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Early Neurodevelopmental Outcomes of Congenital Gastrointestinal Surgical Conditions

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WHAT IS KNOWN ABOUT THE SUBJECT?

1. Surgery in the neonatal period may have an adverse effect on neurodevelopment outcomes.
2. Infection and excessive inflammation are harmful to the developing brain

WHAT THIS STUDY ADDS

1. Infants who have neonatal gastrointestinal surgery were at risk of suboptimal neurodevelopmental outcomes.

2. Lower z scores for birth weight and prolonged hospital stay were associated with increased risk of suboptimal neurodevelopmental outcomes.

3. CRP levels and infections were not associated with suboptimal neurodevelopmental outcomes at 1 year of age.

ABSTRACT

Background: Evidence is emerging that surgery in the neonatal period is associated with increased risk of suboptimal neurodevelopmental outcomes (SNDO). The aim of this study was to describe neurodevelopmental outcomes (at one year) of neonatal surgery for congenital gastrointestinal surgical conditions (CGSC) and to explore risk factors. Griffiths Mental Developmental Assessment Scales (GMDS-II) were used to assess developmental outcomes. Suboptimal neurodevelopmental outcome (SNDO) was defined as one or more of the following: a GQ less than 88 (i.e. >1SD below mean), cerebral palsy, blindness or sensorineural deafness.

Methods: Retrospective study of infants born ≥34 weeks gestation between 2005 and 2014 with CGSC

Results: A total of 413 infants were included, of which 13 died. Median gestation was 37.6 weeks (IQR: 36.4 to 39.1). Information on developmental outcomes was available from 262 out of 400 survivors. A total of 43/262 (16.4%) had SNDO. On univariable analysis, lower z scores for birthweight, prolonged duration of antibiotics, increased episodes of general anaesthesia and prolonged duration of hospital stay were associated with SNDO. On multivariate analysis, higher z scores for birth weight was associated with lower risk (adjusted OR 0.69; 95% CI: 0.49 to 0.98) and prolonged hospital stay with increased risk (adjusted OR 1.03; 95% CI: 1.00 to 1.06) of SNDO.

Conclusions: Late preterm and term infants undergoing surgery for CGSC are at risk for SNDO at one year of age. Studies with longer duration of follow-up are needed to further evaluate the role of potentially modifiable risk factors on their neurodevelopmental outcomes.

Keywords: Surgery, Infant, Neurodevelopment

INTRODUCTION

Survival following neonatal surgery has improved in recent years, but short and long-term complications continue to have significant effects on these infants and their families.[1] A recent population based study that compared developmental outcomes of 124 neonates undergoing non-cardiac surgery versus 92 who underwent cardiac surgery and 162 healthy infants found that cardiac surgery carried the highest risk of developmental delay, but infants undergoing non-cardiac surgeries also had 7-14% incidence of developmental delay.[2]

Factors associated with poor developmental outcomes in neonates undergoing surgery include low birth weight,[3] chromosomal anomalies, growth restriction,[4] prolonged hospital stay,[5] need for Extracorporeal Membrane Oxygenation (ECMO),[6 7] chronic lung disease,[8] increasing number of surgeries,[5] and low socio-economic status.[9] One factor that has not been adequately explored in neonates undergoing surgery is the influence of infection and inflammation. Exploring this area is important because infection and excessive inflammation are potentially harmful to the developing brain.[10-14]

We conducted this retrospective study to evaluate one-year developmental outcomes of late preterm and term infants who underwent surgery for congenital gastrointestinal surgical conditions (CGSC) in our unit and to explore the potential risk factors.

METHODS

This was a retrospective cohort study of all late preterm and term infants born at $\geq 34^{0/7}$ week's gestation between January 2005 and December 2014 with CGSC who underwent surgery in the neonatal period at a single tertiary neonatal intensive care unit.

The following conditions were included in the study- Gastroschisis, exomphalos, duodenal atresia, malrotation, Jejuno-ileal atresia, large bowel atresia, meconium ileus, Hirschsprung disease, multiple gut anomalies, gut perforations/stenoses, short bowel syndrome, biliary atresia, ano-rectal anomalies and benign abdominal cysts. We included oesophageal atresia

and congenital diaphragmatic hernia because they also involve the gastrointestinal tract and have long-term gastrointestinal complications.

Infants were identified by interrogating the departmental database. Infants with chromosomal anomalies and syndromes known to adversely affect developmental outcomes were excluded. Infants born at <34 weeks' gestation were excluded because they carry a higher risk of adverse developmental outcomes due to prematurity compared to late preterm and term infants.

Clinical characteristics of study infants were extracted from their medical records by one author (VB) and verified for accuracy by a second author (SR). Two neonatologists with expertise in developmental follow up (DW, JT) provided information on one-year outcomes based on Griffiths Mental Development Scales (GMDS-II). The GMDS-II assesses development in five areas: locomotor, personal and social, hearing and speech, eye and hand coordination, and performance. The five subscales are assessed and scored separately and then combined to provide an overall general quotient (GQ) reflecting the child's developmental performance level relative to the general population. On these scales, a combined general quotient (GQ) of 100.2 (SD 12) is considered normal.[15] The GMDS-II is a well-recognised tool for identifying neurosensory disability and is used widely.[16 17]

Outcome of interest for this study was suboptimal neurodevelopmental outcomes (SNDO) at one year of age. SNDO was defined as one or more of the following: (i) a GQ of <88 (i.e. >1SD below mean) on GMDS-II[15], (ii) cerebral palsy (based on assessment by neurologist or developmental paediatrician) (iii) blindness (visual acuity of <6/60 in the better eye), and (iv) sensorineural deafness (based on audiometry assessment) requiring hearing aids.

Healthcare associated infection (HAI) included urinary tract infection or healthcare associated blood stream infection (HABSI), meningitis or surgical site infection or any type

of viral infection. HABSI was defined as positive blood culture on a sample taken 48 hours after admission to the NICU. UTI was defined as positive culture based on a sample collected from suprapubic sample or in-and-out catheter. Meningitis was diagnosed based on positive culture on CSF samples collected with aseptic precautions. The diagnosis of wound infection was based on the presence of erythema/oedema/induration at the surgical site and positive culture on the wound swab. Respiratory viral infection was diagnosed based on PCR on postnasal aspirate samples taken in infants who presented clinical symptoms of respiratory illness.

C Reactive Protein (CRP) was used as the marker of inflammation. We stratified the CRP levels based on the timing in relation to the surgical procedure. A CRP done in the preoperative period was considered to be a surrogate marker of early onset sepsis, whereas CRP performed within 72 hours of surgery was considered to be related to the degree of surgical injury and CRP performed after 72 hours of surgery to indicate hospital acquired infection.

Statistical analysis was done using the STATA 16 software (Stata Corp. 2019 Stata Statistical Software: Release 16 College Station, TX; Stata Corp. LP). The summary statistics for normally distributed continuous variables were expressed as mean and standard deviations; those with skewed distribution were expressed as median and interquartile range (IQR). Categorical variables were expressed as frequency and percentage. Univariable and multivariate random effects logistic regression models were carried out to derive unadjusted and adjusted odds ratio and 95% confidence intervals for outcome of interest. A generalized linear mixed model was used for all univariable and multivariate analyses. One-sample t-test was used to compare the mean GQ scores to the population mean (100.2). For all analyses, a two-tailed p-value of <0.05 was considered statistically significant.

This retrospective study was approved by the institutional ethics committee as a quality assurance activity. STROBE guidelines were used to report this study.[18] This retrospective research was done without patient involvement. Patients were not invited to comment on the study design and were not consulted to develop patient relevant outcomes or interpret the results. Patients were not invited to contribute to the writing or editing of this document for readability or accuracy.

RESULTS

A total of 460 neonates underwent surgery for CGSC during the study period, of which 43 were excluded because of chromosomal anomalies or syndromes that are known to adversely affect neurodevelopmental outcomes. Four infants were excluded because they had moderate to severe hypoxic ischemic encephalopathy due to perinatal asphyxia. The remaining 413 infants were included in the study. Of them 13 died, and of the 400 surviving infants, full information on developmental outcomes was available for 262/400 (65%) surviving infants. The flow diagram of patient selection process is given in figure 1.

The major surgical conditions were gastroschisis (92; 22.3%), malrotation (48; 11.6%), oesophageal atresia with or without tracheo-oesophageal fistula (44; 10.6%), Hirschsprung disease (44; 10.6%), congenital diaphragmatic hernia (42; 10.2%), ano-rectal anomalies (39; 9.4%), duodenal atresia (19; 4.6%), gut perforations and stenoses (19; 4.6%), Jejuno-ileal atresia (16; 3.9%), exomphalos (13; 3.1%), meconium ileus (12; 2.9%), multiple gut anomalies (10; 2.4%), short bowel syndrome (5; 1.2%), large bowel atresia (5; 1.2%), benign cysts and tumours (4; 0.97%) and biliary atresia (1; 0.24%).

