SURFACTANT FOR THE TREATMENT OF RESPIRATORY DISTRESS SYNDROME IN VERY LOW BIRTH WEIGHT INFANTS AT A LEVEL 2 HOSPITAL: A DESCRIPTIVE RETROSPECTIVE COHORT STUDY — SAFETY AND EFFICACY

Mnqobi Njabulo Nxumalo (NXMMNQ001)

Thesis presented for the degree of Master of Medicine in Paediatrics

Department of Paediatrics and Child Health

Faculty of Health Sciences

University of Cape Town

Supervisor: Dr Yaseen Joolay

Co-Supervisor: Dr Ilse Els-Goussard

Co-Supervisor: Dr Kenneth Sprenger

Declaration:

I, Mnqobi Njabulo Nxumalo, hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

I empower the university to reproduce for the purpose of research either the whole or ontents in any manner whatsoever.

Signature: Signed by candidate

Supervisors Declaration:

The planned publication meets all requirements to be included in the dissertation, namely:

The journal publishing the paper is accredited by the department of higher education and training or it has been approved by the UCT Health Sciences Specialist Training Committee and:

- The candidate is the first author on the paper
- The candidate contributed the most to the paper
- The candidate developed the protocol and wrote the paper under supervision
- The candidate was involved in the analysis, presentation and interpretation of results
- The other authors and their contributions to the paper are stated:

Co-supervisor: Dr Ilse Els-goussard: research question formulation and protocol development.

Co-supervisor: Dr Kenneth Sprenger: methodology development, editing final write up.

Primary supervisor: Dr Yaseen Joolay: Protocol editing, statistical analysis and final write up editing.

Signature: … Signed by candidate

Date.....28/03/2023

Acknowledgements; Format and Contributions:

To my family, I could not do anything without their support. To my supervisors, for their expert guidance over great distances and conflicting schedules. Finally to the amazing team at George Regional Hospital, the results are a reflection of your dedication to saving the lives of premature infants.

This thesis is an unpublished original work by the authors. The data was collected from electronic patient folders with the approval of the George Regional Hospital and University of Cape Town Department of Health Sciences Human Research Ethics Committees.

The format is in publication ready format in keeping with author guidelines for the South Africa Medical Journal including word count and referencing style, see annexure A. The research is not submitted for another degree at another university.

Table of Contents

List of Tables

Abbreviations:

CI	Confidence interval
CPAP	Continuous Positive Airway Pressure
ECM	Electronic content manager
FiO2	Fraction of inspired oxygen
GSA	Geographical Service area
HIV	Human immunodeficiency virus
HFOV	High Frequency Oscillation Ventilation
INSURE	Intubation surfactant and extubation
IQR	Interquartile range
LISA	Less invasive surfactant administration
NCPAP	Nasal continuous positive airway pressure
NICU	Neonatal intensive care unit
NIPPV	Non-invasive positive pressure ventilation
NNT	Numbers needed to treat
N	Number
PDA	Patent Ductus Arteriosus
PEEP	Positive End Expiratory Pressure
PPIP	Perinatal problem identification programme
RR	Relative risk
RDS	Respiratory distress syndrome
RCT	Randomised control trial
SPB	Surfactant protein B
SPSS	Statistical package for social sciences
SPTL	Spontaneous preterm labour

TRR	Typical relative risk
US$	United States of America dollar
WC	Western Cape
WMD	Weighted mean difference

Abstract:

Background and rationale: Respiratory Distress Syndrome (RDS) is common in pre-term infants and is related to immaturity of the lungs. Surfactant therapy is now being widely used outside of tertiary neonatal centres. The purpose of this study is to describe the demographics and the incidence of adverse events in very low birth weight preterm infants with RDS treated with surfactant at a regional Hospital in the Western Cape Province of South Africa.

Methods: This was a retrospective observational study of infants treated with surfactant during the study period 2017 to 2019 at George Regional Hospital. We conducted an electronic folder review of infants with a birth weight of 800g to 1200g. Outborn infants and those with congenital abnormalities were excluded.

Results: The total number of patients included in the study was 66. The median birth weight was 965g (Interquartile range (IQR) 880-1060g) with a median gestational age of 28 weeks (IQR 28-29 weeks. The median time to first dose of surfactant was 5 hours (IQR 2-16). The mortality rate was 25.8% (17/66). The incidence of bronchopulmonary dysplasia was 6% (4/66).The incidence of pulmonary air leak was 3% (2/66) and pulmonary haemorrhage was 9.1% (6/66). The median number ofdays on mechanical ventilation for the patients who were ventilated was 3 days (IQR 2-6). The median total number of days on respiratory support was 9 days (IQR 4-29).

