AN ANALYSIS OF NEONATES WITH SURGICAL DIAGNOSES ADMITTED TO THE NEONATAL INTENSIVE CARE UNIT AT CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL

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A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfillment of the requirements for the degree of Master of Medicine in the branch of Paediatrics.

Johannesburg 2018

DECLARATION

I, Robin Terence Saggers, declare that this research report is my own work. It is being submitted for the degree of Master of Medicine in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

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___ day of _____ 20_____.

PRESENTATIONS ARISING FROM THIS RESEARCH REPORT

Oral Presentation: Wits Paediatrics Research Day,
26 November 2016,
University of the Witwatersrand, Johannesburg.

Oral Presentation: 3rd Biennial USANA Conference
(United South African Neonatal Association),
15 September 2017,
Southern Sun OR Tambo Hotel, Johannesburg

Oral Presentation: 8TH Cross-Faculty Postgraduate Symposium
(Showcasing Postgraduate Research at Wits),
25 October 2017,
University of the Witwatersrand, Johannesburg.

ABSTRACT

Introduction: The burden of neonatal surgical conditions is not well documented in lower to middle income countries (LMICs), yet neonatal surgical conditions are thought to be relatively common with a considerable proportion of neonates admitted to the neonatal intensive care unit (NICU) requiring surgical intervention. The NICU at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) is combined with a paediatric intensive care unit, to a total of 15 beds, and serves as a referral hospital.

Objectives: To review neonates with surgical conditions admitted to the Neonatal Intensive Care Unit (NICU) in our hospital setting.

Methods: This was a retrospective, descriptive study of neonates admitted to the NICU at CMJAH with surgical conditions between 1 January 2013 and 31 December 2015. The characteristics and the survival of these neonates were described using univariate analysis.

Results: There were 923 neonates admitted to the NICU, of which 319 (34.6%) neonates had primarily surgical conditions. Of the 319 neonates, 205 survived (64.3%). There were 125/319 (39.2%) neonates with necrotizing enterocolitis (NEC), 55 of whom survived (55/125, 44.0%), making the presence of NEC significantly associated with poor outcome (p=<0.001). Other significant predictors of poor outcome were: the patient being outborn (p=0.029); the presence of late sepsis (p=<0.001) – with *Gram-negative* (p=0.005) organisms; as well as lesser gestational age (p=0.001) and lower birth weight (p=<0.001). Major birth defects were present in 166/319 (52.0%) of neonates.

Conclusions: Neonates with major surgical conditions account for one third of NICU admissions in the present study. Paediatric surgical services, with a proper referral and neonatal transport system, must be a priority in planned healthcare interventions to reduce neonatal mortality in LMICs.
(Word count 269)

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ABBREVIATIONS

ANC:	Antenatal care
ARM:	Ano-rectal malformations
CDH:	Congenital diaphragmatic hernia
CMJAH:	Charlotte Maxeke Johannesburg Academic Hospital
ENT:	Ear, nose and throat
GUT:	Genito-urinary tract
HIV:	Human immunodeficiency virus
IQR:	Inter-quartile range
MSK:	Musculoskeletal
NEC:	Necrotizing enterocolitis
NICU:	Neonatal Intensive Care Unit
PDA:	Patent ductus arteriosus
REDCap:	Research Electronic Data Capture
SD:	Standard deviation
TOF:	Tracheo-oesophageal fistula
VLBW:	Very low birth weight
VON:	Vermont Oxford Network

SUBMISSIBLE PAPER

AN ANALYSIS OF NEONATES WITH SURGICAL DIAGNOSES ADMITTED TO THE NEONATAL INTENSIVE CARE UNIT AT CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL

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Major birth defect;
Low and middle-income countries;
South Africa.

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Conclusions: Neonates with major surgical conditions account for one third of NICU admissions in the present study. Paediatric surgical services, with a proper referral and neonatal transport system, must be a priority in planned healthcare interventions to reduce neonatal mortality in LMICs.
(Word count 269)

1.0 INTRODUCTION

The burden of neonatal surgical diseases in Africa is not well documented, yet neonatal surgical conditions are thought to be relatively common, with a considerable proportion of neonates admitted to the neonatal intensive care unit requiring surgical intervention.(1, 2) A survey among paediatric surgeons practicing in Africa indicated that 10-20% of their paediatric surgical workload resulted from neonatal surgery.(1) There is no specific data in South Africa which results in inadequate planning and delivery of neonatal surgical services.

The World Health Organization estimates that approximately 10% of all neonatal deaths in sub-Saharan Africa and South Asia are due to congenital malformations, and many of these congenital malformations are only amenable to operative intervention.(1) In Africa, congenital malformations made up more than a quarter of paediatric surgical admissions, and accounted for nearly half of emergency procedures.(3, 4)

Common surgical problems encountered in Africa are (but not limited to): necrotizing enterocolitis (NEC), congenital diaphragmatic hernia (CDH), anorectal malformations (ARM), Hirshprung's disease, omphalocoele, gastroschisis, oesophageal atresia and trachea-oesophageal fistula (TOF), intestinal atresia, and intestinal perforation.(1)

Resources for neonatal surgery vary widely between high and low to middle income countries (LMICs).(3) There is variability with regards to conditions admitted in hospital, as well as the neonatal surgical workload, within Africa.(1) This could be attributed to a number of factors, such as: availability of antenatal diagnosis, primary health care and transport facilities, distance, poverty, cultural methods of treatment, as well as time of presentation, death before arrival, access to paediatric surgery, access to intensive care, access to neonatal anaesthesia, and genetic predisposition within the various populations.(1, 4)

In high income countries, much progress has been made in the management of neonatal surgical conditions, resulting in a decrease in the neonatal surgical mortality rates, from more than 50% in the 1950s to less than 5% in recent years.(1, 5, 6) However, in Africa there remain multiple challenges leading to high morbidity and mortality, with mortality figures being reported to be between 16% and 45%.(1, 4, 5)

A major post-operative complication is the development of sepsis, which results in serious morbidities and mortalities. Surgical interventions have been shown to have a strong association with the development of infection, with the risk rising as the number of interventions increases.(2, 7, 8) Infections may be septicaemia, related to supportive interventions (e.g. ventilator associated pneumonia, urinary tract infections, central line associated sepsis), or localized to the surgical site.

Neonates who require surgical intervention require mechanical ventilation for longer periods and have increased duration of hospitalisation. The site of surgery determines the site of infection: laparotomies (generally considered to be a contaminated procedure) have a higher rate of surgical site infections than thoracic surgeries (generally considered to be a clean procedure).(2) Notably, very low birth weight (VLBW) neonates as well as neonates who underwent gastroschisis closure are at the greatest risk of developing surgical site infections.(2)

Many hospitals in sub-Saharan Africa do not have paediatric surgical facilities or neonatal intensive care units and neonates with surgical conditions are thus referred to central hospitals. The impact of neonatal surgical patients on the limited neonatal intensive care facilities available is not known.

This study aims to review neonates with surgical conditions admitted to the neonatal intensive care unit (NICU) of Charlotte Maxeke Johannesburg Academic Hospital (CMJAH), a large quaternary referral hospital in South Africa.

2.0 METHODS

This was a retrospective, descriptive study of neonates (<28 days of life) admitted to the NICU at CMJAH with surgical diagnoses between 1 January 2013 and 31 December 2015. Neonates with incomplete records were excluded. Outcome was defined as death or survival to discharge.

The NICU at CMJAH was combined with a paediatric intensive care unit, to a total of 15 beds, and a neonatal high care unit with 35 beds. Neonates with surgical conditions admitted to the CMJAH NICU are managed by neonatologists, in conjunction with paediatric surgeons. Owing to limited resources, the NICU functions essentially as a ventilator unit – neonates who require intensive observation are not routinely admitted.

Neonates with surgical conditions admitted to the NICU and treated by paediatric surgeons were included in the analysis. Neonates with surgical conditions who were admitted to high care wards were not included in this analysis. Thus, neonates with minor conditions (for example circumcision) were not included. Similarly, neonates who underwent surgical procedures in the high care wards, including insertion of central catheters, were not included. A neonate who had more than one surgical condition or congenital abnormality (e.g. TOF and cardiac defect) was included in the different categories.

During the period studied patent ductus arteriosus (PDA) ligations were performed by paediatric surgeons, and so were included in the analysis. All other forms of congenital heart defects were repaired by cardiothoracic surgeons in a separate unit and were thus excluded from the analysis. Myelomeningocoeles were repaired by neurosurgeons in a separate unit and were excluded from the analysis of surgical procedures, but since they were admitted to the NICU post-operatively, they were included in the analysis of the frequencies of major birth defects. Head and neck surgery was performed by ENT surgeons in a separate unit and was excluded from the analysis.

Major birth defects included lethal or life-threatening anomalies as defined in the Vermont Oxford Network database (www.vtoxford.org). Sepsis was classified as culture proven only, with onset within 72 hours of birth being classified as early-onset and after 72 hours as late-onset sepsis.

