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Original Research

Kidney disease improving global outcome for predicting acute kidney injury in traumatic brain injury patients

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Abstract

Aim: To determine the incidence of acute kidney injury (AKI) based on Kidney Disease Improving Global Outcome (KDIGO) criteria in patients with severe traumatic brain injury and to study AKI in relation to risk factors and outcomes.
Method: This trial was a descriptive analytic study on 83 patients with severe traumatic brain injury admitted to Poursina Hospital (Rasht, Iran). The incidence of AKI was determined based on KDIGO criteria over a 12-month period. The correlation of mortality rates, multi-organ failure (MOF), and neurologic outcome to AKI were studied.
Results: Of 83 eligible patients who entered the study, 25.3% ($N = 21$) developed AKI based on KDIGO criteria. Glasgow Outcome Scale on admission was the only risk factor significantly associated with the incidence of AKI ($p = 0.001$). Mortality rates (62% vs. 22.6%, $p = 0.002$) and the occurrence of MOF were significantly higher in patients who developed AKI (23.8% vs. 0% MOF based on Sequential Organ Failure Assessment, $p < 0.0001$; 19% vs. 0% MOF based on Multiple Organ Dysfunction score, $p < 0.0001$). Poor neurologic outcome was observed in 95% and 92% of patients with and without AKI, respectively ($p = 0.674$).
Conclusion: The incidence of AKI among patients with severe traumatic brain injury is striking. The association of Glasgow Outcome Scale with AKI helps to identify patients at a higher risk of developing AKI. Significant rates of mortality and MOF among patients with severe traumatic brain injury and AKI, necessitates consideration of renoprotective measures from the early days of hospital admission.

Keywords: acute kidney injury; brain–kidney crosstalk; KDIFO; traumatic brain injury

1. Introduction

Traumatic brain injury (TBI) is among the leading causes of mortality and morbidity worldwide. Primary and secondary injuries to the brain could lead to hypoperfusion and ischemic insult to non-neurologic organs.

Acute kidney injury (AKI) develops as a result of brain insult or as a consequence of secondary inflammatory or septic reactions. Using drugs with nephrotoxic side effects, such as mannitol for the management of intracranial pressure, may lead to complications like rhabdomyolysis due to trauma which might play a considerable role in kidney injury and should be taken into account.[1]

Several scoring systems are available to use in an intensive care unit (ICU) setting, predicting mortality based on organ failure. Sequential Organ Failure Assessment (SOFA) and Multiple Organ Dysfunction (MOD) scoring systems are implicated in the ICU for assessment of multi-organ failure (MOF). Both systems consist of six components evaluating renal, respiratory, coagulation, neurologic, cardiovascular, and hepatic systems. Based on creatinine levels, scores of renal component range from 0 to 4. Scores of 1 and 2 classify the

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renal insult as a dysfunction and scores of 3 and 4 are indicators of renal failure. The threshold of creatinine which classifies an insult into dysfunction or failure differs between two scoring systems.[2,3]

Many systems have been developed for diagnosing and staging AKI in ICU patients. Acute Kidney Injury Network (AKIN), Risk, Injury, and Failure, and Loss, and End-stage Kidney Disease (RIFLE), and Kidney Disease Improving Global Outcome (KDIGO) are panels with different criteria. AKIN criteria evaluates renal function based on serum creatinine or urine output during 48 hours.[4,5] RIFLE criteria observes the creatinine level and glomerular filtration rate and urine output over a span of 7 days.[6] KDIGO criteria, which was formed in 2012, monitors alterations in kidney function similar to AKIN criteria but within 7 days, similar to that of RIFLE criteria; thus including both previously designed systems.[7]

Although limited studies have been performed, the incidence of AKI among patients with severe TBI has been reported as a variable range with regard to different definitions of AKI.[8,9] Studies of non-neurologic organ failure in patients with TBI reported an incidence of <2% of AKI using SOFA and MOD scoring systems.[3,10–12] Based on different criteria, AKI is estimated to have an incidence of 1.5–23% in a neurotrauma setting[8,10,13,14] and contributes to higher rates of mortality and morbidity[8,15] and poor neurologic outcome.[6]

The aim of this study was to define the incidence of AKI based on KDIGO criteria in patients with severe head trauma, and to evaluate AKI in association with risk factors and outcomes of mortality, neurologic deterioration, and MOF.