Conclusion and recommendations: Regional hospitals have limited capacity for ventilatory support of preterm newborns. The mortality rate was comparable to outcomes at South African central hospitals. Further research should explore how the incidence of adverse events can be reduced in very low birth weight infants.

Publication –ready Manuscript

Surfactant for the treatment of respiratory distress syndrome in very low birth weight infants at a level 2 hospital: a descriptive retrospective cohort study – safety and efficacy

Authors: Nxumalo, M; Els-Goussard, I; Sprenger, K; Joolay, Y

Abstract:

Background and rationale: Respiratory Distress Syndrome (RDS) is common in pre-term infants and is related to immaturity of the lungs. Surfactant therapy is now being widely used outside of tertiary neonatal centres. The purpose of this study is to describe the demographics and the incidence of adverse events in very low birth weight preterm infants with RDS treated with surfactant at a regional Hospital in the Western Cape Province of South Africa.

Methods: This was a retrospective observational study of infants treated with surfactant during the study period 2017 to 2019 at George Regional Hospital. We conducted an electronic folder review of infants with a birth weight of 800g to 1200g. Outborn infants and those with congenital abnormalities were excluded.

Results: The total number of patients included in the study was 66. The median birth weight was 965g (Interquartile range (IQR) 880-1060g) with a median gestational age of 28 weeks (IQR 28-29 weeks. The median time to first dose of surfactant was 5 hours (IQR 2-16). The mortality rate was 25.8%(17/66).The incidence of bronchopulmonary dysplasia was 6%(4/66).The incidence of pulmonary air leak was 3%(2/66) and pulmonary haemorrhage was 9.1%(6/66). The median number of days on mechanical ventilation for the patients who were ventilated was 3 days (IQR 2-6). The median total number of days on respiratory support was 9 days (IQR 4-29).

Conclusion and recommendations: Regional hospitals have limited capacity for ventilatory support of preterm newborns. The mortality rate was comparable to outcomes at South African central hospitals. Further research should explore how the incidence of adverse events can be reduced in very low birth weight infants.

Introduction:

Despite improvements, South Africa has many challenges in providing neonatal care. The neonatal mortality rate for South Africa is currently at 12/1 000 live births, which has remained stagnant for the past decade according to the saving babies triennial report. [1]

Neonatal deaths accounts for over 70% of the under 5 mortality rate. [1] Prematurity related causes accounted for 49.2% of neonatal deaths in South Africa in 2018. [2] The proportion of early and late neonatal deaths occurring at a tertiary institution ranged from 14.6-18.9% nationally in 2019. [2] This highlights the fact that a majority of neonatal deaths occur outside of tertiary institutions.

The Eden district in the Western Cape (WC) province is outside the main urban hub of the WC and has no tertiary hospital, the closest tertiary neonatal unit is over 400km away. In the year 2019 the Eden district of the Western Cape recorded 1415(10.8%) infants born with a birth weight less than 1.5kg. Survival for this group was 91.6% according to the Perinatal Problem Identification Program (PPIP). [1]

Respiratory Distress Syndrome (RDS) is common in pre-term infants and is related to immaturity of the lungs and insufficient endogenous surfactant. Exogenous surfactant administration combined with non-invasive or invasive mechanical ventilation is now the mainstay of treatment for RDS. This has significantly improved the outcomes of very low birth weight infants, resulting in lower mortality rates and decreased incidence of adverse outcomes. [3]

Surfactant is a combination of lipids and proteins that lines the alveoli and lower airways. It lowers the surface tension at the alveolar membrane. This prevents alveolar collapse and improves lung compliance resulting in rapid oxygenation and a decreased work of breathing.
[3] Surfactant treatment was shown to result in significant improvements in oxygenation, less pulmonary air leaks and interstitial disease as compared to controls. [4]

The method known as the INtubation SURfactant Extubation (INSURE) method combined with CPAP was found to be the most effective way of administering surfactant resulting in a decreased incidence of pulmonary air leak, less need for mechanical ventilation and less progression to chronic lung disease and lower mortality (5-7, 10-13) when compared to surfactant administration and continued mechanical ventilation. Patients with a birth weight < 1200g and a gestational age <30 weeks have been shown to be the most at risk of adverse outcomes. But they also have the highest benefit from treatment. [7]

The neonatal viability criteria as defined by the Western Cape Policy Document for secondary hospitals allow for the administration of surfactant in infants with a birth weight > 800g. [8] Level 2 Hospitals around the Western Cape have access to non-invasive mechanical ventilation and surfactant. They also have access to short term mechanical ventilation. George Regional Hospital also has access to High Frequency Oscillation Ventilation (HFOV) and they have a full time Neonatologist as one of their consultants.

