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Observational study shows that it is feasible to provide neuroprotective treatment for neonatal encephalopathy in low-income countries

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Abstract

Aim: Perinatal asphyxia is one of the most frequent causes of neonatal morbidity and mortality worldwide and 96% of the burden of neonatal encephalopathy occurs in low-income countries. This study investigated the feasibility of providing neuroprotective treatment for neonatal encephalopathy in low-income countries.

Methods: Neonates with a gestational age of at least 36 weeks, with signs of perinatal asphyxia, were included in this 2015 observational study in three hospitals in Kinshasa, capital of the Democratic Republic of Congo. Their characteristics were described, including the time to admission and Thompson score on admission.

Results: We found that 42/134 patients (31.3%) reached the hospital within six hours of birth with a Thompson score of at least seven on admission. Another 15 patients (11.2%) had a five-minute Apgar score of up to five, without a Thompson score, and were eligible for treatment. Of the 57 (42.5%) eligible patients 31 were discharged (54.4%), 25 died (43.9%) and one (1.8%) remained in hospital at the end of the study.

Conclusion: Interventional studies are feasible and necessary, especially in countries where the burden of neonatal encephalopathy is largest. A Thompson score of 7-15 might be a useful entry criterion for neuroprotective treatment in low-income countries.

Keywords: low-income countries, neonatal encephalopathy, neuroprotection, perinatal asphyxia, Thompson score.

Keynotes:

- The main burden of neonatal encephalopathy (96%) occurs in low-income countries and this study of 134 patients showed that it is feasible to provide neuroprotection in these settings.
- More than 40% of the patients in this study from the capital of the Democratic Republic of Congo were eligible for neuroprotective treatment
- A Thompson score of more than 7-15 may be used as the inclusion criterion for treatment.

INTRODUCTION

Perinatal asphyxia is one of the most important causes of perinatal morbidity and mortality. It accounts for about one quarter of global neonatal deaths (1) and about 96% of the total burden occurs in low-income countries (2). According to the Global Burden of Disease, in 2010 neonatal encephalopathy accounted for 50.2 million disability-adjusted life years, 44 million years of life lost and 6.0 million years lived with disability worldwide (3). Reducing neonatal deaths is increasingly being recognised as a public health priority and that is why one of the United Nations Millennium Goals was to reduce under-five mortality. Although progress have been made in reducing under-five child mortality, the progress on intrapartum-related conditions has been slow (4). If the present trend progresses, sub-Saharan Africa will account for 33% of the births with neonatal encephalopathy and 60% of the deaths in 2030, compared with 25% and 50%, respectively, in 2013.

For that reason, reducing newborn deaths is at the top of the child mortality agenda in the post-Millennium era (5). To achieve this in low-income countries, especially Sub-Saharan Africa, prenatal care needs to be improved, to reduce preterm births and breech deliveries. In

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addition, neonatal infections, such as sepsis, pneumonia and meningitis, should be recognised and treated early. Furthermore, neuroprotective treatment strategies should be investigated after the occurrence of perinatal asphyxia to reduce neonatal encephalopathy.

Neonatal encephalopathy can be identified using the Thompson score (6). This score is a clinical assessment tool, which describes tone, level of consciousness, fits, posture, Moro reflex, grasping, sucking, breathing and fontanel tone. It can be used to identify neonates with neonatal encephalopathy, who would be eligible for neuroprotective treatment (7,8). A cut-off value of seven or more within the first six hours after birth is often used as an entry criterion for intervention (8-10).

In order to administer the neuroprotective treatment within the therapeutic window, the baby should be transported to a neonatal ward facility within six hours of birth. In low-income countries, such as Sub-Saharan Africa, there can be a lack of transport systems, communications systems and many cannot afford private transport.

The aim of this study was to investigate whether it would be feasible in low-income countries, such as the Democratic Republic of Congo, to reach the hospital in time for neuroprotective treatment in neonates with neonatal encephalopathy. We also wanted to see if the Thompson score could be used as an inclusion criterion for referral.

