Management of tetanus complication

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Abstract. The mortality rate of tetanus is still high; it is because of various complications due to muscle spasms, autonomic dysfunction, as well as due to prolonged critical care. Management of tetanus with its complications is in intensive care facilities. Management goals include stopping toxin production, neutralization of unbound toxin, management of the airway, muscle spasm control, treatment of autonomic dysfunction and general supportive management. Currently, diazepam is still an effective medication to control of muscle spasm and rigidity. Therapy for autonomic dysfunction that supported by evidence is MgSO4. Also, general supportive management for long-term care remains necessary to prevent other complications such as thromboembolism, infection, malnutrition, and others.

1. Introduction

Tetanus is an often fatal disease if left untreated. However, it is preventable by effective immunization. Until now tetanus is still a threatening health problem in low- and middle-income developing countries. Globally reported tetanus death rate in 2015 ranged from 56.743 (95% uncertainty interval: 48.199 to 80.042).[1] The mortality rate of tetanus in the area with limited healthcare facilities of intensive care and ventilator support was more than 50 % due to airway obstruction, respiratory failure, and renal failure. There are reported a decreasing of death into 15% when intensive care was available.[2]

Tetanus is an infectious disease caused by Clostridium tetani that release tetanolysin and tetanospasmin toxins. Tetanospasmin is binding with ganglioside of presynaptic membrane, both in the neuromuscular junction and in the central nervous system. Tetanospasmin acts by preventing the release of inhibitory neurotransmitters such as glycine, Gamma Amino Butyric Acid (GABA), dopamine and noradrenaline in the inhibition synapses of the central nervous system. The incubation period is range from 1 day until months, mostly eight days. Tetanus is a clinical diagnosis characterized by the clinical triad of rigidity, muscle spasms, and autonomic dysfunction, stimulus-induced tetany with the history of injury within the last three weeks. The laboratory test is rarely used for diagnoses tetanus, however, some reference labs would help rule out the differential diagnosis of tetanus. Tetanus has some classification; generalized tetanus (all the muscles of the body affected), localized tetanus (spasm and rigidity that occur in the muscles of the body in certain areas), cephalic tetanus (tetanus that occurs in head wounds affecting the cranial nerve) and neonatorum tetanus. There are complications of tetanus associated with tetanus illness and long-term complication of critical care.[2,3] The existence and improvement of critical care facility provide a better tetanus management.[4] The following will briefly discuss the management of tetanus complications.

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2. Complication

The complications of tetanus result from muscle spasm, autonomic dysfunction, and prolonged critical illness.[2,3] Tetanus complications on organ system are in table 1.

Table 1. Complications of tetanus.

Body system	Complication
Airway	Aspiration
	Laryngospasm/obstruction
	Sedative associated obstruction
	Apnoea
Respiratory	Hypoxia
	type I respiratory failure (atelectasis, aspiration, pneumonia)
	type II respiratory failure (laryngeal spasm, prolonged truncal spasm, excessive sedation)
	ARDS
	Complication of prolonged assisted ventilation (e.g.pneumonia), Tracheostomy complication (e.g.tracheal stenosis)
Cardiovascular	Tachycardia
	Hypertension
	Ischaemia
	Hypotension
	Bradycardia
	Tachyarrhythmias
	Bradyarrhythmias
	Asystole
	Cardiac failure
Renal	High output renal failure
	Oliguric renal failure
	Urinary stasis
	Infection
Gastrointestinal	Gastric stasis
	Ileus
	Diarrhoea
	Haemorrhage
Miscellaneous	Weight loss
	Thromboembolus
	Sepsis and multiple organ failures
	Fracture of vertebrae during spasms
	Tendon avulsion during spasms.

3. Management

Management of tetanus should be in the intensive care unit; it is related to tetanus complication management particularly for early and aggressive airway management and other supportive therapy.[2-4] The tetanus management panel is in table 2. In general tetanus management are: [2-4]

1. Neutralization of tetanus toxin
2. Prevent of tetanus toxin release by *C. tetani* eradication and wound debridement
3. Control of muscle spasm
4. Treating the complication such as autonomic dysfunction and supportive care

3.1. Neutralization of Tetanus Toxin and Clostridium tetani Eradication

Neutralization of tetanus toxin and *C. tetani* eradication should be done on the first day of treatment as the diagnosis confirmed. Toxins that have not been in the tissues can be neutralized by passive immunization using human tetanus immunoglobulin 500IU intramuscularly or equine tetanus

immunoglobulin 1500 – 3000IU intramuscularly or intravenously. In the use of equine antitoxin, ask in test will need a dose of 0.1ml in 1/10 dilution to identify the hypersensitivity reaction.[3]