Alternative, less invasive methods such as nebulisation, administration though a Laryngeal mask airway and introduction by thin catheter in a spontaneously breathing patient are currently under investigation. Preliminary evidence from these trials shows that less invasive techniques result in a decrease in mortality and the incidence of chronic lung disease. [5-7,9, 11, 14-17]

In 2017 a systematic review was published comparing less invasive surfactant administration (LISA) and INSURE. [18] In this study the surfactant was administered using a soft thin catheter, McGill's forceps and laryngoscope. The study compared 6 Randomised controlled trials with a pooled infant number of 895 infants. They found that LISA was associated with less need for mechanical ventilation (RR=0.71 (0.53 to 0.96), p=0.02) and a decreased incidence of Bronchopulmonary dysplasia (RR) =0.75 (95% CI 0.59 to 0.94), p=0.01). [18]

The surfactant preparation used at George Hospital is Beractant. The dose used is the manufacturer recommended dose of 100mg/kg/dose or 4mls of the 25mg/ml preparation. The predominant method of surfactant administration was using the Less Invasive Sufactant Administration (LISA) technique, Infants who are mechanically ventilated receive surfactant via the endotracheal tube. The Intubation surfactant administration and extubation (INSURE) method was used in some infants.

The guideline recommends surfactant for infants with a FiO2 35-45% on NCPAP. A repeat dose is recommended in 6 to 12 hours if the oxygen requirements or the work of breathing are increased. George regional hospital also has access to HFOV and the indications to start treatment are if there is a high pCO2 not responding to mechanical ventilation or oxygen index. To date there has been little published data on the outcomes of infants treated with surfactant outside of tertiary centres.

The purpose of this study is to assess the safety of surfactant treatment in a level 2 hospital and to describe the patient demographics and the incidence of adverse outcomes of preterm infants with RDS treated with surfactant.

Methods:

We conducted a retrospective descriptive study based on folder review of electronic patient records at George Regional Hospital, a level 2 Hospital in the Eden district of the Western Cape. The study period was from January 2016 to December 2019. Ethics approval was obtained for both the George Regional Hospital Ethics Committee and the Human Research Ethics Committee at the University of Cape Town. There was no need for individual infant informed consent as this was a folder review based on data in an existing database. We included inborn infants with a birth weight of 800g to 1200g. We excluded outborn infants and infants with congenital abnormalities.

The pharmacy provided a record of folder numbers for all patients given surfactant during the study period. The pharmarcy issues surfactant per patient once a prescription is received, after hours this is recorded in the emergency cupboard register, thus all patient who receive surfactant are recorded. The folder numbers were then used to access patient records on the Electronic Content Manager (ECM) system used at George Hospital to store patient records. Each physical patient file is scanned and uploaded to ECM including the nursing notes, patient results sheets and any prescription charts.

We then conducted an electronic folder review of patients treated with surfactant during the study period and collect the data on the case report form (Annexure C). The case report form results were then recorded on a coded data sheet to protect identifying information and ensure confidentiality to patients. The data regarding the use of antenatal steroids with incomplete in the infant folders and there was limited access to maternal records and thus this was excluded from the analysis.

The data was then analysed using the Statistical Package for Social Sciences (SPSS). The data were found to have a skewed distribution therefore we reported the median and the interquartile range for the demographic data and the outcomes of interest. Due to the limited sample size and the distribution no inferential statistics were done. Thus a descriptive analysis was done.

The primary outcomes were mortality and the incidence of adverse events; namely pulmonary air leak which includes pneumothorax, pneumomediastinum, pneumopericardium and pulmonary interstitial emphysema. Pulmonary haemorrhage as evidenced by blood suctioned from the trachea post intubation. Bronchopulmonary dysplasia defined as need for supplementary oxygen at 36 weeks post menstrual age if born before 32 weeks or need for supplementary oxygen at 56 days post menstrual age if born after 32 weeks. The secondary outcomes were the duration of mechanical ventilation, number of days on supplementary oxygen; number of days admitted and the number of doses of surfactant required.

Results:

The total number of patients identified through pharmacy records that received surfactant was 213. Of these, 124 patients wereexcluded due to birth weight out of range, 4 had congenital abnormalities and 19 were out-born. This left a total of 66 patients that were included in the analysis.

