FACTORS ASSOCIATED WITH MORTALITY IN VERY LOW BIRTH WEIGHT NEONATES TREATED WITH INVASIVE MECHANICAL VENTILATION AT A TERTIARY HOSPITAL IN SOUTH AFRICA

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0604434T

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 Paediatrics.

Johannesburg

21-12-2022

DECLARATION

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

21 December 2022

PRESENTATIONS ARISING FROM THIS RESEARCH REPORT

Oral Presentation: 5th Biennial USANA Conference

(United South Africa Neonatal Association)

10 September 2022

Century City Conference Centre, Cape Town

ACKNOWLEDGEMENTS

A special thank you to my supervisors Prof Daynia Ballot and Dr Robin Saggers for all their expertise, advice and support throughout this process.

To my wife, for all her encouragement and constant belief.

Lastly, to my entire family for always believing in me.

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ABBREVIATIONS

BPD:	Broncho-pulmonary dysplasia
CMJAH:	Charlotte Maxeke Johannesburg Academic Hospital
EOS:	Early onset sepsis
HFOV:	High frequency oscillatory ventilation
HIV:	Human immunodeficiency virus
IMV:	Invasive mechanical ventilation
IQR:	Interquartile range
LMIC:	Low to Middle income countries
LOS:	Late onset sepsis
NCPAP:	Nasal continuous positive airway pressure
NEC:	Necrotising enterocolitis
NICU:	Neonatal intensive care unit
RDS:	Respiratory distress syndrome
REDCap:	Research electronic data capture
ROP:	Retinopathy of prematurity
SD:	Standard deviation
VLBW:	Very low birth weight

SUBMISSIBLE PAPER

FACTORS ASSOCIATED WITH MORTALITY IN VERY LOW BIRTH WEIGHT NEONATES TREATED WITH INVASIVE MECHANICAL VENTILATION AT A TERTIARY HOSPITAL IN SOUTH AFRICA

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Key Words: *Neonates*
Mortality
Invasive mechanical ventilation
Very Low Birth Weight
South Africa

ABSTRACT

Introduction: Respiratory support with invasive mechanical ventilation (IMV) is a critical intervention available to neonates, especially amongst very low birthweight (VLBW) neonates. Since its introduction in the 1960s it has been associated with an increased survival amongst VLBW neonates.

Objectives: To describe the characteristics and outcomes of VLBW neonates who received IMV in the neonatal intensive care unit (NICU) at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH).

Methods: This was a retrospective, descriptive study of neonates who required IMV admitted to the NICU at CMJAH, between 1 January 2013 and 31 December 2019. The characteristics and outcomes of these neonates were described using univariate analysis. The NICU is combined with the paediatric ICU and comprises of 15 beds.

Results: There were 3 484 VLBW neonates admitted during the study period of which 849 required IMV (24.4%). Of the 849, 445 survived (52.4%). 44 infants required high frequency oscillatory ventilation, 16 of whom survived (16/44, 36.4%) making the need for HFOV one of the factors strongly associated with a poor outcome ($p<0.001$). Other significant associations with poor outcomes were lower birth weight ($p<0.001$), lower gestational age ($p=0.003$), the presence of metabolic acidosis ($p<0.001$), the diagnosis of NEC ($p<0.001$), pathological cranial sonar findings ($p<0.001$), and longer length of hospital admission ($p<0.001$).

Conclusion: One quarter of VLBW neonates admitted at CMJAH required IMV during their hospital admission. We demonstrated a survival rate of 52% for ventilated VLBW infants. The only predictive factor for mortality was the presence of metabolic acidosis, likely a surrogate for severity of illness.

1. INTRODUCTION

Since the introduction of invasive mechanical ventilation (IMV) in the 1960's there has been a significant reduction in the mortality of premature neonates. The use of IMV contributes to improve the survival of critically ill neonates, especially amongst those diagnosed with respiratory distress syndrome (RDS).(1) Through various refinements in technology and ventilator design, as well as ventilatory technique, the survival of very low birthweight (VLBW) neonates and our ability to rescue extremely premature infants has improved drastically.

It is particularly prudent we continue to improve if we are to meet the Sustainable Development Goals, particularly those directly related to neonatal mortality. The key indicators being referred to are *"3.2 By 2030, end preventable deaths of newborns and children under 5 years of age, with all countries aiming to reduce neonatal mortality to at least as low as 12 per 1000 live births and under-5 mortality to at least as low as 25 per 1000 live births*" and "*3.4 By 2030, reduce by one third premature mortality from non-communicable diseases through prevention and treatment and promote mental health and well-being.*"(2)

The improvement in survival of VLBW neonates has not come about through the introduction of IMV alone. The use of surfactant therapy in the management of RDS, the use of antenatal steroids and the introduction and widespread use of non-invasive ventilation, particularly nasal Continuous Airways Pressure (nCPAP) have contributed significantly to the overall reduction in both morbidity and mortality observed through the years.(3-6)

However, IMV is associated with a myriad of morbidities and conditions that may lead to an increase in mortality. IMV itself may lead to lung injury, which in turn may cause "air-leak syndromes" such as pneumothorax, as well as prolonged duration of ventilation. One of the most significant conditions associated with lung injury is broncho-pulmonary dysplasia (BPD) which is associated with lifelong morbidity as well as a significantly increased risk of mortality.(7)

Outside of the lung IMV is also associated with retinopathy of prematurity (ROP), brain white matter damage with its adverse neurodevelopmental consequences, late onset sepsis (LOS), necrotising enterocolitis (NEC) and many other complications.(8-10)

Resources for neonatal intensive care including the availability of IMV vary greatly between high-income countries and low- and middle-income countries (LMICs). In a South African context, there have been a handful of studies published looking at mortality of VLBW neonates and within these it is sometimes possible to extract survival data of neonates that were ventilated. Ntuli *et al* in a study published in 2020 showed a survival rate of 45% when reviewing VLBW neonates admitted between January to July 2015 at Mankweng Hospital NICU. When Tshelhla *et al.* reviewed survival data at Steve Biko Academic Hospital they had a survival rate of 53% for ventilated VLBW neonates. Looking at data published previously from within the unit at CMJAH, Ballot *et al.* reviewed all neonates admitted between 1 January 2013 and 31 December 2015. There were 1590 VLBW neonates admitted, of which 299 required IPPV (18.8%). The overall mortality for VLBW neonates was 30.1% (n=479/1590).(11-13)

This study aimed to review VLBW neonates who were ventilated at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH), a large quaternary referral hospital in South Africa, to describe the population requiring ventilation as well as their mortality and morbidity rates.

2. METHODS

This was a retrospective, descriptive study of VLBW (weighing <1500g) neonates who were admitted to the neonatal intensive care unit (NICU) at CMJAH who required IMV from 1 January 2013 – 31 December 2019. Neonates with incomplete records regarding ventilation were excluded. Outcome was defined as death or survival to hospital discharge.

The neonatal unit at CMJAH consisted of a NICU combined with a paediatric intensive care unit for a total of 15 beds, a neonatal high care unit of 35 beds and a low dependency unit of 40 beds. The NICU essentially functioned as a ventilator unit and patients admitted to the NICU were managed by neonatologists.

2.1 DATABASE

Patient data was captured by the attending neonatal team on to the REDCap database at discharge. Data was managed using REDCap (Research Electronic Data Capture), hosted by the University of the Witwatersrand.(14, 15). REDCap is a secure web application for building and managing online surveys and databases. The platform was developed with the specific intent of aiding in data capture for the purposes of clinical audit and quality assurance.

The information was verified at various stages throughout the data collection process. All data was anonymised on export of the database. The following data was collected from the database: (i) maternal characteristics – demographics, antenatal care, place of delivery, mode of delivery, antenatal steroids, other maternal comorbidities such as hypertension, diabetes, HIV status (ii) neonate characteristics – gestational age, birth weight, sex, 5 minute APGAR score, details around delivery room resuscitation, admission details including temperature, (iii) ventilation details – diagnosis, indication for IMV, age at IMV initiation, duration of ventilation, mode of ventilation, surfactant use, (iv) complications and comorbidities – any comorbid conditions, details around sepsis, cranial sonar and ROP findings, any surgical diagnosis, oxygen requirements on day 28 of life and (v) outcome at discharge.

2.2 STATISTICAL ANALYSIS

Data was exported to MS Excel (Microsoft, USA) for the purposes of data cleaning. For statistical analysis the spreadsheet was imported into statistical software package SPSS version 28 (IBM, USA). Categorical variables were described with frequencies and percentages. Means and standard deviations were used to describe continuous variables with a normal distribution, while medians and interquartile ranges (IQR) were used to describe skewed variables. Survivors and non-survivors were compared in terms of demographics, diagnoses, interventions and complications using univariate analysis. For categorical variables Chi-square tests were used for comparison, continuous variables were compared using unpaired t-tests or non-parametric tests depending on whether they were normally distributed or had a skewed distribution. Statistical significance was defined as a p-value of < 0.05. Within variables, cases with

missing data were excluded from the analysis. A binary logistic regression analysis was then performed with survival to discharge as the outcome variable for those with a statistically significant difference with a p-value of < 0.05 were included.

Definitions

Invasive Mechanical Ventilation (IMV) was defined as any modality of ventilation administered via an endotracheal tube. **Necrotising Enterocolitis (**NEC) was defined as NEC grades 2 or 3 diagnosed either clinically or radiologically according to modified Bells criteria.(16) Low Apgar score was defined as a 5 minute Apgar score of ≤ 5. Non-pathological cranial sonar was defined as either normal findings or grade 1 and 2 intraventricular haemorrhage, according to Papiille classification.(17) Pathological cranial sonar included grade 3 and 4 intraventricular haemorrhage.

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

2.3 ETHICS

The study was granted ethics approval from the Human Research Ethics Committee of the University of the Witwatersrand, Johannesburg (certificate number M211141). Permission to conduct the study was obtained from the CEO of Charlotte Maxeke Johannesburg Academic Hospital before embarking on the study.

