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Clinical profile of severe generalised tetanus patients

Shastri M[1], Gupta R[1], Lakhani N[2], Patel H[2], Thakkar S[2], Kansara T[1]

1. Sir SayajiRao General Hospital & Medical College, Vadodara, India
2. Intern doctor, Sir SayajiRao General Hospital & Medical College, Vadodara, India

RESEARCH

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Corresponding Author:
Dr Tikal Kansara
Sir SayajiRao General Hospital & Medical College
Vadodara, Gujarat, India
Email: tikalkansara@gmail.com

ABSTRACT

Background
Tetanus, a rare disease in today's world, when occurs, takes a devastating course. However, with proper treatment and ventilatory support, patients with tetanus can survive and lead a healthy event-free life.

Aims
To describe the clinical features, course, complications, treatment and outcomes in patients admitted to the medical intensive care unit (MICU) with severe generalised tetanus requiring mechanical ventilation.

Methods
A prospective study was conducted between September 2014 to February 2016, on 40 patients who had severe generalised tetanus. Adult patients (above 12 years age) who required mechanical ventilatory support were included. A detailed history, laboratory parameters, medications, supportive medical care, duration of mechanical ventilation and outcome were studied. Outcomes were defined as complete recovery or death.

Results
This study showed male to female ratio of 3:1, with 67.5 per cent patients under the age of 40 years. Most of the patients (95 per cent) were from rural population and all patients were unimmunized. Mortality was 82.6 per cent, when period of onset was less than two days. Autonomic dysfunction was the attributed cause of death in first seven days of hospital stay, while from second week onwards death was due to secondary complications (sepsis, ventilator associated pneumonia, etc.). Overall mortality rate was 52.5 per cent.

Conclusion
Shorter the period of onset, more severe the disease, and high the mortality. Early mortality was attributed to autonomic dysfunction, while late mortality is attributed to secondary complications. These results matched with the existing literature and historical studies.

Key Words
Tetanus, ventilatory support, period of onset, vecuronium

What this study adds:

1. What is known about this subject?
The incidence of tetanus has been decreasing due to effective primary immunization and prophylactic methods of prevention after exposure. However, there are instances of sporadic cases in developing world, especially from rural population.

2. What new information is offered in this study?
On review of literature, there has not been any large scale study which included 40 patients of tetanus, requiring paralytic agent and mechanical ventilatory support in the last decade. Our attempt was to study the clinical profile, management, outcomes and correlate with the existing literature to find out whether with advances in critical care management, were we able to further improve the outcome of these patients.

3. What are the implications for research, policy, or practice?
In the past decade, very few clinical studies have discussed

severe generalised tetanus and studied the importance of human tetanus immunoglobulin, magnesium sulphate and mechanical ventilatory support in them. Allocation of resources to patients of severe generalised tetanus and further penetration of immunisation program to rural population is required. In practice, early tracheostomy and mechanical ventilatory support leads to a favourable outcome in patients with tetanus.

Background

The Centre for Disease Control and Prevention (CDC) defines tetanus as "the acute onset of hypertonia or painful muscular contractions (usually of the muscles of the jaw and neck) and generalised muscle spasms without other apparent medical cause.[1]" For the purpose of this study, a severe case of generalised tetanus is defined as a case requiring use of paralytic agent over and above benzodiazepines to control spasms and hence requiring mechanical ventilatory support. They are the cases of severe generalised tetanus and only these patients are included in the study. The incubation period of tetanus is 8 to 12 days.[2] The period of onset is the time from appearance of first symptom to first spasm.[2] Lesser the period of onset, more severe the disease. Mortality from dysautonomia occurs commonly in first seven days. Features of dysautonomia comprises of rapid fluctuations in blood pressure and heart rate, heart blocks, gastrointestinal stasis, sudden severe sweating, increased tracheal secretions and acute high output renal failure.[2] In past treatment of tetanus was limited to isolation of patients in a dark, noise free environment and use of equine antiserum. Over time, it has progressed to the use of muscle relaxants with mechanical ventilator support, human tetanus immunoglobulin, sedatives, antibiotics, analgesics and magnesium sulphate. The incidence of tetanus has been decreasing due to effective primary immunization and prophylactic methods of prevention after exposure. The World Health Organisation (WHO), national and international guidelines, have made it possible to penetrate childhood immunisation programs to rural populations of developing countries. Still we still come across isolated cases of tetanus. It is important to provide prompt treatment in intensive care unit as most of these patients are young and otherwise healthy prior to occurrence of tetanus. If properly treated they can lead a healthy life without any residual effects of tetanus. As there are very few data published in the past decade about tetanus, our objective is to follow up these patients during their critical phase of illness in medical ICU (MICU), study their signs, symptoms and management protocol and compare it with the literature available to increase the recent data pool of a dreadful acute but curable disease.

