Successful management of severe generalized tetanus in a 23-year man with Phenobarbital adjuvant: a case report

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Abstract

With a mortality rate of up to 50%, generalized tetanus is still a global concern, especially in low and middle-income countries. A 23-year-old man from Afghanistan was admitted to Sina Hospital, affiliated with Tehran University of Medical Sciences, with the chief complaint of generalized severe spasms and lockjaw. The patient had a history of skin lesions and had never been vaccinated against tetanus. He admitted to the intensive care unit after intubation in emergency room, with diagnose of severe generalized tetanus. After receiving tetanus immunoglobulin and intravenous metronidazole, a combination therapy of midazolam, propofol, atracurium and morphine was administered. Due to the refractory muscular spasms intravenous phenobarbital started and little by little recovery was achieved. With no symptom recurrence, after receiving the first 2 doses of the Td vaccine, the patient was discharged on day 42.

Keywords: Tetanus, phenobarbital, Intensive care

Introduction:

Tetanus is caused by Clostridium tetani and has a mortality rate of 4.2% to 50%, but it is a vaccine-preventable disease (1). Higher mortality rates have been reported from centers with limited intensive care and ventilator support (2). Despite the dramatic reduction in the prevalence of the disease thanks to vaccination programs, tetanus remains a global problem, particularly in low and middle-income countries due to lack of vaccination or not receiving the booster dose (3, 4).

As a toxin-producing, anaerobic gram-positive spore-forming bacterium, Clostridium tetani produces tetanolysin and tetanospasmin. Besides the role of tetanolysin in intensifying wound damage and providing anaerobic condition for bacterium growth, most of the clinical manifestations of tetanus result from tetanospasmin, which inhibits gamma amino butyric acid (GABA)-ergic and glycinergic neurons (5, 6).

The diagnosis of generalized tetanus is based on the history of the injury and clinical features (7). Due to the limited capacity for clinical trials and available management options, there is still limitations in evidence-based management strategies for the disease (8). Nevertheless, treatments such as early tracheostomy and administering benzodiazepines, magnesium sulfate, and morphine are effective and recommended as first line therapy alongside supportive care. Also, admission to intensive care unit (ICU) is offered for patients with high-risk tetanus (4). Phenobarbital is a barbituric acid derivative that acts as a non-selective central nervous system inhibitor by mimicking the action of GABA in the brain. It enhances the effects of GABA by facilitating the passage of Cl through Cl channels in GABA receptors. Therefore, it appears that phenobarbital may be able to reverse the inhibitory effects of tetanospasmin on the GABA receptor.

In this paper, we introduce a case of severe generalized tetanus with respiratory failure, whose spasm did not improve with full doses of benzodiazepines and muscle relaxant agents, but it was finally managed with propofol and phenobarbital.

Case report:

A 23-year-old man (wt= 70kg), construction worker from Afghanistan with no notable medical history, was admitted to the emergency department of Sina hospital, affiliated with Tehran University of Medical Sciences. The patient presented lockjaw leading to dysphagia and intermittent intense muscular spasm in the upper and lower limbs. 3 days before admission, a nail stuck into his right sole. The patient was not vaccinated against tetanus. On the admission day, he had stable hemodynamics (BP = 121/79 mmHg, HR = 90 beat/min, RR = 21 breath/min, SPO2=98 %, Temperature = 37.5 °C oral) and normal laboratory results (CBC, ESR, CRP, LFT, Cr, BUN, VBG, and serum electrolytes). He received 1 vial (250 IU) of tetanus immune globulin and the first dose of the Td vaccine intramuscularly before leaving the emergency department with personal consent. Three days later he was readmitted to the emergency department, and presented loss of consciousness (GCS= 10) and generalized severe spasm and rigidity in the lower and upper limbs. Other clinical manifestations included sustained spasms of the facial muscles (Risus sardonicus), severe contractions of masseter muscles (lockjaw), and sweating, and his hemodynamics were unstable (BP = 178/90 mmHg, HR = 180 beat/min, RR = 45 breath/min, SPO2=85 %, Temperature = 38.5 °C). According to the Ablett classification of tetanus severity (9), the patient's condition was very severe. The patient was intubated in the emergency department and admitted to the ICU. His laboratory results upon admission to the ICU and discharge time are given in Table 1, indicating elevated levels of ESR, CRP, LDH, and CPK, and diminished serum calcium (Ca corrected= 7.6), as well as negative blood and urine culture.

