A REVIEW OF SURFACTANT USE IN NEONATES AT CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL FROM JANUARY 2013 – JUNE 2016.

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Declaration

I Oluwakemi Zainab Ayodele declare that this is all my own work and has not been submitted for examination at any other institutions or for publication. This research report is submitted for the Degree of Master of Medicine in Paediatrics at the University of Witwatersrand.

Signed: _____

Dr Oluwakemi Zainab Ayodele

Date: JULY 2019

Acknowledgment

I acknowledge the support of the following individuals, without their support and encouragement, this work would not have been possible. Prof D Ballot, Dr. T Ramdin, Department of Paediatrics, Charlotte Maxeke Hospital and the support staff.

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Dedication

To my late son Ayodeji Khalil Ayodele

(3.5.2012-26.11.2015)

I was privileged to be his mother. He died shortly before this project was commenced. His smile and enthusiasm touched lives and inspired everyone he met. He is greatly missed.

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List of abbreviations

BPD	**Bronchopulmonary dysplasia**
CMJAH	**Charlotte Maxeke Johannesburg Academic Hospital**
FMV	**Face mask ventilation**
HIC	**High-income countries**
RDS	**Respiratory distress syndrome**
IPPV	**Intermittent positive pressure ventilation.**
IVH	**Intraventricular haemorrhage**
IR	**Interquartile range**
LMIC	**Low and middle-income countries**
MAS	**Meconium aspiration syndrome**
MDG	**Millennium development goals**
NCPAP	**Nasal continuous positive airway pressure**
NEC	**Necrotizing enterocolitis**
OR	**Odds ratio**
PPHN	**Persistent pulmonary hypertension of the new-born**
PDA	**Patent ductus arteriosus**
RCT	**Randomized controlled trials**
ROP	**Retinopathy of prematurity**
SDG	**Sustainable development goals**
SRT	**Surfactant replacement therapy**
SD	**Standard deviation**
VLBW	**Very low birth weight**

List of figures and tables

MAIN ARTICLE

TITLE PAGE

A review of surfactant uses in neonates at Charlotte Maxeke Johannesburg Academic hospital from January 2013 to July 2016

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Table of Content Summary:

Little recent information is known on the use of surfactant therapy in sub-Saharan Africa. This study is a review of surfactant therapy in a tertiary hospital in South Africa.

What is known? Surfactant therapy is the mainstay of management of preterm neonates with respiratory distress syndrome.

What this study adds? This study reviews the use of surfactant replacement therapy in a tertiary hospital in South Africa.

ABSTRACT

Background: Surfactant replacement therapy (SRT) is an established treatment of respiratory distress syndrome globally. However, in sub-Saharan Africa there is limited recent information on the use of SRT.

Objectives: To review the use of surfactant replacement therapy in neonates at Charlotte Maxeke Johannesburg Academic Hospital.

Methods: This was a cross-sectional descriptive study. The population included all neonates, term and preterm, admitted within 72hours after birth at Charlotte Maxeke Johannesburg Academic Hospital between 1 January and 30 June 2016. Maternal and neonatal characteristics of neonates who received surfactant were compared to those who did not receive surfactant therapy.

Results: A total of 5517 neonates were included in the study. Surfactant replacement therapy was strongly associated with birth weight – 69.7% (1179/1609) very low birth weight (<1500 g) neonates received surfactant compared to 16.3% (624/3828) LBW ($p<0.001$). In very low birth weight neonates, surfactant replacement therapy was associated with the presence of a patent ductus arteriosus ($p=0.03$), respiratory distress syndrome ($p<0.001$), the use of mechanical ventilation ($p<0.001$), the use of nasal CPAP ($p<0.001$) and supplemental oxygen at 28 days ($p=0.012$). In LBW, surfactant replacement was similarly associated with respiratory distress syndrome ($p<0.001$), the need for nasal CPAP ($p<0.001$) and resuscitation at birth ($p=0.026$). In all neonates, surfactant replacement was associated with increased duration of hospital stay. SRT was used in term and near-term neonates for the treatment of meconium aspiration syndrome (8.6%), persistent pulmonary hypertension of the neonate (4.3%) and congenital pneumonia (5.1%).

