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A Review on Pharmacological Management of Generalised Tetanus

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Abstract

Background: Tetanus is a major public concern in the developing world and is still encountered in the developed world. The evidence regarding the management of the tetanus is limited making the protocol based treatment of tetanus an unmet goal especially in low to middle-income countries. This article was our endeavour to review the management of the patient.

Methods: Two authors extensively searched electronic databases like MEDLINE/Pub Med and Google Scholar, searched with Mesh (Medical Subject Headings) terms like "tetanus", "treatment", "benzodiazepines", " Tetanus immunoglobin" from the earliest possible date of 1966 to January 2018.

Conclusion: We found that diazepam was the drug of choice for controlling muscle spasm, magnesium sulphate controls the autonomic instability, human tetanus immunoglobin bind the unbound toxin, and proper wound care is a must.

Keywords: Tetanus; Management; Benzodiazepines; Magnesium sulphate; Tetanus immunoglobin; Tracheostomy; Wound management

Abbreviation: GABA: Gamma-Aminobutyric Acid; TIG: Tetanus Immunoglobin; WHO: World Health Organisation; TT- Tetanus Toxoid

Introduction

Tetanus is a major public health concern in the developing world and is still encountered in the developed world. Most of the deaths of tetanus occurred in low to middle-income countries [1]. The mortality rate of generalised tetanus ranges from 4.2% to 50% [2]. Even though protocol based management is a practised to abate the mortality and disability associated with generalized tetanus, it is still an unmet goal in low to middle-income countries. The substantial evidence regarding the management of tetanus is limited. Abbate et al. in their study conducted at the public hospitals in Italy, demonstrated that only 1.5% of the physicians correctly adhere to guidelines on tetanus prophylaxis while managing the tetanus-prone wound in acute care [3]. This is our endeavour to review on the treatment of generalised tetanus based on the evidence published in the recent literature.

Methods

Two authors extensively searched electronic databases like MEDLINE/Pub Med and Google Scholar, searched with Mesh (Medical Subject Headings) terms like " tetanus", "treatment", " benzodiazepines", " Tetanus immunoglobin" from earliest possible date of 1966 to January 2018. We select the articles published in any language with preference to randomised control trial and published in recent years. We analyse the 41 articles to write this review article.

Pharmacological treatment

The pharmacological treatment of tetanus is guided by the following principles;

Management of the muscle spasm

(a) Management of autonomic dysfunctions

(b) Controlling the toxin production

(c) Management of unbound toxin

(d) Supportive care

Management of the muscle spasm

Benzodiazepines: The characteristic feature of tetanus is a muscle spasm, which occurs due to the blockage of the release of inhibitory neurotransmitter Gamma-aminobutyric acid (GABA) in the spinal cord interneuron and brainstem [4]. Repeated muscle spasms lead to respiratory paralysis, aspiration pneumonia, rhabdomyolysis and acute kidney injury. Benzodiazepines are considered as the drug of choice for tetanus as it has combined muscle relaxant, anticonvulsant, sedatives and anxiolytic action [5]. Benzodiazepines modulate the GABA-A transmission and enhance presynaptic inhibition at the level of spinal internuncial, ascending reticular activating system and amygdala [6]. Okoromoh et al. in their review concluded that diazepam monotherapy was more effective than the combination of phenobarbitone and chlorpromazine in the management of tetanus [7]. The dose of diazepam required for muscle relaxation is 1-10 mg/kg/day. It can be given up to 600 mg/day. It can be administered in a bolus or continuous infusion [8]. However, Diazepam therapy has several limitations such as the need for prolonged recovery time due to the large volume of distribution [9] and propensity to cause metabolic acidosis. Withdrawal reaction is common with diazepam therapy hence it should be tapered slowly over weeks [10]. The alternative to diazepam therapy in the management of muscle spasm is tetanus is short-acting midazolam. Gyasi et al. reported that midazolam can be used as a sedative and muscle relaxant for a patient with tetanus [11]. The use of midazolam, a relatively short-acting benzodiazepine, is a theoretically better option than diazepam. However, the substantial evidence showing the efficacy of midazolam is limited. The dose of midazolam is for controlling spasm is 5-15 mg/hour [12]. Pondering upon the fact, Diazepam should be used to control the muscle spasm of a patient with tetanus.

Neuromuscular blocker: In a patient with tetanus on mechanical ventilation, the neuromuscular blocker can be used to control the

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muscle spasm if it continues despite the use of sedatives. Vecuronium is a short-acting neuromuscular blocker. It has minimal cardiovascular effects and it lacks histamine-releasing properties [13]. Fassoulki et al. reported the successful use of vecuronium in managing the two cases of generalised tetanus [14]. Other neuromuscular blockers like pancuronium and atracurium were used in the past to control the muscle spasm. However, their use was not recommended as Pancuronium causes tachycardia [15] and atracurium such as bradycardia and hypotension [16] which may trigger mortality in the patient with tetanus. Based on the above evidence, Vecuronium is now recommended to be used as a neuromuscular blocker in Tetanus.

