ORIGINAL ARTICLE

Tetanus in Adults – A Continuing Problem: An Analysis of 217 Patients Over 3 Years from Delhi, India, with Special Emphasis on Predictors of Mortality

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Summary

Tetanus is still widely prevalent in many parts of the world especially in the developing countries. This study was conducted to assess the demographic and clinical features, treatment and outcome of tetanus in adults with a special emphasis on identification of predictors of mortality. This was a retrospective study of all adult patients admitted with tetanus over a three-year period from 1998 to 2000 at Lok Nayak Hospital, New Delhi, India. The demography, clinical features, treatment and complications of the patients were assessed and were evaluated against two possible outcomes- survival or death, to identify the predictors of mortality. There were 217 adults (148 males, 69 females) admitted with generalized tetanus during the study period. The mean age of the patients was 36.08 ± 18.84 years. In most instances (63.5%), wounds / injuries served as the source of infection. Overall 31.8% had mild, 21.7% had moderate and 46.5% had severe disease at presentation. Respiratory failure and dysautonomia were the frequently observed complications. Of the 217 patients, 82 died – a mortality rate of 37.78%. Parameters that were significantly associated with increased mortality were: age (especially > 60 years); shorter duration of symptoms – trismus, rigidity and dysphagia; severe disease at presentation and shorter period of onset. Tetanus is a preventable disease associated with a high fatality rate. Universal coverage of immunization programme and appropriate wound prophylaxis is the corner stone of tetanus eradication. The treatment of tetanus is difficult and requires specialized and intensive care. The presence of parameters indicating an adverse outcome at the beginning in the patients will help identify the subset of patients that need more intensive management especially in resource poor nations.

Key Words: Tetanus, Adults, Prognostic indicators

Introduction

Tetanus is a global health problem. Despite the availability of a highly effective vaccine making it preventable, tetanus continues to be a significant burden on the health resources worldwide. The WHO included tetanus in its Expanded Programme of Immunization (EPI) with the aim to eradicate the disease. In spite of the efforts of the WHO and various other health authorities, it is estimated that the annual incidence of tetanus is about 1 million cases[1,2]. The majority of these cases occur in the developing countries and the disease is very uncommon in the developed world – there were only 33 cases of tetanus reported in the US in 1999[3]. Tetanus is still widely prevalent in India and about 50% of all cases occur in neonates. Tetanus is associated with a high mortality rate varying from 30-50% and the mortality rates are even higher in the third world nations where the burden of disease is more.

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Tetanus is caused by *Clostridium tetani*, gram-positive bacilli, the spores of which are highly resistant to temperature and humidity and survive for extended periods in the soil. Contaminations of wounds leads to the inoculation of the spores that then germinate into the toxin producing bacilli. *C.tetani* produces 2 main toxins – Tetanospasmin- it is responsible for all the clinical manifestations of tetanus. Tetanospasmin enters the peripheral nerves and by retrograde axonal transport reaches the central nervous system (CNS). There it enters into the presynaptic neurons and prevents the release of the inhibitory neurotransmitters gamma amino butyric acid (GABA) and glycine. The resulting uninhibited discharge from the neurons produces the characteristic muscle spasms and autonomic instability. The role of the other toxin, tetanolysin is still unclear.

Though the majority of cases of tetanus occur as neonatal tetanus, the problem is increasing in magnitude especially in the elderly population. The present study was done to assess the demographic and clinical profile of tetanus with special emphasis on the assessment of outcome and evaluation of predictors of mortality in adults with tetanus.

Materials and Methods

The study was conducted in the department of Medicine of Maulana Azad Medical College and associated Lok Nayak Hospital, New Delhi, India, which is the only referral hospital for all cases of adult tetanus in Delhi and neighboring areas. This study was a retrospective analysis of all patients admitted over a 3-year period from January 1998 to December 2000.

