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Effect of magnesium sulfate administration on the survival of adult and pediatric non-neonatal tetanus patients in a tertiary hospital in the Philippines: A retrospective cohort study

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Abstract

Background & Objective: Locally, there are no recommendations on the use of magnesium sulfate (MgSO4) among tetanus patients. Moreover, some neurologists are unaware of its benefits in this cohort. Most start MgSO4 only when the patients are in the severe stage, have signs of dysautonomia, or if the physician is confident in its administration. This paper will determine the effect of MgSO4 on the survival of adult and pediatric non-neonatal tetanus patients in a tertiary hospital in the Philippines. *Methods:* This study utilized a retrospective cohort study design. Data from a previous study by Lanuza *et al.* (2024) was utilized. Baseline comparisons of MgSO4 versus non-MgSO4 groups were done using Wilcoxon rank sum test or independent t-test for continuous data while a Fisher Exact test was used for comparison of proportions. Those with a p-value lower than 0.2 were used for Cox regression analysis. *Results:* Crudely, survival is better in the MgSO4 group, and although this became non-significant when confounders were accounted, the survival in the MgSO4 group was still markedly higher than non-MgSO4 group. In terms of age group, MgSO4 was beneficial in both pediatric and adult patients, but only significant on the latter. The survival of MgSO4 administered non-neonatal tetanus patients was significantly higher among severe tetanus patients and among those without dysautonomia. *Conclusion:* Administration of MgSO4 in non-neonatal tetanus patients, may be effective in improving survival. Moreover, its benefit is magnified among adult patients, with severe tetanus and those with no dysautonomia.

Keywords: Tetanus, MgSO4, pediatrics, generalized tetanus, neurocritical care

INTRODUCTION

Tetanus is a life-threatening condition acquired by exposure to anaerobic clostridium tetanus bacteria toxin called tetanospasmin. Once exposed, tetanospasmin is absorbed in the motor neuron pre-synaptic terminal and brought to inhibitory neurons in the spinal cord through retrograde transport via microtubules, where it inhibits VAMP and SVA. This prevents the release of inhibitory GABA and glycine to motor and autonomic neurons, resulting to hyperactive muscle and irregular sympathetic and parasympathetic activities, respectively.[1] While tetanus is uncommon in developed countries due to successful vaccination, it is still a common cause of mortality in low to middle income countries, with a case fatality rate of 20 to 40%. In the Philippines, it has an incidence of 6.9 cases per 1 million population in 2022.[2]

Clinical signs and symptoms of tetanus include generalized painful muscle spasms aggravated by induction of any stimuli, whether visual, auditory, or tactile. Dysautonomia, manifested by lability of blood pressure, heart rate, temperature, and gastrointestinal functions, is another life-threatening complication of this infection. Among tracheostomized patients supported by mechanical ventilation, sudden cardiac arrest due to autonomic dysfunction leads the cause of mortality.[3] Other complications of tetanus include kidney injury from rhabdomyolysis due to excessive muscle contraction, pneumonia from prolonged intubation, and sepsis.[2]

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Treatment of tetanus includes early tracheostomy, use of antibiotics, isolation from any forms of stimuli, and control of spasms with the use of benzodiazepines, GABA agonists, neuromuscular junction blockers such as vecuronium, and Magnesium Sulfate (MgSO4).[1] Although the use of MgSO4 for tetanus has started since 1912, its efficacy and safety for generalized tetanus has not yet been concretely established.[4] Among pre-eclamptic patients, it is widely and safely used by obstetricians to decrease the risk of eclampsia.[5] MgSO4 decreases neuromuscular transmission of action potential by acting on the pre-synaptic terminal and by decreasing calcium levels. In theory, this is supposed to decrease muscle spasms and autonomic dysfunction. At extremely high levels however, MgSO4 may reduce the patellar reflex, cause further respiratory depression possibly leading to prolonged admission, or worst, sudden cardiac arrest.[1,6] Hence, some physicians are still wary to include MgSO4 in their armamentarium of treatment for generalized tetanus.

