Impact of nighttime versus daytime emergency surgery on the outcome of necrotising enterocolitis

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by

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Declaration

I, Akhona Maud Mbonisweni hereby declare that the work on this dissertation/thesis is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university. I empower the university to reproduce for the purpose of research either the whole or any portion of the contents in any manner whatsoever.

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Abstract

Background
Necrotising enterocolitis (NEC) is the most common neonatal gastrointestinal surgical emergency, with a high mortality. We hypothesised that nighttime (NT) surgery was associated with higher mortality, intra-operative adverse events (AE) and post operative complications.

Objectives
To determine differences in mortality, intra operative AE and post operative complications between NT and DT surgery for NEC.

Methods
Patients with NEC (n=96) who needed surgical intervention (2015 - 2019) were retrospectively reviewed at a free-standing tertiary paediatric hospital. Differences in mortality, intraoperative AE, post operative surgical complications and length of intensive care unit stay were assessed for NT versus daytime (DT) surgery.

Results
Thirty-three patients (34.4%) were operated during NT. Demographics of the two groups were similar for gestational age, birth weight, sex, and age at operation. NT patients required increased inotropic support pre-operatively (p=.013) and had shorter time from diagnosis to surgical intervention (p<.001). Other preoperative characteristics (SNAPPE II score, haemoglobin, platelet count, C-reactive protein, and serum sodium) showed no statistically significant differences. Duration of anaesthesia and operative time were shorter at NT (p=.01 and p=.002 respectively). Red blood cell transfusion rates were higher at NT (p=.03). "Damage control" surgery was more common at NT (p=.01) and associated with 25% 30-day mortality compared to 33% for other patients (p=.03). Other operative characteristics and intra-operative AE were similar. Thirty-day mortality and enterostomy complications were higher for NT surgery (p=.02 and p=.013), while overall mortality and incidence of other post-operative surgical complications were not significantly different between groups. Longer duration of surgery collerated with increased risk of mortality for both DT and NT surgery (p=.009 and p=.023 respectively).

Conclusion
Patients operated at night required more inotropes and red cell transfusion, and had an increased 30-day mortality and post-operative enterostomy complications. The incidence of intraoperative AE and other post operative complications were similar between groups. A damage control mindset was more prevalent at NT and may reduce mortality. The time of day for surgery for NEC depends on acuity of disease and local resources. NT surgery was found to be as safe as DT surgery in our institution. Further research on damage control surgery outcomes and reduction of stoma complications is needed.

Abbreviations

- AE: adverse events
- CRP: C-reactive protein
- DT: daytime
- ICU: intensive care unit
- IQR: interquartile range
- LMIC: low- and middle-income countries
- NEC: necrotising enterocolitis
- NT: nighttime
- SNAPPE II score: score for neonatal acute physiology with perinatal extension II (see Appendix)
- WCC: white cell count
- RCWMCH: Red Cross War Memorial Children's Hospital

Definitions, terms, and parameters

Listed below are explanations of various parameters as well as definitions of terms used within the text.

- Daytime: The start of induction of anaesthesia between 08h00 till 17h59
- Nighttime: The start of induction of anaesthesia between 18:00 till 07h59
- Duration of operation: Time from skin incision to dressing application
- Anaesthetic time: Time from induction of anaesthesia to the time when patient is awake at the end of procedure, or when the child is taken off the operating table.
- Wound infection/dehiscence: documented retraction of laparotomy wound edges requiring dressing or other intervention including antibiotics or debridement or secondary sutured closure within 30 days of surgery
- Enteric stoma complications: stomas that require repeat surgical intervention e.g., retraction, stenosis, prolapse
- 30-day mortality: death within 30-day post-operative period
- Overall mortality: was the patient still alive at the end study period (follow-up ranged from 3 to 8 years)
- Anastomotic breakdown: need for relook laparotomy due to leak of enteric content after anastomosis
- Damage control surgery with clip-and-drop: resection of necrotic bowel, the viable bowel ends being clipped or ligated, and replaced in the abdomen with a planned second laparotomy performed 48 to 72 hours later
- Open and close: findings at laparotomy dictate no further surgical intervention is needed due to extensive bowel necrosis, with limited viable bowel length incompatible with life
- Desaturation: oxygen saturation level below 90% measured using transcutaneous saturation monitor
- Hypothermia: recorded intraoperative temperature of less than 36.5 degrees Celsius measured using an internal oesophageal probe
- Intra-operative inotropes: commencement of pharmacological inotropes during the surgical procedure

- Intraoperative transfusion: receiving more than 10ml/kg red blood cell concentrate intraoperatively
- Length of ICU stay: Stay at Red Cross War Memorial Children's hospital ICU until the child was deemed stable to transfer to the neonatal unit

Chapter 1

Introduction

Background

Necrotising enterocolitis (NEC) is a bacterial-mediated, dysregulated inflammatory process that affects the bowel of premature infants, leading to bowel necrosis. Sepsis management guidelines recommend urgent source control via laparotomy for perforated or necrotic bowel. Surgery and anaesthesia for babies with NEC is a high risk undertaking and challenging even in experienced hands. Data in other conditions suggests that surgery outside regular office hours is associated with poorer outcomes; this has not been assessed for NEC.

Necrotising enterocolitis

NEC is the most common severe neonatal gastrointestinal emergency, predominantly affecting premature infants. The incidence of NEC is 7% in very low birth weight babies (< 1500g), but it can also affect full term neonates(1). It is the most common cause of death in neonates undergoing surgery. The mortality for patients operated for NEC ranges between 10% to 40% and is higher in low-income countries(2).