The diagnosis of tetanus was entirely clinical, based on the presence of typical symptoms and signs. The patients were classified into 3 groups according to severity[4,5] at presentation into:

Mild : presence of trismus, mild rigidity but no spasms.

Moderate: severe trismus, rigidity. Mild to moderate spasms occurring only on provocation

Severe : spontaneous, protracted spasms, generalized rigidity, autonomic disturbances.

The demography, clinical features, treatment and complications of the patients were evaluated against two possible outcomes- survival or death. For continuous data, the 2 groups were compared using the Students T test and for non-continuous data, the non-parametric Mann Whitney test was applied. An observed p value of < 0.05 was considered significant. Individual variables were also tested in a univariate analysis by logistic regression and the odds ratio was calculated where applicable. Values are presented as mean ± S.D wherever applicable.

Results

There were 219 adults admitted with a clinical diagnosis of tetanus from 1998 to 2000. One patient each had localized (restricted to the upper limb) and cephalic tetanus. The remaining 217 had generalized tetanus and the data of these patients was analyzed. The mean age of the patients was 36.08 ± 18.84 years (range 12 –90). The age distribution of the patients is summarized in Table I. Approximately 57% of the patients were <40 years of age and 11% were > 60 years. The male: female ratio was 2.14:1 (148 males, 69 females).

Source of infection: In 63.5% of patients, there was an identifiable wound or injury that served as the portal of entry for the organism – Table II. In most instances, the patients did not seek any medical attention for their wounds and resorted to only local / home remedies for them. Upper limb wounds were the commonest (51.6%) followed by wounds on the lower limb (38.3%). Wounds on the face / head and trunk were seen in 7.8% and 2.3% respectively. Obstetric causes accounted for 4.6% of cases. Rare instances of an ulcerated breast carcinoma, diabetic foot ulcer, and i.v drug abuse were present. In 59 / 217, i.e. 27.2% of patients, no definite source of infection could be identified.

Immune status: Almost all of the patients had no prior immunization against tetanus. Even the younger patients who had been immunized in childhood did not receive the recommended booster doses of vaccine and therefore did not have adequate protection against tetanus.

Clinical features: Trismus, rigidity and dysphagia were the common presenting features of tetanus in adults – Table III. The patients first noticed a difficulty in opening the mouth – "lock-jaw" or trismus. In the mild cases, this was the predominant and often the only symptom. A generalized stiffness or rigidity in the muscles was the next prominent symptom. Rigidity, dysphagia, muscle aches and pain occurred after the onset of trismus.

Contraction of the muscles of the back leading to a

bowing / arching of the back – ophisthotonos and 'risus sardionicus' – sustained facial contraction leading to a grimace were frequently observed. With increasing severity of disease, spasms appeared. Spasms reflect a sustained tonic contraction of the rigid muscles. In the milder forms, spasms occurred infrequently and for a brief duration, occurring only on provocation by touch or light or occasionally by auditory stimuli. In the more severe cases spasms were spontaneous, sustained, protracted and painful. The frequent, prolonged spasms were responsible for the respiratory difficulty and hypoxia in the severe cases.

Severity: Based on the clinical criteria described earlier, patients were classified into mild, moderate and severe disease – Table IV. Overall 31.8% had mild, 21.7% had moderate and 46.5% had severe disease at presentation. When the grades of severity were assessed within the individual outcome groups of survivors and non – survivors, it is evident that most of the survivors had mild – moderate disease compared to 98.8% of patients having severe disease among the non – survivors ($p< 0.001$). Incubation period (IP) and Period of Onset (PO): It is important to define these two terms in tetanus.

Incubation Period (IP) – It is defined as the interval between the injury / entry of the organism in the body to the development of the first symptom.

Period of Onset (PO) – It is the interval between the first symptom and the first spasm.

The IP could be determined in only 118 out of 217 patients in whom the source of entry could be identified. Still, in many instances the exact point of wound contamination cannot be precisely ascertained and so IP is presumed from the point of first supposed contamination. The IP varied in our study from 1 to 40 days with mean 8.2 ± 6.5 days.