The median gestation was 37.6 weeks (IQR: 36.4 to 39.1) and median birth weight 3000 grams (IQR: 2590 to 3405). The median duration of hospital stay was 18 days (IQR: 11 to 26 days, range: 1 to153 days). There were 13 deaths, all of which were during initial hospital

stay. There were no deaths after discharge from the hospital. Table 1 summarises the clinical characteristics in detail.

Table 1: Characteristics of study infants

Clinical characteristic	Median or number (percentage)	IQR	Range	N
Gestation (weeks)	37.6	36.4 to 39.1	34.1 to 41.5	413
Gender (Male: Female)	57%:43%	NA	NA	413
Birth weight (grams)	3000	2590 to 3405	1664 to 5060	413
Birth weight z scores	-0.23	-0.87 to 0.41	-2.81 to 4.78	413
Birth length (cm)	49	47 to 51	40 to 58	403
Birth Length z scores	-0.03	-0.75 to 0.57	-3.38 to 4.23	403
Birth head circumference (cm)	34	32.5 to 35	28.5 to 47	409
Birth head circumference z scores	0.07	-0.62 to 0.78	-3.32 to 3.29	408
APGAR 5min	9	9 to 9	4 to 10	409
Pre-Surgery CRP levels (mg/dl)	7.5	5 to 20	1 to 188	933
CRP levels within 72 hours of initial surgery (mg/dl)	35.5	19 to 69	3 to 346	747
CRP levels after 72 hours of surgery (mg/dl)	15	7 to 29	1 to 325	2912
Health care associated blood stream infection (HABSI)	27(6.5%)	NA	NA	413
CSF culture positive	1 (0.25%)	NA	NA	413

Lumbar puncture done	14 (3.4%)	NA	NA	413
Viral infections (all respiratory)	17 (4.1%)	NA	NA	413
UTI (urinary tract infections)	1 (0.24%)	NA	NA	413
Culture positive surgical site infections	14 (3.4%)	NA	NA	413
Any health care associated infection (HAI) (Blood stream or CSF or viral or UTI or wound infection)	51 (12.4%)	NA	NA	413
Number of antibiotic courses	2	1 to 2	1 to 14	406
Cumulative duration of antibiotics (days)	6	4 to 8	1 to 56	406
Surgery episodes under GA	1	1 to 2	1 to 5	413
Number of episodes of hypoglycaemia (blood glucose<2.6 mmol/L)	0	0 to 0	0 to 15	413
Length of stay (days)	18	11 to 26	1 to 153	413
Post conception age at discharge (weeks)	41	39.4 to 42.4	35.4 to 60.2	413
Death before discharge	13 (3.1%)	NA	NA	413
Death before 1 year	13 (3.1%)	NA	NA	413
Corrected age at Griffiths assessment (months)	12	12 to 12.5	10 to15.5	270
GQ scores at 12 months	96.5	92 to 102	49 to 131	270
SNDO	43/262 (16.4%)	NA	NA	262

AGA: Appropriate growth for gestational age; SGA: small for gestational age;

LGA: large for gestational age; NA: not applicable; SNDO: Suboptimal developmental outcomes

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A total of 43/262 (16.4%) infants had SNDO, with 9 infants having a GQ<76 (i.e. more than 2SD below the mean). One infant had deafness, one had cerebral palsy, and none had blindness. The mean GQ was 96.3 (SD 10.3), which was significantly lower than the population mean of 100.2; p<0.001. Infants with multiple gut anomalies, oesophageal atresia, Hirschsprung disease, exomphalos and congenital diaphragmatic hernia had highest rates of SNDO amongst survivors (Table 2).

Table 2: Developmental outcomes of neonates with CGISC*

Major gastrointestinal anomaly	**Number**	**Mortality**	**SNDO among infants who were assessed**	**Median GQ (n=numbers assessed)**
Multiple Gut Anomalies	10 (2.4%)	1/10 (10%)	3/7 (42.8%)	88 (IQR:84 to100) n=7
Oesophageal Atresia	44 (10.6%)	1/44 (2.3%)	10/27 (37%)	93 (IQR:85 to100) n=27
Hirschsprung Disease	44 (10.6%)	1/44 (2.3%)	6/32 (18.7%)	98 (IQR:93 to102) n=33
Exomphalos	13 (3.1%)	0/13 (0%)	1/6 (16.7%)	99 (IQR:89 to100) n=7
Congenital Diaphragmatic Hernia	42 (10.2%)	1/42 (2.4%)	5/34 (14.7%)	94.5 (IQR:92 to105) n=34
Gastroschisis	92(22.3%)	3/92 (3.3%)	8/55 (14.5%)	98.5 (IQR:92.5 to103) n=60
Ano-Rectal Anomalies	39 (9.4%)	0/39 (0%)	3/21 (14.3%)	96 (IQR:90 to101) n=22
Malrotation	48 (11.6%)	3/48 (6.2%)	4/33 (12.1%)	96 (IQR:93 to103) n=34
Jejuno-Ileal Atresia	16 (3.9%)	0/16 (0%)	1/9(11.1%)	97.5 (IQR:95 to102) n=10

Gut Perforations and Stenoses	19 (4.6%)	1/19 (5.3%)	1/12 (8.3%)	101.5 (IQR:94.5 to106) n=12
Duodenal Atresia	19 (4.6%)	0/19 (0%)	1/13 (7.7%)	99 (IQR:94 to110) n=15
Meconium Ileus	12 (2.9%)	0/12(0%)	0/5 (0%)	98 (IQR:96 to 99) n=5
Short Bowel Syndrome	5 (1.2%)	2/5 (40%)	0/1 (0%)	95 n=1
Large Bowel Atresia	5 (1.2%)	0/5 (0%)	0/1(0%)	104 n=1
Benign Abdominal Cysts and tumours	4 (0.97%)	0/4 (0%)	0/1(0%)	103 n=1
Biliary Atresia	1 (0.24%)	0/1 (0%)	0/1(0%)	92 n=1

*For all outcomes, infants who underwent at least one episode of surgery were included; infants who died prior to undergoing any surgery were excluded. The information on neurodevelopmental outcomes was available for 65% of survivors.

Healthcare associated bloodstream infection (HABSI) occurred in 27 infants (6.5%). A total of 51 (12.4%) infants developed at least one episode of healthcare associated infection (HAI) (urinary tract infection or HABSI or viral infection or surgical site infection). None of the infants had early onset sepsis. Coagulase negative staphylococcus, *Klebsiella* sp. and *Eschericia Coli* were the most common pathogens isolated (table 3).

Table 3: Micro-organisms isolated from infants with healthcare-associated infections

Micro-organism	**Blood**	**CSF**	**Urine**	**Viral infections**	**Wound/skin swab**
CONS*	16	1	-	-	3
E.Coli	4	-	-	-	3

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Klebsiella	3	-	-	-	-
Pseudomonas	1	-	-	-	2
Strep. Mitis	1	-	-	-	-
Moraxella	1	-	-	-	-
Enterococcus	1	-	-	-	1
Candida Albicans	-	-	1	-	2
Staph. Aureus	-	-	-	-	2
Enterobacter Cloacae	-	-	-	-	1
Rhino virus	-	-	-	12	-
RSV*	-	-	-	2	-
Influenza A	-	-	-	2	-
Parainfluenza	-	-	-	1	-
Total	27	1	1	17	14

*CONS-Coagulase Negative Staphylococcus; RSV- Respiratory Syncytial Virus

Association between neonatal risk factors and SNDO among survivors

On univariable analysis, lower birth weight z scores, prolonged duration of antibiotic therapy increasing episodes of general anaesthesia and prolonged duration of hospital stay were associated with higher odds of SNDO among survivors (Table 4). On multivariate analysis, lower birth weight z scores and longer duration of hospital stay were associated with increased odds of SNDO among survivors (Table 4).

Table 4: Risk factors for SNDO

Variable	**Unadjusted odds ratio and 95% CI**	**P value**	**Adjusted odds ratio and 95% CI**	**P value**
Gestational age at birth (>37 weeks)	1.07 (0.53 to 2.19)	0.840	1.54 (0.65 to 3.63)	0.321

Birth weight z scores	0.64 (0.47 to 0.89)	**0.008**	0.69 (0.49 to 0.98)	**0.038**
Female gender	0 .71 (0.36 to 1.39)	0.313	0.53 (0.24 to 1.16)	0.112
Number of episodes of hypoglycaemia (<2.6mmol/l)	1.06 (0.75 to 1.49)	0.730	0.98 (0.60 to 1.58)	0.923
General anaesthesia (>3 episodes)	3.31 (1.29 to 8.50)	**0.013**	0.77 (0.17 to 3.59)	0.745
Pre-Operative CRP levels	0.90 (0.59 to 1.37)	0.627	0.92 (0.60 to 1.40)	0.698
CRP levels within 72 hours of surgery	0.90 (0.63 to 1.28)	0.555	1.06 (0.69 to 1.62)	0.769
CRP levels after 72 hours of surgery	0.64 (0.41 to 1.01)	0.053	0.99 (0.63 to 1.56)	0.985
Any Infection	1.20 (0.49 to 2.96)	0.683	0.44 (0.11 to 1.77)	0.247
Cumulative duration of antibiotics	1.05 (1.01 to 1.10)	**0.043**	1.00 (0.91 to 1.10)	0.990
Degree of postnatal growth restriction	2.00 (0.59 to 6.81)	0.265	1.56 (0.62 to 3.97)	0.348
Length of stay	1.02 (1.00 to 1.03)	**0.003**	1.03 (1.00 to 1.06)	**0.034**

DISCUSSION

Our study found an overall mortality rate of 3.1% and SNDO in 16.4% of neonates undergoing surgery for CGSC. These findings are similar to a recent study that reported an incidence of 7-14% in various domains of assessment at three years among 124 children who

underwent surgery for non-cardiac conditions in the neonatal period.[2] While the mean GQ of 96.3 in our cohort might not appear too low, it is important to note that the GMDS-II norms are based on population sample more than two decades ago. It is well known that developmental quotients and intelligence quotients in the general population increase by 2 to 3 points each decade (Flynn effect)[19]. If assessed using the GMDS-II tools, healthy 12-month old infants during the study period of 2005-2014 would probably have scored a mean of 103 rather than 100.

