ACUTE KIDNEY INJURY IN TETANUS PATIENTS AT INTENSIVE CARE UNIT OF A PEDIATRIC TERTIARY CARE HOSPITAL

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ABSTRACT

Background: Tetanus is one of the fatal diseases and is amongst major health problems in developing countries. Acute kidney injury (AKI) is a common and lethal complication of tetanus and has a direct association with tetanus mortality. To determine the frequency of acute kidney injury (AKI) in tetanus patients, hospitalized at pediatric intensive care unit (PICU) of a tertiary care hospital.

Material and Methods: This prospective cross-sectional study was conducted from January 2020 to December 2020. Diagnosed tetanus patients hospitalized at PICU of National Institute of child health were included in the study. Detailed history, clinical signs and symptoms were recorded and laboratory tests including serum urea and creatinine were performed on admission, at 48 hours and at 1 week. Input and output charting was documented. AKI was diagnosed and further categorized into Risk, Injury and Failure as per pRIFLE criteria. Data was analyzed using SPSS 25.

Results: Total 52 patients with tetanus were enrolled. Mean age of patients was 8.56 ± 2.57 years including 71.2% males and 28.8% females. Most common presentation was lock jaw in 90.4% and foot injury was the predominant (57.7%) site of trauma. AKI was seen in 13.46% at the time of admission and in 58.69% at 1st week, out of which 28.8% needed dialysis. Mortality was 34.6% and 5.8% developed chronic kidney disease. Higher rates of deaths were observed in patients who presented with a pRIFLE criteria of risk or injury at the time of admission (p-value 0.010).

Conclusion: AKI is a common complication in tetanus patients and is associated with high mortality. Monitoring patients for AKI and implementation of pRIFLE criteria is important to find out patients at risk for AKI.

Keywords: Tetanus, Acute kidney injury, Vaccination, pRIFLE

BACKGROUND

Among many infectious diseases, tetanus is one of the fatal disease in developing countries and still is being encountered in developing countries.[1] Worldwide incidence of tetanus cases is 12476 per year as reported by WHO in 2017 including 478 reported cases from Pakistan in pediatrics age group which is underestimated because of poor reporting system but it's still alarming.[2] Mortality from generalized tetanus is 4.2% to 50% which is specifically very high in low to middle income countries and deaths are more common in neonates.[3,4] Mortality is high when patient presents with short duration of onset, with high severity of disease and autonomic involvement.[5-7]

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Aim of treatment is to neutralize toxin, to control muscle spasm and to stabilize autonomic instability, management of wound and to monitor vital organ functions.[8] Severe tetanus is still a major issue in developing countries and the only strategy to prevent tetanus is vaccination, health care authorities should pay more concern on awareness programs and vaccination strategies.[9]

Tetanus often presents with lockjaw, dysphagia, opisthotonus along with spasms of respiratory, laryngeal, and abdominal muscles, which may cause respiratory failure.[6] Diagnosis of tetanus is entirely clinical.[4] Different factors are related to the high rate of mortality in tetanus like severity of tetanus itself, development of different variety of complications like cardiovascular, renal and pulmonary and need for mechanical ventilation with it.[8]

AKI is a common and lethal complication of tetanus and is reported to have direct association with tetanus mortality.[8,10] Pathophysiology of AKI in tetanus is not clearly known but several factors have been attributed

to development of AKI in tetanus, including rhabdomyolysis, autonomic dysfunction, sepsis, nephrotoxic drugs usage, complications of mechanical ventilation, dehydration and secondary to catecholamine surge alteration in kidney circulation.[11] According to different studies worldwide, frequency of AKI ranged from 1.8 % to 60% and study done in Pakistan showed 31% of tetanus patients developed AKI as complication[8,10]

This study was conducted to determine frequency of AKI in tetanus in pediatric age group in order to highlight the need for routine monitoring of kidney parameters, early diagnosis of AKI and its early management in order to improve the outcome in tetanus patients.

