Factors Associated with Mortality in Neonates with Gastroschisis

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Key words
- neonate
- gastroschisis
- mortality

Abstract

Purpose: The ongoing epidemic of gastroschisis has created multiple challenges and continues to raise questions concerning the optimal management of these high-risk patients. Although the overall survival rate has increased over the past 3 decades, morbidity and mortality remain significant. The purpose of this study was to analyze the main factors associated with mortality in neonates admitted to an intensive care unit for the management of this abdominal wall defect.

Methods: This study is a retrospective review of a large de-identified neonatal intensive care dataset encompassing 284 institutions in 32 states and Puerto Rico, from 1/1/1997 to 1/1/2010. Of the 629 440 neonates in the dataset, a total of 3 456 newborns were diagnosed with gastroschisis (5.5/1 000 hospital discharges). Of these, 685 were transferred to other centers and data was missing on 22, leaving 2 749 infants available for analysis.

Results: Out of these 2 749 infants of whom we knew the outcome, 115 (4.2 %) died. Multivariate logistic regression showed that the factors independently associated with an increased risk of death were male gender, immature gestational age, low birth weight, low 5 min Apgar Score, the need for vasopressors during the first week after birth and the need for high levels of oxygen support. The presence of associated anomalies, vaginal delivery, treatment with surfactant and the need for ventilator support on the day of birth were not independent risk factors associated with an increased mortality.

Conclusion: Premature delivery and low birth weight are the most important factors associated with an increased risk of mortality. Cesarean section does not appear to reduce the risk.

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Introduction

Gastroschisis is a life-threatening congenital malformation of the abdominal wall associated with significant neonatal morbidity and mortality. For reasons that are not well understood, an epidemic-like increase of the condition has been observed worldwide [1,2]. Because of the major anatomical and physiological derangement, nearly all infants with this anomaly exhibit a high degree of morbidity, including feeding intolerance, failure to thrive and prolonged duration of hospitalization.

Although the mortality rate for gastroschisis has been reduced to just under 10 %, many questions concerning the ideal pre- and post-natal management remain (notably the timing and mode of delivery) [3,4]. The purpose of this study was to evaluate the factors associated with mortality in neonates admitted to intensive care for the management of their gastroschisis.

Methods

Study type

A retrospective review was performed of a de-identified neonatal intensive care patient dataset. Neonates were included in our study sample if they required admission to a NICU. This study included patients who were managed between 1 January 1997 and 31 January 2008.

Clinical data warehouse

Pediatrix Medical Group is a consortium that provides intensive care services in 284 hospitals in 33 states of the USA and Puerto Rico. 9 centers offer extracorporeal membrane oxygenation. Clinicians providing care to patients interact with the patients' electronic data on a daily basis to generate progress notes and provide billing information. Each day's notes are stored with the diagnoses. The local data are consolidated within the Pediatrix Medical Group data warehouse, de-

Table 1 Demographics.

