Gastroschisis in a developing country: poor resuscitation is a more significant predictor of mortality than postnatal transfer time

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Background: The time from birth to the first paediatric surgical consultation of neonates with gastroschisis is a predictor of mortality in developing countries. This is contrary to findings in the developed world. We set out to document this relationship within our population.
Methods: Neonates with gastroschisis who were transferred to Steve Biko Academic Hospital within the study period were included. The association between mortality and demographic, clinical and biochemical variables was assessed. Significant variables after univariate analysis were subjected to multivariate regression.
Results: Sixty patients were included. The mortality rate was 65%. Mean transfer time and distance were 14.9 hours and 225km. Forty-eight per cent of the neonates were either dehydrated or in hypovolaemic shock clinically on arrival. Eight neonates arrived hypothermic. It was shown through univariate analysis that female sex, appropriate weight for gestational age, hydration status, gestation, transfer time, serum urea, base deficit and serum bicarbonate (HCO3) were significant predictors of mortality. Only female sex, appropriate weight for gestational age and serum HC03 were shown to be significant using ultivariate analysis.
Conclusion: Our high mortality rate was not due to lengthy transfer times. The poor clinical condition of the patients on arrival at our hospital, which relates to deficiencies in the neonatal transfer system, had a direct impact on the survival of neonates with gastroschisis.

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Gastroschisis is the most common congenital anterior abdominal wall defect treated in our hospital. Currently, the incidence is 2.0–4.9 per 10 000 live births, and is increasing throughout the world.[1,2] A similar increase has been reflected in South Africa.[3]

The mortality of infants born with gastroschisis in developed countries is ≤ 10%,[4] whereas mortality in developing countries is from 35–80%.[3,5–8]

Delays in transferring these neonates from the peripheral hospitals to specialised institutions has been shown to result in increased mortality in developing nations.[6,7] However, it has been shown in multiple studies in First World countries that the absence of a prenatal diagnosis and the consequent postnatal transfer does not influence morbidity and mortality.[9-12] A routine antenatal ultrasound examination is uncommon in the South African public health system, and not part of the antenatal workup of uncomplicated pregnancies in all provinces. As a result, the postnatal transfer of neonates diagnosed with gastroschisis at birth to institutions where specialised paediatric surgical care is available is the norm. Mortality associated with gastroschisis at our institution was previously shown to be at least 39%.[3]

It was not known whether or not the mortality of neonates born with gastroschisis within our population catchment area could be explained by a delay in transfer, similar to that in other developing countries.

In this study, we set out to document the relation between the time from the birth of neonates born with gastroschisis within our population catchment area to their admission to our paediatric surgical unit, their clinical condition on arrival and their mortality.

Method

Setting

Steve Biko Academic Hospital is a public tertiary referral hospital in Tshwane (Pretoria), South Africa, attached to the University of Pretoria medical campus. The Department of Paediatric Surgery is one of two paediatric surgical referral centres for the City of Tshwane, and the only referral centre for the adjacent Mpumalanga province. The paediatric surgical department serves a population of approximately 7 million people,[13] with an average of approximately 124 000 births per year.[14] Six intensive care unit (ICU) beds and five neonatal ward beds are available for the treatment of all neonatal surgical admissions.

Study design

This study was conducted prospectively from February 2011 until September 2013. Neonates born with gastroschisis and transferred to Steve Biko Academic Hospital during this period were eligible for inclusion in the study. Neonates born with gastroschisis at Steve Biko hospital (inborn) were not eligible for inclusion. The study was undertaken with the approval of the University of Pretoria's MMed and ethics committees, and was therefore performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Informed consent was obtained from the parents of the infants included in the study.

Data collection

Data were collected by the admitting doctor in the paediatric surgical department at initial admission. Data on demographics, the birth history, transfer time and transfer distance were collected. Clinically relevant dates and times of birth and admission were recorded. The clinical condition of the child on arrival, as well as the method of bowel coverage by the referring doctor, was also recorded. If birth information was unavailable, the transferring hospital was contacted to supply the missing information from its birth register. On admission, blood was also taken for analysis of the patient's metabolic status in the form of arterial blood gas, serum urea and serum creatinine. Dates of discharge or mortality were recorded following the outcome. Data were collected according to definitions (Table 1).

Outcomes

Survival to hospital discharge or in-hospital mortality was the primary outcome studied.

