Review Article

Tetanus : An update on Management

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Tetanus is endemic in developing countries. There is no definitive diagnostic test available for this only depends the clinical progression of disease and classical symptoms. Common clinical features includes intense muscles spasm, rigidity, and autonomic instability.The mortality depends on delay in diagnosis and other comorbidities of the patients. Prevention of disease by dressing of wound and debridement, early initiation of antibiotics and early diagnosis of the disease are the key for the survival of patient. The principal of management are the control of muscles spasm, dysautonomia, and administration of human anti tetanus immunoglobulins and ventilatory support and prevention of secondary infections. It is ethically incorrect to do and randomization studies on tetanus for the treatment options when there are already some evidence based treatment exist but this review will the best for the physician to treat a patient, based on available evidence. [*J Indian Med Assoc* 2020; **118(12):** 18-23]

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Tetanus is a disease that is affects the central nervous system and muscles, leads to intense muscle spasms, it's caused by the anaerobic spore forming bacteria known as Clostridium*tetani*, that is produces a toxin and commonly found in the dirty soil, saliva, dust. The clinical features of tetanus and it association with soil was well known is past. The term "lockjawor trismus (spasm of jaw muscles) is the one of the hallmark features of tetanus. Accidental tetanus are more common in underdeveloped and developing countries. The mortality rate of accidental tetanus depends on multiple factors including the age of the patients, severity of disease, types of wound, associated with involvement of other organs such respiratory and renal failure and the treatment facility availability.[1]

Tetanus is a vaccine preventable disease less common in the developed countries then under-developed world, the disease is founds in the all unvaccinated population, particularly in developing countries. The only proper treatment of traumatic injury are the mainstay of prevention of tetanus because it is difficult to eliminate the spore of clostridium tetani from the environment.

Clostridium tetani bacteria produce two exotoxins, named as tetanolysin and tetanospasmin. Tetanospasmin is potent neurotoxin that's inhibits the release of neurotransmitters from the presynaptic membrane. This toxin affects central motor system, autonomic nervous system and N-M junctions. The clinical features of disease depends of involvement of type and site of neuronal cells. Tetanus toxin inhibits release of inhibitory neurotransmitters (glycine, GABA). These inhibitory neurons helps in muscles relaxation and control the activity of motor neurons. The excess firing of motor neurons causes muscles spasm. Due to over activity of the motor neuron patient develops hypertonia and spasticity.Tetanus also affects the autonomic nervous system, develops symptoms of dysautonomia such as sweating, fever, tachycardia, labile blood pressure, cardiac arrythemias.[2]

Editor's Comment :

- **Tetanus is still common in India, early initiation of antibiotics and debridement of wound can prevent the disease**
- **Trismus and rigidity, and autonomic instability are the main features of tetanus.**
- **Diazepam, baclofen, magnesium sulphate are the main pharmacological treatment options.**
- **Mortality depends on early diagnosis, other comorbidities of the patient and availability of ventilator (ICU) facility**

Epidemiology :

It is estimated that tetanus causes 213000 – 293000 deaths worldwide each year and that it is responsible for 5-7% of all neonatal deaths and 5% of maternal deaths globally, with a case fatality rate which ranges from 6% to 72%, depending on the availability of well-equipped intensive care units.[3]

Most reported cases occur in adults. From 2009–2017, more than 60% of the 264 reported cases were among people 20 through 64 years of age. In addition, a quarter of those reported cases were among people 65 years old or older. The risk of death from tetanus is

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highest among people 65 years old or older.[4] In developing countries the immunization coverage still is not 100%, peoples are at higher risk then the developed world. The protective immunity is declines with time so booster dose required at a frequent interval. Elderly people are great risk because they have less protective antibodies.[4,5] Tetanus is endemic In India, and it remains a public health problem. Studies shows that mortality by tetanus is still high in India due to poor health facility. According to who report total around 7000 patient having tetanus in years 2018.[6]

Pathogenesis :