The diagnosis of NEC rests on the signs and symptoms of sepsis and intestinal ischaemia. Early signs of NEC are non-specific, with specific signs only evident in advanced disease, making optimal timing for surgery difficult. To aid in the clinical diagnosis, Bell and colleagues developed a clinical staging system that combines physical findings, laboratory data, and radiographic evidence of NEC. Modified Bell Stage III indicates severe disease, with stage IIIb implying features of bowel perforation that requires surgical intervention to resect necrotic gut and for peritoneal cavity toilet(3). The intra-operative finding of extensive diseased bowel is associated with high morbidity and mortality(4).

The mortality risk associated with NEC has been studied extensively. Lower birth weight and low Abgar scores has been shown to be associated with increased risk of mortality(5). There are multiple other factors associated with increased mortality and these include laboratory investigations such as low serum haemoglobin, low white cell count, low platelet count, high serum lactate and high base excess as well as disease severity (amount of necrotic bowel) and associated congenital heart disease(6).

Optimal timing for exploration is after the development of necrosis, but before perforation occurs. This avoids surgery in neonates destined to recover with medical therapy but facilitates necessary intervention before complications of advanced intra-peritoneal sepsis ensue. Identifying this “window of opportunity” has proven to be extremely challenging. The main surgical approach is laparotomy with bowel inspection to identify and resect any necrotic areas(1). Some studies have shown the mortality to be as high as 86% in pan-intestinal disease, 39% in multifocal disease and 21% in focal disease(2). The aim of surgery for NEC is to remove necrotic bowel and evacuate peritoneal cavity contamination, with potential for diversion of the faecal stream if immediate restoration of gastrointestinal continuity is not feasible. Surgical control of sepsis is thus the focus of initial surgery.

Timing of surgery

The evidence is conflicting regarding the timing of surgery, urgent or emergency, and its effect on the incidence of intraoperative adverse events (AEs) and postoperative outcomes. The performance of a preoperative team during NT might be affected by human factors, including mental or physical fatigue. These factors may increase the risk of intraoperative AEs and post operative complications. Furthermore, fewer healthcare workers, clinicians with less experience, and compromised early postoperative care might all compromise quality with night-time surgeries(7). At night, there is the potential for poorer adherence to 'best practice' and guidelines, potentially leading to a higher incidence of perioperative AEs(7–9).

The updated Surviving Sepsis guidelines recommend that the anatomical diagnosis of infection requiring consideration for emergency source control should be sought and diagnosed or excluded as rapidly as possible, and that intervention should be undertaken for source control within the first 6 to 12 hours after diagnosis is made. It is important to be cognisant of the fact that most of the data is extracted from adult studies, due to the paucity of paediatric data, and that these recommendations cannot necessarily be extrapolated to paediatric care(10).

According to a large national database study in the United States of America, children undergoing common urgent surgical procedures during a weekend admission had a higher adjusted risk of death, blood transfusion, and procedural complications compared to those who were operated on during the weekdays(8). While the exact aetiology of these findings was not clear, the timing of surgical procedures should be considered in the context of systems-based deficiencies that may be detrimental to paediatric surgical care(11).

There is currently no literature on daytime versus night-time surgery in NEC. The effect of daytime versus night-time surgery may be less relevant in high income countries with high staff number resources but is of relevance in low- and middle-income countries (LMIC) with limited resources.

Anaesthesia in the neonate

Anaesthesia during the neonatal period is challenging, even in the hands of an experienced anaesthetist. The NEonate and Children audit of Anaesthesia pRactice IN Europe (NECTARINE) study reported a mortality as high as 3.2% in neonates undergoing anaesthesia, and that more than 25% of these patients had critical events requiring intervention(12). This risk is likely higher after hours when there is limited clinical staff and expertise, and possibly higher in LMICs.

In Europe, the "APRICOT study" of Incidence of severe critical events in paediatric anaesthesia reported that the incidence of severe peri-operative adverse events (AE) attributable to anaesthesia was 5.2%. The incidence of cardiovascular and respiratory critical events was significantly higher in neonates and infants, with neonates having the highest rate of cardiovascular complications. Prematurity was identified as a risk factor that increased the incidence of respiratory events 2-fold. An experienced anaesthetist decreases the risk of severe cardiac critical events by 2% per year of experience(13). There is no literature related to anaesthetic adverse events specific to NEC.

The South African Paediatric Surgical Outcomes Study (SAPSOS) showed an overall incidence of 15.9% in severe anaesthetic-related critical incidents, which is significantly higher than high income countries (HICs). Younger age, increased ASA PS (American Society of Anaesthesiology Physical Status), urgent/emergent surgery, preoperative respiratory infection, severity of surgery and chronic respiratory comorbidities were all independent risks for severe anaesthetic- related critical incidents(14).

Anaesthesia and surgery may be prolonged if an anaesthetist or surgeon is inexperienced, leading to prolonged anaesthetic exposure, and increased risk of surgical complications. Exposure of the developing brain to anaesthetic volatile agents may increase the incidence of behavioural and developmental difficulties, with duration of exposure postulated to have a positive correlation(15).

The neonate presenting for urgent major surgery is therefore considered to be at high risk and raises concerns about anaesthesia after-hours when staffing may be constrained, and fatigue is a consideration. It is therefore important that decisions regarding timing for surgery are made in accordance with the patients' clinical condition and available resources.

Data is needed regarding the outcome for night-time surgery in comparison to daytime surgery in the neonatal population in South Africa. This will inform timing of surgery to decrease morbidity and mortality.

Purpose of study

This study compared outcomes between daytime and nighttime surgery for necrotising enterocolitis, looking specifically at mortality, intraoperative adverse events, and post-operative complications in a tertiary referral hospital in South Africa.

Chapter 2

Methods

Objectives

1. Primary objective:

To evaluate difference in post operative mortality in patients with necrotising enterocolitis (NEC) operated on during the nighttime (NT) compared to those operated during the daytime (DT) at Red Cross War Memorial Children's Hospital (RCWMCH) over a five-year period.