Table 1: Definitions with respect to the collection of the study data

Transfer time	Time from the birth to admission at our unit (hours)
Distance of transfer	Distance (kilometres) from the referring hospital to Steve Biko Academic Hospital using the shortest available driving route
Gestation	Obtained from the antenatal card or mother if there was certainty about the dates, or the Ballard score if there was uncertainty
Hydration status	Each neonate was grouped into one of three groups (Table 2), based on the clinical parameters of skin turgor, capillary refill time, the presence of a sunken fontanelle, mucous membrane moisture, pulse rate and blood pressure
Respiratory distress	Regarded as positive in the presence of at least one of the following: • Tachypnoea ≥ 60 breaths per minute • Subcostal or intercostals recessions • Nasal flaring
Place of birth	At a referring hospital or clinic (healthcare facility) or at home
ICU admission	The patient was admitted to the ICU if a bed was available, or to the neonatal cubicle of the paediatric surgical ward if not
Weight for gestational age[15]	Small for gestational age less than 10th centile weight for gestation Appropriate for gestational age from 10–90th centile
Birthweight category	• Normal birthweight of ≥ 2.5 kg • Low birthweight from 1.5–2.49 kg • Very low birthweight from 1.0–1.49 kg • Extremely low birthweight < 1.0 kg
Sepsis	Regarded as positive at any point during the admission if the patient had clinical features of sepsis, with a positive blood culture result

ICU: intensive care unit

Table 2: Univariate analysis of the categorical variables as potential predictors of mortality

Categorical variables	*n*	Mortality rate (%)	*p*-value
Sex			
Male	24	50.0	0.058
Female	36	75.0	
Weight category			
Normal birthweight	21	71.4	
Low birthweight	37	59.5	0.471
Very low birthweight	2	100.0	
Weight for gestational age			
Appropriate for gestational age	31	80.7	0.014
Small for gestational age	29	48.3	
Place of birth			
Healthcare facility	51	87.2	0.706
At home	9	12.8	
Respiratory distress*			
Present	16	29.0	0.766
Absent	43	71.1	
Clinical hydration status			
Well hydrated	31	51.6	
Dehydrated	20	75.0	0.074
Shock	9	88.9	
Type of dressing applied to viscera			
Modified intravenous bag	36	63.9	
Other form of plastic	14	71.4	0.543
Gauze	9	66.7	
None	1	0.0	
Admission ward on arrival			
Intensive care unit	19	63.16	1.000
Paediatric surgical ward	41	65.85	
Sepsis during admission			
Present	33	57.58	0.277
Absent	27	74.07	

*: Data were not collected for one patient. Therefore, the respiratory status of only 59 patients was analysed

Results

Sixty-two patients with gastroschisis were admitted from referring hospitals during the study period. Two patients were excluded from the study. One patient was excluded because the admission data were not recorded adequately, and one because the patient received specialist paediatric surgical care prior to transfer to our department. Four inborn patients were ineligible for admission to the study during the study period. Sixty patients were subjected to statistical analysis.

The mortality rate for the cohort was 65%. Univariate analysis of the categorical variables is shown in Table 2, and that of the continuous variables in Table 3.

A male to female ratio of 2:3 was evident. The mean birthweight was 2.4 kg and gestation 36 weeks. Most neonates were born < 2.5kg (65%), while there were similar numbers of small-for-gestational-age (SGA) and appropriate-for-gestational-age (AGA) neonates. The mean maternal age was 21 years. The minority of births occurred outside a healthcare facility (17%).

The mean transfer time was 14.9 hours (a median of 9 hours and a range of 3.3–106.4 hours). The transfer distance was 225 km (19–439km).

Table 3: Univariate analysis of the continuous variables as potential predictors of mortality

Continuous variables	Range	Mean (95% CI) for the survivor and mortality groups		*p*-value
		Survive to discharge	Mortality	
Birthweight (kg)	1.00–3.45	2.20 (2.05–2.36)	2.26 (2.08–2.45)	0.611
Gestation (weeks)	32–42	36.70 (35.76–37.67)	35.80 (35.24–36.44)	0.120
Maternal age (years)	15–42	22.00 (19.36–24.64)	20.80 (19.69–21.96)	0.401
Apgar score (1 minute)	4–9	7.53 (6.92–8.13)	7.94 (7.41–8.46)	0.290
Apgar score (5 minutes)	6–10	9.29 (8.72–9.86)	9.38 (8.99–9.78)	0.791
Transfer time (hours)	3.30–104.00	11.20 (6.80–15.49)	17.00 (10.70–23.21)	0.123
Transfer distance (km)	19–439	197.62 (135.50–259.20)	239.20 (193.40–285.00)	0.270
Temperature (°C)	≤ 35.00–39.50*	36.40 (36.10–37.00)	37.30 (35.90–38.80)	0.196
Serum urea (mmol/l)	2.10–14.60	5.33 (4.01–6.66)	7.25 (5.17–9.43)	0.131
Serum creatinine (mmol/l)	39–236	85.45 (64.65–106.25)	90.91 (75.07–106.76)	0.668
pH	6.81–7.60	7.36 (7.32–7.40)	7.32 (7.27–7.63)	0.178
PCO2 (mmHg)	10.20–128.00	33.99 (21.66–46.32)	26.74 (24.08–29.40)	0.241
Base deficit (mmol/l)	2.00–29.20	8.71 (7.22–10.20)	10.64 (8.90–12.38)	0.088
Serum HCO3 (mmol/l)	8.70–21.50	16.67 (15.46–17.85)	14.61 (13.49–15.73)	0.013

