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The profile and outcome of neonates presenting for exploratory laparotomy for necrotising enterocolitis at a South African academic hospital

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

Johannesburg, 2022

Declaration

I, Natalie Botha, declare that this research report is my own unaided work. It is being submitted for the Degree of Master of Medicine in the discipline of Anaesthesiology at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University.

NBotha

25 May 2022

Abstract

Introduction:

The anaesthetic management of the neonate presenting for emergency surgery can be challenging. Current evidence has limited data to advise best practice. The aim of this study was to describe the patient profile, anaesthetic management and outcome of neonates presenting for emergency laparotomy for necrotising enterocolitis (NEC).

Methods:

A retrospective, descriptive study was conducted of surgical and anaesthetic neonatal records at Chris Hani Baragwanath Academic Hospital. Records of all neonates presenting for exploratory laparotomy for NEC from 1 January 2019 to 31 December 2020 were included in the study. Categorical variables were described using frequencies and percentages. Continuous parametric variables were described using means and standard deviations, non-parametric variables were described using medians and interquartile ranges. In records with incomplete data the total number of complete records were used to calculate mean and medians. Factors associated with 28-day mortality were compared with logistical regression analysis. A p-value of < 0.05 was considered statistically significant.

Results:

A total of 48 records were analysed. The mean gestational age and weight at birth of the neonates were 31.7 (SD ± 3.5) weeks and 1415 (IQR1199-1800) grams respectively. The mean day of life at presentation to surgery was day 8 (IQR6.0-13.3) . Intraoperatively, 9 (18.8%) cases received Sevoflurane, while 18 (37.5%) received a combination of fentanyl and midazolam. Blood products were used in 35 (73.0%) cases. Preoperative inotropic support was required in 22 (45.8%) cases and a further 6 (12.5%) cases required intraoperative inotropic support. The overall 28-day mortality rate post laparotomy for NEC was 27 (56.3%) cases. Logistical regression analysis showed a significant association between mortality and four factors: Firstly, anaesthesia administered by a consultant anaesthesiologist (OR 3.81; CI: 1.13 to 12.90; p=0.03); secondly, surgery <2 hours (OR 4.00; CI: 1.14 to 14.09; p=0.03); thirdly, surgery performed during working hours (OR 3.95; CI: 1.05 to 14.85; p=0.04) and lastly surgery performed in the neonatal intensive care unit (OR 4.00; CI: 1.14 to 14.09; p=0.03).

Conclusion:

This study described not only the patient profile of neonates presenting for exploratory laparotomy for NEC but also the variations in anaesthetic management of these patients. The higher mortality in a developing country in comparison with developed countries was highlighted. In addition, further analysis demonstrated possible associations between mortality and anaesthesiologist level of expertise; duration of surgery; time of day of surgery; and location of surgery.

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Abbreviations

CHBAH	Chris Hani Baragwanath Academic Hospital
ELBW	Extremely low birth weight
GA	Gestational age
GAS	General anaesthesia spinal trial
LBW	Low birth weight
NEC	Necrotising enterocolitis
NICU	Neonatal intensive care unit
PANDA	Paediatric anaesthesia neurodevelopmental assessment
UNICEF	United National international children's emergency fund

Statement

The Research Report consists of a literature review, draft article, study proposal, and annexures. The study proposal is included for background reference and is not for examination.

The formatting of this Research Report complies with the University of the Witwatersrand's Style Guide for Theses, Dissertations and Research Reports. The formatting of the draft article may differ from the author guidelines of the Southern African Journal of Anaesthesia and Analgesia, the journal to which it is intended to be submitted, in order to comply with the university's style guide.

Section 1: Review of the literature

1.1 Introduction

Necrotising enterocolitis (NEC) is an inappropriate inflammatory process initiated in the intestine of neonates (1). It occurs more commonly in preterm, low birth weight (LBW) and extremely low birth weight (ELBW) neonates (1). Despite a number of medical advances and improved understanding of the disease process, more than 10% of these neonates will develop NEC, and 30% will demise from the complications (2). NEC is a multifactorial disease. Formula feeding, bacterial colonization of the intestine, and prematurity are regarded as key risk factors for NEC development (3-5).

Diagnosis and staging of NEC is based on Bell's criteria (6), which includes clinical and radiological findings (6). Clinical findings range from mild abdominal distension and emesis to severe peritonitis, haematochesia, and haemodynamic collapse (6). Radiological findings include dilated loops of bowel, pneumatosis, portal venous gas, and pneumoperitoneum (6). It should be noted that many neonates with clinical evidence of severe NEC may present with normal radiological imaging (7). In these circumstances, abdominal ultrasound may be of value in confirming the diagnosis (7). According to Bell's criteria (6), stage Ia and Ib are suspected NEC, IIa and IIb are definite NEC with mild or moderate symptoms respectively, and stage IIIa and IIIb are advanced NEC with intact bowel or perforated bowel (6).

Management of NEC may either be medical or surgical, depending on the clinical presentation, radiological findings and staging. In stable neonates without evidence of bowel perforation, supportive medical management is preferred (1). This includes fluid resuscitation, haemodynamic and ventilatory support, correction of electrolyte abnormalities, cessation of enteral feeds, and gastrointestinal decompression (1). Initiation of prophylactic antibiotics is also recommended as this has been shown to reduce the number of NEC related deaths (8).

Surgical management is indicated in cases of full thickness necrosis or bowel perforation (1). This may present as a sudden change in clinical status or be visualised on radiological imaging. Peritoneal drainage and a laparotomy can be considered depending on the severity of the perforation (1). Peritoneal drainage is likely to be a temporary solution and the majority of neonates will require a laparotomy for definitive treatment (9).

In situations where surgery is required, the anaesthetic management of the neonate is extremely challenging, even for the experienced anaesthesiologist (10). There is limited available data to advise appropriate perioperative management of these neonates (11). It is therefore necessary to individualise perioperative management according to the patient profile and the anaesthesiologist's clinical judgement (10). A number of factors should be considered when planning the perioperative management of the neonate (10).

1.2 Type of anaesthetic for laparotomy for NEC

When planning the type of anaesthetic to be administered for emergency laparotomy, both intravenous and inhalational agents need to be considered (10). As clinical trials rarely include neonates, no validated guidelines are available to advise best practice (11).

Intravenous agents such as propofol, benzodiazepines and ketamine can be considered (10). Propofol is the most widely used induction agent, despite its tendency to cause severe hypotension and decreased cerebral perfusion in an immature cardiovascular system (12,13). Benzodiazepines should not be used alone as this may result in increased risk of neuro-excitability and potential for seizures in the neonate (14). Ketamine use has increased in popularity due to its relatively safe haemodynamic and respiratory characteristics (10). It is still a controversial agent as both neurotoxic and neuroprotective effects of its use have been described (15).

With regards to inhalational agents, sevoflurane is the most commonly used volatile anaesthetic agent in neonates (10). According to the general anaesthesia spinal (GAS) trial (16) and Paediatric Anaesthesia Neurodevelopmental Assessment (PANDA) study (17), sevoflurane has minimal long term neurodevelopmental adverse effects when used for short periods of time (16, 17).

1.3 Administration of blood products in the neonate

Administration of blood and blood products is an important consideration in neonates (18). The development of symptomatic anaemia may have catastrophic long-term effects (18). Anaemia occurs commonly in hospitalised neonates (18). Regular phlebotomy is thought to play a role in its development (18). This is supported by Howarth et al (18) who reported 10-30% loss of total blood volume from phlebotomy loss during admission (18).

The debate regarding conservative and liberal transfusion is still ongoing (18). The Australian blood transfusion guidelines have a conservative approach and recommend transfusing if haemaglobin is < 7 g/dl in stable neonates and < 10 g/dl in unstable neonates (19). The Canadian blood transfusion guidelines have a more liberal approach and recommend transfusion if haemaglobin is < 8g/dl in stable neonates and < 12 g/dl in unstable neonates (20). In addition, the Canadian guidelines state that transfusion is required in acute blood loss of more than 10% of blood volume (20). Both the Australian and Canadian guidelines suggest a transfusion dose of 10 to 20 ml/kg of packed red cells as tolerated (19, 20).

Similarly, there is disagreement in the literature with respect to the threshold for platelet transfusions (19-21). However, it is clear that the decision to transfuse should be based on gestational age of the neonate and not the severity of the thrombocytopenia (19-21). Preterm neonates are at increased risk of bleeding and therefore a higher platelet count should result in transfusion (19-21). A dose of 5-10 ml/kg is recommended by the Canadian guidelines (20).

1.4 Resuscitative agents for the neonate

Inotropic support is often necessary to maintain organ perfusion during surgery (22, 23). Dopamine, dobutamine, adrenaline and noradrenaline are commonly used resuscitative agents for the neonate. Dopamine is an endogenous noradrenaline precursor (23). It stimulates dopaminergic receptors at low dose and adrenergic receptors at higher doses (23). It exerts its inotropic effects indirectly via the release of noradrenaline (23). Multiple studies have recommended dopamine as the first line agent (22, 23). When compared to dobutamine, it is more effective in treating hypotension in neonates and has a lower risk of failure (22,23).

Depletion of endogenous noradrenaline stores may result in an attenuated effect over time (23). For this reason, dopamine is not recommended for long-term use (23). Dobutamine is a synthetic catecholamine (23). It increases cardiac contractility by stimulating β1 adrenergic receptors (23). While dobutamine is less effective in increasing blood pressure, it has been shown to increase cardiac output without causing vasoconstriction (23). It is therefore more suitable for long-term use (23). Adrenaline is an endogenous catecholamine (23). At low doses it produces inotropic activity via stimulation of α2, β1 and β2 adrenergic receptors (23). At higher doses it is an effective vasopressor via stimulation of α1 adrenergic receptors (23). Adrenaline has similar effects to dopamine on elevation of neonatal blood pressure (22, 23). In addition, no difference has been found in long-term morbidity and mortality between dopamine and adrenaline (23). Noradrenaline is an endogenous amine (23). It stimulates α1 and, to a lesser extent β1 adrenergic receptors to provide both inotropic effects and peripheral vasoconstriction (23). Noradrenaline is the preferred agent for refractory shock as it increases blood pressure, oxygenation and pulmonary vasodilation (23).