2.1 DATABASE

The neonatal records at CMJAH are stored on the REDCap (Research Electronic Data Capture) database, hosted by the University of the Witwatersrand.(9) REDCap is a secure web-based programme that aids data capture for the purposes of clinical audit and quality improvement. Upon discharge of patients, data were captured on to the REDCap database. The information was verified at several stages of collection. The following data were collected from the database: (i) maternal data – demographics, antenatal care (ANC), place of delivery, mode of delivery; and (ii) infant data – gestational age, birth weight, sex, 5-minute Apgar score, necrotizing enterocolitis (NEC), other surgical conditions, duration of ventilation, late sepsis

(occurring after 72 hours) and outcome at discharge (death or survival.) The information regarding surgery was correlated with a corresponding surgical database.

2.2 STATISTICAL ANALYSIS

An MS Excel (Microsoft, USA) spreadsheet was used to enter the data which was then imported into statistical software package SPSS version 23 (IBM, USA). Frequencies and percentages were used to describe categorical variables. Means and standard deviations (SDs) were used to describe normally distributed continuous variables, and skewed continuous variables were described using medians and interquartile ranges (IQR). Neonates who died were compared to those who survived, with regards to characteristics, surgical diagnoses, and interventions using univariate analysis. Grades 2 and 3 of NEC (diagnosed both clinically and radiologically according to the modified Bell's staging criteria) were included in the NEC variable.(10) Neonates were deemed to have a low 5-minute Apgar score if they had Apgar scores ≤ 5 at 5 minutes. For the purposes of analysis, survivors were classified as those neonates who were transferred out to other hospitals and those who were discharged from NICU. The characteristics of survivors versus non- survivors were compared using univariate analysis. Chi-square tests were used to compare categorical variables, and continuous variables were compared using unpaired t-tests (for those that were normally distributed) and non-parametric tests (for those with skewed distribution). A p-value of <0.05 was considered significant. Only valid cases were analysed for each variable (i.e. cases with missing data were excluded from the analysis.)

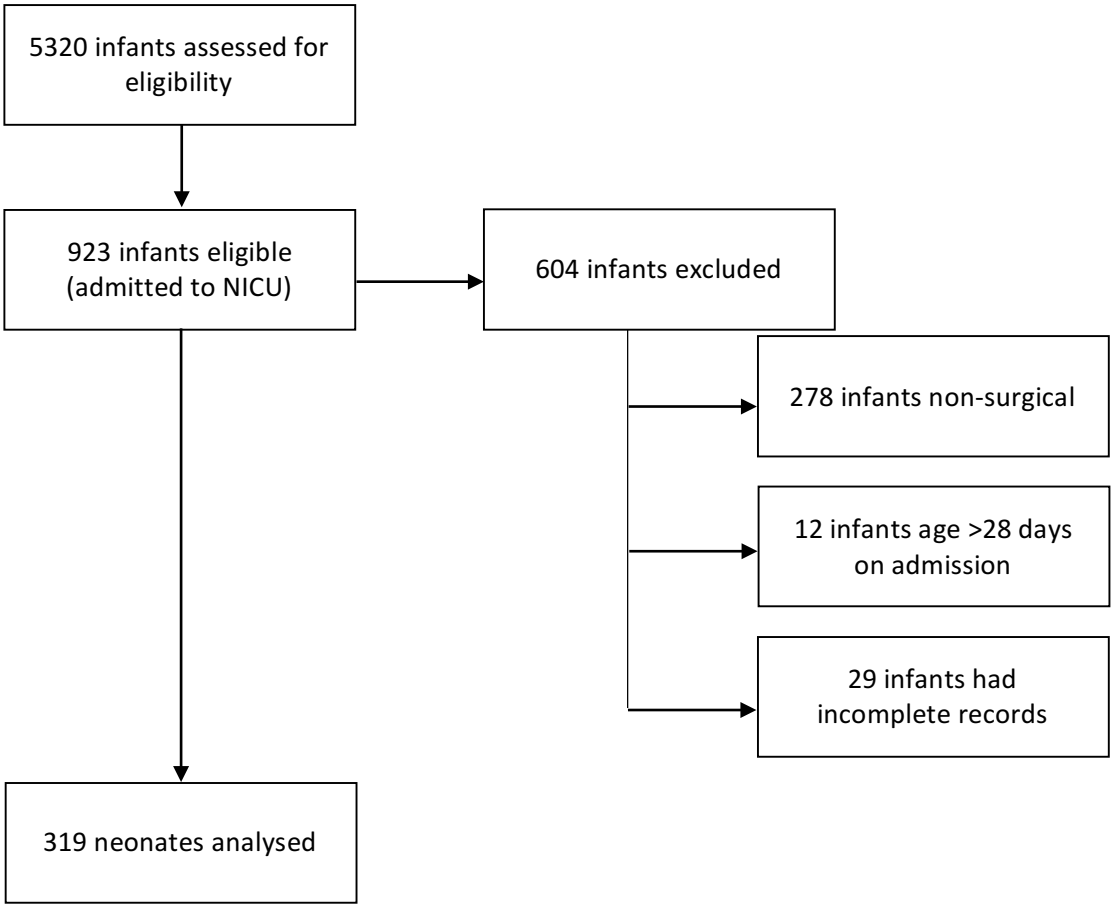
2.3 ETHICS

The Human Research Ethics Committee of the University of the Witwatersrand, Johannesburg granted ethics approval for the study (clearance certificate number M160338).

3.0 RESULTS

During the study period, 5320 infants were admitted to CMJAH, of which 923 infants were admitted to the NICU. 319 neonates fulfilled the inclusion criteria and were included in the analysis (see Figure 1).

Figure 1: Study participants included in an analysis of neonates with surgical diagnoses admitted to the Neonatal Intensive Care Unit at Charlotte Maxeke Johannesburg Academic Hospital, 1 January 2013 – 31 December 2015.



The clinical characteristics of neonates admitted with surgical diagnoses are presented in Table 1. The majority were male (n=178, 55.8%). For those neonates in which the mode of delivery was recorded, normal vaginal delivery was more common (n=115/202, 56.9%). The majority of neonates with surgical conditions were out-born (n=196/299, 65.6%).

Table 1: Characteristics of neonates with surgical diagnoses admitted to the Neonatal Intensive Care Unit at Charlotte Maxeke Johannesburg Academic Hospital, 1 January 2013 – 31 December 2015.

Clinical characteristics	Neonates with surgical diagnoses (n=319)
Gestational age, weeks (mean, SD)	34.2 (4.7)
Birth weight, g (mean, SD)	2028 (801)
Head circumference, cm (mean, SD)	29.3 (3.2)
Age on admission, days (median, [IQR])	1 (1-5)
Duration of ventilation, days (median, [IQR])	5 (1-10)
Length of stay in NICU, days (median, [IQR])	13 (1-29)
Age at outcome, days (median, [IQR])	19 (1-28)

SD = standard deviation, IQR = inter-quartile range.

The majority of mothers were black (287/319, 90.0%) with 176/210 (83.8%) attending antenatal care. Most mothers were multiparous (81/128, 63.3%). The mean maternal age was 27.8 (SD 7.1) years.

Maternal demographics were not significant when comparing survivors with non-survivors, nor was attendance at ANC, and mode of delivery. The infant's sex and presence of a low 5-minute Apgar score was not significant between survivors and non-survivors.

The overall survival rate was 64.3% (205/319). Prematurity and lower birth weight were significant risk factors for death, both with p-values <0.001 (see Table 2).

The significant variables relating to survival are summarized in Tables 2 and 3.

Table 2: Continuous variables relating to outcome (Died vs. Survived) of neonates with surgical diagnoses admitted to the Neonatal Intensive Care Unit at Charlotte Maxeke Johannesburg Academic Hospital, 1 January 2013 – 31 December 2015.

Variable	Died	Survived	p-value
Birth weight, g (mean, SD)	1722.52 (684.85)	2203.32 (810.99)	<0.001
Head circumference, cm (mean, SD)	28.67 (2.63)	30.06 (3.67)	0.029
Gestational age, weeks (mean, SD)	32.44 (4.35)	35.22 (4.58)	<0.001
Age on admission, days (median [IQ])	0 [0-4]	1 [0-6]	0.042
Age at outcome, days (median [IQ])	17 [0-21.3]	20 [0-31.5]	0.037

Table 3: Categorical variables relating to outcome (Died vs. Survived) of neonates with surgical diagnoses admitted to the Neonatal Intensive Care Unit at Charlotte Maxeke Johannesburg Academic Hospital, 1 January 2013 – 31 December 2015.