The patients had a median gestational age of 28 weeks (IQR 28-29) and a median birth weight of 965grams (IQR 880-1060g). Of these, 71.8%(47/66) were born by caesarean section. There was incomplete data regarding the use of antenatal steroids with limited access to maternal records and thus this was excluded from the analysis. The patient demographic data is outlined in table 1. The total number of days on supplementary oxygen was 9 days (IQR 4-29.5). All the infants who had a pulmonary haemorrhage demised. The patient outcomes data for the entire cohort is outlined in table 2

Table 1: Demographic data

	Median(IQR)
Gestational age (weeks)	28(28-29)
Birth weight (grams)	965(880-1060)
5 min Apgar	7(5-8)
Mode of delivery:	**(N)**
Caesarean section	77.3%(51/66)
Normal vaginal delivery	19.6%(13/66)
Breech delivery	3.1%(2/66)
Risk factors for Pre-term delivery:	
Pre-eclampsia	57.7%(38/66)
Antepartum hemorrhage	14.1%(9/66)
Spontaneous preterm labour	25.4%(16/66)
Unbooked	7%(4/66)
Other	14.1%(9/66)
HIV exposure	9.9%(6/66)

The number of patients who received a single dose of surfactant was 66.7% (44/66). The median time to first dose was 5 hours (IQR 2-16). Twenty-two patients received a second dose of surfactant. The median age at second dose was 18 hours (IQR 8-26 and 50% (11/22) required mechanical ventilation. Pulmonary haemorrhage and pulmonary air leak occurred in 13% (3/22) patients respectively. Death occurred in eight of these patients

Table 2: Infant outcomes for all included infants

	(N)/Median(IQR)
Mortality	25.8%(17/66)
Pulmonary air leak	3%(2/66)
Pulmonary hemorrhage	9.1%(6/66)
Bronchopulmonary dysplasia	6%(4/66)
Days on supplementary oxygen	9(4-29.5)
Mechanical ventilation	25%(17/66)
Days ventilated	3(2-6)
Length of hospital stay in days	52(32-69)

The total number of days on oxygen was 8 (IQR 4.5-19.5) days for those who received a single dose of surfactant and the median total days admitted was 28 (IQR 7.5-55) days. They had an incidence of pulmonary haemorrhage of 6.8% (3/48) and BPD of 9% (4/48). In this group incidence of death was18.8% (9/48).

There were 31 patients with a birth weight greater than 1000g, of which 39.1% (12/31) required mechanical ventilation. There were 35 patients who had a birth weight less than 1000g, of which 14.3%(5/35) required mechanical ventilation. A comparison of their outcomes can be found in table 3.

Table 3: Infant outcomes by mode of ventilation and birth weight

	Mechanical Ventilation	Non-invasive ventilation	BW < 1000g	BW > 1000g
Total patients = 66	18	48	35	31
Mortality	44.4%(8/18)	18.8%(9/48)	34.3%(12/35)	16.1%(5/31)
Pulmonary air leak	5.6%(1/18)	2.1%(1/48)	5.7%(2/35)	0/31
Pulmonary hemorrhage	16.7%(3/18)	6.3%(3/48)	11.4%(4/35)	6.5%(2/31)
BPD	0%(0/18)	8%(4/48)	11%(4/35)	0%(0/31)
Days ventilated*	3(2-6)	-	2(1-6)	4(3-7)
Number of doses*	2(1-2)	1(1-1)	1(1-1)	2(1-2)
Days on oxygen*	12(4-28)	8(4-36)	7(3-39)	10(6-28)
Length of hospital stay*	46(3-65)	47(19-65)	46(3-65)	30(18-59)

Abbreviations: BW: birth weight; BPD: Bronchopulmonary dysplasia
*Median(Interquartile range)

There were 17 patients who demised. They had a median birth weight of 900g (IQR 880-1010), and a median gestational age of 28weeks (IQR 27-29). The number of patients who demised that required mechanical ventilation was 47% (8/17)). The median number of days alive in hospital was 3 days (IQR 2-12 days). The incidence of pulmonary haemorrhage was 35.3%(6/17).

Discussion:

This study shows that surfactant can be given safely at level 2 hospitals. Our study found that there was a lower incidence of mortality than those seen in tertiary institutions. This may be due to more unwell patients or complex cases seen in tertiary centers. The incidence of BPD and Pulmonary air leaks was similar to findings in tertiary centres. The number of days on mechanical ventilation was longer than those published in a recent study at a tertiary institution.

The patients who died were very premature and of extreme low birth weight. There was a higher incidence of Pulmonary Haemorrhage in the infants who died, this commonly occurred in smaller infants <1000g and those who needed repeated doses of surfactant. Infants less than 1000g are not routinely offered mechanical ventilation. This may influence the outcomes in this category of infants.

The management of Pulmonary Haemorrhage is largely supportive therefore we do not think these patients would have had better outcomes in a tertiary setting. Due to the resource limitations in the country these patients form the lower limit of birth weight criteria to qualify for surfactant treatment in a majority of level 2 neonatal intensive care units in the country.

The distance from the study site to the nearest tertiary hospital is over 400km, therefore transferring infants is very challenging. George also has a full time Neonatologist and the benefit of having access to mechanical ventilation including HFOV.

