

ADJUNCTIVE PYRIDOXINE FOR SEVERE TETANUS : A CASE REPORT WITH LITERATURE REVIEW

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ABSTRACT

Introduction : Tetanus is an acute, potentially fatal infectious disease that is characterized by seizure (general motor spasm), lockjaw, opisthotonus, defans muscular, rhisus sardonicus. A high mortality case remains tetanus need special attention. Pyridoxine 100mg orally introduced as adjunctive therapy for spasm, aimed to reduce mortality rate.

Case report : A 38-years-old man with lockjaw (< 1cm) accompanied by severe seizures (general motor spasm) that arise many-times caused the patient body arched back (opisthotonus), rhisus sardonics and defans muscular categorized severe tetanus (5 points of Dakar score). Based neuroinfection study grup of Indonesian Neurologist, tetanus patient treated with Human Tetanus Immune Globulin (HTIG) to neutralized toxins, antibiotics penicillin and metronidazole to eradicated causative bacterial, and diazepam (benzodiazepine) to handle seizures (general motor spasm). Pyridoxine (vitamin B6) 100mg used as adjuntive therapy for treated seizure aimed to reduce mortality risk. Patient hospitalized for 18 days and discharged with good condition (free spasm).

Conclusion : The role of pyridoxine in the management tetanus may sinergism with diazepam for reduced general motor spasm (seizures), but it should be re-examined in a blind randomised trial.

Key word : tetanus, seizures (general motor spasm), lockjaw, pyridoxine, diazepam.

Introduction

Tetanus was described by Hippocrates approximately 30 centuries ago.¹ It is an acute, potentially fatal disease that is characterized by generalized increased rigidity and

convulsive spasms of skeletal muscles.^{2,3,4,5,6} Tetanus remains an important cause of death and associated with a high case fatality, particularly in the developing world. The global incidence of etanus is about 18 cases per

100.000 population per year with case fatality ranging between 20% to 50%.¹

About one million cases of tetanus occur annually worldwide, resulting in death of about half a million people each year. Mortality from tetanus approaches close to fifty percent in developing countries like Pakistan. Amerika recorded the highest incidence of tetanus occur under age 20 and more than 60 years, contrary with our patient with age 38 years. It became first reason we raised this case.¹⁸ Secondly, an adult tetanus case report uncommon reported in Indonesia.

Tetanic spasm (seizure) induced sudden burst of tonic contractions of one or more muscle groups may cause complication such as fractures of the long bones, dislocation of the temporomandibular and shoulder joints. Reflex spasm also become majority present in tetanus patient and can be set off by external stimuli (sound, light). Laryngeal spasm can occur any time in this disease that can lead to asphyxia heading to high mortality. According tetanus guideline benzodiazepines used to handle spasm, but unfortunately sometimes muscle spasm refractory to

benzodiazepines. Using pyridoxine orally beside diazepam to handle spasm became last reason we reported this case.

Case Report

A man-38-years-old admitted to General Hospital Centre Wahidin Sudirohusodo with lockjaw (less than one cm) occurred slowly two days ago before admitted to hospital. Initially patient was able to open his mouth and ate as usual. Approximately two days ago patient began feel stiffness in the jaw, more severe time after time then difficult to open. Patient also felt tight in his abdomen and complaint rigidity entire his body accompanied by seizures that arise many-times (general spasm) caused the body arched back. The patient felt pain throughout the main body back, abdomen and nape. Hematemesis occurred six hours before admitted to hospital.

There was history of high fever with sweating about four days ago cured with antipiretic drugs. History punctured timber in the left big toe eight days ago while cleaning the yard / garden, left hand screwdriver impaled nine days ago, and left thumb chipped when sawing ten days

ago before admitted to hospital (picture 1). Patient often punctured by timber on both feet while working in the yard. Patient never get tetanus toxoid injection after that several accident that he experienced. A history of ear disease denied. Vaccination history of tetanus toxoid unknown, nor diphtheria toxoids and acellular pertussis (DTaP) vaccine when he was a child.



The result of vital signs show the blood pressure was 130/80 mmHg, pulse rate was 122 per minute, regular. Respiratory rate was 28 per minute thoracoabdominal type and temperature was 39,5⁰C. There was no anemis, jaundice, nor cyanosis. From neurological examination, Glasgow Coma Scale (GCS) E4M6V5, there was lockjaw (trismus) less than 1 cm, rhisus sardonicus, defans muscular, and opisthotonus.

