

The value of a conscious patient in the intensive care management of tetanus - maximizing magnesium and minimizing midazolam

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The value of Mg therapy for patients with tetanus, which minimizes heavy sedation and paralysis in keeping with the goals of modern intensive care, is discussed.

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Times have changed - and more so in intensive care units (ICU). Gone are the days when patients were heavily sedated and paralysed. On the principle that it is "better to treat the disease than mask it", hypnotic sedation is minimized, with the goal of achieving a calm, lucid, pain free, interactive and co-operative patient, with reduced ICU stay, mortality and morbidity^{1,2}. The goals we require for tetanus are no different^{3,4}.

In the first half of the last century, tetanus patients were heavily sedated and nursed in quiet dark rooms. Mortality was high (30-70%), deaths being due to spasms causing early respiratory failure, aspiration, and exhaustion. In the latter half, the scenario changed, with patients being paralysed and ventilated in ICU. Mortality rates dropped (12-23%), deaths occurring later in the course of the disease due to sudden cardio-vascular events. Complications of prolonged ventilation with neuro-muscular blocking agents (such as ventilator acquired pneumonia, pulmonary embolism, atelectasis, sepsis, respiratory infections, malnutrition) also took their toll⁵.

Today in the 21st century new concepts of ICU management incorporate the PAD guidelines triad (Pain, Agitation, Delirium) and the ABCDE bundle (Awakening, Breathing, Coordination, Delirium monitoring, Exercise), the rationale being lighter sedation and earlier mobilization¹.

Traditional therapy with "heavy sedation"

Benzodiazepines and opioids were given in large doses (diazepam 40-150mg/day)⁵ for the control of paroxysmal spasms and autonomic dysfunction of

tetanus. Spasms were controlled, although the rigidity often persisted causing reduced chest compliance and hypoventilation requiring artificial ventilation. Sympathetic over-action (SOA) causing episodes of fluctuating tachycardia, labile hypertension, sweating and pyrexia needed additional beta blockade⁵. Parasympathetic over-activity caused profuse salivation and bronchial secretions. Accumulation, dependence and withdrawal agitation were added problems.

Magnesium sulphate therapy

Mg has the unique advantage of being able to reduce both spasms and autonomic dysfunction without sedation. By its central action it is a mild central depressant and an effective anti-convulsant. Peripherally, it competes with Ca ions for pre-junctional sites and inhibits release of acetyl choline. It reduces catecholamine release (from both adrenal medulla and adrenergic nerve endings), and receptor responsiveness. It competes with calcium in skeletal, smooth and cardiac muscle and is a generalized vasodilator, improving cerebral and renal blood flow. By antagonizing calcium metabolism, it causes muscle weakness (and even paralysis with toxic doses).

Thus, MgSO₄ should be used as first line therapy in tetanus titrated to the clinical end points of control of spasms and rigidity sufficient to allow swallowing of saliva, mouth care and physiotherapy, while maintaining adequate respiration which should be closely monitored^{3,4}. Clinicians should initially predict severity (Ablett classification) to individualize therapy.

The loading dose is 5g i.v. given over 20 minutes, and the maintenance dose 2g/hr, increased by 0.5 g/hr until spasms are relieved, or the patellar reflex disappears. The patellar reflex maybe an unreliable guide (unlike in pre-eclampsia) due to basal muscle rigidity, and is lost earlier in the elderly while within the therapeutic range³. Mg may safely be used for prolonged therapy as long as renal function is adequate.

Need for ventilatory support

Although in the majority of patients, Mg controls spasms and rigidity without the need for ventilator support or sedation^{3,6}, the elderly, and those with respiratory complications, will often need ventilatory support. Also in very severe tetanus with resistant rigidity, spasms or hypertensive crises, where very high doses of Mg (4-5g/h) are needed, respiratory depression may occur. Prolonged SOA in tetanus may sometimes end with profound hypotension and bradycardia, and Mg should then be discontinued or reduced, and spasms controlled with muscle relaxants and artificial ventilation³.

The effects of Mg are synergistic with other CNS depressants, cardiac depressants and neuromuscular blocking drugs and combinations should be used with caution. The danger is highlighted in the case report published in this journal. Thwaites⁷ showed that Mg therapy reduced the requirement of midazolam from 7.1 to 1.4mg/kg/day and pipecuronium from 2.3 to 0mg/kg/day to control spasms, and the need to treat SOA was 4.7 times less.

Overdose of Mg is easily detected clinically (warmth, flushing, double vision, slurred speech, muscle weakness). Toxic levels will cause severe cardiac and respiratory depression, but all effects are easily and immediately reversed with calcium gluconate i.v. ensuring safety.