1.5 Intraoperative variations in physiological parameters

The long-term effect of variations in physiological parameters during anaesthesia have not been fully described (24). The Neonate and Children Audit of Anaesthesia Practice in Europe (NECTARINE) trial (24) is a multicenter, prospective, observational cohort study (24). The authors recruited 5609 neonates and infants up to 60 weeks post menstrual age from 31 European countries. The primary aim of the NECTARINE study was to determine thresholds of physiological parameters that lead to intervention by the anaesthesiologist (24). The authors determined that hypotension (30% reduction in mean arterial pressure), hypoxaemia (oxygen saturation of less than 85%), and anaemia (Haemoglobin less than 8.6g/dL) triggered medical intervention (24). End tidal carbon dioxide of less than 25mmHg or higher than 50mmHg were often thought to be artifacts and therefore rarely corrected (24). Blood glucose was measured in 50% of cases and values less than 2.8mmol/L or greater than 14.6 mmol/L were corrected (24). Temperatures as low as 34.5 degrees Celsius triggered intervention (24). Complications from hypothermia included coagulopathy in five neonates and cardiovascular instability in eight (24). The study recommendations included intervening earlier to improve outcome (24).

1.6 Location of surgery for laparotomy for NEC

The preferred location for surgical management of NEC is the emergency theatre (25). This is because it has been designed to facilitate an easy working environment for surgeons, anaesthesiologists, and nursing staff (25). However, the change of environment from the stable neonatal intensive care unit (NICU) to the unstable out of NICU environment, places added risk to the already vulnerable neonate (26-28).

The risk of adverse events during transportation of a neonate are as high as 20% (26, 27). Adverse events include equipment failure, extubation or bronchial intubation, ineffective mechanical ventilation, hypoxia, haemodynamic instability, accidental removal of intravenous access, and cardiopulmonary arrest (28, 29). Patients who are manually ventilated are also more likely to be hyperventilated with 62% of patients having end tidal carbon dioxide of less than 35mmHg (30). Adverse events specifically related to the transfer of neonates include hypoglycaemia in 19% of cases and hypothermia in 27% of cases (26).

To avoid the adverse events which may occur during intra-hospital transport of neonates, bedside surgery in the neonatal ICU could be considered. Performing procedures in the NICU has proven to be both safe and feasible and should be recommended in unstable or ELBW neonates (31-39). Unfortunately, bedside surgery is not without its faults. Limitations within this environment include inadequate lighting, inadequate surgical access, a lack of inhaled volatiles for anaesthesia, limited space, and increased risk of infection (33). However, NICU equipment has improved in recent years and may aid in a better working environment. Technology for transport monitors and ventilators have also improved and may influence the outcome of patient transport (40).

1.7 Factors associated with increased mortality rate

The first 28 days of life is known as the neonatal period and is the most vulnerable period for the neonate, with an estimated 2.4 million deaths per year globally (41). The United Nations international children's emergency fund (UNICEF) estimates the global average mortality rate of neonates at 17 deaths per 1000 live births (41). Neonates from sub-Saharan Africa are at increased risk with 27 deaths per 1000 live births (41).

In addition, UNICEF (41) estimates that these children are 10 times more likely to die in the first month compared to those born in a high-income country (41).

The NECTARINE study described the mortality rate of neonates undergoing surgery (24). The authors reported a mortality rate of 4.1% at 30-days, mainly as a result of sepsis or multi-organ failure (24). Increased risk of mortality was associated with a number of factors including co-morbidities (respiratory, cardiovascular, neurological, renal, metabolic or congenital abnormalities), prematurity (post menstrual age less than 32 weeks), and out-of-hours surgery (24). An episode of perioperative hypotension, hypoxaemia or anaemia were associated with a higher mortality rate. A confounding factor may include general instability during the 30 days (24).

Whithers et al (42) conducted a prospective, observational study of 198 neonates who underwent a surgical procedure at a South African hospital (42). Their primary aim was to describe the frequency of neonates requiring surgery and to describe the 30-day morbidity and mortality (42). The morbidity rate was largely due to nosocomial sepsis and surgical complications (anastomotic leaks, compulsory relook operations post “clip and drop surgery”, and adhesiolysis for bowel obstruction) (42). The authors reported an overall mortality rate of 21% (42), which is higher than the NECTARINE study. NEC was found to be the most frequent indication for surgery with a 30-day mortality rate of 23% (42). Nosocomial sepsis was noted to be the main cause of mortality in 87% of cases (42). Additional causes of mortality included disease progression, respiratory failure, pulmonary haemorrhage, multi-organ failure not due to sepsis and palliation (42).

Saggers et al (43) described the factors associated with mortality before discharge of 319 surgical neonates admitted to the NICU of another South African academic hospital (43). In this study records were reviewed retrospectively over 3 years. The authors reported an overall mortality rate of 32% (43). NEC contributed to the highest proportion of surgical neonates in this group (43). The mortality rate amongst this population was 52%, which was double the mortality rate found by Whithers et al (42).

Prematurity, low birth weight, major birth defects, “out-born” patients and sepsis were associated with a poor outcome, while maternal demographics, infant gender and low 5-minute APGAR scores did not affect the outcome (43).

Ammar et al (44) conducted a retrospective review of hospital records on 182 neonates who underwent a surgical procedure in a Tunisian hospital (44). The aim of their study was to determine factors that predict early mortality (44). Unlike Whithers et al (42) and Saggers et al (43), oesophageal and small bowel atresia were the most common indications for surgery (44). NEC accounted for the highest mortality rate at 66%. It should be noted that the small sample size (n=6) may have resulted in an unreliable estimation (44).

1.8 Conclusion:

NEC is a common condition of the preterm, LBW and ELBW neonate (1). Surgical management is indicated in full thickness necrosis or bowel perforation (1). The mortality rate for surgical NEC in developed countries is up to 30% and ranges from 23-66% in developing countries (24, 42-44). These studies have described factors associated with mortality, specifically prematurity, ELBW, disease progression, nosocomial sepsis, and multiorgan failure and focus on surgical and intensive care management (24, 42-44). The results of the studies assist the paediatric surgeon and the neonatologist. (42-44). Specific data on laparotomies for NEC and implication of perioperative management to assist the anaesthesiologist is lacking. The need for data in this area is apparent in order to provide appropriate intraoperative patient care.

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Section 2: Author's guidelines

Southern African Journal of Anaesthesia and Analgesia (SAJAA)

Submitted manuscripts that are not in the correct format and without the required supporting documentation specified in these guidelines will be returned to the author(s) for correction and will delay publication.

2.1 Authorship

Named authors must consent to publication by signing a covering letter which should be submitted as a supplementary file. Authorship should be based on substantial contribution to:

(i) conception, design, analysis and interpretation of data;

(ii) drafting or critical revision for important intellectual content; and

(iii) approval of the version to be published. These conditions must all be met (uniform requirements for manuscripts submitted to biomedical journals; refer to **www.icmje.org**); and

(iv) exact contribution of each author must be stated.

2.2 Declaration of conflict of interest

Authors must declare all sources of support for the research and any association with a product or subject that may constitute a conflict of interest. If there is no conflict of interest to declare please include the following statement: The authors declare no conflict of interest.

2.3 Funding Source

All sources of funding should be declared. Also define the involvement of study sponsors in the study design, collection, analysis and interpretation of data; the writing of the manuscript; the decision to submit the manuscript for publication. If the study sponsors had no such involvement, this should be stated as follows: No funding source to be declared.

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The submitting author must provide written confirmation of Research Ethics Committee approval for all studies including case reports. The ethics committee as well as the approval number should be included.

2.5 Statistical analysis

Authors are advised to involve medical statisticians at the protocol stage of their research project: to plan sample size, and the selection of appropriate statistical tests for analysis and presentation.

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Identifying information should not be published in written descriptions, photographs, and pedigrees unless the information is essential for scientific purposes and the patient (or parent or guardian) gives informed written consent for publication. The patient should be shown the manuscript to be published. Refer to **www.icmje.org**.

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The rationale for analysis based on racio-ethnic-cultural categorisation should be indicated.

2.8 Categories of submission

Shorter items are more likely to be accepted for publication, owing to space constraints and reader preferences.

Original articles: Research relevant to anaesthesia and analgesia should not exceed 3 200 words, no more than 30 references, with up to 6 tables or figures. A structured abstract under the following headings, Background, Methods, Results, and Conclusions is a requirement and should not exceed 300 words.

Clinical Review articles: Research relevant to anaesthesia and analgesia should not exceed 2 400 words, with a maximum of 20 references and no more than 6 tables or figures. A summary of 300 words or less is required.

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Letters to the editor: Letters to the editor should be 800 words or less with only one image or table.

2.9 Manuscript preparation

Refer to articles in recent issues for the presentation of headings and subheadings. If in doubt, refer to 'uniform requirements' - **www.icmje.org**. Manuscripts must be provided in UK English.

Qualification, affiliation and contact details: This information must be provided for ALL authors and must be submitted as a supplementary file. Email addresses of all author must be provided. ORCID number of ALL authors must be provided - if authors do not have ORCID, please register at https://orcid.org/

Abbreviations: All abbreviations should be spelt out when first used and thereafter used consistently, e.g. 'intravenous (IV)' or 'Department of Health (DoH)'.

