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## The Administration of Botulinum Toxin in a Case of Generalized Tetanus

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### Summary

Tetanus is a serious infectious disease that is associated with high morbidity and mortality. The treatment of tetanus has many implications for anesthesiologists and critical care physicians, but most physicians in developed countries lack experience in dealing with such cases. The aim of this report was to present a case whose foot was injured in the field and who developed serious generalized tetanus due to delay in referral with fatal outcome. In this case, botulinum toxin was administered to most intensively involved muscle groups for treatment.

**Keywords:** Muscular spasm; Tetanus; Botulinum toxin; Intensive care

### Background

Tetanus is a disease led to rigidity and spasm in skeletal muscles whose agent is *Clostridium tetani* which is a, Gram (+) anaerobe bacteria [1,2]. Transmission occurs via wounds most commonly [3]. There is no specific laboratory test for diagnosis [4]. Demonstration of toxin in body fluids may be tried. The demonstration of bacillus at wound site may not be much significant [5]. Mean duration of incubation period is 3-21 days [6]. The shorter incubation period is the worst prognosis [7]. At the prodromal period, fatigue, restlessness, headache, pain at wound site, and lethargy may occur. Involvement progresses from upper parts to lower parts with cervical, facial and masseter muscles being influenced first. Subsequently, difficulty in swallowing, abdominal rigidity and opisthotonus may develop. With the effect on respiratory muscles, laryngospasm and difficulty in breathing develops [8]. As a consequence of strong contractions, rhabdomyolysis may develop. There is no loss of consciousness and fever is not expected except for complications [7,8]. Disease course is 10-14 days, becoming more severe meanwhile. Deaths are usually due to autonomic dysfunction. Although its toxoid vaccine is present, it still occurs in developing countries, and in unvaccinated or inadequately vaccinated subjects [4]. Two toxins produced by the bacterium are tetanolysin and tetanospasmin. Tetanospasmin is one of the strongest toxins known and leads to the clinical effects of the disease [3]. Toxin leads to excitatory effect by preventing the release of glicin and GABA, which hinder the transmission of motor nerve impulses and targets central nervous system [8]. Autonomic nervous system is also influenced and a hypersympathetic clinical picture develops. It is thought that this is due to the inadequacy of the inhibition of the release of catecholamines from adrenal gland [3,8]. As there is no laboratory test confirming diagnosis, diagnosis is based upon clinical findings and in the presence of clinical suspicion, tetanus treatment is commenced. Botulinum toxin, unlike the toxin of tetanus, is one that causes paralysis and is produced by *Clostridium botulinum*. It irreversibly inhibits the release of acetylcholine in neuromuscular junction. Therefore, the injection of botulinum toxin to the muscles in which tetanosis led to rigidity may be beneficial in the prevention of clinical complications.

### Case Presentation

A 74 year old male patient applied to emergency service with difficulty speaking, swelling in tongue and restriction of mouth and neck movements ten days after being injured with a foreign body in the field. In physical examination, sub febrile fever, tachypnea, risus sardonicus, trismus, nuchal rigidity and cervical rigidity were detected. Sample was obtained from the wound site in left foot and in the sample the growth of a gram (+) bacillus in the form of a drum stick was seen. White cell, C-reactive protein and creatine kinase values were high and patient was admitted to infectious diseases service with the diagnosis of tetanus. Then, tetanus immunoglobulin was administered and for the infection in the wound, 4\*4 MU i.v penisilin (Benzatin penisilin G, I.E. Ullagay, Turkey) and 4\*500 mg intravenous (iv) Flagyl 500 mg (Metronidazol, Eczacibasi, Turkey) treatment was initiated. Upon the development of respiratory failure one day later, patient was intubated and admitted to our intensive care unit. For sedation, midazolam 20 mg/h (Demizolam, Dem, Turkey) fentanyl (Fentanyl, Abbott, USA) and propofol (Lipuro, Braun, Germany) were commenced and as the patients also had generalized muscular rigidity and spasm, which impaired compliance with mechanic ventilator, magnesium sulphate 80 mg/h infusion was initiated. I.m. tetanus antitoxin and 3000 IU i.m. tetanus immunoglobulin was administered. For the prophylaxis of deep vein thrombosis Enoksaparine sodium (Clexane, Sanofi, Turkey) was instituted. On the fourth day of admission to intensive care unit, pneumonia was detected clinically and with lung graphy and ceftazidime (Fortum, Glaxo SmithKline, Turkey) was initiated. While the patients was in intensive care unit, botulinum toxin was administered to the muscles which were established to be most intensively involved i.e temporal, masseter, paravertebral, abdominal, sternocleidomastoideus and leg muscles. Spasms were decreased in regions where toxin was administered. On the 30<sup>th</sup> day of admission, patient was lost on account of lung infection and development of septic shock.