In 2006, Thwaites and colleagues conducted the first randomized placebo controlled clinical trial for MgSO4 among adult Vietnamese tetanus patients.[6] In this trial, although survival was not different in the two groups and the primary outcome was not significant, they have concluded that administration of MgSO4 may decrease the use of medications for muscle spasms and dysautonomia such as benzodiazepines. Moreover, they have concluded that MgSO4 may also be safely given even to non-tracheostomized patients.[6] In a recent systematic review, MgSO4 was found to be effective in reducing spasms, dysautonomia, and the need for mechanical ventilation. Nevertheless, mortality was not observed to improve even when the previously mentioned outcomes were better. Lack of power and selection bias were few of the reasons why such findings exist.[3] Moreover, external validity of these studies is limited to adult patients only, hence further studies are still needed.

In the Philippines, there are no recommendations on the use of MgSO4 among tetanus patients.[7] Moreover, some adult and pediatric neurologists are unaware of its benefits in this cohort. Most start MgSO4 only when the patients are in the severe stage, have signs of dysautonomia, or if the physician is confident in its administration. This paper determines the effect of MgSO4 on the survival of adult and pediatric non-neonatal tetanus patients in a tertiary hospital from 2012 to 2023.

METHODS

Research design

This study utilized a retrospective cohort study design. Data from a previous study by Lanuza *et al.* (2024)[2] with UPM-REB approval (UPMREB code 2023-0345-01) was used. Another ethics approval was obtained for this manuscript (UPMREB2025-071-01).

Inclusion and exclusion criteria

All tetanus patients admitted in the University of the Philippines-Philippine General Hospital (UP-PGH) and included in the previous study by Lanuza et al.2, regardless of age were analyzed. Those with incomplete data, especially of the main intervention and outcome were excluded.

Operational definition of variables

Main independent factor:
MgSO4 group: Tetanus patients who received any dose of MgSO4.
Non-MgSO4 group: Tetanus patients who did not receive any dose of MgSO4

Main dependent factor:
Survival: Defined by hospital days as survival time and mortality as the failure event. Hospital days were determined from admission until an event occurs, whether the event is considered censored or a failure event

Other independent factors/ Possible confounders: These were the possible factors that may be related to the main intervention and/or outcome which were controlled to isolate the effect of the main independent factor. The following factors were controlled in this study: age, sex, ICU days, co-morbidities, characteristics of tetanus diagnosis, other medications used, and presence of complications.

Administration of MgSO4 based on local guidelines

MgSO4 is only optional in the Philippines and can only be given based on the discretion and comfort of the managing neurologist. Most of the time, it is given in severe patients with frequent and difficult to control muscle spasms and dysautonomia. For adults, 2 grams of MgSO4 is loaded and followed by infusion at a rate of 2 to 3 grams per hour. Serum calcium and magnesium, and ankle reflexes, are checked every 12 hours and 1 hour, respectively to avoid

complications. All patients are linked to a cardiac monitor. The target serum Mg is 2-4 mmol/l. Infusion of MgSO4 is only stopped once spasms are controlled or if complications are observed. Standard management of tetanus, including emergency tracheostomy, immediate removal of tetanus source, administration of necessary vaccines for neutralization of toxin and for active immunity, admission to non-stimulating ICU, administration of metronidazole, administration of medications to reduce muscle spasms including non-depolarizing sodium channel blockers and benzodiazepines was given to all patients. DVT prophylaxis for all patients was also given. Among pediatric patients, MgSO4 is used variably by pediatricians depending on age, weight and other factors.