2. Secondary objective:

To assess the incidence of intra-operative AE, post-operative complications, ICU stay and the time from diagnosis to surgical intervention in the above population.

Study design

The study was a retrospective review of patients' medical records for a period of 5 years, from 1 January 2015 until 31 December 2019. Patients were classified into two groups: those who underwent surgery during the daytime (08h00-17:59) and nighttime (18:00-07:59). Baseline characteristics and outcomes were compared.

Source of data

Data was collected from the following:

1. Paediatric Surgery Division's operative database (names, dates of birth, folder numbers, operation dates, type of operation)
2. Patient medical records (demographics, clinical risk factors for disease severity, gestational age, length of ICU stay, post operative care and post operative complications)
3. Anaesthetic records (induction and duration of anaesthesia, intraoperative AE, duration of surgery)
4. Red Cross War Memorial Children's Hospital Intensive Care Unit discharge summaries
5. Referring Neonatal Intensive Care Units records
6. National Health Laboratory Service (NHLS) records
7. Picture Archive and Communication System ("PACS") Radiological database (radiological evidence of bowel obstruction or perforation)
8. Department of Western Cape Clinicom administrative database (date of demise if not at RCWMCH)

The following data was assessed:

1. Demographics
- Age
- Sex
- Gestation age
- Birth weight
- Age at operation

2. Preoperative characteristics
- SNAPPE II score (described in Appendix)
- Preoperative pharmacological inotropic support
- Preoperative sodium level on day of surgery
- Preoperative platelet count on day of surgery
- Preoperative haemoglobin on day of surgery
- Preoperative CRP on day of surgery
- Preoperative WCC on day of surgery
- Time lapse from arrival to Red Cross Hospital to start of anaesthesia

3. Operation characteristics and intraoperative adverse events at index operation
- Duration of anaesthesia
- Duration of surgery
- Types of surgical intervention- is the surgery done at the index operation
    - Open and close
    - Damage control surgery with “clip and drop”
    - Stoma creation
    - Bowel anastomosis
- Last intraoperative measured blood lactate level
- Intraoperative adverse events
    - Hypothermia
    - Oxygen desaturation
    - Intra-operative Transfusion > 10ml/kg red cell concentrate
    - Initiation of intraoperative pharmacological inotropic support to maintain MAP for age

4. Post-operative outcome
- 30- day mortality
- Overall mortality
- Stoma complication after index operation
- Wound sepsis after index operation
- Anastomotic breakdown after index operation
- Length of ICU stay
- Total number of abdominal operations

Inclusion criteria:

Neonates diagnosed with necrotising enterocolitis who underwent exploratory laparotomy during the study period.

Exclusion criteria:

Patients with inadequate data available from medical records; patients greater than 44 weeks corrected gestational age at time of index surgery; patients with delayed presentation >72 hours from time of presentation with Bell Stage III NEC including patients with post-NEC strictures.

Data collection and storage:

Retrospective data was collected and stored electronically in a password-protected database. Data was anonymised, each patient assigned a study number, and no identifying data e.g., name and surname or hospital number. All data used was routinely collected information used in the management of these patients. Access to information was restricted to study personnel.

Statistical Data Analysis:

Data was analysed with IBM SPSS Statistics Data Editor (version: 28.0.1.0(142) using Shapiro-Wilk test to test for normality. Non-parametric data was summarized by median and interquartile range (IQR) values. Parametric data was analysed using student's T test and nonparametric data was analysed using the Mann Whitney U and Chi square tests for continuous and categorical data respectively. P value < 0.05 was considered statistically significant.

Ethical consideration:

This research protocol was approved by Human Research Ethics Committee (HREC) at the University of Cape Town and was carried out according to internationally-accepted ethical standards and guidelines (University of Cape Town HREC approval number 527/2021).

Motivation for waiver of informed consent from patients:

This is routinely collected data needed for patient management; no caregiver/patient interaction was necessary for data collection. All information extracted was stored in a excel database and access restricted to the investigators and password protected. Consent for data collection was obtained from the medical manager and RCWMCH research and ethics committee after ethical approval.

Privacy and confidentiality:

Data was held securely with access restricted to study investigators only, and anonymisation of data to protect patient confidentiality. A study number connecting data to the relevant patient record numbers was stored separately from the database under password protection.

Chapter 3

Results

A total of 118 patients underwent surgery during the study period, but complete data was only available for 96 patients (81%), who were then included in the study. There were 63/96 (65.6%) patients operated during DT, and 33/96(34.4%) patients operated during the NT.

1. Demographics

Demographics of the cohort are summarised in table 1.

Sex

The total cohort comprised 57/96 males (59.4%). The DT surgery group had a preponderance of 42/63(66.7%) males while the NT surgery group was made of 15/33(45.5%) males. There was no significant sex difference between DT and NT (p=0.05).

Birth weight

The median birth weight of the cohort was 1365g and was similar between the two groups, with DT surgery group being 1300g and NT surgery group being 1400g.

Gestational age

Gestational age (GA) was under 37 weeks in 91/96 (94.7%) with 5/96 (5.3%) being term babies. The median GA was 31.0 weeks for the cohort with DT surgery group gestational age being 30 weeks and NT surgery group gestational age being 31 weeks. There was no significant difference in the gestational age between the two groups (p=0.38).

Age at operation

Median age at operation between the two groups was similar (p= 0.36), with age at operation for DT surgery group and NT surgery group being 8 days and 7 days respectively.

Table 1: Demographics

Variable		Total = 96	Daytime	Nighttime	P value
Sex (males)		57/96 (59.4%)	42/63 (66.7%)	15/33 (45.5%)	p=0.05
Birth weight (g)	Median	1365.0	1300.0	1400.0	p=0.50
	IQR	1041.2- 1812.5	980-1980	1190-1785	
Gestational age (weeks)	Median	31.0	30	31.0	p=0.38
	IQR	28.2- 33.0	28-34	29.0- 33.0	
Age at operation (days)	Median	8	8	7	p=0.36

	IQR	4- 23	4-29	4-10	

2. Preoperative characteristics

Preoperative characteristics of the cohort are summarised in table 2.