3. RESULTS

During the study period, 3 484 VLBW neonates were admitted to the CMJAH neonatal unit, of which 849 (24%) met the inclusion criteria and were included in the analysis. Of those, 87 neonates were excluded. See Figure 1 below

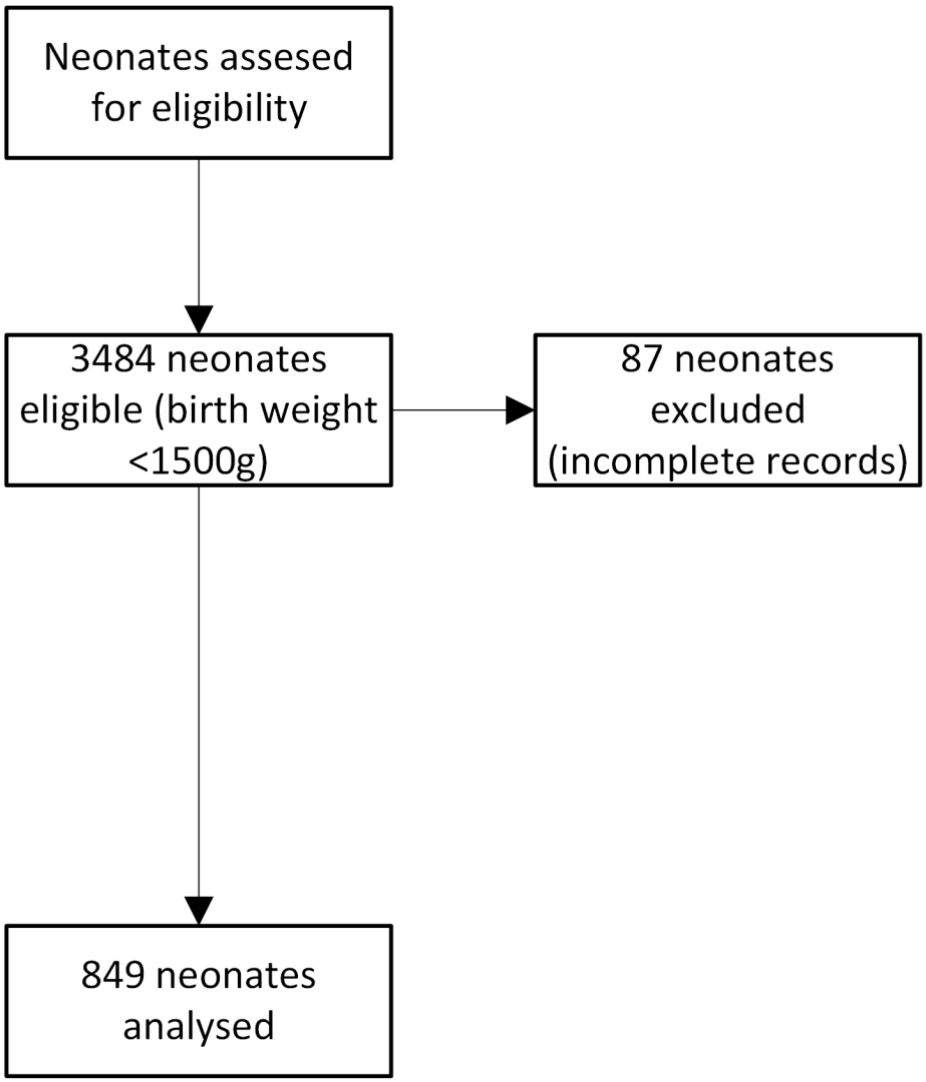

Figure 1: Study participants included in the analysis at Charlotte Maxeke Johannesburg Academic Hospital, 1 January 2013 - 31 December 2019

The clinical characteristics of the study participants are presented in Table 1. Other varaibles as related to outcome are demonstrated in Tables 2 and 3 below. The majority were male (n=470/849, 55.4%). Mode of delivery was almost evenly split with 53.3% being born via caesarean section (n=399/749). The majority of neonates requiring IMV were inborn (n=545/849, 64.2%). The overall survival rate was 52.4% (n=445/849). There was no difference in sex between survivors and non-survivors.

Table 1: Clinical characteristics of ventilated VLBW neonates at Charlotte Maxeke Johannesburg Academic Hospital, 1 January 2013 - 31 December 2019

Clinical Characteristics	Ventilated neonates (n=849)
Gestational age, weeks (mean, SD)	29 (2)
Birth weight, g (mean, SD)	1111 (193)
Age when first ventilated, days (median, [IQR])	3 [0-10]
Duration of ventilation, days (median, [IQR])	4 [2-8]
Length of hospital admission, days (median, [IQR])	27 [9-53]

The majority of mothers had received antenatal care (n=549/725, 75.7%). However, the majority of mothers did not receive antenatal steroids (n=365/651, 56.1%). The mean maternal age was 28.7 (SD 6.378) years.

When analysing maternal characteristics between survivors and non-survivors the only statistically significant difference was the place of birth, delivery outside the hospital was associated with increased survival (185/445, 45.1%, p<0.001)

The most common respiratory diagnosis was RDS, with 737 (737/753, 98%). The remainder included congenital pneumonia, atelectasis and acquired pneumonia.

The most common indication for ventilation was failing a trial of nCPAP (129/572, 22.3%). There was a statistically significant difference in proportions between the various indications for ventilation (p=0.004). All pairwise comparisons however were not statistically significant. Figure 2 below demonstrates the various indications for ventilation according to outcome.

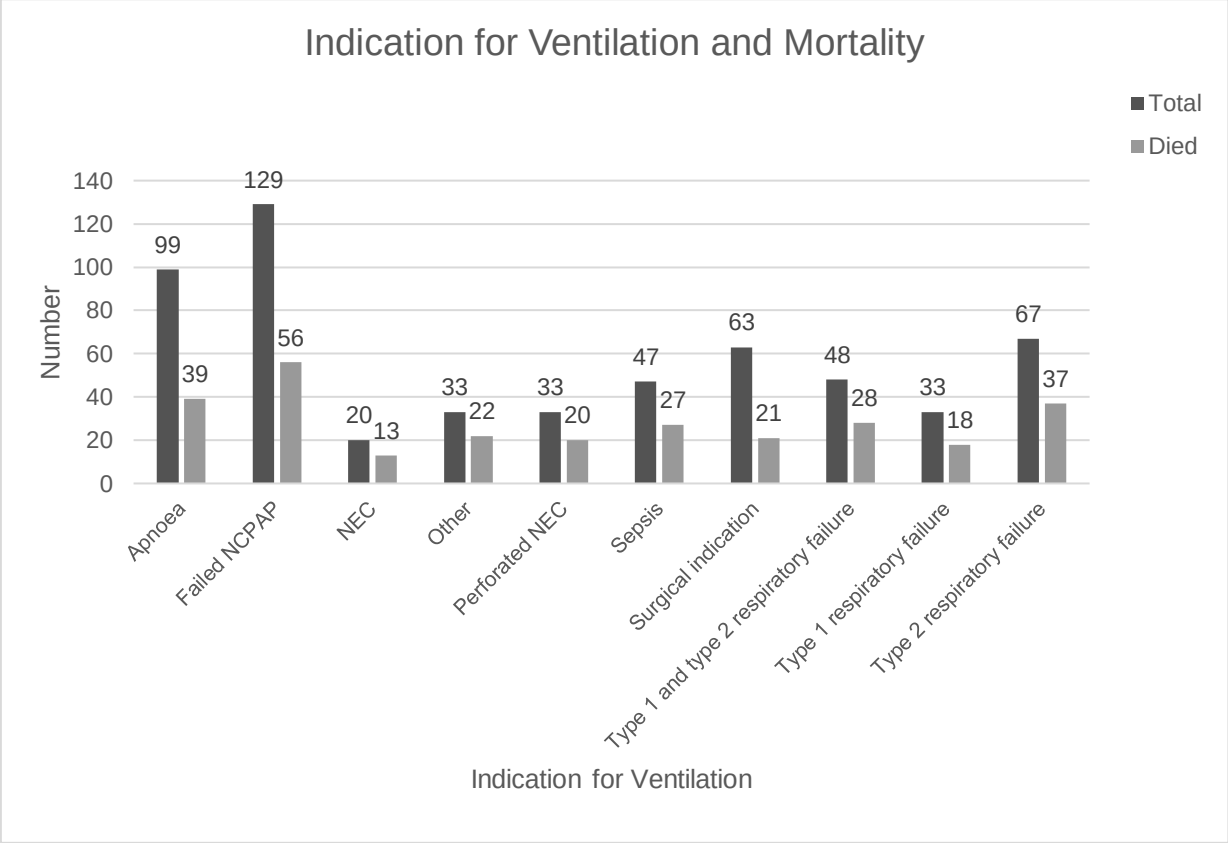

Figure 2: The frequencies of indication for ventilation with outcome (Died vs Survived) at Charlotte Maxeke Johannesburg Academic Hospital, 1 January 2013 - 31 December 2019

There were 666 infants that received surfactant (78.4%) of which 357 survived (357/666, 53.6%) which was significantly associated with an increased chance of survival (p=0.011). Being treated with steroids for the prevention of BPD (176/199, 88.4%, p<0.001) was also significantly associated with an increase chance of survival in VLBW neonates.

Table 2: Continuous variables relating to outcome (Died vs Survived) of ventilated VLBW neonates at Charlotte Maxeke Johannesburg Academic Hospital, 1 January 2013 - 31 December 2019

Variable	Died	Survived	p-value
Maternal age, years (mean, SD)	28.88 (6.31)	28.48 (6.31)	0.42

Birth weight, g (mean, SD)	1076.22 (193.16)	1143.52 (186.73)	<0.001
Gestational age, weeks (mean, SD)	28.7 (2.15)	29.12 (2.07)	0.003
Duration of ventilation, days (median, [IQR])	3 [1-8]	5 [3-8]	0.006
Age at first surfactant dose, minutes (median, [IQR])	120 [73-180]	120 [70-240]	0.479
Age at outcome, days (median, [IQR])	10 [4-22]	49 [30-68]	<0.001

Table 3: Categorical variables relating to outcome (Died vs Survived) of VLBW ventilated neonates at Charlotte Maxeke Johannesburg Academic Hospital, 1 January 2013 - 31 December 2019

Variable	**Died**		**Survived**		**p-value**
	n	**%**	**n**	**%**	
Male	221/402	55.0	249/445	56.0	0.774
Outborn	119/404	29.5	185/445	41.6	<0.001
Apgar > 5	304/335	90.7	302/330	91.5	0.727
Antenatal care	264/351	75.2	285/374	76.2	0.756
Antenatal steroids	149/320	46.6	137/331	41.4	0.184
Caesarean Section	181/365	49.6	211/384	54.9	0.142
HFOV	38/404	9.4	16/445	3.6	<0.001
Received surfactant	309/375	82.4	357/402	88.8	0.011
Metabolic Acidosis	151/404	37.4	52/445	11.7	<0.001
EOS	29/345	8.4	20/418	4.8	0.104
LOS	214/398	53.7	260/442	58.8	0.144
Oxygen on day 28	71/292	24.3	273/416	65.6	<0.001
Steroids for BPD	23/386	6	176/417	42.2	<0.001

NEC	132/404	32.7	96/445	21.6	<0.001
NEC surgery	64/132	48.5	49/96	51.0	0.944
Pathologic Cranial Sonar	79/251	31.4	45/353	12.7	<0.001

There were 54 (6.4%) neonates who required HFOV, 38 of which demised (38/54, 70.4%). Other factors significantly associated with death were the presence of metabolic acidosis (151/203, 74.4%, p<0.001) and the presence of NEC 132/228, 57.9%, p<0.001). However, the need for surgery in NEC was not significantly associated with outcome in our cohort.