Clostridium tetani is spore forming obligate anaerobic bacteria, normally present in soil and gut of mammals. When it is inoculated in the tissues its transforms in a vegetative state which is rode shape. This vegetative form produces a metalloprotein known as tetanospami. Tetanospasmin binds tightly to the receptors in the spinal cord and brain after reaching via retrograde axonal and blocks neurotransmission by its cleaving action on membrane proteins involved in neuroexocytosis.[7,8]

The net effect of tetanospamin is disinhibition of anterior horn cells, motor cortex and autonomic neurons leads to muscles spasm, hypertonia and widespread of autonomic instability. The recovery and regrowth of new axonal terminals took time, so that the effects of toxin remains long-lasting.

Tetanus toxin is produce in an inactive form mediated by genes located in an intracellular plasmid. It is initially inactive polypeptide which is activated by bacterial or tissue proteases after the death of bacteria. The active form of toxin contains two chain, a heavy chain necessary for binding and entry into neurons and a light chain responsible for its toxic properties[8-10].

Heavy chains are further cleaved by pepsins into specific fragments, which individually mediate binding to specific types of neural cells. Inhibition of presynaptic neurotransmitter release is mediated via light chains. There is increase in the resting firing rate of disinhibited motor neurons and lack of inhibition of reflex motor responses to afferent sensory stimuli this leads to muscles rigidity.[10] Symptoms of sympathetic over activity occurs due to loss of neuronal control of catecholamine's by adrenal[11].

Predisposing Factors In Adults :

1. Any types of injury that causes inoculation of bacterial spores in the tissues
2. Uncontrolled Diabetes with diabetic foot
3. Sepsis and Septic abortion
4. Patients of I.V drugs abusers
5. Unsterile surgical procedure
6. Dental infection
7. Circumcision
8. Foreign body inoculation.
9. Cryptogenic Tetanus — in this type patients have signs and symptoms of tetanus but no obvious history of any type of injury is identified. Only small amount of abrasions presumed as a source of infection.

Clinical Features :

Incubation period : — depends on the distance of injury site from the CNS, its range from 3 to 22 days. Mortality is high in those patients who has short incubation period.

Clinical classification of tetanus :

1. Local tetanus : — occurs only 1% of cases, only localised to a particular muscles group that is involves in type of tetanus. In some patients this can be proceeds to in generalised form. The contraction of muscles groups may extends to many weeks then gradually subsides.

2. Cephalic tetanus : — is similar as local tetanus localised involvement of cranial nerves of facial area. Occasionally occurring with otitis media or following head injury and neurosurgical procedures.

3. Generalized tetanus : — most common type, about two third of total reported cases of tetanus in literature are of this category. The disease presented with fever, episodic tachycardia, associated with sweating and muscles spasm. First group of muscles involves are the jaw muscles leads to lockjaw (trismus). Then disease usually descends and involves neck muscles and muscles of deglutition and abdominal muscle. This may leads to difficulty in swallowing, and rigid abdomen. The muscles spasms occur frequently and remains for minutes.

The most common symptom in generalizes tetanus is trismus found in 50% of cases. Dysautonomia was found in almost 100% of patients with generalized tetanus, have symptoms of autonomic over activity. Early phases they may manifest as excessive irritability, restlessness and over sensitive to light and sound, excessive sweating, and profound tachycardia. In later phases of illness they manifest as profuse sweating, any types of cardiac arrhythmias such as VT, VF, and PSVT and labile blood pressure.

