SUCCESSFUL THERAPEUTIC PLASMA EXCHANGE THERAPY IN SEVERE TETANUS

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ABSTRACT

Introduction: Tetanus is an acute toxemia condition caused by neurotoxin produced by *Clostridium tetani* manifested as periodic muscular spasm. Manifestation could range from localized tetanus into generalized tetanus and cephalic tetanus. Severe forms of tetanus complicating management and mostly resulted in death because of asphyxia and hyperactivity of sympathetic system. Therapeutic plasma exchange (TPE), in which plasma separated from whole blood and replaced with normal saline, albumin, or fresh frozen plasma, could improve survival in toxemia condition although studies about the use of TPE in the treatment of tetanus still lacking.

Case Illustration: A man in his 60s presented to the ER with complaint of generalized stiffness on belly, legs, arms and jaw in which the patient hardly open his mouth. Patient was diagnosed with tetanus due to history of unhealed wound on patient's left pinky toe two weeks prior. Patient condition worsened through period of admission that requiring intensive care and mechanical ventillation on fifth day after admission. Two TPE therapy on fifth and eighth day of admission was given with improvement of patient's clinical condition after two days of second TPE therapy.

Discussion: Indication of TPE has expanded, and severe tetanus could be indicated as one of TPE indications inline with principle of management of tetanus to prevent the spread and toxicity of neurotoxins. The general principle of TPE is to remove a circulating molecule from the blood in the hope of improving the clinical condition of the patient.

Conclusion: Tetanus is pretty common case in developing countries related to high mortality rate. Management of severe tetanus could be tricky in several case. Therapeutic plasma eschange (TPE) may be a better therapeutic alternatives with some successful use reported in treatment of neurological cases.

Keywords: Severe tetanus; Therapeutic plasma exchange

INTRODUCTION

Tetanus is an acute toxemia condition caused by neurotoxin produced by *Clostridium tetani*.[1] Manifested as periodic muscular spasm, tetanus is still a problem especially on developing countries with global incidence around 1.000.000 cases yearly and estimated incidence of 0,2/100.000 populations in Indonesia.[2,3] Tetanus is a preventable disease by means of immunization espceially on children, pregnant mother as well as hygienic and adequate wound care. But because this is and intoxication and not an infection, tetanus is not transmissible, and vaccination does not include "herd" effect.[4] Tetanus, including neonatal tetanus, still a growing problem in developing countries due to inadequate knowledge about tetanus and lacking coveraege of tetanus toxoid (TT) vaccine.[5]

Manifestation could range from localized tetanus into generalized tetanus and cephalic tetanus. Although protocols and pharmacological intervention have limit the mortality and morbidity of tetanus, severe forms of tetanus complicating management and mostly resulted in death because of asphyxia and hyperactivity of sympathethic system.[4] Management of tetanus involving preventing the further release of toxins, neutralizing toxins and reduce the toxicity of the toxins.[4,6] Therapeutic plasma exchange (TPE) is one of model of therapy in which plasma separated from whole blood and replaced with normal saline, albumin, or fresh frozen plasma. Plasma exchange potentially improve survival in toxemia condition by removal of harmful substances and replacement of deficient blood components, but studies about the use of TPE in the treatment of tetanus still lacking.[7,8] In this case report, we reported a successful case of therapeutic plasma exchange (TPE) in case of acute toxemia condition of severe tetanus.

CASE PRESENTATION

A man in his 60s presented to our Emergency Department unit with chief complaint of generalized stiffness on belly, legs, arms and jaw in which the patient hardly open his mouth. Patient was a farmer with no history of diabetes, hypertension or other chronic ilnesses. There was no history of seizure nor prior sign of fever, acute respiratory tract infection, allergy or other significant medical history. Two weeks prior, patient's left pinky toe got stuck on motorcycle kickstand resulting in open wound that was cleaned and stitched on local clinic. There was no injection or vaccination given at that time. One week after, the wound still not healed with oozing, pus and pain especially when movement. Examination of the left fifth toe revealed 2x1 cm grade II ulcer with pus, surrounding erythema and edema. Patient's vital sign was normal. On physcial examination, abdominal wall rigidity was found on all part of abdomen and stiffness of patient's jaw, patient can only open his mouth by two fingerwidth wide. Neurological examination was normal and no other abnormalities was found. Routine blood examination, electrocardiography, chest x-ray and blood gas analysis showed no sign of abnormalities.

Figure 1. Wound on patient's left pinky toe

On suspicion of tetanus, scoring was done using Ablett score (Grade II) and tetanus severity score (7, low risk). Patient then admitted to tetanus isolation ward with minimal light, minimal touch and minimal noise). Intralesional (500 IU) and intramuscular gluteal injection of human tetanus immunogluboulin (Tetagram®) (2500 IU) were given as well as diazepam via syringe pump (1.5cc/hour), intravenous metronidazole, intravenous metamizole and throughout debridement of the wound. Patient condition deteriorated over the next four days with complaint of worsening stiffness and difficulties in mouth opening. Wound culture was done with ceftriaxone as suggested antibiotic that was started on fifth day of admission. Blood gas analaysis was done resulted in partially compensated metabolic alkalosis. Patient then moved into intensive care unit, requiring mechanical ventilation and planned to undergo therapeutic plasma exchange therapy two times on fifth and eight days of admission.

Two days after the second therapeutic plasma exchange therapy, patient's condition got better and he started to be able to open his mouth one fingerwidth wide. Patient's condition continually improved and he was discharged after eighteenth day of admission. One week after discharged, patient able to start walking with help and patient can eat and drink normally.