Cranial sonars were performed on 604 (78.1%) neonates during the study period. Of those 124 had an abnormal finding, which was significantly associated with non-survival (79/251, 31.4%, p<0.001)

During the study 254 neonates underwent ROP screening while still in hospital. Of those 216 had normal screening studies (n=216/254, 85%).

A binary logistic regression analysis was performed with survival to discharge as the outcome variable, the results of which are listed in Table 4 below. According to the analysis, metabolic acidosis was the only variable found to be statistically significant and was associated with a decrease in survival.

Table 4: Binary logistic regression model for factors associated with survival to discharge of VLBW ventilated neonates at Charlotte Maxeke Johannesburg Academic Hospital, 1 January 2013 - 31 December 2019

Variable	**Odds ratio**	**95% CI**	
		Lower	**Upper**
Duration of ventilation	1.023	0.978	1.069
Birth weight	1.001	0.999	1.003
Gestational Age	1.059	0.870	1.287
Metabolic Acidosis	0.342	0.148	0.796
Normal Cranial Sonar Findings	2.203	0.800	6.062
NEC Surgery	0.573	0.262	1.253
HFOV	0.561	0.144	2.188

Constant	0.003		

4. DISCUSSION

Despite IMV being widespread and frequently used, there is a paucity of data looking specifically at VLBW neonates who undergo IMV as an intervention in and of itself, rather than as a part of larger study or dataset. In our study up to 24% of VLBW neonates required ventilation at some point during the course of their admission. This also needs to be understood in the context of limited capacity for IMV and stricter criteria for the initiation of IMV than one might find in a setting of relatively unrestricted resources.

In our study we demonstrated a survival rate of 52% amongst ventilated VLBW neonates. This is comparable to other LMICs. In a study from the University Hospital of the West Indies published in 2006, they demonstrated a survival rate of 48% for ventilated VLBW neonates. In a study done by Riyas et al. conducted at a NICU in India, there was a survival rate of 30% amongst ventilated VLBW neonates. Even compared to a high income setting like Saudi Arabia, in a study published in 2002, there was an observed survival rate of 51.2% for ventilated neonates.(18-20)

The most common indication for ventilation was RDS. In the context of the study population being VLBW neonates, this was expected. Surfactant administration was associated with survival benefit. Predictably, lower birth weight and prematurity are significant risk factors for death. It was interesting to note that time to administration of surfactant had no impact on survival.

There was no significant association with early or late onset sepsis and mortality. Metabolic acidosis was the only variable significantly associated with mortality. This likely is an indication on severity of illness and thus is logical that the neonates with more severe illness were more likely to demise. In our setting IMV is generally used as a rescue therapy for neonates who have failed a trial of nCPAP and thus are generally further down the disease progression. Metabolic acidosis was also seen as a significant risk factor for mortality in VLBW neonates on binary logistic regression by Ballot *et al*. in their paper published in 2016.(11)

Of interest, many of the antenatal factors and interventions (for example, antenatal steroids) which we expected to impact on mortality, did not show any significant survival benefit in our population. This would need to be investigated further as the fact that we only studied ventilated neonates may be masking the expected survival benefit. We also demonstrated a relatively low rate of antenatal steroid usage. Although comparable to previous studies at CMJAH, this is however lower than rates in other LMICs. A study by WHO in 2014 had a median use across multiple countries of 54%, still much lower than the usage rates of 80% in high income countries. Considering the impressive benefit antenatal steroids have demonstrated on not just lung maturity, but overall improvement in morbidity and mortality this is something that we should endeavour to improve upon. (21-23)

Being outborn was associated with increased survival on univariate analysis. This is contrary to what we expected, when reviewing the literature, as being outborn was either associated with an increased mortality or tended to have no effect on mortality.(12, 24) This may be due to an inherent selection bias within the group of neonates being transferred in, as in order to survive transfer the neonate in question would have to be in a relatively stable condition. Many neonates that may have been candidates for ventilation within our unit unfortunately may have been simply too ill to survive the hospital transfer.

We also noted that the vast majority of our neonates who required ventilation are inborn. CMJAH is a specialist obstetric unit receiving many referrals for obstetric complications. In our study we only studied VLBW, premature infants which are all considered to be complicated deliveries, thus we may consider that these are in-utero transfers as they are all at high risk for requiring specialist neonatal care.

Low 5-minute Apgar score also was not associated with an increase in mortality. However due to CMJAH being in a resource limited setting, there may be selection bias influencing this result.

5. LIMITATIONS

This study was a retrospective database analysis, therefore some data was missing. As this is not a population based study and the fact that we are dealing with admissions

into an ICU setting, the proportions and severity of disease may be overrepresented and overestimated. This was a single centre study from a tertiary referral centre so the results may not be generalisable to all populations. As this was a database timing of events were not captured.

6. CONCLUSION

In our study one quarter of VLBW neonates admitted at CMJAH required IMV during their hospital admission. We demonstrated a survival rate of 52% for ventilated VLBW infants. The only predictive factor for mortality was the presence of metabolic acidosis, likely a surrogate for severity of illness.

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APPENDICES

APPENDIX A: INSTRUCTION FOR AUTHORS

Author Guidelines

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Author contributions should be listed/described in the manuscript.

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- Abbreviations should be spelt out when first used and thereafter used consistently, e.g. 'intravenous (IV)' or 'Department of Health (DoH)'.
- Scientific measurements must be expressed in SI units except: blood pressure (mmHg) and haemoglobin (g/dL).
- Litres is denoted with an uppercase L e.g. 'mL' for millilitres).
- Units should be preceded by a space (except for % and ºC), e.g. '40 kg' and '20 cm' but '50%' and '19ºC'.
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- Human Gene Mapping Workshop (HGMW): genetic notations and symbols
- HUGO Gene Nomenclature Committee: approved gene symbols and nomenclature
- OMIM: Online Mendelian Inheritance in Man (MIM) nomenclature and instructions
- Bennet et al. Standardized human pedigree nomenclature: Update and assessment of the recommendations of the National Society of Genetic Counselors. J Genet Counsel 2008;17:424-433: standard human pedigree nomenclature.

Preparation notes by article type

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Guideline word limit: 3 000 words (excluding abstract and bibliography)

Research articles describe the background, methods, results and conclusions of an original research study. The article should contain the following sections: introduction, methods, results, discussion and conclusion, and should include a structured abstract (see below). The introduction should be concise – no more than three paragraphs – on the background to the research question, and must include references to other relevant published studies that clearly lay out the rationale for conducting the study. Some common reasons for conducting a study are: to fill a gap in the literature, a logical extension of previous work, or to answer an important clinical question. If other papers related to the same study have been published previously, please make sure to refer to them specifically. Describe the study methods in as much detail as possible so that others would be able to replicate the study should they need to. Where appropriate, sample size calculations should be included to demonstrate that the study is not underpowered. Results should describe the study sample as well as the findings from the study itself, but all interpretation of findings must be kept in the discussion section, which should consider primary outcomes first before any secondary or tertiary findings or post-hoc analyses. The conclusion should briefly summarise the main message of the paper and provide recommendations for further study.

- May include up to 3 illustrations or tables.
- A max of 20 - 25references

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- This should be no more than 250words, with the following recommended headings:
    - **Background:** why the study is being done and how it relates to other published work.
    - **Objectives:** what the study intends to find out
    - **Methods:** must include study design, number of participants, description of the intervention, primary and secondary outcomes, any specific analyses that were done on the data.
    - **Results:** first sentence must be brief population and sample description; outline the results according to the methods described. Primary outcomes must be described first, even if they are not the most significant findings of the study.
    - **Conclusion:** must be supported by the data, include recommendations for further study/actions.
    - Please ensure that the structured abstract is complete, accurate and clear and has been approved by all authors. It should be able to be intelligible to the reader without referral to the main body of the article.
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Illustrations/photos/scans

- If illustrations submitted have been published elsewhere, the author(s) should provide evidence of consent to republication obtained from the copyright holder.
- Figures must be numbered in Arabic numerals and referred to in the text e.g. '(Fig. 1)'.
- Each figure must have a caption/legend: Fig. 1. Description (any abbreviations in full).
- All images must be of high enough resolution/quality for print.
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- Scans/photos showing a specific feature e.g. *Intermediate magnification micrograph of a low malignant potential (LMP) mucinous ovarian tumour. (H&E stain).* –include an arrow to show the tumour.
- Each image must be attached individually as a 'supplementary file' upon submission (not solely embedded in the accompanying manuscript) and named Fig. 1, Fig. 2, etc.

Tables

- Tables should be constructed carefully and simply for intelligible data representation. Unnecessarily complicated tables are strongly discouraged.
- Large tables will generally not be accepted for publication in their entirety. Please consider shortening and using the text to highlight specific important sections, or offer a large table as an addendum to the publication, but available in full on request from the author.
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- Number each table in Arabic numerals (Table 1, Table 2, etc.) consecutively as they are referred to in the text.
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- Ensure each table has a concise title and column headings, and include units where necessary.
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Do not: Use [Enter] within a row to make 'new rows':

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Each row of data must have its own proper row:

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Combine into one column, *n* (%):

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- Authors must verify references from original sources.
- Citations should be inserted in the text as superscript numbers between square brackets, e.g. These regulations are endorsed by the World Health Organization,[2] and others.[3,4-6]
- 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 three names should be given followed by et al.
- Volume and issue numbers should be given.
- First and last page, in full, should be given e.g.: 1215-1217 **not** 1215-17.
- Wherever possible, references must be accompanied by a digital object identifier (DOI) link). Authors are encouraged to use the DOI lookup service offered by CrossRef:
    - On the Crossref homepage, paste the article title into the 'Metadata search' box.
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    - Click Actions > Cite
    - Alongside 'url =' copy the URL between { }.
    - Provide as follows, e.g.: https://doi.org/10.7196/07294.937.98x

Some examples:

- *Journal references:* Price NC, Jacobs NN, Roberts DA, et al. Importance of asking about glaucoma. Stat Med 1998;289(1):350-355. http://dx/doi.org/10.1000/hgjr.182
- *Book references:* Jeffcoate N. Principles of Gynaecology. 4th ed. London: Butterworth, 1975:96-101.
- *Chapter/section in a book:* Weinstein L, Swartz MN. Pathogenic Properties of Invading Microorganisms. In: Sodeman WA, Sodeman WA, eds. Pathologic Physiology: Mechanisms of Disease. Philadelphia: WB Saunders, 1974:457-472.
- *Internet references:* World Health Organization. The World Health Report 2002 - Reducing Risks, Promoting Healthy Life. Geneva: WHO, 2002. http://www.who.int/whr/2002 (accessed 16 January 2010).
- Legal references
- Government Gazettes:

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

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

- Provincial Gazettes:

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

- Acts:

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

- Regulations to an Act:

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

- Bills:

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

- Green/white papers:

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

- Case law:

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

Rex v Jopp and Another: Name of the parties concerned

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

(4): Volume number

SA: SA Law Reports

11: Page or section number

(N): In this case Natal - where the case was heard. Similarly, (C) woud indicate Cape, (G) Gauteng, and so on.

