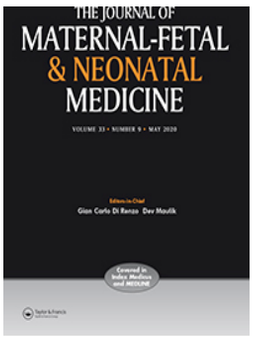

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ORIGINAL ARTICLE

Birthplace is a risk factor for exchange transfusion in outborn infants admitted for jaundice in Myanmar: a case-control study

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ABSTRACT

Aim: To evaluate the role of pathway to admission for jaundice among the risk factors for exchange transfusion in outborn infants in a low resource setting.

Methods: This retrospective case-control study (1:1 ratio) was carried out at the Yankin Children's Hospital in Yangon (Myanmar). All cases were neonates admitted for treatment of jaundice between March 2013 and February 2014 and who required an exchange transfusion. Each control was the next noncase neonate admitted for treatment of jaundice and treated with phototherapy. Infant characteristics, pathways of admission and clinically relevant factors for exchange transfusion were collected.

Results: One hundred thirty-four cases and 134 controls were included in the study. Among cases, home was the most common place of birth while public hospital was the most frequent source of referral. Among controls, private/public hospitals were the commonest places of birth and referral. At multivariable analysis, homebirth was associated with increased likelihood of receiving exchange transfusion at admission (OR 3.30, 95% C.I. 1.31–8.56).

Conclusion: Homebirth was an independent risk factor for exchange transfusion at admission for jaundice in a low-resource setting. Appropriate health education of pregnant women and traditional/home birth attendants may contribute to reduce the need for exchange transfusion in low-resource settings.

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KEYWORDS
Exchange transfusion; jaundice; low-resource setting; phototherapy

Background

Severe neonatal hyperbilirubinemia (SNH) is one of the most frequent reasons for hospitalization or readmission in the first week of life worldwide [1]. SNH is an important cause of neonatal morbidity and mortality, especially in low- and middle-resource countries [2].

Exchange transfusion (ET) is a common and effective treatment for SNH with the goal of preventing bilirubin-induced neonatal mortality and long-term morbidity, but it is also associated with procedure-related complications [3,4]. Although improvements in prevention and in treatment have reduced the requirement for ET in high-resource countries [5], high rates of avoidable ET are still reported in low- and middle-resource countries [6,7].

In low- and middle-resource countries, facility-based constraints introduce additional challenges inadequate risk-assessment and logistical support [8]. In addition, clinical guidelines for neonatal jaundice do not exist in many low- and middle-resource countries [6]. The adaptation of existing guidelines from high-resource countries is actually limited by the interactions with multiple causes linked to population and environment [9]. Therefore, a recent review highlighted the need for additional knowledge on specific risk factors that may be relevant in these settings [2]. Understanding the pathways to admission may provide information on organizational aspects that could be targeted with interventions.

The aim of the present study was to evaluate the role of pathway to admission among the risk factors

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for ET in outborn infants in order to plan adequate prevention strategies in a low resource setting.

Materials and methods

Study design

This retrospective case-control study (1:1 ratio) was carried out at the Yankin Children's Hospital in Yangon (Myanmar), as part of a research project on neonatal admission for jaundice. The study was performed in accordance with the Helsinki Declaration of 1975, as revised in 1983, and was approved by the Ethics Committee on Medical Research Involving Human Subjects of Myanmar Department of Health (No. 14/2014).

Setting

The Yankin Children's Hospital (YKCH) is a tertiary referral pediatric hospital in Yangon (Myanmar), covering a geographical catchment area of about 8 million people [10]. In this area, admissions for neonatal jaundice are responsible for around 46% of all hospital admissions for conditions originating in the perinatal period [11]. Admissions at YKCH include neonates born at home, those born in private or public health facilities and discharged home and those transferred directly from lower level facilities [10].

Patients

The cases were all consecutive neonates admitted at YKCH for treatment of jaundice between 1 March 2013 and 28 February 2014 and who required ET according to local protocols based on AAP guidelines [3]. The case-control ratio was 1:1. Each control was the next noncase neonate admitted for treatment of jaundice and treated with phototherapy. All neonates were followed until discharge or death during hospital stay.