Baclofen: Baclofen is a GABA-B receptor agonist that inhibits pre-synaptic acetylcholine release and synaptic medullar reflexes. The cumulative effects help in an anti-spastic action. They act by lowering calcium permeability in primary afferents. Intrathecal administration of baclofen had caused decrease muscle spasm in generalised tetanus. In a study by Santosh et al. of 22 patient with grade III tetanus treated by intrathecal baclofen with bolus dose followed by 20 ug/hour, 21 patients recovered [17]. A similar finding was reported by the prospected study conducted by the Guglielmino et al. that the use of intrathecal baclofen had a good response to treatment [18]. However, randomised controlled trial has not been conducted to confirm the aforementioned finding. Th adverse effects associated with intrathecal baclofen therapy are drowsiness and meningitis.

Management of autonomic dysfunction

Magnesium sulphate: Magnesium sulphate functions as a physiological antagonist of calcium at the cellular level causing vasodilatation, neuromuscular blockade and prevention of catecholamine release from the presynaptic neurons. Attygalle et al. reported in their observational study of 40 patients of generalised tetanus that Magnesium sulphate reduces the need of other drugs to control muscle spasm, autonomic instability and need for mechanical ventilation [19]. However, Mathew et al. in their prospective clinical trial among 33 patients of generalised tetanus where magnesium sulphate was used at a dose of 70 mg/kg followed by 0.5 g/hour 6 hourly demonstrated that magnesium there alone was not efficacious for treatment of severe tetanus [20]. Thwaites et al. in the randomised controlled trial conducted over 256 severe tetanus patients reduce the need for other drugs to control spasm and cardiovascular instability but didn't reduce the mortality and need of mechanical ventilation [21]. On meta-analysis of 3 studies by Rodrigo et al. reported that magnesium sulphate didn't reduce the mortality of the patients [22]. The therapeutic level of the magnesium sulphate to be maintained is 2-4 meq/L [19]. The adverse effects of magnesium therapy were hypocalcemia, hypotension, arrhythmia, respiratory depression and renal failure [17,20,22]. Based on the above evidence, Magnesium sulphate can be used as an adjunctive to other therapy to control muscle spasm and autonomic instability in a patient with generalised tetanus.

β Blockers: The autonomic instability which occurred to excessive release of adrenaline and noradrenaline was the most common cause of death among patients in mechanical ventilation [23]. Antisympathomimetic therapy should be considered only when adequately sedated, well hydrated and unstimulated patients have features of sympathetic overactivity [24]. Esmolol was used to treat to autonomic instability in generalised tetanus owing to its short-acting nature; however, the evidence is not adequate to recommend the use of esmolol routinely [25]. In a study done by Wesley et al. on 15 patients with generalised tetanus where labetalol was given to a patient with cardiovascular instability (Heart Rate >120/minute, Systolic blood pressure >160 mmHg, diastolic blood pressure >100 mmHg). Even though labetalol blocked both alpha and beta receptor, the blockage was profound on the beta receptor, this imbalance leads to depression in cardiac centrality without a significant increase in peripheral vasodilation [24]. Propranolol should be better avoided as there is a chance of sudden death with its use [26].

Other pharmacological drugs: Clonidine is the selective partial alpha-2 adrenergic receptor agonist, inhibits the sympathetic outflow in the central nervous system leading to bradycardia and hypotension. A case report Kumar et al. by the report the efficacy of clonidine in controlling the muscle spasm and sympathetic overactivity [27]. Gregorakos et al. reported the effectiveness of clonidine in maintaining the blood pressure in a patient with tetanus and autonomic dysfunction [28]. Rocke et al. reported that morphine in an average daily dosage of 103 ±36 mg reduces the blood pressure by 18% (P-0.07) and heart rate by 12% (P-0.01) [16]. Dolar D reported the successful use of atropine in the management of bradycardia of tetanus patients [29].

Controlling toxin production

Wound debridement: Surgical debridement of the wound is must to halt the toxin production in tetanus patient. Povidone-iodine 10% or cetrimide 15% and chlorhexidine gluconate 1.5% should be applied to the wound. All the tetanus prone wound which illustrated in Table 1. As listed World Health Organisation (WHO) should undergo soap water washing for at least 10 minutes and proper debridement [30]. The vaccination and use of immunoglobin as recommended by WHO during management of wound are illustrated in Table 2**.**