A study done by Nitin M Apte and colleagues in 1995 to demonstrate a bedside diagnostic test known as spatula test (reflex spasm of pharyngeal muscles by touching the posterior pharyngeal wall by wooden spatula). They selected 400 patient and found this test positive in 359 (94%) of patients with sensitivity of (94%) and specificity of (100%).[11]

Patients of with generalized tetanus they have

painful tonic contractions of muscles aggravated by noise and light. In the course of disease the consciousness of patients does not affect so patient felt intense pain due to muscles spasm. The spasm may also triggered by physical stimuli such as touch. Tonic and periodic spastic muscular contractions are responsible for most of the classic clinical findings of tetanus such as:

1. Stiffness of neck
2. Opisthotonus position
3. Risussardonicus
4. Rigid abdomen
5. Periods of apnoea and upper airway obstruction due to persistent contraction of the thoracic muscles and/or glottal or pharyngeal muscles
6. Dysphagia

During the tetanic spasm patient suddenly clinch his fists and jaw, the back of patient become like bow, arm flex and adduct with extension of his leg. During this phase of tetanic spasm the respiratory movement of patient is affected and he develops apnoea for some time.

Diagnosis : — The diagnosis of tetanus based clinical features. No diagnostic test available only the detail history of injury with contaminated wound and inadequate immunization may support in the diagnosis of the patient. The clinical features of tetanus mimics many other diseases.

Differential Diagnosis :

1. Drug-induced dystonia — It is characterized as abnormal rhythmic movement of neck, face, with history of drugs intake mainly the antipsychotic and antiemetic such as haloperidol. The dystonia includes the variety of movements such as torticollis, grimacing, dysarthria, oculogyric crisis. The dystonic movements usually subsides by the anticholinergic and antihistaminic drugs treatment within 30 minutesbut not in case of tetanus.

2. Malignant neuroleptic syndrome — A group of neurological symptoms characterised by, altered mental status, fever, muscles rigidity, and autonomic dysfunction. This syndrome usually develops as due to side of antipsychotic drugs both typical and atypical (haloperidol, risperidone) which act as dopaminergic receptor antagonistor withdrawal of dopaminergic drugs (levodopa,tolcapone). In this, patient has rhabdo-myolysis (increased CPK) causes renal tubular damage and renal failure. The mental status of the patient suddenly changes from agitation to deep. This syndrome is managed by bromocriptine, datrolene, cooling of body and proper hydration of patient. The presence of history of antipsychotics and rhabdomyolysis can differentiate it's from the tetanus

3. Trismus other than tetanus — Such as dental infection, deep seated neck infection, fracture of mandible neck etc.

4. Rat poisoning — Strychnine is a bitter plants alkaloid used for pesticide and rodenticide. The clinical feature of strychnine poising are similar to tetanus. Strychnine inhibits post synaptic release of neurotransmitter glycine in spinal cord and the medulla. After ingestion strychnine absorbed from the mucus surface and stomach act fast within 15 to 20 minutes leads to neuronal hyper excitability causing muscles spams similar to tetanus. This poisoning easily differentiated by history of ingestion and quick development of symptoms and can be identified by serum strychnine levels

5. Stiff man syndrome — It is an autoimmune mediated neurological disorder associated with other autoimmune diseases such as vitiligo, pernicious anaemia, diabetes, and thyroiditis. The clinical feature are similar to tetanus characterised by painful muscular rigidity. The rigidity is increased by physical stimuli such as noise, touch and sudden movement and patient is very anxious to go outside the house. Management includes diazepam and immunoglobulins rapid response to diazepam and association of other autoimmune diseases distinguish this from true tetanic spasms.

6. Management of Tetanus — Management of tetanus includes in the following headings:-

1. General Measurements

a. Admit in dark and quit room
b. Management airway, circulation, and other supportive measures
c. Well-equipped ICU

2. Wound management

a. Debridement of wound

3.Antibiotics (Adult dose)

a. Metronidazole 500mg 6 to 8 hourly
b. Penicillin G 2 to 4 MU I.V TDS4. Ceftriaxone 2g TDS if mixed infection is suspected

4.Human tetanus immunoglobulin (HTIG)

a. 3000 to 6000 units intramuscular single dose
b. 200 IU to 1,000 IU intrathecal single dose

5. Treatment of muscles spasm, Sedation and muscles relaxant

a. Dark and quit room
b. Diazepam 1 to 10 mg/kg/day3. Propofol infusion

6. Neuromuscular blockers

a. Pancuronium traditionally used
b. Intrathecal baclofen bolus 40 to 200 mcg followed by a continuous infusion of 20 mcg/hour

7. Management of dysautonomia

a. MgSO4 loading dose of 40 mg/kg for 30 minutes was used followed by a 2 g/hour infusion.