The PO is however determined more accurately and especially when the spasms are witnessed for the first time during hospitalization. The mean PO in the patients was 2.13 ± 1.7 days with range from <1 to 6 days. The IP and PO have a bearing on the outcome as will be discussed later. Duration of hospital stay: The mean duration of hospital stay in the patients who recovered was 17.7 ± 9.8 days (range 2 –56 days). The mean interval from admission to death in the patients who expired was 5.7 ± 4.8 days (1-23 days).

Treatment: Being a very large hospital catering to the population of Delhi and also neighboring states, there is a huge burden of patients on the limited resources. All the patients with tetanus are not admitted to the ICU. However, there is a special, separate ward available for tetanus patients providing a quiet environment for them.

Wounds, when present, were thoroughly cleaned and surgically debrided if necessary. Most patients received crystalline penicillin 10-20 MU i.v daily in divided doses for 7-10 days. Metronidazole 500 mg i.v 8 hourly was administered as an alternative to some patients. Tetanus toxoid was given to all patients. Human tetanus immunoglobulin (TIG) was administered to all patients. Human TIG was given intrathecally in a dose of 500 IU in most patients. In those patients in whom a lumbar puncture could not be done due to technical reasons, intramuscular doses of 1000-2000 IU of TIG was given. No adverse reactions to TIG were observed.

Spasms were controlled using infusions of diazepam the dose varying with disease severity. Chlorpromazine (25-50mg) i.m was added if and when required. Adequate supportive care of nutrition, hydration, antibiotics (when required), and prophylaxis against deep vein thrombosis (in patients admitted beyond 15 days) was provided.

Tracheostomy was done in 85 /217 i.e. 39.2% patients. Among those who expired, 64.6% underwent a tracheostomy. Mechanical ventilation with paralysis was provided in 21 / 217 i.e. 9.7% patients. Complications: Dysautonomia (62.1%) and respiratory complications (38.3%) were the most frequently observed complications observed in the patients. Septicemia (12.6%), wound related complications (11/.1%) and UGI bleed and renal failure were also infrequently seen. Presence of autonomic disturbances characterized severe form of tetanus and manifested as tacchycardia, labile or sustained hypertension, and diaphoresis and in very severe cases, as bradycardia and hypotension. Sudden cardiac death as a consequence of autonomic dysfunction was seen in 24 patients. Respiratory infections and septicemia - pneumonia, atelectasis, septicemia were also common complications and added to morbidity and mortality of the patients. They were chiefly due to gram negative infections and were more frequent in those with severe disease and those on mechanical ventilation.

Outcome: Two outcomes were defined – survival and death. Of 217 patients 82 died – a mortality rate of 37.78%.

Prognostic indicators and indicators of mortality: The following variables were tested separately in the 2 primary outcomes to determine the significance of their association with mortality – age, sex, duration of clinical features, site of wound, IP, PO, severity of disease at admission, requirement for tracheostomy. The results are summarized in Table V.

Ages, sex, IP, PO were separately tested by univariate analysis and logistic regression. Age ≥40 years and PO ≤3 days emerged as strong predictors of mortality with odds ratio of 3.73 and 6.19 respectively – Table VI. A significant difference in outcome was observed among the different age groups. Patients who were younger had a much better chance of survival than the older patients where the outcome was poorer- ($p<0.001$) Table – VII.