This study confirms that most preterm neonates with respiratory distress syndrome in the study hospital were treated with surfactant replacement therapy and nasal CPAP. This is in keeping with global neonatal practices. Protocols to decrease neonatal mortality in low and middle income countries must include the provision of surfactant replacement therapy and nasal CPAP for the treatment of preterm infants.

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INTRODUCTION

The neonatal period represents the most vulnerable time for a child's survival. Neonatal mortality is of great concern globally, accounting for 41% of child deaths under the age of five years (1). The fourth-millennium development goal(MDG), aimed at reducing mortality in children under five by two-thirds in 2015, was not achieved by most developing countries (2) including South Africa. The neonatal mortality rate in South Africa is on a decline but it is approximately five-fold that of high-income countries (HIC)(2). About 99% of neonatal deaths occur in low and middle-income countries (LMIC) with poverty being the major risk factor(3). Most neonatal deaths occur in the first week of life and could mostly be prevented by the provision of adequate health care (1).Globally ,the main direct causes of neonatal deaths are estimated to be preterm birth(28%),severe infection(26%) and asphyxia(23%) (3). The global rate of preterm birth is estimated as 9.6% accounting for 13 million preterm birth every year. Of these, 1 million are born in HIC countries and 12 million in LMIC countries. Asia and Africa contribute to 80% global preterm birth(3).

To achieve the sustainable development goal SDG (3) aimed to reduce neonatal mortality to as low as 12 neonatal deaths per 1000 births by 2030, causes of neonatal deaths need to be determined and addressed (4). A high-risk group with considerable mortality is the very low birth weight (VLBW) neonates. Survival of VLBW infant in South Africa is reported to have improved between 2006 and 2013 (5). Although survival rate is better than other African countries, it is still worse than in HIC (6). Measures to reduce neonatal mortality, and especially that of VLBW must be made a health priority in South Africa.

Respiratory distress syndrome (RDS) is one of the morbidities that results in deaths in preterm neonates. In addition to this, it also contributes indirectly to increase the risk of intraventricular hemorrhage (IVH), bronchopulmonary dysplasia (BPD) and nosocomial infections such as ventilator acquired pneumonia (7). Respiratory distress syndrome is a major cause of

respiratory failure in preterm neonates (8). Respiratory distress syndrome is caused by a deficiency of endogenous pulmonary surfactant in preterm neonates. The physiologic function of surfactant is its ability to reduce alveolar surface tension for gaseous exchange to occur.

Fujiwara et-al in 1980 reported the first successful use of surfactant replacement therapy(SRT) in a newborn with RDS (9). Since then, several randomized controlled trials (RCTs) have established the efficacy of SRT in reducing morbidity and mortality in neonates with RDS (10) , in addition to decreasing risk of intraventricular hemorrhage (IVH), bronchopulmonary dysplasia(BPD), pulmonary air leaks, and duration of mechanical ventilation (11) . Today SRT,CPAP and antenatal steroids forms the mainstay in the management of RDS (12) worldwide, although only a few LMIC use SRT routinely due to its high cost or availability of skilled healthcare workers. In South Africa, SRT became commercially available in November 1991 in public hospitals that provide level II and III neonatal care. Cooper et al. in South Africa (13) compared survival in VLBW neonates born before SRT was introduced in South Africa in 1990/1991 (64%), to those born after SRT was introduced in 1996(84%). Another study by Ballot et-al (5) showed a marked improvement in survival of extremely low birth weight (ELBW) infants and neonates between 2006/2007 and 2013 in South Africa, most likely due to the use of SRT and nasal continuous airways pressure (NCPAP).

Most studies reviewing the efficacy and safety of SRT were conducted in HIC, hence SRT is the standard of care for neonates with RDS in these countries. A recent systematic review was done by Sankar MJ et al. (14) on the safety and efficacy of SRT in LMIC, this confirmed its safety and feasibility in level III units, and its ability to reduce neonatal mortality and air leak.

Inactivation and secondary dysfunction of surfactant may occur as a result of various clinical conditions such as meconium aspiration syndrome (MAS), congenital pneumonia and pulmonary hemorrhage (15) . Whilst surfactant treatment for preterm neonates with RDS is

well established, there are limited high-quality RCTs to recommend its use in the above-mentioned conditions.