Scientific measurements: Scientific measurements must be expressed in SI units except blood pressure (mmHg) and haemoglobin (g/dl). Litres is denoted with a lowercase 'l' e.g. 'ml' for millilitres). Units should be preceded by a space (except for %), e.g. '40 kg' and '20 cm' but '50%'. Greater/smaller than signs (> and 40 years of age) should also be preceded by a space e.g. > 20 years. No spaces should precede ± and °, i.e. '35±6' and '19°C'.

Numbers: should be written as grouped per thousand-units, i.e. 4 000, 22 160...

Quotes: should be placed in single quotation marks: i.e. The respondent stated: '...'
Round **brackets** (parentheses) should be used, as opposed to square brackets, which are reserved for denoting concentrations or insertions in direct quotes.

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Disclaimers should follow the Conclusion and it should be in the following order: Acknowledgements, Declaration conflict of interest, Funding source, Ethics declaration and ORCID.

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If tables or illustrations submitted have been published elsewhere, the author(s) should provide consent to republication obtained from the copyright holder.

Tables: may be embedded in the manuscript file and provided as 'supplementary files'. They must be numbered in Arabic numerals (1,2,3...) and referred to consecutively in the text (e.g. 'Table 1'). Tables should be constructed carefully and simply for intelligible data representation. Unnecessarily complicated tables are strongly discouraged. Tables must be cell-based (i.e. not constructed with text boxes, tabs or enters) and accompanied by a concise title and column headings. Footnotes must be indicated with consecutive use of the following symbols: * † ‡ § ¶ || then ** †† ‡‡ etc.

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All references should be listed at the end of the article in numerical order of appearance in the Vancouver style (not alphabetical order). Approved abbreviations of journal titles must be used; see the List of Journals in Index Medicus. Names and initials of all authors should be given; if there are more than six authors, the first four names should be given followed by et al. First and last page, volume and issue numbers should be given. Wherever possible, references must be accompanied by a digital object identifier (DOI) link and PubMed ID (PMID)/PubMed Central ID (PMCID). Authors are encouraged to use the DOI lookup service offered by CrossRef. Crossref DOIs should always be displayed as a full URL link in the form https://doi.org/10.xxxx/xxxxx

Journal references:

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A covering letter to the editor is mandatory and must include statements that the manuscript has not been published previously and is not under review elsewhere. It should state details of any prior publication of the research in abstract form or in Congress proceedings.

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Section 3: Draft article

The profile and outcome of neonates presenting for exploratory laparotomy for necrotising enterocolitis at a South African academic hospital

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Key words: Necrotising enterocolitis; neonate; anaesthetic management; mortality.

Abstract

Introduction:

The anaesthetic management of the neonate presenting for emergency surgery can be challenging. Current evidence has limited data available to advise best practice. The aim of this study was to to describe the patient profile, anaesthetic management and outcome of neonates presenting for emergency laparotomy for necrotising enterocolitis (NEC).

Methods:

A retrospective, descriptive study was conducted of surgical and anaesthetic neonatal records at Chris Hani Baragwanath Academic Hospital. Records of all neonates presenting for exploratory laparotomy for NEC from 1 January 2019 to 31 December 2020 were included in the study. Categorical variables were described using frequencies and percentages. Continuous parametric variables were described using means and standard deviations, non-parametric variables were described using medians and interquartile ranges. In records with incomplete data the total number of complete records were used to calculate mean and medians. Factors associated with 28-day mortality were compared with logistical regression analysis. A p-value of < 0.05 was considered statistically significant.

Results:

A total of 48 records were analysed. The mean gestational age and weight at birth of the neonates were 31.7 (SD ± 3.5) weeks and 1415 (IQR1199-1800) grams respectively. The mean day of life at presentation to surgery was day 8 (IQR6.0-13.3). Intraoperatively, 9 (18.8%) cases received Sevoflurane, while 18 (37.5%) received a combination of fentanyl and midazolam. Blood products were used in 35 (73.0%) cases. Preoperative inotropic support was required in 22 (45.8%) cases and a further 6 (12.5%) cases required intraoperative inotropic support. The overall 28-day mortality rate post laparotomy for NEC was 27 (56.3%) cases. Logistical regression analysis showed a significant association between mortality and four factors: Firstly, anaesthesia administered by a consultant anaesthesiologist (OR 3.81; CI: 1.13 to 12.90; p=0.03); secondly, surgery <2 hours (OR 4.00; CI: 1.14 to 14.09; p=0.03); thirdly, surgery performed during working hours (OR 3.95; CI: 1.05 to 14.85; p=0.04) and lastly surgery performed in the neonatal intensive care unit (OR 4.00; CI: 1.14 to 14.09; p=0.03).

Conclusion:

This study described not only the patient profile of neonates presenting for exploratory laparotomy for NEC but also the variations in anaesthetic management of these patients. The higher mortality rate in a developing country in comparison with developed countries was highlighted. In addition, further analysis demonstrated possible associations between mortality and anaesthesiologist level of expertise; duration of surgery; time of day of surgery; and location of surgery.

Introduction

The first 28 days of life are known as the neonatal period (1). The United Nations international children's emergency fund (UNICEF) reports 2.4 million neonatal deaths annually (1). In addition, a child born in sub-Saharan Africa is 10 times more likely to die in the first month compared to those born in a developed country (1).

Necrotising enterocolitis (NEC) is an inappropriate inflammatory process initiated in the intestine of neonates (2). It occurs more commonly in preterm, low birth weight (LBW) and extremely low birth weight (ELBW) neonates (2). Despite a number of medical advances and improved understanding of the disease process, more than 10% of these neonates will develop NEC, and 30% will demise from the complications (3).

In situations where surgery is required, the anaesthetic management of the neonate is extremely challenging, even for the experienced anaesthesiologist (4). Clinical trials rarely include neonates, and although there are current practice recommendations in the literature, no validated guidelines are available to advise best practice (5). It is therefore necessary to individualise perioperative management according to the patient profile and the anaesthesiologist's clinical judgement (4).

A number of studies describe the outcome of surgical neonates in developing countries (6-8). These studies consistently report an increased mortality rate compared to developed countries (6-9). However, the main focus of these studies was surgical and intensive care management to assist the paediatric surgeon and the neonatologist (6-8). No studies related to the anaesthetic management of neonates in developing countries could be found. The need for data in this area is apparent in order to provide appropriate patient care, specifically for the anaesthesiologist.

The aim of this study was to describe the patient profile, anaesthetic management and outcome of neonates presenting for emergency laparotomy for NEC at a South African academic hospital.

Methods

Study Design: A retrospective, descriptive study of neonatal records at Chris Hani Baragwanath Academic Hospital (CHBAH) was conducted. CHBAH is tertiary academic hospital located in Johannesburg, South Africa and is affiliated with the University of the Witwatersrand to provide a training environment for medical students. The hospital has more than 3 000 beds and receives referrals from the entire province. The neonatal complex consists of 26 ventilated neonatal intensive care unit (NICU) beds and can accommodate up to 60 additional neonates in the transitional unit. The unit is managed by both paediatric surgeons and neonatologists.

Sample selection: Records of all neonates presenting for exploratory laparotomy for NEC at CHBAH from 1 January 2019 to 31 December 2020 were included in the study. Missing records were excluded from the study.

Data Collection: Data were obtained from the neonatal theatre registry, anaesthesia charts and the paediatric electronic database.

Data Analysis: Microsoft Excel® data spread sheet and the statistical programme STATA® version 17 were used to analyse data. Categorical variables were described using frequencies and percentages. Continuous parametric variables were described using means and standard deviations, non-parametric variables were described using medians and interquartile ranges. In records with incomplete data the total number of complete records were used to calculate means and medians. Factors associated with 28-day mortality were compared with logistical regression analysis. A p-value of < 0.05 was considered statistically significant.

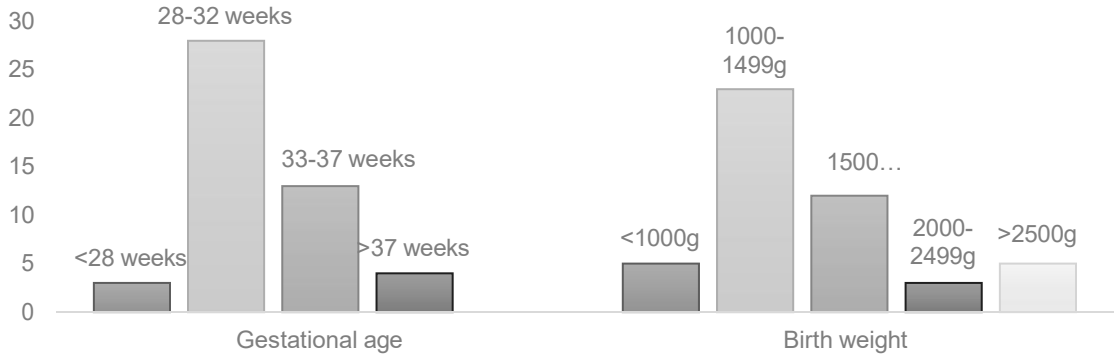
Ethical Considerations: Approval to conduct the study was obtained from the Human Research Ethics Committee (Medical) and the Graduate Studies Committee of the University of the Witwatersrand before commencement of the study (M200849). As this is a retrospective, observational record review with anonymous data, the need for informed consent was waivered.

Results

All neonates in the first 28 days of life who had undergone an index exploratory laparotomy from 1 January 2019 to 31 December 2020 at CHBAH for NEC were included in the study. A total number of 48 neonatal records were analysed.

The mean gestational age (GA) at birth was 31.7 (SD ± 3.5) weeks and the median weight at birth was 1415g (IQR 1199-1800g). The number of neonates according to GA and weight at birth are represented in figure one. The median day of life at the index presentation for surgery was day 8 (IQR 6.0-13.3).