Table I: Age Distribution of the Patients

Age group (years)	Number	%
<20	62	28.6
20-40	84	38.7
40-60	48	22.1
>60	23	10.6

Table II: Source of Infection in the Patients

Source	%
• Wounds	
- lacerated / crush wounds	25.3%
- puncture wounds	14.7%
- abrasions	2.3%
- minor wounds	14.3%
- injection / cut wounds	6.9%
• Otogenic	5.5%
• Obstetric related	4.6%
• Burns	1.8%
• Others	1.4%
• Unknown	27.2%

Table III: Clinical Features of Tetanus in the 217 Patients

Clinical manifestation	Frequency %	Duration (days) Mean ± S.D
Trismus	97.7	3.0 ±2.2
Rigidity	70.5	2.5 ± 1.9
Dysphagia	27.2	2.5 ± 1.7
Pain	27.2	2.6 ± 1.8
Ophisthotonus	49.3	1.1 ± 0.3
Spasms	52.2	1.2 ± 0.5

Table IV: Severity of Disease at Admission

Grade of Severity	Overall (N=217)	Survivor group (N=135)	Mortality group (N=82)
Mild	31.8	51.1	--
Moderate	21.7	34.1	1.2
Severe	46.5	14.8	98.8

Table V: Assessment of Predictors of Mortality

Outcome	Age (years) Mean ± S.D	IP (days) Mean ± S.D	PO (days) Mean ± S.D	Severe disease at admission	Requirement for tracheostomy
Overall (n= 217)	36.1 ± 18.8	8.2 ± 6.5	2.1 ± 1.7	46.5%	39.2%
Survivors (n= 135)	30.6 ± 14.5	8.4 ± 5.3	3.01 ± 1.7	14.8%	23.7%
Expired (n= 82)	45.1 ± 21.6	8.1 ± 7.9	1.74 ± 1.0	98.8%	64.6%
P value	<0.001	NS	<0.001	<0.001	<0.001

Table VI: Evaluation of Predictors of Mortality by Univariate Analysis

Variable	Group	P value	Odds ratio of death
Age	<40 years ≥ 40 years	<0.001	3.74
Sex	Male Female	NS	--
IP	< 7 days ≥7 days	NS	--
PO	<3 days ≥ 3 days	<0.001	6.19

Table VII: Association of Demographic and Clinical Parameters with Outcome

Outcome	Age (years)- Frequency %				Sex		Clinical features (duration in days) Mean ± S.D				
	<20	20-39	40-59	>60	Male	Female	Trismus	Rigidity	Dysphagia	Ophisthotonus	Spasms
Survivors (n=135)	34.8	44.4	18.5	2.2	68.1	31.9	3.48 ± 2.2	2.92 ±1.83	1.11±0.37	2.83 ± 1.83	1.31 ± 0.65
Expired (n= 82)	18.3	29.3	28.0	24.4	68.3	31.7	2.30 ± 2.1	1.86 ±1.47	1.68 ± 1.16	1.02 ± 0.15	1.13 ± 0.33
P value	<0.001				0.98 (NS)		<0.001	<0.001	=0.016	0.11(NS)	0.06(NS)

Table VIII: Prophylaxis for Tetanus

Primary Immunization		Tetanus – prone wound		non tetanus- prone wound
		TT	TIG	TT
Incomplete		yes	yes	yes
Completed	<5 years	no	no	no
Last booster	> 5 years	yes	no	no
	>10 years	yes	no	yes

Discussion

The profile of the adult patients with tetanus in the present study was similar to that reported in other large studies[3,5]. There was a male preponderance of cases reflecting a probable greater exposure to tetanus prone injuries. However, there was no significant difference in outcome between male and females – Table VII. Wounds or injuries were the chief source of infection in the patients. Though lower limb wounds have been observed more frequently in earlier reports[3,5], upper limb wounds were commoner in the present series of patients. The site of the wound however was not associated with outcome.

Trismus, rigidity and dysphagia were the prominent clinical manifestations, with almost all patients having trismus. The mean duration (days) of these 3 major manifestations was significantly less in the patients who expired compared to the survivors ($p< 0.001$, $p<0.001$ and $p=0.016$ respectively)- Table VII. This is reflective of the faster progression of disease in the patients who expired. Severity of disease at presentation was also an important predictor of outcome – mild to moderate disease predominating in the survivors while majority of patients who expired had severe disease – Tables III and V. Similar observations regarding disease severity and outcome have been reported earlier[3].

