Magnesium Sulfate Use in Adult Patients with Tetanus at Mariano Marcos Memorial Hospital & Medical Center

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Abstract

Objective. This study aimed to determine whether adjunctive therapy with magnesium sulfate is more effective than diazepam alone in reducing mortality and morbidity rates among adult patients with tetanus admitted to Mariano Marcos Memorial Hospital and Medical Center (MMMH & MC) from January 1, 2012, to January 1, 2022.

Methods. Retrospective cohort study using chart review and descriptive statistics.

included patients admitted at East Avenue Medical Center for DFU. The primary endpoint was major amputation of the lower extremities. Data were analyzed using Receiver Operating Characteristic (ROC) analysis and logistic regression.

Results. A total of 51 patients were included in the study, with 17 patients in the adjunct magnesium sulfate group and 34 patients in the diazepam group. Based on the results of this study, at a 95% confidence interval, ICU stay was significantly longer in the magnesium sulfate group compared to the diazepam group, along with an increased average hospital stay. There was no significant difference in patient mortality in terms of treatment, age, severity, ICU stay, or duration of mechanical ventilation.

Conclusion. The use of magnesium sulfate as an adjunct treatment for tetanus is not superior to standard stand-alone diazepam, regardless of severity. Magnesium sulfate use is associated with a longer overall hospital stay. Lastly, hospital-acquired pneumonia and aspiration pneumonia significantly increase the risk of mortality among patients with tetanus, regardless of age, treatment, or severity.

Keywords. Tetanus, Magnesium Sulfate, Diazepam, Adjunctive Therapy

Introduction

Tetanus is a life-threatening disease prevalent in third-world countries, requiring advanced medical care. Sedation and ventilatory support are the mainstays of management, but they are not always available in developing countries where the disease is common. The complications of tetanus, resulting in long-term sedation and artificial ventilation, contribute to 60% of total mortality.[1]

The mainstay and initial treatment is sedation with benzodiazepines to control muscle rigidity, spasms, and autonomic dysfunction. However, there is a lack of comparative or controlled studies on the treatment approach for autonomic dysfunction.[3]

Magnesium sulfate is a promising treatment that has been used in the management of spasms and autonomic overactivity.[4] However, magnesium sulfate alone has been found to be inadequate as a sedative and relaxant, but is an effective adjunct in controlling autonomic disturbance.[3]

In one meta-analysis conducted by Rodrigo et al., there was no evidence that magnesium sulfate affects mortality in patients with tetanus. Whether it changes the total duration of ICU stay or hospital stay remains uncertain, as different studies have provided conflicting results.[7]

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Conducting trials on different treatment modalities for tetanus is challenging due to both logistical and ethical reasons. However, it is imperative that physicians be aware of the best evidence-based treatment strategies currently available to improve patient outcomes. Without timely diagnosis and proper treatment, severe tetanus is fatal, with mortality also influenced by the patient's comorbidities.[2]

MMMH & MC is the only Department of Health accredited tertiary hospital located in the northwestern Luzon region of the Philippines and aims to be the premier center of healthcare in Ilocandia. As an apex hospital situated in an agricultural community with diverse geographical features that pose challenges to specialized healthcare provision, it primarily serves Region 1, the northern Cordillera Autonomous Region, and northern Region 2. Tetanus remains one of the reasons for referral to the institution. Magnesium sulfate was first introduced as an adjunct muscle relaxant for tetanus when the supply of conventionally used intravenous benzodiazepines became scarce, prompting the search for alternative muscle relaxants.[6] However, magnesium sulfate use is generally more tedious, requiring titration, tapering, and serial serum level monitoring compared to benzodiazepines.[13] For this reason, its use may be challenging in any clinical setting, hence the need to further study its clinical benefit in the management of tetanus.

Lastly, results from different studies regarding the use of magnesium sulfate in tetanus have been conflicting, and there are not enough recent studies on its use. This study aims to determine whether adjunctive therapy with magnesium sulfate is more effective than diazepam alone in reducing mortality and morbidity rates among adult patients with tetanus grades I–III. Specifically, it seeks to: describe the demographics of adult patients with tetanus admitted to MMMH & MC, compare patients treated with adjunct magnesium sulfate or diazepam alone in terms of mortality based on demographic (age > 60 and < 60 years old) and clinical criteria (severity of tetanus by Ablett classification I–III); length of ICU and/or ward hospital stay (in days), and duration of mechanical ventilation (in days); and determine the factors associated with mortality.