Tetanus patients should have wound debridement to eradicate spores and necrotic tissue. The recommended antibiotic for the eradication of *C. tetani* is metronidazole 500mg intravenously every 6 to 8 hours, and the alternative antibiotic is Penicillin G 2-4 million units intravenously every 4-6 hours, with the duration of treatment, is 7-10 days.[3]

3.2. Muscle Spasm Control

Generalized muscle spasm is a life-threatening condition, which can lead to complications of respiratory failure, aspiration and induced generalized exhaustion. Treatment of patients with controlled room light or noise greatly helps avoid muscle spasm provocation.[3]

Diazepam is a derivative of Benzodiazepines is a very effective drug in tetanus management. Diazepam acts by increasing GABA agonism through resistance to endogenous inhibitors of the GABAA receptor. The benefits of diazepam are as anti-convulsant and muscle relaxants that acts to control rigidity and muscle spasms. In addition, diazepam has sedative and anxiolytic effects.[2,3,5] Diazepam dose in adults is 5mg then titrated until spasm is resolved without causing excessive sedation and hypoventilation.[6] Administration of high-dose diazepam may cause mild respiratory depression. Diazepam may be administered orally via nasogastric tube, per rectum, or intravenous infusion. In intramuscular administration, there is an erratic absorption. Bioavailability after oral administration and rectal reportedly good, with an almost complete absorption and peak plasma levels achieved in 30-90 minutes.[2,3,5] When there is no diazepam, midazolam can be used with little cumulation. Midazolam is a relatively short-acting benzodiazepine, theoretically better than diazepam. However, until now, there is only few evidence of the use of this drug in tetanus patients.[5]

Other drugs that have sedation effects and as anticonvulsants, which can be used for tetanus include phenobarbitone, chlorpromazine (50-150 mg by intramuscular injection every 4-8 hours in adults), propofol.[2,3,5] In a meta-analysis study in children found that the use of diazepam alone gave a better chance of survival compared to the combination of phenobarbitone and chlorpromazine (RR of death 0:36; 95% CI 0:15 to 0.86; risk difference - 12:22; 95% CI -0.38 to - 0.06). On the other hand, the administration of diazepam alone or diazepam with other anticonvulsants (phenobarbitone and chlorpromazine) was reported to be significantly associated with the milder clinical course and shorter hospital stay.[7]

If sedation alone is inadequate, neuromuscular blocking agents and intermittent positive pressure ventilation may be necessary for prolonged periods. Some of the aminosteroid neuromuscular blocking agents that can be used are vecuronium, pancuronium, rocuronium,and pipecuronium. Pancuronium inhibits catecholamine re-uptake and may aggravate autonomic instability in severe cases. Vecuronium has no cardiovascular side effects and histamine release, but relativelyshort-acting. Long-term use of aminosteroid neuromuscular blocking agent through infusion is reported to be associated with neuropathy and myopathy. Intrathecal baclofen which is a $GABA_B$ agonist can be administered at a dose of 500 - 2000 ug daily can be given a bolus or perinfusion. Larger doses and boluses are associated with greater side effects. In some cases, the side effects can be reversible with $GABA_A$ flumazenil antagonist. The disadvantage of this drug is the invasive administration technique, the price is expensive and requires the mechanical ventilation facilities that are available anytime.[2]

3.3. Management of Autonomic Dysfunction

The mechanism of action of morphine includes replacement of endogenous opioids, reduction of sympathetic reflex activity and histamine release.[2,3,5] Morphine is very useful in maintaining cardiovascular stability. The dose of morphine sulfate 0.5 - 1.0mg/kg per h by continuous intravenous infusion.[3]

Phenothiazine especially chlorpromazine which acts as anticholinergic and α adrenergic antagonism also play a role in maintaining cardiovascular stability and used as a sedative. Agent β-adrenergic blocking agents such as propranolol, labetalol may be used to control episodes of

hypertension and tachycardia.[2,3,5] Labetalol with a dose of 0.25 -1.0 mg per min has the effect of α blocking and β blocking, compared to propanolol which has only β-blocking effects.[3]