Variables

Infant characteristics (gestational age, birth weight, sex, age at admission and weight at admission), the pathway of admission to YKCH (birthplace, referral source, and timing of admission) and risk factors for hyperbilirubinemia were collected from local medical records. The risk factors included gestational age $<$38 weeks, significant bruising, previous sibling receiving phototherapy, feeding poorly, asphyxia, sepsis, ABO incompatibility, rhesus incompatibility and glucose-6-phosphate dehydrogenase (G6PD) deficiency [2,12]. The recording of (suspected) infection/sepsis was at the discretion of the clinician completing the admission paper and was not subjected to pre agreed diagnostic rules (e.g. laboratory confirmation) [13]. The use of natural/traditional medicine was also recorded. This form of medicine is very common in Myanmar and is available at any store without a prescription. These medicines are plant based and taken orally by mothers for an unspecified period before and after delivery. Information on total serum bilirubin (TSB), kernicterus at admission [14] and phototherapy elsewhere before admission at YKCH were also retrieved.

Statistical analysis

Continuous data were expressed as medians and interquartile ranges (IQRs), and categorical data as number and percentage. Continuous data were compared between cases and controls using the Mann–Whitney test, and categorical data using Fisher's test. A logistic regression model was estimated to identify independent predictors of ET among the pathway of admission, clinically relevant factors (age at admission, natural/traditional medicine) and known risk factors for hyperbilirubinemia (listed in Variable section). Time of referral was not included in the model due to large quantities of missing data. Use of natural/traditional medicine was included because local health providers suggested its possible role in delaying the treatment. Model selection was performed by minimizing the Akaike information criterion (AIC). A p value less than .05 was considered statistically significant. Statistical analysis was performed using R 3.2.2 (R Foundation for Statistical Computing, Vienna, Austria) [15].

Results

Patients

In total, 134 cases and 134 controls were included in the study (Table 1). ET was not performed in 14 cases due to patient instability (13 cases) or to parental refusal (one case). ET was performed in 120 cases at a median of 6.2 hours after admission (IQR 4.3–9.0) and reduced TSB from median 26.2 mg/dl (IQR 24.3–28.0) to median 14.9 mg/dl (IQR 12.2–19.3). All controls received phototherapy at admission, while 25 cases received phototherapy before ET.

Table 1. Patient characteristics at admission.

	Cases	Controls
Number of subjects	134	134
Exchange transfusion		
No	0	134
Required and performed	120	0
Required but not performed	14	0
Phototherapy elsewhere, prior to admission		
Yes	29 (21.6)	31 (23.1)
No	42 (31.4)	54 (40.3)
Unclear	63 (47.0)	49 (36.6)
Phototherapy at admission		
Yes	25 (18.7)	134 (100.0)
No	109 (81.3)	0
TSB at admission		
TSB at admission, mg/dl[a]	25.6 (20.9–28.0)	16.8 (14.3–20.0)
Kernicterus at admission		
Signs of impeding kernicterus[b]	21 (15.7)	0
Signs of kernicterus[c]	17 (12.7)	0

Data expressed as *n*(%) or [a]median (IQR). Exchange transfusion (ET) was planned but not performed in 14 cases due to patient instability (13 cases) or to parental refusal (one case). TSB: total serum bilirubin. [b]Presence of lethargy, floppiness and poor feeding. [c]Presence of opisthotonos, high-pitched cry and convulsions.

Pathway to admission

Among cases, home was the most common place of birth (43.3%) while public hospital was the most frequent source of referral (41.8%) (Table 2). Among controls, private and public hospitals were the commonest places of birth (41.0% each) and the commonest source of referral (40.3 and 33.6%) (Table 2). Overall, infants were referred directly from their birthplace in 198 instances (91, 67.9% in cases versus 107, 79.9% in controls; $p = .04$). The proportion of selfreferral among infants born at home was similar in the two groups (29 out of 58, 58% in cases versus 12 out of 20, 60% in controls; $p = .60$).

Risk factors for requiring exchange transfusion at admission for jaundice

At admission, cases were younger than controls (median age 81 versus 100 hours, $p = .0006$). Median birth weight was 3000 grams (IQR 2778–3500) in cases and 3076 grams (IQR 2800–3466) in controls ($p = .43$), while median weight at admission was 3000 grams (IQR 2500–3200) in cases and 3000 grams (IQR 2800–3350) in controls ($p = .03$). Risk factors for ET are shown in Table 2. Place of birth and source of referral were different in the two groups (Table 2), with shorter time of referral in cases (median 50 versus 70 hours in controls, $p = .0002$). Use of natural medicine during pregnancy was similar in the two groups ($p = .99$). Significant bruising ($p = .004$), feeding poorly ($p < .0001$), sepsis ($p < .0001$) and G6PD deficiency ($p = .005$) were more frequent in cases than in controls (Table 2).

