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Short Report

Neonatal tetanus in eastern Uganda: improved outcome following the implementation of a neonatal tetanus protocol

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Abstract

Neonatal tetanus remains a significant, yet avoidable, cause of neonatal death. Despite the 34,000 deaths that occur globally from neonatal tetanus every year, there has been little research into the management of neonatal tetanus. Until worldwide elimination of neonatal tetanus is achieved, the case management of this devastating illness needs to be improved. We describe an improved outcome of neonatal tetanus following the introduction of a neonatal tetanus protocol including diazepam, magnesium sulphate, bubble continuous positive airway pressure and broad-spectrum antibiotics in a low-resource setting in eastern Uganda.

Keywords

Neonatal tetanus, developing countries, newborn

Introduction

Neonatal tetanus can be prevented by public health measures, including maternal immunisation, clean facility-based delivery and safe cord care.[1–6] However an estimated 34,000 neonatal tetanus deaths continue to occur every year, almost all in low-resource settings.[5,7]

The World Health Organization (WHO) defines confirmed neonatal tetanus as an illness occurring in a neonate who has the normal ability to suck and cry in the first two days of life, but who loses this ability between days 3 and 28 of life and becomes rigid or has spasms.[8] Respiratory failure and airway obstruction from laryngeal

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spasm follow.[9,10] Autonomic dysfunction can occur causing hypertension, tachycardia and pyrexia. Both respiratory failure and autonomic dysfunction are important causes of mortality in post-neonatal tetanus.[11–14] In neonates, low birth weight, early onset, delayed presentation, fever and generalised rigidity have all been associated with poor outcome.[15,16] Without medical care, mortality is virtually 100%. With hospital care, this remains as high as 88% in low-resource settings.[17] With intensive care, mortality in older patients may be <10%, but intensive care is uncommonly available in low-resource settings.[18–24]

There are five key objectives in the treatment of neonatal tetanus: preventing further production of toxin with debridement of the umbilical cord; neutralising circulating toxin with tetanus immunoglobulin; controlling muscle spasms; preventing respiratory failure; and preventing autonomic dysfunction.[8]

Most data for tetanus therapy are from adult studies with few randomised controlled trials.[14,23,25,26] Diazepam is known to improve survival in children compared to a combination of phenobarbital and chlorpromazine.[27] When benzodiazepines fail to control spasms, neuromuscular blockade is advocated. However, mechanical ventilation is a prerequisite and is rarely available in low-resource settings. There is a need to explore alternative therapies that can still control spasms and autonomic dysfunction without mechanical ventilation.[17,28] Magnesium sulphate causes muscle relaxation, vasodilation and lowering of heart rate, which can help mitigate autonomic dysfunction.[29] There is conflicting evidence for the addition of intravenous magnesium sulphate in adults.[14,23,26,30–33] However, a recent Vietnamese study demonstrated improved outcome of neonatal tetanus after introducing a bundle of care including magnesium sulphate in a setting with limited intensive care including mechanical ventilation.[34] In settings where neuromuscular blockade is not feasible, the use of this inexpensive drug could have a great impact. We describe the introduction of a protocol including broad-spectrum antibiotics, bubble continuous positive airway pressure (bCPAP), immediate sedation with diazepam and magnesium sulphate, and subsequent continuous infusion of magnesium sulphate and diazepam.

Methods

Mbale Regional Referral Hospital (MRRH) serves a population of 4.5 million people in eastern Uganda. MRRH has a dedicated Neonatal Unit (NNU) providing Level 2 Neonatal Care to >2000 neonates, including up to 20 cases of neonatal tetanus as defined by the WHO above, every year.[35]