While many variables were found to be associated with increased risk of SNDO on univariable analysis, only lower birth weight z scores and longer duration of hospital stay were found to be having significant association on multivariate analysis. Lower birth weight z scores indicate fetal growth restriction and prolonged hospitalisation is usually related to the complex nature of the underlying surgical condition. Hence their association with adverse neurodevelopmental outcomes is not unexpected.

The burden of HAI and HABSI in neonates with CGSC has not been explored adequately. Donnell and van Saene et al. conducted a prospective study of surgical infants<6 months to find infection rates.[20 21] Thirty-two infants developed blood culture positive sepsis (15%); predominant micro-organisms (86%) were coagulase-negative staphylococci and enterococci. Other pathogens, including aerobic gram-negative bacilli, were responsible for the remainder. They suggested that gut translocation was the main factor behind sepsis in surgical infants rather than central lines and cautioned that prevention is unlikely to be successful if abnormal gut flora is ignored.[21] Another study by Bishay et al reported that 31 out of 112 surgical infants (28%) had a total of 65 episodes of septicaemia.[22]

In very preterm infants, it is well established that neonatal sepsis is associated with higher risk of adverse neurodevelopmental outcomes. A recent systematic review by Cai et al[23] found that preterm infants with neonatal sepsis were at a higher risk of neurodevelopmental

impairments such as cerebral palsy and neurosensory deficits, compared with infants without sepsis (OR 3.18; 95% CI 2.29-4.41)[23]. Hence, we had expected similar findings in our cohort of surgical infants. However, in our study, HAI was not associated with increased risk of SNDO, either on univariable or multivariate analysis. Similarly, higher levels of CRPs were not associated with SNDO irrespective of the timing in relation to the surgeries. This could be related to the resilience of the brain of late preterm and term infants to the harmful effects of infection and inflammation, unlike the vulnerable extremely preterm infants. However, prolonged duration of antibiotic therapy, which could be a surrogate marker of clinically suspected infection, was associated with SNDO on univariable, but not multivariate analysis. Further studies with larger sample size and a longer duration of follow up beyond 1 year of age are needed to explore the role of infection and inflammation in late preterm and term infants undergoing neonatal surgery.

The harmful effect of exposures to general anaesthesia on developing brain is an area of debate and active research.[24] [25] While animal studies have consistently shown general anaesthesia to be toxic to the developing brain,[26] one recent large RCT (GAS study),[27] and a large prospective cohort study (PANDA)[28] found no significant association. Both these studies evaluated a single exposure to general anaesthesia, and hence do not address the issue of repeated exposures. A recent large data linkage study found that children exposed to general anaesthesia before four years have poorer development outcomes at school entry and school performance.[29] In another cohort study[30], children who had multiple exposure to GA before 3 years of age scored 1.3 points (95% CI, -3.8 to 1.2; P = 0.32) less than unexposed children on intelligence tests; children who had one exposure to GA scored 0.5 points (95% CI, -2.8 to 1.9; P = 0.70) less than unexposed children. However, the parents of children who had multiple exposure to GA reported increased problems related to executive function, behaviour, and reading[30]. In our cohort, increasing episodes of general anaesthesia were

associated with higher risk of SNDO on univariable analysis, but not on multivariate analysis. Further studies with long duration of follow up are needed in this area.

One of the limitations of our study was the shorter duration of follow up of one year and the findings may not track subsequently. In a recent study, Fairbairn et al reported that Bayley-III results for all domains at one year of age were a weak predictor of outcomes at three years of age in infants who had early major cardiac and non-cardiac surgery and healthy infants[31]. Hence all infants, irrespective of the results of developmental assessments at one year should be followed with formal developmental assessments at least until five years of age. At the same time, infants identified as high risk based on the one-year assessments could be provided early developmental interventions to optimise their outcomes. Only recently, we have commenced routine developmental follow up until two years of age with Bayley Scales of Infant Development (BSID-III) to all infants undergoing surgery in the neonatal period. The other limitations of our study were: a) retrospective design without healthy controls, b) the indication for doing CRP levels was at the discretion of clinicians rather than based on a standardised protocol, c) full information on developmental outcomes was missing from nearly 35% of survivors, d) lack of information on socio-demographic status of family and e) missing information about duration of general anaesthesia which can have significant influence on developmental outcomes. The main strength of the study is the large sample size of surgical infants and the use of regression analyses to adjust for confounders.

Conclusions: Late preterm and term infants undergoing surgery for CGSC are at risk for suboptimal neurodevelopmental outcomes at one year of age. Studies with long-term follow-up are needed to further evaluate the influence of potentially modifiable risk factors on neurodevelopmental outcomes in such infants.

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Contributors' Statements:
A/Prof Rao conceptualized and designed the study, coordinated and supervised data collection, verified the data for accuracy, drafted the initial manuscript, and reviewed and revised the manuscript.

Dr Batta collected the data, assisted with drafting of the initial manuscript and reviewed the manuscript

Prof Patole and Prof Simmer critically reviewed and revised the manuscript. They also provided feedback at the design and analysis stage of the study

Dr Wagh and Dr Tan provided information regarding the developmental outcomes of all study infants. They critically reviewed and revised the manuscript.

Dr Gollow critically reviewed and revised the manuscript.
Prof Bulsara conducted the statistical analysis of the data, reviewed and revised the manuscript.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Data Sharing Statement: Individual de-identified participant data (including data dictionaries) that underlie the results reported in this article will be shared beginning 3 months and ending 5 years after publication of the article to researchers who provide a methodologically sound proposal. All such requests should be directed to the corresponding author. To gain access, the data requestors will need to sign a data access agreement.

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Response to reviewers' comments

Title: Early Neurodevelopmental Outcomes of Congenital Gastrointestinal Surgical Conditions

Manuscript ID: bmjpo-2019-000555

Reviewer 1 [Dr Sarah Nevitt, University of Liverpool, United Kingdom]

1. I have conducted a statistical review of the manuscript "Early Neurodevelopmental Outcomes of Congenital Gastrointestinal Surgical Conditions."

Comment: The authors conduct a retrospective audit and analysis of a hospital database examining risk factors of adverse neurodevelopmental outcomes following CGSC. I consider the analysis methods to be appropriate and results are well interpreted.

Response: Thank you for the encouraging comments

Comment: 1) Abstract, methods: $34^0/7$ – I think I understand what this means, i.e. 34 weeks gestation is defined as anything from 34 weeks 0 days to 34 weeks and 7 days, but this is not immediately clear. Perhaps for the purposes of the abstract, just 34 weeks could be used, and the definition of 34 weeks gestation could be described further in the main methods section of the manuscript.

Response: Done

Comment: Page 8: "STROBE guidelines were used to report this study" This is good, I suggest including a STROBE checklist as an appendix to the manuscript for completeness.

Response: Done

Comment: Within the Tables and text where IQRs and ranges are reported, it can be a little difficult to read numbers separated with a comma. I suggest using 'to' instead (i.e. range 0 to 10).

Response: Done

4) Table 4: Adjusted odds ratio p-value for birth weight should be bold?

Response: Thank you for the suggestion. In this table, we have now used bold font for all results that were statistically significant.

5) Page 15: "Excessive inflammation has the potential to be harmful and hence every effort should be undertaken to minimise this risk" While I do not doubt this statement, it should also be highlighted that no association was actually shown in this study between infection / inflammation and disability. Furthermore, although I appreciate investigating the association between infection / inflammation and disability was one of the prespecified hypotheses, as no association was found within this study, perhaps it is not a good idea for two of the points for "What this study adds" to concentrate on inflammation. Certainly, one as it was a pre-specified hypothesis, but I suggest using one of the other points to highlight an additional finding of this study

Response: We agree with your thoughts. We have now updated the "what this study adds" section to reflect the results.

Reviewer 2 [Prof Neil Marlow, UCL, London UK]

This is a retrospective chart review of a large number of babies with surgical procedures for GI conditions from a large surgical centre. The hypothesis was that disability would be more frequent in the surgical cases exposed to high levels of CRP as a marker of inflammation. In fact, although associated with "disability" at 12m any relationship disappeared in adjustment for known confounders. There was no association with HAI which might also be associated with inflammation.