Preoperative inotropic support

There were 23/96 (24%) patients in the whole cohort who received inotropes. Only 10/63 (15.9%) patients in the DT surgery group had inotropes compared to 13/33 (39.4%) in the NT surgery group, a significant difference (p=0.013).

SNAPPE II score

The median SNAPPE II score was 22 for the whole cohort, with no significant difference in median scores in the DT versus NT surgery groups (p=0.39). However, 26/96 (29%) of the cohort had SNAPPE II score above 38 indicating an increased risk for mortality(16). 30-day mortality was seen in 12/26 (46%) of these patients.

White cell count

The preoperative white cell count was a median of 7 $x10^9$/L for the cohort with no significant difference between the two groups (p=0.30).

C reactive protein

The median preoperative CRP was 72.5 mmol/L for the cohort, with a median daytime surgery group value of 75mmol/L and median nighttime surgery group value of 65mmol/L. This difference was not significant (p=0.70).

Haemoglobin

The median preoperative level for haemoglobin was 12g/dl in the whole cohort with no significant difference between the groups (p=0.24).

Platelets

The median preoperative value for platelets was 106 $x10^9$/L in the cohort, with daytime surgery group values being 129 $x10^9$/L and nighttime surgery group values being $61x10^9$/L but no statistically significant difference between the two groups (p=0.20).

Time from arrival at Red Cross Hospital to surgery

The median time from arrival to Red Cross to surgical intervention was 8 hours for the cohort, with the DT surgery group taking 11 hours and NT surgery group taking a significantly shorter time of 4 hours (p<0.001).

Sodium

The median preoperative value of serum sodium was not significantly different (p=0.17) between the two groups and was 133 mmol/L for the cohort.

Table 2: Preoperative characteristics

Variables		N=96	Daytime	Night- time	P value
Pre op inotropes		23/96 (24.0%)	10/63 (15.9%)	13/33 (39.4%)	p= 0.013
SNAPPE II score	Median	22	22	23	p=0.39
	IQR	16- 40	16-35	14- 42	
WCC ($x10^9$/L)	Median	7	6	9	P=0.30
	IQR	3- 13	3-14	4-13	
CRP (mg/L)	Median	72.5	75	65	p=0.70
	IQR	30.0- 163.0	22-184	32- 118	
Haemoglobin (g/dl)	Median	12.0	12	12.0	p=0.24
	IQR	10.0- 14.7	9.0- 14.0	11.0- 15.0	
Platelets ($x10^9$/L)	Median	106	129	61	p=0.20
	IQR	41- 220	52- 217	40-254	
Time from arrival to operation(hrs)	Median	8	11	4	p<0.001
	IQR	3- 14	5-16	2- 5	
Sodium (mmol/L)	Median	133	134	131	p=0.17
	IQR	130-136	131-136	128- 135	

3. Procedure characteristics and intraoperative adverse events

Procedure characteristics and intraoperative adverse events of the cohort are summarized in table 3.

All of the surgical interventions were done with both an anaesthetic and paediatric surgery consultant in theatre. A sub-analysis of years of experience of the consultant was however not performed.

Duration of anaesthesia

The median duration of anaesthesia was 160 minutes; it was 180 minutes for the daytime group, but significantly shorter for the nighttime group, only taking 140 minutes (p= 0.01).

Duration of surgery

The median duration of surgery was 85 minutes, with DT surgery being longer at 90 minutes and significantly shorter for NT being only 70 minutes (p= 0.002).

Last intraoperative lactate level

Measured blood serum lactate was a mean value of 4.7mmol/L in the cohort with no statistical significance between the two groups.

Type of surgery- for procedures done at index laparotomy

Primary anastomosis

Primary anastomosis was undertaken as an initial procedure in 26/96 (27%) of the cohort. It was more commonly performed in DT surgery at 20/63 (31.7%) versus 6/33 (18.2%) in the NT group (p=0.23).

Stoma

Enteral stomas were created as an initial procedure in 35/96 (36,5%) of the cohort. This was done 23/63 (41.3%) in the DT group and 9/33 (27.3%) patients in the NT group (p=0.12).

Damage control surgery with 'clip and drop'

'Clip and drop' was performed in 24/96 (25%) of patients and were performed more frequently in the NT group compared the DT group [(13/33 (39.4%) vs 11/63 (17.5%)] (p=0.01).

"Open and close"

"Open and close" non-therapeutic laparotomy was performed in 11/96 (11.5%) of the cohort, 6/63 (9.5%) in the DT group and 5/33 (15.2%) in the NT group (p=0.30).

Intraoperative adverse events

The risk of intraoperative adverse events (see table 3 below) was not significant between groups. The incidence of hypothermia was 41/95 (43%), with no significance between the NT and DT group(p=0.82). Desaturation was similar amongst the DT and NT groups (11/62 (17.7%) and 5/33 (15.2%) respectively), with no statistical significance (p=0.97). Use of intraoperative inotropes support was higher in the NT surgery group 17/33 (51.5%) compared to DT surgery group 20/62(32.2%) but this difference was not of statistical significance (p=0.05). Intraoperative red cells transfusion was seen in 66/95 (69.4%). This happened more commonly in the NT group 27/33 (84.4%) when compared to the DT group 39/62 (62.9%) and was of significance (p=0.03).