	Died	Lived	Transfer	Lived vs. Died
number of patients	115	2634	685	
birth weight, median (10–90th)	1.9 (1.05–2.8)	2.4 (1.8–3.1)	2.4 (1.7–3.1)	0.001
gestational age, median (10–90th)	34 (29–37)	36 (33–38)	36 (33–38)	0.001
male, N (%)	65 (56.5)	1359 (51.6)	348 (50.8)	0.2
outborn, N (%)	13 (11.3)	307 (11.7)	83 (12.1)	0.5
cesarean section, N (%)	88 (76.5)	1820 (69.1)	442 (64.5)	0.1
multiple births (twins, triplets, quadruplets)	3 (2.6)	47 (1.8)	9 (1.3)	0.1
APGAR 1 min, median (10–90th)	6 (1–9)	8 (4–9)	8 (3–9)	0.001
APGAR 5 min, median (10–90th)	8 (4–9)	9 (8–9)	9 (7–9)	0.001
reported associated anomalies	22 (19.1)	209 (7.9)	59 (8.6)	0.001
gastrointestinal anomalies*	4 (3.5)	68 (2.6)	27 (3.9)	
renal*	3 (2.6)	83 (3.2)	18 (2.6)	
brain anomalies*	4 (3.5)	19 (0.7)	2 (0.3)	
heart*	1 (0.9)	7 (0.3)	3 (0.4)	
chromosomal anomalies*	2 (1.7)	4 (0.2)	0 (0)	
other	8 (7)	28 (1.1)	9 (1.3)	
race/ethnicity, N (%)				0.1
American/ native Alaskan	2 (1.7)	67 (2.5)	10 (1.5)	
Asian	2 (1.7)	45 (1.7)	18 (2.6)	
black	16 (13.9)	172 (6.5)	77 (11.2)	
hispanic	36 (31.3)	803 (30.5)	170 (24.8)	
other	7 (6.1)	145 (5.5)	31 (4.5)	
white	52 (45.2)	1402 (53.2)	379 (55.3)	
Treatments				
surfactant	26 (22.6)	140 (5.3)	38 (5.5)	0.001
vasopressors during first week	47 (40.9)	298 (11.3)	62 (9.1)	0.001
high frequency ventilation	13 (11.3)	55 (2.1)	11 (1.6)	0.001
any ventilation on day of birth	93 (80.9)	1714 (65.1)	333 (48.6)	0.003
max FiO_2 on day of birth, median (10–90th)	0.35 (0.21–1)	0.25 (0.21–0.6)	0.21 (0.21–0.9)	0.001
inhaled nitric oxide	7 (6.1)	7 (0.3)	4 (0.6)	0.001
hospital days, median (10–90th)	6 (0–82)	31 (18–77)		0.01

* 81% of the associated gastrointestinal anomalies were bowel atresias; 91% of the renal anomalies were hydronephrosis. Brain anomalies included hydrocephalus (n=4), absent septum pellucidum (n=3), porencephalic cyst (n=2), meningomyelocele (n=3), holoprosencephaly (n=3). Heart anomalies included coarctation of aorta (n=4), pulmonary valve stenosis (n=3), atrioventricular canal (n=1), hypoplastic left heart syndrome (n=2). Chromosomal anomalies included trisomy 21 (n=2), Turner syndrome (n=1), trisomy 13 (n=1), and trisomy 18 (n=1). Data are presented as n (%) or median (10–90th percentile)

identified, and made compliant with the Health Insurance Portability and Accountability Act of 1996 regulations. These data are stored in a consolidated dataset and used for quality assurance, research, and billing purposes. Using the de-identified dataset, from which several other observations have been reported [5–7], we performed a retrospective case series review of neonates with a diagnosis of gastroschisis. Duplicate entries resulting from a transfer between consortium units were excluded. Neonates who died in the delivery room or those who were not admitted to the neonatal intensive care unit were not included in the dataset. The gestational age assignment was based on the best obstetrical estimate prior to delivery and was recorded as completed weeks.

The Greenville Memorial Hospital, Greenville SC, USA, institutional review board approved our use of the de-identified dataset.

Statistical methods

Differences in the demographic characteristics of patients with gastroschisis who died were compared to those who were discharged home. We compared the 2 population samples using univariate analysis. Continuous variables (e.g., estimated gestational age and birth weight) were evaluated with 2-tailed *t*-tests. Categorical variables (e.g., race and gender) were evaluated with 2-tailed chi-square tests. Nonparametric data were assessed by Kruskal-Wallis analysis of variance. All statistical analyses were performed using JMP 7 software (SAS Institute, Cary, NC, USA).

We evaluated all the factors listed in **Table 1** to determine which was associated with an increased risk of mortality. After bivariate analysis, multivariate logistic regression was used to calculate the adjusted odds ratio for death by comparing the neonates who died with those who were discharged home. Transferred patients were not included in this analysis. The descriptive data for transferred patients is included as a reference. We incorporated into the logistic regression analysis the variables that had a probability of <0.1 of being associated with an increased risk of mortality. Birth weight and gestational age were entered into the model as continuous variables. Cases with missing values for any of the independent variables were excluded from the analyses.