This retrospective study used the neonatal admissions register to identify all neonatal tetanus cases admitted to MRRH-NNU between 1 January 2016 and 31 March 2017. Additional data were collected from the medical files of these patients. Before the neonatal tetanus protocol was introduced on 1 October 2016, management consisted of tetanus immunoglobulin, intermittent intravenous diazepam and metronidazole. The new protocol (Figure 1) consists of: immediate sedation with intravenous diazepam followed by its continuous infusion, loading with intravenous magnesium sulphate followed by its continuous infusion if suspected autonomic dysfunction is present. Autonomic dysfunction was defined as either tachycardia >180/min or fever >40°C or both. Blood pressure was not considered as it was not available in this setting. Although ventilation was not available in MRRH-NNU, bCPAP was. When the neonatal tetanus protocol was commenced, if respiratory distress was present, bCPAP was administered if a machine was available. Broad-spectrum antibiotics were given to all cases to cover for concurrent septicaemia and possible meningitis.[36] To prevent further production of toxin, if still attached, the umbilical cord was removed with a surgical blade and hydrogen peroxide was applied to the stump.

Descriptive analysis, t-test and Fisher's exact test were used to compare the differences before and after the protocol was introduced; a P value < 0.05 was statistically significant. Analyses were done in SPSS version 22.

The MRRH Research & Ethics Committee (MRRH-REC) approved the study and local permission to conduct the study was obtained from Mbale Clinical Research Institute.

Results

A total of 21 cases were identified from the neonatal admissions register (13 cases before and eight after introduction of the protocol). The mortality rate reduced from 84.6% (11/13) to 25.0% (2/8, $P = 0.02$). Owing to social and financial constraints, it is not uncommon for families to self-discharge, but there was no significant difference in the rate of self-discharges in both groups: 15.4% (2/13) and 25.0% (2/8). From our experience, it is highly likely that these patients died at home. If this was the case, the mortality in the period before and after the protocol could be as high as 100% and 50%, respectively. Although there were no differences in the duration of hospital admissions between the two periods for those who self-discharged and died, following the introduction of the protocol, the overall mean duration of admission increased significantly (Table 1). There were no significant difference in admission weight, gender, age at presentation and duration of symptoms before presentation (Table 1).

Only 52.4% of mothers reported attending two or more antenatal clinics, the minimum number of attendances needed for tetanus vaccination.[4] The receipt of at