The awake patient

With individualized infusion rates titrated to the changing needs of the tetanus patient, close clinical monitoring of the respiratory and cardiovascular systems, and sedation scoring, the goal of a conscious, cooperative, mobilized patient, tolerating enteral feeding should be achieved³.

Studies of outcomes in intensive care focus on mortality and duration of stay in ICU which give simple, concrete end points with finite numbers. Indeed most studies comparing Mg and traditional treatment conclude that Mg did not reduce mortality⁸. Mortality depends on the severity of the disease, age, co-morbidity and stage of presentation which factors clinicians have no control over. It is time studies focused on patient comfort and quality of life during their stay in ICU⁹. It is surely not acceptable for a patient to lie comatose on mechanical ventilation for a month (masking all symptoms) and wake up from the nightmare frightened, confused, agitated, unable to write his own name (due to neuropathy and myopathy). It would be far better to aim for a conscious patient able to communicate his needs, fears and distress. It is time to supplement sedation scoring with a patient perception scoring where comfort, communication, natural sleep, etc are assessed. The advantages of having a conscious co-operative patient without the complications of heavy sedation and ventilation, are well known to nursing staff and relatives. It would also have an immense cost-benefit, especially in countries where tetanus is widely prevalent and should be the goal of all clinicians, specially for long term intensive care. Mg used as first line therapy (with additives as and when necessary) should help achieve this for tetanus patients.

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A PROTOCOL FOR THE USE OF MAGNESIUM AS THE FIRST LINE THERAPY FOR TETANUS

This protocol is suitable for all patients diagnosed as tetanus having generalised muscle rigidity with or without spasms. Patients should be managed in a high dependency unit or ICU with immediate access to ventilatory support if needed.

DIAGNOSIS (Ablett classification):

Grade	Clinical Features
Grade 1(mild)	Trismus with little or no dysphagia
Grade 2 (moderate)	Trismus, dysphagia, generalised muscle rigidity with fleeting spasms, not embarrassing respiration
Grade 3a (severe)	Trismus, marked dysphagia and generalised muscle rigidity with severe spasms , embarrassing respiration
Grade 3b (very severe)	All symptoms of Grade 3a with autonomic dysfunction

History of injury: Not always present since the injury is often trivial.

History of immunization - Tetanus cannot be excluded if immunization was 7 years prior.

Clinical features: Diagnosis is based on clinical features which have a typical progression of descending rigidity of muscles first affecting the cranial nerves (trismus, dysphagia) then the trunk (opisthotonus, and generalised rigidity) and limbs. Spasms occur with intervening rigidity.

Negative findings: no alteration of consciousness, or CSF biochemistry.

Spatula test is very specific for tetanus.

Ask the patient to open the mouth and insert a tongue depressor gently to touch the back of the pharynx. Clamping down on the blade is positive and a gag response negative for tetanus.

ASSESSMENT OF SEVERITY

Incubation period (period between injury and first symptom) - <14 days predicts severe tetanus (with spasms).

Onset time (period between first symptom and first spasm) - < 72 hours predicts severe tetanus

Age > 60 years and co- morbid factors increase the morbidity and mortality.

Grading: Ablett classification of severity

MANAGEMENT

Neutralisation of the toxin:

Antitoxin should be given as soon as the diagnosis is made to neutralise the circulating toxin before it enters the CNS via axons. It has no action once the toxin is bound to the nerves.

Anti-tetanus serum –ATS- 5000U IM and 5000U infiltrated around the wound (after Sensitivity Testing) or

Human tetanus immunoglobulin 500IU IM
Toxoid first dose as soon as the diagnosis is made, the second dose after one month and the third after 6 months. The disease does not confer immunity.

Eradication of the organism

Wide wound debridement under general anaesthesia

Antibiotics – Metronidazole 500mg i.v. 8 hourly for 10 days (Penicillin is contraindicated since it is a GABA antagonist and will potentiate the tetanus toxin)

Prevention of early complications

Pulmonary aspiration and laryngeal obstruction are common causes of mortality in tetanus. Therefore, it is recommended that once the diagnosis is established, patient should be transferred to an ICU for monitoring and further care.