Table 3: Procedure characteristics and intraoperative adverse events

		Cohort	Daytime	Night- time	P value
Duration of anaesthesia (mins)	Median	160	180	140	**p=0.01**
	IQR	120- 210	138-236	100-185	
Duration of surgery (mins)	Median	85	90	70	**p=0.002**
	IQR	60- 120	60-136	45- 90	
Intraoperative adverse events	Hypothermia	41/95(43%)	26/62(41.9%)	15/33(45.5%)	p=0.82
	Desaturation	16/95(16.7%)	11/62(17.7%)	5/33(15.2%)	p= 0.97
	Transfusion	66/95(69.4%)	39/62(62.9%)	27/33(84.4%)	**p=0.03**
	Inotropes	37/95(38.5%)	20/62(32.3%)	17/33(51.5%)	**p= 0.05**
Last intraoperative lactate (mmol/L)	Mean	4.7	4	4	p=0.30
	IQR	4.1-5.3	2-6	3-7.75	
Primary anastomosis		26/96 (27.0%)	20/63 (31.7%)	6/33 (18.2%)	p= 0.23
Stoma		35/96 (36,5%)	26/63 (41.3%)	9/33 (27.3%)	p=0.12
Damage control with Clip and drop		24/96 (25.0%)	11/63 (17.5%)	13/33 (39.4%)	**p=0.01**
Open and close		11/96 (11.5%)	6/63 (9.5%)	5/33 (15.2%)	p=0.30

4. Outcomes

Outcomes of the cohort are summarised in table 4.

30-day post-operative mortality

The 30-day mortality was seen in 27/96 (28.1%) in the cohort. This was seen 13/63 (20.6%) in the DT group and significantly higher in the NT group 14/33 (42.4%) (p=0.02). After excluding patients who were palliated for pan-necrosis [DT group 6/63 (9.5%) and NT group 5/33 (15.2%)] mortality for damage control "clip and drop" surgery was associated with a lower 30-day mortality seen in 7/27 (25.9%) compared to 9/27 (33.3%) of the patients who didn't undergo damage control surgery with 'clip and drop'. This was however not of statistical significance (p=0.3). Post-hoc power analysis of the study for 30- day mortality was 61.3%.

Overall mortality

The overall mortality was 39/96 (40.6%). It was 22/63 (34.9%) in the DT group and 17/33 (51.5%) in the NT group. This was not statistically significant (p=0.08).

Total number of abdominal operations for each patient

The median number of abdominal operations was 2, being the same for both DT and NT surgery group (p=0.76).

Length of ICU stay

The median length of ICU stay was 7 days but was shorter in the NT group with median length of stay being 5 days compared to 7 in the DT group (p=0.50).

Postoperative complications

Wound sepsis

The rate of wound sepsis was 11/96 (11.5%) overall. It was 6/63 (9.5%) in the DT group and 5/33 (15.2%) in the NT group, not significantly different (p=0.30).

Stoma complications

Stoma complications were seen in 9/35 (25.7 %) in patients who had enterostomies. This was 4/26 (15.3%) in the DT group, and significantly more at 5/9 (55.5%) in the NT group (p=0.013).

Anastomotic leak

The incidence of anastomotic leaks was 2/25 (8%) in the cohort, with 2/19 (10%) seen from the DT group and none in the NT group (p=0.4).

Table 4: Outcomes

		Cohort (n=96)	Daytime	Nighttime	p value
30-day mortality		27/96 (28.1%)	**13/63 (20.6%)**	**14/33 (42.4%)**	**p=0.02**
Overall mortality		39/96 (40.6%)	22/63 (34.9%)	17/33 (51.5%)	p=0.08
Total number of abdominal surgeries	Median	2	2	2	p=0.76
	IQR	1-3	1-3	1-3	
Wound sepsis		11/96 (11.5%)	6/63 (9.5%)	5/33 (15.2%)	p=0.30
Stoma complications		9/35 (25.7%)	**4/26 (15.3%)**	**5/9 (55.5%)**	**p=0.013**
Anastomotic leaks after PA		2/25 (8%)	2/19 (10.5%)	0/6 (0%)	p=0.4
Length of ICU stay (days)	Median	7	7	**5**	p=0.5
	IQR	3-14	4-14	**3-14**	

On multivariate analysis there was a strong association between length of operative procedure and 30-day mortality and overall mortality. Preoperative inotropes and blood transfusion were not deemed independent and so were duration of anaesthesia and duration of surgery. Longer duration of surgery was associated with increased mortality for both DT (p=0.014) and NT (p=0.025) surgery. This further highlights the role of damage control surgery in NEC.

Table 5: Logistic regression on 30-day mortality

30 day mortality		Daytime			Nighttime		
Characteristics		OR	95% CI	p- value	OR	95% CI	p- value
Arrival to surgery		0.96	0.84,1.08	p= 0.5	1.00	0.77,1.25	p= >0.9
Duration of surgery		0.98	0.96,0.99	**p= 0.014**	0.96	0.93,0.99	**p= 0.025**
blood transfusion	Yes	2.99	0.72,16.3	p= 0.2	1.02	0.10,9.91	p= >0.9
	No	-	-	-	-	-	

OR- odds ratio; CI- confidence interval

Table 6: Logistic regression on overall mortality

Overall mortality		Daytime			Nighttime		
Characteristics		OR	95% CI	p- value	OR	95% CI	p- value
Diagnosis to surgery		0.97	0.87, 1.07	p= 0.5	1.12	0.99, 1.47	p= 0.3
Duration of surgery		0.98	0.97, 0.99	**p= 0.009**	0.97	0.93, 0.99	**p= 0.023**
blood transfusion	Yes	1.27	0.40, 4.24	p= 0.7	0.98	0.09, 9.45	p= >0.9
	No	-	-	-	-	-	