Apgar: appearance, pulse, grimace, activity and respiration, CI: confidence interval, PCO2: partial pressure of carbon dioxide in arterial blood, HCO3: bicarbonate

*: The minimum recordable temperature was indicated as ≤ 35 °C on the digital thermometer used on all patients

Statistical analysis

The modelling approach was used to consider the associations between mortality and the individual demographic, clinical and biochemical variables in order to determine the risk factors for mortality. Univariate analysis was performed using Fisher's exact test for the categorical data and Welch's t-test for continuous data. Factors that were significant at a liberal *p*-value of 0.150 were included in a multivariate regression model. A stepwise model was then used to determine the significant factors retained in the final model (p = < 0.05).

The hydration status of 48% of the neonates was assessed as either dehydrated or in hypovolaemic shock. Only one patient arrived without any coverage of the viscera, while the exposed viscera of 68% of the neonates were covered with a modified intravenous fluid bag. Eight patients arrived with a temperature of < 36°C, five of whom had a temperature of ≤ 35°C. The majority of the neonates were admitted to the paediatric surgical ward (68%) and not to the ICU. Two patients experienced complete midgut necrosis on admission, were not actively managed further, and were transferred back to the referring hospitals for palliative care after the parents had been counselled. Both were included in the mortality group.

The mean blood gas analysed (serum HCO3) for those who survived was 16.67mmol/l, while the mean serum HC03 on admission of the neonates who died was 14.61mmol/l, the pH was 7.32 and partial pressure of carbon dioxide in arterial blood 26.74mmHg.

It was revealed through univariate analysis that variables associated with mortality at a liberal *p*-value of 0.150 included the female sex, AGA, a hydration status of dehydrated or in hypovolaemic shock, gestation, transfer time, serum urea, arterial base deficit and serum HCO3.

Table 4: Logistic regression analysis of factors associated with mortality

Factors	Odds ratio	95% CI	*p*-value
Female sex	5.80	1.31–25.66	0.020
Appropriate weight for gestational age	6.86	1.60–29.34	0.009
Serum HCO3	1.37	1.08–1.74	0.009

CI: confidence interval, HCO3: bicarbonate

It was found following logistic regression analysis (Table 4) that only female sex, AGA and serum HCO3 on admission were significantly associated with mortality (p = < 0.050). The odds of mortality in a female neonate with gastroschisis were 5.8 times greater that of a male neonate (p = 0.020). There was a 6.8-fold greater odds of mortality during their admission for neonates with gastroschisis and

AGA than those who were SGA (p = 0.009). A decrease of 1mmol/l in serum HCO3 measured on admission resulted in a 1.4-fold increase in the odds of mortality (p = 0.009).

Interestingly, 48 cases of gastroschisis over a 20-year period (1981–2001) were identified in the previous study,[3] whereas the 60 patients in this study were admitted over a 32-month period. This is in keeping with the rise in the incidence of gastroschisis worldwide,[2] and also reflects a likely increase in the population within our drainage area. Our cohort was far greater than the 19 neonates with gastroschisis reported over a four-year period in Cape Town,[16] and similar to the cohort of approximately 17 patients per year reported in Durban.[17] Further epidemiological studies are required to accurately assess the incidence of this disease across South African paediatric surgical centres.

The mean maternal age of 21 years in this study was in keeping with the reported data of a higher incidence of gastroschisis in the infants of young mothers.[18]

A lower gestational age did not result in a greater odds of mortality in our study, despite the mean gestation being preterm, i.e. 36 weeks. Spontaneous preterm labour is more common in pregnancies complicated by foetal gastroschisis,[19] and our results are in keeping with these findings.

The finding that there was a lower odds of mortality in the SGA neonates in our cohort than that in their AGA counterparts was counterintuitive. It is accepted that SGA neonates experience greater mortality than those of an appropriate weight, especially in the preterm neonate.[20] With a mean gestation of 36 weeks in our cohort, it was difficult to explain the significant difference in mortality (48.3% vs. 80.7%) between the SGA and AGA groups, which remained consistent after multivariate analysis. Controlling for prematurity also did not change the findings as equal numbers of SGA and AGA births were preterm.