Figure 1: The number of neonates according to gestational age and weight at birth



Prior to coming to theatre, 13 (27.1%) of the cases had episodes of glucose instability, 21 (43,8%) had a metabolic acidosis, and 33 (68.8%) had suspected or confirmed sepsis. Preoperative ventilation was required in 41 (85.4%) of the cases, one (2.1%) of which required high frequency oscillation. The remaining seven (14.6%) received supplemental oxygen via nasal canulae.

With regards to induction of anaesthesia, all seven (14.6%) neonates who arrived in theatre on nasal canulae were induced with propofol. Maintenance of anaesthesia varied. Nine cases (18.8%) received Sevoflurane.

No sevoflurane was used in 39 cases of which 12 (25.0%) cases received fentanyl only, 18 (37.5%) received a combination of fentanyl and midazolam, and 9 (18.8%) received a combination of fentanyl and ketamine.

Physiological parameters that were investigated included oxygen saturation, end tidal carbon dioxide ($ETCO_2$), mean arterial blood pressure (MAP), heart rate, and temperature. The median values, including those at the start of the procedure, end of the procedure as well as the maximum and minimum values during the procedure are summarised in table one. $ETCO_2$ was not reported in 22 (45.8%) of the cases, as they were performed in NICU where capnography was not available. No heart rate values were documented in one (2.1%) of the cases and no temperature values were documented in five (10.4%) of the cases. Blood glucose was documented in 37 (77.1%) cases. At the start of surgery, a blood glucose value of less than 2.8 mmol/L was found in 7 (18.9%) of the cases and a value of more than 10 mmol/L was found in 10 (27.0%) of the cases. At least one haemaglobin value was documented in 47 (97.9%) cases. At the start of surgery 44 (93.6%) cases documented haemaglobin with a mean value of 11.29 (SD±2.58) g/dL. A value of less than 10 g/dL was found in 16 (34.0%) of the cases. At the end of surgery 26 (55.3%) cases documented haemaglobin with a mean value of 11. 93 (SD±2.95). A value of less than 10 g/dL was found in seven (15.9%) of the cases at the end of surgery.

Table 1: Median values for intraoperative physiological parameters

	Oxygen saturation (%)	End tidal carbon dioxide (mmHg)	Mean arterial pressure (mmHg)	Heart rate (Beats/minute)	Temperature (Degree Celsius)
At the start	94 (IQR 92-96)	35(IQR 30-44)	44 (IQR 35-59)	170 (IQR 160-180)	36.6 (IQR 36.4-37.0)
At the end	94 (IQR 92-96)	33 (IQR 27-36)	42 (IQR 34-46)	163 (IQR 145-180)	36.5 (IQR 36.1-36.8)
Minimum	90 (IQR 85-92)	28 (IQR 25-34)	37 (IQR 27-40)	145 (IQR 132-165)	36.4 (IQR 35.4-36.5)
Maximum	97 (IQR 95-99)	41 (IQR 35-45)	55 (IQR 45-64)	175 (IQR 161-194)	36.9 (IQR 36.5-37.1)

Packed red cells were administered in 33 (68.8%) cases, fresh frozen plasma in 20 (41.7%) cases and platelets in 28 (58.3%) cases. The mean volume of packed red cells was 25.8mls/kg, fresh frozen plasma was 19.1mls/kg and platelets were 17.4mls/kg. No cryoprecipitate was given in any of the cases.

Preoperative inotropic support was required in 22 (45.8%) of the cases. The most commonly used inotrope was dobutamine in 18 (81.8%) of those cases, followed by adrenaline in 14 (63.6%) and then dopamine in four (18.2%) of the cases.

A further six (12.5%) cases required intraoperative inotropic support, resulting in a total of 28 (58.3%) cases requiring inotropes during the procedure. The most commonly used inotrope was adrenaline in 21 (75.0%), followed by dobutamine in 19 (67.9%) and dopamine in 6 (21.4%). No cases reported the use of noradrenaline, phenylephrine or ephedrine preoperative or intraoperatively. The percentage and mean dose of preoperative and intraoperative inotropic agents are summarised in table two.

Table 2: Percentage and mean dose of preoperative and intraoperative inotropic agents

	Pre-Operative (n=22)	Intra-operative (n=28)
Single therapy		
Dobutamine	5 (22.7%)	4 (14.3%)
Adrenaline	4 (18.2%)	7 (25.0%)
Dopamine	0 (0%)	1 (3.6%)
Double therapy		
Adrenaline and dobutamine	9 (40.9%)	11 (39.3%)
Dobutamine and dopamine	3 (13.6%)	2 (7.1%)
Dopamine and adrenaline	0 (0%)	1 (3.6%)
Triple therapy		
Dobutamine, adrenaline and dopamine	1 (4.5%)	2 (7.1%)
Mean dose (mcg/kg/min)		
Dobutamine	17.5 (SD±9.8)	18.6 (SD±6.9)
Adrenaline	0.5 (SD±0.3)	0.5 (SD±0.3)
Dopamine	18.75 (SD±5.2)	13.0 (SD±5.8)

The overall 28-day mortality rate was 27 (56.3%) of the 48 cases. One (2.1%) death occurred intraoperatively and the remainder demised postoperatively in the NICU.

Factors associated with the 28-day mortality rate were assessed. These included birthweight, GA and preoperative inotropic support. The association between professional level of the surgeon and anaesthesiologist (consultant versus registrar) were also assessed.

Additional factors assessed included normal working hours compared to after working hours, as well as the duration of the procedure and location of the procedure. Figure two demonstrates the distribution of factors associated with 28-day mortality in the 27 neonates who demised. Logistical regression analysis was performed on these factors to determine their association with mortality amongst the whole group of 48 patients. Anaesthesia administered by a consultant anaesthesiologist, surgery <2 hours duration, surgery during working hours and surgery performed in the NICU were all associated with a significant increase in mortality rate. The results are represented in table four.

Figure 2: Distribution of factors associated with 28-day Mortality

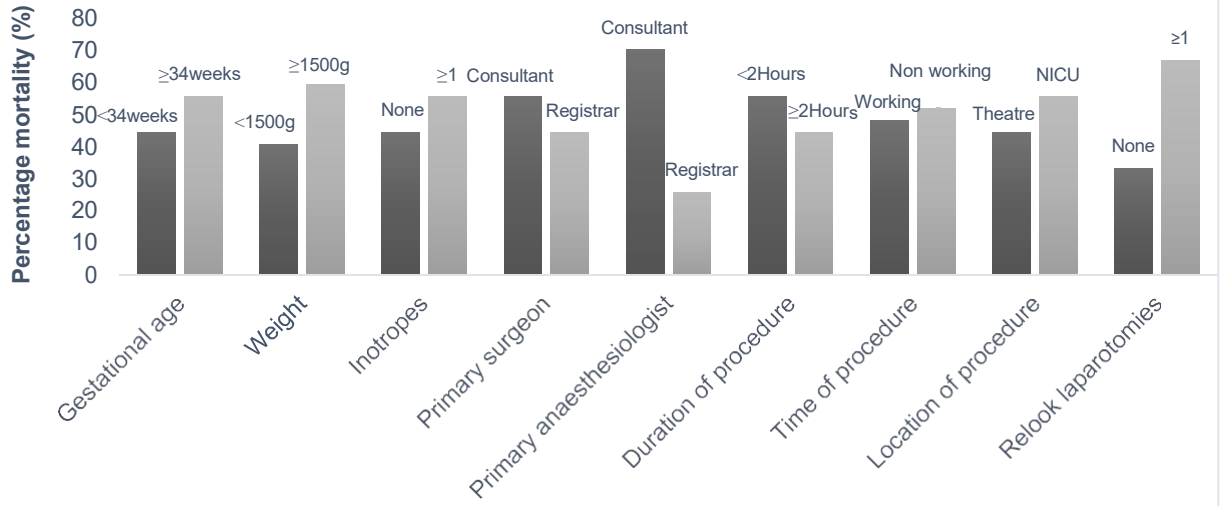


Table 3: Logistical regression analysis for factors associated with 28-day mortality

	Odds Ratio	P-value	95% Confidence Intervals
Gestational age < 34 weeks	0.77	0.66	0.24 to 2.45
Weight < 1500g	1.60	0.42	0.51 to 5.03
Use of preoperative inotropes	1.09	0.88	0.34 to 3.47
Primary surgeon: Consultant	1.88	0.33	0.53 to 6.72
Primary anaesthesiologist: Consultant	3.81	0.03	1.13 to 12.90
Duration of procedure < 2 hours	4.00	0.03	1.14 to 14.09
Time of procedure in working hours	3.95	0.04	1.05 to 14.85
Location of procedure in NICU	4.00	0.03	1.14 to 14.09
Number of relook laparotomies	1.00	1.00	0.30 to 3.35

Discussion

The aim of our study was to describe the patient profile, anaesthetic management and the 28-day mortality of neonates presenting for laparotomy for NEC.

In our study more than 85% of the neonates were premature with LBW and ELBW. The patient profile in our study was similar to the profile described by studies conducted in both developed and developing countries (6-8, 10).

Preopertive Metabolic acidosis, glucose instability and inotropic support were present in a large number of the cases from our study. These markers of disease progression were not reported in studies similar to ours (6-8). Two thirds of the cases in our study had suspected or confirmed sepsis prior to coming to theatre. This is in keeping with findings from Whithers et al (6) who reported the median time to sepsis of 2.5 days in neonates with NEC. Preoperative ventilatory support was required in 85% of the cases in our study. Although their study was not specific to neonates with NEC, Ammar et al (8) reported a preoperative ventilation rate of 22.5%. The inconsistency in results may be explained by the high number of premature cases and the patient profile in our study.

Propofol was the induction agent of choice in all cases of our study. It's use in neonates is controversial (11-13). De Kort et al (13) described a 34% decrease in mean arterial blood pressure in more than 50% of neonates post endotracheal intubation with propofol. They recommended alternative induction agents in haemodynamically unstable, preterm neonates (13). It should be noted that the cases requiring induction in our study were all haemodynamically stable.