Multivariable analysis (Table 3) identified homebirth (OR 3.30, 95% C.I. 1.31–8.56), sepsis (OR 8.57, 95%C.I. 4.22–18.26), feeding poorly (OR 7.52, 95%C.I. 3.64–16.26), significant bruising (OR 3.79, 95%C.I. 1.12–14.41) and G6PD deficiency (OR 3.26, 95%C.I. 1.57–7.07) as independent predictors for requiring ET at admission for jaundice. Older age at admission (OR 0.995, 95%C.I. 0.990–0.999) was associated with lower likelihood of requiring ET (Table 3).

Outcome at discharge

The median length of stay was shorter in cases than in controls (median 132 [IQR 96–251] versus 61 [IQR 46–107] hours, $p < .0001$). Mortality was 26.1% in cases and 0.7% in controls. The cause of death included kernicterus (28 cases), sepsis (20 cases and one control), encephalopathy (eight cases), hyperbilirubinemia (seven cases), respiratory failure or asphyxia (two cases) and congenital heart defect (one case).

Discussion

The present study investigated the role of pathway to admission among the risk factors for receiving ET for jaundice in outborn infants in a low resource setting. Homebirth, but not source of referral, was an independent risk factor for ET at admission. Sepsis, feeding poorly, significant bruising and G6PD deficiency were also associated with increased likelihood of receiving ET.

Neonatal jaundice is common and usually benign, but SNH can lead to kernicterus or chronic bilirubin encephalopathy. Kernicterus results from injury to the

Table 2. Univariate analysis of risk factors for requiring exchange transfusion at admission for jaundice.

	Cases ($n = 134$)	Controls ($n = 134$)	p value
At admission			
Males	87 (64.9)	90 (67.3)	.80
Age at admission, hours[a,b]	81 (58–110)	100 (74–177)	.0006
Natural/traditional medicine	59 (44.0)	60 (44.8)	.99
Pathway of admission			
Place of birth:			<.0001
Home	58 (43.3)	20 (15.0)	
Other public facilities	14 (10.4)	4 (3.0)	
Public hospital	43 (32.1)	55 (41.0)	
Private hospital	19 (14.2)	55 (41.0)	
Source of referral:			.001
Home	36 (26.9)	21 (15.7)	
HC/clinic	17 (12.7)	14 (10.4)	
Public hospital	56 (41.8)	45 (33.6)	
Private hospital	25 (18.6)	54 (40.3)	
Time of referral (from referral source to Yankin), hours[a,c]	50 (26–80)	70 (46–109)	.0002
Selected risk factors for hyperbilirubinemia			
Gestational age <38 weeks[d]	12 (9.2)	13 (9.8)	.99
Significant bruising	21 (15.7)	6 (4.5)	.004
Previous sibling had phototherapy	7 (5.2)	7 (5.2)	.99
Feeding poorly	87 (64.9)	17 (12.7)	<.0001
Asphyxia	10 (7.5)	3 (2.3)	.08
Sepsis	89 (66.4)	21 (15.7)	<.0001
ABO incompatibility	25 (18.7)	37 (29.6)	.11
Rhesus incompatibility	3 (2.2)	5 (3.7)	.72
G6PD deficiency	59 (44.0)	36 (26.9)	.005

Data expressed as n (%) or [a]Median (IQR). Data not available in [b]one, [c]53 and [d]5 subjects. G6PD: glucose-6-phosphate dehydrogenase.

Table 3. Multivariable analysis of risk factors for requiring exchange transfusion at admission for jaundice.

	Variables	p value	Odds ratio (95%C.I.)
At admission	Age at admission (hours)	.03	0.995 (0.990–0.999)
	Natural/traditional medicine	.65	–
Pathway of admission	Place of birth:	<.0001	
	Home		3.30 (1.31–8.56)
	Other public facilities		2.55 (0.54–14.23)
	Public hospital		1.45 (0.63–3.43)
	Private hospital		Reference
	Source of referral:	.46	–
	Home		
	HC/clinic		
	Public hospital		
	Private hospital		
Selected risk factors for hyperbilirubinemia	Gestational age <38 weeks	.48	–
	Significant bruising	.04	3.79 (1.12–14.41)
	Previous sibling had phototherapy	.53	–
	Feeding poorly	<.0001	7.52 (3.64–16.26)
	Asphyxia	.79	–
	Sepsis	<.0001	8.57 (4.22–18.26)
	ABO incompatibility	.22	–
	Rhesus incompatibility	.51	–
	G6PD deficiency	.002	3.26 (1.57–7.07)