NOTE: no . after the v

- *Other references (e.g. reports) should follow the same format:* Author(s). Title. Publisher place: Publisher name, year; pages.
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- Unpublished observations and personal communications in the text must **not** appear in the reference list. The full name of the source person must be provided for personal communications e.g. '...(Prof. Michael Jones, personal communication)'.

APPENDIX B: RESEARCH PROTOCOL

Factors Associated with Mortality in Very Low Birth Weight Neonates Treated with Invasive Mechanical Ventilation at a Tertiary Hospital in South Africa

Dr Rowan Goldstein

Research Proposal

University of Witwatersrand

Student number: A0025893

Supervisors: Prof D Ballot

Dr R Saggers

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1. INTRODUCTION, BACKGROUND AND RATIONALE FOR THE STUDY

Introduction

According to the Global Burden of Disease Study 2016, 35% of the under-5 mortality rate is accounted for by neonatal deaths (15.2 of 43.4 deaths per 1000 live births). (1) Considering that two of the key indicators to be achieved by 2030 according to the Sustainable Development Goals are directly related to neonatal mortality, it is of particular importance to analyse all aspects surrounding child health and neonatal care. The specific indicators are *"3.2 By 2030, end preventable deaths of newborns and children under 5 years of age, with all countries aiming to reduce neonatal mortality to at least as low as 12 per 1000 live births and under-5 mortality to at least as low as 25 per 1000 live births."* And *"3.4 By 2030, reduce by one third premature mortality from non-communicable diseases through prevention and treatment and promote mental health and well-being." (2)*

Some of the earliest work investigating and perfecting the technique for successfully using Invasive Mechanical Ventilation (IMV) in neonates was done in Cape Town at the Red Cross War Memorial Children's Hospital in an effort to successfully treat Tetanus Neonatorum. The technique was first used in 1958 in Cape Town and over the following decade the team was able to reduce morality from Tetanus Neonatorum from over 90% to 10%. (3) IMV was introduced in the 1960's as a means to try and reduce the mortality and morbidity from respiratory distress syndrome (RDS) in premature neonates. This intervention was associated with an increased survival amongst very low birth weight infants (VLBW). (4) In the United States, infant mortality from RDS decreased drastically from 268 per 100 000 live births in 1971 to 14.7 per 100 000 live births in 2008. (5) This decrease coincides with the introduction of IMV as well as other advancements in neonatal care, such as exogenous surfactant administration. In a paper published by Lui et al, outcome trends for VLBW neonates from 11 different high-income countries showed an overall decrease in mortality from 2007 – 2015. (6)

Two other major advances in the early 1970's contributed significantly to the improvement in mortality and morbidity in VLBW neonates and the treatment of RDS. The first was the advent of continuous positive airway pressure (CPAP), which initially was applied via the use of an endotracheal tube (ETT) as a mode of ventilation. However, through the decade this was simplified to be applied via specialised nasal cannula, thus eliminating the need for "invasive" mechanical ventilation in a large proportion of VLBW neonates. (7)

The use of Nasal Continuous positive airway pressure (nCPAP) is now considered the modality of choice for providing respiratory support in the initial management of

RDS.(8) The use of nCPAP has been reviewed extensively. Within our own unit a retrospective analysis of the use of nCPAP was undertaken by Jardine et al. They showed an overall survival of 87.6% of VLBW infants, with 18.2% of those infants failing CPAP therapy and requiring IMV.(9) At Chris Hani Baragwanath Hospital (CHBH), Bopape-Chinyanga *et al.* reviewed all VLBW neonates started on nCPAP within the first 72 hours of life. Similarly, they had a survival rate of 87% although the rate of nCPAP failure requiring IMV was higher than that of CMJAH with 34%.(10)

One of the next major breakthroughs was the discovery that antenatal corticosteroids administered to the mother prior to delivery of a premature neonate helped to accelerate the maturity of the lungs and thus prevent a large portion of neonates being born with RDS. (11) Since the seminal work published by Liggins et al, this has been re-evaluated multiple times through the years, with the latest systematic review published by the Cochrane database in 2017 showing an overall reduction in RDS of 34%, as well as significantly less need for IMV amongst numerous other benefits. (12)

However, as with most interventions there are always adverse effects and complications to consider. The aim of mechanical ventilation is to allow for successful gaseous exchange to aid in homeostasis, while avoiding lung injury caused by too high or too low-pressure delivery. This is essential as significant morbidity and mortality is associated with lung injury, such as Broncho-pulmonary dysplasia (BPD), air leak syndromes and pneumothorax as well as longer duration of ventilation. Ventilation at too low pressures can result in “atelecto-trauma” as well as inflammation. (8)

Choi et al. found in their study of ventilated VLBW neonates in Korea, that the cumulated duration of ventilation correlated with mortality. They also found that BPD as the cause of death increased from 15 days of ventilation and became the leading cause of death after three months of IMV. They also found that longer duration of ventilation was associated with more morbidity such as peri-ventricular leukomalacia (PVL), progression of retinopathy of prematurity (ROP) and impaired auditory response. (13)

Another significant cause of morbidity and mortality in VLBW neonates is late-onset sepsis (LOS), defined as clinically suspected or proven sepsis after 72 hours of life. A study on the Brazilian Neonatal Research Network, reported that 24% of all VLBW neonates developed proven LOS. In these infants, IMV was more frequent and prolonged. It is impossible from this study to determine whether IMV caused the higher rates of LOS or if neonates who acquired LOS were more likely to subsequently need IMV or if it is a combination of both. The mortality rate was significantly higher in those with LOS. (14)

In discussing all of this it is also prudent to consider the associated increased hospital costs associated with the significant burden of morbidity in the care of VLBW neonates. In a study conducted in America, Johnson et al. found that LOS had an increase of $10,055 (±R171 631) of direct costs to the hospital, BPD had an increase of $31,565 (±R538 792) and necrotising enterocolitis had an increase of $15,440(±R263 550). They also found that the absolute number of morbidities was associated with significantly higher costs. (15) A good understanding of morbidities

and costs associated with IMV is crucial in a resource limited setting, such as in South Africa.

IMV is one of the most critical interventions performed especially amongst VLBW neonates. In a South African context, there have been a handful of studies published looking at mortality of VLBW neonates and within these it is sometimes possible to extract survival data of neonates that were ventilated. Ntuli *et al.* found that between January to July of 2015 at the Mankweng Hospital neonatal intensive care unit (NICU) in Limpopo province, of the 252 VLBW neonates admitted, only 51 received mechanical ventilation (20%) and of those only 23 survived to discharge (45%).(16) At Steve Biko Academic Hospital in Tshwane, Tshehla *et al.* observed that between June 2016 and May 2017, of the 231 VLBW neonates admitted, 72 required invasive mechanical ventilation (31%) of which 38 survived to discharge (53%). (17)

Within our own unit, Ballot et.al published a paper in 2010 on the determinants of survival in VLBW neonates. Of the 474 VLBW neonates born at a tertiary academic hospital over a two-year period (2006 – 2007), 99 were offered mechanical ventilation (21%) and of those infants, 71 survived to discharge (72%). (18)

The survival rate observed in the above South African studies is higher than survival rates observed in some other NICUs in low-middle income countries. In a prospective observational study conducted in a NICU in Southern India between 2000 and 2002, of the ten VLBW neonates that were ventilated, only three survived, with a survival rate of 30%. (19) Even when compared to some upper middle- or high-income countries we still see higher survival rates in a South African setting. In

a study from the University Hospital of the West Indies (upper-middle income), published in 2006 by Trotman *et al*, of the 73 VLBW neonates that were ventilated, 35 survived with a survival rate of 48%. (20) This is comparable to a study conducted in the high-income economy of Saudi Arabia in January 2002 (by Karthikeyan *et al*.) – they observed a mortality rate of 48.6% for ventilated VLBW neonates (18/37). (21)

While the overall survival rates are interesting to compare, it is more prudent to try to understand the various factors associated with the survival of ventilated VLBW neonates. The survival rate observed within our unit is higher than what could be expected within a resource limited setting, and it is valuable to try to understand if this could be translated to better outcomes in other centres with similar resources.

Despite this, it seems there is an overall paucity of data looking specifically at outcomes of VLBW neonates who have undergone mechanical ventilation as an intervention on its own, and not as part of larger data set as one factor in the myriad of complications that premature infants may acquire throughout their care within a neonatal ICU. This study aims to review the characteristics and outcomes of VLBW neonates who received IMV within the NICU at the Charlotte Maxeke Johannesburg Academic Hospital over a seven-year period.

2. OBJECTIVES OF THE STUDY

2.1 Primary objectives

a. To describe the characteristics and outcomes of VLBW neonates who received IMV

2.2 Secondary objectives

To determine the outcome of VLBW neonates who are ventilated multiple times vs those who are only ventilated once

To determine factors associated with mortality in VLBW neonates who received IMV by comparing survivors with non-survivors.

3. METHODOLOGY

3.1 Study Design

Retrospective descriptive study, secondary analysis of an existing database.

3.2 Study Population

All neonates who received invasive mechanical ventilation at Charlotte Maxeke

Johannesburg Academic Hospital from 1 January 2013 – 31 December 2019.

a. Inclusion criteria

Neonates with a birthweight of less than 1500g.

b. Exclusion criteria

1. Study participants with no information on mechanical ventilation

3.4 Study Setting

Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) has a 15-bed combined neonatal and paediatric ICU. The ICU is serviced by 2 paediatric registrars during the day and 1 on call registrar after hours. The staff are supervised by Neonatology consultant or fellow.

NICU admissions are generally reserved for neonates with a birth weight above 800g or neonates who were born less than 800g who have now grown to more than 800g.

Management strategies for various conditions included criteria for ventilation and ICU admission are outlined in units' protocol.

Indications for mechanical ventilation are outlined as such, recurrent apnoea, respiratory failure defined as either PaCO2 of >55 mmHg with acidaemia (pH <7.25); PaO2 <50 or oxygen saturations of <90% on an FiO2 of >70% oxygen. An attempt at non – invasive ventilation (nasal CPAP) should precede mechanical ventilation.

3.3 Data Collection

a. Data collection instrument

See Appendix A.

b. Data collection method

Data will be extracted from a pre-existing neonatal database run and maintained by the neonatal unit at the Charlotte Maxeke Johannesburg Academic Hospital. The data is managed using Research Electronic Data Capture (REDCap), which is hosted by the University of the Witwatersrand. (12) Patient details are captured at discharge for each patient onto the database for the purpose of clinical audit and quality improvement. Once captured they are checked and verified at multiple points. Only de-identified data will be analysed.