Both volatile agents and total intravenous anaesthesia (TIVA) were used for maintenance of anaesthesia in our study. Sevoflurane was the agent of choice. This is in-keeping with practice recommended by the literature (14,15).

Less than 20% of cases were maintained on a volatile agent. This is likely due to lack of access to volatiles in cases done in NICU, due to intolerance of volatiles in cases with severe haemodynamic instability or due to anaesthesiologist preference. A combination of midazolam and fentanyl were the preferred agents for TIVA maintenance of anaesthesia. Midazolam and fentanyl were used in 37.5% of the cases. Consistent with recommendations in NICU practice from Hall et al (16) who suggest that both midazolam and fentanyl provide adequate conditions for mechanical ventilation and procedural pain (16). Fentanyl was used in all 48 cases, either for pain management, or for maintenance of anaesthesia. This is consistent with literature which reports reduced pain, lower heart rates and fewer side effects in neonates receiving fentanyl (16).

When reviewing physiological parameters, our study found that the median value for oxygen saturation, $ETCO_2$, MAP, heart rate and core body temperature at the start of surgery were similar to those at the end of surgery. Intraoperative variations were noted when reviewing the minimum and maximum values. These findings suggest that although variations did occur, they were managed effectively to re-establish preoperative values. The Neonate and Children Audit of Anaesthesia Practice in Europe (NECTARINE) trial (9) determined the thresholds of physiological parameters that lead to intervention by the anaesthesiologist (9). They reported a minimum threshold for oxygen saturation of less than 85%, $ETCO_2$ of less than 25 mmHg, MAP of 30% reduction, and core body temperature of less than 34.5 degrees Celsius. While the focus of our study was not to determine these thresholds, the median parameters reported in our study did not exceed the thresholds documented in the NECTARINE trial (9). Hence, the threshold values are likely to be higher in our setting. In addition, we found that glucose was recorded in 77% of cases at the start of surgery. This exceeds the 50% of cases reported in the NECTARINE trial (9).

Furthermore, our study found 36.4% of neonates had haemaglobin levels <10 g/dl prior to initiation of surgery. A possible reason for this could be iatrogenic blood loss caused by repeated phlebotomy. This is supported by Howarth et al (17) who reported 10-30% loss of total blood volume from phlebotomy during admission (17).

Intraoperatively, 68.8% of the cases received packed red cells. The debate regarding appropriate transfusion triggers is still ongoing (17-19). The Australian Blood Transfusion Guidelines (19) recommend transfusing asymptomatic neonates if haemoglobin is < 7 g/dl and symptomatic neonates if haemaglobin is < 10 g/dl (19). The Canadian Blood Transfusion Guidelines (18) recommend transfusion if haemoglobin is < 8g/dl in asymptomatic neonates and < 12 g/dl in symptomatic neonates (18). In addition, Canadian Blood Transfusion Guidelines (18) stipulate that acute blood loss of more than 10% blood volume should trigger a transfusion (18). In our study, a mean volume of 23 ml/kg was given. This is comparable to the Canadian Blood Transfusion Guidelines (18) which suggest a dose of 10 to 20 ml/kg of packed red cells as tolerated (18). In our study we found that 58% of the cases received platelets with a mean volume of 17 ml/kg. This far exceeds the recommended dose of 5-10 ml/kg (18). The literature describes that, preterm neonates are at increased risk of bleeding and therefore a higher platelet count should result in transfusion compared to term neonates (17-19). In addition, the decision to transfuse platelets should be based on GA of the neonate and not the severity of the thrombocytopenia (17-20). Our results show that this centre may not follow current practice in the literature. We recommend that transfusion trigger protocols for developing countries be developed and implemented to prevent inappropriate blood administration.

Inotropic support is often necessary to maintain organ perfusion during surgery (21, 22). In our study we found that 45.8% of cases required preoperative inotropic support. The majority (81.5%) of neonates received dobutamine as first line therapy prior to surgery. The choice of inotropic agent in neonates remains controversial (21, 22). Multiple studies have reported that dopamine is more effective at increasing MAP in neonates and has a lower risk of failure compared to dobutamine (21, 23). Despite these benefits, dopamine acts indirectly via the release of endogenous noradrenaline, thus depletion of these stores may result in an attenuated effect over time (21, 22). For this reason, long term use of dopamine is not recommended (21). This may explain why dobutamine is used more frequently in our setting. In addition, dobutamine is more effective at increasing superior vena cava blood flow without a substantial increase in MAP (22). Intraoperatively, 58.3% of the patients required support.

Adrenaline was the inotropic agent of choice compared to dobutamine and dopamine. Dopamine and adrenaline have comparable effect on neonatal blood pressure, cerebral oxygenation and mortality (21-23). Importantly, while adrenaline has been shown to increase lactate levels, and heart rate, it also improved the base excess and blood glucose (22). Initiation of adrenaline intraoperatively is likely due to ease of access to adrenaline as well as the anaesthesiologist's preference. None of the cases in our study used noradrenaline. Noradrenaline is recommended in refractory septic shock (21). It would therefore be a suitable agent for inotropic support in NEC. Noradrenaline may not be freely available in some settings. Further randomised trials are necessary to determine the most appropriate inotropic agent for neonates with NEC, including the use of noradrenaline.

A mortality rate of 56.3% in neonates with confirmed NEC was found in our study. This exceeds the 30% mortality rate previously reported in developed countries (3). These results are consistent with the increased mortality rate in Sub-Saharan Africa reported by UNICEF (1). Ammar et al (8) reported a mortality rate of 66% in a Tunisian hospital (8). However, their sample size was extremely small (n=6) and should be viewed with caution. Whithers et al (6) and Saggers et al (7), conducted studies in two South African hospitals, the authors reported a mortality rate of 23% and 52% respectively in neonates with NEC who underwent surgery (6,7). Whithers et al (6) and our study were conducted in the same hospital and over a similar period, by different departments. In their study, the mortality rate of 68 neonates was assessed, compared to our study with 48 neonates. The inconsistency in the sample size and mortality rate is largely due to differing inclusion and exclusion criteria, as well as a high number of missing anaesthetic records. It should be noted that our study was conducted during the covid 19 pandemic and therefore co-infection with the virus may have contributed to the higher mortality rate. Working in the pandemic also provided logistical challenges that may have resulted in delay to surgery which could have influenced outcomes of the neonates. In addition during this time theatre staff may have conducted the procedure in full personal protective equipment (PPE). This may have had an impact on patient outcomes.

Multiple studies have attempted to addresses the major risk factors associated with mortality in surgical neonates (6-9). No association was found between mortality and GA <34 weeks (OR: 0.77; CI: 0.24 to 2.45), but a nonsignificant (p=0.42) association was found between mortality and birthweight <1500g (OR: 1.60; CI: 0.51 to 5.03).

While the results for birthweight are consistent with these studies, a possible reason for the discrepancy in GA may be differing GA values. Gestational age <34 weeks in our study compared to GA <32 weeks in these studies (7,9). Furthermore, an association between mortality and preoperative inotropic use was found (OR: 1.09; CI:0.34 to 3.47), but this was not significant (p=0.88). The NECTARINE trial (9) reported an increased morbidity with preoperative cardiovascular support (9).

In addition, our study found an association between mortality in cases where surgery was performed by a consultant surgeon (OR: 1.88; CI: 0.53 to 6.72; p=0.33) or anaesthetised by a consultant anaesthesiologist (OR: 3.81; CI: 1.31 to 12.90; p=0.03) as compared to registrars. While this was not significant for consultant surgeons, the reason for the increased mortality is likely to be the same in both cases. This may be due to the unstable preoperative condition of the neonate, necessitating more specialized care from consultant surgeons and anaesthesiologist. Surgeries with a duration of < 2 hours were associated with increased mortality (OR: 4.00; CI: 1.14 to 14.09; p = 0.03). These results are not in keeping with previous studies which report increased mortality with longer duration of surgery (8-9). The shorter duration of surgery noted in our study may be explained by the presence of NEC Totalis. In this situation, surgery is immediately abandoned and palliative care is instituted resulting in short surgical time with inevitable mortality.

A significant increase in mortality during working hours (OR: 3.95; CI:1.05 to 14.85; p= 0.04) was found in our study. This is in contrast to the NECTARINE study which reported an increased mortality during after working hours (9). Of note is that the NECTARINE study included all elective and emergency surgical cases, compared to our study in which only emergency cases were included (9). Hence, the higher mortality found in the NECTARENE study may be due to the nature of the surgery. Surgeries performed in the NICU were also significantly associated with an increased mortality (OR: 4.00; CI: 1.14 to 14.09; p=0.03). These results are comparable with previous studies which reported increased mortality in NICU due to the unstable condition of the neonate (24). Finally, no association was found between mortality and the number of relook laparotomies (OR:1.00; CI: 0.30 to 3.53; p=1.00). The NECTARINE trial (9) reported an increased mortality with increased number of relook laparotomies. Our study did not find this association.

This may again be explained by the presence of NEC Totalis where no relook laparotomies are performed as mortality was inevitable. Prospective studies with preoperative and post operative objective assessment with scoring systems may be of benefit to fully understand the factors associated with mortality.

Limitations to our study include a small sample size as a result of missing records. In addition, our study was conducted in a single centre. The results of our study rely on retrospective record keeping from multiple sources from different departments and therefore is subject record keeping bias.

Conclusion

Emergency laparotomies in neonates can prove to be complex anaesthetic cases. The results obtained in this study gives us further insight into the clinical profile and perioperative anaesthetic management of neonates presenting for emergency laparotomy for NEC. Although most variables described are similar to those recommended in the literature, the 28-day mortality rate in our study was significantly higher than those reported in developed and developing countries (6-9). Despite the small sample size, our study highlights the importance of perioperative anaesthetic management of a neonate in order to provide safe quality care to these patients. Future studies may benefit from multicentre, prospective studies.