Data collection

A post-hoc analysis of previously derived data was performed. In brief, a chart review of all tetanus patients who satisfied the inclusion and exclusion criteria was done. Charts obtained and extracted were from the census of a tertiary hospital from 2012 to 2023. Relevant information including the demographics, risk factors, management, as well as outcomes were extracted and recorded using a pre-made abstraction form. All information were coded using a coding manual and transferred to an excel file prior to analysis. The previous study was cleared by the local ethics board (UPMREB 2023-0345-01) prior to data collection.[2] The primary author of the previous study consented for post hoc analysis of the data. This current study was likewise approved by UPM Research ethics board (UPMREB2025-071-01) on March 25, 2025.

Data analysis

In this paper, continuous variables were presented as medians (range) while categorical variables were presented as proportions. Baseline comparisons of MgSO4 versus non-MgSO4 groups were done using Wilcoxon rank sum test or independent t-test for continuous data while Fisher exact test was used for comparison of proportions. Comparisons with a p-value lower than 0.2 were later used for Cox regression analysis. Kaplan-Meier Curves of each group were generated and compared using log rank test. Moreover, crude and adjusted hazard ratio of MgSO4 use were computed using Cox regression analysis. In the use of survival analytic methods, mortality served as the failure event while other outcomes were labelled as censored events. Hospital days, defined as days from admission to outcome served as the survival time. Prior to survival analysis, proportionality hazard assumption was globally tested using Schoenfeld residuals and through creation of log-log survival curves. All analysis were conducted using STATA SE 18.0 with a p-value of less than 0.05 serving as statistical significance cutoff.

RESULTS

Baseline characteristics

There were 79 non-neonatal tetanus patients included in this study. These patients had a median age of 39 years (range:2-72), around 75% were adults, and majority were males (69.1%). The median hospital and ICU stays were 25 and 15 days respectively. Some of patients had cancer (18.5%) hypertension (12.5%) and DM (7.4%) and some reported trauma (49.4%) as their possible main source of infection, with around 30% acquiring it through puncture wound. Some patients had their trauma at the lower extremity (44.6%) with majority initially presenting with trismus (62.8%). Almost all patients had generalized tetanus (94%) at stage III (60.5%). Around 52% of patients received MgSO4, 54.3% received benzodiazepine, 31% received rocuronium, and 61% received baclofen during their stay at the hospital. More than half of the patients developed pneumonia, while around 20% had dysautonomia. Twenty one percent of patients died; of these, septic shock and fatal arrhythmia appeared to be the most common causes. (See Table 1)

Magnesium sulfate Vs no magnesium sulfate

More adult neurologists used MgSO4 than pediatricians (85.7% vs 64.1%, p=0.03). Moreover, patients who received MgSO4 had significantly longer ICU stay (22 vs 9.5 days, p=0.005), higher proportion of Baclofen use (69% vs 41%, p=0.01), higher proportion of developing pneumonia (68.3% vs 43.6%, p=0.03) and higher proportion who had dysautonomia (31% vs 12.8%, p=0.0001). The mortality rate in the non-MgSO4 group was significantly higher (38.5% vs 4.8%, p=0.0001).

Effect of MgSO4 on survival of tetanus patients

Proportional hazard assumption was met using both the global test (chi^2=10.16, p=0.18) and graphing methods. Crudely, the incidence death

Table 1: Baseline characteristics (N=79)