METHODS

Participants

We studied neonates with a gestational age of at least 36 weeks, who were admitted with signs of perinatal asphyxia to the neonatology wards of three large public hospitals in Kinshasa, the country's capital. Gestational age was determined prenatally by early ultra

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sound in 50% of cases or by the last menstrual period. Perinatal asphyxia was defined as a five-minute Apgar score of up to five or the need for resuscitation until 10 minutes after birth. The three study locations were the University Hospital in south-west Kinshasa, Clinique Ngaliema, a well-equipped hospital in north-west Kinshasa, and the Saint Joseph hospital, a conventional Catholic hospital in the centre of Kinshasa that receives many referrals from local maternity units. The three hospitals have vital signs monitors and incubators, but no access to neonatal ventilation or blood gas analysis. The study was performed from 1 January 2015 until 30 September 2015, according to the guidelines for clinical studies laid down by the ethical committee of the University of Kinshasa and informed consent was obtained from the parents.

Procedure

Before the start of the study, a meeting was organised to train local midwives, gynaecologists and paediatricians to recognise a baby with signs of perinatal asphyxia. The Apgar score was recorded at one, five and 10 minutes after birth and all the doctors in the three hospitals were trained to perform a Thompson score on when the neonate was admitted to the hospital. At the time of admission, the birth weight, gestational age and whether the baby was inborn or outborn were noted. The outcome of the patient was recorded as death, discharged or still hospitalised.

The presence of encephalopathy was defined as a Thompson score of seven or more within the first six hours of birth. Neonates with severe congenital or chromosomal malformations were not included in this study, as they would be excluded from neuroprotective treatment. When no Thompson score was available, patients with a five-minute Apgar score of up to five and signs of perinatal asphyxia were considered to be eligible for neuroprotective treatment.

Statistics

The data are expressed as means and standard errors of the mean. Percentages were calculated. Results were tabulated or depicted as graphs. ANOVA or Fisher's exact test was performed to test differences between groups or distributions. A p value of <0.05 was considered statistically significant.

RESULTS

During the nine-month period, 134 neonates were admitted with signs of perinatal asphyxia in the three Kinshasa-based hospitals: 21 in the University hospital of Kinshasa, 14 in the Clinique Ngaliema and 99 in the Saint Joseph hospital. The characteristics of the admitted infants with signs of perinatal asphyxia are described (Table 1).

Of the 134 patients, 77 (57.5%) would not have been eligible for neuroprotective treatment because of a low Thompson score and, or, because they arrived in the hospital more than six hours after birth (37/77, 49.4%). A Thompson score of seven or more was recorded in 24 (31%) patients, a five or six in 24 (31%) patients and 16 (21%) had a Thompson score below five. In 13 (17%) patients, no Thompson score was recorded. Of the 77 patients who were not eligible for treatment, 57 (74%) were discharged, 17 (22%) died and three (4%) were still in hospital at the end of the study at the age of two, 10 and 14 days.

Of the 134 patients evaluated for perinatal asphyxia, 42 (31.3%) had a Thompson score of seven or more within six hours of birth and would have been eligible for neuroprotective treatment: six were admitted to the University Hospital of Kinshasa, seven to the Clinique Ngaliema and 29 to the St Joseph Hospital. Another 15 patients (11.2%) had a five-minute Apgar score of up to five without a Thompson score and were eligible for treatment. These

children were all admitted to the St Joseph Hospital. In total, 42.5% of the neonates would have been eligible for neuroprotective treatment.

The patients who were eligible for neuroprotective treatment, had a mean admission time to the hospital of 1.5 ± 0.2 hours, a gestational age of 38.4 ± 0.2 weeks, a birth weight of $2,878 \pm 74$ grams and their mothers had a mean age of 30.7 ± 0.8 years. The mean Thompson score was 10.3 ± 0.4 and the Apgar scores at one, five and 10 minutes were 3.3 ± 0.1 ; 4.5 ± 0.2 and 5.9 ± 0.3 , respectively (Figure 1).

There was a significant difference in the one-minute Apgar scores between the three centres: at Clinique Ngaliema it was 2.1 ± 0.3 , at the University hospital it was 3.0 ± 0.3 and at the St Joseph Hospital it was 3.6 ± 0.2 ($p=0.011$; post-hoc analysis St Joseph versus Clinique Ngaliema $p=0.004$). There were no significant differences in the five and 10-minute Apgar scores or the Thompson score at admission.

