



Large versus Small Dose Magnesium Sulfate Infusion in Tetanus

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ABSTRACT

Introduction: Evidence based guidelines regarding the use of magnesium sulfate in tetanus is lacking. Hence, our objective was to compare two infusion doses of magnesium sulfate to control the tetanic spasms.

Methods: Data of 14 adult male patients admitted in the intensive care unit were retrieved. Twelve adult ventilated patients received magnesium infusion as an adjunct to diazepam therapy to control tetanic spasms. We retrospectively divided them into two groups for comparison. Group 1 patients (n=7) received a smaller dose (<1 g.h⁻¹) than group 2 (n=5) (1.5 to 2 g.h⁻¹).

Results: The duration of symptoms before arrival to hospital was significantly longer in group 1 than group 2. The Ablett severity grade was II in three patients in group 1 and III in all patients of group 2. In Ablett severity grade III patients, the diazepam dose used was significantly higher in group 1 (n=4) (292±48 mg.d-1) than group 2 (n=3) (106±9 mg.d-1) as magnesium infusion dose was restricted due to hypotension in group 1. Amongst the patients who received MgSO₄ for ≥10 days, the requirement of diazepam was significantly reduced in the second week (174.1±59.2 mg/d) than the first week (325.4±105.9 mg.d-1) of infusion in group 2 (n=4) but not in group 1 patients (n=4).

Conclusions: The larger dose of MgSO₄ infusion was titrated to control tetanic spasms as an adjunct to diazepam in select group of patients without hypotension. Uncontrolled hypotension, cardiac arrhythmia and renal failure were the factors to limit its infusion dose.

Keywords: MgSO₄; magnesium sulphate; tetanus.

INTRODUCTION

Tetanus is resurging globally due to rise in acquired immunodeficiency syndrome, use of immunosuppressive drugs and increased migration of the unimmunized population.¹ Its management is challenging because of uncertainty about the optimum care of the respiratory compromise and the cardiovascular instability.²

Magnesium sulfate has been reported for the treatment of tetanus since 1906.³ It controls spasms and the associated sympathetic over activity, hence minimizes the use of artificial ventilation and sedation.⁴ However, it can cause muscle weakness, hypotension

and bradyarrhythmia.⁵ Magnesium sulfate has been investigated as a therapeutic option in variable infusion doses ranging from 80 mg to 4 gm per hour.^{1,6-8} Since there is no report on the comparison of different infusion doses, we carried out this retrospective study to compare the outcome of the two different infusion doses used in our intensive care unit (ICU).

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METHODS

In this retrospective observational study, the hospital records (paper based as well as electronic) were reviewed for the period of the four years (from 2007 to 2011) after obtaining clearance from the institutional ethical review board of B. P. Koirala Institute of Health Sciences. Total 84 patients suffering from tetanus got admitted to hospital emergency unit and overall 14 tetanus patients got admitted in our general intensive care unit (ICU). Rest of the patients had no access to ICU because of non-availability of beds.

These 14 patients were identified and their data were retrieved from the ICU record (paper based) as well as the central hospital record section (electronic). A predetermined data abstraction form was filled by the principal investigator for the detailed retrospective data recording and analysis. From the record of fourteen ICU patients, after initial management in the emergency unit, the majority of patients ($n = 11$) had a varied period of the treatment in the medical ward before getting bed in the ICU where magnesium sulfate infusion was given. Only three patients were directly transferred to ICU from the emergency unit and received magnesium sulfate infusion immediately.

Management of all the patients included cleaning and debridement of the wound, administration of intravenous metronidazole, and human tetanus immunoglobulin and intramuscular tetanus toxoid. In addition a titrated dose of diazepam was given as a continuous intravenous infusion with intermittent top up boluses as and when necessary. Subsequent general management included administration of subcutaneous heparin, intravenous antibiotics, stress ulcer prophylaxis and enteral nutrition. Other supportive therapy included skin and oral care, chest and limb physiotherapy, early tracheostomy and tracheal suctioning. In ICU, all the patients received mechanical ventilator support. This was followed by administration of intravenous magnesium as per our protocol to control tetanic spasm. In group 1 ($n = 7$), small infusion dose ($< 1 \text{ g.h}^{-1}$) of magnesium sulfate was given in patients requiring diazepam infusion ($< 15 \text{ mg.h}^{-1}$) or if patients were hypotensive (systolic arterial blood pressure $< 90 \text{ mmHg}$) requiring inotrope infusion. The magnesium sulfate infusion was titrated to keep tetanic spasms less than two episodes in one hour and the mean arterial pressure above 60 mmHg .

