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# Therapeutic plasma exchange (TPE) in management of patients with tetanus: A case report

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**Abstract**

**Tetanus is an infection caused by a neurotoxin produced by a bacterium called Clostridium tetani. One of tetanus management is to use therapeutic plasma exchange (TPE) facilities as a therapeutic modality, which is rarely available in most severe tetanus populations. TPE is therapeutic apheresis that is applied either as primary or secondary therapy in various kinds of diseases. We reported a case of a 60-year-old man diagnosed with observed general onset tonic-clonic seizure with trismus due to tetanus. The patient came with a chief complaint of mouth stiffness with difficulty opening his mouth (mouth opening of 5 cm). His condition was followed by generalized spasms, especially when triggered by loud noises and light. The patient had a 2- week history of tooth pain due to dental caries with no response to pain relievers. The patient then received TPE on the eighth day of treatment, two times with 3000 ml plasma exchange, 2500 ml albumin 5%, and 500 ml NaCl 0.9%. Based on clinical evidence, TPE effectively eliminates toxins released by Clostridium tetani in tetanus patients. Removing circulating autoantibodies, immune complexes, cytokines, and other inflammatory mediators is fundamental to this process. Cytokines are one of the molecules that potentially cause damage but can be removed through TPE. Significant clinical outcomes were shown after the patient received TPE. TPE can maintain hemodynamic stability and faster extubation time and reduce trismus, muscle spasms, and seizure frequency until they no longer appear.**

**Key words**: TPE, tetanus, plasmapheresis, intensive care.

## Introduction

Tetanus is an infection caused by a neurotoxin produced by the Clostridium tetani bacterium. (1) Tetanus can affect anyone of any age. However, it is most commonly reported in patients younger than neonates. Despite immunization being widespread in infants and children since the 1940s, the disease remains a significant public health problem in many parts of the world, especially in poor and developing countries. This health problem is due to underemployment and infrequent practice. World Heart Organization (WHO) estimates that in 2018, 25,000 newborns died from neonatal tetanus. (2,3)

In many countries, including Indonesia, neonatal tetanus cases have not been frequently reported, so actual prevalence rates are not available. Even though it is still a big problem among adults, the current higher rates of tetanus in older adults are due to those not vaccinated or adequately vaccinated according to the protocol. In 2019, 14,751 cases of tetanus were reported to the WHO, with developing countries holding a high prevalence, causing a high mortality rate. (2,3)

One of tetanus management is to use therapeutic plasma exchange (TPE) facilities as a therapeutic

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modality, which is rarely available in most severe tetanus populations. TPE is clinical apheresis that includes various blood processing techniques that can improve the outcome of various diseases. TPE can be applied as primary therapy in certain diseases or as a secondary or adjunct therapy in various other diseases. Primary, secondary, and adjunctive therapy of TPE treatment is considered effective and beneficial. (4)

TPE is often combined with immunosuppressive treatment, such as intravenous immunoglobulin (IVIG), prednisone, and azathioprine, to avoid rebound effects and maintain improvement. IVIG and TPE are effective disease-stabilizing therapies for patients with tetanus. Neither IVIG nor TPE has a clear clinical predominance for treating tetanus up until now. There are no adequate randomized controlled trials, but there have been a few of case reports of short-term benefits of plasma exchange in tetanus. (5)

This case report discusses a 60-year-old male with tetanus. The writing of this case report aims to analyze experiences related to the indications, complications, and outcomes of TPE as a treatment for tetanus patients.

**Case report**

A 60-year-old male patient came to the hospital with mouth stiffness and difficulty opening, as chief complaints, four days before admission. The patient also complained of generalized spasms for approximately 15 minutes twice daily. According to the patient's relatives, complaints of stiffness appeared when the patient was triggered by loud noises and light. However, the patient was still conscious. Vomiting, headache, and fever were denied. Previously, the patient complained of tooth pain due to dental caries for two weeks which had not improved despite taking a pain reliever. The history of being pierced by nails or other metals was denied. There was also no history of hypertension or diabetes mellitus. The patient was referred to the Intensive Care Unit (ICU) for intensive care.