OR- odds ratio; CI- confidence interval

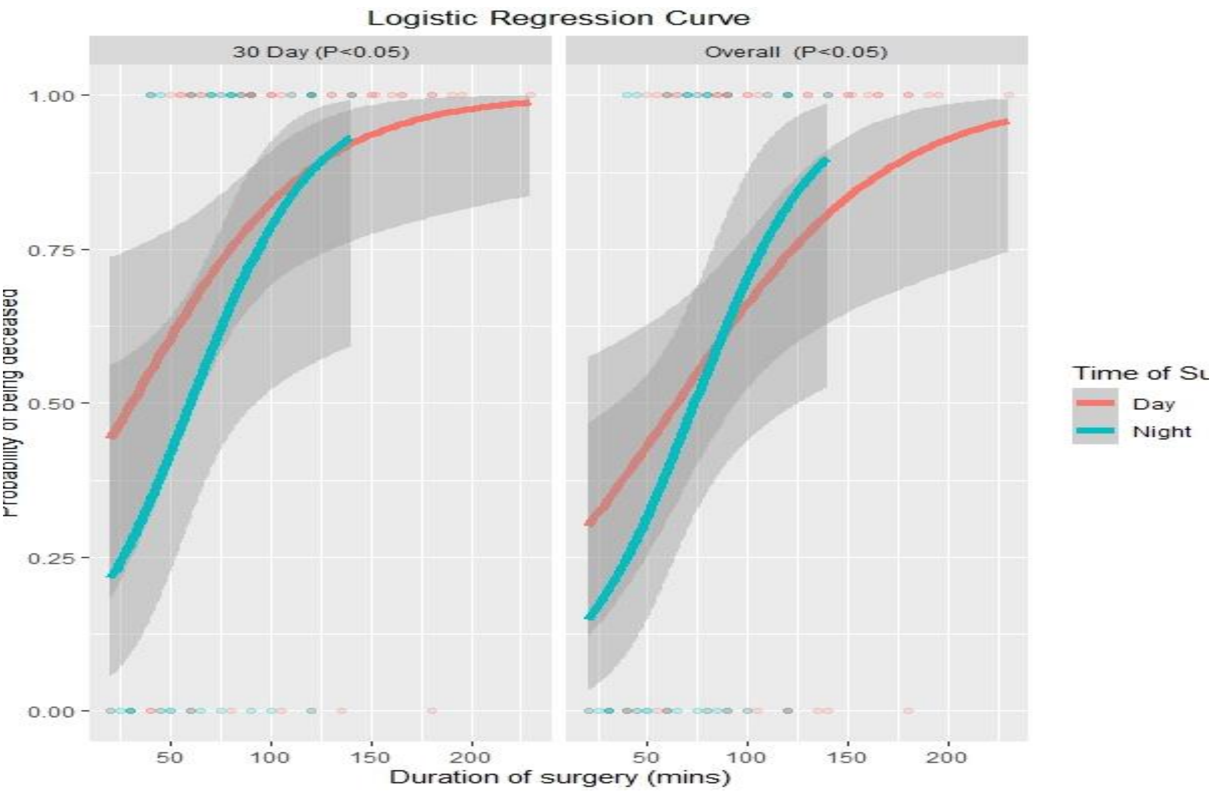

Figure 1: 30 day and overall mortality relative to duration of surgery for DT compared to NT surgery

Chapter 4

Discussion:

NEC remains a challenging disease for paediatric surgeons and anaesthetists. Critical questions regarding surgical care remain unanswered after over 30 years of research. These include: optimal timing for operative intervention, and recommendation for specific surgical techniques. This study of the impact of the time of day on NEC surgical outcomes is the first of its kind.

The demographics of the two groups were similar. Many of the patients were males with a median birth weight of 1365g. Most of our patients were premature (94.7%; median GA 31 weeks), with median age at surgery for NEC towards the end of the first week after birth for both the daytime and nighttime groups, making them a high risk for both anaesthetic and surgical intervention.

The baseline preoperative characteristics were similar except for a trend towards lower platelet count and higher use of preoperative inotropes in the NT group. Median platelet count in the nighttime group was less than half that of the daytime group ($p=0.2$). NT patients were significantly more likely to require pre-operative inotropic support, compared to a DT patient. These indicate that the children in the NT group were sicker compared to DT counterparts, despite the median SNAPPE II score being the same for both groups.

The time from arrival at our institution to the operating room was significantly longer for the DT surgery group compared to the NT surgery group - 11 hours vs 4 hours respectively. This suggests that the neonates in the DT group waited overnight for the surgical intervention or transport during daylight hours. This may be attributed to the clinical condition as they appeared more haemodynamically stable preoperatively and therefore negating the need for surgery at night. Even though these patients waited longer for surgical intervention, there was no increased mortality in the DT group.

Critical adverse events requiring an intervention occurred in 41.9% in our study. The initiation of intraoperative inotropic support to maintain blood pressure was seen more commonly in the NT group. This is most likely because these children were sicker, as suggested by the increased thrombocytopenia and pre-operative need for inotropic support in the NT group.

Hypoxic events were similar between DT and NT groups but timing of desaturation (e.g. whether at induction of anaesthesia or during surgery) was not specifically documented. Hypothermia was common and was similar between groups. The high rate of perioperative hypothermia is concerning as it is associated with increased risk of acidosis and apnoea, increased oxygen consumption, altered pharmacokinetics, decreased action of various enzyme systems, impaired coagulation, and platelet function, and increased risk of wound sepsis and cardiac arrhythmias. This results in increased risk of bleeding and the potential for increased blood transfusion. Active preventative and therapeutic measures are undertaken to prevent and treat hypothermia; which include wrapping the neonates' arms and legs with padding material, putting the baby on a forced-air warming blanket, covering the whole baby with plastic except over the abdomen, using warmed intravenous fluids and blood products and warmed saline for peritoneal irrigation. The high incidence of hypothermia in our study suggests that more focus needs to be placed on strict adherence to these measures throughout the procedure, with an emphasis on minimising anaesthesia and surgical time.

