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Prognosis of neonatal tetanus in the modern management era: an observational study in 107 Vietnamese infants

Phung Khanh Lam [a], Huynh T. Trieu [b], Inke Nadia D. Lubis [c,d], Huynh T. Loan [b], Tran Thi Diem Thuy [b], Bridget Wills [a,c], Christopher M. Parry [a,e], Nicholas P.J. Day [a,c,f], Phan T. Qui [b], Lam Minh Yen [b], C. Louise Thwaites [a,c,*]

[a] Oxford University Clinical Research Unit, Hospital for Tropical Diseases, 764, Vo Van Kiet, Ho Chi Minh City, Vietnam
[b] Hospital for Tropical Diseases, Ho Chi Minh City, Vietnam
[c] Centre for Tropical Medicine and Global Health, Nuffield Department of Medicine, University of Oxford, Oxford, UK
[d] University of North Sumatera, Medan, Indonesia
[e] Clinical Sciences, Liverpool School of Tropical Medicine, Liverpool, UK
[f] Mahidol Oxford Tropical Medicine Research Unit, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand

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SUMMARY

Objectives: Most data regarding the prognosis in neonatal tetanus originate from regions where limited resources have historically impeded management. It is not known whether recent improvements in critical care facilities in many low- and middle-income countries have affected indicators of a poor prognosis in neonatal tetanus. We aimed to determine the factors associated with worse outcomes in a Vietnamese hospital with neonatal intensive care facilities.

Methods: Data were collected from 107 cases of neonatal tetanus. Clinical features on admission were analyzed against mortality and a combined endpoint of 'death or prolonged hospital stay'.

Results: Multivariable analysis showed that only younger age (odds ratio (OR) for mortality 0.69, 95% confidence interval (CI) 0.48–0.98) and lower weight (OR for mortality 0.06, 95% CI 0.01–0.54) were significantly associated with both the combined endpoint and death. A shorter period of onset (OR 0.94, 95% CI 0.88–0.99), raised white cell count (OR 1.17, 95% CI 1.02–1.35), and time between first symptom and admission (OR 3.77, 95% CI 1.14–12.51) were also indicators of mortality.

Conclusions: Risk factors for a poor outcome in neonatal tetanus in a setting with critical care facilities include younger age, lower weight, delay in admission, and leukocytosis.

1. Introduction

The worldwide incidence of neonatal tetanus has reduced significantly following a sustained initiative by the World Health Organization (WHO) and its partners The United Nations Children's Fund (UNICEF) and The United Nations Population Fund (UNFPA). Latest figures (June 2014) show only 24 countries out of 59 originally targeted have still to eliminate the disease.[1] The initiative attempts to eliminate maternal and neonatal tetanus through improvements in maternal vaccination programmes, delivery practices, and surveillance systems. In some 'high-risk' areas, supplementary immunization programmes targeting all women of child-bearing age have been employed.[2]

Despite these advances, the disease continues to occur. Elimination of neonatal tetanus is defined as 'less than one case per thousand live-births in every district of a country'.[3] However, this does not mean complete eradication, as the causative agent of tetanus, *Clostridium tetani*, is ubiquitous in the environment throughout the world and is able to cause disease in any vulnerable individual (i.e., neonate with unvaccinated mother).

Maintaining a country's neonatal tetanus elimination status requires continued efforts and further resources to strengthen vaccination programmes, reproductive health services, and surveillance systems. These can be threatened by war or natural disasters. Tetanus clusters have been reported following tsunamis and earthquakes in Indonesia, Kashmir, and Haiti.[4] It is still not clear how maternal HIV and malaria affect transplacental protective

* Corresponding author. Tel.: +84 8 3923 7954; fax: +84 8 9238 904.
E-mail address: lthwaites@oucru.org (C.L. Thwaites).

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antibody transfer,[5,6] although maternal HIV reduces the maternal response to tetanus vaccination.[7]

In neonatal tetanus, entry of tetanus toxin into the central nervous system results in muscle spasms, initially interfering with the ability to suck and feed, but later involving the chest muscles, impeding respiration. Without medical treatment mortality rates are very high (some reports are of 99% fatality).[8,9] As tetanus evolves over days in a characteristic manner, the recognition of prognostic features on presentation may enable timely intervention and triage.

Generally, rapid disease progression in tetanus is associated with a worse outcome.[8,10] Most studies have been performed in adults, but several case series in neonates have found similar indicators of prognosis.[11–13] Lambo and Anokye recently performed a meta-analysis and included data from 4535 neonates to ascertain which features are most relevant in neonates. They concluded that low birth weight and age at onset were the most important factors in determining the outcome.[14] The authors criticized the studies included in the analysis for limited prospective data and lack of control for gestational age. They noted that only one out of the 16 studies included all of the prognostic factors selected for the analysis and they were unable to find consistent reporting on delay in admission to hospital or duration of hospital stay to include these in their analysis, as originally intended. In some studies, current standard therapies such as tetanus anti-toxin were not necessarily used. Many of the studies included were conducted over 40 years ago, and even relatively recent studies used patient data from preceding decades. (The study by Patel and Mehta published in 1999 and including 1490 neonates, used data from the period 1954–68.[8]) In total, 3648 out of 4535 cases were admitted before 1996. Most of the studies were therefore either conducted in settings without facilities for mechanical ventilation or were performed before such facilities were readily available.