Method

Study sample

A prospective study was conducted in medical intensive care unit (MICU) at Sir SayajiRao General Hospital, Vadodara during the period of September 2014 to February 2016 and 40 consecutive patients of severe generalised tetanus requiring mechanical ventilatory support were enrolled after taking ethics committee approval and consent of the patient's relatives.

Inclusion criteria

All patients, above 12 years of age, clinically diagnosed as having severe generalized tetanus requiring mechanical ventilatory support for their management and admitted in MICU. Children 12 years and younger were admitted in paediatric ICU and were not included in the study.

Exclusion criteria

Patients less than 12 years of age diagnosed as severe tetanus requiring mechanical ventilatory support, localised tetanus (e.g., only trismus) and generalised tetanus whose spasms were controlled only by monitored benzodiazepine infusions and not requiring paralytic agents as well as not requiring mechanical ventilatory support.

History and Clinical Examination

A detailed history of each patient enrolled in the study was taken including antecedent history of trauma, pregnancy/delivery, otitis media and immunization history in reference to vaccination for tetanus. The frequency of spasms, severity of autonomic dysfunction, respiratory distress and urine output were noted and taken care of on daily basis and treated accordingly. Incubation period and period of onset was noted in all the patients.

Hemogram, renal and liver profile, electrocardiogram, chest X-ray and arterial blood gas analysis (ABG) were done in all patients. Tracheostomy cultures and other cultures were ordered when clinically indicated.

Standard treatment protocol for management of patients with severe generalized tetanus was followed. This included giving human tetanus immune globulin immediately after admission. Tracheostomy was performed as soon as possible in all patients to relieve upper airway obstruction due to laryngospasm via surgical route and they were kept on mechanical ventilatory support. A cocktail therapy of sedatives, analgesics and paralytic agents along with

sympathetic alpha and beta receptor blockers for autonomic dysfunction were also used. Sedatives included benzodiazepines as intravenous continuous drip or infusion form, most commonly diazepam. Vecuronium as a muscle relaxant was used as intravenous continuous drip or infusion form along with bolus doses of atracurium, as and when required. All patients were treated with third generation cephalosporins. Magnesium sulphate was given at the earliest possible time and further doses were given as per requirement.

There were two end points of the study. Either the patient died during their hospital stay or was shifted to medical ward after tracheostomy closure. In medical wards, they spent variable amount of time for rehabilitation and some were followed up with physiotherapy department for months. So, for our study, once a patient was out of medical ICU and shifted to medical ward, he was deemed survived (in relation to tetanus).

Analysis

For the purpose of simplicity, the patients were divided into three main groups according to their age. Group A had adolescent children between 13–19 years of age. Group B had young adults between 20–39 years of age. Group C had older patients above 40 years of age. Data entry and analysis was done using Microsoft Excel. Chi-square test was used to determine statistical significance. Mean was derived for age and period of onset.

Results

The results of the study are summarised in the following Tables 1–11.

Table 1: Occurrence of tetanus according to age with tetanus

Age Group	Males	Females	Total
13–19 years	11	05	16
20–39 years	09	02	11
40 years and above	11	02	13

In our study, the mean age of presentation was 30.20 years ±17.20 years. Minimum age of presentation was 13 years and maximum was 79 years. Interquartile range (IQR) was 23 (Q1=17; Q2=22; Q3=40). Our study had 27 out of 40 (67.5 per cent) of patients under the age of 40 years. Among them, more than 2/3rd was males. Adolescent children were the most commonly affected group. This was not statistically significant. (x^2=1.198; p>0.05)

Tetanus from rural and urban areas

Our study had most of the patients (38 out of 40, 95 per cent) patients from rural population.

Table 2: Tetanus Outcome according to both age and sex

Age group (years)	Male		Female	
	Survived	Death	Survived	Death
13-19	5	6	2	3
20-39	6	3	0	2
40 and above	5	6	1	1
Total	16	15	3	6

Out of a total of 31 males, 16 survived. The age distribution was nearly equal among all three age groups. Mortality was half in the age group of 20–39 years as compared to both adolescence and old age group patients. Out of nine females, six died.