Variable	Died		Survived		p-value
	n	%	n	%	
Outborn	66/114	57.9	103/205	50.2	0.029
NEC	70/114	61.4	55/205	26.8	<0.001
Late sepsis	70/114	61.4	82/205	40.0	<0.001
Gram-positive organisms	37/70	52.9	59/82	72.0	0.015
Gram-negative organisms	49/70	70.0	39/82	47.6	0.005
Major birth defect	41/114	36.0	125/205	61.0	<0.001

There were 125 (39.2%) neonates with NEC, 55 of whom survived (55/125, 44.0%), making the presence of NEC significantly associated with poor outcome (p=<0.001). The majority of neonates with NEC (57.6%, 72/125) underwent surgery of which 34/72 survived (47.2%). Patients requiring surgery for NEC had a mortality of 52.8% (n = 38/72) despite surgery. There were 200 (62.7%) neonates with other surgical diagnoses – six of whom had concurrent NEC. Forty-six neonates within the study did not undergo surgery (46/319, 14.7%). Most of these were neonates with NEC (34/46, 73.4%).

The distribution of duration of ventilation was not significantly different between survivors and non-survivors (median 5 [IQR 8.5] days versus median 4 [IQR 12] days, p=0.549). Likewise, the distribution of length of stay was not significantly different between survivors and non-survivors (median 13 [IQR 31.5] days versus median 12 [IQR 21.8] days, p=0.155).

The presence of sepsis within the first 72 hours of life was not significantly different between survivors (3/205, 1.5%) and non-survivors (2/114, 1.8%) p=1.000, whereas the presence of sepsis after 72 hours was significant (survivors 82/205 (40.0%) versus 70/114 (61.4%) p=<0.001). Within the late sepsis variable, a number of other factors were analysed: the presence of septicaemia was significant (p=<0.001), but the presence of wound sepsis was not significant (p=1.0). Regarding septicaemia within late sepsis, infection with gram-negative organisms was significant (p=<0.001), yet infection with gram-positive organisms (p=0.525), multi-drug resistant organisms (p=0.016) or fungal organisms (p=0.479) was not significant.

There was a total of 258 patients who underwent surgical procedures, with a mortality rate of 32.9% (85/258). The vast majority of surgical procedures occurred in the abdomen (n = 216/258, 83.7%), with a mortality rate of 76/216, 35.2%. Surgery for NEC was the biggest contributor to mortality with 38/72 patients demising (52.8%).

Surgery to repair intestinal obstruction (oesophageal, duodenal, jejunal, ileal, large bowel atresias) made up 47 cases with a mortality of 4 patients (8.5%). Surgery to repair abdominal wall defects comprised of gastroschisis repair (n = 36) and omphalocoele repair (n = 13). Gastroschisis repair had a mortality rate of 50% (18/36).

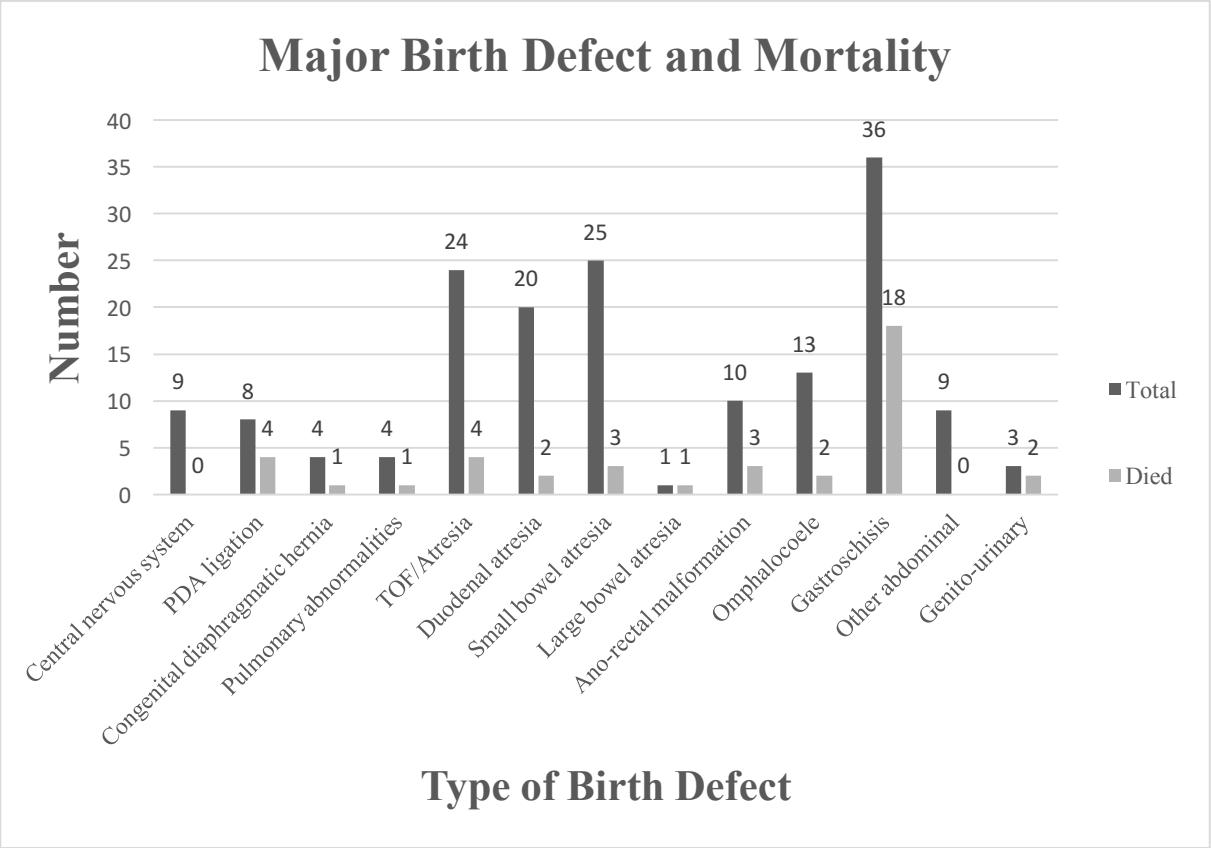
Other abdominal surgery included laparotomy for other causes, ileostomy and colostomy placement or reversal, anorectal malformation repair, congenital diaphragmatic hernia repair, and pyloroplasty.

The predominant surgical procedure conducted in the thorax was TOF repair accounting for 23/33 cases with a mortality of 13.0% (n = 3/23). The remainder included patent ductus arteriosus ligation, aortopexy, congenital cystic adenomatoid malformation repair and bronchoscopy.

Genito-urinary tract surgery included cystostomy and inguinal hernia repair. The musculoskeletal surgeries were all arthrotomies.

Major birth defects were present in 166/319 (52.0%) of neonates (see Table 3). The frequencies of the major birth defects, with respective outcomes are shown in Figure 2.

Figure 2: The frequencies of major birth defects according to system, with outcome, of patients with surgical diagnoses admitted to the Neonatal Intensive Care Unit at Charlotte Maxeke Johannesburg Academic Hospital, 1 January 2013 – 31 December 2015.



There was a total of 166 neonates with birth defects with a mortality rate of 24.7 % (41/166). Gastrointestinal defects were the most common major birth defects making up 138/166 cases (83.1%). Gastroschisis was the most common of these with a 50.0% mortality (n = 18/36). Intestinal atresias together made up a large percentage (46/138, 33.3%) with a mortality of 13% (n = 6/46). Tracheo-oesophageal and oesophageal atresia had a combined mortality of 16.7% (n = 4/24).

Central nervous system abnormalities consisted of myelomeningocoeles and congenital hydrocephalus. Genito-urinary conditions were patients with polycystic kidneys and obstructive uropathy.

4.0 DISCUSSION

There is limited information on neonatal surgical conditions in LMICs. The present study, conducted in a large academic referral centre in Johannesburg, South Africa, showed that one third of neonatal admissions to NICU were surgical. Of this third of admissions to the NICU, a third of neonates demised. This highlights the large burden of surgical diseases and the associated high mortality rate.

In this study, most neonates with surgical conditions were outborn and referred in, which was associated with increased mortality. Firstly, this indicates the need for improved access to antenatal screening, which could enable counselling of mothers to deliver in a hospital where paediatric surgical services are available.(11) Secondly, an efficient referral and neonatal transport system is essential in this setting. Thirdly, earlier and wider access to specialist care would be of benefit, as well as easier access to NICU beds at this and other centres.

The most common neonatal surgical problems were abdominal conditions, accounting for almost 80% of all cases. The overall mortality was 34.7% with mortality being highest in neonates with NEC. Other predictors of poor outcome were the presence of sepsis and major birth defects. The overall mortality rate found in this study correlates with other studies in Africa which report a mortality range of 16 – 45%.(1, 5)

Major birth defects were present in 52.0% of patients. The presence of a major birth defect was associated with survival. An explanation for this is that more than 80% of birth defects were gastro-intestinal abnormalities, which are amenable to surgical correction. The abnormalities were predominantly intestinal atresias (29.5%), followed by gastroschisis (21.7%). Without a paediatric surgical facility, none of these neonates would have survived. Antenatal screening, genetic counselling and planned termination of pregnancy are not commonly available in LMICs, so a large number of neonates with life threatening birth defects requiring paediatric surgery in this setting is to be expected.

