Full Length Research Paper

Comparison of the efficacy of magnesium sulphate and diazepam in the control of tetanus spasms

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Tetanus though preventable through vaccination, it continues to be a major scourge and a common cause of death in developing countries. The objective of this study is to compare the efficacy of magnesium sulphate and diazepam in controlling the tetanus spasm. This was a randomized double blind controlled trial. A total of 42 patients with clinical diagnosis of tetanus, received continuous infusion of either magnesium sulphate or diazepam. The outcome variable was cessation of spasm, uncontrollable spasm, death and presence of signs of magnesium toxicity or of excessive sedation of diazepam. The knee jerk reflex was use to monitor magnesium sulphate overdose. Observations from the patients were entered into the data sheets and analysis was done using Epi info version 6. A total of 42 patients were enrolled for the study, of whom 31(72.8%) were males and 11(27.2%). The age range of the patients was between 15 years and 70 years, with a mean age of 31.38 ± 14.89 years. Twenty one patients were randomly assigned to each arm of the trial. The outcome variables measured were frequency of spasms, and duration of spasms, which were were similar in the first five hours of commencing the trials. The mean spasm frequency in the Magnesium sulphate group reduced from 4.1±1.6 spasms/h at the onset of study to 0.13±0.05 spasms/h in the second week of trial compared to 3.4±1.5 spasms/h to 0.33±0.2 spasms/h in the diazepam group. This difference was statistically significant (p =0.010). The mean duration of spasm was also shorter in the magnesium sulphate group compared to the diazepam group (3.9±0.7 s versus 6.2±2.0 s) but without statistical significance (p value of 0.055). In magnesium sulphate group 11 (52.4%) patients survived and 10 (47.6%) patients died, while in the diazepam group 12 (57.14 %) patients survived, and 9 (42.86%) patients died during the trial . the Risk Ratio was 0.91( 95% C.I) . Magnesium sulphate is a suitable alternative to diazepam for the control of spasms in moderate tetanus.

Key words: Tetanus spasms, magnesium sulphate, diazepam.

INTRODUCTION

Tetanus, now a rare disease in the developed world (Cook et al., 2001) is regarded as a third world disease which requires modern intensive care management (Books et al., 1965). Tetanus is preventable through vaccination of pregnant women, children and high risk groups such as farmers, but it continues to be a major scourge and a common cause of death in Sub-Saharan Africa (Osuntokun et al 1993). The prevalence of tetanus has been reported to be between 2.8 to 7.9% of medical in-patients in Nigeria (Ogun et al., 2000) in contrast to an annual incidence of between 50-70 cases and 12-15 in the United States and Britain, respectively (Farrar et al., 2000; Gergen et al., 1995).

Tetanus is a major infectious cause of death in Nigeria, with high case fatality rate ranging between 55 to 70% (Adetuyibi et al., 1973; Ogun et al., 2000). In the developed countries, the mortality in the at - risk - group remains about 50% (Sandford, 1995; Centre for Disease Control, 1985).

Management of tetanus and the outcome of treatment depend on severity and the type of disease (Farrar et al., 2000). Modern intensive care management may become
necessary, especially in very severe illness with acute respiratory failure or other cardiovascular complications resulting from autonomic instability (Cook et al., 2001). Death resulting from cardiovascular dysfunction has not been adequately reduced by the use of sedative regimens (Attygalle et al., 1997). The complications resulting from long term sedation and artificial ventilation contributed significantly to morbidity and mortality resulting from this disease (Attygalle et al., 1997). Conventional treatment of tetanus involves the use of sedatives (Cook et al., 2001; Attygalle et al., 1997), and in severe cases, ventilatory support (with or without muscle relaxants), and these are not always available to tetanus patients in the developing countries where the disease is prevalent (Attygalle et al., 1997). It was difficult to control tetanus-induced overactivity of the sympathetic nervous system (Attygalle et al., 1997). The problems of autonomic dysfunction and altered circulatory haemodynamics with direct myocardial damage and other effects of catecholamines such as renal impairment remain unresolved.

Magnesium is a physiological calcium antagonist that acts presynaptically as a neuromuscular blocker (Mellanby, 1968). It blocks catecholamine release from nerves and adrenal medulla reduces receptor responsiveness to released catecholamines, thus acting as an anticonvulsant and a vasodilator (Witlin et al., 1998). It antagonizes calcium in the myocardium and at the neuromuscular junction and inhibits parathyroid hormone release so lowering serum calcium. These effects constitute added advantage over other muscle relaxants. The therapeutic range of magnesium in the serum is 2-4 mmol/l (Attygalle et al., 1997). Areflexia occurs when serum level is above 4 mmol/l and muscle paralysis occurs at levels above 6 mmol/l (Attygalle et al., 1997). Therefore, the knee jerk reflex can also be clinically used to detect magnesium toxicity when it is difficult to monitor serum levels of magnesium. At higher doses, magnesium can cause central sedation, hypotension and bradycardias. The efficacy of magnesium sulphate as the sole muscle relaxant in the management of tetanus has been demonstrated in earlier studies (Cook et al., 2001; Prys-Roberts et al., 1969; James et al., 1985; Valve et al., 1993; Edlich et al., 2006).