Comment: The authors do not describe "disability" but low Griffiths scores at 12m with one child with deafness and one with CP.

Response: We thank you for this comment. We have now used the term suboptimal neurodevelopmental outcomes (SNDO) instead of "disability". This is because as mentioned by this reviewer below, the results of GMDS at one year may not track subsequently. SNDO has now been defined as one or more of the following: (i) a GQ of <88 (i.e. >1SD below mean) on GMDS-II (iii) cerebral palsy (based on assessment by neurologist or developmental paediatrician) (iv) blindness (visual acuity of <6/60 in the better eye), and (v) sensorineural deafness (based on audiometry assessment) requiring hearing aids.

Comment: The use of the GMDS-II does need some qualification as it was standardised 20+ years ago and may severely overestimate developmental scores, as per the Flynn effect.

Response: We agree with these comments. We have added the following information in the manuscript now, highlighting this issue along with the following reference: Trahan LH, Stuebing KK, Fletcher JM, Hiscock M. The Flynn effect: a meta-analysis. Psychol Bull. 2014 Sep;140(5):1332-60.

While the mean GMDS-II GQ of 96.3 in our cohort may not appear too low, it is important to note that the GMDS-II norms are based on population sample more than two decades ago; developmental quotients in the general population increase by 2 to 3 points each decade (Flynn effect). If assessed using the GMDS-II tools, healthy 12-month old infants during the study period of 2005-2014 would probably have scored a mean of 103 rather than 100.

Comment: The use of 12m outcomes is unusual although it is a later preterm/term population, but these findings are unlikely to track.

Response: We agree that the 12-month findings may not track subsequently. But infants who are identified as high risk based on the one-year assessments could be provided early intervention to optimise their outcomes. All infants, irrespective of the results of GMDS at one year should be followed with formal developmental assessments at least until five years of age. We have added this information in our manuscript.

As the reviewer points out, our study cohort was a late preterm/term surgical population and hence our unit had been following them only until one year of age. Recently we have introduced Bayley Scales of Infant development-III for our surgical infants in addition to GMDS at one year.

Comment: No sociodemographic variables were included which might be stronger predictors of development than surgery at 12m age.

Response: We apologise that being a retrospective study, we were unable to incorporate those variables. We have added it as a limitation of our study. In future prospective long-term outcome studies, we will incorporate those variables.

Comment: The use of GMFCS at 12 months needs justifying as standardisation below 18-24m is not available and the predictive value of grades at 12m are unclear and not referenced.

Response: We have edited the definition of CP as based on diagnosis by a paediatric neurologist or developmental paediatrician.

Comment: CRP is described using non-parametric statistics in the table but in the text, means are used with large SD's – clearly the data are not normally distributed and non-parametric descriptors and tests should be used.

Response: We have now used non-parametric descriptions for CRP at all places.

Comment: It isn't good practice to put both BWt and Gestation in the same analysis as they are highly inter-related; the use of z-scores for BWt would be more appropriate to isolate the effect of being small for gestational age leaving GA to account for immaturity.

Response: Thank you for this very important suggestion. In addition to gestational age, we have now used z scores for birth weight instead of actual birth weight in the regression analysis. Lower z scores for birth weight were associated with higher odds of SNDO even on multivariate analysis.

Comment: The first paragraph of the discussion ends "Future studies should explore the developmental trajectory of infants identified as having disability or risk for disability at 12 months and whether preschool interventions are effective." This is not well placed there, certainly is not supported by the paper, and might be a concluding speculation.

Response: We have removed this sentence from the discussion

Comment: Despite having found no association between CRP and outcome after adjustment they persist in declaring one. After adjustment the direction of the CRP association reverses and there was no association with a broadly defined HAI variable

Response: We have now made the correct interpretation of results based on the multivariate analysis and concluded that no significant association was found between CRP or infections and adverse neurodevelopmental outcomes.

Comment: I am left with several questions – a. Can we finesse the relationship if any with CRP – were some immediate post-surgery and others later in the course, and did the timing of the CRP rise modify the relationship?

Response: Thank you for this very important suggestion. We have now stratified CRP levels based on the timing in relation to the surgical procedure. A CRP done in the preoperative period was considered to be a surrogate marker of early onset sepsis, whereas CRP performed within 72 hours of surgery was considered to be related to the degree of surgical injury and CRP performed after 72 hours of surgery to indicate hospital acquired infection.

HAI was not associated with increased risk of suboptimal neurodevelopmental outcomes, either on univariable or multivariate analysis. Similarly, higher levels of CRPs were not associated with adverse neurodevelopmental outcomes irrespective of the timing of CRP in relation to the surgeries.

Comment: Length of stay was associated with outcome and number of anaesthetic procedures – this suggests "illness" might predict outcome – no duration of anaesthesia was included – this might be a better measure of exposure than the number of procedures

Response: We agree with the reviewer. In our updated analysis, suboptimal neurodevelopmental outcomes were defined based on GMDS-II only and the results of ASQ were not used as per suggestion of reviewer 3. Higher number of anaesthetic procedures were no longer a significant association for adverse outcomes on the updated multivariate analysis. We have updated the discussion section thoroughly now. Unfortunately, we could not get reliable information regarding the duration of anaesthesia.

Comment: Is there really any relationship between CRP levels and outcomes?

Response:

Higher levels of CRPs were not associated with adverse neurodevelopmental outcomes irrespective of the timing of CRP in relation to the surgeries, either on univariable or multivariate analyses. We have updated the manuscript to reflect these results. On univariable analysis, lower birth weight z scores, prolonged duration of antibiotic therapy increasing episodes of general anaesthesia and prolonged duration of hospital stay were associated with higher odds of suboptimal neurodevelopmental outcomes (Table 4). On multivariate analysis, lower birth weight z scores and longer duration of hospital stay were associated with increased odds adverse outcomes (Table 4).

Reviewer: 3 [Prof Francesco Morini, Ospedale Pediatrico Bambino Gesù, IRCCS, Rome, Italy]

Comment: This is a retrospective study, analysing developmental outcome at 1 year of age in infants operated on for congenital gastrointestinal disorders. The Authors found a 16% prevalence of disability. Factors associated with developmental delay were birth weight, C-reactive protein (CRP) level > 95th centile, multiple (>3) general anesthesia, length of hospital stay (LOS). At multivariate analysis, gestational age >37 weeks, birth weight, and LOS were independently associated with developmental delay. This is an interesting and well-written study on the issue of follow-up of surgical neonates, an issue that will most likely become increasingly important as more surgical neonates survive.

Response: Thank you for the encouraging comment. The following are the results in our updated analyses in which the results of ASQ were no more used to define suboptimal neurodevelopmental outcomes. The definition of adverse outcome is now based on GMDS-II only as per your suggestion.

On univariable analysis, lower birth weight z scores, prolonged duration of antibiotic therapy increasing episodes of general anaesthesia and prolonged duration of hospital stay were associated with higher odds of suboptimal neurodevelopmental outcomes (Table 4). On multivariate analysis, lower birth weight z scores and longer duration of hospital stay were associated with increased odds adverse outcomes (Table 4).

Comment: What is known/what this study adds: several factors were associated with adverse developmental outcome, but the Authors focus their attention only on CRP and inflammation. Either the other factors that were associated with adverse developmental outcome are already known, and they should be included in the "What is known" section, or they are not already definitely accepted as risk factors, and they should also be reported in the "What this study adds".

Response: We have now updated this section to correctly reflect the results.

Comment: Methods: how do the Authors define infections? Blood culture positive or other definitions? This should be specified.

Response: We have now provided definitions for all types of infections.

Comment: Methods: did the Authors choose 95th centile as a cut-off for CRP because it is the 2SD limit? If so, I would suggest specifying this.

Response: Yes, that was the reason for choosing 95% centile. In the updated analysis, we have used the median values to ensure almost equal number of CRPs above and below the cut-offs.

Comment: Results: page 8, lines 53-60 and page 9, lines 3-8, I suggest that the prevalence of disability in the different anomalies is reported in decreasing order, rather than in alphabetical order.

Response: Done.

Comment: Results: page 11, lines 36-39, among the anomalies with higher prevalence of disability, the Authors do not report some with the highest prevalence such as oesophageal atresia, multiple gut anomalies.

Response: We have now mentioned the top five conditions with highest prevalence of suboptimal neurodevelopmental outcomes.

Comment: Results: table 2: maybe the Authors can specify that not all survivors had development tested. This may make more strait the understanding of the changing numbers in the columns. For example, for anorectal anomalies, one might expect 39 survivors in the "Disability among survivors" column instead of 26.

Response: We have now stated in the manuscript of the surviving 400 infants, information on developmental outcomes was available for 262 infants (65%). The same information has been written at the bottom of table 2.

Comment: Results: page 14, lines 3-17, the risk factors are neither reported in the order of decreasing significance nor in the order they appear in the table (tab 4). I understand that the Authors want to highlight the association of inflammation with developmental delay, but I think that the order of factors should follow a coherent logic.