Methodology

A retrospective chart review was conducted on 89 patients admitted with tetanus from January 1, 2012, to January 1, 2022. Patients aged 19 years old and above who were clinically diagnosed with tetanus admitted to MMMH & MC, and who were treated with diazepam alone or with adjunct magnesium sulfate, were included in the study. Patients who were pregnant or had and underlying or coexisting chronic kidney disease or chronic renal insufficiency, cardiac dysrhythmia, psychological impairment and who were previously treated with magnesium sulfate and/or any benzodiazepines, on mechanical ventilation at another institution prior to admission at the study site were excluded. Data were extracted through a review of the patient's clinical history and ward course. The significant sample size was computed with a 5% margin of error and a 95% power to detect a difference, using the proportion of tetanus cases in MMMH & MC from 2012-2022 to the total tetanus cases in the Philippines from 2012-2021, as reported by the WHO, which is 1.3%.[9] The sample size was calculated using the Lynch's formula, which yielded a required sample size of 17.[12] Microsoft Excel was used to tabulate and summarize the data gathered.

This research was reviewed and approved by the institutional Research Ethics Review Committee.

Results and Analysis

A total of 51 patients were included in the study; 34 patients were treated with diazepam alone, and 17 patients received adjunct magnesium sulfate. Descriptive statistics were used to summarize the demographic and clinical characteristics of the patients. Frequency and proportion were used for categorical variables, the median and interquartile range were used for non-normally distributed continuous variables, and the mean and standard deviation (SD) were used for normally distributed continuous variables.

The Independent Samples t-test, Mann-Whitney U test, and Fisher's exact/Chi-square test were used to determine differences in mean, rank, and frequency, respectively, between patients treated with magnesium sulfate and those treated with diazepam alone. The odds ratio and corresponding 95% confidence intervals from binary logistic regression were computed to identify significant predictors of mortality. All statistical tests were two-tailed. The Shapiro-Wilk test was used to assess the normality of continuous variables. Missing values were neither replaced nor estimated. Null hypotheses were rejected at a 0.05 α-level of significance. STATA 13.1 was used for data analysis.

Table 2: Factors Associated with Patient's Mortality

Parameters	Crude odds ratio	95% CI	P-value
Treatment group			
Magnesium Sulfate	1.2429	0.2593 to 5.9564	0.786
Diazepam Alone	(reference)	-	-

Age, years	0.9832	0.9340 to 1.0351	0.519
< 60	1.0897	0.2298 to 5.1674	0.914
≥ 60	(reference)	-	-
Ablett class			
Class I	(reference)	-	-
Class II	0.1939	0.0213 to 1.7604	0.145
Class III	-	-	-
HAP/Aspiration Pneumonia			
With	18.083	2.0063 to 162.99	**0.010**
Without	(reference)	-	-
ICU stay, days	0.9857	0.8787 to 1.1057	0.806
Ward stay, days	-	-	-
Mechanical Ventilation use, days	1.0721	0.8572 to 1.3409	0.542

Table 2 presents the factors included in the study to determine their association with the mortality of tetanus patients. There was no significant difference in patient mortality concerning treatment, age, severity, ICU stay, or duration of mechanical ventilation. There was no statistically significant difference in the incidence of HAP/aspiration pneumonia between the diazepam-only group and the group receiving adjunct magnesium sulfate. However, regardless of treatment, patients with HAP/aspiration pneumonia had an 18.083 times higher risk of death compared to those without these complications. In a study by Kole et al., which assessed the use of magnesium sulfate alongside diazepam in moderate to severe tetanus cases, the incidence of aspiration pneumonia decreased from 10% in the diazepam-only group to 5% in the combination group. Although this reduction was not statistically significant (P = 0.149), it suggests that adding magnesium sulfate to standard therapy may help lower the risk of pneumonia.[14]

Discussion

Vaccination has significantly reduced the incidence of tetanus, but cases remain high in Africa and Southeast Asia.[8] Management primarily involves sedation and ventilatory support; however, these are not always available, especially in developing countries. Their limited availability contributes to 60% of the total mortality.[1]

The principles of treating tetanus include reducing muscle spasms, rigidity, and autonomic instability (with ventilatory support when necessary); neutralizing the tetanus toxin with human antitetanus immunoglobulin or equine antitetanus sera; wound debridement; and administering antibiotics to eradicate locally proliferating bacteria at the wound site.[2]

Autonomic instability is a major concern and usually develops a few days after the onset of the disease. Manifestations include labile or sustained hypertension, tachycardia, arrhythmias, hyperpyrexia, profuse sweating, peripheral vasoconstriction, hypotension, and bradycardia. Dysrhythmia and myocardial infarction are the most common fatal events.[4]

Benzodiazepines remain to be the mainstay treatment for tetanus and have gained popularity over other agents due to their combined muscle relaxant, anticonvulsant, sedative, and anxiolytic effects, which are particularly useful in managing patients with tetanus.[2]

Magnesium sulfate is a promising treatment that has been used in the management of spasms and autonomic overactivity. By competitively inhibiting calcium channels, similar to calcium channel antagonists, it decreases calcium availability at presynaptic terminals, causing presynaptic neuromuscular blockade, blocking the release of catecholamines, and reducing receptor sensitivity to released catecholamines. In addition, it has anticonvulsant and vasodilator properties. Thus, patients with tetanus who suffer from repetitive spasms may benefit from the use of magnesium sulfate thereby, potentially reducing the need for mechanical ventilation.[4,8] Despite these principles supporting its utility, the safety of magnesium sulfate has not been well established in tetanus patients.[8]