MATERIAL AND METHODS
National Institute of Child Health (NICH) Karachi from January till December 2020 after approval from institutional ethical committee (IERB No 19/2019). NICH is one of the largest public sector tertiary care children Hospital of Pakistan with 500 beds including a PICU of 13 beds. The hospital receives pediatric patients from all over Sindh and also from Southern Punjab and Balochistan.

All children admitted in PICU with diagnosis of tetanus during study period with age ranging from 1 month to 14 yrs were enrolled. Patients with history renal disease were excluded.

After taking informed consent from patient's attendant detailed medical history and clinical examination was performed. Baseline laboratory investigations including hemoglobin, platelets and total leukocyte counts were recorded in the proforma. Serum urea and creatinine were done at arrival, at 48 hours and at 7-days. Input and output charting was documented and pRIFLE criteria was applied in all tetanus patients to determine AKI which was further categorized into

1. Risk (R); decrease in GFR by 25% or urine output <0.5ml/kg/hr for 8 hr.
2. Injury (I): decrease in GFR by 50% from baseline or urine output <0.5ml/kg/hr for 16hr.
3. Failure (F): decrease in GFR by 75% from baseline or urine output <0.3 ml/kg/hr for 24 hr or anuric for 12 hr.[12]

All patients received standard care as per ICU management protocols of NICH. Children with AKI were followed at 3 months and repeat serum creatinine

and GFR measurement was done. CKD was defined as GFR <90ml/min/1.73m^2 at 3 months.[13]

Data was analyzed by SPSS version 25. Numerical variables like (age, duration of stay) are reported as mean and standard deviation. Categorical variables (gender, vaccination status) are presented as frequency and percentages. Effect of AKI development on length of hospital stay and duration of mechanical ventilation was determined using t-test for independent sample. Comparison of patients' outcome with respect to different factors was also studied using chi square test for categorical variables like gender, antibiotic used, vaccination status etc. and t-test for independent samples in case of numerical variables like age. For all statistical analyses p-value less than 0.05 was taken as significant.

RESULTS
Total 52 patients were enrolled with mean age of 8.56 ±2.57 years (1.5 to 13 years of age), out of which 37 (71.2%) were male and 15 (28.8%) were female. Mean duration of illness before hospitalization was 6.10 ± 2.56 days (3 to 13 days). Clinical signs and symptoms included lock jaw 47 (90.4%), fits 43 (82.7%) with mean frequency of fits 2.56 ± 1.74 per day (range 0 - 6 fits per day), fever 43 (82.7%). Also seen were hypertonia in 22 (42.3%) and hyper-reflexia in 20 (38.5%). Common site of injury was foot 30 patients (57.7%), hand 9 (17.3%) and other sites 23 (44.23%). With respect to EPI, Pakistan protocols 12 (23%) patients were completely vaccinated, 17 (32.7%) were partially vaccinated while 23 (44.2%) were unvaccinated. Laboratory findings at the time of admission, at 48 hours and 7-days have been presented in Table-1.

According to pRIFLE criteria, at the time of admission 5 (9.6%) patients were in risk category and 2 (3.8%) patients were in injury category of AKI. At 48 hours AKI was seen in 21(40.38%) patients including 16 (30.8%) in risk category, 4 (7.7%) had injury while 1 (1.9%) patient had kidney failure. After 7 days of admission 46 (88.46 %) patients were left while 6 (11.5%) patients had less than 1 week of intensive care unit stay. Among these AKI was seen in 27(58.69%) patients as per pRIFLE criteria including 12 (26.08%) patients in risk category (26.08 %), 7 (15.21%) in renal injury, renal failure in 8 (17.39%) patients. Patients who developed AKI and who did not develop

AKI were compared in terms of length of hospital stay and duration of mechanical ventilation. Both hospital stay and duration of mechanical ventilation were prolonged in case of AKI however, no statistical significant association was observed (Table-2).