Half the neonates with gastroschisis in the current study demised. While this is a high mortality rate, it does compare to a study done at Inkosi Albert Luthuli Central Hospital in Durban, in which a mortality rate of 43% in all neonates with gastroschisis admitted over a six year period (2002-2007) was found.(12) Through the rest of Africa, mortality rates are as high as 84% (n = 80/95) in a study at Harare Children's Hospital in Zimbabwe for a year period (2013) and

100% (n = 20/20) in a study at Mulago Hospital Uganda over the same period.(13) (14) Mortality rates in Africa, are considerably higher than those reported in high-income countries, where survival exceeds 90%.(15)

Prematurity and low-birth-weight are predictably a risk for death. A high proportion of surgical neonates had NEC. Although severe cases of NEC are managed surgically, medical management of the condition is just as important. In addition, measures to prevent NEC should be emphasized, including avoidance of broad spectrum antibiotic use in VLBW neonates and promotion of breast feeding.(16)

Associated bacterial, not fungal, infection was associated with poor outcome in the present study. Previous studies in our unit have shown that neonatal surgical patients are at increased risk of fungal sepsis.(17) Gram-positive sepsis appeared to be associated with survival. This is confounded by the fact that sepsis was classified as culture-proven and thus may reflect many coagulase negative *Staphylococcus* that was not clinically significant.

The importance of neonatal mortality as a cause of childhood deaths increases as the under-5 mortality rate due to a decline in mortality due to communicable diseases, including HIV related causes(18). Paediatric surgery, particularly neonatal surgery, with a proper referral and transport system is an essential component in any health care intervention to reduce neonatal mortality, and hence, childhood mortality.

5.0 STUDY LIMITATIONS

This was a retrospective analysis of an existing database, so some information was missing. In addition, certain data, such as the time of onset of infection in relation to the surgery and catheter related infections were not routinely collected in the database and were therefore not analysed. As stated under Methods, the study does not account for neonates with surgical conditions not admitted to the NICU. If neonates managed in the high care unit and outlying wards were included, the demonstrated burden of disease could be higher. Furthermore, this is not a population based study.

6.0 CONCLUSION

Neonates with major surgical conditions account for one third of NICU admissions in the present study. This study highlights the large burden placed on paediatric surgical services at a large quaternary referral hospital in South Africa. Earlier identification and easier access to NICU with paediatric surgery coverage is essential to improve outcomes. Paediatric surgical services, with a proper referral and neonatal transport system, must be a priority in planned healthcare interventions to reduce neonatal mortality in LMICs.

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APPENDICES

Appendix A: Instructions for authors

Author Guidelines

Author Guidelines

Please view the Author Tutorial for guidance on how to submit on Editorial Manager.

To submit a manuscript, please proceed to the *SAJCH* Editorial Manager website: Editorial Manager

To access and submit an article already in production, please see the guidelines here.

Author Guidelines

Please take the time to familiarise yourself with the policies and processes below. If you still have any questions, please do not hesitate to ask our editorial staff (tel.: +27 (0)21 532 1281, email: submissions@hmpg.co.za).

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- Human Gene Mapping Workshop (HGMW): genetic notations and symbols
- HUGO Gene Nomenclature Committee: approved gene symbols and nomenclature
- OMIM: Online Mendelian Inheritance in Man (MIM) nomenclature and instructions
- Bennet et al. Standardized human pedigree nomenclature: Update and assessment of the recommendations of the National Society of Genetic Counselors. J Genet Counsel 2008;17:424-433: standard human pedigree nomenclature.

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***Scientific letters*/short reports**

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- *Book references:* Jeffcoate N. Principles of Gynaecology. 4th ed. London: Butterworth, 1975:96-101.
- *Chapter/section in a book:* Weinstein L, Swartz MN. Pathogenic Properties of Invading Microorganisms. In: Sodeman WA, Sodeman WA, eds. Pathologic Physiology: Mechanisms of Disease. Philadelphia: WB Saunders, 1974:457-472.
- *Internet references:* World Health Organization. The World Health Report 2002 - Reducing Risks, Promoting Healthy Life. Geneva: WHO, 2002. http://www.who.int/whr/2002 (accessed 16 January 2010).
- Legal references
- Government Gazettes:

  National Department of Health, South Africa. National Policy for Health Act, 1990 (Act No. 116 of 1990). Free primary health care services. Government Gazette No. 17507:1514. 1996.

  In this example, 17507 is the Gazette Number. This is followed by :1514 - this is the notice number in this Gazette.

- Provincial Gazettes:

  Gauteng Province, South Africa; Department of Agriculture, Conservation, Environment and Land Affairs. Publication of the Gauteng health care waste management draft regulations. Gauteng Provincial Gazette No. 373:3003, 2003.

- Acts:

  South Africa. National Health Act No. 61 of 2003.

- Regulations to an Act:

  South Africa. National Health Act of 2003. Regulations: Rendering of clinical forensic medicine services. Government Gazette No. 35099, 2012. (Published under Government Notice R176).

- Bills:

  South Africa. Traditional Health Practitioners Bill, No. B66B-2003, 2006.

- Green/white papers:

  South Africa. Department of Health Green Paper: National Health Insurance in South Africa. 2011.

- Case law:

Rex v Jopp and Another 1949 (4) SA 11 (N)

Rex v Jopp and Another: Name of the parties concerned

1949: Date of decision (or when the case was heard)

(4): Volume number

SA: SA Law Reports

11: Page or section number

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Appendix B: Research Protocol

Research Protocol:

Title: An analysis of neonates with surgical diagnoses admitted to the Neonatal Intensive Care Unit at Charlotte Maxeke Johannesburg Academic Hospital.

Investigator: Robin Saggers
MBBCh, DCH

Student no: 0404428P

Degree: MMed (Paediatrics)

Supervisors: Prof Daynia Ballot
MBChB, FC Paed, MMed (Paeds)

Dr Andrew Grieve
MBChB, FC Paed Surg, MMed (Surgery)

INDEX

1. Introduction – Background Information

The burden of neonatal surgical diseases in Africa is not well documented.(1) This lack of data results in inadequate planning and delivery of neonatal surgical services in Africa. This being said, neonatal surgical conditions are thought to account for a large burden of disease, with a considerable proportion of neonates admitted to the neonatal intensive care unit requiring surgical intervention.(2) A survey among paediatric surgeons practicing in Africa indicates that 10-20% of their paediatric surgical workload results from neonatal surgery.(1)

The World Health Organization estimates that approximately 10% of all neonatal deaths in sub-Saharan Africa and South Asia are due to congenital malformations. Many of these congenital malformations are only amenable to operative intervention.(1) In Africa, congenital malformations make up more than a quarter of paediatric surgical admissions, and accounted for nearly half of emergency procedures.(3, 4)

Common surgical problems encountered in Africa are (but not limited to): necrotizing enterocolitis (NEC), congenital diaphragmatic hernia (CDH), anorectal malformations (ARM), Hirshprung's disease, omphalocoele, gastroschisis, oesophageal atresia and trachea-oesophageal fistula, intestinal atresia, and intestinal perforation.(1)

Resources for neonatal surgery vary hugely between the developed countries and Africa.(3) There is a variability between developed and developing countries with regards to conditions admitted in hospitals. There is also variability of neonatal surgical workload within Africa.(1) This could be attributed to a number of factors, such as: availability of antenatal diagnosis, primary health care and transport facilities, distance, poverty, cultural methods of treatment, as well as time of presentation, death before arrival, access to paediatric surgery, access to intensive care, access to neonatal anaesthesia, and genetic predisposition within the various populations.

In developed countries, much progress has been made in improving neonatal surgical mortality rates, decreasing from more than 50% in the 1950s to less than 5% in recent years.(1, 5, 6) However, in Africa there remains multiple challenges leading to high morbidity and mortality, with mortality figures being reported to be between 16% and 45%.(1, 5) There are multiple reasons for this: resource limitations (manpower, equipment, and facilities) late presentation

and poor transportation, difficulty with anaesthesia and peri-operative care, limited data and research, and poor follow-up.(1, 4)

A major post-operative complication is the development of sepsis, which results in serious morbidities and mortalities. Surgical interventions have been shown to have a strong association with the development of infection, with the risk increasing as the number of interventions increase.(2, 7, 8) The sepsis may be systemic in the form of septicaemia, related to supportive interventions (e.g. ventilator associated pneumonia, urinary tract infections, central line associated sepsis), or localized to the surgical site.