In group 2 ($n = 5$), larger infusion dose (1.5 to 2 gm.h^{-1}) of magnesium sulfate was used in patients where tetanic spasms were refractory to intravenous diazepam ($> 15 \text{ mg.h}^{-1}$) infusion. After the intravenous loading dose of 40 mg.kg^{-1} given over 30 min, magnesium was infused at 1.5 g.h^{-1} in patients weighing $\leq 45 \text{ kg}$ and 2 g.h^{-1}

weighing $> 45 \text{ kg}$. Magnesium infusion was titrated to control tetanic spasms as above.

Patients receiving magnesium were closely monitored for the signs of its toxicity with continuous ECG monitoring, hourly urine output, knee jerks every four hour, 12 lead ECG and serum calcium everyday and serum magnesium on alternate days. Magnesium was not administered to patients with serum creatinine greater than 2 mg.dL^{-1} , urine output less than $1 \text{ ml.kg}^{-1}.\text{h}^{-1}$, ECG evidence of conduction abnormality or arrhythmia, or hypotension {systolic blood pressure (SBP) $\leq 80 \text{ mmHg}$ } unresponsive to fluid challenge of 500 ml crystalloid and/or inotropic support. If a patient developed hypotension during magnesium infusion, inotropic support was started and magnesium dose titrated to keep the mean blood pressure above 60 mmHg . If urine output fell but not lower than $0.5 \text{ ml.kg}^{-1}.\text{h}^{-1}$, then magnesium dose was lowered on the discretion of the treating intensivist.

All the patients were given slow intravenous boluses of thiopental (50 mg) before the endotracheal suctioning or changing positions and until the spasms got controlled. Control of spasm was defined as less than two brief episodes of spasm in one hour.⁶ Vecuronium was added only if spasms were refractory to the above therapy.

Intravenous morphine (0.1 mg.kg^{-1}) was administered every 4-6 hours if autonomic dysfunction occurred (unexplained SBP $> 160 \text{ mmHg}$ or heart rate $> 120 \text{ bpm}$ sustained for more than one hour).⁶ In addition, hypotension was managed with fluid boluses and inotropes (dopamine and/or noradrenaline) as required. We compared the two groups for the patient characteristics, injury sites, Ablett grades (table 1),⁹ need for the inotropic support, diazepam requirement to control tetanic spasms, duration of ventilation, length of ICU stay and hospital stay and the outcome.

Statistical analysis: The collected data were entered into Microsoft Excel Spreadsheet and analyzed using SPSS version 11.5. To make comparisons between the two groups, Fisher exact test was used for categorical values and Man Whitney U test for not normally distributed continuous data. Wilcoxon signed ranks paired test was applied to analyze the weekly change in diazepam requirement after starting magnesium therapy within each group. A P value of < 0.05 was considered significant.

RESULTS

Out of the 14 patients transferred to ICU for mechanical ventilation, two patients did not receive magnesium therapy as one died within two hours of ICU admission

and the other developed acute renal failure (fig 1). Early tracheostomy was performed in all patients. Median (interquartile range) time to tracheostomy was 3.5 (0.5-24) hours after the arrival of patients in the hospital. The duration of symptoms before arrival to hospital was significantly longer in group 1 than group 2 (table 2). The Ablett severity grade of tetanus was <III in three patients in group 1 and was III in all the patients in group 2.

All the patients had well controlled spasms with either doses of the magnesium infusion. However, in group 1, the patients with Ablett severity grade III (n=4) required significantly (p<0.05) larger doses of diazepam (12.2±2.0 mg.h-1) to control the tetanic spasms compared to patients with Ablett severity grade II (n=3) (4.4±0.4 mg.h-1). The dose of magnesium infusion in

these four patients requiring larger amount of diazepam in group 1 could not be increased as they developed significant hypotension and cardiac arrhythmia (fig 1). Four patients in group 2 recovered and were discharged from the ICU after 21 (14-25) days and none of them expired while only two patients recovered in group 1 and were discharged from the ICU after 36 (32-41) days and two expired due to septicemia. Three patients from group 1 and one from group 2 left against the medical advice on the request from relatives who were not interested to pursue therapy due to financial problems (table 3).