The use of surfactant therapy and CPAP has significantly improved the outcomes of pre-term infants with respiratory distress syndrome. Most of the research done in developing countries has been conducted in tertiary institutions. This study explores the demographics and outcomes of very low birth weight infants treated for respiratory distress syndrome with surfactant at a regional level 2 hospital.

A recent retrospective study done in South Africa found no significant difference in outcomes comparing infants with a birth weight less than 1500g treated with either Poractant alfa or

Beractant. [19] Poractant alfa and Beractant were both previously available in the public sector. Poractant alfa was removed due to costs and the evidence to support its use in the public sector was deemed to be insufficient.

Our study outcomes were in keeping with a recent study by Boshoff et al of very low birth weight infants treated with surfactant at a tertiary hospital (see Table 4 for comparisons.) [19] The primary outcome in both studies was mortality and the incidence of adverse events. Although the study included infants that were of very low birth weight therefore the infants in this study were larger than the infants in our study. The study was the best local comparison we found.

The incidence of death in the study 17/66(25.8%) was lower than the incidence of death in the aforementioned study 67/208(32,2%), as well as a study done at a central hospital in Johannesburg 241/633(38.1%). [19, 20]

The median number of days on mechanical ventilation for the cohort 3(2-6) was higher than the outcomes of a recent study done at a central hospital in South Africa 1(IQR 0-2). [19]

Table 4: Comparison with published data from Boshoff et al[19]

	Boshoff et al.	Nxumalo et al.
Mortality	32.2%(67/208)	26%(17/66)
BPD	5.3%(11/208)	6%(4/66)
Days on vent: median(IQR)	1(0-3)	3(2-6)

We found that patients with a higher birth weight, who only required a single dose of surfactant, had better outcomes. There was a high incidence of pulmonary haemorrhage and death in the patients who required mechanical ventilation. We also found that patients who did not require mechanical ventilation had a lower incidence of adverse events such as pulmonary air leaks or haemorrhage.

One of the limitations in the study was the relatively small number of patients that could be included. The retrospective nature of the study made it prone to misclassification bias from the variable amount of detail available in patient records. This was due to the fact that the study was performed at a regional hospital where there were a limited number of deliveries of very low birth weight infants.

We utilized this by utilizing a convenience method of sampling with limited exclusion criteria, this may introduce bias as the sample may not be a true reflection of the population but rather a reflection

of the patients who were admitted during the study period.

Access to maternal records was limited and the majority of mothers had not had an early ultrasound. Therefore we used the consensus gestational age in our study. This was estimated by taking the ballard score, the foot length and the last day of the Mom's last normal menstrual period into consideration.

The study period was selected to include the earliest electronic case records available at the study site. This was done to mitigate the effects of missing data and incomplete or lost case records.

Conclusion:

Regional hospitals have limited capacity for ventilatory support of preterm newborns. This study showed that adverse outcomes in very preterm infants with RDS treated with surfactant at a regional Western Cape hospital were similar to outcomes at central hospitals in South Africa.We recommend further research be done to explore how the incidence of adverse events can be reduced in very low birth weight infants

Funding and conflicts of interest:

The investigators are not affiliated with any drug company nor have we received any external funding. The statistical support will be paid by the University of Cape Town Department Of Paediatrics and Child health.

This research is intended for submission as a mini-dissertation for the MMed in Paediatrics and Child health at the University of Cape Town. Any intellectual property emanating from this research project will belong to the University of Cape Town

Authors:

Dr Mnqobi Njabulo Nxumalo. MBChB. FC Paeds (SA). Medical Registrar: Paediatrics. George Regional Hospital & Groote Schuur Hospital. University of Cape Town.

Dr Ilse Els-Goussard. MBChB, FC Paeds (SA), Cert Neonatology Neonatologist: George Regional Hospital

Dr Kenneth Sprenger. MD, MBBCh, BSc (Med), FC Paeds (SA), Cert Cardiology Paediatric Cardiologist: George Regional Hospital

Dr Yaseen Joolay. MBChB, MMed, FC Paeds (SA), Cert Neonatology: Neonatologist, Senior Lecturer Groote Schuur Hospital / University of Cape Town

References

1. The National Perinatal Morbidity and Mortality Committee. Saving babies report 2017-2020. Triennial report on perinatal mortality in South Africa. Available from: www.gov.za/documents/saving-mothers-report-confidentioal-enquiries-maternal-deaths-south-africa

2. Rhoda N, Velaphi S, Gebhardt GS, Kauchali S, Barron P, Reducing neonatal deaths in South Africa: Progress and challenges. South African Medical Journal [Internet]. South African Medical Association NPC; 2018; 108(3a):0. Available from: http://dz.doi.org/10.7196/samj.2017.v108i3b.12804