2. Materials and methods

The present study was performed as a descriptive analytic trial, after the approval of the Ethics Committee of Guilan University of Medical Science (Rasht, Iran) and gathering informed consent. All patients with severe TBI who were admitted to the neurosurgery ICU of Poursina Hospital from March 2013 to April 2014 were included. Enrolled in study were patients with a TBI (due to traffic accidents) and one of the following conditions: an initial resuscitation (systolic blood pressure > 90 mmHg and arterial oxygen saturation > 90%); Glasgow Coma Score (GCS) of ≤ 8 at ICU admission; a postresuscitation GCS at presentation to the Poursina Neurosurgery ICU of ≤ 8 in the absence of any type of sedation and drug or alcohol overuse; indication for intracranial pressure monitoring; or the presence of a clinical herniation syndrome diagnosed by a neurosurgeon.[16] Excluded from the study were patients with concomitant trauma to the chest, abdomen, or pelvis, that resulted in vital organ damage, patients with a previous history of vital organ involvement, and patients with an unknown past medical history. Acute Physiology and Chronic Health Evaluation (APACHE) II score was calculated for all patients on the 1st day of admission to ICU. During the period of the study, SOFA and MOD scores were calculated daily for all patients based on original guidelines. For any organ compartment, Score 0 was considered normal, Score 1 and 2 represented organ dysfunction, Score 3 and 4 was demonstrative of organ failure, and scores of ≥ 6 represented a state of MOF.[2,3]

Table 1
Definition of acute kidney injury (AKI) based on Kidney Disease Improving Global Outcome (KDIGO) panel.

KDIGO defines AKI as any of the following:
Increase in serum creatinine by ≥ 0.3 mg/dL within 48 h or
Increase in serum creatinine to ≥ 1.5-times baseline within the last 7 d or
Urine output < 0.5 mL/kg/h for 6 h

A daily screening program based on KDIGO panel guidelines for AKI was applied for all patients during the study period (Table 1). For statistical data analysis, SPSS version 21 (SPSS Inc., Chicago. IL, USA) was used. Incidence of AKI defined by KDIGO criteria and frequency of MOF, based on SOFA and MOD scores, were calculated. Fisher's exact test and Pearson's Chi-square test were used to correlate the AKI with risk factors and outcomes of mortality, MOF, and neurologic outcome. In order to report the neurologic outcome, Glasgow Outcome Scale (GOS) was dichotomized into favorable (GOS: 4, 5) and unfavorable (GOS: 1, 2, 3).[8] Multivariable linear regression analysis was used to detect the relationship of risk factors with AKI. All tests were two-sided and $p < 0.05$ was considered to be statistically significant.

3. Results

Of all patients who were admitted to the ICU of Poursina Hospital during the study period, 83 were eligible to enroll. Most of the patients diagnosed with severe TBI were men (93.9%) and were young (mean age: 33 ± 18 years). Mortality rate was 27.7% ($N = 23$) and 79.5% of the study population had shown a poor neurologic outcome (GOS = 1, 2, 3). The incidence of AKI was reported as high as 25.3% ($N = 21$). Basic characteristic features are shown in Table 2.

The only risk factor shown to be significantly related to AKI was GOS on admission ($p = 0.001$). Age, sex, GCS,

Table 2
Basic characteristic features of the study population.

Age (y)	33 ± 18
Sex (M/F)	78/5
GCS on admission	5.9 ± 1.7
GOS on admission	2.4 ± 1.1
MAP on admission (mmHg)	93.2 ± 11.1
APACHE II	14.1 ± 3.8
SOFA score on 1st d of admission	5.5 ± 1.6
MODS score on 1st d of admission	5.4 ± 1.6
Maximum SOFA score during hospital stay (d)	8.4 ± 2.4
Maximum MODS score during hospital stay (d)	8 ± 2.1
Incidence of AKI	25.30% ($n = 21$)
Mortality	27.7% ($n = 23$)
Poor neurologic outcome (GOS ≤ 3)	79.5% ($n = 66$)

AKI = acute kidney injury; APACHE II = Acute Physiology and Chronic Health Evaluation; F = female; GCS = Glasgow Coma Score; GOS = Glasgow Outcome Scale; M = male; MAP = mean arterial pressure; MODS = Multiple Organ Dysfunction Score; SOFA = Sequential Organ Failure Assessment.