Healthcare protocols need to be reviewed and modified to incorporate new therapies and protocols in view of inadequate resources. This is particularly relevant in LMIC where resources are scarce and must be diligently utilized. For instance, a study was done by Ballot et al (16) on the selection of infants for SRT in a resource-constrained setting. It showed that there was no difference in outcome after SRT administration in those with moderate RDS compared to those with severe RDS. This raises the issue of prudence in use of scarce resources in situations of this nature. Owing to financial constraints, infants below 850 g are not routinely ventilated in South Africa (16). A practice in South Africa is the use of nasal continuous positive airway pressure (NCPAP) as the primary mode of management of RDS, and SRT reserved for non-responders to NCPAP (17). Therefore, introducing a policy on judicious use of SRT in respiratory conditions, and its cost-effectiveness becomes relevant.

The present study is an overview of the characteristics, demographic variables, and outcomes of neonates who received SRT compared to those who did not receive SRT at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) between the time 2013 and 2016. The acquired information will be useful for updating health care protocols to save cost and improve outcome in these group of infants in sub-Saharan Africa.

METHOD

Study Design

This was a cross-sectional descriptive study. All neonates, term (>37weeks) and preterm (<37weeks) admitted within 72 hours of birth at CMJAH in the period between 1 January 2013 and 30th June 2016, were eligible for inclusion. Babies with major birth abnormalities, death in the delivery room and those with incomplete records were excluded. Early rescue surfactant therapy was administered as intubate surfactant and extubate (INSURE), and NCPAP was provided as first-line therapy in all VLBW infants >750 g at birth with RDS. Ventilation (IPPV) was provided to those infants >900 g who showed evidence of respiratory failure on NCPAP or become apnoeic.

Respiratory distress syndrome was diagnosed clinically (tachypnoea, subcostal, and intercostal recessions) and using chest radiographs in preterm neonates requiring oxygen after delivery, at CMJAH. Resuscitation at birth was defined as the need for bag mask ventilation, chest compressions or intubation and ventilation. Cranial ultrasound was performed on all VLBW within the first week of life. Necrotising enterocolitis (NEC) was classified as modified Bell's stage 2 and 3 (18). Meconium aspiration syndrome was diagnosed based on clinical and radiologic findings. Persistent pulmonary hypertension in the new-born was diagnosed based on clinical presentation. At CMJAH, two doses of antenatal steroids, betamethasone 12mg is given 12hours apart intramuscularly to mothers <34weeks gestational age, or if the estimated fetal weight was less than two kilograms. Intraventricular hemorrhage (IVH) was defined grade 3 and 4 based on the classification by Papile (19). Retinopathy of prematurity (ROP) was diagnosed by ophthalmologic screening.

Data

This was a secondary review of an existing database. Data was captured on hospital discharge for all neonates by attending clinicians. The data was verified at different stages. Data were

managed using Research Electronic Data Capture (REDCAP) hosted by the University of Witwatersrand, Johannesburg (20).

***Data Analysis*:**

Standard statistical methods were used to analyze data. Continuous variables were described using mean and standard deviations or median and range, depending on the distribution. Categorical data were described using percentages and frequencies. The primary outcome was survival to discharge from the hospital. Secondary outcomes were rates of complications and therapeutic interventions and risk factors for mortality. The total sample was stratified by birthweight into two groups: babies weighing < 1500grams and babies weighing >1500 g. Each of the two groups was further divided into SRT exposed group and SRT unexposed group, and the maternal and neonatal characteristics of these babies were compared. Only valid cases were analyzed (i.e. missing data was excluded for each variable).

Student's T-Test was used to compare continuous variables with normal distribution and non-parametric tests were used for skewed data. Chi-square test was used to compare categorical variables A p-value of <0.05 was considered statistically significant. The analysis was done using SPSS version 24. Association with the use of SRT was determined using binary logistic regression. All significant variables ($p<0.05$) on univariate analysis were explored.

Ethics

This study was approved by Human Research Ethics Committee of the University of Witwatersrand; clearance certificate number M170231.