Antibiotics: Cambell et al. in their study reported that all isolated of Clostridium tetani from the wound of 45 patients with tetanus were susceptible to metronidazole and penicillin but resistant to co-trimoxazole [31]. A prospective study on tetanus where one group were given procaine penicillin 1.5 MU intramuscularly and another group metronidazole 500 mg 6 hourly for 7-10 days demonstrated that metronidazole group had lesser mortality than procaine penicillin group (7% *vs.* 24%) [32]. AV Ganesh Kumar et al conducted an open-label randomised controlled trial on tetanus patients making three arms of benzathine penicillin (1.2 million unit), metronidazole(600 mg QID for 10 days) and benzylpenicillin (2 million units 4 hourly for 10 days) which showed that three antibiotics were equally effective [33]. Penicillin produces non-competitive voltage-dependent inhibition

List of tetanus-prone wounds
Wound that requires surgical intervention and delayed by 6 hours
Punctured wound
Wound with devitalized tissue or foreign bodies
Wound with contact with soil or manure
Compound fracture
Wound with sepsis

Table 1: List of tetanus-prone wounds.

Age group	Tetanus Immunoglobin	TT or DTaP
<10 years	250 unit intramuscular	0.5 ml intramuscular or deep subcutaneous Stat, follow up doses at 6 weeks and 6 months
>10 years	250 unit intramuscular	0.5 ml Stat, follow up doses at 4 weeks and 8 weeks
NB: a dose of tetanus immunoglobin is 500 IU if the duration of the wound is more than 12 hours or risk of heavy contamination or if the patient weighs more than 90 kg. TT: Tetanus toxoid; DTap: Diptheria, attenuated Tetanus, Pertusis		

Table 2: Dosage of Tetanus Human Immunoglobin and tetanus toxoid for a patient with tetanus-prone wound.

GABA-A receptor and suppresses the postsynaptic inhibitory response [34] the above-mentioned evidence suggests that metronidazole is preferred as the first line antibiotic for Clostridium tetani.

Management of unbound toxin

Human Immunoglobulin: Human TIG (HTIG) neutralises the circulating tetanus toxin before it binds to neuronal cell membranes [10]. Randomised controlled trial conducted by Miranda Filho Dde et al. demonstrated that the duration of spasm, hospital stay and respiratory assistance is significantly shorter in intrathecally tetanus immunoglobin than intramuscular tetanus immunoglobulin (P-0.0001). In a meta-analysis of 942 patients from 12 trials by Kabura et al. concluded that intrathecal administration of tetanus immunoglobin is more beneficial than intramuscular administration in the treatment of tetanus (Relative risk-0.71, 95% CI,0.62-0.81) [35]. The cost of the drug, need of expertise in placing the spinal catheter and associated complications may limit the use of the intrathecal human immunoglobin. The dose of human tetanus immunoglobin is 500 IU via Intramuscular or intravenous route [36].

Supportive care

Airway management: The most common cause of death of generalised tetanus was an acute respiratory failure due to repeated muscle spasm [37]. Once the tetanospasmin reach to spinal cord it irreversibly inhibits the release of GABA forms inhibitory neurons for a prolonged period of time, hence, the airway management with a tracheostomy is warranted. Prolonged endotracheal intubation was associated with subglottic stenosis, vocal cord immobility and laryngeal granuloma [38,39]. Saeed et al. conducted randomised control trial among 60 patients with tetanus which showed that tracheostomy in the early stages group had lesser mortality than medically managed group (40% versus 66.7%) [40]. The caregiver may have a concern regarding the complications in early tracheostomy group, however, Waldron et al. reported that there was no difference in early tracheostomy versus emergency tracheostomy group [41]. The side effects of tracheostomy are haemorrhage, chest infection, tracheal stenosis, transcutaneous tracheal fistula etc.

Nutrition: Oral feeding is not possible in tetanus to due to the trimus. Once the muscle spasm gets controlled, enteral feeding should be started through a nasogastric tube. The high calories nutritional supplement is required to meet the high metabolic demand of tetanus for which total parental nutrition is preferred [42]. Other supportive measures are the deep vein thrombosis prophylaxis, foot drop splint to prevent ankle contracture, limb physiotherapy; care in dark room with minimal stimulus should be instituted to the entire patient with tetanus.

Strength: This article extensively reviews the various aspects of the management of the patients with tetanus in a simplified manner.

Limitation: The meta-analysis of the literature was not done. Even though authors have a serious concern to minimise the biases in choosing the article, this reviews may have some unintentional bias in selecting the article. This review doesn't include the results of unpublished research and conference proceeding.

Future direction: This review reflects the need to conduct multicentric randomised controlled trial with large sample size to confirm the efficacy of different therapeutics such as benzodiazepines, magnesium sulphate, baclofen and immunoglobin in the management of patients with tetanus.

Conclusion

For management of generalised tetanus, the evidence favours the use of Diazepam infusion for controlling muscle spasm, magnesium sulphate for autonomic instability, intrathecal human tetanus immunoglobin binding the unbound toxin, and early tracheostomy for airway management. For prevention, all tetanus-prone wound should undergo proper wound care with surgical debridement, tetanus toxoid vaccination, tetanus human immunoglobin administration, and antibiotic therapy.

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