### Discussion

*Clostridium tetani* bacillus can thrive in all kinds of land and its germinative spores produce tetanospasmin or tetanus toxin, which leads to muscular rigidity with simultaneous contraction of agonist and

antagonist muscles by stopping the inhibition of excitator impulses [9]. Tetanospasmin is one of the strongest toxins in the nature and an amount as small as 240 g is enough to kill all people in the world [10]. This toxin has single type of antigen. Toxin enters from peripheral nerves and targets all central nervous system, including peripheric motor end plates, spinal cord, sympathomimetic nervous system and exerts its effect by preventing the release of GABA and glycine [9]. Specifically, toxin degrades synaptobrevin, which is a protein required for the contact between inhibitor transmitter vesicles and release regions in presynaptic membrane [2]. It influences autonomous nervous system by means of the inhibition of stimuli preventing catecholamine release and produces sympathetic hyperactivity [2]. Toxin also decreases the release of norepinephrine, acetylcholine and encephalin and is also epileptogenic. It may also lead to flaccid type paralysis by preventing the release of acetylcholine. Facial paralysis occurring in cephalic tetanus is explained by this effect [7]. For differentiating tetanus from other problems, it is important to keep in mind that tetanus is not an infection and will not produce any symptoms before reaching nerves [11]. Antitoxin exerts effect by protecting only the neuron to which toxin has not been bound yet. As the effect of the toxin is irreversible, recovery takes place solely by the formation of new nerve endings and new synapses [9]. Although the use of drugs and interventions has increased within the last half century, the target of tetanus treatment remains unchanged [9]. Anesthetists participate in tetanus treatment process due to their experience with muscular relaxants, tracheal intubation and mechanical ventilation [9]. The management of tetanus in intensive care units is still guided by the information presented in case reports owing to the lack of treatments based upon evidence based medicine [9] and it focuses on three areas, namely: 1) toxin control, 2) treatment of spasms, 3) hemodynamic management.

### Decreasing active toxin

It involves debridement of wound site and its aeration in order to control toxin, and to improve anaerobic environment contributing to the growth of the bacillus and to decrease bacterial burden [9]. Metronidazole is the first choice and it can be used in combination with penicillin whose use is controversial [10]. In our patient, metronidazole and penicillin treatment was instituted following the diagnosis of tetanus. The treatment of tetanus toxins in circulation is carried out by human tetanus immunoglobulin (HTIG) or equine anti serum. This treatment has no effect on toxin in neurons [9]. Some authors suggested that repetition of HTIG treatment is not necessary while some others stated that it should be administered again since new toxin release may take place [13]. Our patient was administered 5000 unit immune globulin both in the clinic and in intensive care unit. In addition, tetanus toxoid may also be administered during disease process. However, it should be administered to a different location in order to avoid interaction.

### Management of muscular spasms and mechanical ventilation

The preliminary treatment of the management of muscular spasms involves sedation in a dark and silent room. In the literature, it has been reported that benzodiazepin, barbiturates, anticonvulsants, narcotics, baclofen, dantrolene and propofol were used for sedation [14,15]. After the admission of the patient to our intensive care unit, in the dark and silent isolation room, sedation, analgesia, and in order to decrease muscular spasms benzodiazepin, opioid, barbiturate, propofol and neuromuscular relaxants were employed. Botulinum toxin released by *Clostridium botulinum* bacillus is bound to, VAMP, SNAP 25 and syntaxin proteins, preventing the release of acetylcholine [16]. Based upon the fact that botulinum toxin A does not influence central and adrenergic nervous system, it is used at therapeutic doses in the treatment of strabismus, dystonia, torticollis and similar skeletal muscle rigidities [17]. Although it does not completely abolish the rigidity caused by tetanus, it may help to

reduce it. Prevention of mouth, teeth and tongue injuries which may occur due to the contraction of masseter muscle, prevention of the increase in gastric pressure in association with abdominal contractions, decreasing rhabdomyolysis and administration of botox to these muscles at doses which will not exceed safety margins for the prevention of possible bone fractures may considerably relieve the severity of the course of the disease [18]. In 6 cases reports published on this issue, its beneficial effects were shown by injection to different regions. Maximum effect was seen within three weeks [19]. In our case, botulinum was injected to temporal, masseter, paravertebral, abdominal, sternocleidomastoides and leg muscles established to be involved most markedly by electromyography. Spasms were improved in regions which are administered toxin.

### Treatment of circulatory impairment

Autonomic instability is the most challenging part of tetanus treatment, and is also the most frequent cause of death in the progressive period of the disease [20]. Unfortunately, the optimal treatment of this condition is far from clear [20]. Although there is no event precipitating autonomic instability, it is characterized by hypertension and tachycardia. This autonomic storm is frequently followed by severe and recalcitrant hypotension, bradycardia and even asystole [9]. In our patient, in the first 20 days after admission to intensive care unit, disease coursed with hypertension and tachycardia and in the remaining ten days, hypotension requiring vasopressor support, bradycardia and ultimately asystole developed. Ventilator induced pneumonia associated with prolonged ventilation also occurred with the development of septic shock and hence vasopressor support was required. It could not be determined whether vasopressor was required due to septic shock or to hypotension and bradycardia following autonomic storm period.

### Conclusion

Botulinum toxin treatment alone does not reduce the need for mechanical ventilation but its use reduces the requirement for other muscle relaxants. Further work is needed to define its role in the less severely ill and in settings with limited facilities.

**Conflict Of Interest:** The authors declare that they have no conflict of interest.

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