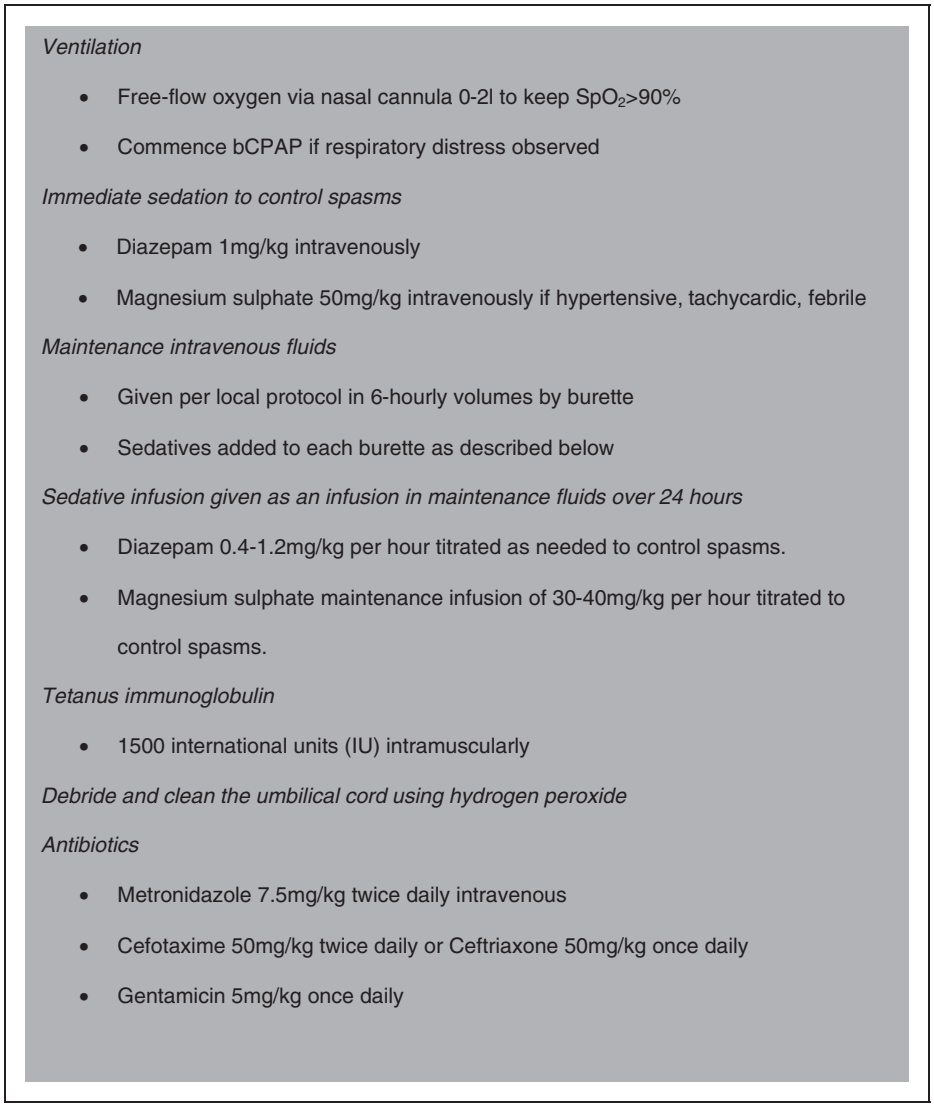

Figure 1. The neonatal tetanus protocol.

least two tetanus vaccinations was lower, suggesting that opportunities for tetanus immunisation were not optimised. There was no significant difference in the rate of maternal immunisation between the groups (38.5% and 12.5%, $P = 0.34$). There was a high rate of home delivery within both groups, which was non-significantly higher in the post-intervention group (38.5% and 75.0%, $P = 0.08$). All cases were delivered vaginally but only half (52.4%) by a skilled birth attendant. When the method of cord-cutting was known, it was reportedly done using a new razor blade. The practice of applying ash or herbs to the umbilical cord is still common in eastern Uganda. In this study, when the method of cord care was known, it was poor: three applied herbs; one soil; one ash; and two baby powder. All babies presented with difficulty feeding, fever, stiff neck and spasms, over half (57.1%, 12/21) presented with respiratory distress. All were noted to have features of autonomic dysfunction at presentation as defined above. The treatments received by the two groups are described in Table 1.

Discussion

Although progress has been made towards the elimination of neonatal tetanus in many countries, low-resource settings still experience deaths from this preventable illness. Two ongoing considerations highlighted by this study are maternal immunisation and facility-based delivery. While efforts towards elimination continue, improved recognition and case management is needed.

The WHO recommends two doses of maternal tetanus toxoid a minimum of four weeks apart and at least two weeks before delivery.[4] The majority of women in this study did not receive two doses of tetanus toxoid; this is probably because of poor antenatal clinic attendance.[37]

Table 1. Characteristics and management of patients before and after the neonatal protocol.