Discussion

Tetanus was caused by neurotoxin produced at the site injury by *Clostridium tetani*, an aerobic, gram positive bacillus.^{10,11,13,14} Spores of *C. Tetani* are present in soil worldwide,^{15,16,17,19,20} and portals of entry resulting in human disease include traumatic and surgical wounds, injection sites (especially among parenteral drug abusers), skin ulcers, burns, and infected umbilical cords.² There are no laboratory test that can support the exac diagnosis of tetanus. Wound culture only 30% sensitive, also can occur in the presence of “protective” levels of antitixin (more than 0,1 UI by ELISA standard), therefore serology cannot exclude the diagnosis tetanus.^{6,7,9,13}

Chalya et al (2011) studied 102 patients in Tanzania for 10 years of all group and gender who presented with clinicals diagnosis of tetanus. The diagnosed was wholly clinical and based on the presence of one or more of the following trismus (Agerberg measurement), rigidity of the neck, and or abdomen spasm (defans muscular), opisthotonus, and general spasm.⁸ Kakheli et all (2013) studied 22 patients, 95,5%

had generalized tetanus with symptoms general spasm (100%), trismus (100%), body arched (opisthotonus) 23,5%.⁹ Based on history of disease, typically physical examination (trismus, rhisus sardonicus, opisthotonus) tetanus diagnose we enforced

Study by Patel et al in 8697 tetanus cases, 29.4% cases were because of otitis and 18.1% cases had unidentified injury. Eman et al found 36.4% cases to be injection drug users. In this case, tetanus possibly occurred from puncture wound by chamber about 4 days ago before fever (incubation period), then 2 days ahead patient got lockjaw less than 1cm but we suggested mild lockjaw occurred earlier 1 day ahead after fever (onset period). . The usual incubation period in neonatal tetanus (NT) is five to ten days, thus most cases of NT have their onset in the later part of first week or early in the second week of life.^{1,18} In a study at BP Koirala Institute of Health Sciences (BPKIHS) on paediatric and NT, mean incubation period was 7.7 days with a range of two to 17 days. Mean onset time was 16.9 hours with a range of two to 72 hours.¹

The spores *C. Tetani* germinate and produce Tetanus Toxin (TeNT) that is tetanolysin—a hemolysin substance with no recognized pathologic activity and tetanospasmin—toxin that responsible for the clinical manifestations of tetanus; by weight, it is one of the most potent toxins known, with an estimated minimum lethal dose of 2.5 ng/kg body weight.^{1,18}

L chain of TenT is a zinc-dependent metalloproteinase that targets synaptobrevin (on VAMP), when the toxin reaches the spinal cord, it enters central inhibitory neurons. The TenT cleaves the protein synaptobrevin (SNARE-component), as a result, gamma-aminobutyric acid (GABA)-containing and glycine-containing vesicles are not released. Because GABA and glycine as important spinal inhibitory neurotransmitter in synaptic cleft from inhibitory interneuron not released caused α -motorneurons are under no inhibitory control-undergo sustained excitatory discharge causing the characteristic motor spasm of tetanus.^{1,4,8,12.}

Loss of central inhibition because TeNT caused an autonomic hyperactivity, as well as uncontrolled muscle

contractions (spasm) in response to normal stimuli such as noises or lights. Once the toxin becomes fixed to neurons, it cannot be neutralized with antitoxin. Recovery of nerve function from tetanus toxins requires sprouting of new nerve terminals and formation of new synapses. General motor spasm occurred for 10 days, risus sardonicus for 6 days, defans muscular for 9 days, and trismus ≥ 3 cm for 9 days in this patient. We treated spasm with benzodiazepines (diazepam), because benzodiazepines augment GABA agonism, by inhibiting an endogenous inhibitor at the GABA_A receptor. We used diazepam because it is cheap and may be given by various route, in this case we used intravenous^{12,18,19,20}