There was a large discrepancy between the surgical and anaesthetic times. The time from onset of anaesthesia to time of surgical incision was protracted, irrespective of the time of day. This is due to multiple reasons; the insertion of central venous catheters and arterial lines is performed by the anaesthetic team after induction of anaesthesia, and surgical preparation of the operating field is also done after the lines have been inserted. These procedures then result in the patient being under anaesthesia for much longer than the surgical intervention.

There is no consensus on the most appropriate surgical technique for the management of NEC. Traditionally, resection of compromised bowel and proximal diverting enterostomy with or without mucous fistula has been performed. Enterostomy was commonly performed in the DT group, compared to more damage-control laparotomy with "clip and drop" at NT. Damage-control laparotomy may improve survival, as seen by a trend towards lower 30-day mortality, especially in NT where patients are typically more haemodynamically unstable; more research is required to evaluate this.

Enterostomy increases the risk of fluid and electrolyte imbalance, poor weight gain, and stoma complications such as prolapse, retraction and peristomal excoriation(17). All patients with enterostomies require further surgery, either to manage complications, or for closure of the enterostomy. Complications related to enterostomies were seen more commonly in the NT group and 10/35 (28%)of patients who had enterostomies died during the study period. It is unclear if these deaths were related to stoma complications, sepsis or complications related to prematurity.

In our institution, almost all patients who have enterostomies created have a distal mucus fistula created at the same time. This helps to initiate distal fistuloclysis in the postoperative period to address high enterostomy losses, use the distal bowel and aid weight gain, since the whole bowel length is involved in absorption of fluid and nutrients. Fistuloclysis is beneficial in allowing faster weaning off parenteral nutrition, maintains fluid and electrolyte balance and matures the distal bowel(18).

Damage control laparotomy with 'clip and drop' was performed more commonly at NT. This indicates a damage-control mindset during nighttime surgery, which is most likely due to the clinical condition of this group of patients. 'Clip and drop' is an accepted surgical strategy for the management of multifocal NEC or the child who is clinically unstable for extensive surgery. The 'clip and drop' procedure did not seem to increase the number of abdominal operations per patient in the NT group. More research is needed to know to what degree 'clip and drop' allows for future anastomosis at relook or improves survival.

Primary bowel anastomosis has been described after intestinal resection without diversion and has been shown to have better outcomes when compared to enterostomy formation(19). The decision to perform a resection and primary anastomosis versus resection and enterostomy is based on the surgeon's preferences, intraoperative findings and the patient's clinical condition. Primary anastomosis was performed more commonly during the day compared to night, but this difference was not of statistical significance. However, this trend may point to a more stable daytime population where primary anastomosis is considered less risky for anastomotic leak. This approach has the added advantage of fewer complications associated with enterostomies, such as peristomal dermatitis, prolapse, fluid and electrolytes disorders, and poor weight gain as well as the need for a second procedure to close the enterostomy.

Anastomotic leak needing surgical intervention was found in 8% of our patients who had primary anastomosis, which was lower than the complication rate for enterostomy. None of the patients with anastomotic leak died during the study period, and the leak was managed with resection and primary anastomosis in most cases, while some patients had enterostomies. Primary anastomosis should be considered in patients who are haemodynamically stable.

Our hypothesis that 30-day mortality was increased for patients undergoing NT surgery was confirmed in this study. The higher 30-day mortality in the NT group is likely because these patients are sicker, as evidenced by higher baseline inotropic requirements, and increased intra-operative red cell transfusion. Red cell transfusion has been found to be associated with increased mortality in preterm neonates(20). The most commonly occurring intraoperative adverse event (69.4%) was the need for red cell transfusion greater than 10ml/kg. This was significantly higher in the group who had surgery at NT. These baseline characteristics help explain why damage control surgery was more than twice as common at night. This in turn led to decreased anaesthetic and surgical duration. Surgical duration was the only significant factor associated with mortality on multivariate regression, a factor that both reflects the extent of disease and peritoneal soiling as well as choice of surgical approach.

While increased overall long-term mortality persisted in the NT group, this trend was not of statistical significance. This could be due to earlier surgical sepsis source control in the NT group, as indicated by decreased time from diagnosis of pneumoperitoneum to the start of surgery, mitigating the illness severity in the NT group. It would also be interesting to investigate the late cause of mortality in these children, whether related to complications of short bowel syndromes or other childhood diseases. More research is needed to clarify why 30-day mortality, but not overall mortality, was of statistical significance between groups, as it could also be an effect of small sample size.

Our 30-day mortality rate of 28% is very similar to other studies for surgical NEC, conducted in HICs, with some studies having mortality rates as high as 35% for patients who undergo surgery(21). Due to our institution being a dedicated children's hospital without an attached maternity unit, only neonates stable for transfer can be operated. Furthermore, current government policy restricts access to surgery for extreme low birth neonates with birth weights <1000g, unless born within a tertiary institution. This led to only 20% of our cohort being of extreme low birth weight, limiting generalisation of our findings to this population group. Patients with presentation of Bell stage III NEC beyond 72hours from diagnosis at base hospital to surgery were excluded to avoid bias from delayed surgical source control of sepsis.

There was a trend towards a longer median ICU stay in the DT group. Length of ICU stay in turn correlated with increased mortality and may explain the reduced difference in overall compared to 30-day mortality. Larger studies are needed to assess the impact of time from diagnosis to surgery on length of ICU stay. Wound sepsis was seen more frequently in patients who had enterostomies at their index operation, highlighting the complications associated with enterostomy. More research is needed on factors impacting sepsis control in this vulnerable population, including aspects already mentioned such as time to surgical source control, and impact of intra-operative blood transfusion and hypothermia.