G6PD: glucose-6-phosphate dehydrogenase.

brain in areas that are susceptible to bilirubin staining, including the bilateral globus pallidus, subthalamic nuclei, brainstem, and cerebellum [16]. This type of brain injury results in severe quadriplegic cerebral palsy with the classic extrapyramidal signs of choreoathetosis and/or dystonia. Kernicterus has been referred to as one of the few preventable causes of cerebral palsy [17], but it remains a significant burden in low- and middle-resource countries [6]. Moreover, patients with SNH requiring ET have an increased risk of mortality [2].

In low- and middle-resource countries, additional challenges are presented by environmental and sociocultural factors, which may affect the pathways to admission for care [9,10]. In our data, infants requiring ET were more likely to born at home and referred from home than those requiring phototherapy. Interestingly, most infants were referred directly from

their birthplace, either home or hospital. These findings may suggest the presence of cultural or socioeconomic issues regarding birthplace, given that to physical access care does not appear to be an issue in the Yangon geographical area. At multivariable analysis, homebirth, but not referral source, was a risk factor for requiring ET at admission. Homebirth has been suggested to be a proxy for other factors, rather than being a risk factor *per se* [13]. These factors include racial differences correlated with genetic risk, socioeconomic status, cultural aspects and geographical barriers to facility access [13]. Appropriate training on essential newborn care for traditional/home birth attendants, and home visits by nurses/midwives in the first week of life are crucial [9]. Such interventions have been planned in Myanmar, but lack of resources has hampered full implementation [18]. In our study, one out of four cases selfreferred from home, thus stressing the need for education of parents on a selected subset of signs that need urgent selfreferral to a tertiary referral hospital.

In the present study, sepsis, feeding poorly, significant bruising and G6PD deficiency were also associated with increased likelihood of receiving ET. Prevention of early-onset infections may contribute to reducing the need for ET at admission as well as the associated mortality, but some recommended practices are often not followed in low-resource settings [19]. Previous studies showed a wide maternal knowledge gap on recognition and care of neonatal jaundice in southeastern Asia [20,21]. In addition, breastfeeding discontinuation has been observed in mothers of infants admitted for jaundice [22]. Health education of pregnant women including teaching the signs of jaundice (as significant bruising or feeding poorly) may reduce the failure to recognize clinical signs. G6PD deficiency can cause SNH through severe hemolysis if triggered (i.e. by naphthalene or sepsis); nevertheless, G6PD-deficient infants are at higher risk of acute and chronic bilirubin encephalopathy even if not triggered [2]. In areas with a high prevalence of G6PD deficiency, universal screening has been suggested, but the implementation is limited in many settings due to resource constraints [6,23]. Although TSB assessment in all newborns before discharge from an obstetric facility may prevent readmissions for SNH [24], it may not be readily affordable in many resource-limited settings [9]. The development and validation of accurate low-cost devices for TSB assessment should provide an affordable screening system in these settings [6,25].

Natural/traditional medicine is still very common during pregnancy in low- and middle-resource countries [2,7,9]. Although this cultural approach was believed to limit or delay care-seeking for jaundice [9,26], it was not associated with increased ET in our data.

The findings of the present study contribute to identify areas of intervention in low- and middle-resource countries. However, the present study has some limitations. First, it is a retrospective single-center study, so the generalizability of the findings may be limited to similar settings. However, our findings were in broad agreement with previous studies performed in Africa and southeastern Asia, thus contributing to identify possible areas of intervention and gaps in knowledge. Second, it would be interesting to evaluate the effect of prophylactic phototherapy on need for ET for jaundice [27], but this aspect could not be evaluated due to the lack of clear information on phototherapy before admission.

Conclusion

Homebirth was a risk factor for ET at admission for jaundice in a low-resource setting. Sepsis, feeding poorly, significant bruising and G6PD deficiency were also risk factors for ET. Recognition of such factors and appropriate health education of pregnant women and traditional/home birth attendants may contribute to reducing the need for ET in low-resource settings.

Disclosure statement

No potential conflict of interest was reported by the authors.

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