Infants who require surgical intervention require mechanical ventilation for longer periods and have longer hospital stays. Regarding surgical site infections, the site of surgery is important: laparotomies (generally considered to be a contaminated procedure) had a higher rate of surgical site infections than thoracic surgeries (generally considered to be a clean procedure). Notably, VLBW infants as well as infants who underwent gastroschisis closure are at the greatest risk of developing surgical site infections.(2)

With the progress made in developed countries with regards to neonatal surgery mortality rates, cost effectiveness becomes an important consideration.(6) Neonatal surgical conditions are thought to account for a large burden of disease, but they are also costly and highly sophisticated interventions requiring specialized training and specialized perinatal care.(5) This becomes important when determining equitable distribution of health and health care, particularly in a developing country such as South Africa. The conditions of ano-rectal malformations and congenital diaphragmatic hernia were found to be the most cost effective.(6)

Justification for the study

The number, characteristics, and outcome of patients who are admitted to a neonatal intensive care unit in developing countries are not well documented. Specifically, the number, characteristics and outcomes of those patients admitted with various surgical diagnoses, and those that have surgery related complications and/or death or factors associated with poor outcomes in our hospital are not known. It is important to determine characteristics of patients admitted for surgical conditions, differentiate the different conditions and in so doing determine the characteristics of patient who die or develop complications. Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) where this study will be conducted has approximately 14 000 births a year, and is the referral centre for a number of other regional hospitals. CMJAH caters for high risk patients and is a referral hospital for such high-risk patients. The large number of patients requiring admission to the neonatal intensive care unit places a burden on limited resources. In this environment, there is a higher risk of complications developing. Such complications prolong hospital stays and have serious effects on morbidities and mortalities.

2. Aim

To review neonates with surgical diagnoses admitted to the Neonatal ICU at CMJAH.

3. Objectives

a. To describe the demographics, disease profile and management of neonates with surgical diagnoses at CMJAH NICU.
b. To determine the survival rate and risks for poor survival in neonates with surgical diagnoses at CMJAH.

4. Definitions

i. Neonate – a child presenting within the first 28 days or life. A preterm infant will be classified as a neonate according to their chronological age corrected for gestational age (e.g. a 5-week old preterm infant born at 28 weeks will be corrected to 31 weeks and hence is a neonate).
ii. Low birth weight – birth weight < 2500g.
iii. Very low birth weight – birth weight < 1500g.
iv. Extremely low birth weight – birth weight <1000g.
v. Confirmed sepsis – positive blood culture of organism deemed to be significant.
vi. Surgical diagnosis – any diagnosis requiring a surgical procedure for correction.

5. Methods

a. Study Design

It will be a retrospective cross sectional descriptive study, reviewing an existing database of all neonates admitted to CMJAH NICU who underwent a surgical procedure from 1st January 2013 to 31st December 2015.

b. Sample Population

The sample population includes all neonates admitted to CMJAH NICU (either born in the hospital, or referred to the NICU).

i. Inclusion Criteria

Neonates with surgical diagnoses (including Necrotizing Enterocolitis) admitted to CMJAH NICU within the study period.

ii. Exclusion Criteria

Neonates with missing information.

Neonates undergoing minor surgical procedures in the ward (e.g. vascular access, incision and drainage of superficial skin abscess) will not be included.

c. Procedures/ Data Collection

The neonatal database at CMJAH will be reviewed to identify all neonates who had a surgical procedure and were admitted to NICU from 1 January 2013 to 31 December 2015. Discharge information is captured for all neonates admitted to the CMJAH NICU on a computerized database. Data is managed using Research Electronic Data Capture (REDCap) which is hosted by the University of the Witwatersrand.(9) REDCap is a secure, web-based programme that has been designed to aid data capture for the purpose of clinical audit and quality improvement. The information is verified at several different stages of collection. The data will be collected and entered onto a prepared data sheet (appendix A). The data sheet will capture demographic information (Maternal age, parity, infants' gestational age and birth weight, gender), place of birth, age on admission to NICU, clinical diagnoses, number of surgeries, duration of ventilation, duration of NICU stay and surgical procedure, congenital abnormality, died or survived. Details regarding the surgical diagnosis and surgical procedures will be obtained from a corresponding paediatric surgical database.

d. Data Analysis

Data will be described using standard statistical methods. Continuous variables will be described using measures of central tendency – mean and standard deviation for those variables with a normal distribution and median and range for those variables with a skewed distribution. Categorical variables will be described using frequencies and percentages. Variables will be compared between survivors and non-survivors. Continuous variables will be compared using Student's t test or Mann Whitney U analysis, as appropriate. Categorical variables will be compared using Chi Square analysis. Binary logistic regression, considering survival as the primary outcome measure, will be done to establish predictors of poor outcome.

e. Sample Size

The expected number of neonates meeting the inclusion criteria is 350 - 400 neonates.

6. Significance

The findings of this study will be shared with both the paediatric medical and surgical teams to highlight any improvements that can be made to medical and surgical care to the neonates admitted to CMJAH. This will be done by presenting the information at local research days and conferences. Identifying the incidence of different surgical conditions, characteristics related to the development of complications, and outcome of neonates with different surgical conditions will assist in highlighting the need to improve medical and surgical care of neonates in our hospital and South Africa at large.

7. Limitations

The study is a retrospective audit of an existing database, so some data is not captured and not all records are complete. The study does not include neonates with surgical diagnoses who were not admitted to NICU, or who were transferred out to other hospitals or other surgical disciplines.

8. Ethical Considerations

The proposal for this study will be submitted to the University of the Witwatersrand Protocol Review Committee and Human Research Ethics Committee (HREC) of the University of the Witwatersrand for approval. As this is a retrospective audit, no consent will need to be obtained from individual patients. Data sheets will only contain a study number. The patient's name, hospital number and age on admission will be stored in a separate database at a different, secure location so that only the investigator and the supervisors will have access to this information. The study will not be started until clearance from the ethics and hospital committee has been received.

9. Time Lines

	Dec 2015	Jan 2016	Feb 2016	Mar 2016	Apr 2016	May 2016	Jun 2016	Jul 2016	Aug 2016	Sep 2016	Oct 2016	Nov 2016	Dec 2016
Literature review													
Protocol preparation													
Protocol assessment													
Ethics approval													
Post-grad approval													
Data collection													
Data analysis													
Write-up report													
Write-up paper													

10. Cost/Funding

The cost involved in the study is for stationery, printing and binding. The budget is R 5 000 – to be borne by the investigator.

11. References

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12. Appendix A: Data Collection Sheet

Study No:

Maternal details:

Age---- Parity---- Gravity----

ANC booking: Y/N

If Yes ----- no. of visits

Antenatal scan: Y/N

If Yes ----- Normal/Abnormal

If abnormal

Antenatal diagnosis:

Delivery

Place of birth:

Mode of delivery

NVD---- C/Section----

If C/Section----indication?

Infant details

Weight---- Length---- OFC----

Gestation: (

Apgar score at 5 minutes:

Surgical condition

Surgical condition:

Congenital abnormality:

Chromosomal abnormality:

Surgical procedure:

Number of procedures:

Hospital stay

Age on admission:

Days in NICU:

Transferred to another hospital: Y/N

Discharged to surgical ward: Y/N

Discharged to neonatal ward: Y/N

Readmitted to NICU: Y/N

Age at outcome:

Died: Y/N

Laboratory results

Blood culture: +ve---- -ve----

Organism

Appendix C: Plagiarism Declaration

PLAGIARISM DECLARATION TO BE SIGNED BY ALL HIGHER DEGREE STUDENTS

SENATE PLAGIARISM POLICY: APPENDIX ONE I, **Robin Saggers** (Student number: **0404428P**), am a student registered for the degree of **MMed (Paeds)** in the academic year **2018**.

I hereby declare the following:

- I am aware that plagiarism (the use of someone else's work without their permission and/or without acknowledging the original source) is wrong.

- I confirm that the work submitted for assessment for the above degree is my own unaided work except where I have explicitly indicated otherwise.

- I have followed the required conventions in referencing the thoughts and ideas of others.

- I understand that the University of the Witwatersrand may take disciplinary action against me if there is a belief that this is not my own unaided work or that I have failed to acknowledge the source of the ideas or words in my writing.

- I have included as an appendix a report from "Turnitin" (or other approved plagiarism detection)

software indicating the level of plagiarism in my research document.

Signature: _____ Date: _____

Appendix D: Ethics Clearance Certificate

R14/49 Dr Robin Terence Saggers

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M160338

NAME: (Principal Investigator)	Dr Robin Terence Saggers
DEPARTMENT:	Paediatrics and Child Health Charlotte Maxeke Johannesburg Academic Hospital
PROJECT TITLE:	An Analysis of Neonates with Surgical Conditions Admitted to the Neonatal Intensive Care Unit at Charlotte Maxeke Johannesburg Academic Hospital, 1 January 2013 - 31 December 2015
DATE CONSIDERED:	01/04/2016
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Prof Daynia Ballot
APPROVED BY:	Professor P. Cleaton-Jones, Chairperson, HREC (Medical)
DATE OF APPROVAL:	08/06/2016

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary in Room 10004,10th floor, Senate House/2nd floor, Phillip Tobias Building, Parktown, University of the Witwatersrand. I/We fully understand the the conditions under which I am/we are authorised to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated,from the research protocol as approved, I/we undertake to resubmit to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. in this case, the study was initially review in March and will therefore be due in the month of March each year.