All patients received tetanus toxoid vaccination and tetanus immunoglobulin on admission. Antibiotic treatment during hospital stays included ceftriaxone and metronidazole in 32 (61.5%) patients, ceftriaxone in 10 (19.2%) patients and meropenem in other 10 (19.2 %) patients. Different variety of antibiotics were chosen on basis of severity of infection clinically as well as on basis of biochemistry and septic markers. Sedation was given in 46 (88.5%) patients. Forty-three (82.7%) patients required mechanical ventilator support.

Overall mortality was observed to be 18 (34.6%). Three patients were found to develop chronic kidney disease (CKD) at 3-months follow-up. Table-3 presents the association of different factors with reference to outcome. Results of comparative analysis show that mean age of patients who survived was slightly higher than non-survivors but statistically not significant, similarly more deaths were observed in females, partially or not vaccinated patients, those who received meropenem and who developed AKI but none of these exhibited a statistically significant association. Statistically significant higher rates of deaths were observed in patients who presented with a pRIFLE criteria of risk or injury at the time of admission (p-value 0.010).

Table-1: Laboratory investigation and renal functions of tetanus patients at time of admission, at 48 hours and at the end of 1st week.

Parameter	At the time of admission	After 48 hours of admission	After 7 days of admission
Hemoglobin (g/dl)	10.02 ± 1.9		
Total leucocytes count ($\times 10^3/\mu l$)	18.45 ± 7.4		
Platelets count ($\times 10^3/\mu l$)	300 ± 80.27		
Serum urea (mg/dl)	35.2 ± 1.0	55.4 ± 48.58	84.7 ± 66.31
Serum creatinine (mg/dl)	0.66 ± 0.65	0.66 ± 0.65	1.493 ± 1.15
GFR (ml/min)	108 ± 20.7	100 ± 28.9	85.17 ± 34.10

Table-2: Comparison of patients with respect to AKI development.

		AKI	No AKI	p-value
Length of hospital Stay (Mean ± S.D)		20.31±9.15	16.64 ±14.20	0.276
Duration of mechanical ventilation(Mean ± S.D)		17.27±9.45	12.30±12.47	0.113
Outcome	Survived	18 (69.2%)	15 (60%)	0.490
	Expired	8 (30.8%)	10 (40%)	

Table-3: Comparison of tetanus patients with respect to outcome.

VARIABLES		Survived N=33	Expired N= 18	p-value
Mean Age of Patients (Years)		8.73±2.24	8.31±3.20	0.585
Gender	Male	27 (73%)	10 (27%)	
	Female	6 (42.9%)	8 (57.1%)	0.093
Antibiotic Treatment Used	Ceftriaxone	9 (90%)	1 (10%)	
	Ceftriaxone + metronidazole	20 (64.5%)	11 (35.5%)	0.051
	Meropenem	4 (40%)	6 (60%)	
pRIFLE on Admission	Normal	32 (72.7%)	12 (27.3%)	
	Risk	1 (20%)	4 (80%)	0.010
	Injury	0(0%)	2 (100%)	
Vaccination Status	Complete	10 (83.3%)	2 (16.6%)	
	Partial	12 (70.6%)	5 (29.4%)	0.116
	Unvaccinated	11 (50%)	11 (50%)	
Booster dose of tetanus	Yes	6 (85.7%)	1 (14.3%)	0.398
	No	27 (61.4%)	17 (38.6%)	
AKI	Yes	18 (69.2%)	8 (30.8%)	0.490
	No	15 (60%)	10 (28.2%)	

DISCUSSION

Tetanus remains a morbid illness and a major health issue in Pakistan, despite availability of free of cost-effective vaccination through expanded program of immunization (EPI) and is associated with significant morbidity and mortality.[14]