Table 1. Showing the Ablett grades classification for severity.

Grade	Clinical Features
I (mild)	Mild trismus, general spasticity, no respiratory embarrassment, no spasms, no dysphagia
II (moderate)	Moderate trismus, rigidity, short spasms, mild dysphagia, moderate respiratory involvement, respiratory rate > 30, mild dysphagia
III (severe)	Severe trismus, generalized spasticity, prolonged spasms, respiratory rate > 40, severe dysphagia, apnoeic spells, pulse > 120
IV (very severe)	Grade 3 plus severe autonomic disturbances involving the cardiovascular system

Table 2. Summary of the characteristics of patients and disease. Values are expressed as mean ±SD, number or median (interquartile range) as applicable.

	Group 1 (n=7)	Group 2 (n=5)
Magnesium sulphate infusion (g.d-1)	6.03±3.5	41.1±6.0
Age	50 (45-58)	40 (24-56.5)
Age ≥50 : <50 y	5:2	2:3
Site of trauma foot : hand : none	6:1:0	4:0:1
Incubation period (day)	6 (4-10)	7 (2-18.5)
≤7 : >7d	4:3	3:1
Unknown	0	1
Duration of symptoms before arrival (d)	2 (1-5)*	2 (1.5-2.5)*
Time interval between the first symptom and transfer to ICU	1:6	1:4
Transferred to ICU after first symptom (d)	4(1-5)	7(4-12)
Ablett grade II: III: IV	3:4:0	0:5:0
Patients requiring inotropic support	4	2
Patients requiring paralysis	5	2

** - p<0.05- statistically significant difference

Table 3. Comparison on the patient outcome between groups. Values are expressed as median (interquartile range).

	Group 1 (n = 7)	Group 2 (n = 5)	
Outcome recovered:died:LAMA	3:2:2	4:0:1	
Duration in ICU (d)	26 (7-32)	21 (8-24)	
Length of ventilation (d)	22 (7-30)	13 (7-21)	
Duration of hospital stay (d)	34 (9-42)	37 (19.5-39)	
Complications	Ventilator associated pneumonia/ARDS	3	2
	Acute coronary syndrome	1	0
	Metabolic acidosis	1	0
	Acute renal failure	1	0
	Hypotension (mean arterial pressure <60 mmHg)	5	0
	Bradycardia (heart rate <50 bpm)	1	0

When data of the patients who received magnesium sulfate for ≥ 10 days (n=8) were analyzed in two groups, the amount of diazepam needed to control tetanic spasms in group 2 was significantly ($p < 0.05$) lower by 151.3 ± 79.1 mg.d⁻¹ in the second week than the first week of magnesium therapy in group 2 (n=4). However in group 1 (n=4) the diazepam doses in first week remained insignificantly affected on both the weeks (fig 2).

One patient in group 1 who received higher dose diazepam therapy (30 mg.h⁻¹), developed lactic acidosis and midazolam was used instead of diazepam. Ventilator associated pneumonia and hypotension were the most frequent complications during ICU stay (table 3).

DISCUSSION

Role of diazepam in controlling spasm in tetanus is well established and has been used in various doses; up to 100 mg.hr⁻¹ in tetanus patients on ventilator.² However, a continuous high dose infusion for longer duration may cause lactic acidosis because of its preservative propylene glycol.¹⁰ In our ICU, we too had one patient in whom diazepam was stopped because of the severe lactic acidosis and instead midazolam was used to control the tetanic spasms.

A combination therapy of magnesium sulfate and diazepam has been reported to reduce the dose requirements of each drug to control the tetanic spasms and the autonomic dysfunction with a possibility of reducing side effects of each drug.^{3,6,7} We too observed that the diazepam requirement was significantly reduced from 13.6 mg.h⁻¹ in the first week to 7.2 mg.h⁻¹ in the second week after the titrated infusion of magnesium

sulfate. However, this finding has to be interpreted with caution because the reduction in dose might be a part of natural disease process itself. A randomized control trial involving a larger sample size is awaited to explore this observation. As the magnesium has a narrow therapeutic window, use of titrated dose in combination with benzodiazepines to control tetanic spasms may be safer than using it as a sole agent at very large doses (2-3.5 g.h⁻¹).⁴ Use of magnesium as a sole agent to control tetanic spasms in higher dose (2-3.5 g.h⁻¹) was proposed by Attygalle and colleagues to control spasms without sedation and possibly the mechanical ventilation to avoid related complications.⁴ In contradiction, the only randomized controlled trial on the magnesium infusions in tetanus did not support the argument of avoiding mechanical ventilation in adults with severe tetanus and, 74% patients needed mechanical ventilation during magnesium infusion.⁷ Attygalle and colleagues in their subsequent series of 40 patients also used a reduced dosage of magnesium (1-2 g.h⁻¹).¹¹