8. Prophylaxis

a. Immunization

- **General Measurements: -**Tetanus is rapidly progressive disease, when there is clinically suspicious it is recommended that patient should be admitted in ICU regardless of the severity.[12,13] A retrospective multicentre study done in France in 2017 suggestive that in high income country where ICU facility is available the mortality of tetanus is significantly less (1-year mortality 16%) compare to low income countries[14]. A Ten years retrospective study done in India shows mortality is around 42.2% in total admitted patient in general ward and ICU.[15] A study done in Bangladesh shows the mortality only 28.6% patients managed without ventilator only 2 patient out of 42 required ventilator support.[16] A Brazilian study shows that the final mortality rate 44.5%, patients those have high APACHE 2 has high mortality.[17] Another study done in Nigeria shows higher mortality rate in ICU admission probably due more sever patients admitted in ICU[18].
- **Wound management : -** All patients with tetanus will go for wound debridement to prevent further bacterial growth. There is no role of local installation of human tetanus immunoglobulins.[19]
- **Role of antibiotics : -** There is minimal role of antibiotics in treatment of tetanus. A prospective open label non randomization clinical trial done in Indonesia shows that mortality is less in patients treated with Metronidazole 500 mg thrice daily compare to penicillin group.[20] Another RCT between benzathine penicillin, metronidazole, and benzyle penicillin done in Mumbai in India shows single dose of benzathine penicillin (1.2 Million Units I.M) is equally effective as other two drugs.[21]
- **Neutralization of free toxin : -** The role of anti-toxin is to neutralise the circulating toxins and it should be given as early as possible. The human anti tetanus immunoglobulin are has better outcome then the equine anti-tetanus serum because it has lot of side effects. The various RCT shows that the intrathecal rout for administration of anti-tetanus toxin is better than intramuscular route.[22]
- **Role of intrathecal HTIG: -**A meta- analysis showed there is no difference in outcome by intrathecal therapy in neonates but has benefit in adults with tetanus.[23] Few small non randomization studies shows benefits of intrathecal immunoglobulin in view of length of hospital stay and less complications[24-26]. The dose of therapy range from 300 IU to 3000 IU. A pilot study done to assess the safety and efficacy of intrathecal immunoglobulin in tetanus showed it is feasible with less adverse effects.[27] Recently a randomization clinical trial is registered to see the efficacy of intrathecal immunoglobulins.[28]
- **Treatment of muscles spasm :-** The physical stimulus are the aggravating factors for painful muscles spasm, patient must be kept in dark sound proof room with minimal physical stimuli to prevent muscles spasm. This muscles spasm can causes respiratory arrest and exhaustion in the patients.
- **Sedation and control of muscles spasm : -** Diazepam is sedative, anticonvulsant, muscles relaxant and anxiolytic so it is the drug of choice in tetanus. A Cochrane databases study review published in 2004 that compared diazepam to other anticonvulsant such as phenobarbitone and chlorpromazine, they found better outcome in patient treated with diazepam.[29] Another comparative study done between diazepam, and combination with chlorpromazine or propranolol shown that there no additional benefit compare to diazepam alone.[30] Another study done in paediatric patients with a continuous infusion ofdiazepam (20-40 mg/kg per day) and intra-gastric phenobarbitone (10-15 mg/kg per day in 4 divided doses) shows reduction in mortality significantly.[31] A case report of severe tetanus showed effect of midazolam with propofol to reduce severe muscles spasm.[32] The continuous infusion of midazolam also effective for management of muscles spasm.[33] Diazepam is a potent GABA-ergic agonist this drug has a fast onset of action when given as a bolus, which is useful for spasm control. The dose required to provide relaxation may be high, ranging from 1 to 10 mg/kg/day according to the desired degree of relaxation. This drug can be used as a bolus (10-30 mg/hour) or a continued infusion with extra 10-mg boluses as required. Additionally, continuous infusion provides a effect more stable and allows more appropriate dose titration. Infusion of propofol may also control spasms and rigidity. Its prolonged use has been associated with lactic acidosis, hypertriglyceridemia, and pancreatic dysfunction.
- **Neuromuscular blockers :-** When sedation alone is not effective then N-M blocking agent may be use. Pancuronium is a long-acting agent, has been traditionally used. However, it may worsen autonomic instability because it is an inhibitor of catecholamine reuptake. Vecuronium can also be administered and is less likely to cause autonomic problems, but since it is short acting, it must be given as continuous infusion to provide adequate effects. Monitoring of patients on these drugs is extremely important to avoid