Disclaimers

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Section 4: Proposal

The profile and outcome of neonates presenting for exploratory laparotomy for necrotising enterocolitis at a South African academic hospital

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4.1 Introduction

Necrotising enterocolitis (NEC) is an inappropriate inflammatory process initiated in the intestine of neonates (1). It occurs more commonly in preterm, low birth weight (LBW) and extremely low birth weight (ELBW) neonates (1). Despite a number of medical advances and improved understanding of the disease process, more than 10% of these neonates will develop NEC, and 25% will demise from the complications (2). NEC is a multifactorial disease. However, formula feeding, bacterial colonisation, and prematurity are regarded as key risk factors for NEC development (3–5).

Diagnosis and staging of NEC is based on Bell's criteria, which includes clinical and radiological findings (6). Clinical findings range from mild abdominal distension and emesis to severe peritonitis, haematochesia, and haemodynamic collapse (6). Radiological findings are less subtle and include dilated loops of bowel, pneumatosis, portal venous gas, and pneumoperitoneum (6). However, many neonates with clinical evidence of severe NEC may present with normal radiological imaging (7). In these circumstances, abdominal ultrasound may be of value in confirming the diagnosis (7). Clinical and radiological findings assist in staging the degree of NEC (6). Stage Ia and Ib are suspected NEC, IIa and IIb are definite NEC with mild or moderate symptoms respectively, and stage IIIa and IIIb are advanced NEC with intact bowel or perforated bowel respectively (6).

Management of NEC may either be medical or surgical, depending on the clinical presentation, radiological findings and staging. In stable neonates without evidence of bowel perforation, supportive medical management is preferred (1). This includes fluid resuscitation, haemodynamic and ventilatory support, correction of electrolyte abnormalities, cessation of enteral feeds, and gastrointestinal decompression (1). Initiation of prophylactic antibiotics is also recommended as this has been shown to reduce the number of NEC related deaths (8).

Surgical management is indicated in cases of full thickness necrosis or bowel perforation (1). This may present as a sudden change in clinical status or be visualised on radiological imaging. Peritoneal drainage and a laparotomy can be considered depending on the severity of

the perforation (1). However, peritoneal drainage is likely to be a temporary solution and the majority of neonates will require a laparotomy for definitive treatment (9).

In situations where surgery is required, the anaesthetic management of the neonate is extremely challenging, even for the experienced anaesthesiologist (10). There is limited available data to advise appropriate peri-operative management of these neonates (11). It is therefore necessary to individualise peri-operative management according to the patient profile and the anaesthesiologist's clinical judgement (10). A number of factors should be considered when planning the peri-operative management of the neonate. These include type of anaesthetic administered, management of variations in physiological parameters, as well as location of surgery (10, 12).

When planning the type of anaesthetic to be administered for emergency laparotomy, both intravenous and inhalational agents need to be considered (12). As clinical trials rarely include neonates, no validated guidelines are available to advise best practice (11).

Intravenous agents such as propofol, benzodiazepines and ketamine can be considered (10). Propofol is the most widely used induction agent, despite its tendency to cause severe hypotension and decreased cerebral perfusion in an immature cardiovascular system (13, 14). Benzodiazepines commonly worsen haemodynamic instability in the premature neonate, however, it is in these situations that they are most likely to be used (15). Ketamine has increased in popularity due to its relatively safe haemodynamic and respiratory characteristics (10). However, it is still a controversial agent as both neurotoxic and neuroprotective effects of its use have been described (16).

Inhalational agents can also be considered. Sevoflurane is the most commonly used volatile anaesthetic agent in neonates (10). According to the general anaesthesia spinal (GAS) trial (17) and Paediatric Anaesthesia Neurodevelopmental Assessment (PANDA) study (18), sevoflurane has minimal long term neurodevelopmental adverse effects when used for short periods of time (17, 18).

Management of variations in physiological parameters is likely to affect long term outcome, however, this has not been fully described (12). The Neonate and Children Audit of Anaesthesia Practice in Europe (NECTARINE) trial (12) is a multicentre, prospective, observational cohort study (12). Which recruited 5609 neonates from 31 European countries.

The primary aim of the NECTARINE study was to determine thresholds of physiological parameters that lead to intervention by the anaesthesiologist (12). They determined that hypotension (30% reduction in mean arterial pressure), hypoxaemia (oxygen saturation of less than 85%), and anaemia (Haemoglobin less than 8.6g/dL) triggered medical intervention (12). End tidal carbon dioxide of less than 25mmHg or higher than 50mmHg were often thought to be artifacts and therefore rarely corrected (12). Only 50% of cases measured blood glucose and values Less than 2.8mmol/L or more than 14.6 mmol/L were corrected (12). Temperatures of as little as 34.5 degrees Celsius triggered intervention (12). They recommended that intervening earlier might improve outcome (12).

In addition, the NECTARINE study aimed to describe the mortality rate of neonates undergoing surgery (12). The authors reported a mortality rate of 4.1% at 30-days, mainly as a result of sepsis or multi-organ failure (12). Increased risk of mortality was associated with a number of factors including co-morbidities (respiratory, cardiovascular, neurological, renal or metabolic or congenital abnormalities), prematurity (post menstrual age less than 32 weeks), and out-of-hours surgery (12).

An episode of peri-operative hypotension, hypoxaemia or anaemia were associated with a higher mortality rate. However, it is unclear if this was a result of peri-operative instability or instability throughout the 30-days (12).

Whithers et al (19) conducted a prospective, observational study of 198 neonates who underwent a surgical procedure at a South African hospital (19). Their primary aim was to describe the frequency of neonates requiring surgery and to describe the 30-day morbidity and mortality (19). The morbidity rate was largely due to nosocomial sepsis and surgical complications (anastomotic leaks, compulsory relooks post clip and drop surgery, and adhesiolysis for bowel obstruction) (19). The authors reported an overall mortality rate of 21% (19), which is significantly higher than the NECTARINE study.

NEC was found to be the most frequent indication for surgery with a mortality rate of 24% (19). Nosocomial sepsis was noted to be the main cause of mortality in 87% of cases (19).

Additional causes of mortality included disease progression, respiratory failure, pulmonary haemorrhage, multi-organ failure not due to sepsis and palliation (19). Anaesthesia related complications as a cause of morbidity or mortality were not studied or discussed.

The preferred location for surgical management of NEC is the emergency theatre (20). This is because it has been designed to facilitate an easy working environment for surgeons, anaesthesiologists, and nursing staff (20). However, the change of environment from the stable neonatal intensive care unit (ICU) to the unstable out of ICU environment, places added risk to the already vulnerable neonate (21-23).

The risk of adverse events during transportation of a neonate is as high as 20% (21, 22). Adverse events include equipment failure, extubation or bronchial intubation, ineffective mechanical ventilation, hypoxia, haemodynamic instability, accidental removal of intravenous access, and cardiopulmonary arrest (23, 24). Patients who are manually ventilated are also more likely to be hyperventilated with 62% of patients having end tidal carbon dioxide of less than 35mmHg (25).

In addition, adverse events specifically related to neonates include hypoglycaemia in 19% of cases and hypothermia in 27% of cases (21).

To avoid the adverse events that occur during intra-hospital transport of neonates, bedside surgery in the neonatal ICU could be considered. Performing procedures in the neonatal ICU has proven to be both safe and feasible and should be recommended in all unstable or ELBW neonates (26-34). Unfortunately, bedside surgery is not without its faults. A number of limitations to ease of surgery and anaesthesia do exist. Limitations within this environment include inadequate lighting, inadequate surgical access, a lack of inhaled volatiles for anaesthesia, limited space, and increased risk of infection (28). However, neonatal ICU equipment has improved in recent years and may aid in a better working environment, technology for transport monitors and ventilators has also improved and may influence the outcome of patient transport (35).

Only one South African study looking at outcome of surgical neonates was found, and the main focus of the study were surgical complications and sepsis related to morbidity and mortality (19). No other African studies related to patient profile of neonates undergoing emergency laparotomy, the anaesthetic management thereof, or the outcome of these procedures, could be found. The need for data in this area is apparent in order to provide appropriate patient care, specifically for the anaesthesiologist.

4.2 Problem statement

NEC is a common disease of neonates and often requires surgical intervention (1). The patient profiles and outcome of neonates undergoing surgical intervention for NEC has been documented in European counties (1, 2, 12). However, limited data is available regarding patient profile and outcome in African countries (19). In addition, no validated guidelines exist to advise the anaesthesiologist on appropriate anaesthetic management for these neonates (10, 11). This information is important in guiding anaesthesiologists, paediatric surgeons, and neonatologists with respect to peri-operative management of these patients, especially in resource limited countries.

4.3 Aim

The aim of this study is to describe the patient profile, anaesthetic management and outcome of neonates presenting for emergency laparotomy for NEC at a South African academic hospital.

4.4 Objectives

The primary objectives of this study are to:

- Describe the patient profile of neonates who have undergone an emergency laparotomy.
- Describe the type of anaesthetic, type and amount of resuscitative drugs, and blood products administered by the anaesthesiologist during the emergency laparotomy.
- Describe variations in physiological parameters noted during the emergency laparotomy (oxygen saturation, end tidal carbon dioxide, mean arterial pressure, heart rate, blood glucose, haemoglobin, core body temperature).
- Describe the 28-day mortality rate of neonates who have undergone an emergency laparotomy.

The secondary objectives of this study are to:

- Describe the association of the following surgical, anaesthetic and patient factors with 28-day mortality: physiological profile (gestational age, birth weight, inotropes), level of expertise of most senior surgeon, level of expertise of most senior anaesthesiologist, location of surgery, time of surgery, duration of surgery and number of relook laparotomies.

4.5 Research assumptions

Neonate: an infant in the first 28 days of life.

Outcome: alive or demised within 28 days of index laparotomy.