On admission to the HDU or ICU

1. USE MAGNESIUM AS FIRST LINE THERAPY
2. OMIT ALL SEDATIVES.
3. Maintain urine output at $>0.5 \text{ ml.kg}^{-1}\text{h}^{-1}$
4. Start on i.v. fluids and do not feed till the airway is protected

5. Airway protection

Send the patient to the operating theatre for the following under general anaesthesia :

- 1) Urgent early tracheostomy within 24 hours of diagnosis in all patients predicted to develop moderate or severe tetanus.
- 2) Insert naso-gastric tube for feeding
- 3) Wide debridement of the wound

6. Symptomatic management

Control of rigidity and spasms with intravenous magnesium therapy

Loading dose: 5g (80 mg/kg) in 30 mins

Maintenance dose to be started with:
 <60 years - 2 g per hour and ≥ 60 years or moderate tetanus (no spasms) - 1g per hour
 Increments of 0.5 g (<60yrs) or 0.25g (≥ 60 yrs) six hourly (as serum level takes 6 hours to achieve new level) till spasms are controlled.

If spasms are very severe the higher increment doses can be used. Titrate to the control of spasms and a degree of rigidity acceptable to the patient.

If the patellar reflex is suppressed (when the rigidity is severe the patellar reflex often cannot be

elicited) and spasms are not controlled continue to increase the dose but monitor respiration more carefully.

If spasms are uncontrolled with increasing respiratory rate $> 30/\text{min}$ or tidal volume (TV) $< 4\text{ml/kg}$, support ventilation but continue to titrate the Mg dose to spasms. Give chest physiotherapy and suction clearance. Continue ventilator support.

Once spasms are controlled, attempt to reduce the dose by 0.25g/hr, to ensure that the minimum effective dose is being given.

If hypotensive ($<80\text{mmHg}$ of systolic) or bradycardic ($<40\text{bpm}$) occur, STOP Mg.

If unresponsive, send blood for serum Mg^{2+} , stop Mg therapy, and give Ca gluconate i.v. When stable continue at a lower dose.

Titration of Mg dose after loading dose

Rigidity	Spasms	Patella reflex	TV	BP /HR	Adjustment of dose
++ After 6h	++ After 6h	+	Normal	Normal	Increase dose by 0.25- 0.5g/h. Monitor patella reflex & TV
++	+	-	Normal	Normal	Increase dose. Monitor TV. Prepare to support ventilation
+	-	-	Normal <4ml/kg	Normal	No support Ventilator support-SIMV/PS
Flaccid Deep sedated	-	-	<4ml/kg	LOW	Reduce dose to 2g/h & increase again when spasm commence.
Flaccid	+	-	<4ml/kg	LOW	Reduce dose & supplement with relaxants

Control of autonomic dysfunction

Magnesium therapy as in above

If hypotensive (<80mmHg systolic) stimulate patients, and if bradycardic (<40beats.min⁻¹) give atropine.

If hypertensive (>170 mmHg systolic) or tachycardic (>120 beats.min⁻¹ for > 1 hour), give intravenous morphine.

Sedatives and muscle relaxants

In the event of maximum therapeutic range of Mg being reached or if Mg toxicity occurs, sedatives and neuromuscular blockers can be supplemented. As a sedative, Midazolam is preferred over diazepam.

7. Monitor

- a. Hourly urine output (>0.5ml/kg/h)
- b. Ability to cough, patellar reflex, respiratory rate, tidal volume, arterial blood gases
- c. Blood pressure, ECG, pulse oximetry
- d. 12 lead ECG every third day and daily if serum Mg exceed therapeutic levels.
- e. Chest X-ray after tracheostomy
- f. Sedation score
- g. Serum Mg daily, more frequently if signs of overdose are seen (normal range : 2-4 mmol/l)
- h. Clinical signs of hypocalcaemia and serum calcium every third day
- i. Serum electrolytes, albumin, blood sugar, urinary urea

The elderly group show signs of suppression of patellar reflex, respiratory inadequacy

and even cardiac depression before 4mmol/l are reached and therefore require support much earlier.

8. Supportive therapy

Tracheostomy care:

Maintain humidification

Suctioning can induce spasms. It may have to be done regularly if secretions are profuse.

Check the tracheostomy cuff pressure 8 hourly.

Careful management of tracheostomy site by application of dry dressings 4 hourly.

Adhere to ventilator care bundle

Head up tilt of 30 degrees

LMWH(enoxaparin) 1mg/kg subcutaneously if no contraindication

Gastric ulcer prophylaxis

Oral care - Chlorhexidine mouth washes at least 3 times a day

Feeding

Start feeding after tracheostomy. Continuous drip feeding via the nasogastric tube is best.

Energy requirement- 35kCal/kg/day (can go up to even 40-45kCal/kg/day)

Constipation is a problem.

Add laxatives and fiber to the diet.

Physiotherapy specially to the chest and limbs are important and may need sedation.

Maintain constant communication to keep up the morale of the patient.

Attempt mobilising patient in the 2nd week.

Attempt weaning fromMg in the 3rd week.

Fill the communicable disease surveillance forms for tetanus.