RESULTS

A total of 6228 neonates were on the REDCap database (accessed on 1 June 2017) at CMJAH between January 2013 and June 2016. Of the 6228, there were 4374 neonates with a birth weight >1500 grams and 1854 neonates with a birth weight <1500 grams. Three hundred and eighteen neonates admitted after 72hours of life were excluded, three hundred and twenty neonates with major birth defect were excluded and seventy-six neonates with no record of SRT or birth weight were also excluded, resulting in a final sample size of 5517 neonates.

VLBW NEONATES

There were 1609 VLBW with a mean birth weight of 1124.0 (SD=240.9) and mean gestational age of 29.1 (SD=2.5). A total of 1179/1609 (69.7%) received surfactant. Survival rate was 1241/1670 (74.3%). Neonatal and maternal characteristics with significant differences between those VLBW neonates who received surfactant and those who did not are shown in Table1.

TABLE 1. Neonatal and maternal characteristics significantly associated with SRT in VLBW.

Variables	<1500g			
	Total n/N (%)	*SRT n/N (%)	*No* SRT n/N (%)	*P*- value
Apgar score in 5mins- >5	1338/1530 (87.5)	919/1066 (86.2)	419/464 (90.3)	0.026
Outcome- Survived n/N (%)	1241/1670 (74.3)	847/1162 (72.9)	394/508 (77.6)	0.0045
Resuscitation-FMV	673/1588 (42.4)	529/1098 (48.2)	144/490 (29.4)	<0.001
Pneumothorax	11/1662 (0.7)	11/1157 (1,0)	0/505 (0)	0.028
Pulmonary haemorrhage	29/1671 (1.7)	25/1162 (2.2)	4/509 (0.8)	0.049

*IPPV	310/1670 (18.6)	276/1162 (23.8)	34/509 (6.7)	<0.001
*RDS	1492/1671 (89.3)	1153/1162 (99.2)	339/509 (66.6)	<0.001
*PDA	165/1662 (9.9)	159/1157 (13.7)	6/505 (1.2)	<0.001
*NCPAP	1036/1671 (78.0)	994/1162 (85.5)	42/509 (8.3)	<0.001
Maternal hypertension	426/1521 (28.0)	277/1062 (26.1)	149/459 (32.5)	0.011
Antenatal care	1261/1605 (78.8)	866/1118 (77.5)	395/487 (82.0)	0.044
Oxygen on day28	393/1646 (23.9)	349/1143 (30.5)	44/503 (8.7)	<0.001
*FMV: Face mask ventilation; IPPV: Intermittent positive pressure ventilation; RDS: Respiratory distress syndrome; PDA: Patent ductus arteriosus; NCPAP: Nasal continuous positive airway pressure				

Place of birth, gender, congenital pneumonia, ROP, NEC, home oxygen, IVH, maternal age, the temperature on admission, maternal race, receipt of antenatal steroids, chorioamnionitis, maternal diabetes and multiple gestations were not significantly associated with SRT. Continuous variables associated with SRT are shown in Table2.

Table 2. Continuous variables associated with surfactant replacement therapy in VLBW<1500grams

Variable	<1500 g		
	*SRT	No SRT	P value
Length of stay in days- *Median (Interquartile Range)*	31(31)	21(21)	<0.001
Birth weight in grams	1100(350)	1260(370)	<0.001

Median (Interquartile Range)			
Gestational age in weeks *Mean (Standard deviation)*	28.78(2.18)	29.91(3.14)	<0.001

The most significant association with SRT using logistic regression (see Table 3) were patent ductus arteriosus (P=0.031), conventional ventilation (P=0.001), respiratory distress syndrome (P<0.001), nasal continuous positive airway pressure (P<0.001) and oxygen on day 28 (P=0.012). Other variables were not significantly associated with SRT.