Physical examination revealed that the patient was conscious with a blood pressure of 119/84 mmHg, heart rate of 101 beats per minute, respiratory rate of 20 breaths per minute, a temperature of 36.5 ºC, and oxygen saturation of 93%. In the examination of the head, it was found that the eyes were not anemic nor icteric, and a trismus was found with the mouth opening 5 cm. The thoracic examination was symmetric, with no retraction, clear breath sounds in both lung fields, and no crackles and wheezing heard. The first heart sound was more dominant than the second, regular, and no murmurs and gallops were heard. There were no abdomen abnormalities, distension, and peristalsis within normal limits. The upper and lower extremities were warm, the capillary refill was less than 2 seconds, and no edema was found.

The laboratory examination showed hemoglobin of 15.4 g/dl, hematocrit of 43%, erythrocytes of 5000/$mm^3$, leukocytes of 15,500/$mm^3$, platelets of 277,000/$mm^3$, urea of 31 mg/dl, creatinine of 0.9 mg/dl, the blood sugar level of 137 mg/dl, natrium of 143 mmol/l, potassium of 4.1 mmol/l, and chloride of 108 mmol/l. In addition, chest x-ray imaging of the patient's heart and lungs were within normal limits (**Figure 1**).

The patient was diagnosed with observed general onset tonic-clonic seizure with trismus due to tetanus based on the patient's complaints, including mouth stiffness with difficulty opening, generalized spasms, and a history of dental caries, physical examination that showed trismus with a mouth opening of 5 cm, and the laboratory and radiology examinations were within normal limits.

Subsequently, the patient was given therapy in the form of intravenous amikacin with a dose of 1 g/6 hour, paracetamol drip with a dose of 1 g/8 hour, intravenous procaine penicillin 1.2 g/12 hours, oral diazepam 5 mg thrice followed by intravenous diazepam 5 mg/8 hour, intravenous omeprazole 40 mg/12 hours, metronidazole drip 500 mg/8 hour, and TPE was given twice on the eighth day of treatment with 3000 ml plasma exchange with 2500 ml albumin 5% and 500 ml NaCl 0.9%. The patient's hemodynamic status during treatment was relatively stable, especially after performing TPE (**Figure 2**). The patient was extubated two days after TPE, and on the 20th day of treatment, the patient was transferred from the ICU to the High Care Unit (HCU) for further treatment.

**Discussion**

TPE is a therapeutic modality in tetanus. Although it is not listed in the American Society for Apheresis (ASFA) consensus, based on clinical evidence, this therapy is quite effective for eliminating toxins released by Clostridium tetani. *The bacterium* enters through a 0.5-1.7 cm x 2.1-18.1 cm wound and produces tetanospasmin weighing 150 kDa. Removing circulating autoantibodies, immune complexes, cytokines, and other inflammatory mediators is the basis of this process's mechanism of action. Cytokines are one of the molecules that potentially cause damage but can be removed through TPE. (6-8)

Tetanus is a clinical diagnosis defined by hypertonia accompanied by painful muscle contractions or spasms. Generalized tetanus is a disease character-

ized by the progression from trismus to neck muscle stiffness with difficulty swallowing. Patients may experience generalized muscle spasms, including abdominal muscle spasms, which may present as abdominal stiffness. These were the things that the patient complained about. In our patient, stiffness of the body occurred gradually. Stiffness initially appeared in the masseter muscle, causing difficulty in mouth opening, trismus, or lockjaw. Then the complaint developed into the body's stiffness for 15 minutes twice daily. This body stiffness indicated that the patient had seizures, a typical symptom of tetanus. (9,10)

The patient previously had tooth pain due to dental caries for two weeks, which the painkiller could not relieve. Dental caries was suspected as a port of entry for tetanus germs. After that, the patient was consulted by the Dental and Oral Department, but because acute symptoms presented, especially trismus, the extraction of the carious tooth could not be done. (11)

There were no typical laboratory findings of tetanus. The diagnosis was entirely clinical and did not depend on bacteriological confirmation. The incubation period of tetanus is 3 to 21 days, and the shorter the incubation, the higher the risk of death. As in this patient, the initial symptom of tetanus was trismus. If left untreated, this jaw spasm can progress to dysphagia, laryngospasm, respiratory muscle spasm, cardiac arrest, and even death. Thus, the most recommended action to avoid these risks is to treat patients in the ICU. (9,12)