Table 3
Comparison of patients with and without acute kidney injury (AKI).

	AKI	No AKI	*p*
Age (y)	36.3 ± 19.6	32.3 ± 17.6	0.398
Sex (M/F)	20/1	58/4	0.626
GCS on admission	5.8 ± 1.9	6 ± 1.7	0.738
GOS on admission	1.7 ± 1	2.6 ± 0.9	0.001
MAP on admission (mmHg)	93.7 ± 12	93 ± 10.9	0.798
APACHE II	14.9 ± 4.5	13.8 ± 3.6	0.317
SOFA score on 1st d of admission	5.6 ± 1.7	5.5 ± 1.5	0.756
MODS score on 1st d of admission	5.1 ± 1.7	5.5 ± 1.6	0.389

APACHE II = Acute Physiology and Chronic Health Evaluation; F = female; GCS = Glasgow Coma Score; GOS = Glasgow Outcome Scale; M = male; MAP = mean arterial pressure; MODS = Multiple Organ Dysfunction Score; SOFA = Sequential Organ Failure Assessment.

mean arterial pressure, SOFA, MOD scores on admission, and APACHE II score were not significantly different between the patients with and without AKI (Table 3).

Mortality rates (62%) and the proportion of patients who developed MOF (23.8% based on SOFA and 19% based on MODS) were significantly higher in patients with AKI ($p = 0.002$ for mortality rates and $p \leq 0.0001$ for MOF rates; Table 4).

Finally, using the multivariable regression analysis, the only feature shown to be significantly related to AKI was APACHE II score on admission day ($p = 0.044$, 95% confidence interval = 1.005–1.410; Table 5).

4. Discussion

This descriptive analytic study was performed at a Level I trauma center to estimate the incidence of AKI among patients with severe TBI admitted to ICU, and to evaluate the association of AKI with risk factors and outcomes. SOFA and MOD scores were used to detect the MOF, and KDIGO criteria were used to diagnose AKI during the period of the ICU stay. Based on KDIGO criteria, the incidence of AKI reported was as high as 25%. APACHE II score and GOS on admission day were significantly related to the development of AKI. Mortality rate was 62% in the cohort with AKI; MOF rate was 23.8% based on SOFA and 19% based on the MODS system.

Table 4
Comparison of multi-organ failure (MOF), poor neurologic outcome, and mortality rates between patients with and without acute kidney injury (AKI).

	AKI	No AKI	*p*
	n = 21	*n* = 62	
MOF (SOFA)	23.8%	0%	0.0001
	n = 5	*n* = 0	
MOF (MODS)	19%	0%	0.0001
	n = 4	*n* = 0	
Poor neurologic outcome	95%	92%	0.674
	n = 20	*n* = 57	
Mortality	62%	22.6%	0.002
	n = 13	*n* = 14	

MODS = Multiple Organ Dysfunction Score; SOFA = Sequential Organ Failure Assessment.

Table 5
The relationship between patient characteristic features on admission and acute kidney injury.

	p	95% confidence interval
Sex (M/F)	0.959	0.078–11.294
Age (y)	0.717	0.972–1.043
GCS	0.515	0.796–1.046
SOFA score	0.163	0.823–3.188
MODS score	0.082	0.449–1.050
APACHE score	0.044	1.005–1.410

APACHE = Acute Physiology and Chronic Health Evaluation; F = female; GCS = Glasgow Coma Score; M = male; MODS = Multiple Organ Dysfunction Score; SOFA = Sequential Organ Failure Assessment.

Rodling Wahlstrom et al[17] reported 0.1% renal dysfunction in 93 patients with severe TBI and no patients with renal failure defined by SOFA. Zygun et al[18] conducted a study using MOD score to establish non-neurologic organ failure among 209 patients with severe TBI. They reported an incidence of 7% renal failure and 0.5% renal dysfunction. None of the ICU predicting scoring systems, including MODS and SOFA, are validated for the diagnosis of AKI.[18]

Although the study population in both trials were patients with severe TBI, the SOFA and MOD scoring systems have been applied for the diagnosis of renal dysfunction/failure. We applied the KDIGO system, which resulted in the diagnosis of 25.3% patients as having AKI.