APGAR Score: a newborn health score developed in 1953 by Virginia Apgar. The score assesses the heart rate, respiratory effort, reflex irritability, muscle tone and colour of the newborn baby (36).

Sepsis: dysregulated response to infection leading to life-threatening organ dysfunction. Based on clinical parameters including new onset fever (more than 38.3C), new onset tachycardia (more than 160 beats/min), elevated white cell count, C-reactive protein or positive blood cultures.

Septic shock: occurs in a portion of patients with sepsis. Defined as hypotension (mean arterial pressure of 65mmHg) despite the use of vasopressors and elevated serum lactate (more than 2mmol/L) despite adequate hydration.

Metabolic Acidosis: accumulation of acids or loss of bicarbonate in the blood. Defined as a blood pH of <7.35.

Glucose instability: variations in blood glucose concentration, with episodes of either hypoglycaemia (Less than 2.5mmol/L) or hyperglycaemia (More than 7.0mmol/L) or both.

Levels of seniority for anaesthesiologists and paediatric surgeons:

- Medical officer.
- Junior registrar (0-2 years experience).
- Senior registrar (3-4 years experience).
- Specialist or career medical officer.

4.6 Demarcation of study field

The study will be conducted in the neonatal theatre complex and neonatal ICU of Chris Hani Baragwanath Academic Hospital (CHBAH) affiliated to the Department of Anaesthesiology and the Department of Paediatrics at the University of the Witwatersrand.

CHBAH is a 2888 bed central hospital. The hospital has 25 theatres of which one is a neonatal theatre. The neonatal ICU consists of 18 beds which all provide ventilated care.

4.7 Ethical considerations

4.7.1 Approval

Approval to conduct the study will be obtained from the Human Research Ethics Committee (Medical) and the Graduate Studies Committee of the University of the Witwatersrand before commencing the study.

Approval to conduct the study has been obtained from:

- Dr Mogane of Department of Anaesthesiology (Appendix A).
- Dr Nakwa, Head of Neonatal Intensive Care Unit (Appendix B).
- Professor Loveland, Head of Paediatric Surgery (Appendix C).

4.7.2 Informed consent

As this is a retrospective record review, no informed consent will be required.

4.7.3 Anonymity and confidentiality

In order to ensure anonymity and confidentiality, data will be collected using a study number without identifying information. A Microsoft Excel® spreadsheet containing the patients' name and hospital number linking them to a specific study number will be kept separately. Only the researcher and supervisors will have access to the raw data.

Data will be stored securely for six years after completion of the study on a password protected electronic database.

4.8 Research methodology

4.8.1 Research design

A retrospective, contextual, descriptive research design will be followed in this study.

A retrospective study implies that the information that will be collected has occurred before the study commenced (37). This study will obtain data from neonatal ICU death books, anaesthetic charts, and paediatric surgical notes that have already been completed.

A contextual study relates to a small-specified group (38). This study will focus on a small, specified group of neonates at CHBAH.A descriptive study describes variables: the researcher does not manipulate the variables or intervene in the outcome of the variable (37). This study will describe the patient profile of neonates, the anaesthetic management of the neonate and the 28-day mortality rate without manipulating the outcome.

4.8.2 Study population

The study population consists of all neonates presenting for exploratory laparotomy for NEC at CHBAH from 1 January 2019 to 31 December 2020.

4.8.3 Study sample

Sampling method: the sampling method was determined in consultation with a biostatistician. A purposive sampling method will be used (39). Purposive sampling allows for subjects to be selected based on the purpose of the study. Each subject selected will provide information of value to the study (39). In this study every neonatal record that fulfills the criteria for the study will be included in the sample.

Sample size: the sample size was determined in consultation with a biostatistician. As a purposive sampling method will be used, the sample size is dependant on the amount of data collected and not statistical power analysis (39). The sample size will be determined by the number of subjects that fit the criteria during the period 1 January 2019 to 31 December 2020. Using this time frame approximately 65 subjects will be included in the study.

Inclusion and exclusion criteria:

The inclusion criteria for this study are:

- Neonates within the first 28 days of life.
- Neonates presenting for exploratory Laparotomy for NEC.

The exclusion criteria for this study are:

- Neonates with incomplete or missing records.

4.8.4 Collection of data

Once the relevant departments have approved the study, data will be collected from CHBAH.

The neonatal theatre registry will be used to locate all neonates who have undergone a laparotomy during the time period 1 January 2019 and 31 December 2020. Each neonate will be assigned a study number, which will be recoded on a separate Microsoft Excel® spreadsheet (Appendix D). This will allow for the patient's details to remain confidential. Their details will only be used during collection of data and not during analysis of data.

The details of the neonate will be used to locate their anaesthetic charts from the anaesthesiology records department, their theatre notes from the paediatric surgery database and their 28-day mortality from the neonatal ICU death book.

Data will be collected and entered into the data collection sheet (Appendix E). The data collection sheet includes the following information.

- Demographics:
    - Day of life.
    - Birth weight and birth post-menstrual age.
    - Laparotomy weight and laparotomy post-menstrual age.
    - Mode of delivery.
    - 5-minute APGARS.
- Pre-operative clinical examination and investigations.
- Intra-operative type of anaesthetic, type and amount of resuscitative drugs and blood products.
- Intra-operative change in oxygen saturation, end tidal carbon dioxide, mean arterial blood pressure, heart rate, blood glucose, haemoglobin, and core body temperature.
- 28-day mortality rate.
- Level of expertise of most senior surgeon and anesthesiologist, location of surgery, duration of surgery, time of surgery, number of relooks and grade of NEC.

Data capturing will be done in the Department of Anaesthesiology at CHBAH. No records will be removed from the hospital premises.

4.8.5 Data analysis

All data will be entered onto a Microsoft Excel® spreadsheet and analysed in consultation with a biostatistician. The statistical programme STATA version 15 (STATACorp, USA) will be used.

Descriptive and inferential analysis will be done. Categorical variables will be described using frequency and percentages. Continuous variables which are normally distributed will be described using means and standard deviations and those not normally distributed using medians and interquartile ranges. Factors associated with 28-day mortality rate will be compared with logistical regression analysis.

A p-value of <0.05 will be considered statistically significant.

4.9 Significance of study

The results obtained from this study will provide information on the patient profile, anaesthetic management and outcome of neonates presenting for exploratory laparotomy for NEC at CHBAH. This data may assist anaesthesiologists, paediatric surgeons and neonatologists in improving the peri-operative management of neonates for exploratory laparotomy for NEC.

4.10 Validity and reliability of the study

Validity of the study is determined by how accurately the findings of the study reflect the variables that have been measured (40). Reliability of the study is determined by the ability to consistently repeat the variables that have been measured (32). To ensure the validity and reliability of the study, the following steps have been taken:

Appropriate study design.

- Data collected retrospectively to prevent change in practice by the anaesthesiologists, paediatric surgeons or neonatologists.
- Data collected by a single researcher.
- Data analysis in consultation with a biostatistician.

4.11 Potential limitations of the study

The study may be limited by the quality and completeness of records. As well as by difficulty obtaining the relevant information from different departments, specifically those that do not have electronic databases. The study will be conducted in a single centre. Some of the data collected (within the time period of 1 January 2020 to December 2020) may be influenced by the presence of Coronavirus pandemic as it could have an influence over patient assessment and management. The study is a retrospective, observational study and a randomized control trial may provide better data.

4.12 Project outline

	January to April	**May**	**June**	**July**	**August**	**September**	**October**	**November**	**December**
Proposal preparation									
Proposal submission									
Postgraduate approval									
Postgraduate corrections									
Ethics approval									
Data collection									
Data analysis									
Draft article									
Submission									

4.13 Financial plan

Costs for the study include printing costs. The Department of Anaesthesiology at the University of the Witwatersrand will incur the costs of the printing and paper.

Printing	Number of pages	Cost per page	Total
Postgraduate submission	125	R1	R125
Ethics submission	50	R1	R50
Final report	100	R1	R100
Total	**275**	**R1**	**R275**

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4.15 Appendices

Appendix A: Permission to conduct study from the head of department of anaesthesiology

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL
DIRECTORATE - ANAESTHESIA
Enquiries: Dr P. Mogane
Tel. number: (011) 933-9334
Email: Palesa.Mogane@wits.ac.za

Department of Anaesthesiology
Chris Hani Baragwanath Academic Hospital
PO Bertsham
2013
20th October 2020

To whom it may concern

RE: PERMISSION TO CONDUCT RESEARCH

This serves to confirm that I grant permission for Dr Natalie Botha to conduct research involving the Department of Anaesthesia at the Chris Hani Baragwanath Academic Hospital. The research topic is titled: **The profile and outcome of neonates presenting for exploratory laparotomy for necrotizing enterocolitis at a South African academic hospital.**

I'd like to wish her luck in this endeavor and I am happy to support her wherever possible.

Kind regards.

Dr Palesa Mogane
Chief specialist and Head of Department
Department of Anaesthesiology
Chris Hani Baragwanath Academic Hospital
University of Witwatersrand
Email: Palesa.Mogane@wits.ac.za

Appendix B: Permission to conduct study from the head of department of neonatal intensive care unit

Dear Dr Nakwa

My Name is Natalie Botha, I am a 2nd year registrar in anaesthesia. The topic of my MMed is to describe the patient profile of neonates presenting for emergency laparotomies in the emergency theatre and those presenting for bedside laparotomies in the Neonatal Intensive Care Unit. I will also be describing the changes in physiological status peri-operatively and 28day survival rate of these neonates. The study is retrospective and will include the period 1st January 2019 to 31st December 2019. The research is based on a study done in Australia in 1999 by Frawley et el.

In order for me to have a comprehensive picture of the patient profile of these neonates, as well as the peri-operative physiological status and 28day survival rate, I would need to review the neonate's intensive care unit chart, anaesthetic chart and surgical notes.