Previous studies suggest that tetanus infection is commonly observed in children aged 6 years with predominance noted in male children. Current study further confirms these findings as it also showed that majority of patients were male (71.2%) with a mean age of 8.56 $\pm$ 2.57 years.[4,14,19] Male predominance in tetanus is usually associated with the fact that boys are likely more prone to have trauma due to more outdoor activities.[14-19]

It was also observed that almost 77% of tetanus patients were either unvaccinated or had received incomplete tetanus vaccination. High rates of incomplete vaccination among tetanus patients was also reported by Khurshid et al and Animasahun *et al*.[15-17] Complete vaccination according to EPI was received in only 23% of the cases. Infection besides complete vaccination is also alarming. Extended program for Immunization (EPI) Pakistan provides only 3 doses of tetanus which is protective for next 3 to 4 years of life, after which antibody levels fall and results in children being susceptible to tetanus infection again.[4,16] This raises the need of booster vaccination at 15 to 18 months and at 4 to 6 years of age to provide long term immunity against tetanus in vaccinated children.

Present study identified foot injury as the predominant (57%) site of infection. This finding is also supported by other studies where researchers have reported foot as a common site of injury.[20,22]

This study showed that 58.69 % patients developed AKI according to pRIFLE criteria. A study from India reported similar findings of 63.3% AKI among tetanus patients.[16] However, an earlier study from Karachi reported AKI in 31.81% in pediatric tetanus patients.[1] Authors from Afghanistan reported 33% AKI among tetanus patients.[17] While few other studies showed AKI as complication of tetanus with wide variation in frequency from 1.8 % to 19.4%. Except for the Indian study we have observed higher rates of AKI in our patients but it is important to note that these studies have not mentioned timing of development of AKI as in our study at the time of admission, AKI was in 13.46% which progressed to 58.69% at the end of 1st week. Secondly most of these studies have collected data from both pediatric and adult population.[5,15,20] Also our study was Intensive Care Unit based study that included critically ill patients only while other studies enrolled all tetanus patients from general pediatric ward as well as ICU. In our patients 15 (28.8%) needed dialysis, similar findings are reported by Angurana *et al*.[16]

In present study 34.6% patients died due to tetanus, similar rates of tetanus associated mortality have been reported by Angurana *et al* (40%), Awoke *et al* (32.7%), Shruti *et al* (32%), Kiran *et al* (31%) and Faizia *et al* (26%).[1,16,17,22]

Among 18 children who expired almost 50% patients had associated complication of AKI suggesting it to be among one of the major risk factors for mortality in tetanus patients and it is also supported by study of Ali et al in which mortality among tetanus children was high with associated complication of AKI.[19]

Out of 18 patients who survived after AKI, 15 children visited for follow up at 3 months and 3 children (5.8%) had persistent deranged renal function after 3 months and were labelled as chronic kidney disease.

LIMITATIONS

We had certain limitations in our study. We didn't include general pediatric ward patients. So, outcome related to AKI and mortality in tetanus children may be little better if we had included patients in general ward. Second our study is a single centered study which limits its generalization of results. Further multicentre large-scale studies are needed for generalization of results

CONCLUSION

AKI is common complication in tetanus patients and is associated with high mortality. Monitoring of AKI and implementation of pRIFLE criteria is important to find out patients at risk for AKI. Early recognition is necessary to start early management to prevent further progression into kidney failure.

RECOMMENDATION

We recommend to add booster vaccination of tetanus in EPI program at 18 months of age and then at 4 to 6 years of age to prevent this illness in vaccinated

children. Public health awareness is key for tetanus vaccination after injury and implementation of routine EPI vaccine and booster vaccinations.

AUTHOR CONTRIBUTION

Faryal Ayub: Conception, Manuscripts writing, analysis, data collection, revised manuscript

Misbah Anjum: Conception, manuscripts writing

Safia Bibi: Data analysis, revised

Aisha Khan: Data collection

Shazia Soomro: Data collection

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