Table3. Logistic regression for significant variables in VLBW neonates exposed to SRT

Variables	Odds Ratio	95% Confidence Interval	P value
Patent ductus arteriosus	3.50	1.12-10.93	0.03
Conventional ventilation	5.39	1.53-5.91	0.001
Respiratory distress syndrome	22.70	8.28-62.717	<0.001
Nasal continuous positive airway pressure	67.649	42.50-107.65	<0.001
Oxygen on day 28	2.00	1.16-3.429	0.012

LBW

There were 3828 LBW with a mean birthweight of 2262.6 (SD=739.4) and mean gestational age of 34.6 (SD=3.87). A total of 624/3828 (16.3%) received surfactant. Survival rate was 3609/3826 (94.3%). Maternal and neonatal characteristics with a significant difference between those who received surfactant and those who did not are shown in Table 4. Place of birth, chorioamnionitis, survival, maternal diabetes, gender, Apgar score at 5minutes, IVH, congenital pneumonia, MAS, pulmonary hemorrhage, the temperature on admission and maternal age were not significantly different. Continuous variables significantly associated with SRT are shown in Table 5.

Table 4. Maternal and neonatal characteristics significantly associated with SRT in LBW (>1500 g)

Variables	>1500 g			
	Total n/N (%)	*SRT n/N (%)	No SRT n/N (%)	*P*- value
Resuscitation at birth-FMV	945/3827 (24.7)	199/624 (31.9)	746/3203 (23.3)	<0.001
Pneumothorax	25/3827 (0.7)	10/624 (1.6)	15/3203 (0.5)	0.001
*PPHN	67/3827 (1.8)	27/624 (4.3)	40/3202 (1.2)	<0.001
*RDS	748/3827 (19.3)	505/624 (80.9)	243/3203 (7.3)	<0.001
*NCPAP	630/3827 (16.5)	511/624 (81.9)	119/3203 (3.7)	<0.001
*NEC	54/3802 (1.4)	21/620 (3.4)	33/3182 (1.0)	<0.001
*PDA	113/3827 (3.0)	27/624 (4.3)	86/3203 (2.7)	0.027
Antenatal steroid	284/2350 (12.1)	91/385 (23.0)	193/1965 (9.8)	<0.001
Multiple Gestations	341/3802 (9.1)	99/624 (15.9)	242/3178 (7.6)	<0.001

Maternal hypertension	312/3668 (8.5)	68/598 (11.4)	244/3070 (7.9)	0.006
Antenatal care	3183/3743 (85.0)	504/619 (81.4)	2679/3124 (85.8)	0.006
*NEC: Necrotising enterocolitis; *PDA: Patent ductus arteriosus; *SRT: Surfactant replacement therapy; *RDS: Respiratory distress syndrome; *PPHN; Persistent pulmonary hypertension of the newborn; *NCPAP: Nasal continuous positive airway pressure				

Table 5. Continuous variables significantly associated with surfactant replacement therapy in LBW

Variable	>1500 g		
	*SRT	No SRT	P value
Length of stay in days- *Median (Interquartile Range)*	9(10)	4(5)	0.001
Birth weight in grams *Median (Interquartile Range)*	2052.2(537.8)	2762.2(772.2)	<0.001
Gestational age in weeks- *mean (standard deviation)*	33.6(3.16)	37.2(3.25)	<0.001

Table 6. Logistic regression for significant variables in neonates >1500 g exposed to SRT

Variables	Odds ratio	95% Confidence interval	P value
Respiratory distress syndrome	10.57	7.12-15.68	<0.001
Nasal continuous positive airway pressure	51.65	34.81-76.63	<0.001
Resuscitation at birth- face mask ventilation	1.64	1.06-2.54	0.026

The variables with most significant association using logistic regression were respiratory distress syndrome ($p<0.001$), nasal continuous positive airway pressure ($p<0.001$) and face mask ventilation resuscitation ($p=0.026$).

DISCUSSION

This study, of over 5000 neonates, is the first to review the use of surfactant in a tertiary hospital in sub-Saharan Africa in the 21st Century. The results confirm the liberal use of SRT in preterm infants. Surfactant therapy was strongly associated with birth weight and gestational age. Surfactant was provided to almost two-thirds of VLBW neonates and almost one-fifth of LBW. The use of SRT was, not unexpectedly strongly associated with RDS and the use of NCPAP. There was, however a reduction in the use of SRT in VLBW infants compared to a study conducted in the same unit in 2013 (5).This could be attributed to use of NCPAP as initial respiratory support for VLBW with RDS, and babies being weaned on NCPAP without requiring SRT. The practice of early use of NCPAP concurs with the European consensus guideline on the management of RDS in preterm neonates (12).