Table 1

In addition to wound cleaning and debridement, the patient received the second dose of tetanus immune globulin (500 IU), diazepam (20 mg), and labetalol 10 mg/hr in the emergency department. The patient was isolated in a dark, quiet room in the ICU because any sensory stimuli—including light, touch, and loud noise—would trigger the spasms. Despite receiving intravenous midazolam 30 mg/hr, morphine 2-3 mg/hr, MgSO4 5 cc/hr, and intravenous metronidazole, the patient experienced severe, painful and refractory spasms permanently. Because of the insufficiency of these medications to manage the spasms, a neuromuscular

blocking agent, atracurium 40 mg/hr, was administered as well. The spasm was refractory to all these medications, and we had to start propofol infusion 10cc/hr on the third day of ICU admission for 48 hours. This regimen was followed by intravenous phenobarbital 1 gr as loading dose and 100mg/8hr as maintenance dose. The tracheostomy was performed on the sixth day of ICU admission. The spasm gradually decreased after administering phenobarbital on day 10 of ICU admission; therefore, atracurium and midazolam were gently tapered down to discontinue the medication on day 12 and 25 of ICU admission, respectively. Finally, he was extubated from mechanical ventilation in day 30 of ICU admission. It is worth mentioning that the phenobarbital serum level was at the therapeutic range (between 25-30 mg/L, therapeutic level is 10-40 mg/L in our hospital laboratory) during the survey.

It should be noted that because of MgSO4 infusion and the patient's low calcium level at baseline, we also administered calcium gluconate supplement intravenously to keep his corrected calcium level above 8.5 mg/dl. Meanwhile, he received pantoprazole and heparin for stress ulcer and DVT prophylaxis from the first day of ICU admission. On the other hand, the patient need high energy due to continuous muscle overactivity and spasms, but he could not tolerate enteral nutrition and had excessive residue volume, so total parenteral nutrition (TPN) started on day 4. The ESR, CRP, LDH, and CPK levels decreased gradually and normalized on day 28. Finally, on day 42 of hospitalization and after receiving the second dose of the Td vaccine, the patient was discharged with no symptom recurrence. A written informed consent was obtained from the patient in order to publish this case report, and it was approved by the Research Ethics Committee of Sina Hospital.

Discussion:

Tetanus is still a global concern since the World Health Organization reported 14751 tetanus cases in 2019 (8). Generalized tetanus was the most common type, accounting for about 80% of patients (10). It has been suggested that ICU admission results in better monitoring, and timely diagnosis of complications will reduce morbidity and mortality rates (5, 11). Although there are some protocols for tetanus management, there is a lack of substantial evidence for tetanus management strategies (1, 11). Hence, the management of tetanus is challenging even for the most experienced physicians.

In this case, although we administered tetanus immune globulin (500 IU) and intravenous metronidazole on the first day of admission, the spasms continued to worsen over the first 5 to 10 days of hospitalization. This might be due to the toxin that had already entered the motor neurons and was progressing toward the central nervous system (6). It has been reported that tetanospasmin inhibits the action of enkephalins, which may play a role in modulating the autonomic nervous system (12). Midazolam, morphine sulfate, and MgSO4 were administered from the first day of admission to control muscle spasms and pain. There are several reports about the role of MgSO4 in patients with tetanus. It might be used to resolve muscle spasms and autonomic instability (including hypertension and tachycardia) and reduce the need for benzodiazepines and neuromuscular blockers. On the other hand, some studies suggest that MgSO4 has no significant effect on mortality and should not be used as monotherapy in these patients (13).