3. Henry L. Halliday. History of Surfactant from 1980. Biol Neonate 2005; 87:317-322 DOI: 10.1159/000084879

4. Alan H Jobe. Pharmacology Review: Why Surfactant works for Respiratory Distress Syndrome. Neo Reviews 2006; 7:e95-e106. DOI: 10.1542/neo7-2-e95

5. Seung Hye Han; Rama K Mallampali. The role of Surfactant in Lung disease and Host Defence against pulmonary infections. Annals ATS 2015 12(5):765-774

6. Christopher Cheng-Hwa Ma; Sze Ma. The Role of Surfactant in Respiratory Distress Syndrome. The Open Respiratory Medicine Journal 2012;6:44-53

7. Collaborative European Multicentre Study Group: Surfactant replacement therapy for severe neonatal respiratory distress syndrome: An international randomized clinical trial. Pediatrics 1988; 82: 683–691.

8. Western Cape Department of Health. Standard post-natal interventions for peri-viable preterm birth in extremely low birth weight infants in the Western Cape Province Department of Health – Decision Support Framework. [Internet] Circular H10-2017

9. Richard A Polin; Waldemar A. Carlo et al. Surfactant Replacement therapy for Preterm and term neonates with Respiratory Distress Syndrome. Paediatrics 2014;133-156 DOI:10.1542/peds.2013-3443

10. Bahadue FC; Soll R. Early versus delayed selective surfactant treatment for Neonatal Respiratory Distress Syndrome. Cochrane Database of Systematic Reviews 2012; issue 11; Art No: CD001456. DOI:10.1002/14651858.CD001456.pub2

11. Robert H Pfister, Roger F. Soll. Initial Respiratory Support of Preterm infants. The Role of CPAP, The INSURE method and non-invasive ventilation. Clin Perinatol 2012;39: 459-481

12. Morley CJ, Davis PG, Doyle LW, et al. Nasal CPAP or intubation at birth for very preterm infants. N Engl J Med 2008;358(7):700–8.

13. Tetsuya Isayama; Hroko Iwami et al. Association of Non-invasive ventilation strategies with mortality and Bronchopulmonary Dysplasia. Systematic review and meta-analysis. JAMA 2016;316(6); 611-624

14. Stevens TP; Blennow M et al. Early surfactant administration and brief ventilation versus selective surfactant and continued mechanical ventilation for Preterm Infants with or at risk of Respiratory Distress Syndrome. Cochrane Database of Systematic Reviews 2007 Issue 4; Art No: CD003063. DOI:10.1002/1461858.CD003063.pub1

15. Sandri F, Plavka R, Ancora G, et al. Prophylactic or early selective surfactant combined with nCPAP in very preterm infants. Pediatrics 2010;125(6):e1402–9

16. Ga Won Jeon. Surfactant preparations for Preterm infants with Respiratory Distress Syndrome: Past; present and future. Korean Journal of Paediatrics 2019;62(5):155-161

17. Smeeta Sardesai; Manoj Biniwale; Fiona Wertheimer; Arlene Garingo and Rangasamy Ramanathan. Evolution of Surfactant therapy for Respiratory Distress Syndrome: Past, present and Future. Paediatric RESEARCH 2017;81:240-248

18. Singh N: Halliday HL et al. Comparison of animal derived Surfactants for the prevention and treatment of Respiratory Distress Syndrome in Preterm Infants. Cochrane Database of Systematic Reviews 2015. Art No. CD010249

19. Lize Boshoff Coyles, MBChB, FCPaed, Yaseen Joolay, MBChB, FCPaed, MPhil, Lloyd Tooke, MBChB, FCPaed, MMed, Bovine or Porcine: Does the Type of Surfactant Matter?, Journal of Tropical Pediatrics, , fmaa011, https://doi.org/10.1093/tropej/fmaa011

20. Ingemyr K, Elfvin A, Hentz E, Saggers RT, Ballot DE. Factors influencing survival and short-term outcomes of very low birth weight infants in a tertiary hospital in Johannesburg. Frontiers in Pediatrics. 2022;10

Annexure A: Human research ethics committee approval letter

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room G50- Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6492
Email: hrec-submissions uct.ac.za
Website: www.health.uct.ac.za fhs research humanethics forms

13 April 2021

HREC REF: 221/2021

Dr Y Joolay
Department of Neonatology
Room 62, H46 OMB
Email: Yaseen.˙oola uct.ac.za
Student: mn obi.nxm mail.com

Dear Dr Joolay

PROJECT TITLE: SURFACTANT FOR THE TREATMENT OF RESPIRATORY DISTRESS SYNDROME IN VERY LOW BIRTH WEIGHT INFANTS AT A LEVEL 2 HOSPITAL: A DESCRIPTIVE RETROSPECTIVE COHORT STUDY– SAFETY, EFFICACY AND COSTS-MMED-CANDIDATE-DR MNQOBI NXUMALO

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee (HREC) for review.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

This approval is subject to strict adherence to the HREC recommendations regarding research involving human participants during COVID -19, dated 17 March 2020 & 06 July 2020.