The results of the present study indicate that SRT was used in the smallest and sickest neonates. There was an association between SRT and PDA . The reason for this is not clear, although there is a report that SRT may increase the shunt across a PDA (21) . Necrotising enterocolitis, an important complication of prematurity was not associated with SRT exposure in VLBW neonates. Those VLBW neonates who received SRT had a longer duration of hospitalization and an increased need for mechanical ventilation. Supplemental oxygen at 28 days was also increased in VLBW neonates who had received SRT.This could be due to inexperienced doctors and no CPAP available. This is in contrast to the findings of Rojas et al (22) who reported that early SRT reduced the incidence of BPD. In addition, the present study found an increase in survival in those VLBW neonates who had not received SRT on univariate analysis, although this finding was not significant after logistic regression.

Interestingly, pneumothoraces was significantly higher in the group who received SRT, on univariate analysis, however, adjusted odds ratios were not significant. This may reflect a failure to wean positive pressure sufficiently rapidly after SRT administration. However, other studies have shown SRT is associated with reduced incidence of pneumothorax (23). Although a small percentage (1.7%) of VLBW babies had pulmonary hemorrhage, it was significantly associated with SRT, as more babies who had pulmonary hemorrhage received surfactant.

In the current study, babies whose mothers were diagnosed with hypertension had a reduced need for SRT. This could be attributed to maternal hypertension causing intrauterine stress which matures the lungs and reduces the risk of RDS. In addition, maternal attendance at antenatal care was associated with a lower requirement for SRT. This is in keeping with results reported by Robert D et al.(24).

LBW in the present study who received SRT were also of lower birth weight and gestational age than those who did not and most commonly had RDS, indicating that this group of neonates was well grown preterm infants. However, SRT was also used for other conditions, in near-term and term neonates, including PPHN, MAS and congenital pneumonia. Our study showed an association between SRT, PPHN, and RDS in larger babies. This was in keeping with a study done by Donn SM et al on use of SRT beyond RDS (15). Reports on the use of SRT for respiratory conditions other than RDS were mainly carried out in HIC, more studies need to be done on the use of SRT in LMIC.

The obstetric policy at the study site was to give antenatal steroids to all mothers with anticipated preterm deliveries at a gestational age less than 34weeks, based on the NICE guidelines(25).The use of antenatal steroid was however not significantly associated with SRT in the current study.

LIMITATIONS AND CONCLUSION

Study limitations

This study was retrospective, so additional information, such as the timing, dosage volume, and brand of SRT was not documented. Additional clinical information, such as the initial oxygen saturation of neonates was not available for analysis. Similarly, the cost-benefit of SRT was not evaluated, which would be of relevance in LMICs. This was a retrospective descriptive study, so only associations with SRT can be noted.

Conclusion

This large review of the use of SRT in neonates in a tertiary hospital in South Africa, confirms that most preterm neonates with RDS received SRT and were treated with NCPAP, which is in keeping with global neonatal practices (Although, this study was conducted in a tertiary centre, the results are generalizable to regional and district hospitals, as both SRT and NCPAP can be provided in this setting). Health protocols to decrease neonatal mortality in sub-Saharan Africa should include the provision of both SRT and NCPAP for the management of RDS in preterm infants, in addition to the provision of antenatal steroids.

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Appendix A: SAMJ Guidelines

SAMJ

Submissions

- » Online Submissions
- » Author Guidelines
- » Copyright Notice
- » Privacy Statement

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AUTHORSHIP

Named authors must consent to publication. Authorship should be based on: (i) substantial contribution to conception, design, analysis and interpretation of data; (ii) drafting or critical revision for important intellectual 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**).

CONFLICT OF INTEREST

Authors must declare all sources of support for the research and any association with a product or subject that may constitute conflict of interest.

RESEARCH ETHICS COMMITTEE APPROVAL

Provide evidence of Research Ethics Committee approval of the research where relevant.