Tetanus outcome by status of immunisation

All patients who presented with severe generalised tetanus were not immunised. Tetanus toxoid at the time of trauma was given to only one patient. (x^2=1.134; p>0.05)

Table 3: Tetanus outcome according to incubation period

Incubation period	Survived	Death	Total
<7 days	7	7	14
≥7 days	8	7	15
Not calculable	4	7	11
Total	19	21	40

In our study, there was no difference in outcome among patients with incubation period of less than seven days or more than seven days (x^2=0.787; p>0.05).

Table 4: Tetanus outcome according to period of onset

Period of onset	Survived	Death	Total
<2 days	4	19	23
≥2 days	15	2	17
Total	19	21	40

In our study, mean duration of period of onset was 1.98 days. Patients admitted with period of onset less than two days showed poor prognosis with a mortality rate of 82.6 per cent (x^2=16.935; p<0.0001).

Table 5: Tetanus outcome by autonomic dysfunction

Autonomic dysfunction	Survived	Death	Total
Present	14	20	34
Absent	5	1	6
Total	19	21	40

In our study, 34 patients developed autonomic dysfunction in the form of sinus tachycardia, hypotension or bradycardia. Mortality among patients with autonomic dysfunction was 58.82 per cent (20 out of 34) while mortality among patients without autonomic dysfunction was 16.67 per cent (x^2=2.141; p>0.05)

Table 6: Tetanus outcome by type of injury

Type of injury	Survived	Death	Total
Trauma	15	10	25
Electrical burns	0	1	1
Post partum	0	1	1
Ear infection	0	1	1
Gangrenous limb	0	1	1
Idiopathic	4	7	11
Total	19	21	40

27.5 per cent (11 out of 40) had no antecedent history of injury, infection or history of post partum state as is evident from the table 6 above.

Table 7: Outcome of tetanus in relation to secondary complications

Complications	Survived	Death	Total
Urinary tract infection	4	2	6
Ventilation associated pneumonia	7	5	12
Bed sores	6	1	7
Thrombophlebitis or deep vein thrombosis	2	0	2
Sepsis	3	5	8
Total	21	13	35

Table 8: Outcome of tetanus with timing of tracheostomy

Tracheostomy done	Survived	Death	Total
Immediately after admission	19	19	38
Delayed	0	2	2
Total	19	21	40

Both patients in whom tracheostomy was delayed by a few hours to days expired (x^2=1.905; p>0.05). Tracheostomy was performed, 12–16 hours after hospital stay in one patient, while in the others; it was performed on the second hospital stay.

Table 9: Outcome of tetanus in relation with timing of onset of symptoms and administration of tetanus immunoglobulin

Human tetanus immunoglobulin given	Survived	Death	Total
≤2 days after symptoms	3	13	16
>2 days after symptoms	16	8	24
Total	19	21	40

In our study, when tetanus immunoglobulin was given two days after the symptom onset, the patients had a favourable outcome (x^2=8.839; p<0.05), but had a confounding agent as “period of onset”, hence, a spurious association.

Mortality in patients with severe tetanus admitted in MICU:

Table 10: Outcome with severe tetanus

Outcome	Number
Survived	19
Expired	21
Total	40

Thus in our study, patients of severe tetanus admitted in MICU had a mortality rate of 52.5 per cent.

Table 11: Duration of ICU stay and outcome in patients with tetanus

Duration in MICU	Survived	Death	Total
≤1 week	0	15	15
1-2 week	0	2	2
>2 week	19	4	23
Total	19	21	40

In our study, out of 40 patients, 15 died in first week, two died in the second week (x^2=26.749; p<0.0001). All patients who died in the first week were due to severe autonomic dysfunction. Out of 23 patients who were admitted in MICU for more than two weeks, 19 patients survived. Two

patients who died in the second week had developed ventilation associated pneumonia. Thus our study shows that tetanus carries mortality rate of 37.5 per cent in the first week of the disease. After this period, mortality is mainly due to secondary complications due prolonged bed ridden state in the MICU.