There were no significant differences in admission time, gestational age and birth weight between the three hospitals. However, a significant difference for maternal age was found, namely 25.2 ± 1.0 years at the Clinique Ngaliema, 27.7 ± 1.4 years at the University Hospital, and 31.9 ± 0.9 years at the St Joseph Hospital ($p<0.021$; post-hoc analysis St Joseph Hospital versus Clinique Ngaliema $p=0.01$).

Of the 57 eligible patients, 10 were outborn and were referred from the surrounding clinics and 47 were inborn. The mean time until admission to the neonatology ward of the inborn patients was 1.3 ± 0.2 hours and it was 2.5 ± 0.3 hours for the outborn patients. In this group,

31 were discharged (54.4%), 25 died (43.9%) and one (1.8%) was still in hospital at the end of the study (see Figure 2).

We found that 30 of the 57 eligible patients had a Thompson score of 7-11, nine had a score of 12-15 and three had a score of at least 16. The Thompson score was not recorded for 15 patients. Deaths occurred in 8/30 of the patients admitted with a Thompson score of 7-11, 6/9 (67%) with a score of 12-15 and all patients with a score of 16 or more (Fisher's exact test $p=0.0082$) (Figure 3).

DISCUSSION

This study describes perinatal asphyxia the Democratic Republic of Congo, which is one of the poorest countries in the world and has the most daunting infrastructure on the African continent (11). Several studies have been performed in the country and these reported that the incidence of perinatal asphyxia was 39-45 per 1,000 live births at the University Hospital of Kinshasa and that the early neonatal death rate was 32 per 1,000 live births in rural Congo, of which 34% were caused by perinatal asphyxia (12-14). In 2013 a survey was undertaken to estimate the incidence of perinatal asphyxia in the three large hospitals featured in our study. Perinatal asphyxia was defined as a five-minute Apgar score up to five or the need for resuscitation until 10 minutes after birth. Of the 1,478 children admitted to the neonatal wards, 187 (12.7%) had asphyxia and 134 were analysed for perinatal asphyxia over a nine-month period, which equated to 179 infants per year. This was almost the same as our figure of 187 infants admitted with signs of perinatal asphyxia in 2013.

Several grading systems have been developed to assess neonatal encephalopathy in infants with perinatal asphyxia. The Thompson score, which was derived from the Sarnat and Sarnat grading system, is a simple clinical method based on the neurological examination and assessment of respiration and fontanel tension (6). The method is quick to perform, requires no additional training for medical and paramedical personal and requires no equipment. Therefore, it is strongly recommended for use in low-income countries, where sophisticated equipment such as continuous electroencephalogram registration, near-infrared spectroscopy, and, or, magnetic resonance imaging are unavailable to assess neonates with neonatal encephalopathy. Within six hours of birth, a Thompson score at least seven is a sensitive predictor of either an abnormal six-hour amplitude integrated electroencephalography or moderate to severe encephalopathy presenting within 72 hours of birth (7). This Thompson score may be used to assist with the triage and selection of infants for neuroprotective treatments, such as therapeutic hypothermia (8-10).

In our study 27% of the patients with a Thompson score on admission of 7-11, 67% with a score of 12-15, and all patients with a score of 16 or more died. This was in line with the findings of Thorsen et al who reported that in the cooled population a Thompson score of 12 or more was associated with increased odds for death before discharge (odds ratio 3.9, 95% confidence interval 1.3-11.2) (8). Also Horn et al reported that 75% of the patients with a Thompson score of 16 or more three to five hours after birth had a severely abnormal amplitude integrated electroencephalography or died within 48 hours, even when they were cooled (7). With regard to future clinical trials, patients with a Thompson score of 7-15 might be eligible for neuroprotective treatment.

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In this study more than 40% of the patients with perinatal asphyxia were born in the hospital or reached the hospital in time to receive neuroprotective treatment, making an intervention study feasible, even in a low-income countries like the Congo. About half of the patients (49.4%) with signs of perinatal asphyxia arrived too late to receive neuroprotective treatment. These findings show the real problem experienced in low-resource settings where numerous factors may explain why patients cannot reach the hospital in time. These factors may be related logistical problems, like infrastructure, private transport or communication, or to the parents' financial situation, as referral and treatment might be too expensive.