Aside from enterostomy complications, intraoperative AE, and post-operative complications were similar between groups, suggesting that NT surgery for NEC is as safe in our institution as DT surgery. This should be interpreted with caution and cannot be generalised to other institutions, where availability of experienced staff may be more limited at NT. The number of intraoperative adverse events in our study varied from 16% to more than 70%, highlighting that neonatal anaesthesia for urgent major surgery is a risky undertaking, irrespective of the time of day, and even in high income countries(13,22).

Chapter 5

Conclusion

5.1 Summary of key findings

About a third (34.4%) of our patients with NEC were operated during NT. Baseline demographics of DT and NT groups were similar for gestational age, birth weight, sex, and age at operation. Patients operated at NT were more haemodynamically unstable with increased pre-operative inotropic support (p=.013) and increased intraoperative red cell transfusion(p=.03). Other preoperative characteristics (SNAPPE II score, haemoglobin, platelet count, C-reactive protein, and sodium) were similar between groups. Time from presentation at our institution to surgical intervention was shorter for the NT surgery group (p<.001). Damage control surgery with "clip-and-drop" procedures were more common at NT (p=.01) while other operative characteristics and intra-operative AE were similar. Duration of anaesthesia and operative time were shorter at NT (p=0.01 and p=0.002 respectively). 30-day mortality and enterostomy complications were higher for NT surgery (p=0.02 and p=0.013) while overall mortality and other post operative surgical complications were similar. Duration of surgery collerated with risk of mortality for both DT and NT surgery (p=.009 and p=.023 respectively).

There is inadequate data from this small retrospective study to fully answer how long it is safe to wait for surgery in patients with perforated NEC however this study confirms that expediting surgery to be done at nighttime is safe in our institution. The study raises potential research topics for future large multicentre prospective studies on timing for surgery for NEC and outcomes.

5.2 Strengths of the study

This is the first study looking at outcomes for NEC comparing nighttime and daytime surgery. The study has identified a significant impact of damage control surgery on the initial operative and anaesthetic time for these vulnerable and critically ill neonates, highlighting the usefulness of this approach. This study has identified this as a point for further research as total anaesthetic exposure for these neonates and impact on neurodevelopment is unknown. The information is valuable in local decision-making, knowing that intra-operative adverse events and post-operative complications are similar between nighttime and daytime surgery.

5.3 Weaknesses of the study

Due to poor record keeping and lost records in a paper-based system, complete data was only available for 80% of patients during the study period. A future prospective study will be beneficial; however, this has ethical challenges.

This study has the inherent limitation of a retrospective study including decision making for NT surgery may be biased by easily measurable patient clinical features and intraoperative decision making may not have been done in a systematic manner and was based on individual surgeons.

As RCWMCH is a free-standing hospital and all the neonatal units are not within the premises, this excludes patients who are clinically unstable for transfer and those patients who do not meet the provincial guidelines in term of birth weight(<1000g).

The SNAPPE II score is not designed specifically for NEC but rather a mortality score that has been used and validated in the neonatal intensive care unit. It only looks at the haemodynamic of the patients in the 1st 12 hours and doesn't account for haemodynamic changes thereafter.

5.4 Recommendations:

1. This study supports the current clinical stratification of patients with NEC to expedited surgery even if at nighttime, particularly if there are signs of haemodynamic instability.

2. A prospective study in our institution is recommended to assess whether decreasing delay from diagnosis to operative intervention would decrease mortality, given the longer time to surgery in the daytime group.

3. Further prospective study is recommended to validate markers of haemodynamic instability as best predictors of mortality as well as the relationship to surgical outcomes in comparison to other markers of NEC disease severity.

4. More research is required into whether a "clip and drop" approach in haemodynamically unstable patients improves outcomes compared to immediate enterostomy formation, as well as seeing if it increases primary anastomosis at the relook laparotomy, as well as improving survival.

5. Quality-improvement initiatives are suggested to address the high incidence of intra-operative hypothermia found in this study at our institution, as well as addressing stoma formation techniques.

6. Improved record-keeping, and a transition to electronic record-keeping or database, which would prevent lost data and possibly mitigate against medicolegal risks.

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Appendix

SNAPPE II score

1. Indication for use:

The SNAPPE II score was used in this study as an objective measure of neonatal illness severity and mortality risk. There are no validated scoring systems predicting morality in NEC, however the SNAPPE II compared to other scoring systems includes metabolic and laboratory parameters some of which have been shown to correlate to NEC outcomes.

2. Description of score:

This physiological score consists of 6 variables, including vital signs and laboratory values, as listed below. It was developed in 2001 following adaptations of the Score for Neonatal Acute Physiology (SNAP) (1993, Richardson et al. and SNAP-II (1998, Richardson et al.(1) Multiple studies have been done to validate this scoring system for morbidity and mortality(2), although there are no specific studies related to necrotizing enterocolitis outcomes. There is evidence to suggest an increased mortality in patients with scores of 37 and above(3,4) even though this hasn't been proven for morbidity.

The following parameters and score points are used in the SNAPPE II score and are measured in the first twelve hours of admission, as applied to admission to the Red Cross War Memorial Children's Hospital Paediatric Intensive Care Unit in this study.

Parameter range	Score
Mean blood pressure (mm Hg)	
>30	0
20-29	9
<20	19
Lowest temperature (degrees C)	
>36	0
35-36	8
<35	15
PO2 (kPA)/FiO2 ratio	
>2.4	0
1-2.29	5
0.3-0.99	16
<0.2	28
Lowest serum pH	
>7.2	0
7.1-7.19	7
<7.1	16
Seizures	
No	0
Yes	19
Urine output (ml/kg/hr)	

>1	0
0.1-0.9	5
<0.1	18
APGAR score	
>7	0
<7	18
Birth weight (g)	
>1000	0
750- 999	10
<750	17
Small for gestational age	
< 3rd percentile	12

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