Response: We have now reported the results in a more coherent logical way.

Comment: Discussion: The Authors should try to give an explanation for the association of higher gestational age and developmental delay.

Response: As per suggestion, we have now reanalysed the data without using the results of ASQs. Hence our follow up rates are low at 262/400. Upon the new analysis, gestational age was no more a significant association either on univariable or multivariate analysis.

Major comments

Comment: Methods/Results: The Authors use two different methods to analyze the development of their patients, the GMDS which is a direct analysis, and the ASQ, that is a parent-reported test. From the description in the methods I assume that most of the patients likely performed both tests. I suggest that in such patients with both tests, the authors report if the two tests are in agreement in detecting disability, so that it can be assumed that in this specific set of patients the two tests have the same ability in disability detection. If the opposite is true, patients with only ASQ test should be excluded (being less).

Response: We thank the reviewer for this important suggestion. We looked at the data from 150 infants where simultaneous recording of ASQ and GMSD-II was available.

Among 21 infants who were considered as disabled on GMSD-II, 8 had passed ASQ (false negative) and the remaining 13 had failed ASQ (True positive). Among 129 infants who did not have disability based on GMSD-II, 105 had passed ASQ (true negative) and 24 had failed ASQ (false positive). Hence the overall sensitivity of ASQ was 61.9% (95% CI: 38.4 to 81.9%) and specificity of 81.4% (95% CI: 73.5 to 85.7). Given the low sensitivity of ASQ to predict disability on GMDS-II, we decided to use only the results of GDMS-II. While it has decreased the follow up rate from 313 to 262, we feel assured that the definition of disability is now more reliable.

Comment: Methods/results: The Authors decided to include in the study very different congenital anomalies in terms of pathophysiology. For example, CDH is quite different from intestinal atresia because patients with CDH are more likely to experience hypoxic episodes that may have an impact on developmental outcome. The Authors should include the type of anomaly among the risk factors for disability and analyse if the prevalence of disability is statistically different between the different anomalies

Response: We thank the reviewer for this comment. Since there were 16 types of surgical anomalies, we could not include them in the multivariate analysis. Instead we have given the disability rates for individual anomalies in table 2. Infants with multiple gut anomalies, oesophageal atresia, Hirschsprung disease, exomphalos and congenital diaphragmatic hernia had highest rates of suboptimal neurodevelopmental outcomes (Table 2).

Comment: Discussion: in my opinion, the results of this paper emphasize the fact that the developmental outcome of surgical neonates with congenital gastrointestinal conditions is associated with the severity of the patient itself. This is suggested by the significance of low birth weight, episodes of acute inflammation, number of anaesthesia (that may be a predisposing factor, but also an indirect marker of severity of the patient) and LOS, all markers of a more complex patient, on univariable analysis, and lower birth weight and LOS on multivariate analysis. I would suggest to the authors to emphasize this aspect, instead of (or in addition to) focusing mainly on the association of inflammation with developmental delay.

Response: In our updated analysis, neither infection nor CRP levels were associated with adverse developmental outcomes. Only lower birth weight z scores and longer duration of hospital stay were associated with adverse outcomes on multivariate analysis. We have updated the discussion section now to correctly reflect the results.

Comment: One of the aims of the study was specifically to explore the association between developmental outcome and infections; however, very limited space is dedicated to this aspect in the Discussion. This should be amplified, or the aim should be less specific.

Response: In our updated analysis, infection and CRP levels were not associated with increased risk of adverse developmental outcomes, either on univariable or multivariate analysis. However, prolonged duration of antibiotic therapy, which could be surrogate marker of clinically suspected infection, was associated with adverse outcomes on univariable, but not multivariate analysis. We have added this information in the discussion section of the manuscript and also advocated for further studies with larger sample size to explore this area.

Associate Editor [Mr. Nigel Hall]

Comments to the Author:

Comment: Whilst we find some merit in your work our reviewers have identified a number of areas that we would like to invite you to address, if you are able to. In particular we invite you to consider the use of a longer-term neurodevelopmental outcome and if you are unable to do so justify the use of the outcome you have used and discuss further its limitations.

Response: We thank the editor for giving us an opportunity to address the reviewers' comments**.** We have addressed all the comments, which hopefully the reviewers will find satisfactory. Since our unit follows surgical infants only up to one year of age, we are unable to report on the longer-term outcomes such as at 2-5 years of age. We have added it as a significant limitation of the study. We have also justified the use of GMDS-II at one year of age, to enable the early identification of high-risk infants. In addition, we have recommended that irrespective of the results of one-year outcomes, all surgical infants should be followed at least until 3-5 years of age.

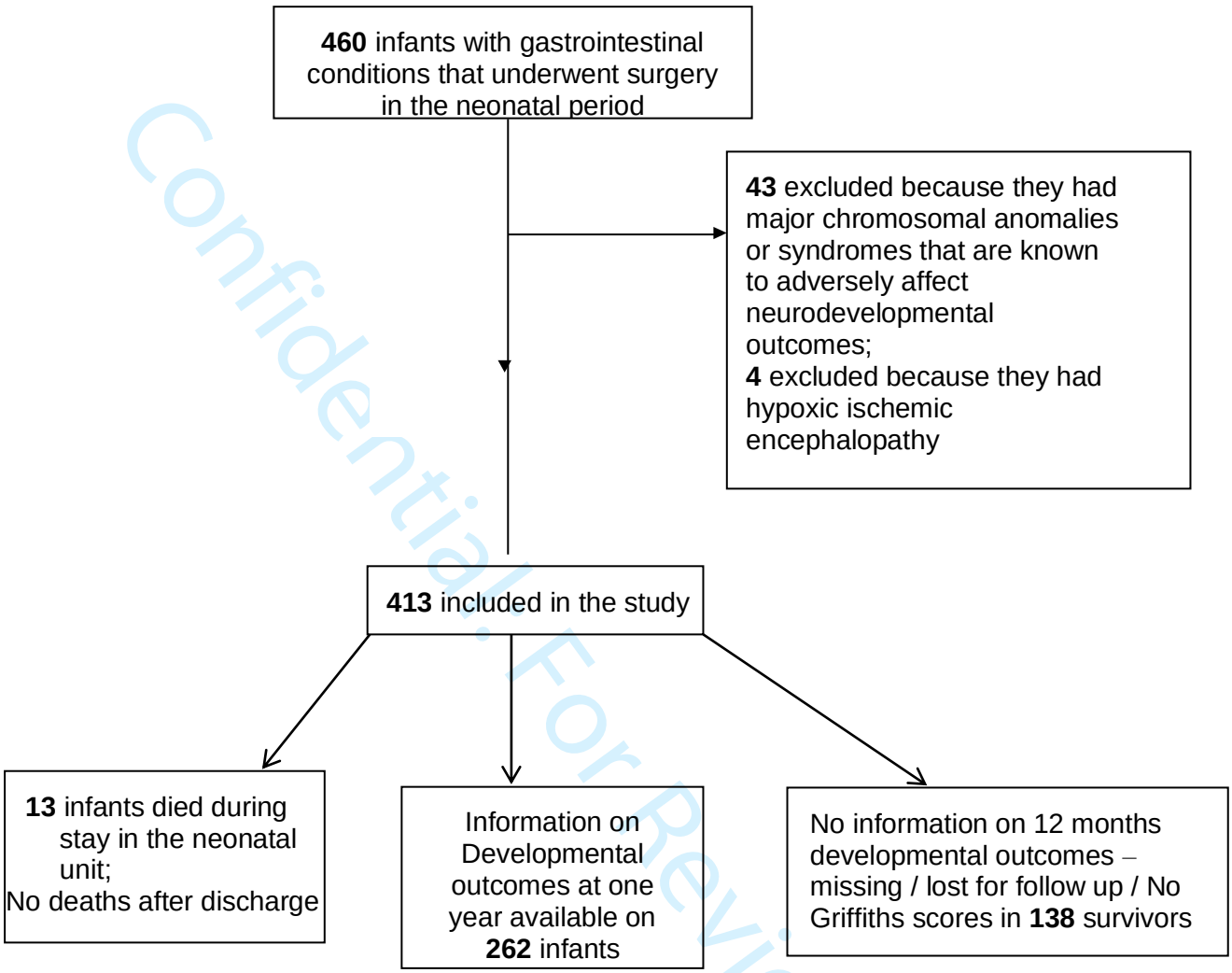
Comment: Additionally, as per one of the reviewers please consider your analysis of CRP levels in relation to outcome, the limitation that they were not drawn in a standardised way and the fact that a raised CRP in relation to a post-operative state may be completely different in meaning to a raised CRP associated with a bloodstream infection.

Response: We thank you and the reviewer for this very important suggestion. We have now stratified the timing of CRP levels under three groups: "Before initial surgery", "within 72 hours after surgery" and more than "72 hours after surgery". A CRP done in the preoperative period prior to the initial surgery was considered to be a surrogate marker of early onset sepsis, whereas CRP performed within 72 hours after surgery was considered to be related to the severity of surgical injury (reflecting the complexity of the surgical condition) and CRP performed after 72 hours to indicate hospital acquired infection.