I would like to request permission from your department to have access to the neonatal intensive care charts for all neonates who have undergone a laparotomy during this period. I have attached a copy of the data collection chart, which I intend to use for record keeping, as well as the Frawley et al study. Your assistance in the matter will be greatly appreciated.

If you agree, please sign and date below.

Kind regards
Dr Natalie Botha

Nakwa I agree with the use of the files for the above research.

Appendix C: Permission to conduct study from the head of department of paediatric surgery



GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL
Directorate: Paediatric Surgery
Enquiries: Prof. J.A. Loveland
Tel. number: (011)933 8138; Email: Loveland@wol.co.za

28 January 2020

Dear Dr Botha,

RE: PROVISIONAL PERMISSION TO CONDUCT A STUDY

Your request to conduct a cross-sectional study titled **"The profile of neonates presenting for exploratory laparotomy for necrotizing enterocolitis at Chris Hani Baragwanath Academic Hospital"**, intended for your Ethics application, on Paediatric Surgery Patients at Chris Hani Baragwanath Academic Hospital is granted.

You therefore can obtain relevant information from patients' files once full Ethics clearance is obtained. Please be advised that you are to submit a full copy of your final protocol and final Ethics Clearance Certificate from Wits HREC before you are to commence data collection.

Regards,

Professor JA Loveland
Academic Head
Department of Paediatric Surgery
School of Clinical Medicine
University of the Witwatersrand

_28/01/2020___
Date

Appendix D: Data collection Excel spreadsheet for patient details

Study no.	Patient's Name	Patient's Hospital no.	Date of Laparotomy
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
13			
14			
15			

Appendix E: Data collection chart

PATIENT PROFILE										
Day of life										
PMA and weight at birth	weeks						Grams			
PMA and weight at surgery	weeks						Grams			
Mode of delivery:	NVD			Emergency c/s			Elective c/s			
5-minute APGARS	1	2	3	4	5	6	7	8	9	10

PRE-OPERATIVE EXAMINATION and INVESTIGATIONS				
Laboratory:	Glucose instability	Acidosis	Sepsis	
Ventilation	Nasal prongs	Venturi – mask	High flow	
	Ventilated (PS)	Ventilated (PC)	High Frequency Ventilation	
Inotropes	Adrenaline mcg/kg/min	Dobutamine mcg/kg/min	Dopamine mcg/kg/min	Noradrenaline mcg/kg/min

PERI-OPERATIVE ANAESTHETIC MANAGEMENT				
Inotropes	Adrenaline mcg/kg/min	Dobutamine mcg/kg/min	Dopamine mcg/kg/min	Noradrenaline mcg/kg/min
Vasopressors	Phenylephrine mcg/kg		Ephedrine mg/kg	
Blood products	Packed Red cells mls/kg	Fresh frozen plasma mls/kg	Platelets mls/kg	
Propofol based	Yes	No		
Opioid based	Yes	No		
Benzodiazepine based	Yes	No		
Ketamine based	Yes	No		
Inhalation agent based	Yes	No	Not available	

VARIATIONS IN PERI-OPERATIVE PHYSIOLOGICAL PARAMETERS				
Oxygen saturation (%):	At start:	At end:	Maximum:	Minimum:
ETCO2 (mmHg)	At start:	At end:	Maximum:	Minimum:
MAP (mmHg)	At start:	At end:	Maximum:	Minimum:
Heart rate (b/min)	At start:	At end:	Maximum:	Minimum:
Blood glucose	At start:	At end:	Maximum:	Minimum:
Haemoglobin	At start:	At end:	Maximum:	Minimum:
Temperature (C):	At start:	At end:	Maximum:	Minimum:

28-DAY MORTALITY RATE		
28-Day post-surgery	Alive	Demised

POSSIBLE FACTORS CONTRIBUTING TO 28-DAY MORTALITY RATE						
Most senior surgeon level of expertise	Consultant		Senior Registrar		Junior registrar	
Most senior anaesthesiologist level of expertise	Consultant		Senior registrar		Junior registrar	
Duration of surgery	Start time:		End time:		Minutes:	
Date of surgery						
Time of surgery						
Location of surgery	Neonatal theatre		Neonatal ICU			
Number of relooks						
Gestational age						
Grade of NEC	IA	IB	IIA	IIB	IIIA	IIIB

Section 5: Annexures

5.1 Ethics approval – Provisional approval

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

03 September 2020

To Whom It May Concern

SUBJECT: **CONFIRMATION OF PROVISIONAL STUDY APPROVAL**
(This letter is not a clearance certificate - not yet cleared)
Protocol Ref No: M200849
Protocol Title: The profile and outcome of neonates presenting for exploratory laparotomy for necrotising enterocolitis at a South African academic hospital
Principal Investigator: Dr Natalie Botha (du Plessis)
Department: Anaesthesiology

This letter serves to confirm that the Human Research Ethic s Committee (Medical) has provisionally approved the above mentioned study. In order for a clearance certificate to be issued, the researcher is required to submit written approval to conduct the study in your district/institution.

The researcher has been informed that this letter is not a clearance certificate and that the study cannot commence without your approval and receipt of a clearance certificate from the HREC (Medical).

Should you have any queries, you may contact me at tel: 011 717 1234/2700/2656 or by email Rhulani.Mkansi@wits.ac.za or HREC-Medical.ResearchOffice@wits.ac.za

Yours Faithfully,

Mr Rhulani Mkansi
Administrative Officer
Human Research Ethics Committee (Medical)

UNIVERSITY OF THE WITWATERSRAND
OFFICE OF THE DEPUTY VICE CHANCELLOR: RESEARCH
03 SEP 2020
RESEARCH OFFICE HREC (Medical)
JOHANNESBURG

5.2 Ethics approval – Amended approval

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG	HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

2021/09/27

Dr N Botha
School of Clinical Medicine
Department of Anaesthesiology
Medical School
University

Sent by e-mail to: natz.botha@yahoo.co.za

Dear Dr Botha

Re: **Protocol Ref No:** M200849
Protocol Title: *The profile and outcome of neonates presenting for exploratory laparotomy for necrotising enterocolitis at a South African academic hospital*
Principal Investigator: Dr N Botha

Thank you for your undated letter, received here on 2021/09/14.

I confirm that we have noted and approve of your proposal (a) not to use the SNAP score and (b) to extend the data collection window to 2020/12/31.

Thank you for keeping us informed.

Yours Sincerely

I. Burns

.....
Mr I Burns
For the Human Research Ethics Committee (Medical)

CB Penny

.....
Dr CB Penny, Chairperson, Human Research Ethics Committee (Medical)

5.3 Graduate studies approval

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Private Bag 3 Wits, 2050
Fax: 027117172119
Tel: 02711 7172076

Reference: Mrs Sandra Benn
E-mail: sandra.benn@wits.ac.za

04 October 2021
Person No: 0504727A
PAG

Dr N Du Plessis
955 North Riding
Randubrg
2158
South Africa

Dear Dr Natalie Du Plessis

Master of Medicine in Anaesthesia: Approval of Title

We have pleasure in advising that your proposal entitled *The profile and outcome of neonates presenting for exploratory laparotomy for necrotising enterocolitis at a South African academic hospital* has been approved. Please note that any amendments to this title have to be endorsed by the Faculty's higher degrees committee and formally approved.

Yours sincerely

Mrs Sandra Benn
Faculty Registrar
Faculty of Health Sciences

5.4 National health research data base approval

Proposal Details: GP_202011_044

GAUTENG HEALTH RESEARCH COMMITTEE

APPLICATION DETAILS

TITLE OF RESEARCH PROJECT

The profile and outcome of neonates presenting for exploratory laparotomy for necrotizing enterocolitis at a South African hospital

TYPE OF STUDY

Non-academic

STATUS OF APPLICATION

Pending (New Application)

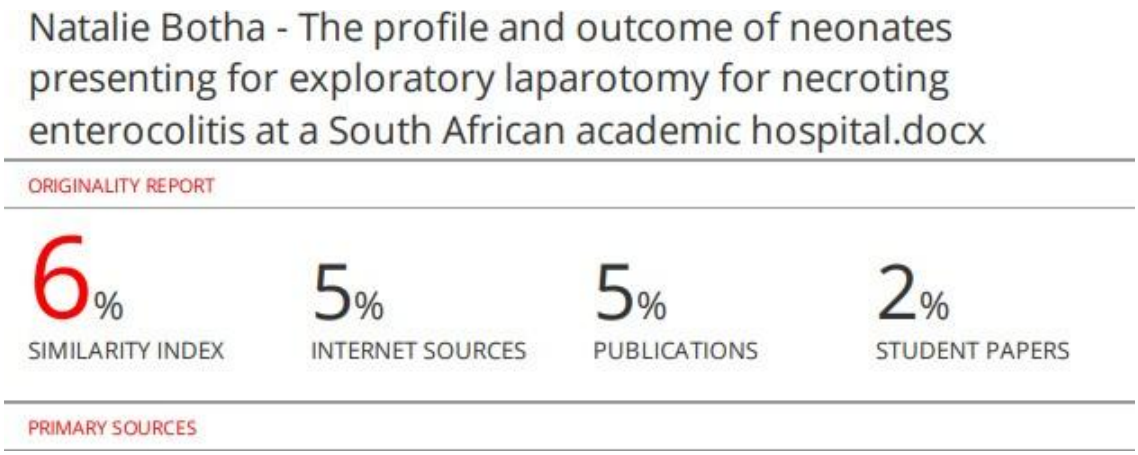
STATUS OF PROJECT

On-Going

PROPOSAL SUBMISSION DATE

2020/11/16

5.5 Turnitin report



Natalie Botha - The profile and outcome of neonates presenting for exploratory laparotomy for necroting enterocolitis at a South African academic hospital.docx

ORIGINALITY REPORT

6%	5%	5%	2%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

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