Evidence based guidelines on the dose of magnesium sulfate in tetanus is lacking. It has also been used as an adjunct to diazepam therapy in doses as low as 80 mg.h⁻¹ Either dose of magnesium sulfate infusion that we used as an adjunct to diazepam therapy in our patients requiring positive pressure ventilation was associated with adequate control of tetanic spasms. However, in a prospective clinical study of thirty two tetanus patients, larger dose magnesium sulphate (>1g.h⁻¹) along with diazepam infusion did not control spasms in six and required neuromuscular paralysis.⁶

Whether magnesium causes centrally mediated sedation or not is still a matter of debate. Its infusion decreases

tidal volume, vital capacity and increases secretions, inability to cough and the need the mechanical ventilation at high doses.² Temporary muscle weakness and paralysis have also been reported.² As suggested by James et al,¹² we also propose that use of magnesium in severe tetanus outside ICU is unsafe and the magnesium therapy for tetanus should not be used in the absence of facilities for the mechanical ventilation and the invasive hemodynamic monitoring.

Magnesium causes presynaptic neuromuscular blockade, inhibits the release of catecholamine and adrenoceptor sensitivity to the released catecholamine. It also causes vasodilatation and has an anticonvulsant properties.² All these properties are desirable in controlling spasms and the sympathetic over activity in tetanus, however, it can lead to hypotension. We found that all our patients, in whom larger dose of magnesium infusion were infused, also required dopamine and adrenaline infusion to support the arterial blood pressure.

Tracheostomy was performed within 48 hours of arrival at hospital in all our patients. It has been found that the tetanus patients with an early tracheostomy stood the best chance of survival and recovery.¹³ A delayed tracheostomy is associated with more chance of aspiration of secretions into the tracheobronchial tree and the consequent bronchopneumonia.¹³ An early tracheostomy and positive pressure ventilation were used in all of our ICU patients in whom magnesium infusion was used and we too suggest the same.

In patients with renal compromise, magnesium can accumulate to an unacceptably high toxic level. Since magnesium can lower heart rate and blood pressure,² it may worsen already existing hypotension or lead to life threatening bradyarrhythmia. Magnesium therapy had to be discontinued in one fifth of patients because of emerging contraindications like acute renal failure, ECG changes, hypotension and cardiac arrest in a Vietnam study involving a large number of patients.⁷ Similarly,

uncontrolled hypotension, cardiac arrhythmia and renal failure were the factors to limit the infusion dose of magnesium sulfate ($< 1 \text{ g.h}^{-1}$) in our patients.

In our study, a patients receiving the smaller dose of magnesium were older than the other group and were not as sick and had longer onset of symptoms, and so perhaps were in the waning phase of the tetanus. It is possible that these dissimilarities in the two groups could have affected results.

Other limitations of our study a include its retrospective nature with inherent weakness of data loss. For example, we could not compare the onset time (time from first symptom to first spasm), an important indicator of severity in tetanus, and the serum levels of magnesium as these were not documented in majority of our patients. There is a small sample size as less number of tetanus patients are coming to ICU. A significant number of patients in ICU were taken away home by their relatives against medical therapy due to financial constraint with poor socio economic status or the disbeliefs in the disease outcome. This could also obviate the outcome data in our study.

CONCLUSIONS

The large doses ($1\text{-}2 \text{ g.h}^{-1}$) of MgSO_4 infusion may be appropriate in a select group of tetanus patients on ventilator support. Its dose needs to be titrated to control tetanic spasms as an adjunct to diazepam in patients where hypotension is a limiting factor. Renal failure and arrhythmias can also limit the dose of infusion. Prolonged infusion (≥ 10 days) of the magnesium in large doses may reduce the diazepam requirement but large prospective controlled trials may be helpful in addressing this issue.

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