In one study, researchers concluded that magnesium sulfate in combination with diazepam may be a better option for the treatment of tetanus, particularly in developing countries with limited intensive care facilities,

due to its morbidity and mortality benefits.[5] However, a systematic review done by Nepal et al. found that magnesium sulfate has no mortality benefit but is effective in reducing spasms when used alongside diazepam, leading to better control of dysautonomia, a reduced need for mechanical ventilation, and a shorter hospital stay by 3–7 days. The incidence of magnesium toxicity was very low in the studies reviewed.[8]

Based on the results of this study, the use of magnesium sulfate as an adjunct to diazepam, compared with diazepam alone, showed no significant differences in age (p=0.271), occurrence of hospital-acquired pneumonia (p=0.365), duration of mechanical ventilation (p=0.171), and mortality (p=1.0). These results do not align with a systematic review that suggested magnesium sulfate reduces the need for mechanical ventilation.[8] However, they are consistent with findings from the largest RCT, which showed no statistically significant reduction in ventilation needs with magnesium sulfate use in severe tetanus.[10]

On the other hand, the use of magnesium sulfate as an adjunct showed a significant difference in terms of severity (p=0.007), with more patients in Ablett Class III receiving magnesium sulfate. The preference for magnesium sulfate in more severe tetanus cases may be due to physicians' clinical decisions based on its hypothesized role in reducing dysautonomia. Additionally, ICU stays were significantly longer among patients treated with adjunct magnesium sulfate compared with those treated with diazepam alone (p<0.001), whereas patients receiving only diazepam had significantly longer ward stays (p=0.024).

Overall, the use of magnesium sulfate significantly increased the average hospital stay (Mean = 17 days) compared to diazepam alone (Mean = 12 days). One factor contributing to the longer ICU stay may be the severity of tetanus, as magnesium sulfate is typically reserved for more severe cases. Additionally, the magnesium sulfate protocol requires serial magnesium monitoring every six hours and continuous cardiac monitoring, which would be challenging in a ward setting. Furthermore, patients requiring adjunctive magnesium sulfate were often high-grade tetanus cases, classified as Class III and IV on the Ablett scale, necessitating intensive care. Other factors depend on overall dysautonomia control and effective spasm management. However, this finding contradicts the systematic review, where most studies indicated that magnesium sulfate shortened hospital or ICU stays compared with diazepam alone.[8] A shorter hospital stay can be beneficial in reducing hospital costs and potentially lowering hospital-acquired infection rates due to earlier discharge.

The difference in mortality was also not significant in this study consistent with findings of a systematic review that reported no significant reduction in mortality among tetanus patients treated with magnesium sulfate compared with diazepam alone.[8]

This study also identified a significant factor associated with higher mortality among tetanus patients. This was the occurrence of HAP or aspiration pneumonia (OR 18.083, 2.0063–162.99, p=0.010). This finding supports a study indicating that in-hospital mortality rates were significantly higher among patients with complications, with hypoxemia and aspiration pneumonia being the most common.[11]

However, age, severity, and mechanical ventilation use did not emerge as significant factors contributing to increased mortality. The lack of significance for age contradicts one article stating that patients aged ≥60 years have a higher likelihood of death. One possible reason for this discrepancy could be the small sample size for patients over 60 years old. Additionally, severity may not be a reliable predictor of mortality, and the case-fatality rate among mechanically ventilated patients appears to be lower.[13]

This study also supports findings that, despite no improvement in mortality rates when comparing magnesium sulfate with benzodiazepines and combined treatment groups, there was no reported increase in mortality among patients receiving magnesium sulfate therapy.[8]

There are several limitations to this study worth mentioning. No patients were diagnosed with tetanus Ablett Class IV, which may have been underdiagnosed by physicians. Data collection was limited to information recorded in medical charts. Additionally, some patients included in the study were treated with midazolam in addition to or as a replacement for diazepam, which could have influenced the mortality and morbidity outcomes.

Conclusion

In this study, we found that the use of magnesium sulfate as adjunct treatment to tetanus is not superior to standard stand-alone Diazepam in reducing morbidity and mortality. Magnesium sulfate use is associated with longer overall hospital stay. However, hospital-acquired pneumonia and aspiration pneumonia greatly increases the risk of mortality among patients with tetanus regardless of age, treatment (benzodiazepine with or without magnesium sulfate), and severity.

Recommendations

1. Diazepam can be used as stand-alone treatment of tetanus Ablett Class I-III.
2. Preventive strategies to reduce risk for aspiration pneumonia and hospital-acquired pneumonia should be implemented to reduce mortality risk.
3. Further study on the benefits of diazepam over magnesium sulfate use among tetanus patients in reducing morbidity and mortality.

4. Further study on the potential use of diazepam alone in the management of tetanus among hospitals with limited access to intensive care.

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