Campbell et al (2009) attempted to isolate and evaluate *C. tetani* from wounds of 84 patients with tetanus, they effectively isolated *C. Tetani* from 45 patients. The study performed at the hospital for Tropical Diseases, Ho Chi Minh City. The results show that all organisms tested had similar sensitivity patterns. Because penicillin is the recommended antimicrobial agent for treatment, the sensitivity to this agent was

of most interest. All strains were sensitive to penicillin; the highest MIC was 0,25 μ g with clearance zone of 29 mm (using a 10- μ g disc). Similarly, all strains were sensitive to metronidazole. The highest MIC to metronidazole was 1.0 μ g, with a zone of 26mm (5- μ g disc). All strain were sensitive with the exception of cotrimoxazole.⁷

Patient treated with antibiotics ampicillin 2 grams every 8 hours intravenous because the structure similar with penicillin, distant to the β -lactam ring, is similar to aminobutyric acid (GABA), the principal inhibitory neurotransmitter in the Central Nervous System (CNS). We also used metronidazole 500mg every 8 hours, considered as the drug of choice in the treatment of tetanus. Patient we treated with Human Tetanus Immune Globulin (HTIG) 3.000 unit IM (adult dose 3.000 – 6.000 IU) to neutralized toxin suitable with guideline.

Dakar score used to assess patient prognosis, with component incubation period (1 point), period of onset (1 point), entry site (0 point), spasm (1 point), fever (1 point), and tachycardia (1 point), totally

5 points, indicated very severe tetanus (score 5 or 6) with mortality rate more than 50%.^{14,15}

General motor spasm (seizures) with severe lockjaw (less than 1 cm) symptoms categorized severe tetanus based Ablett scoring with high mortality rate. It was indicated how important for treated spasms. Pyridoxine (vitamin B6) 100mg as adjunctive therapy seem reduced patient's general motor spasm (seizures). Pyridoxine is a coenzyme with glutamate decarboxylase in the production of GABA from glutamic acid, and increases GABA concentrations in animal models may reduced general motor spasm (seizures). In an unblinded open trial 20 neonates with tetanus were treated with pyridoxine (100 mg/day) and compared with retrospective records. The mortality in the pyridoxine treated group was reduced. The role of pyridoxine in the management of neonatal tetanus should be re-examined in a blind randomised trial.²⁰

Luckily eventhought our patient had poor prognostic, but after 18 days patient discharge with good condition (free spasm). In addition therapy based guideline with Human Tetanus Immune

Globulin (HTIG), antibiotics, and diazepam – pyridoxine may play a role for the improvement condition. It may be need to considered using pyridoxine together with benzodiazepine for treated tetanus spasm.

Tetanus occured annually worldwide, resulting in death of about half a million people each year. Because of the mortality, the best solution for tetanus is prevention. Prevention is through vaccination which is highly safe and efficacious. Active immunisation should be instituted in all partially immunised, unimmunised persons and those recovering from tetanus.^{13,15,16,18,19,20}

Vaccination is instituted in the form of a toxoid, available as a single antigen preparation tetanus toxoid (TT), combined with Diphtheria vaccine as paediatric DT or adult Td, and with both diphtheria and pertusis vaccine as DPT and DTaP (containing acellular pertusis component).^{1,13,19,20}

Children under seven years should receive DPT or DTaP or paediatric DT and children above seven years and adults should receive Td formulation. Single antigen TT is not recommend. In children,

three doses of DPT vaccine are given at an interval of four to eight weeks, starting at six weeks of age. This should be followed by booster at 18 months.^{1,13,19,20}

The second booster is given at five to six years and third up to ten years. The initial series for adults involves three doses. The first two doses are given four to eight weeks apart and the third is given six months after the second. Booster doses are required every ten years. Tetanus was preventable disease, that's why the priorities must be in prevention; universal vaccination, and the development of simple immunisation schedules with longer protection.^{1,13,19,20}

Conclusion

Tetanus is an acute, potentially fatal disease that is characterized by generalized increased rigidity and convulsive spasms of skeletal muscles. It occurs annually worldwide, resulting in death of about half a million people each year.

The role of pyridoxine in the management of tetanus for reduced general motor spasm (seizures) seems to be underlying routine use, but it should be re-

examined in a blind randomised trial. As tetanus was a preventable disease, the priorities must be in prevention so there is no more tetanus case in Indonesia, furthermore worldwide.

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