Principal Investigator Signature _____ Date _____

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix E: Turnitin Report

00820433:paper_for_TURNITIN.docx

by Daynia Ballot

Submission date: 15-Feb-2018 11:05AM (UTC+0200)
Submission ID: 916377244
File name: nts_aae4a10c-9f97-49db-b671-0cd625e8737a_paper_for_TURNITIN.docx (132.55K)
Word count: 4760
Character count: 28660

AN ANALYSIS OF NEONATES WITH SURGICAL DIAGNOSES ADMITTED TO THE NEONATAL INTENSIVE CARE UNIT AT CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL

Robin Terence Saggers

0404428P

A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfillment of the requirements for the degree of Master of Medicine in the branch of Paediatrics.

Johannesburg 2018

DECLARATION

I, Robin Terence Saggers, declare that this research report is my own work. It is being submitted for the degree of Master of Medicine in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

_____.

___ day of _____ 20_____.

PRESENTATIONS ARISING FROM THIS RESEARCH REPORT

Oral Presentation: Wits Paediatrics Research Day,
26 November 2016,
University of the Witwatersrand, Johannesburg.

Oral Presentation: 3rd Biennial USANA Conference
(United South African Neonatal Association),
15 September 2017,
Southern Sun OR Tambo Hotel, Johannesburg

Oral Presentation: 8TH Cross-Faculty Postgraduate Symposium
(Showcasing Postgraduate Research at Wits),
25 October 2017,
University of the Witwatersrand, Johannesburg.

ABSTRACT

Introduction: The burden of neonatal surgical conditions is not well documented in lower to middle income countries (LMICs), yet neonatal surgical conditions are thought to be relatively common with a considerable proportion of neonates admitted to the neonatal intensive care unit (NICU) requiring surgical intervention. The NICU at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) is combined with a paediatric intensive care unit, to a total of 15 beds, and serves as a referral hospital.

Objectives: To review neonates with surgical conditions admitted to the Neonatal Intensive Care Unit (NICU) in our hospital setting.

Methods: This was a retrospective, descriptive study of neonates admitted to the NICU at CMJAH with surgical conditions between 1 January 2013 and 31 December 2015. The characteristics and the survival of these neonates were described using univariate analysis.

Results: There were 923 neonates admitted to the NICU, of which 319 (34.6%) neonates had primarily surgical conditions. Of the 319 neonates, 205 survived (64.3%). There were 125/319 (39.2%) neonates with necrotizing enterocolitis (NEC), 55 of whom survived (55/125, 44.0%), making the presences of NEC a significant predictor of poor outcome (p=<0.001). Other significant predictors of poor outcome were: the patient being outborn (p=0.029); the presence of late sepsis (p=<0.001) – with *Gram-negative* (p=0.005) organisms; the presence of a major birth defect (p=<0.001); as well as lesser gestational age (p=0.001) and lower birth weight (p=<0.001).

Conclusions: Neonates with major surgical conditions account for one third of NICU admissions in the present study. Paediatric surgical services, with a proper referral and neonatal transport system, must be a priority in planned healthcare interventions to reduce neonatal mortality in LMICs.
(Word count 268)

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(Word count 268)

ACKNOWLEDGEMENTS

A special thanks to my supervisors Professor Daynia Ballot and Dr Andrew Grieve who provided guidance and encouragement throughout.

Thank you to my family for their tireless support and understanding.

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ABBREVIATIONS

ANC:	Antenatal care
ARM:	Ano-rectal malformations
CDH:	Congenital diaphragmatic hernia
CMJAH:	Charlotte Maxeke Johannesburg Academic Hospital
GUT:	Genito-urinary tract
HIV:	Human immunodeficiency virus
IQR:	Inter-quartile range
MSK:	Musculoskeletal
NEC:	Necrotizing enterocolitis
NICU:	Neonatal Intensive Care Unit
PDA:	Patent ductus arteriosus
REDCap:	Research Electronic Data Capture
SD:	Standard deviation
TOF:	Trecheo-oesophageal fistula
VLBW:	Very low birth weight
VON:	Vermont Oxford Network

SUBMISSABLE PAPER

AN ANALYSIS OF NEONATES WITH SURGICAL DIAGNOSES ADMITTED TO THE NEONATAL INTENSIVE CARE UNIT AT CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL

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Key Words: *Neonatal surgery;*
Mortality;
Major birth defect;
Low and middle-income countries;
South Africa.

ABSTRACT

Introduction: The burden of neonatal surgical conditions is not well documented in lower to middle income countries (LMICs), yet neonatal surgical conditions are thought to be relatively common with a considerable proportion of neonates admitted to the neonatal intensive care unit (NICU) requiring surgical intervention. The NICU at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) is combined with a paediatric intensive care unit, to a total of 15 beds, and serves as a referral hospital.

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(Word count 268)

1.0 INTRODUCTION

The burden of neonatal surgical diseases in Africa is not well documented, yet neonatal surgical conditions are thought to be relatively common, with a considerable proportion of neonates admitted to the neonatal intensive care unit requiring surgical intervention.(1, 2) A survey among paediatric surgeons practicing in Africa indicated that 10-20% of their paediatric surgical workload resulted from neonatal surgery.(1) There is no specific data in South Africa which results in inadequate planning and delivery of neonatal surgical services.

The World Health Organization estimates that approximately 10% of all neonatal deaths in sub-Saharan Africa and South Asia are due to congenital malformations, and many of these congenital malformations are only amenable to operative intervention.(1) In Africa, congenital malformations made up more than a quarter of paediatric surgical admissions, and accounted for nearly half of emergency procedures.(3, 4)

Common surgical problems encountered in Africa are (but not limited to): necrotizing enterocolitis (NEC), congenital diaphragmatic hernia (CDH), anorectal malformations (ARM), Hirshprung's disease, omphalocoele, gastroschisis, oesophageal atresia and trachea-oesophageal fistula, intestinal atresia, and intestinal perforation.(1)

Resources for neonatal surgery vary widely between high and low to middle income countries (LMICs).(3) There is variability with regards to conditions admitted in hospital, as well as the neonatal surgical workload, within Africa.(1) This could be attributed to a number of factors, such as: availability of antenatal diagnosis, primary health care and transport facilities, distance, poverty, cultural methods of treatment, as well as time of presentation, death before arrival, access to paediatric surgery, access to intensive care, access to neonatal anaesthesia, and genetic predisposition within the various populations.(1, 4)

In high income countries, much progress has been made in the management of neonatal surgical conditions, resulting in a decrease in the neonatal surgical mortality rates, from more than 50% in the 1950s to less than 5% in recent years.(1, 5, 6) However, in Africa there remain multiple challenges leading to high morbidity and mortality, with mortality figures being reported to be between 16% and 45%.(1, 4, 5)

A major post-operative complication is the development of sepsis, which results in serious morbidities and mortalities. Surgical interventions have been shown to have a strong association with the development of infection, with the risk rising as the number of interventions increases.(2, 7, 8) Infections may be septicaemia, related to supportive interventions (e.g. ventilator associated pneumonia, urinary tract infections, central line associated sepsis), or localized to the surgical site.

Infants who require surgical intervention require mechanical ventilation for longer periods and have increased duration of hospitalisation. The site of surgery determines the site of infection: laparotomies (generally considered to be a contaminated procedure) have a higher rate of surgical site infections than thoracic surgeries (generally considered to be a clean procedure).(2) Notably, very low birth weight (VLBW) infants as well as infants who underwent gastroschisis closure are at the greatest risk of developing surgical site infections.(2) Many hospitals in sub-Saharan Africa do not have paediatric surgical facilities or neonatal intensive care units and neonates with surgical conditions are thus referred to central hospitals. The impact of neonatal surgical patients on the limited neonatal intensive care facilities available is not known.

This study aims to review neonates with surgical conditions admitted to the neonatal intensive care unit (NICU) of Charlotte Maxeke Johannesburg Academic Hospital (CMJAH), a large quaternary referral hospital in South Africa.

2.0 METHODS

This was a retrospective, descriptive study of neonates (<28 days of life) admitted to the NICU at CMJAH with surgical diagnoses between 1 January 2013 and 31 December 2015. Neonates with incomplete records were excluded. Outcome was defined as death or survival to discharge.

The NICU at CMJAH was combined with a paediatric intensive care unit, to a total of 15 beds, and a neonatal high care unit with 35 beds. Neonates with surgical conditions admitted to the CMJAH NICU are managed by neonatologists, in conjunction with paediatric surgeons. Owing to limited resources, the NICU functions essentially as a ventilator unit – neonates who require intensive observation are not routinely admitted.

Neonates with surgical conditions who were admitted to high care wards were not included in this analysis. Thus, neonates with minor conditions, for example hernia repair or circumcision were not included. Similarly, neonates who underwent surgical procedures in the high care wards, including insertion of central catheters, were not included. A neonate could have more than one surgical condition or congenital abnormality (e.g. tracheo-esophageal fistula and cardiac defect) and would be analysed in each category.