PROTECTION OF PATIENT'S RIGHTS TO PRIVACY

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

ETHNIC CLASSIFICATION

References to ethnic classification must indicate the rationale for this.

MANUSCRIPTS

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

Research articles (previously 'Original articles') not exceeding 3 000 words, with up to 6 tables or illustrations, are usually observations or research of relevance to clinical medicine and related fields. *References should be limited to no more than 15.* Please provide a structured abstract not exceeding 250 words, with the following recommended headings: *Background, Objectives, Methods, Results,* and *Conclusion.*

Scientific letters will be considered for publication as shorter ***Research articles***.

Editorials, Opinions, etc. should be about 1000 words and are welcome, but unless invited, will be subjected to the *SAMJ* peer review process.

Review articles are rarely accepted unless invited.

Letters to the editor, for publication, should be about 400 words with only one illustration or table, and must include a correspondence address.

Forum articles must be accompanied by a short description (50 words) of the affiliation details/interests of the author(s). Refer to recent forum articles for guidance. Please provide an accompanying abstract not exceeding 150 words.

Book reviews should be about 400 words and must be accompanied by the publication details of the book.

Obituaries should be about 400 words and may be accompanied by a photograph.

Guidelines must be endorsed by an appropriate body prior to consideration and all conflicts of interest expressed. A structured abstract not exceeding 250 words (recommended sub-headings: *Background*, *Recommendations*, *Conclusion*) is required. Sections and sub-sections must be numbered consecutively (e.g. 1. Introduction; 1.1 Definitions; 2. etc.) and summarised in a Table of Contents. References, appendices, figures and tables must be kept to a minimum.

Guidelines exceeding 8 000 words will only be considered for publication as a supplement to the SAMJ*; the costs of which must be covered by sponsorship or advertising. The Editor reserves the right to determine the scheduling of supplements. Understandably, a delay in publication must be anticipated dependent upon editorial workflow.*

MANUSCRIPT PREPARATION

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

Qualification, affiliation and contact details 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)'.

Scientific measurements must be expressed in SI units except: blood pressure (mmHg) and haemoglobin (g/dl). Litres is denoted with a lowercase 'l' e.g. 'ml' for millilitres). Units should be preceded by a space (except for %), e.g. '40 kg' and '20 cm' but '50%'. Greater/smaller than signs (> and 40 years of age'. The same applies to ± and º, i.e. '35±6' and '19ºC'.

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.

General formatting The manuscript must be in Microsoft Word or RTF document format. Text must be single-spaced, in 12-point Times New Roman font, and contain no unnecessary formatting (such as text in boxes, with the exception of Tables).

ILLUSTRATIONS AND TABLES

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

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

Figures must be numbered in Arabic numerals and referred to in the text e.g. '(Fig. 1)'. Figure legends: Fig. 1. 'Title...' All illustrations/figures/graphs must be of **high resolution/quality**: 300 dpi or more is preferable, but images must not be resized to increase resolution. Unformatted and uncompressed images must be attached individually as '**supplementary files**' upon submission (not solely embedded in the accompanying manuscript). TIFF and PNG formats are preferable; JPEG and PDF formats are accepted, but authors must be wary of image compression. Illustrations and graphs prepared in Microsoft Powerpoint or Excel must be accompanied by the original workbook.

REFERENCES

References must be kept to a maximum of 15. Authors must verify references from original sources. *Only complete, correctly formatted reference lists will be accepted.* Reference lists must be generated manually and **not** with the use of reference manager software. 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. First and last page, volume and issue numbers should be given.

Wherever possible, references must be accompanied by a digital object identifier (DOI) link and PubMed ID (PMID)/PubMed Central ID (PMCID). Authors are encouraged to use the DOI lookup service offered by **CrossRef**.

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] [PMID: 2764753]

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 jun, 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: World Health Organization, 2002. http://www.who.int/whr/2002 (accessed 16 January 2010).

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)'.

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2. The submission has not been previously published, nor is it before another journal for consideration.
3. The text complies with the stylistic and bibliographic requirements in **Author Guidelines**.
4. The manuscript is in Microsoft Word or RTF document format. The text is single-spaced, in 12-point Times New Roman font, and contains no unnecessary formatting.
5. Illustrations/figures are high resolution/quality (not compressed) and in an acceptable format (preferably TIFF or PNG). These must be submitted individually as 'supplementary files' (not solely embedded in the manuscript).