Results

During the study period (1/1/1997 to 1/1/2010), out of 629440 neonates included in the dataset, a total of 3456 newborns were diagnosed with gastroschisis (5.5/1000 hospital discharges). Of these, 685 were transferred to other centers and data was missing for 22 neonates, leaving 2749 infants available for analysis. Of the 2749 infants of whom we knew the outcome, 115 (4.2%) died and 2634 (95.8%) were discharged home from the hospital. We compared the characteristics of the 115 neonates who died

Table 2 Results of multivariate logistic regression analysis.

	Adjusted odds ratio (95% confidence interval)	*p*-value
birth weight per 100 g increase in weight	0.5 (0.3–0.9)	0.01
APGAR 5 min per each increase in score	0.6 (0.6–0.7)	<0.0001
gestational age per 1 week increase in gestational age	0.8 (0.7–0.9)	0.003
male compared to female gender	1.6 (1–2.6)	0.02
FiO_2 increase per 10% FiO_2	3.2 (1.4–6.9)	0.03
vasopressors compared to no vasopressors	3.8 (2.3–6.1)	<0.0001

ROC = 0.85

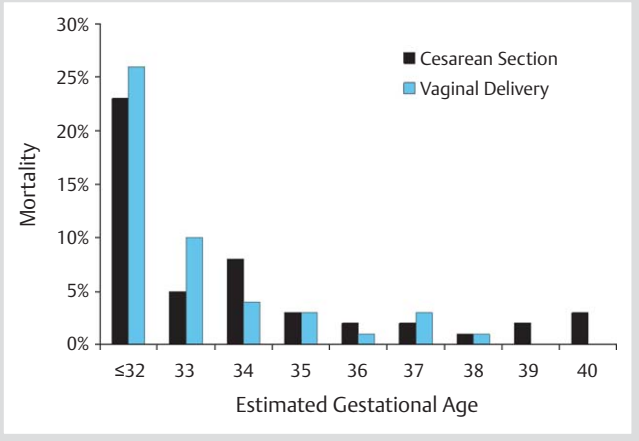

Fig. 1 Mortality (died/[died + lived]) of patients with gastroschisis according to estimated gestational age and route of delivery. Transferred neonates are excluded.

to the 2634 infants who were discharged home. Data on transferred patients is included as a reference sample only.

The demographics of the study population sample are presented in **Table 1**. Bivariate analysis showed that there were no significant differences between the neonates who died and those who survived with regard to mode of delivery, gender, frequency of being outborn, and ethnicity/race. Compared to patients who died, patients who lived were more mature (36 vs. 34 weeks estimated gestational age), were heavier at birth (2.4 vs. 1.9 kg) and, less often, had an associated anomaly (7.9 vs. 19.1%). Neonates who died were treated more often with a surfactant, a vasopressor, high frequency ventilation and/or inhaled nitric oxide than neonates who lived and were discharged home. Patients who died had lower Apgar scores and needed higher levels of oxygen support.

Multivariate logistic regression showed that the factors independently associated with an increased risk of death were male gender, immature gestational age, low birth weight, low 5 min Apgar score, the need for vasopressors during the first week after birth and need for high levels of oxygen support. The presence of associated anomalies, vaginal delivery, treatment with surfactant and the need for ventilator support on the day of birth were not independent risk factors associated with increased mortality (**Table 2**).

The cause of death was unclear in 15 (13%) of the 115 patients who died. 29 (25.2%) patients developed acute respiratory failure and died. There were 22 (19.1%) patients in whom care was discontinued; in 14 the reason for the discontinuation of care was not clear. Of the remaining patients in whom care was discontinued, 6 had brain anomalies, 1 had trisomy 13, and 1 had trisomy 18. Eight (7%) patients died of necrotic bowel associated with a volvulus, 5 deaths (4.3%) were associated with necrotizing enterocolitis, 3 deaths (2.8%) were associated with bowel perforation and 1 death was associated with severe short bowel syndrome. 15 patients (13%) died of complications associated with prematurity, 6 deaths (6.3%) were associated with renal failure, 3 deaths (2.8%) were associated with severe hypoxic-ischemic encephalopathy, 3 deaths (2.8%) were due to shock; and 2 patients (1.4%) died of sepsis. 1 infant each died of hydrops fetalis, hypoplastic left heart syndrome and intracranial hemorrhage.

