this study tramadol was given for the weaning process and during that period acute seizures were not reported. Furthermore, in the present study low dose (50 mg I.V at every 6 h) was used during ventilator weaning, which might attribute to the absence of seizures, tachycardia and hypertension in those patients. Interestingly, a recent study on patients who developed seizures due to tramadol use (either therapeutic or overdose) showed that traumatic injuries occurred in around 25% of these patients.[16]

In our cohort, use of tramadol in patients presented with low GCS has been significantly associated with agitation on multivariate analysis. Therefore, the possible association of tramadol use with a higher rate of agitation and extubation failure in TBI patients raises serious concern in this particular group of patients. These consequences of events could explain

Table 4: Indication and side-effects of medications used for head injury patients in TICU

Medication	Indications/utility	Side-effects	Contraindications
Midazolam	Maintenance of sedation in hypotensive patients; effective for refractory status epilepticus	Metabolites accumulation delayed neurological assessment; withdrawal syndrome; delirium; respiratory depression	Hypersensitivity, shock, hypotension or head injury
Propofol	Induction and maintenance of anesthesia; mechanical ventilation; fast recovery than midazolam	Hypotension; transient apnea; mild myocolonic movements	Adverse respiratory effects with other respiratory depressants
Fentanyl	Induction agent; relative hemodynamic stability	Respiratory depression, diarrhea, nausea, constipation, dry mouth, somnolence and asthenia	Known intolerance to the drug or other opioid agonists
Remifentanyl	Short acting anesthesia; relative hemodynamic Stability	Reduces sympathetic nervous system tone, respiratory depression, dizziness, itching and agitation	Raised ICP; hypersensitivity to fentanyl analogs
Tramadol	Management of moderate to moderately-severe pain in adults	Agitation, fever, hallucinations, seizures and blistering skin rashes	Used with caution in patients with increased ICP; acute intoxication with other CNS depressants

ICP = Intracranial pressure, TICU = Trauma Intensive Care Unit, CNS = Central nervous system

in part the longer hospital stay in those who used tramadol during weaning. The results of our study indicate the necessity of further evaluation of tramadol use during weaning in TBI patients.

Limitations of this study include the retrospective nature of the study, the absence of ICP documentation in every patient and the other causes of agitation in ICU were not ruled out. The wide confidence interval for tramadol use denotes small sample size that may not be well representative to the population. If another study was conducted with a larger sample size, it would yield a narrower and better estimate to the true value in the population.

Conclusion

Tramadol is still one of the commonly used drugs in the management of TBI patients. We report that agitation and subsequent extubation failure and tracheostomy are associated with tramadol use during the weaning from ventilations. However, tramadol use among TBI patients' needs re-evaluation and further prospective studies.

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Conference Calendar 2015

Name of conference	Dates	Venue	Name of organising secretary with contact details
31st Annual National Conference of Indian Society for Study of Pain ISSPCON-2016	February 5th-7th, 2016	Indore	Dr. Pravesh Kanthed Telephone: 91 9301444007 Email Id: secretaryisspcon2016@gmail.com Website: http://www.isspcon2016.com/
17th Annual Conference of Indian Society of Neuroanesthesiology and Critical Care ISNACC 2016	February 5th-7th, 2016	Bengaluru	Dr. Venkatesh H K Telephone: 919739974930 Email Id: isnacc2016@gmail.com Website: http://isnacc2016.org/index.html
22nd Annual Conference of Indian Society of Critical Care Medicine & International Sepsis Forum CRITICARE 2016	February, 5th-9th, 2016	Agra	Dr. Ranvir Singh Tyagi, Dr. Diptimala Agarwal Telephone: 919927778889 Email Id: criticare2016@gmail.com Website: http://criticare2016.com/