Two important determinants of disease outcome are IP and PO. Both IP and PO have been inversely proportional to the risk of mortality i.e. shorter the IP and PO, higher the mortality[3,5,6,7]. Whereas IP may not be determined with great accuracy in some instances, PO can be ascertained with much greater reliability.

Hence, the reliability of PO is more than that of IP. In our series the IP did not show any significant difference among the two outcome groups. However, PO was significantly shorter among those who expired compared to the survivors (1.74 ± 1.0 versus 3.0 ±1.7 days, $p < 0.001$).

The reported incidence of complications observed in the patients in various published series indicate that dysautonomia (from 55-97%)[5,8,9] and respiratory complications (from 55-80%)[5,8,9] were the major complications during the course of the disease.

With the introduction of intensive treatment for tetanus patients, the incidence of respiratory complications has decreased dramatically in the developed countries. Prior to the introduction of ICU care including ventilation, 80% of deaths were related to acute respiratory failure. This reduced to 15% with ICU utilisation[10]. High rates of tracheostomy performed in adults with tetanus are reflective of this. Most developed nations are biased towards early tracheostomy in almost all but the mildest of cases[5,8]. Early tracheostomy facilitates the use of increased doses of sedatives, better chest physiotherapy and early initiation of mechanical ventilation. In contrast to this, in certain developing countries, the use of tracheostomy is very restricted. In fact in some peripheral district centers in Nigeria, Africa, tracheostomy is not resorted to at all for the fear of additional procedure – related morbidity and mortality[3].

At our center, intensive care facility is not available to all patients due to limited resources. We perform tracheostomies in moderation due to the large numbers of patients with tetanus that are admitted. Patients in whom spasms are worsening despite increasing doses of sedatives undergo the procedure. Providing care for the tracheostomy requires additional skilled manpower, which is also limited. Overall, 40% of patients in the present series underwent a tracheostomy and this increased to 65% in patients with severe disease. In a few instances, consent for tracheostomy was refused owing to certain cultural beliefs and practices. Mechanical ventilation was provided to 10% of patients. Our hospital is very large and the ICU caters to multiple specialties and therefore a delay in initiating controlled ventilation was also present due to limited number and availability of ventilators.

The treatment protocol followed at our hospital is as per the general recommendations. Sedatives, chiefly diazepam infusions, and chlorpromazine i.v. are used to control spasms. Among antibiotics, it is postulated that penicillin being a centrally acting GABA antagonist may synergistically act with Tetanospasmin to increase spasms[11]. A study also demonstrated an increase survival benefit in patients receiving i.v. metronidazole 500 mg tid to penicillin[12] and metronidazole is currently recommended as the drug of choice for tetanus[13]. We have been using penicillin for decades widely and even in this study penicillin has been administered to the majority of patients. Recently, we have started using Metronidazole as an alternative. Care of the wound (including surgical debridement), nursing care, nutritional support, thromboprophylaxis for DVT, beta blockers for severe hypertension and / or tacchycardia and prevention of pressure sores are routinely done.

For achieving neutralization of tetanus toxin, human TIG is administered to all patients. The intrathecal route is the preferred route of administration unless there is a technical difficulty in performing a lumbar puncture. The rationale behind the intrathecal use is that Human TIG does not cross the blood brain barrier and hence i.m TIG is ineffective against toxin that has already entered the CNS. Though doubts have been raised on the use of intrathecal TIG (it not recommended by the US FDA), there are large studies that have convincingly shown a clear survival benefit in patients who received intrathecal versus i.m TIG[9,14]. We have been using intrathecal TIG for nearly 8 years at our center now without any adverse reactions to it. TIG is definitely superior to anti tetanus serum (ATS) being free of the allergic reactions seen with the equine preparation. Inc certain parts of the world human TIG is not available and even ATS is in limited supply.