Characteristic	Before NT protocol (n = 13)	After NT protocol (n = 8)	*P* value
Mean age at admission (days)	6.3 ± 2.9	7.4 ± 3.5	0.46
Male (%)	46.2 (6/13)	62.5 (5/8)	0.66
Mean weight at admission (kg)	2.81 (± 0.35)	2.46 (±0.67)	0.126
Mean duration of symptoms (days)	2.1 ± 1.8	2.4 ± 0.7	0.66
Attend ≥ 2 ANC (%)	69.2 (9/13)	37.5 (3/8)	0.20
Tetanus vaccine ≥ 2 (%)	38.5 (5/13)	12.5 (1/8)	0.34
Home delivery (%)	38.5 (4/13)	75.0 (6/8)	0.08
SVD (%)	100	100	1.00
Delivery by skilled birth attendant (%)	69.2 (9/13)	25.0 (2/8)	0.08
Cord cut by:			
New razor (%)	8/13 (61.5)	6/8 (75.0)	0.66
Sterile blade	0	0	
Unknown	5/13 (38.5)	2/8 (25.0)	
Cord care (%)			
Soil/herbs/ash/powder	6/13 (46.1)	3/8 (37.5)	1.00
Dry cord care	0	0	
Saline	0	0	
Antiseptic	0	0	
Water	1/13 (7.7)	0	
Unknown	6/13 (46.1)	5/8 (62.6)	
Symptoms and signs (%)			
Inability to feed	13/13 (100)	8/8 (100)	1.00
Fever	13/13 (100)	8/8 (100)	1.00
Stiff neck	13/13 (100)	8/8 (100)	1.00
Spasms	13/13 (100)	8/8 (100)	1.00
Respiratory distress	8/13 (61.5)	4/8 (100)	0.67
Antibiotics administered (%)			
Ampicillin and Gentamicin	7/13 (53.8)	1/8 (12.5)	
Metronidazole	13/13 (100)	8/8 (100)	
Ceftriaxone and Gentamicin	6/13 (46.1)	7/8 (87.5)	
Respiratory support given			
None	1/13 (7.7)	1/8 (12.5)	
Free flow oxygen only	12/13 (92.3)	3/8 (37.5)	
bCPAP	0 (0)	4/8 (50.0)	
Diazepam administration (mg/kg/h)			
Intermittent boluses	13/13 (100.0)	0/8 (0.0)	
0.4		2/8 (25.0)	
0.8		5/8 (62.5)	
1.2		1/8 (12.5)	
Magnesium sulphate			
Loading 50 mg/kg	0 (0.0)	7/8 (87.5)	
Infusion at 30 mg/kg/h	0 (0.0)	7/8 (87.5)	
Infusion at 40 mg/kg/h	0 (0.0)	0/8	
Mean duration of admission (days)			
All patients	2.9 ± 3.2	7.8 ± 4.8	0.01
Self-discharge	8.0 ± 7.1	5.0 ± 2.8	0.63
Death	1.9 ± 0.8	2.0 ± 0.0	0.88
Inpatient outcome			
Survival to discharge	0 (0/13)	50.0(4/8)	0.04
Self-discharge	15.4 (2/13)	25.0 (2/8)	0.62
Death	84.6 (11/13)	25.0 (2/8)	0.003

However, cases of neonatal tetanus were also reported in infants of mothers who had been immunised. The probable causes of these cases include errors in the dosing interval, poor maternal immune response, maternal HIV, vitamin A deficiency and maternal malaria infection.[38–40] Data on these factors were unfortunately not available in this study but these should be considered in ongoing efforts to eliminate neonatal tetanus.

Delivery by a skilled birth attendant (SBA) encourages clean delivery practices and effectively reduces neonatal tetanus.[1–3] In Uganda, as was observed in this study, a high rate of home deliveries still occurs. In 2016, it was estimated that only 73% of women delivered in a health facility.[37,41,42] Home delivery encourages harmful practices such as cutting the cord with non-sterile equipment or applying ash or cow dung to the umbilical stump, all of which increase the risk of neonatal tetanus.[43]

While efforts towards elimination continue, improved recognition and case management are needed. Although the results of our study should be interpreted with caution owing to the small sample size, our report suggests that introducing a neonatal tetanus protocol, incorporating broad-spectrum antibiotics together with immediate sedation and continuous infusion with diazepam and magnesium sulphate, does have a significant impact on mortality. Almost all patients required respiratory support during both periods but with the introduction of bCPAP, half the patients received bCPAP. The duration of such therapy was not available from the records, but the additional respiratory support from bCPAP may have made a substantial contribution to the overall impact of the protocol.

The improved survival observed may therefore be due to any or all of these measures and may also have been due to improved identification and initiation of treatment. Although the use of magnesium in older patients has so far not been shown to reduce mortality, this is the second study that suggests an improved survival in neonatal tetanus when using a treatment bundle that includes magnesium sulphate.[33,34] Magnesium sulphate and diazepam infusions, broad-spectrum antibiotics and bCPAP are all safe and inexpensive adjuncts for neonatal tetanus in settings where intensive care and mechanical ventilation are not available. Data from adequately powered controlled studies are now needed to confirm this.

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