The aim of this study was to compare the efficacy of magnesium sulphate and diazepam in the control of spasms in moderate to severe tetanus.

**RESEARCH DESIGN AND METHODS**

This double-blind randomized clinical trial was carried out at the Olabisi Onabanjo University Teaching Hospital, Sagamu, Ogun State, Nigeria. Ethical approval for the study was obtained from the institutional ethical committee of the hospital. Informed consent was obtained from the patients or relatives. Consecutive patients presenting with clinical diagnosis of tetanus at Olabisi Onabanjo University Teaching Hospital, Sagamu, Ogun State, Nigeria, were randomly assigned to either the magnesium sulphate group or the diazepam group by the blocking method. The method of allocation of patients, the randomization sequence and the preparation of the active drugs (magnesium and diazepam) in coded and indistinguishable infusion bottles were concealed from the researchers by the hospital’s pharmacy department. Blinding was maintained until all analysis of the collected data was performed. Baseline electrolyte and urea including calcium and phosphate, full blood count and wound culture, when appropriate, were carried out for the patients.

**Intervention**

Subjects in each group were given intravenous metronidazole 500 mg eight hourly for one week, antitetanus serum at the dose of 10,000 units (intramuscular) after a test dose, intravenous fluid as 5% dextrose-saline infusion 500 ml 4 hourly, 50 ml of 50% dextrose in double dilution 8 hourly and parenteral amino acid/vitamins infusion as food supplement daily.

Each patient was given a loading dose of either 5 g of magnesium sulphate in 20 ml of infusion or 20 mg of diazepam in 20 ml of infusion, followed by the maintenance dose of 8 g of magnesium sulphate in 200 ml given 4 hourly or 40 mg of diazepam in 200 ml of infusion given 4 hourly (Attygalle et al., 1997). Hypocalcaemia monitoring was done by clinical signs of Chvostek’s and Trousseau’s. This has been found to be useful and was adopted for this trial due to lack of biochemical facility in our centre. The knee jerk reflex was assessed hourly within the first hour and 4 hourly later. Vital signs were monitored hourly in the first 4 hours then 4 hour later. All the patients that survived were given tetanus immunization on discharge. The outcome variables measured were frequency of spasms, and duration of spasms which were recorded in the spasm chart till cessation was achieved.

**Indications for termination of research therapy with further intervention**

(1) Cessation of spasms. (2) If unacceptable autonomic dysfunction occurred (systolic hypertension > 160 mm or tachycardia > 120/min sustained for over one hour). (3) If excessive sedation with respiratory depression. (4) If signs of magnesium overdose occur-
red (muscle flaccidity with loss of the patella reflex, respiratory depression or prolonged PR interval on the ECG if suspected).

The end points of the research therapy were determined by

Cessation of muscular spasm, death, uncontrollable muscle spasm, signs of magnesium toxicity as evidenced by muscle flaccidity with loss of patella reflex, respiratory depression or prolonged PR interval on the ECG and excessive sedation and respiratory depression from the use of diazepam.

Data analysis

Observations from the patients were recorded in the patients’ case notes and later extracted and entered into the data sheets. Data analysis was done using Epi info version 6. Continuous variables were expressed as means with standard deviation, while categorical variables were expressed as frequencies. Comparison of mean of key parameters between the two groups was done using Student’s t-test, while frequencies were compared using chi-square analysis. Level of significance was fixed at P < 0.05.

RESULTS

Biodata

A total of 42 patients were enrolled for the study, of whom 31 (72.8%) were males and 11 (27.2%) were females giving male to female ratio of 2.8:1. The age range of the patients was between 15 years and 70 years, with a mean age of 31.38 ± 14.89 years. Baseline investigations of the patients showed that serum calcium levels ranged between 8.6 and 10.5 mg/dl with a mean of 9.7 ± 0.4 mg/dl and the serum phosphate level ranged between 3.0 and 4.7 mg/dl with a mean of 3.9 ± 0.3 mg/dl. Baseline PCV ranged between 25 and 45% with a mean of 38.5 ± 4.4%.