In our updated analysis, infection and CRP levels were not associated with increased risk of adverse developmental outcomes, either on univariable or multivariate analysis. However, prolonged duration of antibiotic therapy, which could be surrogate marker of clinically

suspected infection, was associated with adverse outcomes on univariable, but not multivariate analysis. We have added this information in the discussion section of the manuscript and also advocated for further studies with larger sample size to explore this area.

Fig 1. Study Flow Diagram



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Early Neurodevelopmental Outcomes of Congenital Gastrointestinal Surgical Conditions- A Single Centre Retrospective Study

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TITLE PAGE

Title: Early Neurodevelopmental Outcomes of Congenital Gastrointestinal Surgical Conditions- A Single Centre Retrospective Study

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WHAT IS KNOWN ABOUT THE SUBJECT?

1. Surgery in the neonatal period may have an adverse effect on neurodevelopment outcomes.
2. Infection and excessive inflammation are harmful to the developing brain

WHAT THIS STUDY ADDS

1. Nearly 16% of late preterm and term infants who underwent neonatal surgery for congenital gastrointestinal conditions had suboptimal neurodevelopment at one year of age.

2. Lower z scores for birth weight and prolonged hospital stay were associated with increased risk of suboptimal neurodevelopmental outcomes.

3. CRP levels and infections were not associated with suboptimal neurodevelopmental outcomes at 1 year of age.

ABSTRACT

Background: Evidence is emerging that surgery in the neonatal period is associated with increased risk of suboptimal neurodevelopmental outcomes (SNDO). The aim of this study was to describe neurodevelopmental outcomes (at one year) of neonatal surgery for congenital gastrointestinal surgical conditions (CGSC) and to explore risk factors.

Methods: Retrospective study (2005-2014) of infants born ≥34 weeks gestation with CGSC and admitted to the surgical neonatal intensive care unit of Perth Children's Hospital, Western Australia. Clinical details and one-year developmental outcomes based on Griffiths Mental Developmental Assessment Scales (GMDS-II) were collated from the database and by reviewing the medical records of study infants. Suboptimal neurodevelopmental outcome (SNDO) was defined as one or more of the following: a GQ less than 88 (i.e. >1SD below mean), cerebral palsy, blindness or sensorineural deafness. Univariable and multivariable logistic regression analyses were carried out to explore risk factors for SNDO. A total of 413 infants were included, of which 13 died. Median gestation was 37.6 weeks (IQR: 36.4 to 39.1). Information on developmental outcomes was available from 262 out of 400 survivors. A total of 43/262 (16.4%) had SNDO. On univariable analysis, lower z scores for birthweight, prolonged duration of antibiotics, increased episodes of general anaesthesia and prolonged duration of hospital stay were associated with SNDO. On multivariable analysis, lower z scores for birth weight and prolonged hospital stay were associated with increased risk of SNDO.

Conclusions: Late preterm and term infants undergoing neonatal surgery for CGSC may be at risk for SNDO. Studies with longer duration of follow-up are needed to further evaluate the role of potentially modifiable risk factors on their neurodevelopmental outcomes.

Keywords: Surgery, Infant, Neurodevelopment

INTRODUCTION

Survival following neonatal surgery has improved in recent years, but short and long-term complications continue to have significant effects on these infants and their families.[1] A recent population based study that compared developmental outcomes of 124 neonates undergoing non-cardiac surgery versus 92 who underwent cardiac surgery and 162 healthy infants found that cardiac surgery carried the highest risk of developmental delay, but infants undergoing non-cardiac surgeries also had 7-14% incidence of developmental delay.[2]

Factors associated with poor developmental outcomes in neonates undergoing surgery include low birth weight,[3] chromosomal anomalies, growth restriction,[4] prolonged hospital stay,[5] need for Extracorporeal Membrane Oxygenation (ECMO),[6 7] chronic lung disease,[8] increasing number of surgeries,[5] and low socio-economic status.[9] One factor that has not been adequately explored in neonates undergoing surgery is the influence of infection and inflammation. Exploring this area is important because infection and excessive inflammation are potentially harmful to the developing brain.[10-14]

We conducted this retrospective study to evaluate one-year developmental outcomes of late preterm and term infants who underwent surgery for congenital gastrointestinal surgical conditions (CGSC) in our unit and to explore the potential risk factors. Another aim of the study was to analyse the impact of inflammation on neurodevelopmental outcomes of those infants.

METHODS

This was a retrospective cohort study of all late preterm and term infants born at $\geq 34^{0/7}$ week's gestation between January 2005 and December 2014 with CGSC who underwent surgery in the neonatal period at the tertiary neonatal intensive care unit of Perth Children's Hospital, Western Australia.

The following conditions were included in the study- Gastroschisis, exomphalos, duodenal atresia, malrotation, Jejuno-ileal atresia, large bowel atresia, meconium ileus, Hirschsprung disease, multiple gut anomalies, gut perforations/stenoses, short bowel syndrome, biliary atresia, ano-rectal anomalies and benign abdominal cysts. We included oesophageal atresia and congenital diaphragmatic hernia because they also involve the gastrointestinal tract and have long-term gastrointestinal complications.

Infants were identified by interrogating the departmental database. Infants with chromosomal anomalies and syndromes known to adversely affect developmental outcomes were excluded. Infants born at <34 weeks' gestation were excluded because they carry a higher risk of adverse developmental outcomes due to prematurity compared to late preterm and term infants.

Clinical characteristics of study infants were extracted from their medical records by one author (VB) and verified for accuracy by a second author (SR). Two neonatologists with expertise in developmental follow up (DW, JT) collated the results of one-year outcomes based on Griffiths Mental Development Scales (GMDS-II) from the departmental database. The GMDS-II assesses development in five areas: locomotor, personal and social, hearing and speech, eye and hand coordination, and performance. The five subscales are assessed and scored separately and then combined to provide an overall general quotient (GQ) reflecting the child's developmental performance level relative to the general population. On these scales, a combined general quotient (GQ) of 100.2 (SD 12) is considered normal.[15] The GMDS-II is a well-recognised tool for identifying neurosensory disability and is used widely.[16 17]

Outcome of interest for this study was suboptimal neurodevelopmental outcomes (SNDO) at one year of age. SNDO was defined as one or more of the following: (i) a GQ of <88 (i.e. >1SD below mean) on GMDS-II[15], (ii) cerebral palsy (based on assessment by neurologist or

developmental paediatrician) (iii) blindness (visual acuity of <6/60 in the better eye), and (iv) sensorineural deafness (based on audiometry assessment) requiring hearing aids.

Healthcare associated infection (HAI) included urinary tract infection or healthcare associated blood stream infection (HABSI), meningitis or surgical site infection or any type of viral infection. HABSI was defined as positive blood culture on a sample taken 48 hours after admission to the NICU. UTI was defined as positive culture based on a sample collected from suprapubic sample or in-and-out catheter. Meningitis was diagnosed based on positive culture on CSF samples collected with aseptic precautions. The diagnosis of wound infection was based on the presence of erythema/oedema/induration at the surgical site and positive culture on the wound swab. Respiratory viral infection was diagnosed based on PCR on postnasal aspirate samples taken in infants who presented clinical symptoms of respiratory illness.

C Reactive Protein (CRP) was used as the marker of inflammation. We stratified the CRP levels based on the timing in relation to the surgical procedure. Empirically, a CRP done in the preoperative period was considered to be a surrogate marker of early onset sepsis, whereas CRP performed within 72 hours of surgery was considered to be related to the degree of surgical injury and CRP performed after 72 hours of surgery to indicate hospital acquired infection.

Statistical analysis was done using the STATA 16 software (Stata Corp. 2019 Stata Statistical Software: Release 16 College Station, TX; Stata Corp. LP). The summary statistics for normally distributed continuous variables were expressed as mean and standard deviations; those with skewed distribution were expressed as median and interquartile range (IQR). Categorical variables were expressed as frequency and percentage. Univariable and multivariable random effect logistic regression models were carried out to derive unadjusted

and adjusted odds ratios and 95% confidence intervals. Random effect was included in the fitted model to minimise bias due to the presence of correlated data [i.e. multiple measurements of CRP values from individual patients].One-sample t-test was used to compare the mean GQ scores to the population mean (100.2)[15]. For all analyses, a two-tailed p-value of <0.05 was considered statistically significant.

This retrospective study was approved by the institutional ethics committee as a quality assurance activity. All clinical variables and the results of developmental assessments (GMDS-II) collected for this study were retrospective in nature. STROBE guidelines were used to report this study.[18]

Patient and Public Involvement

The development of research question and outcome measures for this retrospective study were not informed by patients' priorities, experience and preferences. Patients were not involved in the design, in the recruitment to and conduct of the study. Patients were not invited to comment on the study design and were not consulted to develop patient relevant outcomes or interpret the results. Patients were not invited to contribute to the writing or editing of this document for readability or accuracy. There are no plans to disseminate the results of this study to study participants.