Moore et al[19] reported an incidence of 9.2% among 207 patients with moderate and severe TBI using RIFLE criteria. Mortality rates were estimated as 42% and 18% in patients with AKI and with no AKI, respectively. They showed a significant correlation between age, severity of illness measured by APACHE III, admittance to hospital, and AKI.

Presenting age and high scores of APACHE III as risk factors for AKI, was the first trial evaluating the risk factors for AKI development. We used the latest criteria for diagnosis of AKI approved by the KDIGO panel in 2012, and we enrolled patients with TBI of severe type not moderate type, and we reported the incidence of AKI as high as 25%. Reporting higher rates of mortality in patients with AKI and without AKI (95% vs. 92%) could be related to our study population, which was of severe type TBI only, unlike moderate and severe which was included in Moore et al's[19] study. Another difference worth mentioning is the applied system for diagnosing AKI; i.e., applying KDIGO instead of RIFLE as in this study.

Li et al[8] reported an incidence of 23% of AKI among 136 patients with severe TBI; of which 55% died and 74% of cases resulted in poor neurologic outcome. Compared with patients with no AKI, patients with AKI showed a poor prognosis and high rates of mortality. The statistical relationship between development of AKI and age, admission GCS, level of blood urea nitrogen, and creatinine on admission was significant. They used AKIN criteria for the diagnosis of AKI.[8]

The association of AKI with higher rates of mortality in Li et al's[8] study is similar to our findings but we found no significant association between AKI and neurologic outcome. In our study GOS and APACHE II were the only features related

to AKI. We found no association between age or admission GCS with AKI. This contradictory finding could be justified by the discrepancy between study populations in terms of size, mean age, mean arterial pressure, and other basic characteristic features on admission.

Postinjury vasoconstriction of kidneys caused by sympathetic overactivity as a response to severe brain damage is a leading cause of AKI.[20] Mannitol used for decreasing the intracranial pressure and preventing further brain edema and herniation might result in nephrotoxicity and thus is a risk factor for developing AKI.[21–23] Application of other nephrotoxic drugs, rhabdomyolysis, and hospital-related complications like sepsis are all factors that play a role.[24]

Kidneys could be affected by inflammatory transmitters released after other organ failures like the lungs and liver.[25] AKI could be the initiator of a process ending in MOF or could be the result of systemic inflammatory transmitters generated in MOF. AKI, when it takes place, can result in brain endothelial damage, inflammation, and finally brain edema and encephalopathy, worsening the patient outcome and increasing the mortality rate.[26–28]

As shown in our study, 62% of patients who developed AKI died and 95% of them showed a poor neurologic outcome. MOF, defined by SOFA, was reported as high as 23.8%, and the MODS system revealed 19% as having MOF.

The association of AKI to high rates of mortality, poor neurologic outcome, and MOF, signifies the role of renoprotective measures and early diagnosis in order to prevent any injury and restore the kidney function.[8,19]

Patients with severe head trauma are a specific subtype of ICU patients with high rates of mortality and morbidity. Unfortunately, most of them are a young population, therefore, the burden on the health system is noteworthy. To our knowledge, few studies provided information about concomitant AKI using KDIGO in this subtype of patients. This study was performed in order to describe the AKI deteriorating the course and the prognosis of severely head injured patients.

Although there is no definitive therapy for early diagnosed AKI and the only available choice to date is resuscitative management, applying renal hygiene guidelines is always protective. Finding new biomarkers to diagnose the at-risk population for renal injury or to detect the AKI in earlier stages will help to save and restore the kidney function. Recent research is investigating new biomarkers like kidney injury molecule-1, neutrophil gelatinase-associated lipocalin, liver fatty-acid binding protein, and interleukin-18 to detect any decrease in renal function in early stages.[29]

Erythropoietin has been proposed as a novel treatment in the setting of brain trauma and a protective therapy for kidneys. Neuroprotective and nephroprotective effects have been shown in multiple rat models, but the exact mechanisms and the efficacy in human patients is an open field of study.[30,31]

New biomarkers for earlier diagnosis of AKI along with effective treatments for AKI with concomitant protective effect on the brain could change the course and prognosis of patients with severe TBI and AKI.

Conflicts of interest

The authors report no conflicts of interest.

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