During the first 24 hours in the Emergency Room (ER), the patient was given oral diazepam 5 mg thrice as the initial management of severe spasms that occurred in the patient. Treating muscle spasms and convulsions in tetanus is essential because it can cause respiratory failure, stridor, dysphagia, and aspiration pneumonia. Diazepam works by increasing the effect of gamma-aminobutyric acid (GABA) on the postsynaptic membrane. Large doses of diazepam are required to achieve adequate muscle relaxation and prevent spasms. Once seizures are controlled, maintenance doses of diazepam should be continued for 2-4 weeks. In this patient, the maintenance dose given was 5 mg/8 hour. (13,14)

On the first day, the patient was given antibiotic therapy with amikacin as empiric therapy before the results of culture and sensitivity tests appeared. Amikacin is an aminoglycoside antibiotic with a broad spectrum against gram-negative bacteria, including Pseudomonas spp, Escherichia coli, Proteus spp, Klebsiella-Enterobacter-Serratia spp, Salmonella, Shigella, Acinetobacter (Minea-Herellae), and others. Gram-positive bacteria that are sensitive to amikacin are Staphylococcus spp. Both produce penicillinase or not, including strains that are resistant to methicillin. Amikacin has activity against other gram-positive bacteria, including strains of Streptococcus pyogenes, Enterococci, and Diplococcus pneumoniae (Streptococcus pneumoniae). The dose given was 1 g/6 hour intravenous. (15)

Metronidazole and procaine penicillin are given to eradicate bacteria. In one study in Indonesia, metronidazole has become the treatment of choice in several health services. Metronidazole is effective in reducing the number of vegetative forms of Clostridium tetani. Procaine penicillin can be given as the second line. Similar to metronidazole, penicillin also kills vegetative forms of Clostridium tetani. Until now, administration of penicillin G 100,000 U/kg/day IV every 6 hours for ten days is recommended in all cases of tetanus. One study suggested that penicillin may act as an agonist against tetanospasmin by inhibiting the release of GABA. (16)

On the third day of treatment, the patient was planned for TPE. However, due to the absence of albumin and filter, TPE can only be performed on the eighth day of treatment. In this patient, TPE was performed twice. The plasmapheresis was carried out around 3000 ml plasma exchange with 2500 ml albumin 5% and 500 ml NaCl 0.9%. (17)

Complications associated with the TPE procedure include allergic reactions, hypokalemia, and hypotension. The patient had hypokalemia as a side effect of plasmapheresis, with potassium levels nearing 3 mmol/l. Therefore, the patient was given potassium chloride of 200 mg/12 hours to restore serum potassium to normal. The patient's condition must be monitored closely during plasmapheresis, including the necessary laboratory tests to minimize side effects. (18)

IVIG treatment can also be given to help neutralize circulating toxins. IVIG could be started at 1 ml/min for the first 15 minutes. It can be increased slowly to a maximum of 4 ml/min over the next 15 minutes if tolerated. It can be directly infused or diluted up to 4 times the volume with compatible liquids. (19)

In IVIG therapy, it is necessary to monitor the patient's response, including hypotension, abdominal pain, headache, redness, chest tightness, dyspnea, rash, nausea, and vomiting. Stop or slow down the infusion rate if necessary and restart at a slower rate once symptoms have alleviated. Infusion reactions are most common in the first hour and at a more rapid rate. Delayed reactions can occur 24 hours after the infusion, including nausea, vomiting, chest pain, stiffness, and leg pain. Anaphylactic reactions are rare but are a medical emergency. Stop the infusion and treat it appropriately. (19)

The use of plasmapheresis in combination with IVIG is not recommended because it does not provide a better outcome. In addition, the use of combination therapy also often leads to complications when compared to a single use. (18)

A study by Bobati in 2017 showed that TPE was not only a safe and effective treatment alternative for IVIG but also had strong evidence in ameliorating neurological disorders. TPE or IVIG is equally effective and significantly better than conservative treatment for recovering from neurological disorders. However, TPE has been reported to have a more significant potential benefit than IVIG. TPE is most effective when started within seven days of the disease onset to control neuroimmunological disorders symptoms. (18)

Clinically, the effect is seen within 24 hours after treatment. There are no adequate randomized controlled trials to prove its effectiveness, but many cases report a benefit of plasmapheresis over IVIG with improved ventilatory status. (18)

The patient's hemodynamic status was continuously monitored and relatively stable during treatment. Especially after plasmapheresis, the patient could breathe spontaneously, and the ventilator could be removed two days later.