or recognize complications. Baclofen which stimulates postsynaptic GABA beta receptors has been used in a few small studies. The preferred route is intrathecal, and it may be given either in a bolus of 1000 mcg or by continuous intrathecal infusion. Intrathecal baclofen given as an initial bolus in a dose ranging from 40 to 200 mcg followed by a continuous infusion of 20 mcg/hour was found to control spasms and rigidity.[34, 35]

- **Management of dysautonomia : -**The pathogenesis of autonomic dysfunction is unclear only few purpose theory are given. Patient develops symptoms of sympathetic overdrive such as tachycardia and systolic blood pressure changes from minute to minutes, and may develops sudden cardiac arrest. One purposed hypothesis suggested that these symptoms are due increase catecholamine levels in the serum which may increase several times from their base line values.[36-38] However, in future studies no correlation was found between the development of symptoms and serum catecholamine levels. Second is tetanospasmin as a zinc-dependent peptidase enzyme its acts similar to ACE, excessangiotensin II in serum leads to hypertension[39,40].
- Buchanan *et al* reported in 1979 that morphine had a significant effect on reducing spontaneous sympathetic over activity in tetanus, though it had little effect on spasms.[41]
- Intra venous Morphine reduces the muscles spasm and symptoms of sympathetic over activitythe loading dose is 5 mg followed by continuous infusion of 0.05 to 0.1 mcg/kg/min or with 5-mg doses every 3 hours.
- Gregorakos et al suggested that intra venous Clonidine has reduces dysautonomia in patient compare to placebo groups.[42]
- **Beta blocker** : - suchintra venous labetalol also effective in controlling of blood pressure and tackles sympathetic overdrive.[43]
- **Role of magnesium :** - Magnesium is a physiological antagonist of calcium at cellular level has properties of vasodilation, presynaptic N-M blocking and inhibition of catecholamine release. Therefore it is very effective in controlling the symptoms of dysautonomia.[44,45] A randomized, placebo-controlled clinical trial conducted by Thwaites and colleagues in Vietnam.[46,47] In this trial, 97 and 98 patients with tetanus of comparable severity (independently verified with three different scoring systems) were allocated to receive either magnesium sulphate or placebo while receiving standard therapy (high dose diazepam for sedation replaced with midazolam as required, neuromuscular junction blockade and respiratory support when necessary). The primary outcome assessed was the need for ventilatory support within the first 7 days of magnesium therapy, which showed no difference between groups No significant difference was observed in the primary endpoint. However, a significant difference was found in the secondary endpoints, ie, reduced needs of sedation, neuromuscular blockers which were considered to be the treatment of choice for dysautonomia. Another case series (n=30) done by Mathew and et all in Chandigarh in India found that magnesium sulphate is beneficial in controlling of muscles spams and dysautonomia[48]
- **Limitations : -** There are limited options for the treatment of tetanus. It is ethically incorrect to do randomization studies on tetanus for the treatment options when there are already some evidence based treatment exist. Diazepam is easily available and safe to use so role of other benzodiazepine are not much studied. Human anti tetanus immunoglobulins are very costly and it's the definitive role for management of tetanus is not stabilized.

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