3.4 Variables to be analysed

The data sheet (Appendix A) will capture demographic information (maternal age, parity, gestational age, birth weight, gender), perinatal details (mode of delivery, APGAR scores, resuscitation details), clinical diagnosis, ventilation details (mode of ventilation, duration, complications), other associated neonatal complications and diseases, surgical diagnoses, and survival details.

3.5 Data Analysis

a. Statistical analysis

Descriptive analysis will be used for the baseline characteristics of study participants, such as age, sex, diagnosis, type of ventilation received, other relevant comorbidities. Continuous variables which are normally distributed will be described with means and standard deviations; those with skewed distribution will be described

using median and inter-quartile range. Categorical data will be described using frequencies and percentages.

All variables will be compared between survivors and non-survivors. For the categorical variables, a chi-squared test will be used to infer if there is statistical significance between the groups. For continuous variables the students t-test or Mann Whitney U analysis will be used, depending on the distribution of the data. A p-value

< 0.05 will be considered statistically significant

All those variables with a p value < 0.1 on univariate analysis will be entered into a binary logistic regression, considering survival as the primary outcome, and will be used to establish associations with poor outcome.

b. Sample size calculation

Based on a review of the database, we can expect approximately 450 VLBW infant admissions per year. Based on the study of the same population in 2010 by Ballot et al, we can expect 20% to require mechanical ventilation. (18) Accordingly, we can expect a total sample of approximately 630 patients.

3.6 Research Assumptions

a. Definitions of terms and abbreviations

i. Neonate – a child within the first 28 days or life. A preterm infant will be classified as a neonate according to their chronological age corrected for gestational age (e.g., a 5-week-old preterm infant born at 28 weeks will be corrected to 31 weeks and hence is a neonate). ii. Very low birth weight – birth weight < 1500g. iii. Extremely low birth weight – birth weight <1000g.

Invasive Mechanical Ventilation (IMV) - Intermittent Positive Pressure Ventilation (IPPV) through an endotracheal tube via either a conventional mechanical ventilator (CMV) or high frequency oscillator ventilator

(HFOV)

Confirmed sepsis – positive blood culture of organism deemed to be

significant.

Early-onset sepsis (EOS) – confirmed sepsis and or meningitis before 72 hours of life.

Late-onset sepsis (LOS) – confirmed sepsis with onset after 72 hours of

life.

Cranial Sonar Findings – intra-ventricular haemorrhage (IVH) graded according to Papile (22) ix. Broncho-pulmonary dysplasia – oxygen at 28 days of life

x. NEC – grade II and III according to modified Bell (23) xi. Other variables are defined according to the Vermont Oxford

Network. (24)

4. SIGNIFICANCE OF THE STUDY

Although many studies have looked at the impact of survival of VLBW neonates, none have looked at what specifically impacts the survival of those that have been ventilated. This may help us to define both positive and negative prognostic factors, which in turn may help us to more accurately select which patients should be prioritised for this crucial, yet very limited resource. It will also help us to evaluate what specific factors we should be focusing on to help improve survival rates amongst ventilated neonates in our continuous efforts of self-evaluation and improvement.

5. POTENTIAL LIMITATIONS

As this is a retrospective review of an existing database there are numerous limitations inherent to this type of research. The biggest limitations are the sources of potential bias, issues surrounding validity, issues around missing data and the fact that we can only establish associations, not causal relationships. (25)

The study site is a tertiary referral centre with a large paediatric surgery service, so the results will not be generalizable to regional and district facilities.

6. ETHICAL CONSIDERATIONS

The proposal for this study will be submitted to the University of the Witwatersrand's Human Research Ethics Committee (HREC). As this is a retrospective database review, no consent will need to be obtained from individual patients. Confidentiality will be ensured as data sheets will only contain a study number. Identifying data (for example, name and hospital number) will be stored in a separate database at a different, secure location so that only the supervisors will have access to this information. The study will not be started until clearance from the HREC and permission from the hospital

(CMJAH) CEO is granted.

7. PROJECTED OUTLINE

7.1 Timeframe

	2020									
	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Jan	Feb
Protocol preparation	x	x	x							
Submission to post grad committee				x	x					
Application for institutional permission				x	x					
Submission for ethics approval					x	x				
Data Collection						x				
Data Analysis							x	x		
Write up							x	x	x	

Submission									x	x

7.2 Budget for the study

Approximate budget of R1000 (for stationery, printing, and binding).

The cost of the study will be borne by the investigator.

7.3 Publication Plan

The final report will first be submitted to the University of the Witwatersrand post graduate research office for assessment as partial fulfilment for the degree of Master of Medicine in Paediatrics. Thereafter, publication may be considered.

8. REFERENCES

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9. APPENDIX

1. Data Capture Instrument

Data Capture Sheet

Database Number:

DEMOGRAPHICS

Birth Weight: (g)

Gestational Age: (weeks) 3) Place of Birth: Inborn

Out born

Clinic / MOU

BBA

Unknown

4) Maternal age: (years)

PRENATAL AND MATERNAL DETAILS

Antenatal Care Received

Antenatal Steroids

Antenatal Magnesium Sulphate

Chorioamnionitis

Maternal Hypertension

Maternal HIV infection

Maternal ART use

7) Maternal Syphilis

a. Received Treatment

8) Maternal Diabetes

PERINATAL AND POSTNATAL DETAILS

Mode of delivery

NVD

Breech

Elective Caesarean Section

Emergency Caesarean Section

Multiple Gestation

APGAR scores

1 minute:

5 minutes:

10 minutes:

Resuscitation in Delivery Room

Oxygen alone

Bag mask Ventilation

Chest Compressions

Endotracheal tube intubation

Adrenaline

Temperature on admission (°C)

Congenital Infection

Early onset Neonatal Sepsis

Metabolic Acidosis

RESPIRATORY COMPLICATIONS

Respiratory Diagnosis:

Indication for Invasive Ventilation

Age at first ventilation: (days)

Duration of ventilation: (days)

Mode of Ventilation

Conventional Mechanical

Ventilation

High Frequency Oscillatory ventilation 6) Surfactant use:

Age at 1st administration: (hours)

Number of doses received:

On Oxygen on day 28 of life

Use of steroids for treatment of Chronic Lung Disease ☐

Discharged on home oxygen

NEONATAL COMPLICATIONS / OTHER DIAGNOSIS

Persistent Ductus Arteriosus

Caffeine administered

Inotropic Support

Pneumothorax ☐

Late Onset Sepsis (after day 3) ☐

Cranial Sonar Findings

Not done

Normal ☐

IVH Grade 1

IVH Grade 2

IVH Grade 3

☐

IVH Grade 4

Peri-ventricular leukomalacia

Surgical Diagnosis

Necrotising Enterocolitis

Stage:

Type of Surgery for NEC

Pencil Drain

Laparotomy

Colostomy ☐

Other Surgical Diagnosis:

Survived to Discharge ☐

FACTORS ASSOCIATED WITH MORTALITY IN VERY LOW BIRTH WEIGHT NEONATES TREATED WITH INVASIVE MECHANICAL VENTILATION AT A TERTIARY HOSPITAL IN SOUTH AFRICA

DR ROWAN GOLDSTEIN

Research Proposal

University of Witwatersrand

Student number: A0025893

Supervisors: Prof D Ballot

Dr R Saggers

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1. INTRODUCTION, BACKGROUND AND RATIONALE FOR THE STUDY

INTRODUCTION

According to the Global Burden of Disease Study 2016, 35% of the under-5 mortality rate is accounted for by neonatal deaths (15.2 of 43.4 deaths per 1000 live births).(25) Considering that two of the key indicators to be achieved by 2030 according to the Sustainable Development Goals are directly related to neonatal mortality, it is of particular importance to analyse all aspects surrounding child health and neonatal care. The specific indicators are *"3.2 By 2030, end preventable deaths of newborns and children under 5 years of age, with all countries aiming to reduce neonatal mortality to at least as low as 12 per 1000 live births and under-5 mortality to at least as low as 25 per 1000 live births."* And *" 3.4 By 2030, reduce by one third premature mortality from non-communicable diseases through prevention and treatment and promote mental health and well-being." (2)*

Some of the earliest work investigating and perfecting the technique for successfully using Invasive Mechanical Ventilation (IMV) in neonates was done in Cape Town at the Red Cross War Memorial Children's Hospital in an effort to successfully treat Tetanus Neonatorum. The technique was first used in 1958 in Cape Town and over the following decade the team was able to reduce morality from Tetanus Neonatorum from over 90% to 10%. (26) IMV was introduced in the 1960's as a means to try and reduce the mortality and morbidity from respiratory distress syndrome (RDS) in

premature neonates. This intervention was associated with an increased survival amongst very low birth weight infants (VLBW).(27) In the United States, infant mortality from RDS decreased drastically from 268 per 100 000 live births in 1971 to 14.7 per 100 000 live births in 2008.(1) This decrease coincides with the introduction of IMV as well as other advancements in neonatal care, such as exogenous surfactant administration. In a paper published by Lui et al, outcome trends for VLBW neonates from 11 different high-income countries showed an overall decrease in mortality from 2007 – 2015.(28)

Two other major advances in the early 1970's contributed significantly to the improvement in mortality and morbidity in VLBW neonates and the treatment of RDS. The first was the advent of continuous positive airway pressure (CPAP), which initially was applied via the use of an endotracheal tube (ETT) as a mode of ventilation. However through the decade this was simplified to be applied via specialised nasal cannula, thus eliminating the need for "invasive" mechanical ventilation in a large proportion of VLBW neonates.(6)

The use of Nasal Continuous positive airway pressure (nCPAP) is now considered the modality of choice for providing respiratory support in the initial management of RDS. (29) The use of nCPAP has been reviewed extensively. Within our own unit a retrospective analysis of the use of nCPAP was undertaken by Jardine et al. They showed an overall survival of 87.6% of VLBW infants, with 18.2% of those infants failing CPAP therapy and requiring IMV. (30) At Chris Hani Baragwanath Hospital (CHBH), Bopape-Chinyanga et al reviewed all VLBW neonates started on nCPAP

within the first 72 hours of life. Similarly they had a survival rate of 87% although the rate of nCPAP failure requiring IMV was higher than that of CMJAH with 34%. (31)

One of the next major breakthroughs was the discovery that antenatal corticosteroids administered to the mother prior to delivery of a premature neonate helped to accelerate the maturity of the lungs and thus prevent a large portion of neonates being born with RDS. (3) Since the seminal work published by Liggins et al, this has been re-evaluated multiple times through the years, with the latest systematic review published by the Cochrane database in 2017 showing an overall reduction in RDS of 34%, as well as significantly less need for IMV amongst numerous other benefits.(4)

However, as with most interventions there are always adverse effects and complications to consider. The aim of mechanical ventilation is to allow for successful gaseous exchange to aid in homeostasis, while avoiding lung injury caused by too high or too low pressure delivery. This is essential as significant morbidity and mortality is associated with lung injury, such as Broncho-pulmonary dysplasia (BPD), air leak syndromes and pneumothorax as well as longer duration of ventilation. Ventilation at too low pressures can result in “atelecto-trauma” as well as inflammation.(29)

Choi et al. found in their study of ventilated VLBW neonates in Korea, that the cumulated duration of ventilation correlated with mortality. They also found that BPD as the cause of death increased from 15 days of ventilation and became the leading cause of death after three months of IMV. They also found that longer duration of ventilation was associated with more morbidity such as peri-ventricular leukomalacia

(PVL), progression of retinopathy of prematurity (ROP) and impaired auditory response.(8)

Another significant cause of morbidity and mortality in VLBW neonates is late-onset sepsis (LOS), defined as clinically suspected or proven sepsis after 72 hours of life. A study on the Brazilian Neonatal Research Network, reported that 24% of all VLBW neonates developed proven LOS. In these infants, IMV was more frequent and prolonged. It is impossible from this study to determine whether IMV caused the higher rates of LOS or if neonates who acquired LOS were more likely to subsequently need IMV or if it is a combination of both. The mortality rate was significantly higher in those with LOS. (9)

In discussing all of this it is also prudent to consider the associated increased hospital costs associated with the significant burden of morbidity in the care of VLBW neonates. In a study conducted in America, Johnson et al. found that LOS had an increase of $10,055 (±R171 631) of direct costs to the hospital, BPD had an increase of $31,565 (±R538 792) and necrotising enterocolitis had an increase of $15,440(±R263 550). They also found that the absolute number of morbidities was associated with significantly higher costs.(32) A good understanding of morbidities and costs associated with IMV is crucial in a resource limited setting, such as in South Africa.