Although no preferred combination therapy is available thus far, some studies suggest the addition of propofol, neuromuscular blockers, or a combination of both when there was no adequate clinical response to benzodiazepines (7, 14). Therefore, we added atracurium and then propofol because of the patient's resistant spasm and high sensitivity to any sensory stimulus.

Intrathecal baclofen has been successfully used in patients with spasms that are resistant to neuromuscular blocking agents. It seems that intrathecal baclofen could shorten the duration of mechanical ventilation and reduce the rate of mortality (15), but since intrathecal baclofen was not available in our setting, we decided to administer oral baclofen.

Since the probability of propofol infusion syndrome was high, we decided to add intravenous phenobarbital to the previous medications. There are some case reports supporting the use of phenobarbital in generalized and neonatal tetanus, although some of them have shown no mortality benefit (16). A meta-analysis of studies on children with tetanus reported diazepam alone is more beneficial on controlling tenues and reducing

mortality than if it is combined with phenobarbital (RR of death 0:36; 95% CI 0:15 to 0.86; risk difference -12:22; 95% CI -0.38 to - 0.06) (17). However, the combination of diazepam and phenobarbital compered to diazepam alone has demonstrated a significantly milder clinical course and shorter hospitalization (18). This evidence confirming the efficacy and safety of phenobarbital in tetanus management, which suggests adding phenobarbital to primary treatment of severe tetanus could be a favorable choice.

On day 10 of ICU admission, the patient showed a significant reduction in clinical manifestations, although intermittent muscle spasms continued until day 32. Due to the use of combination therapy to manage severe muscle overactivity in this case, it is not clear which drug yielded the most clinical benefit. On the other hand, due to the patient's severe pain and spasms and to follow the ethical considerations, we decided to add medications as soon as possible in the failure of a complete response to first-line therapy. Since tetanus infection does not provide natural immunity, patients need a full course of vaccination. Our patient received one dose of Td vaccination on his first admission and the second dose during discharge. The next dose should be administered 6 to 12 months later. Although it has been suggested that vaccine-naïve patients should receive at least one dose of Tdap vaccination (19), due to the unavailability of Tdap in our region we considered Td for all three doses.

Conclusion

Although there are guidelines for managing generalized tetanus, no preferred combination therapy has been established until now. Our study found adding phenobarbital to first-line medicine could reduce sever spasm more quickly with no adverse reaction. However, further studies are required to understand the best combination and dosage of medications for severe tetanus management.

Conflict of interests

On behalf of all of the authors, the corresponding author declares no conflict of interests

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Authorship:

AA, HSH, AN, MM, MahM carried out diagnostic management. EK and RN contributed in writing of manuscript and organizing patient's files. AA revised the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Written informed consent for publication of their clinical details and/or clinical images was obtained from the patient/parent/guardian/ relative of the patient. A copy of the consent form is available for review by the Editor of this journal.

Data availability statement

The data of the study are available from the corresponding author upon rational request.

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Table 1: Patient's laboratory data at the admission and discharge from ICU

Parameter	ICU admission	Discharge from ICU
WBC (cell/mm3)	13100	6200
Hgb (g/dl)	11	11.2
MCV (fl)	88.9	89.6
RBC (million/mm3)	3.58	4.10
Platelet (cell/mm3)	322000	316000
ALT (U/L)	24	18
AST (U/L)	36	28

Bilirubin Total (mg/dl)	0.47	0.62
Bilirubin Direct (mg/dl)	0.17	0.22
ALP (U/L)	426	126
ESR (mmol/hr.)	84	10
CRP (mg/L)	74	6
LDH (U/L)	2518	120
CPK (U/L)	10852	186
PT (second)	16.3	16.3
INR	1.3	1.2
APTT (second)	38.2	36
Serum Cr (mg/dl)	0.92	1.02
Urea (mg/dl)	24	32
Na (meq/L)	139	137
K (meq/L)	3.78	4.2
Mg (mg/dl)	3	2.4
Ca (mg/dl)	6	7.8
P (mg/dl)	2.7	2.2
Alb (g/dl)	2	2.8
[a] Normal range in our hospital's Laboratory	[a] Normal range in our hospital's Laboratory	[a] Normal range in our hospita