Approval is granted for one year until the 30 April 2022.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za fhs research humanethics forms)

The HREC acknowledge that the student: Dr Mnqobi Nxumalo will also be involved in this study.

Please quote the HREC REF 221/2021 in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

Yours sincerely

Signed by candidate

PROFESSOR M BLOCKMAN
CHAIRPERSON, FACULTY OF HEALTH SCIENCES HUMAN RESEAR ETHICS COMMITTEE
Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938
NHREC-registration number: REC-210208-007

This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use: Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH 2006), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI), and Declaration of Helsinki (2013) guidelines. The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

Annexure B: Author guidelines: South African Medical Journal

Author Guidelines

Authorship

Named authors must consent to publication. Authorship should be based on: (i) substantial contribution to conceptualisation, design, analysis and interpretation of data; (ii) drafting or critical revision of important scientific content; or (iii) approval of the version to be published. These conditions must all be met (uniform requirements for manuscripts submitted to biomedical journals; refer to www.icmje.org)

If authors' names are added or deleted after submission of an article, or the order of the names is changed, all authors must agree to this in writing.

Please note that co-authors will be requested to verify their contribution upon submission. Non-verification may lead to delays in the processing of submissions.

Author contributions should be listed/described in the manuscript.

Conflicts of interest

Conflicts of interest can derive from any kind of relationship or association that may influence authors' or reviewers' opinions about the subject matter of a paper. The existence of a conflict – whether actual, perceived or potential – does not preclude publication of an article. However, we aim to ensure that, in such cases, readers have all the information they need to enable them to make an informed assessment about a publication's message and conclusions. We require that both authors and reviewers declare all sources of support for their research, any personal or financial relationships (including honoraria, speaking fees, gifts received, etc) with relevant individuals or organisations connected to the topic of the paper, and any association with a product or subject that may constitute a real, perceived or potential conflict of interest. If you are unsure whether a specific relationship constitutes a conflict, please contact the editorial team for advice. If a conflict remains undisclosed and is later brought to the attention of the editorial team, it will be considered a serious issue prompting an investigation with the possibility of retraction.

Research ethics committee approval

Authors must provide evidence of Research Ethics Committee approval of the research where relevant. Ensure the correct, full ethics committee name and reference number is included in the manuscript.

If the study was carried out using data from provincial healthcare facilities, or required active data collection through facility visits or staff interviews, approval should be sought from the relevant provincial authorities. For South African authors, please refer to the guidelines for submission to the National Health Research Database. Research involving human subjects must be conducted according to the principles outlined in the Declaration of Helsinki. Please refer to the National Department of Health's guideline on Ethics in Health research: principles, processes and structuresto ensure that the appropriate requirements for conducting research have been met, and that the HPCSA's General Ethical Guidelines for Health Researchers have been adhered to.

General article format/layout

Accepted manuscripts that are not in the correct format specified in these guidelines will be returned to the author(s) for correction, which will delay publication.

General:

Manuscripts must be written in UK English.

The manuscript must be in Microsoft Word format. Text must be single-spaced, in 12-point Times New Roman font, and contain no unnecessary formatting (such as text in boxes).

Please make your article concise, even if it is below the word limit.

Qualifications, full affiliation (department, school/faculty, institution, city, country) and contact details of ALL authors must be provided in the manuscript and in the online submission process.

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

Include sections on Acknowledgements, Conflict of Interest, Author Contributions and Funding sources. If none is applicable, please state ‘none’.

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'.

Please be sure to insert proper symbols e.g. µ not u for micro, a not a for alpha, b not B for beta, etc.

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

Quotes should be placed in single quotation marks: i.e. The respondent stated: '...'

Round brackets (parentheses) should be used, as opposed to square brackets, which are reserved for denoting concentrations or insertions in direct quotes.

If you wish material to be in a box, simply indicate this in the text. You may use the table format –this is the only exception. Please DO NOT use fill, format lines and so on.

Research

Guideline word limit: 4 000 words

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. 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. Select figures and tables for your paper carefully and sparingly. Use only those figures that provided added value to the paper, over and above what is written in the text. Do not replicate data in tables and in text .