IMV is one of the most critical interventions performed especially amongst VLBW neonates. In a South African context, there have been a handful of studies published looking at mortality of VLBW neonates and within these it is sometimes possible to

extract survival data of neonates that were ventilated. Ntuli *et al* found that between January to July of 2015 at the Mankweng Hospital neonatal intensive care unit (NICU) in Limpopo province, of the 252 VLBW neonates admitted, only 51 received mechanical ventilation (20%) and of those only 23 survived to discharge (45%).(13) At Steve Biko Academic Hospital in Tshwane, Tshehla *et al* observed that between June 2016 and May 2017, of the 231 VLBW neonates admitted, 72 required invasive mechanical ventilation (31%) of which 38 survived to discharge (53%).(12)

Within our own unit, Ballot et.al published a paper in 2010 on the determinants of survival in VLBW neonates. Of the 474 VLBW neonates born at a tertiary academic hospital over a two year period (2006 – 2007), 99 were offered mechanical ventilation (21%) and of those infants, 71 survived to discharge (72%).(33)

The survival rate observed in the above South African studies is higher than survival rates observed in some other NICUs in low-middle income countries. In a prospective observational study conducted in a NICU in Southern India between 2000 and 2002, of the ten VLBW neonates that were ventilated, only three survived, with a survival rate of 30%.(19) Even when compared to some upper middle or high income countries we still see higher survival rates in a South African setting. In a study from the University Hospital of the West Indies (upper-middle income), published in 2006 by Trotman *et al*, of the 73 VLBW neonates that were ventilated, 35 survived with a survival rate of 48%.(18) This is comparable to a study conducted in the high income economy of Saudi Arabia in January 2002 (by Karthikeyan *et al*.) – they observed a mortality rate of 48.6% for ventilated VLBW neonates (18/37).(20)

While the overall survival rates are interesting to compare, it is more prudent to try to understand the various factors associated with the survival of ventilated VLBW neonates. The survival rate observed within our unit is higher than what could be expected within a resource limited setting and it is valuable to try to understand if this could be translated to better outcomes in other centres with similar resources.

Despite this, it seems there is an overall paucity of data looking specifically at outcomes of VLBW neonates who have undergone mechanical ventilation as an intervention on its own, and not as part of larger data set as one factor in the myriad of complications that premature infants may acquire throughout their care within a neonatal ICU. This study aims to review the characteristics and outcomes of VLBW neonates who received IMV within the NICU at the Charlotte Maxeke Johannesburg Academic Hospital over a seven year period.

2. OBJECTIVES OF THE STUDY

2.1 PRIMARY OBJECTIVES

a. To describe the characteristics and outcomes of VLBW neonates who received IMV

2.2 SECONDARY OBJECTIVES

a. To determine the outcome of VLBW neonates who are ventilated multiple times vs those who are only ventilated once
b. To determine factors associated with mortality in VLBW neonates who received IMV by comparing survivors with non-survivors.

3. METHODOLOGY

3.1 STUDY DESIGN

Retrospective descriptive study, secondary analysis of an existing database.

3.2 STUDY POPULATION

All neonates who received invasive mechanical ventilation at Charlotte Maxeke Johannesburg Academic Hospital from 1 January 2013 – 31 December 2019.

a. INCLUSION CRITERIA

Neonates with a birthweight of less than 1500g.

b. EXCLUSION CRITERIA

1. Study participants with no information on mechanical ventilation

3.4 STUDY SETTING

Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) has a 15 bed combined neonatal and paediatric ICU. The ICU is serviced by 2 paediatric registrars during the day and 1 on call registrar after hours. The staff are supervised by Neonatology consultant or fellow.

NICU admisisons are generally reserved for neonates with a birth weight above 800g or neonates who were born less than 800g who have now grown to more than 800g.

Management strategies for various conditions included criteria for ventilation and ICU admission are outlined in units protocol.

Indications for mechanical ventilation are outlined as such, recurrent apnoeas, respiratory failure defined as either PaCO2 of >55 mmHg with acidemia (pH <7.25);

PaO2 <50 or oxygen saturations of <90% on an FiO2 of >70% oxygen. An attempt at non – invasive ventilation (nasal CPAP) should precede mechanical ventilation.

3.3 DATA COLLECTION

a. DATA COLLECTION INSTRUMENT

See Appendix A.

b. DATA COLLECTION METHOD

Data will be extracted from a pre-existing neonatal database run and maintained by the neonatal unit at the Charlotte Maxeke Johannesburg Academic Hospital. The data is managed using Research Electronic Data Capture (REDCap), which is hosted by the University of the Witwatersrand.(12) Patient details are captured at discharge for each patient onto the database for the purpose of clinical audit and quality improvement. Once captured they are checked and verified at multiple points. Only de-identified data will be analysed.

3.4 VARIABLES TO BE ANALYSED

The data sheet (Appendix A) will capture demographic information (maternal age, parity, gestational age, birth weight, gender), perinatal details (mode of delivery, APGAR scores, resuscitation details), clinical diagnosis, ventilation details (mode of ventilation, duration, complications), other associated neonatal complications and diseases, surgical diagnoses and survival details.

3.5 DATA ANALYSIS

a. STATISTICAL ANALYSIS

Descriptive analysis will be used for the baseline characteristics of study participants, such as age, sex, diagnosis, type of ventilation received, other relevant comorbidities.

Continuous variables which are normally distributed will be described with means and standard deviations; those with skewed distribution will be described using median and inter-quartile range. Categorical data will be described using frequencies and percentages.

All variables will be compared between survivors and non-survivors. For the categorical variables, a chi-squared test will be used to infer if there is statistical significance between the groups. For continuous variables the students t-test or Mann Whitney U analysis will be used, depending on the distribution of the data. A p value < 0.05 will be considered statistically significant

All those variables with a p value < 0.1 on univariate analysis will be entered into a binary logistic regression, considering survival as the primary outcome and will be used to establish associations with poor outcome.

b. SAMPLE SIZE CALCULATION

Based on a review of the database, we can expect approximately 450 VLBW infant admissions per year. Based on the study of the same population in 2010 by Ballot et al, we can expect 20% to require mechanical ventilation. (33) Accordingly we can expect a total sample of approximately 630 patients.

3.6 RESEARCH ASSUMPTIONS

a. DEFINITIONS OF TERMS AND ABBREVIATIONS

i. Neonate – a child within the first 28 days or life. A preterm infant will be classified as a neonate according to their chronological age corrected for gestational age (e.g. a 5-week old preterm infant born at 28 weeks will be corrected to 31 weeks and hence is a neonate).

ii. Very low birth weight – birth weight < 1500g.

iii. Extremely low birth weight – birth weight <1000g.

iv. Invasive Mechanical Ventilation (IMV) - Intermittent Positive Pressure Ventilation (IPPV) through an endotracheal tube via either a conventional mechanical ventilator (CMV) or high frequency oscillator ventilator (HFOV)

v. Confirmed sepsis – positive blood culture of organism deemed to be significant.

vi. Early-onset sepsis (EOS) – confirmed sepsis and or meningitis before 72 hours of life.

vii. Late-onset sepsis (LOS) – confirmed sepsis with onset after 72 hours of life.

viii. Cranial Sonar Findings – intra-ventricular haemorrhage (IVH) graded according to Papile(17)

ix. Broncho-pulmonary dysplasia – oxygen at 28 days of life

x. NEC – grade II and III according to modified Bell (16)

xi. Other variables are defined according to the Vermont Oxford Network.(34)

4. SIGNIFICANCE OF THE STUDY

Although many studies have looked at the impact of survival of VLBW neonates, none have looked at what specifically impacts the survival of those that have been ventilated. This may help us to define both positive and negative prognostic factors, which in turn may help us to more accurately select which patients should be prioritised for this crucial, yet very limited resource. It will also help us to evaluate what specific factors we should be focusing on to help improve survival rates amongst ventilated neonates in our continuous efforts of self-evaluation and improvement.

5. POTENTIAL LIMITATIONS

As this is a retrospective review of an existing database there are numerous limitations inherent to this type of research. The biggest limitations are the sources of potential bias, issues surrounding validity, issues around missing data and the fact that we can only establish associations, not causal relationships.(35)

The study site is a tertiary referral centre with a large paediatric surgery service, so the results will not be generalizable to regional and district facilities.

6. ETHICAL CONSIDERATIONS

The proposal for this study will be submitted to the University of the Witwatersrand's Human Research Ethics Committee (HREC). As this is a retrospective database review, no consent will need to be obtained from individual patients. Confidentiality will

be ensured as data sheets will only contain a study number. Identifying data (for example, name and hospital number) will be stored in a separate database at a different, secure location so that only the supervisors will have access to this information. The study will not be started until clearance from the HREC and permission from the hospital (CMJAH) CEO is granted.

7. PROJECTED OUTLINE

7.1 TIMEFRAME

	2020									
	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Jan	Feb
Protocol preparation	x	x	x							
Submission to post grad committee				x	x					
Application for institutional permission				x	x					
Submission for ethics approval					x	x				
Data Collection						x				
Data Analysis							x	x		
Write up							x	x	x	
Submission									x	x

7.2 BUDGET FOR THE STUDY

Approximate budget of R1000 (for stationery, printing and binding).

The cost of the study will be borne by the investigator.