Parameter	Total (N=79)	Without Magnesium Sulfate (n=39)	With Magnesium Sulfate (n=42)	p-value
Age in years (Median, range)	39(2-72)	36(3-72)	40(2-71)	0.2
Proportion of adult patients	75.3%	64.1%	85.7%	0.03
Proportion of males	69.1%	64.1%	73.8%	0.4
Median hospital days	25(<1-102)	18.5 (<1-102)	31(8-55)	0.052
Median ICU days	15(<1-49)	9.5(<1-49)	22(6-47)	0.0005
Median days to tracheostomy	<1 (<1-19)	<1(<1-19)	<1(0-8)	0.2
Median days from trauma to onset of symptom	7(<1-176)	5(<1-90)	7(<1-176)	0.8
Outcome				
Discharged	77.8%	59.0%	95.3%	<0.0001
HAMA	1.2%	2.6%	0%	
Mortality	21.0%	38.5%	4.8%	
Co-morbidities				
Hypertension	12.5%	12.8%	12.1%	0.9
DM	7.4%	5.1%	9.5%	0.5
Stroke	6.2%	10.2%	2.4%	0.2
Lung disease	11.1%	5.1%	16.7%	0.1
Renal disease	1.2%	2.3%	0%	0.3
Malignant disease	18.5%	17.9%	19.0%	0.9
Source of infection				
0-Trauma	49.4%	48.7%	50%	0.47
1-Surgical	3.7%	2.6%	4.8%	
2-Unknown	37.0%	33.3%	40.5%	
Type of injury Puncture	32.1%	27.8%	35.7%	0.21
Site of Injury				
0-Head	23.0%	25.7%	20.5%	0.3
1-Trunk	18.9%	17.1%	20.5%	
2-Arms	5.4%	8.6%	2.6%	
3-Legs	44.6%	37.1%	51.3%	
4-Perianal	4.1%	2.9%	5.2%	
5-Others	4.1%	8.6%	0%	
Initial symptoms				
0-Trismus	62.8%	63.2%	62.5%	0.8
1-Risus	0%	0%	0%	
2-Dysphagia	11.5%	7.9%	15%	
3-Spasm	11.5%	13.2%	10%	
4-Spasticity	0%	0%	0%	
5-Rigidity	3.9%	2.6%	5%	
6-Neck stiff	10.3%	13.2%	7.5%	
7-Opisthotonus	0%	0%	0%	
Median number of segments with spasm	2(0-4)	2(0-4)	2(0-4)	0.9

Table 1: (continued)

Parameter	Total (N=79)	Without Magnesium Sulfate (n=39)	With Magnesium Sulfate (n=42)	p-value
Type of tetanus				
Generalized	93.8%	89.5%	97.6%	0.15
Localized	6.3%	10.5%	2.4%	
Cephalic	0%	0%	0%	
Stage				
1	5.3%	5.7%	4.9%	0.99
2	32.9%	34.3%	31.7%	
3	60.5%	60%	61.0%	
Proportion given with ATS[#]	95%	97.4%	92.9%	0.34
Proportion benzodiazepine given during admission	54.3%	53.8%	54.8%	0.9
Proportion given rocuronium during admission	30.9%	30.7%	30.9%	0.9
Proportion baclofen given	60.5%	41.0%	69.0%	0.01
Median number of services on board	6(3-13)	5(3-13)	6(3-12)	0.4
Median number of complications during admission	1(0-7)	2(0-6)	1(0-7)	0.92
Complications				
Pneumonia	56.3%	43.6%	68.3%	0.03
CAUTI[$]	12.5%	12.8%	12.2%	0.9
Bacteremia	13.8%	17.9%	9.8%	0.3
CRBSI[&]	3.8%	0%	7.3%	0.08
Rhabdo	7.5%	5.1%	9.8%	0.4
AKI[*] from sepsis	13.8%	20.5%	7.3%	0.09
Pressure ulcer	15%	10.3%	19.5%	0.2
Dysautonomia	22.2%	12.8%	31.0%	0.0001
Causes of mortality				
Septic shock	7.4%	12.8%	2.4%	0.001
Cardiogenic	0	0	0	
Hypovolemic	0	0	0	
Obstructive	1.2%	2.6%	0	
Respiratory	4.9%	7.7%	2.4%	
Fatal arrhythmia	6.2%	12.8%	0	

[#]ATS- anti-tetanus serum; [$]CAUTI- Catheter Associated Urinary Tract Infection; [&]CRBSI- Catheter Related Blood Stream Infection; [*]AKI- Acute Kidney Injury