Discussion

Our study showed 67.5 per cent of cases in age group of less than 40 years similar to study by Chalya et al.[3] which showed 74.5 per cent patients under the age of 40 years, but in contrast to study by Owolabi et al.[4] which had only 29.7 per cent patients less than 40 years and Marulappa et al.[5] which had only 26.7 per cent patients under 40 years. This could be because most of our patients were working farmers with associated occupational risk of trauma.

Our study included 75 per cent males and 25 per cent females which is similar to the study by Marulappa et al.[5] showing incidence of tetanus as 74 per cent males and 26 per cent in females and the study by Lau et al.[6] where 68.2 per cent were males and 31.8 per cent were females, study by Owolabi et al.[4] which had 73.8 per cent males and 26.2 per cent females.

In our study, 95 per cent of patients were from rural area and five per cent from urban area. Studies by Saltoglu et al.[7] showed tetanus in rural population at 77.7 per cent, while a study by Mamtarani et al.[8] showed only 55.8 per cent rural population in cases of tetanus. This could be due to lack of awareness among people about immunization, including post exposure prophylaxis and lack of penetration of immunization programs to rural populations.

Our study showed that none of the patients had history of immunization to tetanus. In a study by Chalya et al.,[3] 76.5 per cent patients were not vaccinated. Several studies and CDC guidelines have demonstrated the efficacy of immunization with tetanus toxoid in decreasing the incidence rate of tetanus. Thus, immunization is a necessary primordial step against tetanus.

Our study showed 50 per cent mortality in patients with incubation period less than seven days similar to Marulappa et al.[5] where mortality was 56.7 per cent with incubation period less than seven days and a study by Saltoglu et al.[7] where mortality was 75 per cent. In the study by Owolabi et al.[4] where the mortality rate was 89.1 per cent in patients with incubation period of less than two days.

As history of injury might not always be available in all patients, incubation period is not a reliable measure to calculate the prognosis of a patient. Instead, period of onset is a better source for the same.

Our study showed 83 per cent mortality in patients with period of onset less than two days and 12 per cent mortality in patients with period of onset greater than two days. Similar to studies by Owolabi et al.[4] where mortality was 84.4 per cent and 6.5 per cent for the same. Thus, shorter the period of onset, higher the mortality rate. In our study, this was highly significant at $p<0.0001$.

Our study showed 58.8 per cent mortality in patients with dysautonomia and 16.6 per cent mortality in patients without dyautonomia. Autonomic dysfunction was present in 86 per cent of patients in a study by Owolabi et al.[4] Hence, patients with dysautonomia showed worse prognosis in the form of early mortality. Several studies like the ones by Twaites et al.[9] and Attagalle et al.[10] have shown importance of magnesium sulfate. These studies stated that although there was no change in the overall mortality whether the patient received magnesium sulphate or not, there was a considerable reduction in the requirement of muscle relaxants and sedatives. A study by Wesley et al.[11] showed that labetolol when used in tetanus with autonomic dysfunction helps in control of sympathethic overactivity.

In our study, death after first week of disease was mainly due to secondary complications due to longer period of admission and longer bedridden state of the patients. These complications must be prevented or diagnosed and treated early. Development of secondary complications shows worse prognosis in the form of multifold increase in mortality.

In our study, all the patients were tracheostomized immediately after admission but in two patients' tracheostomy were delayed due to delayed consent for performing tracheostomy and both of them did not survive. A study by Fasunla showed that delaying tracheostomy lead to increased mortality.[12]

In our study, all patients were given human tetanus immunoglobulin immediately after admission. Yet the mortality was high (81.2 per cent) in patients within two days of onset of symptoms. This could most likely be due to less period of onset which determines grave prognosis in patients with severe tetanus.

In our study, patients with severe injury were very few hence this data cannot be commented.

Our study showed 47.5 per cent survival rate in patients with severe tetanus similar to the study by Trujillo et al.[15] which had 47 per cent survival rate, study by Marulappa et al.[5] which had a survival rate of 57.8 per cent, Owolabi et al.[4] which had a survival rate of 54 per cent. Our study showed that survival rate was higher in the patients who lived for more than a week. Death within one week was mainly due to dysautonomia. After the first week, death was mainly due to secondary complications related to prolonged bedridden state in the ICU.

Conclusion

Shorter the period of onset, more severe the disease, and high the mortality. Early mortality was attributed to autonomic dysfunction, while late mortality is attributed to secondary complications. These results matched with the existing literature and historical studies.

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CONFLICTS OF INTEREST

The authors declare that they have no competing interests.

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