7.3 PUBLICATION PLAN

The final report will first be submitted to the University of the Witwatersrand post graduate research office for assessment as partial fulfilment for the degree of Master of Medicine in Paediatrics. Thereafter, publication may be considered.

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9. APPENDIX

1. Data Capture Instrument

Data Capture Sheet

Database Number:

DEMOGRAPHICS

1) Birth Weight: (g)
2) Gestational Age: (weeks) 3) Place of Birth: Inborn ☐
   Out born ☐
   Clinic / MOU ☐
   BBA ☐
   Unknown ☐
4) Maternal age: (years) ☐

PRENATAL AND MATERNAL DETAILS

1) Antenatal Care Received ☐
2) Antenatal Steroids ☐
3) Antenatal Magnesium Sulphate ☐
4) Chorioamnionitis ☐
5) Maternal Hypertension ☐
6) Maternal HIV infection ☐
   a. Maternal ART use ☐
7) Maternal Syphilis ☐
   a. Received Treatment ☐
8) Maternal Diabetes ☐

PERINATAL AND POSTNATAL DETAILS

1) Mode of delivery
   a. NVD ☐
   b. Breech ☐
   c. Elective Caesarean Section ☐
   d. Emergency Caesarean Section ☐
2) Multiple Gestation ☐
3) APGAR scores
   a. 1 minute:
   b. 5 minutes:
   c. 10 minutes:
4) Resuscitation in Delivery Room
   a. Oxygen alone ☐
   b. Bag mask Ventilation ☐
   c. Chest Compressions ☐
   d. Endotracheal tube intubation ☐

e. Adrenaline ☐

5) Temperature on admission (°C)
6) Congenital Infection ☐
7) Early onset Neonatal Sepsis ☐
8) Metabolic Acidosis ☐

RESPIRATORY COMPLICATIONS

1) Respiratory Diagnosis:
2) Indication for Invasive Ventilation
3) Age at first ventilation: (days)
4) Duration of ventilation: (days)
5) Mode of Ventilation
a. Conventional Mechanical Ventilation ☐
b. High Frequency Oscillatory ventilation ☐ 6) Surfactant use: ☐
    a. Age at 1st administration: (hours)
    b. Number of doses received:
7) On Oxygen on day 28 of life ☐
8) Use of steroids for treatment of Chronic Lung Disease ☐
9) Discharged on home oxygen ☐

NEONATAL COMPLICATIONS / OTHER DIAGNOSIS

1) Persistent Ductus Arteriosus ☐
2) Caffeine administered ☐
3) Inotropic Support ☐
4) Pneumothorax ☐
5) Late Onset Sepsis (after day 3) ☐
6) Cranial Sonar Findings
    a. Not done ☐
    b. Normal ☐
    c. IVH Grade 1 ☐
    d. IVH Grade 2 ☐
    e. IVH Grade 3 ☐
    f. IVH Grade 4 ☐
    g. Peri-ventricular leukomalacia ☐
7) Surgical Diagnosis
    a. Necrotising Enterocolitis ☐
        i. Stage:
        ii. Type of Surgery for NEC
            1. Pencil Drain ☐
            2. Laparotomy ☐
            ☐

3. Colostomy

b. Other Surgical Diagnosis:

8) Survived to Discharge ☐

APPENDIX C: PLAGIARISM DECLARATION

PLAGIARISM DECLARATION TO BE SIGNED BY ALL HIGHER DEGREE STUDENTS

SENATE PLAGIARISM POLICY: APPENDIX ONE

I **Rowan Goldstein** (Student number: **0604434T**) am a student registered for the degree of **MMed (Paeds)** in the academic year **2022**

I hereby declare the following:

- I am aware that plagiarism (the use of someone else's work without their permission and/or without acknowledging the original source) is wrong.
- I confirm that the work submitted for assessment for the above degree is my own unaided work except where I have explicitly indicated otherwise.
- I have followed the required conventions in referencing the thoughts and ideas of others.
- I understand that the University of the Witwatersrand may take disciplinary action against me if there is a belief that this is not my own unaided work or that I have failed to acknowledge the source of the ideas or words in my writing.
- I have included as an appendix a report from "Turnitin" (or other approved plagiarism detection) software indicating the level of plagiarism in my research document.

Signature: _____ Date: 06-10-2022

APPENDIX D: ETHICS CLEARANCE CERTIFICATE

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

R49 Dr R Goldstein

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M2111141

NAME: (Principal Investigator)	Dr R Goldstein
DEPARTMENT:	School of Clinical Medicine Department of Paediatrics and Child Health Medical School University
PROJECT TITLE:	*Factors associated with mortality in very low birth weight neonates treated with invasive mechanical ventilation at a tertiary hospital in South Africa*
DATE CONSIDERED:	2021/11/26
DECISION:	Approved unconditionally
CONDITIONS:	
NOTE:	If contact information regarding student study participants is required, please contact the Registrar's office - <Nicoleen.Potgieter@wits.ac.za>
SUPERVISOR:	Dr R Saggers and Professor D Ballot
APPROVED BY:	Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	2022/03/10

This Clearance Certificate is valid for 5 years from the date of approval. An extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office secretariat on the 3rd floor, Phillip Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated from the research protocol as approved, I/we undertake to submit details to the Committee. **I agree to submit a yearly progress report**. When a funder requires annual re-certification, the application date will be one year after the date when the study was initially reviewed. In this case, the study was initially reviewed in **November** and therefore reports and re-certification will be due in the month of **November** each year. Unreported changes to the study may invalidate the clearance given by the HREC (Medical).

Signature of Principal Investigator _____ Date _____

APPENDIX E: TURNITIN REPORT

Research Report Final submissible paper only-4.docx

by Rowan Goldstein

Submission date: 06-Oct-2022 09:28AM (UTC+0200)

Submission ID: 1918079969

File name: Research_Report_Final_submissible_paper_only.docx (107.48K)

Word count: 3872

Character count: 22003

SUBMISSIBLE PAPER

NEONATES TREATED WITH INVASIVE MECHANICAL VENTILATION

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Ballot[2], FC Paed (.

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.
[2]*School*

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Key Words:

Neonates
Mortality
Invasive mechanical ventilation
Very Low Birth Weight
South Africa

ABSTRACT

Introduction: with available to neonates, especially amongst very low birthweight (VLBW) neonates. Since its introduction in the 1960s it has been associated with an increased survival amongst VLBW neonates.

Objectives: To describe the characteristics and outcomes of VLBW neonates who received IMV in (NICU) (CMJAH).

who required IMV 2019. outcomes . The NICU is combined with the paediatric ICU and comprises of 15 beds.

3 484 neonates of which 849 required IMV (24.4%). Of the 849, 445 survived (52.4%). 44 infants required high frequency oscillatory ventilation, 16 of whom survived (16/44, 36.4%) making the need for HFOV one of the factors strongly associations with outcomes .003), the presence metabolic acidosis ( ), the diagnosis NEC (.001), pathological cranial sonar findings (hospital admission (.001).

Conclusion: One quarter of VLBW neonates admitted at CMJAH required IMV during their hospital admission. We demonstrated a survival rate of 52% for ventilated VLBW infants. The only predictive factor for mortality was the presence of metabolic acidosis, likely a surrogate for severity of illness.

1. INTRODUCTION

Since the introduction of invasive mechanical ventilation (IMV) in the 1960's there has been a significant reduction in the mortality of premature neonates. The use of IMV contributes to improve the survival of critically ill neonates, especially amongst those diagnosed with respiratory distress syndrome (RDS).(1) Through various refinements in technology and ventilator design, as well as ventilatory technique, the survival of very low birthweight (VLBW) neonates and our ability to rescue extremely premature infants has improved drastically.

It is particularly prudent we continue to improve if we are to meet the Sustainable Development Goals, particularly those directly related to neonatal mortality. The key indicators being referred to are "*3.2 By 2030, end preventable deaths of newborns and children under 5 years of age, with all countries aiming to reduce neonatal mortality to at least as low as 12 per 1000 live births and under-5 mortality to at least as low as 25 per 1000 live births*" and "*3.4 By 2030, reduce by one third premature mortality from non-communicable diseases through prevention and treatment and promote mental health and well-being.*"(2)

The improvement in survival of VLBW neonates has not come about through IMV alone. surfactant in management of RDS, the introduction and widespread non-invasive ventilation, particularly nasal Continuous Airways Pressure (nCPAP) have contributed significantly to the overall reduction in both morbidity and mortality observed through the years.(3-5)

However, IMV is associated with a myriad of morbidities and conditions that may lead to an increase in mortality. IMV itself cause "air-leak syndromes" such as pneumothorax, as well as prolonged duration of ventilation. One of the most significant conditions associated with lung injury is broncho-pulmonary dysplasia (BPD) which is associated with lifelong morbidity as well as a significantly increased risk of mortality.(6)

Outside of the lung IMV is also associated with retinopathy of prematurity (ROP), neurodevelopmental , late onset sepsis (LOS), necrotising enterocolitis (NEC) and many other complications.(7-9)

Resources for neonatal intensive care including the availability of IMV vary greatly). In South African context, there have been a handful of studies published looking at mortality of VLBW neonates and within these it is sometimes possible to extract survival data of neonates that were ventilated. Ntuli *et al* in a study published in 2020 showed a survival rate of 45% when reviewing VLBW neonates admitted between January to July 2015 at Mankweng Hospital NICU. When Tshelhla *et al.* reviewed survival data at Steve Biko Academic Hospital they had a survival rate of 53% for ventilated VLBW neonates. Looking at data published previously from within the unit at CMJAH, Ballot *et al.* reviewed all neonates admitted between 1 January 2013 and 31 December 2015. There were 1590 VLBW neonates admitted, of which 299 required IPPV (18.8%). The overall mortality for VLBW neonates was 30.1% (n=479/1590).(10-12)

This study aimed to review VLBW neonates who were ventilated quaternary South Africa, to describe the population requiring ventilation as well as their mortality and morbidity rates.

2.

VLBW (weighing <1500g) who were intensive care (NICU) CMJAH who required IMV from 1 January 2013 – 2019. regarding ventilation hospital

neonatal unit consisted of NICU for neonatal high care 35 beds and a low dependency unit of 40 beds. The NICU essentially functioned as a ventilator unit and patients admitted to the NICU were managed by neonatologists.

2.1 DATABASE

Patient data was captured by the attending neonatal team on to the REDCap database at discharge. Data was managed using .(13, 14). . The platform developed with the specific intent of aiding in assurance.

various throughout the data process. All was anonymised on export of the database. was characteristics – , antenatal steroids, other maternal comorbidities such as hypertension, diabetes, HIV status (ii) neonate characteristics – , details around delivery room resuscitation, admission details including temperature, (iii) ventilation details – diagnosis, indication for IMV, age at IMV initiation, duration of ventilation, mode of ventilation, surfactant use, (iv) complications and comorbidities – any comorbid conditions, details around sepsis, cranial sonar and ROP findings, any surgical diagnosis, oxygen requirements on day 28 of life and (v) outcome at discharge.