The availability of an effective vaccine against tetanus makes the prospects of its eradication very bright. Despite this, it has not been possible to eradicate tetanus from even the most developed countries of the world where immunization programmes cover almost the entire population. Routine immunization involves 3 doses of tetanus toxoid in combination as (DPT) at monthly intervals from 2-3 months of age with booster doses at 1 and 5 years. The immunity provided is not lifelong and in the US booster vaccinations at 10 year intervals lifelong[15] and 2 such boosters at 10 year intervals in the UK[6] are recommended.

It is these booster doses that are neglected in most countries. In the US, 30% of adults do not have

protective antibody levels (>0.01U / ml). This increases to 72% in people aged > 70 years[16]. This waning immunity in the adult population has led to the resurgence of tetanus in the elderly in whom it is associated with a high mortality[17,18].

The immunization status of adults in developing countries is dismal. Firstly, the primary immunization, including maternal immunization coverage is far from adequate. Further the concept of booster doses is almost non-existent. In the present series of patients, almost all were un-immunized and unprotected. Even the younger patients who had received 3 doses of vaccine in infancy had missed the booster doses. We need to focus all our efforts to ensure universal and adequate coverage of our immunization programme. The need of booster vaccines must be emphasized to all the physicians and health care workers.

Another area that requires concerted efforts is wound care. The physicians must be made aware of the identification of 'tetanus – prone' wounds and their appropriate prophylaxis. Wounds that are > 6 hours old, > 1cm deep, stellate, denervated, ischemic, contaminated and infected are categorized as tetanus prone[4]. All physicians must know the CDC recommendations for tetanus prophylaxis – Table VIII[19]. The public must be made aware of good wound toilet and the need to visit a doctor, rather than dismiss the wound as minor. In the present series most patients considered their wounds a "of no consequence".

The observed mortality rate in the present series was 37.78% (82 / 217). The reported mortality rates globally vary from 30 –50%. In the US the case fatality rate is about 20-30% and this increases to 52% in patients over 60 years[20]. The mortality rate in Portugal varies between 32-59% [21] and in Africa, up to 44% mortality has been reported[3]. The case fatality rates depend on a lot of factors – coverage by immunization and most importantly the availability of ICU care for the patients. Studies have shown that with intensive care treatment, mortality rates are as low as 11-13%[22,5].

Most of the published case series of adults involve small numbers of patients. The present study involving 217 patients is one of the largest studies in the world. Such a large number of patients enabled us to perform a detailed statistical analysis of the demographic and clinical parameters that are indicators of mortality.

Parameters that were significantly associated with increased mortality were: age (especially > 60 years) $p< 0.001$; shorter duration of symptoms – trismus $p<0.001$, rigidity $p<0.001$ and dysphagia $p=0.016$; severe disease at presentation $p<0.001$ and shorter PO $p< 0.001$. Sex, portal of entry, nature of wound, and site of wound were insignificant predictors of mortality. Though a short IP has been proposed as a significant predictor of mortality, no such association could be demonstrated in the present series. Even on logistic regression, IP did not emerge as an indicator of mortality. It is possible that in many instances IP was assumed from the day of injury and hence imprecise. On univariate analysis PO <3 days and age ≥ 40 emerged as the strongest determinants of mortality with odds ratio being 6.19 and 3.74 respectively.

To summarize, tetanus is a preventable disease characterized by the presence of classic symptoms and signs and associated with a high fatality rate. Though management in the intensive care settings has reduced the mortality rates in developed nations, limited resources and access to specialized care are the major stumbling blocks in the developing nations. Identification of the poor prognostic markers early in the course of the disease will help identify the subgroup of patients that will need more intensive treatment. Widespread use of appropriate prophylaxis is the cornerstone of effective prevention of tetanus. The WHO and other health authorities of individual nations must act together to ensure universal immunization to help eradicate this disease.

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