The patient's condition showed significant changes after plasmapheresis. On the 20th day of hospitalization in the ICU, the patient was transferred to the High Care Unit (HCU) for further treatment. During treatment, the patient showed very significant progress. Trismus and muscle spasm decreased progressively. The frequency of seizures in patients also reduced until it was not experienced anymore.

## Conclusion

A 60-year-old male came with a chief complaint of mouth stiffness, difficulty opening, and generalized spasms diagnosed with tetanus. The patient was treated with benzodiazepines, antibiotics (metronidazole and penicillin), and mechanical ventilation. One of the modalities of tetanus therapy is TPE. Although not listed in the ASFA consensus, based on the clinical evidence, this therapy effectively eliminates toxins released by Clostridium tetani. Using TPE in combination with IVIG is not recommended because it does not provide a better outcome. TPE or IVIG is equally effective and significantly better than conservative treatment for recovering from neurological disorders. However, TPE has been reported to have a more significant potential benefit than IVIG. The patient's condition showed significant changes after plasmapheresis, and he could be transferred to a regular room. Careful monitoring and adherence to treatment protocols help reduce mortality.

## Statement of ethics

This written case report has obtained consent from the patient and his family.

## Disclosure statement

The authors have no conflicts of interest to declare.

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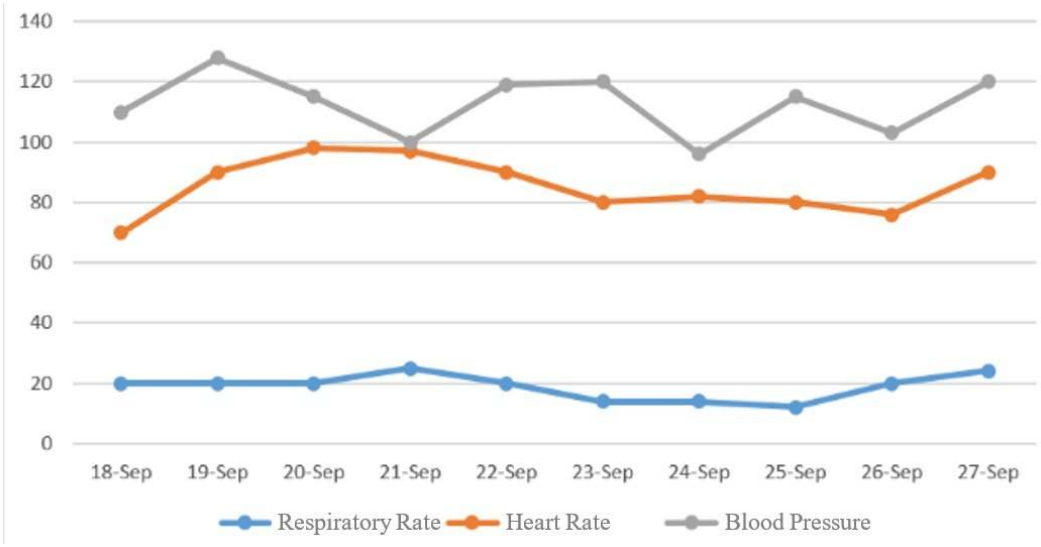
**Figure 1**. Chest x-ray imaging of the patient


Legend: The chest x-ray imaging of the patient was within normal limits (the heart and the lungs were normal).

**Figure 2**. The patient's hemodynamic status




Legend: The patient's hemodynamic status during treatment was relatively stable (respiratory rate, heart rate, and blood pressure), especially after performing a therapeutical plasma exchange.

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