Discussion

We previously reported that the incidence and cost of caring for neonates with gastroschisis continues to increase [8]. In our multivariate analysis (n = 2749), the factors independently associated with an increased risk of death were male gender, immature gestational age, low birth weight, low Apgar score at 5 min, the need for vasopressors during the first week after birth, and the need for high levels of oxygen support. Mode of delivery (specifically cesarean section delivery) did not change the risk of death (**Fig. 1**). A low Apgar score at 5 min, the need for vasopressors and the need for high levels of oxygen support are very likely surrogate markers for severity of illness and not alterable causes for mortality.

Several recent studies evaluated the effect of preterm delivery and cesarean section on morbidity and mortality in neonates with gastroschisis. Gelas et al. [9] performed a retrospective study including all cases of gastroschisis born between 1990 and 2004 (n = 69). Cases were categorized in 2 groups. Group 1 included gastroschisis cases born between 1990 and 1997. Group 2 included cases occurring since 1997, when a new management pathway for gastroschisis was established: weekly evaluation of the fetal gut by ultrasound (>28 weeks), corticosteroids, and delivery by scheduled cesarean section at 35 weeks (or before if evidence of bowel compromise was present). The authors found that scheduled and elective preterm delivery optimized the surgical results and shortened the time to first feeding. Maramreddy et al. [4] conducted a retrospective review of patients with gastroschisis born between 1989 and 2007 and found that compared to term neonates with gastroschisis, preterm neonates with gastroschisis had a higher rate of sepsis, longer duration to reach full enteral feedings, and longer length of stay. Hadidi et al. [10] assessed the value of early elective cesarean delivery for patients with gastroschisis compared with late spontaneous delivery and found that elective cesarean delivery before 36 weeks allowed earlier enteral feeding and was associated with less complications and a higher incidence of primary closure. In contrast, Maramreddy et al. [4] concluded that preterm delivery should be avoided because there is no clear benefit to the gut and prematurity itself is associated with significant morbidity.

Boutros et al. [3] evaluated the effect of gestational age, birth weight and intended and actual route of delivery on outcomes in neonates with gastroschisis (n = 192). Of 145 pregnancies with an antenatal delivery plan, vaginal delivery was intended in 77%

and actually occurred in 119 pregnancies, with the remainder being planned (33; 17 %) or emergency (40; 21 %) cesarean deliveries. A delivery conforming to the antenatal plan occurred in 74 (51 %) cases. Birth weight and gestational age were significant inverse predictors of ventilator and total parenteral nutrition days and length of hospital stay, but not survival. Delivery route did not predict any outcome; however, "nonconformers" were born with lower birth weights and at a younger gestational age than "conformers," and they showed a trend towards poorer, non-lethal outcomes. Boutros et al. [9] concluded that gestational age, birth weight, and conformity to an antenatal birth plan are predictors of outcome in gastroschisis, whereas the actual route of delivery was not.

We previously reported, and the current dataset demonstrates, that neonates with gastroschisis are frequently (83 %) born before 38 weeks. The risk of mortality is increased in immature neonates; especially in neonates born at less than 35 weeks gestational age. It is impossible to know whether this is an alterable risk factor [11]. Lausman et al. [11] reported that the mean gestational age with spontaneous labor was 36.6 weeks, so it is hard to determine how much of the premature birth is driven by a clinical decision to deliver the fetus because the infant has gastroschisis or by other medical factors that cause premature birth. A prematurity rate of 83 %, however, is much higher than the 10–12 % prematurity rate observed in the general population and suggests that to some degree this risk factor may be alterable.

Low birth weight is closely correlated with gestational age; however, the fact that it is a risk factor that is independent of gestational age suggests that intrauterine growth restriction increases the risk of mortality. Like severity of illness and gender this may not be alterable.

Prospective studies are needed to define the best treatment options, but most pressing is the need to discover the cause of the pandemic and, with that, to hopefully discover an intervention that will prevent or diminish the prevalence of this costly anomaly.

Conflict of Interest: None

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