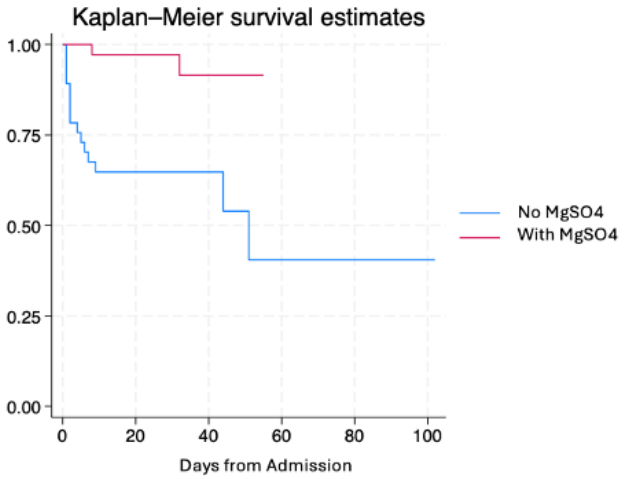

Figure 1. Kaplan Meier curves, MgSO4 vs No MgSO4

rate was significantly higher in the non-MgSO4 group (1.2% vs 0.19%, RR:9.5, p=0.002). Accordingly, patients who were not given MgSO4 were 9.5 times more likely to die from tetanus than those who were given. Moreover, the Kaplan Meier survival curve of the MgSO4 group was better than No MgSO4 (Log Rank Test Chi2=11.49, p=0.0007). At 14th (survival: 97.2% vs 64.8%) and 21st days (survival: 97.2% vs 64.8%), more patients were still alive in the MgSO4 group than non-MgSO4 group. The median survival for the non-MgSO4 was around 50 days while at the same period, around 90% tetanus patient in the MgSO4 group were still alive. Even when stratified log rank test was used, with age as the stratifying factor, administration of MgSO4 still improved survival (Log Rank Test chi2:11, p=0.0009). (See Figure 1 and Figure 2)

Not giving MgSO4 compared to giving MgSO4 will result to 8.4 times more hazard of dying among patients diagnosed with tetanus (HR: 0.12, p=0.005). Nevertheless, controlling possible confounders, although administering MgSO4 still reduced the hazard of dying by 78%, this becomes non-significant (HR:0.22, p=0.13). Interestingly, prolonged ICU stay (HR: 0.08, p=0.003), baclofen use (HR: 0.21, p=0.03)

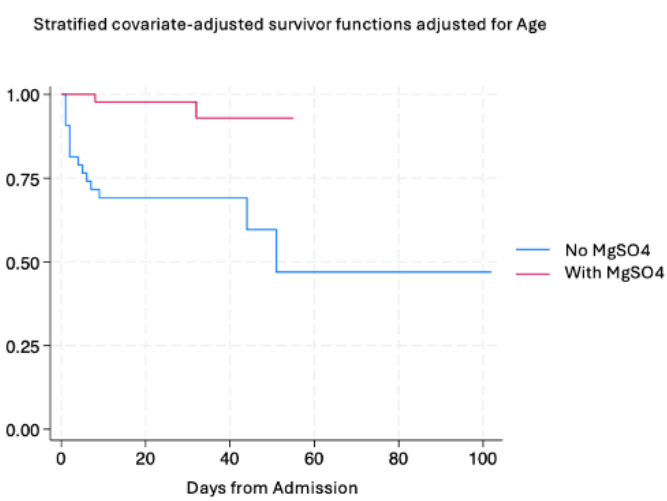

Figure 2. Effect of MgSO4 on survival adjusted for age only. Notice the significantly better survival curve of the MgSO4 group than non-MgSO4 group (log rank test chi2:11.71, p=0.0084)

Table 2: Adjusted hazard ratio

Independent variable	Hazard ratio	P-value
MgSO4	0.22	0.13
Age	1.6	0.5
ICU stay (>14 days)	0.08	0.003
Stroke co-morbidity	1.5	0.7
Pulmonary disease co-morbidity	-	1.000
Type of tetanus	0.91	0.9
Baclofen	0.21	0.03
Pneumonia complication	0.5	0.4
Pressure ulcer complication	0.24	0.01
Presence of dysautonomia	2.7	0.2

and presence of ulcer (HR: 0.24, p=0.01), were significantly associated with better outcome (see Table 2).