RESULTS

A total of 460 neonates underwent surgery for CGSC during the study period, of which 43 were excluded because of chromosomal anomalies or syndromes that are known to adversely affect neurodevelopmental outcomes. Four infants were excluded because they had moderate to severe hypoxic ischemic encephalopathy due to perinatal asphyxia. The remaining 413 infants were included in the study. Of them 13 died, and of the 400 surviving infants, full information on developmental outcomes was available for 262/400 (65%) surviving infants. The flow diagram of patient selection process is given in figure 1.

The median gestation was 37.6 weeks (IQR: 36.4 to 39.1) and median birth weight 3000 grams (IQR: 2590 to 3405). The median duration of hospital stay was 18 days (IQR: 11 to 26 days, range: 1 to153 days). There were 13 deaths, all of which were during initial hospital stay. There were no deaths after discharge from the hospital. Table 1 summarises the clinical characteristics in detail.

The major surgical conditions were gastroschisis, malrotation, oesophageal atresia with or without tracheo-oesophageal fistula, Hirschsprung disease and congenital diaphragmatic hernia (Table 2).

Table 1: Characteristics of study infants

Clinical characteristic	Median or number (percentage)	IQR	Range	N
Gestation (weeks)	37.6	36.4 to 39.1	34.1 to 41.5	413
Gender (Male: Female)	57%:43%	NA	NA	413
Birth weight (grams)	3000	2590 to 3405	1664 to 5060	413

Birth weight z scores	-0.23	-0.87 to 0.41	-2.81 to 4.78	413
Birth length (cm)	49	47 to 51	40 to 58	403
Birth Length z scores	-0.03	-0.75 to 0.57	-3.38 to 4.23	403
Birth head circumference (cm)	34	32.5 to 35	28.5 to 47	409
Birth head circumference z scores	0.07	-0.62 to 0.78	-3.32 to 3.29	408
APGAR 5min	9	9 to 9	4 to 10	409
Pre-Surgery CRP levels (mg/dl)	7.5	5 to 20	1 to 188	933
CRP levels within 72 hours of initial surgery (mg/dl)	35.5	19 to 69	3 to 346	747
CRP levels after 72 hours of surgery (mg/dl)	15	7 to 29	1 to 325	2912
Health care associated blood stream infection (HABSI)	27(6.5%)	NA	NA	413
CSF culture positive	1 (0.25%)	NA	NA	413
Lumbar puncture done	14 (3.4%)	NA	NA	413
Viral infections (all respiratory)	17 (4.1%)	NA	NA	413
UTI (urinary tract infections)	1 (0.24%)	NA	NA	413
Culture positive surgical site infections	14 (3.4%)	NA	NA	413
Any health care associated infection (HAI) (Blood stream or CSF or viral or UTI or wound infection)	51 (12.4%)	NA	NA	413
Number of antibiotic courses	2	1 to 2	1 to 14	406
Cumulative duration of antibiotics (days)	6	4 to 8	1 to 56	406
Surgery episodes under GA	1	1 to 2	1 to 5	413

Number of episodes of hypoglycaemia (blood glucose<2.6 mmol/L)	0	0 to 0	0 to 15	413
Length of stay (days)	18	11 to 26	1 to 153	413
Post conception age at discharge (weeks)	41	39.4 to 42.4	35.4 to 60.2	413
Death before discharge	13 (3.1%)	NA	NA	413
Death before 1 year	13 (3.1%)	NA	NA	413
Corrected age at Griffiths assessment (months)	12	12 to 12.5	10 to15.5	270
GQ scores at 12 months	96.5	92 to 102	49 to 131	270
SNDO	43/262 (16.4%)	NA	NA	262

AGA: Appropriate growth for gestational age; SGA: small for gestational age;

LGA: large for gestational age; NA: not applicable; SNDO: Suboptimal developmental outcomes

A total of 43/262 (16.4%) infants had SNDO, with 9 infants having a GQ<76 (i.e. more than 2SD below the mean). One infant had deafness, one had cerebral palsy, and none had blindness. The mean GQ was 96.3 (SD 10.3), which was significantly lower than the population mean of 100.2; p<0.001. Infants with multiple gut anomalies, oesophageal atresia, Hirschsprung disease, exomphalos and congenital diaphragmatic hernia had highest rates of SNDO amongst survivors (Table 2).

Table 2: Developmental outcomes of neonates with CGISC*

Major gastrointestinal anomaly	**Number**	**Mortality**	**SNDO among infants who were assessed**	**Median GQ**
Gastroschisis	92(22.3%)	3/92 (3.3%)	8/55 (14.5%)	98.5 (IQR:92.5 to103) n=60
Malrotation	48	3/48 (6.2%)	4/33 (12.1%)	96 (IQR:93 to103)

	(11.6%)			n=34
Oesophageal Atresia	44 (10.6%)	1/44 (2.3%)	10/27 (37%)	93 (IQR:85 to100) n=27
Hirschsprung Disease	44 (10.6%)	1/44 (2.3%)	6/32 (18.7%)	98 (IQR:93 to102) n=33
Congenital Diaphragmatic Hernia	42 (10.2%)	1/42 (2.4%)	5/34 (14.7%)	94.5 (IQR:92 to105) n=34
Ano-Rectal Anomalies	39 (9.4%)	0/39 (0%)	3/21 (14.3%)	96 (IQR:90 to101) n=22
Gut Perforations and Stenoses	19 (4.6%)	1/19 (5.3%)	1/12 (8.3%)	101.5 (IQR:94.5 to106) n=12
Duodenal Atresia	19 (4.6%)	0/19 (0%)	1/13 (7.7%)	99 (IQR:94 to110) n=15
Jejuno-Ileal Atresia	16 (3.9%)	0/16 (0%)	1/9(11.1%)	97.5 (IQR:95 to102) n=10
Exomphalos	13 (3.1%)	0/13 (0%)	1/6 (16.7%)	99 (IQR:89 to100) n=7
Meconium Ileus	12 (2.9%)	0/12(0%)	0/5 (0%)	98 (IQR:96 to 99) n=5
Multiple Gut Anomalies	10 (2.4%)	1/10 (10%)	3/7 (42.8%)	88 (IQR:84 to100) n=7
Short Bowel Syndrome	5 (1.2%)	2/5 (40%)	0/1 (0%)	95 n=1
Large Bowel Atresia	5 (1.2%)	0/5 (0%)	0/1(0%)	104

				n=1
Benign Abdominal Cysts and tumours	4 (0.97%)	0/4 (0%)	0/1(0%)	103 n=1
Biliary Atresia	1 (0.24%)	0/1 (0%)	0/1(0%)	92 n=1

*For all outcomes, infants who underwent at least one episode of surgery were included; infants who died prior to undergoing any surgery were excluded. The information on neurodevelopmental outcomes was available for 65% of survivors.

Healthcare associated bloodstream infection (HABSI) occurred in 27 infants (6.5%). A total of 51 (12.4%) infants developed at least one episode of healthcare associated infection (HAI) (urinary tract infection or HABSI or viral infection or surgical site infection). None of the infants had early onset sepsis. Coagulase negative staphylococcus, *Klebsiella* sp. and *Eschericia Coli* were the most common pathogens isolated (table 3).

Table 3: Micro-organisms isolated from infants with healthcare-associated infections

Micro-organism	Blood	CSF	Urine	Viral infections	Wound/skin swab
CONS*	16	1	-	-	3
E.Coli	4	-	-	-	3
Klebsiella	3	-	-	-	-
Pseudomonas	1	-	-	-	2
Strep. Mitis	1	-	-	-	-
Moraxella	1	-	-	-	-
Enterococcus	1	-	-	-	1
Candida Albicans	-	-	1	-	2
Staph. Aureus	-	-	-	-	2
Enterobacter Cloacae	-	-	-	-	1
Rhino virus	-	-	-	12	-

RSV*	-	-	-	2	-
Influenza A	-	-	-	2	-
Parainfluenza	-	-	-	1	-
Total	27	1	1	17	14

*CONS-Coagulase Negative Staphylococcus; RSV- Respiratory Syncytial Virus

Association between neonatal risk factors and SNDO among survivors

On univariable analysis, lower birth weight z scores, prolonged duration of antibiotic therapy increasing episodes of general anaesthesia and prolonged duration of hospital stay were associated with higher odds of SNDO among survivors (Table 4). On multivariable analysis, lower birth weight z scores and longer duration of hospital stay were associated with increased odds of SNDO among survivors (Table 4).