Magnesium sulfate is a pre-synaptic neuromuscular blocker, inhibits catecholamine release from nerves and adrenal medulla, reduces receptor responsiveness to released catecholamines, anticonvulsants, and vasodilators. MgSO4 is a calcium antagonist in the myocardium and neuromuscular junction and inhibits the release of parathyroid hormone thereby decreasing calcium levels. MgSO4 is used in patients using artificial ventilation to reduce autonomic disorders and in non-ventilated patients to control spasms.[2,3,5] MgSO4 doses are initiated with loading dose 75-80 mg/kg in 30 minutes and followed by 2g h in patients under 60 years and 1g/hour for patients over 60 years. The infusion rateincreases every 6-hour interval depending on the comfortable and spasm degree of patients.[5] Clinical signs that are used to predict and assess the therapeutic range of MgSO4 are a patellar reflex, hypocalcemia, over-sedation, cardiovascular and respiratory depression.[5,6]

Among that medication, only MgSO4 has a study with a randomized clinical trial in tetanus patient.[5] As compared to placebo, MgSO4 has been shown to significantly reduce the need for muscle spasm and the need for verapamil to manage cardiovascular instability, about 4.7 times less than that of placebo.[3] However, MgSO4 does not reduce the need for mechanical ventilation.[3,5]

There are several potential medications which can be used to manage this condition in future are sodium valproate acts to block GABA-aminotransferase which results in inhibition of GABA catabolism. Angiotensin-converting enzyme inhibitors inhibit the synthesis of angiotensin II, which leads to the increase in norepinephrine production and its release from nerve ending. Dexmedetomidine, a α_2- adrenergic agonist, which is more potent than clonidine, also shows some effect in reducing sympathetic overactivity. Adenosine decreases presynaptic norepinephrine release and has antagonist inotropic effect of catecholamine.[2]

3.4. Supportive management and complications

Weight loss or malnutrition frequently appears in tetanus patients. Several factors contributing to this condition are swallowing difficulty, gastrointestinal system problem induced by autonomic activity, increase in metabolic rate due to pyrexia, muscular activity problem, and long-standing critical diseases. Nutrition has to be given to these patients. Enteral nutrition feeding is related to lower incidence of complications and is cheaper than parenteral nutrition. Percutaneous gastronomy can reduce the occurrence of complications related to nasogastric tube feeding.[2]

Maintaining airways is essential to prevent aspiration and laryngospasm/obstruction as these may lead to the need for mechanical ventilation. Tracheostomy is the desired access when long-term mechanical ventilation is necessary. Respiratory complication prevention includes meticulous oral care, chest physiotherapy, and regular tracheal suction mainly for saliva and bronchial secretion.[2]

Infection complications, such as ventilator-associated pneumonia and sepsis, frequently take place, so they have to be monitored and managed immediately. Other crucial complications that need attention and management in tetanus are critical care including thromboembolism, gastrointestinal bleeding, decubitus ulcer, and psychological complications.[2]

Table 2. Management of tetanus.

First presentation and admission
• Suspected tetanus case: painful muscle spasms with no known explanation
• Ensure ventilation
• First laboratory tests of serum sample: determination of antitoxin concentration, strychnine, and dopamine antagonist assays, electrolytes, blood urea nitrogen, creatinine, creatine kinase, C-reactive protein, procalcitonin, and urinary myoglobin
• Complete the history of the port of entry, incubation period, period of onset, and immunization
• Use benzodiazepine intravenously (diazepam or lorazepam) to control spasms
• Transfer the patient to a quiet, darkened area in the intensive care unit
First day

- Human tetanus immunoglobulin, 500 IU, intramuscularly; if human tetanus immunoglobulin not available, use equine tetanus immunoglobulin
- Administer adsorbed tetanus toxoid, such as tetanus-diphtheria vaccine (0·5 mL) or diphtheria, pertussis, and tetanus vaccine (0·5 mL), intramuscularly
- Begin metronidazole, 500 mg intravenously every six hours for ten days
- Debride the wound if necessary
- Feed by a soft small-bore nasal tube or a central venous catheter
- Adjust benzodiazepines dose to control spasms and produce sedation

During hospital stay

- Treat sympathetic hyperactivity with labetalol or morphine
- Control blood pressure; insert a pulmonary artery catheter and an arterial line and administer fluids, dopamine, or norepinephrine as indicated
- Begin prophylactic heparin
- If the severity of spasms has diminished substantially, taper the benzodiazepine dose over 14–21 days

Discharge and follow-up

- When spasms are no longer present, begin physical therapy
- Many patients require supportive psychotherapy
- Before discharge, administer another dose of tetanus-diphtheria vaccine or diphtheria, pertussis, and tetanus vaccine
- Schedule the third dose of toxoid to be given four weeks after the second dose

4. Conclusion

Tetanus is still a significant health problem in developing countries. Tetanus mortality rate remains high because of its complications and long-term care for critical illness. Immediate diagnosis, identification of complications, complication management, and quality of supportive management are keys in determining the outcome.

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