Subset analysis

Effect of MgSO4 on survival by age

Among pediatric tetanus patients (n=20), none died in the MgSO4 group compared to 25% in the non-MgSO4 group (0% vs 25%, p=0.26). Nevertheless, the comparison was not significant. Unfortunately, due to lack of mortality in the exposed group, regression methods could not be done.

Among adults (n=56), a significantly lower mortality (6.5% vs 40%, p=0.003) was observed in the MgSO4 group. Crudely, administration of MgSO4 reduced the hazard of mortality by 86% (HR:0.14, p=0.012) compared to non-MgSO4 group. Controlling possible confounders however, rendered this to be not significant (adjusted HR:0.28, p=0.23).

Effect of MgSO4 on survival by severity

Among stage 1 or 2 tetanus, the effect of MgSO4 was not significant (HR:0.5, p=0.6). Among stage 3 cases however, MgSO4 reduced the hazard of mortality by 93% when compared to no-MgSO4 treatment (HR:0.07, p=0.010).

MgSO4 and dysautonomia

There was a tendency to use MgSO4 by a factor of 3 times when dysautonomia was present but this was not statistically significant (p=0.056). Even when other factors were controlled, this tendency was sustained (adjusted OR: 6.9, p=0.061). Among patients who developed dysautonomia, administration of MgSO4 resulted in 82% non-significant reduction of hazard of death when compared to placebo (HR:0.18, p=0.06). Among those without dysautonomia (n=59), no mortality was recorded in the MgSO4 group (0% vs 35%, chi2=11.1, p=0.001) compared to 12 deaths in the no MgSO4 group.

DISCUSSION

Crudely, survival is better in the MgSO4 group and although this became non-significant when possible confounders were accounted, the survival in the MgSO4 group was still markedly higher than the non-MgSO4 group. In terms of age group, MgSO4 was beneficial in both pediatric and adult patients, but only significant in the latter. The survival of MgSO4 administered non-neonatal tetanus patients was significantly higher among more severe patients and among those without dysautonomia, nevertheless a non-significant reduction in mortality can also be observed among those with mild tetanus and those with overt dysautonomia.

MgSO4 exerts its effect by reducing calcium intake in the pre-synaptic terminal through competitive inhibition, leading to reduced muscle contraction and release of catecholamines.[5,8] As consequences, muscle spasm and dysautonomia were expected to be reduced.[1] These effects were demonstrated in multiple observational and controlled trials of MgSO4 in tetanus, specifically in the randomized clinical trial by Thwaites among Vietnamese patients.[6,9] In particular, Thwaites' team observed that MgSO4 administration significantly reduced the use of

midazolam and pancuronium and it significantly decreased the mean heart rate and verapamil use in the same cohort. Midazolam and pancuronium, and mean heart rate and verapamil, were surrogate markers for muscle spasm and dysautonomia respectively. The same findings were found in the recent systematic review by Nepal *et al*.[3] Accordingly, patients in the MgSO4 group had significantly lower duration of muscle spasm and dysautonomia. Moreover, they also concluded that MgSO4 significantly reduced hospitalization and ICU stays in most studies they have included.[3,10]

Unfortunately, due to the retrospective nature of our study, we could not use muscle spasm as an outcome. Moreover, in our institution, MgSO4 was used as a response to presence of dysautonomia and not to primarily prevent it and this may explain the significantly higher proportion of patients with dysautonomia and baclofen use in the MgSO4 group. Furthermore, this may also explain why those on MgSO4 stayed longer in the hospital and ICU. Nevertheless, even when presence of dysautonomia was controlled for, and even when only those without dysautonomia were analyzed in the subset analysis, the beneficial effect of MgSO4 on survival can still be observed. This benefit can also be seen among severe cases of tetanus.