The characteristics biodata distribution of the two groups are shown in Table 1. Twenty one subjects each had magnesium sulphate and diazepam.

Outcome of hospitalization

Of the 42 patients studied, 24 (54.8%) patients survived, while 19 patients (45.2%) died. In magnesium sulphate group 11 (52.4%) patients survived and 10 (47.6%) patients died, while in the diazepam group 12 (57.14%) patients survived, and 9 (42.86%) patients died during the trial. The risk ratio was 0.91 (95% C.I) . There was no significant difference in the survival outcome with a chi square value of 0.10.

Overall, the duration of hospitalization of the survivors in the magnesium sulphate group ranged from 7 to 23 days with a mean of 17.23 ± 4.13 days, while in the diazepam group it ranged from 14 to 24 days with a mean of 20.46 ± 3.12 days (p= 0.055) which showed a better trend toward the magnesium sulphate group.

The total duration of hospitalization of subjects who died in the magnesium sulphate group ranged from 36 h to 216 h with a mean of 50.33 ± 12.78 h, while in the diazepam group, the range was 30 to 68 h with a mean of 42.78 ± 10.79 h (p=0.193).

The commonest complications observed were aspiration (21.6%), sepsis (4.8%) and UTI (4.8%). Though the number of patients that had complication was more in the diazepam group, there was no statistical difference in the complications observed in two treatment groups (p value of 0.398).

The cause of death in all the patients was presumed to be from cardiorespiratory related problems. One patient (2.4%) in the diazepam group discharged himself against medical advice, and one patient in the magnesium sulphate group had the drip discontinued on day 14 due to cardiorespiratory depression.

Relevant historical details

The mean onset time was similar in both groups: it ranged from 11 to 90 h, with a mean of 37.8 ± 21.9 h in the Magnesium Sulphate group compared to a range of 8 to 72 h with a mean of 28.7 ± 17.8 h in the Diazepam group (p=0.42).

Ablett’s grading of the severity of tetanus used in the study (Attygalle et al., 1997) showed that of the 42 patients studied, 4 (4.8%) had mild tetanus, 20 (47.6%) had moderate tetanus and 18 (42.8%) had severe tetanus. None of the patients studied in the two groups presented with very severe form of tetanus. The distribution of these in the two treatment groups is shown in Table 2.

Intervention outcome

The mean frequency of spasm expressed per hour in the first four hours of the trial in the magnesium sulphate group ranged from 2 to 9 spasm/hour with a mean of 4.1 ± 1.6 spasm/hour, while it ranged from <1-6 spasm/hour with a mean of 3.4±1.5 spasm/hour in the diazepam group. The values were similar (p = 0.79). There was no difference in the mean duration of spasms in the two trial groups (p=0.761) within the first four hours of the trial.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Magnesium sulphate (%)</th>
<th>Diazepam (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age±SD</td>
<td>34.29 ± 15.38 years</td>
<td>28.48± 14.1 years</td>
<td>0.21</td>
</tr>
<tr>
<td>Male</td>
<td>16 (76.2)</td>
<td>15 (71.4)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>5 (23.8)</td>
<td>6 (28.6)</td>
<td></td>
</tr>
</tbody>
</table>
Table 2. Characteristics of tetanus in the two groups.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Magnesium sulphate (%), n=21</th>
<th>Diazepam(%), n=21</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>0 (0)</td>
<td>4 (19.1)</td>
</tr>
<tr>
<td>Moderate</td>
<td>13 (61.9)</td>
<td>10 (47.6)</td>
</tr>
<tr>
<td>Severe</td>
<td>8 (38.1)</td>
<td>7 (33.3)</td>
</tr>
<tr>
<td>Very severe</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

Table 3. Comparison of spasm frequency per hour in the studied population.

<table>
<thead>
<tr>
<th>Time</th>
<th>Magnesium sulphate mean spasm freq (SD)</th>
<th>Diazepam mean spasm freq (SD)</th>
<th>t value</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-4 h</td>
<td>4.15 (1.55)</td>
<td>3.42 (1.46)</td>
<td>1.56</td>
<td>0.13</td>
</tr>
<tr>
<td>5-24 h</td>
<td>3.34 (1.54)</td>
<td>3.23 (1.52)</td>
<td>0.22</td>
<td>0.83</td>
</tr>
<tr>
<td>2-7 days</td>
<td>0.87 (1.37)</td>
<td>0.80 (0.324)</td>
<td>0.15</td>
<td>0.88</td>
</tr>
<tr>
<td>8-14 days</td>
<td>0.13 (0.05)</td>
<td>0.33 (0.196)</td>
<td>2.85</td>
<td>0.01</td>
</tr>
<tr>
<td>15-21 days</td>
<td>***</td>
<td>***</td>
<td>***</td>
<td>***</td>
</tr>
</tbody>
</table>

***Cessation of spasm had occurred in all survivors in magnesium group making data not comparable.

There was no difference in the mean frequency of spasm in the two groups (p= 0.83) within the next five to 24 h (Table 3). There was significant difference in the mean duration of spasm during the 5th to 24th hour (p= 0.07) favouring the use of magnesium sulphate.