DISCUSSION

Tetanus

Tetanus is an acute toxemia condition caused by bacteria *Clostridium tetaniI,* a spore producing bactera found on soil and decompensation of organic matter. *Clostridium tetani* spores can withstand months and even years before entering host through infected wound and release neurotoxins named tetanus neurotocin (TeNT). There were two kind of TeNT produced, tetanolysin and tetanospasmin. Tetanolysin, a hemolysin, had questionable clinical importance since this toxins inhibited by oxygen and serum cholesterol. [9,10] In the other hand, tetanospasmin mostly contributed to clinical manifestation of tetanus that spread from the infected wound by hematogen and lympathics spread before reaching motor neurons. Tetanospasmin degraded, internalized in endosome vesicles and transported by means of retrograde axonal transport to pre-synapses nerve mediated by SNARE protein. This toxins then inhibits the release of glycine and gamma-amino butyric acid (GABA), preventing inhibition of motor neurons that manifested as neuroparalytic syndromes such as spastic paralysis and stiffness.[4,11]

Incubation period of tetanus ranged from 3 to 36 days with mean period of 12 days. Manifestation of tetanus classified into local tetanus, generalized tetanus, tetanus neonatorum and cephalic tetanus. [1,4] Localized tetanus commonly manifested as rigidity and spasm on contaminated limb extremites that will evolve into generelazied tetanus in 2/3 of cases. Generalized is the most common form, begins with stiffness of the jaws (trismus, lock-jaw), contracture of facial and neck muscles (opisthotonos), rigidity of abdominal and erector spinal muscles, then evolved into pharyngeal and laryngeal spasms with dysphagia. Spasmodic contraction of respiratory muscless causes asphyxia, the most common cause of death in tetanus. Late autonomical manifestation may develop because over acitivty of sympathetic neuron as results of inibiton of neurotransmitter release from inhbitory neurons of spinal cord.[1,6]

Severity of tetanus determined by location of the wound, size of the wound, extent of necrotic area and number of spores contaminating the wound. Scoring system such as Ablett score and tetanus severity score could predict the severity and prognosis of suspected tetanus condition. [1] Main management of tetanus involving prevent the further release of toxins, neutralize toxins and reduce the toxicity of the toxins. Throughout debridement of the wound and administration of antibiotics could prevent further production and release of toxins. Neutralization of toxins could be achieved by tetanus antitoxin (TAT) and equine/human tetanus immunoglobulin (HTIG). Toxicity affecting respiratory system may bring the need of mechanical ventilation and continuous renal replacement therapy (CRRT).[4,10]

Therapeutic Plasma Exchange

American Society for Apheresis (ASFA) 2019 guidelines defined therapeutic plasma exchange (TPE) as "A therapeutic procedure in which the blood of the patient is passed through a medical device which separates plasma from the other components of blood…". TPE involves removal of plasma and replacement with a solution either a colloid solution, a combination of a crystalloid/colloid solution, or fresh frozen plasma (FFE).[8,12] Initially as a treatment for hematological diseases, TPE has been indicated to a variety of pathologies including kidney, autoimmune, neurological diseases, and gained popularity in the recent Coronavirus disease-19 (COVID-19) pandemic. [7,13] Neurological diseases previously treated by TPE including myasthenia gravis, Guillain-Barré syndrome, neuromyelitis optica spectrum disorder, chronic inflammatory demyelinating polyneuropathy and autoimmune encephalitis. Case reports and small observational studies also report the use of TPE in treatment of septicemia or meningococcemia.[12,14] AFSA classified the indication of TPE therapy in several category, (1) Category I represents diseases for which TPE is a first-line treatment (e.g., Guillain-Barré syndrome [GBS]); (2) Category II includes pathologies for which TPE is accepted as second-line (e.g., acute disseminated encephalomyelitis after steroid failure) therapy; (3) Category III are indications that are not established and are considered on a case-by-case basis (e.g., IgA nephropathy); (4) Category IV are the indications where the literature has proven no benefit or has shown deleterious effects. [7]

The evolution of the understanding of the molecular mechanisms of several pathologies has allowed the expansion of therapeutic plasma exchange (TPE) indications.[7] Severe tetanus could be indicated as one of TPE indications inline with principle of management of tetanus to prevent the spread and toxicity of neurotoxins. The general principle of TPE is to remove a circulating molecule from the blood in the hope of improving the clinical condition of the patient. Although several cases of neurological cases related to inflammatory and infection mechanism already successfully treated with TPE, TPE also has the potential to cause harm by diluting or attenuating the host's adaptive response to infection.[14] Complication of TPE including electrolyte disturbances, depletion coagulopathy, access-associated complications and reaction to FFP (anaphylaxis, rigor, and hypotension).[7,8]

In this case report, we reported man in his mid-40s with severe tetanus that worsened through period of admission that requiring intensive care and mechanical ventillation on fifth day after admission. Two TPE therapy on fifth and eighth day of admission then given with improvement of patient's clinical condition after two days of the second TPE therapy until discharged of patient after good clinical evaluation at eighteenth day of admission. We concluded successfull therapeutic plasma exchange (TPE) therapy in a case of severe tetanus and further studies about this method are needed to help the management of tetanus case in the future.

CONCLUSION

Tetanus is pretty common case in developing countries related to high mortality rate. Management of severe tetanus could be tricky in several case. Therapeutic plasma eschange (TPE) may be a better therapeutic alternatives with some successful use reported in treatment of neurological cases.

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Informed Consent Statement

Informed consent was obtained from the patient involved in the study to publish this paper.

Conflicts of Interest

The authors declare no conflict of interest.

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