The availability of mechanical ventilation allows respiratory muscle spasm to be controlled and prevents respiratory failure – the major cause of death in tetanus. Recent improvements in critical care capacity in many low- and middle-income countries has meant improved supportive therapy is now available for a larger number of cases of neonatal tetanus. However, it is not known whether this has affected the reliability of factors identified to be associated with a worse prognosis in settings without these facilities.

In all settings the ability to rapidly identify those neonates at highest risk of a poor outcome may be especially important to target medical and nursing care appropriately. Knowledge of prognostic factors is also important to determine the efficacy of interventions over time and between locations. Baseline comparison of prognostic factors allows more accurate determination of likely disease progression before any treatment is begun. As some newer interventions in tetanus have been reported to reduce disease progression itself, this is especially important.[15–17]

In adult patients with tetanus, the efficacy of some interventions has been disputed due to potential differences in the severity of disease in the populations studied and the lack of consensus regarding how to quantify this.[18] Some publications have used only overall mortality rates as a marker of disease severity.[19] In neonatal tetanus, with wide variations in management and mortality rates ranging from 0 to 70% in different centres, improved indicators of disease severity are needed.[13,20–22]

In this study, we analyzed data from patients admitted with neonatal tetanus to our intensive care units. We examined multiple prognostic factors associated with outcome over a period of time during which improvements in critical care facilities were made.

2. Methods

All study patients were admitted to the Hospital for Tropical Diseases, Ho Chi Minh City, Vietnam between 1997 and 2012. The Hospital for Tropical Diseases is a tertiary referral hospital for infectious diseases and admits patients from the whole of southern Vietnam (population around 45 million). The reorganization of medical services in 2006 resulted in patients with neonatal tetanus being admitted to a specialist paediatric intensive care unit rather than the dedicated tetanus intensive care unit that had served all age groups and has been described previously.[23] Facilities for the intensive care management of neonates available at the Hospital for Tropical Diseases include mechanical ventilation and invasive blood pressure monitoring. Over the course of the study, these facilities were gradually incorporated into standard neonatal tetanus management. Mechanical ventilation was first used in the management of neonatal tetanus in 2000. Invasive blood pressure monitoring was introduced in 2008 following the transfer of care to the specialist paediatric intensive care unit.

Two datasets were used for the analysis. For most analyses, data from both phases were combined. The first was a prospective collection of data from 87 consecutive neonatal tetanus cases admitted between 1997 and 2003 to the Tetanus Unit at the Hospital for Tropical Diseases as part of an ongoing tetanus surveillance programme.[23,24] The second phase of the study consisted of case record analysis of 20 consecutive patients with neonatal tetanus admitted to the paediatric intensive care unit at the same hospital from January 2010 to December 2012.[25]

Clinical and demographic data were collected (Table 1). The incubation period was defined as the time between birth and first symptom, assuming umbilical portal of entry. The period of onset was defined as the time between first symptom and first generalized muscle spasm. Cases of 'discharge to die at home' or 'discharge against medical advice' were recorded as deaths, as these were felt certain to result in this outcome due to the severity of the disease. In phase 1 of the study, the results of routine neurological examinations performed on discharge were recorded, including screening for gross deficits and general development. Studies were approved by the scientific ethics committee of the Hospital for Tropical Diseases.

All data were entered into a specially designed database and extracted for analysis. Frequencies (%) and the median (with interquartile range, IQR) were used to describe data. Age and weight on admission were compared between phases of the study using the Wilcoxon rank sum test.

As mortality rates declined during the study period, we used a combined poor outcome endpoint of either death or staying in hospital for more than 40 days as a more sensitive means of detecting a poor outcome in a setting of low mortality. The cut-off of 40 days was based on the 75th percentile of the length of hospital stay in patients who survived. Logistic regression was used for both univariate and multivariable analyses. Predefined covariates

Table 1
Clinical and laboratory features of participants on admission ($n = 107$)

Features	n	Median	(IQR)
Age, days	107	8.0	(6.0–11.0)
Time from first symptom to admission, days	104	3.0	(2.0–3.3)
Incubation period, days	105	6.0	(5.0–8.0)
Period of onset, h	102	24.0	(24.0–24.0)
Weight, kg	103	2.8	(2.5–3.0)
Temperature, °C	84	38.0	(38.0–39.0)
Heart rate, beats per min	85	140	(125–150)
White blood cell count, $\times 10^9$/l	98	12.0	(9.0–16.8)
Platelet count, $\times 10^9$/l	69	265.0	(190.0–444.0)
Haematocrit, %	67	47.0	(43.5–52.5)

IQR, interquartile range.