Comparing the mean spasms frequency in the second week was statistically significant (p = 0.01). The mean duration of spasms was also statistically significant (p = 0.003) in the second week (Table 4). Cessation of spasm in the magnesium group was achieved at 17.3 ± 4.1 days, while in the diazepam group the mean was 20.4 days ± 3.142, with a p value of 0.055. Thus after the first week magnesium sulphate group was better.

Respiration variation

There was no remarkable differences in the mean respiratory rate within the first four hours and next 5-24 h of intervention p=0.05 and p=0.12, respectively. During the next one week and following second week the mean respiratory rates in the two groups were statistically significant with p=0.03 and p=0.007, respectively.

Cardiovascular response

There was no differences in the mean pulse rate within the first four hours and next 5-24 h of intervention p=0.76 and p=0.15, respectively. During the next one week and following second week the mean pulse rates in the two groups were also not statistically significant with p=0.33 and p=0.10, respectively.

There was no remarkable differences in the mean systolic blood pressure within the first four hours and next 5-24 h of intervention p=0.34 and p=0.33, respectively. During the next one week and following second week the mean systolic blood pressure in the two groups were not statistically significant with p=0.845 and p=0.83, respectively.

DISCUSSION

The efficacy of magnesium sulphate in the management of tetanus without causing sedation has been demonstrated in many studies in other parts of the world (Farrar et al., 2000; Attygalle et al., 1997; Writght et al., 1989; Towey, 2005; Attaygalle et al., 2004; Fawcet et al., 1999). This study has demonstrated that magnesium sulphate compared favourably with diazepam in terms of controlling frequency and duration spasm of tetanus. However the set goal of 15% fatality rate was not achieved. It is possible that magnesium sulphate has no favourable effect on fatality rate compared to diazepam in moderate and severe tetanus. However it has been shown to have better efficacy in very severe tetanus with significant autonomic disturbance (Attygalle et al., 1997; Attygalle et al., 2004, Fawcet et al., 1999). The mean serum concentration of calcium in the patients in the magnesium group was 9.7±0.4 mg/dl, while the mean serum concentration of phosphate was 3.9±0.3 mg/dl. This could explain the absence of overt clinical signs of hypocalcaemia. The mean frequency of tetanus spasm showed better response to therapy in the magnesium sulphate group by the second week of the trial. In an earlier trial (Attygalle et al., 1997), where the effect of
magnesium sulphate on frequency of spasm was assessed, it reduced the frequency within 3 h; however this reduction was not compared to that of diazepam. There was a better reduction in the mean duration of spasm in the magnesium sulphate group by the second week of therapy. In this study the respiratory rates were consistently lower in the magnesium sulphate group as evidenced by comparing the mean respiratory rate in the first 24 h \((p =0.12)\), first week \((p = 0.03)\) and the second week of therapy \((p =0.007)\).

It is admissible that vital capacity was not routinely measured in all the patients. Magnesium in the therapeutic range has been reported to produce a small but significant reduction of vital capacity in tetanus patient (Dietz et al., 1996; Lipman et al., 1987). Such a reduction could assume a greater clinical significance in tetanus in view of the reduction in vital capacity that is already present due to rigidity. Also magnesium sulphate was said to have the capacity to cause respiratory depression at high doses (Dietz et al., 1996). This could be the reason for the relatively lower mean respiratory rate in the Magnesium group compared to Diazepam group.

There was no significant difference in mean blood pressure of the patients in the two groups and neither was there any noticeable fluctuation in their blood pressure.

**Conclusion**

This study has demonstrated that magnesium sulphate in a dosage titrated to the preservation of the knee jerk reflex could be used as the sole drug to control the spasms of tetanus. Spontaneous respiration in this dose range is adequate using the clinical guide of the knee jerk reflex. Though magnesium sulphate therapy was not found to be superior in terms of outcome it compared well with diazepam in terms of reducing the severity of the spasms.

**Recommendation**

A multi-center study with a larger sample size of patients with severe and very severe form of tetanus may be designed to determine the efficacy of magnesium sulphate in the management of tetanus and its effect on autonomic functions.

**REFERENCES**


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