Structured abstract

This should be 250-400 words, with the following recommended headings:

o Background: why the study is being done and how it relates to other published work.

o Objectives: what the study intends to find out

o Methods: must include study design, number of patients, description of the intervention, primary and secondary outcomes, any specific analyses that were done on the data.

o 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.

o 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.

Do not include any references in the abstracts.

Main article

All articles are to include the following main sections: Introduction/Background, Methods, Results, Discussion, Conclusions.

The following are additional heading or section options that may appear within these:

Objectives (within Introduction/Background): a clear statement of the main aim of the study and the major hypothesis tested or research question posed

Design (within Methods): including factors such as prospective, randomisation, blinding, placebo control, case control, crossover, criterion standards for diagnostic tests, etc.

Setting (within Methods): level of care, e.g. primary, secondary, number of participating centres.

Patients (instead of patients or subjects; within Methods): numbers entering and completing the study, sex, age and any other biological, behavioural, social or cultural factors (e.g. smoking status, socioeconomic group, educational attainment, co-existing disease indicators, etc)that may have an impact on the study results. Clearly define how patients were enrolled, and describe selection and exclusion criteria.

Interventions (within Methods): what, how, when and for how long. Typically for randomised controlled trials, crossover trials, and before and after studies.

Main outcome measures (within Methods): those as planned in the protocol, and those ultimately measured. Explain differences, if any.

Results

Start with description of the population and sample. Include key characteristics of comparison groups.

Main results with (for quantitative studies) 95% confidence intervals and, where appropriate, the exact level of statistical significance and the number need to treat/harm. Whenever possible, state absolute rather than relative risks.

Do not replicate data in tables and in text.

If presenting mean and standard deviations, specify this clearly. Our house style is to present this as follows:

E.g.: The mean (SD) birth weight was 2 500 (1 210) g. Do not use the ± symbol for mean (SD).

Leave interpretation to the Discussion section. The Results section should just report the findings as per the Methods section.

Discussion

Please ensure that the discussion is concise and follows this overall structure – sub-headings are not needed:

Statement of principal findings

Strengths and weaknesses of the study

Contribution to the body of knowledge

Strengths and weaknesses in relation to other studies

The meaning of the study – e.g. what this study means to clinicians and policymakers

Unanswered questions and recommendations for future research

Conclusions

This may be the only section readers look at, therefore write it carefully. Include primary conclusions and their implications, suggesting areas for further research if appropriate. Do not go beyond the data in the article.

Illustrations/photos/scans

If illustrations submitted have been published elsewhere, the author(s) should provide 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.

All illustrations (graphs, diagrams, charts, etc.) must be in PDF or jpeg form.

Ensure all graph axes are labelled appropriately, with a heading/description and units (as necessary) indicated. Do not include decimal places if not necessary e.g. 0; 1.0; 2.0; 3.0; 4.0 etc.

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

Embed/include each table in the manuscript Word file - do not provide separately as supplementary files.

Number each table in Arabic numerals (Table 1, Table 2, etc.) and refer to consecutively in the text.

Tables must be cell-based (i.e. not constructed with text boxes or tabs) and editable.

Ensure each table has a concise title and column headings, and include units where necessary.

Footnotes must be indicated with consecutive use of the following symbols: * † ‡ § ¶ || then ** †† ‡‡ etc.

Do not: Use [Enter] within a row to make 'new rows':

Rather:

Each row of data must have its own proper row:

Do not: use separate columns for n and %:

Rather:

Combine into one column, n (%):

Do not: have overlapping categories, e.g.:

Rather:

Use <> symbols or numbers that don't overlap:

References

NB: Only complete, correctly formatted reference lists in Vancouver style will be accepted. Reference lists must be generated manually and not with the use of reference manager software. Endnotes must not be used.

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.
- Look for the correct, matching article in the list of results.
- 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.

Cited manuscripts that have been accepted but not yet published can be included as references followed by '(in press)'.

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)'.

Copyright Notice

Privacy Statement

The SAMJ is committed to protecting the privacy of the users of this journal website. The names, personal particulars and email addresses entered in this website will be used only for the stated purposes of this journal and will not be made available to third parties without the user's permission or due process. Users consent to receive communication from the SAMJ for the stated purposes of the journal. Queries with regard to privacy may be directed to publishing@samedical.org

Annexure C: Case report form

NEONATES 800g to 1200g DATA SHEET	
Weight:	Gestational age:
Maternal risk factors:	
Antenatal steroids:	Doses:
Surfactant:	
1st dose:	2nd Dose
Days on Mechanical Ventilation:	
Days on CPAP:	
Days on HFNC:	
Days on NPO2:	
Total days on Supplimentary Oxygen	
Pulmonary air leak:	Pulmonary Haemorrhage:
Mortality	Chronic lung Disease:
Clinician:	