During the period studied patent ductus arteriosus (PDA) ligations were performed by paediatric surgeons, and so were included in the analysis. All other forms of congenital heart defects were repaired by cardiothoracic surgeons in a separate unit and were thus excluded from the analysis. Equally, myelomeningocoeles were repaired by neurosurgeons in a separate unit and were excluded from the analysis of surgical procedures, but were included in the analysis of the frequencies of major birth defects. Head and neck surgery was performed by ENT surgeons in a separate unit and were excluded from the analysis.

Major birth defects included lethal or life-threatening anomalies as defined in the Vermont Oxford Network database (www.vtoxford.org).

2.1 DATABASE

The neonatal records at CMJAH are stored on the REDCap (Research Electronic Data Capture) database, hosted by the University of the Witwatersrand.(9) REDCap is a secure web-based programme that aids data capture for the purposes of clinical audit and quality improvement. Upon discharge of patients, data were captured on to the REDCap database. The information was verified at several stages of collection. The following data were collected from the database: (i) maternal data – demographics, antenatal care (ANC), place of delivery, mode of delivery; and (ii) infant data – gestational age, birth weight, sex, 5-minute Apgar score, necrotizing enterocolitis (NEC), other surgical conditions, duration of ventilation, late sepsis (occurring after 72 hours) and outcome at discharge (death or survival.) The information regarding surgery was correlated with a corresponding surgical database.

2.2 STATISTICAL ANALYSIS

An MS Excel (Microsoft, USA) spreadsheet was used to enter the data which was then imported into statistical software package SPSS version 23 (IBM, USA). Frequencies and percentages were used to describe categorical variables. Means and standard deviations (SDs) were used to describe normally distributed continuous variables, and skewed continuous variables were described using medians and interquartile ranges (IQR). Infants who died were compared to those who survived, with regards to characteristics, surgical diagnoses, and interventions using univariate analysis. Grades 2 and 3 of NEC (according to the modified Bell's staging criteria) were included in the NEC variable.(10) Infants were included in the birth asphyxia variable if they had Apgar scores ≤ 5 at 5 minutes. For the purposes of analysis, survivors were classified as those infants who were transferred out to other hospitals and those who were discharged from NICU. The characteristics of survivors versus non- survivors were compared using univariate analysis. X^2 tests were used to compare categorical variables, and continuous variables were compared using unpaired t-tests (for those that were normally distributed) and non-parametric tests (for those with skewed distribution). A p-value of <0.05 was considered significant. Only valid cases were analysed for each variable.

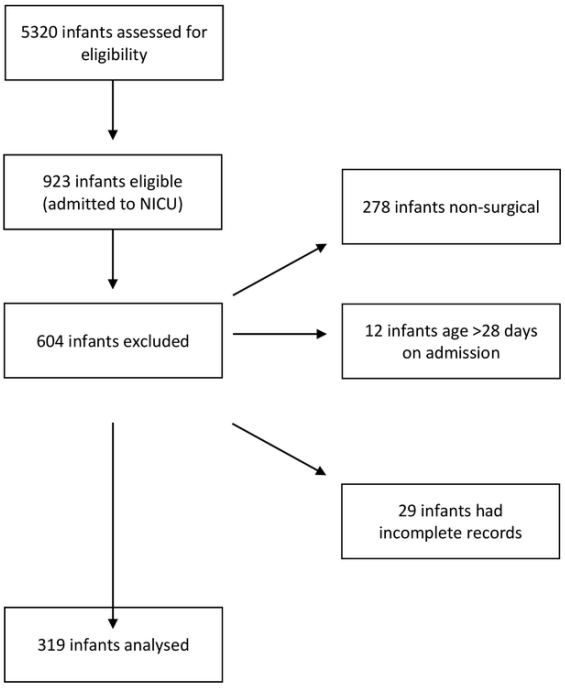
2.3 ETHICS

The Human Research Ethics Committee of the University of the Witwatersrand, Johannesburg granted ethics approval for the study (clearance certificate number M160338).

3.0 RESULTS

During the study period, 5320 infants were admitted to CMJAH, of which 923 infants were admitted to the NICU. 319 infants fulfilled the inclusion criteria and were included in the analysis (see Figure 1).

Figure 1: Study participants included in an analysis of infants with surgical diagnoses admitted to the Neonatal Intensive Care Unit at Charlotte Maxeke Johannesburg Academic Hospital, 1 January 2013 – 31 December 2015.



The clinical characteristics of infants admitted with surgical diagnoses are presented in Table 1. The majority were male (n=178, 55.8%). For those infants in which the mode of delivery was recorded, normal vaginal delivery was more common (n=115/202, 56.9%). The majority of infants with surgical conditions were out-born (n=196/299, 65.6%).

Table 1: Characteristics of infants with surgical diagnoses admitted to the Neonatal Intensive Care Unit at Charlotte Maxeke Johannesburg Academic Hospital, 1 January 2013 – 31 December 2015.

Clinical characteristics	Infants with surgical diagnoses (n=319)
Gestational age, weeks (mean, SD)	34.2 (4.7)
Birth weight, g (mean, SD)	2028 (801)
Head circumference, cm (mean, SD)	29.3 (3.2)
Age on admission, days (median, [IQ])	1 (1-5)
Duration of ventilation, days (median, [IQ])	5 (1-10)
Length of stay in NICU, days (median, [IQ])	13 (1-29)
Age at outcome, days (median, [IQ])	19 (1-28)

The majority of mothers were black (287/319, 90.0%) with 176/210 (83.8%) attending antenatal care. Most mothers were multiparous (81/128, 63.3%). The mean maternal age was 27.8 (SD 7.1) years.

Maternal demographics were not significant when comparing survivors with non-survivors, nor was attendance at ANC, and mode of delivery. The infant's sex and presence of asphyxia was not significant between survivors and non-survivors.

The overall survival rate was 64.3% (205/319). Prematurity and lower birth weight were significant risk factors for death, both with p-values <0.001 (see Table 2).

The significant variables relating to survival are summarized in Tables 2 and 3.

Table 2: Continuous variables relating to outcome (Died vs. Survived) of infants with surgical diagnoses admitted to the Neonatal Intensive Care Unit at Charlotte Maxeke Johannesburg Academic Hospital, 1 January 2013 – 31 December 2015.

Variable	Died	Survived	p-value
Birth weight, g (mean, SD)	1722.52 (684.85)	2203.32 (810.99)	<0.001
Head circumference, cm (mean, SD)	28.67 (2.63)	30.06 (3.67)	0.029
Gestational age, weeks (mean, SD)	32.44 (4.35)	35.22 (4.58)	<0.001
Age on admission, days (median [IQ])	0 [0-4]	1 [0-6]	0.042
Age at outcome, days (median [IQ])	17 [0-21.3]	20 [0-31.5]	0.037

Table 3: Categorical variables relating to outcome (Died vs. Survived) of infants with surgical diagnoses admitted to the Neonatal Intensive Care Unit at Charlotte Maxeke Johannesburg Academic Hospital, 1 January 2013 – 31 December 2015.

Variable	Died	Died	Survived	Survived	p-value
	n	%	n	%	
Outborn	66/114	57.9	103/205	50.2	0.029
NEC	70/114	61.4	55/205	26.8	<0.001
Late sepsis	70/114	61.4	82/205	40.0	<0.001
Gram-positive organisms	37/70	52.9	59/82	72.0	0.015
Gram-negative organisms	49/70	70.0	39/82	47.6	0.005
Major birth defect	41/114	36.0	129/205	62.9	<0.001

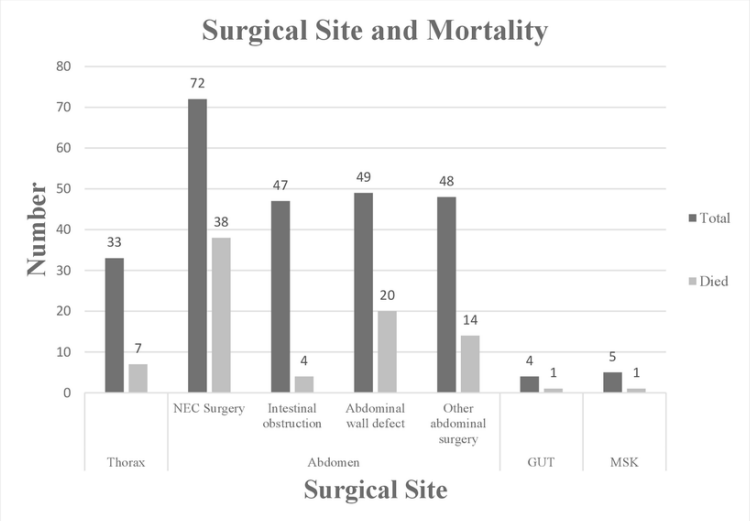
There were 125 (39.2%) infants with NEC, 55 of whom survived (55/125, 44.0%), making the presence of NEC a significant predictor of poor outcome (p=<0.001). The majority of infants with NEC (57.6%, 72/125) underwent surgery of which 34/72 survived (47.2%). Patients requiring surgery for NEC had a mortality of 52.8% (n = 38/72) despite surgery. There were 200 (62.7%) infants with other surgical diagnoses – six of whom had concurrent NEC.