Ideally, reduction of spasm and dysautonomia would lead to better survival.[1] Decreased muscular contraction may lower risk for AKI, hospitalization days and in turn pneumonia, while decreased fluctuation of vital signs may signify reduced risk of death from fatal arrhythmia.[3] However, in most studies, no difference in mortality and survival were observed in MgSO4 and non-MgSO4 groups.[3,6,9] In the randomized trial by Thwaites, survival was the same for both groups despite all factors being equal and the study was sufficiently powered. They attributed this to blinded and controlled nature of the study. As the dose of the MgSO4 was fixed, no adjustment was made despite the fluctuating severity of symptoms. Moreover, the medication was only given for 7 days, and was administered to more benign, non-mechanical ventilation assisted patients.[6] In contrast, we observed a significantly lower reduction in survival in the MgSO4 group than non-MgSO4, albeit crudely. We attributed this to possible muscle spasm and dysautonomia controlled by MgSO4. Should the proportion of patients with dysautonomia and pneumonia be equal between non-MgSO4 and MgSO4 groups, we expect the survival in the latter to be significantly higher than what we have currently computed, whether the hazard ratio was adjusted or not. As to other studies which did not find difference in mortality between the 2 groups, it is advised that in future studies, survival or hazard ratio be used as it utilizes more information as its outcome (survival days, failure event, censored event) than a simple count of mortality as categorical data. Moreover, a well powered randomized controlled trial similar to that of Thwaites, but now with no limitation in the number of days of MgSO4 administration, is recommended in the future to fully determine the effect of MgSO4 on survival. Nevertheless, since tetanus has been widely controlled in developed countries, this recommendation is applicable only to countries where tetanus is still endemic, like the Philippines.

Several studies have already been published about the benefit of MgSO4 in the reduction of muscle spasm and incidence of dysautonomia among adults, but only 1 paper with relatively numerous sample size was published for children.[11] In the single arm study by Shanbag *et al*, 27 pediatric non-neonatal tetanus patients were given 100mg/kg loading dose of MgSO4 for 30 minutes then 40 mg/kg/hr thereafter. Accordingly, 72% (13/18) of the patients with moderate to severe tetanus required other interventions such as diazepam and pancuronium to control muscle spasm for a median period of 4.7 days. None had autonomic dysfunction and 19% (5/27) died due to various causes.[11] Due to its single arm nature however, it could not be determined if MgSO4 offered clinical or survival advantages in this cohort of patients. In contrast, although non-significant, none in the MgSO4 group of our pediatric patients died compared to 25% in the non-MgSO4 group. The small sample size however made the comparison underpowered, and the non-significance was possibly a type 2 error. Nevertheless, we still hypothesize that like adults, MgSO4 can also improve survival among pediatric tetanus patients.

The limitations of this study are: First, to retrospective nature of the study, some details about the use of MgSO4 could not be retrieved. Specifically, the outcome measures for muscular spasm, surrogate marker for dysautonomia and other factors that need to be controlled should have been obtained. Moreover, due to the observational design of the study, selective bias was expected. For example, the distribution of patients with dysautonomia was unequal, as well as the hospitalization and ICU days, and some

complications. Nevertheless, this was adjusted by multiple Cox and logistic regression analyses. Moreover, sensitivity and subset analyses were performed on some factors deemed to possibly affect survival outcomes. Since we only have limited sample size, type 2 error may have been committed in some comparisons. Accordingly, regression analyses require larger sample size as the number of factors included in the model increases while performing subset analysis effectively decreases the sample size for each comparison. A careful and cautious interpretation of the results should be made due to this. Despite this, inclusion of both pediatric and adult patients extends the external generalizability of this study's results.

In conclusion, administration of MgSO4 in non-neonatal tetanus patients, may be effective in improving survival. Moreover, its benefit is magnified among adult patients, with severe tetanus and those with no dysautonomia.

DISCLOSURES

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Conflicting of interests: None

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