Table 4: Risk factors for SNDO

Variable	**Unadjusted odds ratio and 95% CI**	**P value**	**Adjusted odds ratio and 95% CI**	**P value**
Gestational age at birth (≥37 weeks)	1.07 (0.53 to 2.19)	0.840	1.54 (0.65 to 3.63)	0.321
Birth weight z scores	0.64 (0.47 to 0.89)	**0.008**	0.69 (0.49 to 0.98)	**0.038**
Female gender	0 .71 (0.36 to 1.39)	0.313	0.53 (0.24 to 1.16)	0.112
Number of episodes of hypoglycaemia (<2.6mmol/l)	1.06 (0.75 to 1.49)	0.730	0.98 (0.60 to 1.58)	0.923
General anaesthesia (>3 episodes)	3.31 (1.29 to 8.50)	**0.013**	0.77 (0.17 to 3.59)	0.745
Pre-Operative	0.90 (0.59 to 1.37)	0.627	0.92 (0.60 to 1.40)	0.698

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CRP levels				
CRP levels within 72 hours of surgery	0.90 (0.63 to 1.28)	0.555	1.06 (0.69 to 1.62)	0.769
CRP levels after 72 hours of surgery	0.64 (0.41 to 1.01)	0.053	0.99 (0.63 to 1.56)	0.985
Any Infection	1.20 (0.49 to 2.96)	0.683	0.44 (0.11 to 1.77)	0.247
Cumulative duration of antibiotics	1.05 (1.01 to 1.10)	**0.043**	1.00 (0.91 to 1.10)	0.990
Degree of postnatal growth restriction	2.00 (0.59 to 6.81)	0.265	1.56 (0.62 to 3.97)	0.348
Length of stay	1.02 (1.00 to 1.03)	**0.003**	1.03 (1.00 to 1.06)	**0.034**

DISCUSSION

Our study found an overall mortality rate of 3.1% and SNDO in 16.4% of neonates undergoing surgery for CGSC. These findings are similar to a recent study that reported an incidence of 7-14% in various domains of assessment at three years among 124 children who underwent surgery for non-cardiac conditions in the neonatal period.[2] While the mean GQ of 96.3 in our cohort might not appear too low, it is important to note that the GMDS-II norms are based on population sample more than two decades ago. It is well known that developmental quotients and intelligence quotients in the general population increase by 2 to 3 points each decade (Flynn effect)[19]. If assessed using the GMDS-II tools, healthy 12-month old infants during the study period of 2005-2014 would probably have scored a mean of 103 rather than 100.

Since the study spanned over 10 years (January 2005 to December 2014), advances in anaesthesia, surgical techniques, intensive care management, and changes to family and

societal environment during that period could have influenced the in-hospital clinical outcomes and one-year developmental outcomes of study infants. Contemporary multicentre studies with adequate sample size are needed enhance knowledge in this area.

While many variables were found to be associated with increased risk of SNDO on univariable analysis, only lower birth weight z scores and longer duration of hospital stay were found to be having significant association on multivariable analysis. Lower birth weight z scores indicate fetal growth restriction and prolonged hospitalisation is usually related to the complex nature of the underlying surgical condition. Hence their association with adverse neurodevelopmental outcomes is not unexpected. The width of the CI for birth weight z-scores was very wide, ranging between a drop in the odds between 2 and 50%. The probable reason for this wide range could be related to the timing of intrauterine growth restriction (IUGR). For the same degree of IUGR, the one that starts early during pregnancy is known to have worse outcomes compared to late gestation IUGR.

Each additional day of stay in the hospital resulted in a change in the odds of SNDO by 3%. Many surgical infants stay for a protracted period of time in the hospital and hence these odds are likely to be clinically significant.

The burden of HAI and HABSI in neonates with CGSC has not been explored adequately. Donnell and van Saene et al. conducted a prospective study of surgical infants<6 months to find infection rates.[20 21] Thirty-two infants developed blood culture positive sepsis (15%); predominant micro-organisms (86%) were coagulase-negative staphylococci and enterococci. Other pathogens, including aerobic gram-negative bacilli, were responsible for the remainder. They suggested that gut translocation was the main factor behind sepsis in surgical infants rather than central lines and cautioned that prevention is unlikely to be successful if abnormal gut flora is ignored.[21] Another study by Bishay et al reported that 31 out of 112 surgical infants (28%) had a total of 65 episodes of septicaemia.[22]

In very preterm infants, it is well established that neonatal sepsis is associated with higher risk of adverse neurodevelopmental outcomes. A recent systematic review by Cai et al[23] found that preterm infants with neonatal sepsis were at a higher risk of neurodevelopmental impairments such as cerebral palsy and neurosensory deficits, compared with infants without sepsis (OR 3.18; 95% CI 2.29-4.41)[23]. Hence, we had expected similar findings in our cohort of surgical infants. However, in our study, HAI was not associated with increased risk of SNDO, either on univariable or multivariable analysis. Similarly, higher levels of CRPs were not associated with SNDO irrespective of the timing in relation to the surgeries. This could be related to the resilience of the brain of late preterm and term infants to the harmful effects of infection and inflammation, unlike the vulnerable extremely preterm infants. However, prolonged duration of antibiotic therapy, which could be a surrogate marker of clinically suspected infection, was associated with SNDO on univariable, but not multivariable analysis. Further studies with larger sample size and a longer duration of follow up beyond 1 year of age are needed to explore the role of infection and inflammation in late preterm and term infants undergoing neonatal surgery.

The harmful effect of exposures to general anaesthesia on developing brain is an area of debate and active research.[24] [25] While animal studies have consistently shown general anaesthesia to be toxic to the developing brain,[26] one recent large RCT (GAS study),[27] and a large prospective cohort study (PANDA)[28] found no significant association. Both these studies evaluated a single exposure to general anaesthesia, and hence do not address the issue of repeated exposures. A recent large data linkage study found that children exposed to general anaesthesia before four years have poorer development outcomes at school entry and school performance.[29] In another cohort study[30], children who had multiple exposure to GA before 3 years of age scored 1.3 points (95% CI, -3.8 to 1.2; P = 0.32) less than unexposed children on intelligence tests; children who had one exposure to GA scored 0.5 points (95%

CI, -2.8 to 1.9; P = 0.70) less than unexposed children. However, the parents of children who had multiple exposure to GA reported increased problems related to executive function, behaviour, and reading[30]. In our cohort, increasing episodes of general anaesthesia were associated with higher risk of SNDO on univariable analysis, but not on multivariable analysis. Further studies with long duration of follow up are needed in this area.

Whilst we found lower birth weight z scores and prolonged hospital stay to be associated with increased risk of SNDO, one should not ignore the possibility that the underlying surgical condition in itself could be an important risk factor that drives other morbidities leading to SNDO. In our cohort, multiple gut anomalies and oesophageal atresia had the highest incidence of SNDO (42.8% and 37% respectively), which is not unexpected because these infants have significant in-hospital and post-discharge morbidities, which puts them at a higher risk of SNDO.

One of the limitations of our study was the shorter duration of follow up of one year and the findings may not track subsequently. In a recent study, Fairbairn et al reported that Bayley-III results for all domains at one year of age were a weak predictor of outcomes at three years of age in infants who had early major cardiac and non-cardiac surgery and healthy infants[31]. Hence all infants, irrespective of the results of developmental assessments at one year should be followed with formal developmental assessments at least until five years of age. At the same time, infants identified as high risk based on the one-year assessments could be provided early developmental interventions to optimise their outcomes. Only recently, we have commenced routine developmental follow up until two years of age with Bayley Scales of Infant Development (BSID-III) to all infants undergoing surgery in the neonatal period.

Surgical infants who need prolonged duration of mechanical ventilation are at higher risk of hypoxic episodes and hence worse developmental outcomes. At the same time, prolonged ventilation could be a maker of severity of the underlying anomaly. A limitation of our study

was the lack of reliable information on the duration of mechanical ventilation among the study infants.

The other limitations of our study were: a) retrospective design without healthy controls, b) the indication for doing CRP levels was at the discretion of clinicians rather than based on a standardised protocol, c) full information on developmental outcomes was missing from nearly 35% of survivors, d) lack of information on socio-demographic status of family and e) missing information about duration of general anaesthesia which can have significant influence on developmental outcomes and f). The data was from a single centre from a high-income country and hence the findings may not be generalisable. The main strength of the study is the large sample size of surgical infants and the use of regression analyses to adjust for confounders.

Conclusions: Late preterm and term infants undergoing surgery for CGSC may be at risk for suboptimal neurodevelopmental outcomes at one year of age. Studies with long-term follow-up are needed to further evaluate the influence of potentially modifiable risk factors on neurodevelopmental outcomes in such infants.

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Contributors' Statements:

A/Prof Rao conceptualized and designed the study, coordinated and supervised data collection, verified the data for accuracy, drafted the initial manuscript, and reviewed and revised the manuscript.

Dr Batta collected the data, assisted with drafting of the initial manuscript and reviewed the manuscript

Prof Patole and Prof Simmer critically reviewed and revised the manuscript. They also provided feedback at the design and analysis stage of the study

Dr Wagh and Dr Tan provided information regarding the developmental outcomes of all study infants. They critically reviewed and revised the manuscript.

Dr Gollow critically reviewed and revised the manuscript.

Prof Bulsara conducted the statistical analysis of the data, reviewed and revised the manuscript.

Patient advisers were not involved in this retrospective study.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Data Sharing Statement: Individual de-identified participant data (including data dictionaries) that underlie the results reported in this article will be shared beginning 3 months and ending 5 years after publication of the article to researchers who provide a methodologically sound proposal. All such requests should be directed to the corresponding author. To gain access, the data requestors will need to sign a data access agreement.

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Fig 1. Study Flow Diagram