Forty-six infants within the study did not undergo surgery (46/319, 14.7%). Most of these were infants with NEC (34/46, 73.4%). The surgical procedures and outcomes are shown in Figure 2.
The distribution of duration of ventilation was not significantly different between survivors and non-survivors (median 5 [IQ 8.5] days versus median 4 [IQ 12] days, p=0.549). Likewise, the distribution of length of stay was not significantly different between survivors and non-survivors (median 13 [IQ 31.5] days versus median 12 [IQ 21.8] days, p=0.155).

The presence of sepsis within the first 72 hours of life was not significantly different between survivors (3/205, 1.5%) and non-survivors (2/114, 1.8%) p=1.000, whereas the presence of sepsis after 72 hours was significant (survivors 82/205 (40.0%) versus 70/114 (61.4%) p=<0.001). Within the late sepsis variable, a number of other factors were analyzed: site of sepsis was not deemed to be significant, infection with gram-negative organisms was significant, yet infection with multi-drug resistant organisms or fungal organisms was not significant.

There was a total of 258 patients who underwent surgical procedures, with a mortality rate of 32.9% (85/258). The vast majority of surgical procedures occurred in the abdomen (n = 216/258, 83.7%), with a mortality rate of 76/216, 35.2%. Surgery for NEC was the biggest contributor to mortality with 38/72 patients demising (52.8%) (see Figure 2).

Figure 2: Frequencies of surgical procedures according to anatomical site, with outcome, of patients with surgical diagnoses admitted to the Neonatal Intensive Care Unit at Charlotte Maxeke Johannesburg Academic Hospital, 1 January 2013 – 31 December 2015.



Surgery to repair intestinal obstruction (oesophageal, duodenal, jejunal, ileal, large bowel atresias) made up 47 cases with a mortality of 4 patients (8.5%). Surgery to repair abdominal wall defects comprised of gastroschisis repair (n = 36) and omphalocoele repair (n = 13). Gastroschisis repair had a mortality rate of 50% (18/36).

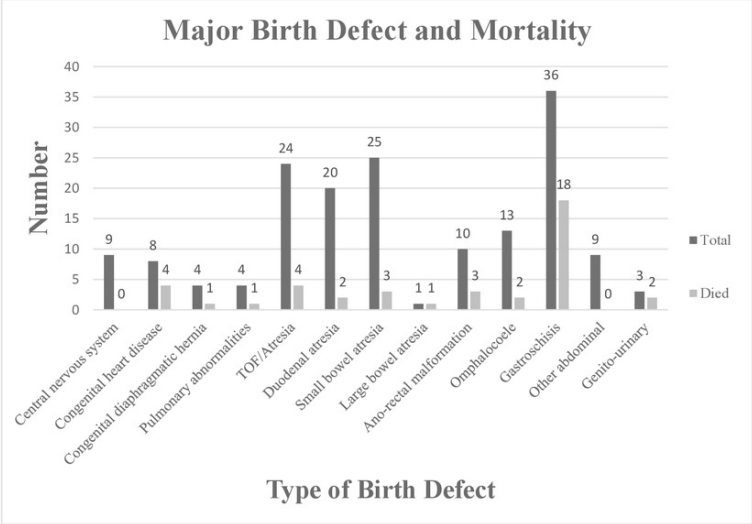
Other abdominal surgery included laparotomy for other causes, ileostomy and colostomy placement or reversal, anorectal malformation repair, congenital diaphragmatic hernia repair, and pyloroplasty.

The predominant surgical procedure conducted in the thorax was trachea-oesophageal fistula repair accounting for 23/33 cases with a mortality of 13.0% (n = 3/23). The remainder included patent ductus arteriosus ligation, aortopexy, congenital cystic adenomatoid malformation repair and bronchoscopy.

Genito-urinary tract surgery included cystostomy and inguinal hernia repair. The musculoskeletal surgeries were all arthrotomies.

Major birth defects were present in 166/319 (52.0%) of infants. The presence of a major birth defect significantly worsened survival (see Table 3). The frequencies of the major birth defects, with respective outcomes are shown in Figure 3.

Figure 3: The frequencies of major birth defects according to system, with outcome, of patients with surgical diagnoses admitted to the Neonatal Intensive Care Unit at Charlotte Maxeke Johannesburg Academic Hospital, 1 January 2013 – 31 December 2015.



There was a total of 166 neonates with birth defects with a mortality rate of 24.7 % (41/166). Gastrointestinal defects were the most common major birth defects making up 138/166 cases (83.1%). Gastroschisis was the most common of these with a 50.0% mortality (n = 18/36). Intestinal atresias together made up a large percentage (46/138, 33.3%) with a mortality of 13% (n = 6/46). Tracheo-oesophageal and oesophageal atresia had a combined mortality of 16.7% (n = 4/24).

Central nervous system abnormalities consisted of myelomeningocoeles and congenital hydrocephalus. Genito-urinary conditions were patients with polycystic kidneys and obstructive uropathy.

4.0 DISCUSSION

There is limited information on neonatal surgical conditions in LMICs. The present study, conducted in a large academic referral centre in Johannesburg, South Africa, showed that one third of neonatal admissions to NICU were surgical. Of this third of admissions to the NICU, a third of neonates demised. This highlights the large burden of surgical diseases and the associated high mortality rate.

Most neonates with surgical conditions were born at other health facilities and were referred in; place of birth was a predictor of mortality. Firstly, this indicates the need for improved access to antenatal screening, which could enable counselling of mothers to deliver in a hospital where paediatric surgical services are available.(11) Secondly, an efficient referral and neonatal transport system is essential in this setting. Thirdly, earlier and wider access to specialist care would be of benefit. Couple this with easier access to NICU beds at this and other centres and the burden of disease at the referral centre may be eased.

The most common neonatal surgical problems were abdominal conditions, accounting for almost 80% of all cases. The overall mortality was 34.7%; most deaths occurred in neonates with NEC. Other predictors of poor outcome were the presence of sepsis and major birth defects. The overall mortality rate found in this study correlates with other studies in Africa which report a mortality range of 16 – 45%.(1, 5)

Major birth defects were present in 52.0% of patients. The presence of a major birth defect was associated with survival. An explanation for this is that more than 80% of birth defects were gastro-intestinal abnormalities, which are amenable to surgical correction. The abnormalities were predominantly intestinal atresias (29.5%), followed by gastroschisis (21.7%). Without a paediatric surgical facility, none of these neonates would have survived. Antenatal screening, genetic counselling and planned termination of pregnancy are not commonly available in LMIC, so a large number of neonates with life threatening birth defects requiring paediatric surgery in this setting is to be expected.

Half the neonates with gastroschisis in the current study demised. While this is a high mortality rate, it does compare to a study done at Inkosi Albert Luthuli Central Hospital in Durban, in which a mortality rate of 43% in all infants with gastroschisis admitted over a six year period (2002-2007) was found.(12) Through the rest of Africa, mortality rates are as high as 84% (n = 80/95) in a study at Harare Children's Hospital in Zimbabwe for a year period (2013) and 100% (n = 20/20) in a study at Mulago Hospital Uganda over the same period.(13) (14) Mortality rates in Africa, are considerably higher than those reported in high-income countries, where survival exceeds 90%.(15)

Prematurity and low-birth-weight are predictably a risk for death. A high proportion of surgical neonates had NEC. Although severe cases of NEC are managed surgically, medical management of the condition is just as important. In addition, measures to prevent NEC should be emphasized, including avoidance of broad spectrum antibiotic use in VLBW neonates and promotion of breast feeding.(16)

Associated bacterial, not fungal, infection was associated with poor outcome in the present study. Previous studies in our unit have shown that neonatal surgical patients are at increased risk of fungal sepsis.(17) Gram-positive sepsis appeared to be associated with survival. This is confounded by the fact that sepsis was classified as culture-proven and thus may reflect many coagulase negative *Staphalococcus* that was not clinically significant.

The importance of neonatal mortality as a cause of childhood deaths increases as the under-5 mortality rate due to a decline in mortality due to communicable diseases, including HIV related causes(18). Paediatric surgery, particularly neonatal surgery, with a proper referral and transport system is an essential component in any health care intervention to reduce neonatal mortality, and hence, childhood mortality.

5.0 STUDY LIMITATIONS

This was a retrospective analysis of an existing database, so some information was missing. In addition, certain data, such as the time of onset of infection in relation to the surgery and catheter related infections were not routinely collected in the database and were therefore not analyzed.

6.0 CONCLUSION

Neonates with major surgical conditions account for one third of NICU admissions in the present study. This study highlights the large burden placed on paediatric surgical services at a large quaternary referral hospital in South Africa. Earlier identification and easier access to NICU with paediatric surgery coverage is essential to improve outcomes. Paediatric surgical services, with a proper referral and neonatal transport system, must be a priority in planned healthcare interventions to reduce neonatal mortality in LMICs.

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