It is our policy to admit neonates with gastroschisis to the ICU facility if a bed is available. As only 32% of the cohort was admitted initially to the ICU, it is evident that we, as with most developing countries, have significant difficulty in caring for these patients in an appropriate ICU setting owing to the lack of available facilities.

The type of material used to cover the viscera by the transferring medical practitioner was not shown to have influenced mortality. Two patients whose exposed viscera had been directly covered with gauze arrived with acute haemorrhage from their livers due to erosion by the dried-out gauze. Neither survived. Therefore, the use of a soft plastic covering of the viscera is advocated, in keeping with the published guidelines.[9,21] There was a significantly greater odds of mortality in our female cohort. This contradicts the previous results which indicated a higher mortality risk in males.[22]

The chief aim in our study was to evaluate if the transfer time was a significant predictor of mortality in neonates born with gastroschisis in our drainage population. It was shown, contrary to previous studies in developing countries,[6,7] that the transfer time did not seem to be a predictor of mortality. However, the impact that a prolonged transfer time had on the ongoing dehydration of these neonates and its influence on their serum HCO3 needs to be factored in, especially as serum HCO3 was shown to be a significantly associated with mortality. The metabolic findings on admission indicated a state of compensated metabolic acidosis in those neonates who eventually died, likely to have resulted from the fluid and heat losses that these neonates experience if not appropriately managed. None of the clinical variables withstood logistic regression to be significant. It was shown by Mills et al. that clinical variables, in the form of the Score for Neonatal Acute Physiology II (SNAP II), were a significant predictor of mortality and survival outcomes in gastroschisis.[23] A review of our data, and the inclusion of SNAP II on admission, would have allowed a direct comparison to be made between our cohort and this study. A structured overall clinical impression for comparison purposes would have been achieved with the use of SNAP II, rather than having to use individual clinical factors. Unfortunately, the data required to complete SNAP II had not been completely recorded to allow its utilisation in retrospect.

Despite advice being given to referring doctors, it is not uncommon for patients to arrive from the transferring hospital without a functional intravenous line, a finding in our study that was to similar to that for Hadley and Mars.[24] While it can only be speculated as to whether or not these were functioning prior to transfer, the management of neonates prior to and during transfer is brought into question by their poor clinical state on arrival. Poor neonatal transfer systems in South Africa have been shown to contribute to poorer outcomes.[24,25] Transfer times and the poor clinical state of the patients on arrival at hospital is further testament to deficiencies in neonatal transfer within the healthcare system.

It must be noted that some patients were not able to be transferred timeously owing to the lack of available beds in our hospital. These patients were diverted to other paediatric surgical centres, or were transferred to the nearest hospital with the highest available level of care, while awaiting a bed in our unit. Reasons for the lengthy transfer time and poor condition of the child on arrival were not included in this study. Therefore, an opportunity exists for further research to accurately identify these causes and aid in addressing the high mortality of gastroschisis in our unit and elsewhere in South Africa.[17] Likely areas of concern include a delay in the initial consultation from the peripheral hospital, a delay with the ambulance collecting the patient, inadequate initial resuscitation prior to transportation, failure of the referring doctor to adhere to telephonically communicated management, as well as equipment and medication shortages at the peripheral hospitals and during ambulance transport.

The influence of varying methods of definitive surgical gastroschisis treatment on the outcomes was not included in this study. The majority of patients were initially stabilised in our study with the application of a preformed silo bag with delayed closure of the abdomen because of long transfer times and the poor clinical condition of the cohort on arrival. However, some patients were closed primarily. This decision was made by the treating surgeon based on the

appearance of the bowel, the clinical condition of the patient and the availability of a postoperative ICU bed. Therefore, the relationship of treatment method and outcome at our institution remains to be studied, but the cohort would have to be far larger in order for any significant difference in outcomes to be demonstrated as very few patients are closed primarily. As the state of the bowel and condition of the patient at initial presentation determine the method of surgical treatment employed, the findings of the relationship between the treatment used and outcomes would not be independent of the clinical condition of the patient on arrival in our unit.

In conclusion, while it was shown that our high mortality rate did not seem to be directly due to lengthy transfer times, the poor clinical condition of the patients on arrival at our hospital, likely related to deficiencies in the neonatal referral and transfer system, had a direct impact on the survival of neonates with gastroschisis. A decline in the high mortality rate of gastroschisis within our population might result if these patients are adequately resuscitated prior to and during transfer.

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