2.2 STATISTICAL ANALYSIS

Data was exported to MS Excel (Microsoft, USA) for the purposes of data cleaning. For statistical analysis the spreadsheet was SPSS 28 ( ). with , while skewed . Survivors and non-survivors were compared in terms of demographics, diagnoses, interventions and complications using univariate analysis. For , unpaired depending on whether they were normally distributed or had a skewed . Within variables,

binary analysis was then performed with those with a statistically significant difference .05 .

Definitions

IMV was defined as any modality of ventilation administered via an endotracheal tube. NEC was defined as NEC or either or Bells .(15) ≤ 5. Non-pathological cranial sonar was defined as either normal findings or grade 1 and 2 intraventricular haemorrhage, according to Papiille classification.(16) Pathological cranial sonar included grade 3 and 4 intraventricular haemorrhage.

by defined before .

2.3 Ethics

The study was granted , Johannesburg (M211141).

3.

, 3 484 neonates CMJAH , of which 849 (24%) . 87 neonates were excluded.

The majority were male (n=470/849, 55.4%). Mode of delivery was almost evenly split with 53.3% being born via caesarean section (n=399/749). The majority of neonates

requiring IMV were inborn (n=545/849, 64.2%). The overall survival rate was 52.4% (n=445/849). sex .

Table 1: Clinical characteristics of ventilated VLBW neonates 2019

Clinical	Ventilated neonates (n=849)
	29 (
)	1111 (193)
)	
Age when first ventilated (median, [IQR])	3 [0-10]
])	4 [2-8]
hospital admission (median, [IQR])	27 [9-53]

The majority of mothers had received antenatal care (n=549/725, 75.7%). However, the majority of mothers did not receive antenatal steroids (n=365/651, 56.1%). .7 (.378) years.

When analysing maternal characteristics between survivors and non-survivors the only statistically significant difference was the place of birth, delivery outside the hospital was associated with increased survival (185/445, 52.4%, p<0.001)

The most common respiratory diagnosis was RDS, with 737 (737/753, 98%). The remainder included congenital pneumonia, atelectasis and acquired pneumonia.

The most common indication for ventilation was failing a trial of nCPAP (129/572, 22.3%). proportions various indications for ventilation (p=0.004). 2

however . Figure 2 below demonstrates the various indications for ventilation according to outcome.

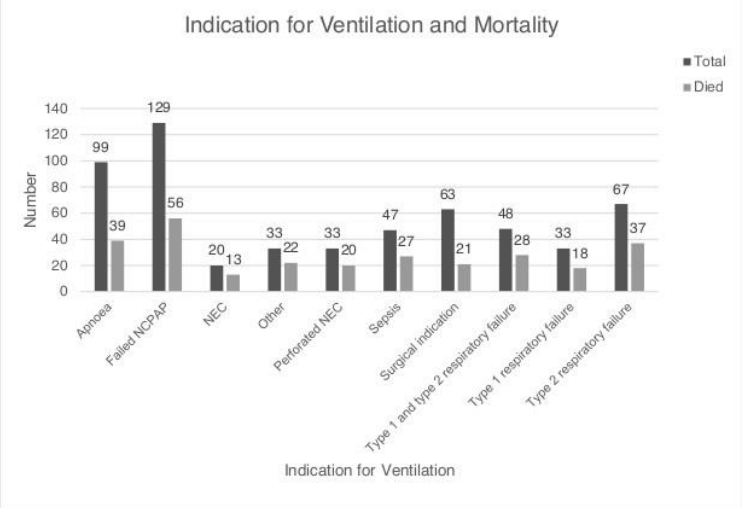

Figure 1: The frequencies of indication for ventilation with outcome (Died vs Survived) of VLBW ventilated neonates 2019

There were 666 infants that received surfactant (78.4%) of which 357 survived (357/666, 53.6%) which was significantly associated with an increased chance of survival (p=0.011). Being treated with steroids for the prevention of BPD (176/199, 88.4%, p<0.001) chance of survival VLBW neonates.

Further [redacted] outcome [redacted] presented [redacted].

[redacted] vs [redacted] ventilated VLBW [redacted] 2019

[redacted]	[redacted]	[redacted]	[redacted]
Maternal age, years ([redacted])	28.88 (6.31)	28.48 (6.31)	0.42
Birth weight, g (mean, SD)	1076.22 (193.16)	1143.52 (186.73)	<0.001
[redacted]	[redacted] .15)	29.12 ([redacted].07)	[redacted].003
[redacted]	[redacted]	[redacted] -8]	0.006
Age at first surfactant dose, minutes (median, [IQR])	120 [73-180]	120 [70-240]	0.479
Age at outcome, days (median, [IQR])	10 [4-22]	49 [30-68]	<0.001

[redacted] vs [redacted] VLBW ventilated [redacted] 2019

[redacted]	[redacted]		[redacted]		[redacted]
	n	%	n	%	
Male	221/402	55.0	249/445	56.0	0.774
Outborn	119/404	29.5	185/445	41.6	<0.001
Apgar > 5	304/335	90.7	302/330	91.5	0.727
Antenatal care	264/351	75.2	285/374	76.2	0.756
Antenatal steroids	149/320	46.6	137/331	41.4	0.184
Caesarean Section	181/365	49.6	211/384	54.9	0.142
HFOV	38/404	9.4	16/445	3.6	<0.001
Received surfactant	309/375	82.4	357/402	88.8	0.011
Metabolic Acidosis	151/404	37.4	52/445	11.7	<0.001
EOS	29/345	8.4	20/418	4.8	0.104
LOS	214/398	53.7	260/442	58.8	0.144
Oxygen on day 28	71/292	24.3	273/416	65.6	<0.001
Steroids for BPD	23/386	5.6	176/417	42.2	<0.001
NEC	132/404	32.7	96/445	21.6	<0.001
NEC surgery	64/132	48.5	49/96	51.0	0.944
Pathologic Cranial Sonar	79/251	31.4	45/353	12.7	<0.001

There were 54 (6.4%) neonates who required HFOV, 38 of which demised (38/54, 70.4%). Other factors significantly associated with death were the presence of metabolic acidosis (151/203, 74.4%, p<0.001) and the presence of NEC 132/228, 57.9%, p<0.001). However, the need for surgery in NEC was not significantly associated with outcome in our cohort.

Cranial sonars were performed on 604 (78.1%) neonates during the study period. Of those 124 had an abnormal finding, which was significantly associated with non-survival (79/251, 31.4%, p<0.001)

During the study 254 neonates underwent ROP screening while still in hospital. Of those 216 had normal screening studies (n=216/254, 85%).

A binary logistic regression analysis was performed with survival to discharge variable, which listed 4 below. According to the analysis, metabolic acidosis was the only variable found to be statistically significant and was associated with a decrease in survival.

Table 4: model of ventilated 2019

	Odds ratio	95% CI	
		Lower	Upper
Duration of ventilation	1.023	0.978	1.069
Birth weight	1.001	0.999	1.003
Gestational Age	1.059	0.870	1.287
Metabolic Acidosis	0.342	0.148	0.796
Normal Cranial Sonar Findings	2.203	0.800	6.062
NEC Surgery	0.573	0.262	1.253
HFOV	0.561	0.144	2.188
Constant	0.003		

4. Discussion

Despite IMV being widespread and frequently used, there is a paucity of data looking specifically at VLBW neonates who undergo IMV as an intervention in and of itself, as opposed to part of larger study or dataset. In our study up to 24% of VLBW neonates required ventilation at some point during the course of their admission. This also needs to be understood in the context of limited capacity for IMV and stricter criteria for the initiation of IMV than one might find in a setting of relatively unrestricted resources.

In our study we demonstrated a survival rate of 52% amongst ventilated VLBW neonates. This is comparable to other LMICs. In a study from the published 2006, they demonstrated survival rate of 48% for ventilated VLBW neonates. In Riyas at a NICU

India, there was a survival rate of 30% amongst ventilated VLBW neonates. Even compared to a high income setting like Saudi Arabia, in a study published in 2002, there was an observed survival rate of 51.2% for ventilated neonates.(17-19)

Commented [RS1]: 3 studies referenced, only 2 mentioned. Please mention the Indian one too.

was RDS. In context the study population being VLBW neonates, this was expected. Surfactant administration was associated with survival benefit. Predictably, lower birth weight and prematurity are significant risk factors for death. administration of surfactant had no

with early or late onset sepsis and mortality. Metabolic acidosis significantly . This likely an indication on severity of illness and thus is logical that the neonates with more severe illness were more likely to demise. In our setting IMV is generally used as a rescue therapy for neonates who have failed a trial of nCPAP and thus are generally further down the disease progression. Metabolic acidosis was also seen significant neonates on binary logistic regression by Ballot *et al.* in their paper published in 2016.

Of interest, many of the antenatal factors and interventions (for example, antenatal steroids) which we expected to impact on mortality, did not show any significant survival benefit in our population. This would need to be investigated further as the fact that we only studied ventilated neonates may be masking the expected survival benefit. We also demonstrated a relatively low rate of antenatal steroid usage. Although comparable to previous studies at CMJAH, this is however lower than rates in other LMICs. A study by WHO in 2014 had a median use across multiple countries of 54%, still much usage rates .(20-22) Considering the impressive benefit antenatal steroids have demonstrated on not just lung maturity, but overall improvement in morbidity and mortality this is something that we should endeavour to improve upon.

Being outborn was associated with increased survival on univariate analysis. This is in opposition to what we expected, when reviewing the literature, as being outborn was either associated with an increased mortality or tended to have no effect on mortality.(12, 23) This may be due to an inherent selection bias within the group of neonates being transferred in, as in order to survive transfer the neonate in question would have to be in a relatively stable condition. Many neonates that may have been

candidates for ventilation within our unit unfortunately may have been simply too ill to survive the hospital transfer.

We also noted that the vast majority of our neonates who required ventilation are inborn. CMJAH is a specialist obstetric unit receiving many referrals for obstetric complications. In our study we are only studying VLBW, premature infants which are all considered to be complicated deliveries, thus we may consider that these are in-utero transfers as they are all at high risk for requiring specialist neonatal care.

Low [redacted] also [redacted] not [redacted] increase in [redacted]. However due to CMJAH being in a resource limited setting, there may be selection bias influencing this result.

5. LIMITATIONS

[redacted] database [redacted], therefore some data was missing. As [redacted] and the fact that we are dealing with admissions into an ICU setting, the proportions and severity of disease may be overrepresented and overestimated. [redacted] centre [redacted] from [redacted] centre so [redacted] generalisable [redacted] all populations. As this was a database timing of events were not captured.

6. CONCLUSION

In our study one quarter of VLBW neonates admitted at CMJAH required IMV during their hospital admission. We demonstrated a survival rate of 52% for ventilated VLBW infants. The only predictive factor for mortality was the presence of metabolic acidosis, likely a surrogate for severity of illness.

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17

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