The conduct of a clinical trial in a low-income country is a challenge. It is not only patient-related factors that are important. Hospitals do not always have the necessary equipment, pharmacies do have the facilities to safely use and store medication and power shutdowns are frequent and voltage fluctuations can damage equipment. We found that the logistics of such a study were feasible, with the help of a strong, locally trained mobile doctor team, help from a clinical research organisation and the availability of generators and voltage stabilisers,.

Several neuroprotective treatment strategies are currently being investigated to reduce cerebral damage during neonatal encephalopathy,. Therapeutic hypothermia has become the standard of care for neonatal encephalopathy in high-income countries (15). However, a meta-analysis on therapeutic hypothermia in low-income countries using low-cost cooling techniques, did not show a significant reduction in neonatal mortality (16). It was concluded that adequately randomised controlled trials are required before cooling can be offered in low-income countries (17).

Pharmacological strategies include treatments that are affordable for the people in low-income countries, are cost-effective and can be easily administered, with storage conditions that are compatible with a high temperature environment. Potential drugs include melatonin and 2-iminobiotin (18-19), a vitamin B7 analogue that has to be stored in temperatures above 10 degrees Celsius, can be easily administered either through an umbilical catheter or a venous infusion and is affordable. Melatonin is a drug with the same capacities for oral administration, although the available intravenous formulation contains ethanol, which might not be acceptable for neonatal administration (20). Erythropoietin is an alternative and frequently-studied drug for neuroprotection, although storage in a refrigerator is necessary, and that is not affordable for people in low-income countries (21).

We believe that together with supporting strategies in prenatal and perinatal care to prevent perinatal asphyxia, it is time to think about neuroprotective interventions in low-income countries, such as the Congo, where the neonatal encephalopathy burden is the largest. Efforts should be made to explore new interventions for neonatal encephalopathy that are feasible, cost-effective and safe in low-income countries. This was also stated in a commentary by Tagin et al, who advocated complementary contributions by high-income countries, who have established expertise in medical trials, to low-income countries that bear the burden of neonatal encephalopathy (22).

In such interventional studies, infants with neonatal encephalopathy would be invited to attend follow ups at four, six, nine, 12, 18 and 24 months to assess neurological outcomes using the Bayley Scales of Infant and Toddler Development - Third Edition

CONCLUSION

Our study showed that more than 40% of neonates with neonatal encephalopathy were born in the three study hospitals or reached them in time in time to receive neuroprotective treatment. By improving prenatal care and increasing the knowledge of local obstetricians and pediatricians, we can create greater awareness of perinatal asphyxia and the incidence can be lowered. A Thompson score of 7-15 might be eligible for neuroprotective treatment in low-income countries.

Funding

TB received money from Neurophyxia to organise a meeting for all the local midwives and paediatricians to discuss the study.

Conflicts of interest

HT and CPS work as consultants for, and are shareholders of, Neurophyxia, a drug development company that aims to develop new drugs for newborn infants.

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Table 1: Characteristics of patients admitted with signs of asphyxia (n=134)

Factors	Mean $\pm$ SEM
Maternal age (years)	28.3 $\pm$ 0.5
Postmenstrual age (weeks)	38.5 $\pm$ 0.1
Birth weight (grams)	2907 $\pm$ 47.2
Apgar score at 1 minute	3.5 $\pm$ 0.1
Apgar score at 5 minutes	4.5 $\pm$ 0.1
Apgar score at 10 minutes	6.0 $\pm$ 0.2
Thompson score at admission	8.1 $\pm$ 0.3
Outborn (%)	40 (29,9%)

SEM: standard error of the mean.

Figure legends

Figure 1: Thompson score on admission and the Apgar score at one, five and 10 minutes after birth of all 57 eligible patients. Data represents mean $\pm$ standard of the mean.

Figure 2: Outcomes of the 57 eligible patients with encephalopathy in the three public hospitals.

Figure 3: Outcomes of the 57 eligible patients, according to the Thompson score at admission

Figure 1

Figure 2

Figure 3