6. For illustrations/figures or tables that have been published elsewhere, the author has obtained written consent to republication from the copyright holder.
7. Where possible, references are accompanied by a digital object identifier (DOI) and PubMed ID (PMID)/PubMed Central ID (PMCID).
8. An abstract has been included where applicable.
9. The research was approved by a Research Ethics Committee (if applicable)
10. Any conflict of interest (or competing interests) is indicated by the author(s).

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Appendix B: Research Protocol

Protocol

A Review of Surfactant use in Neonates at Charlotte Maxeke Johannesburg Academic Hospital from January 2013-June 2016

DR AYODELE OLUWAKEMI ZAINAB

Student Number: 1596239

Staff Number A0048043

For MMED in Paediatrics

Supervisor:

Prof Daynia. E Ballot; MBChB, FCPaeds (SA), PhD (Wits).

BACKGROUND

Preterm birth is a major cause of morbidity and mortality as it results in complications such as respiratory distress syndrome(RDS) which is a major cause of respiratory failure in them(1).Respiratory distress syndrome(RDS) is caused by deficiency of endogenous pulmonary surfactant. Its incidence increases with decreasing gestational age. Pulmonary surfactant is predominantly a combination of phospholipids, lipids and surfactant proteins. The physiologic function of surfactant is its ability to reduce surface tension and its ability to rapidly adsorb, spread and reform a monolayer in the dynamics of the respiratory cycle(2)

Surfactant replacement therapy forms the mainstay in the management of respiratory distress syndrome (3). In the 1980s, Fujiwara et-al reported the first successful use surfactant in new born with respiratory distress syndrome (RDS) (4). It is an effective and safe therapy for management of respiratory distress syndrome (RDS)(5).Meta-analysis of randomised controlled trials (RCTs)have confirmed that animal derived surfactant administration in preterm infant with established respiratory distress syndrome(RDS) reduces mortality, decreases the risk of intraventricular haemorrhage(IVH) and reduces risk of bronchopulmonary dysplasia(BPD)(6).A wide variety of surfactant products have been studied in clinical trials, these includes animal derived surfactant extract and synthetic surfactant (6). Multiple systematic reviews have addressed the use of animal derived surfactant preparation or synthetic surfactant preparation in the prevention or treatment of RDS(7).

Surfactant may be prophylactically administered to infants considered to be at risk of respiratory distress syndrome (RDS) in the delivery room or as rescue treatment in infants with established respiratory distress syndrome (RDS) within the first 12hours after birth provided specified threshold criteria of severity of RDS are met, as defined by fractional inspired oxygen concentration (Fio2) requirement (16). Recent randomised controlled trials(RCTs) indicate

that the benefit of prophylactic surfactant are no longer evident in groups of infants when continuous positive airway pressure(CPAP) is used routinely(7). There doesn't seem to be any advantage to the prophylactic use of surfactant replacement therapy(SRT)over rescue treatment except in extreme premature infants <30 weeks gestation(8).

Surfactant has been administered through an intra-tracheal route using an endotracheal tube to introduce it into the trachea and extubating the patient afterwards(IN-SUR-E Technique)(9) or a minimally invasive technique(MIST)(10) which allows administration of surfactant using a feeding tube without intubating the patient or Less invasive surfactant administration(LISA)(10) which allows the administration of surfactant without intubation via a laryngeal mask or a feeding tube in spontaneously breathing infants. However, a small clinical trial of human premature infants showed no significant difference in clinical outcome (11). Because data are conflicting and limited, the optimal method of administration in premature infants is yet to be proven. There is limited evidence to recommend the optimal number of doses of surfactant (11).

Surfactant inactivation and secondary dysfunction may occur as a result of conditions such as meconium aspiration syndrome (MAS),primary pulmonary hypertension of the new-born (PPHN) congenital pneumonia and pulmonary haemorrhage(12).Whilst the treatment of respiratory distress syndrome(RDS) with surfactant in preterm is well established, and evidence for its use in non-respiratory distress syndrome(RDS) conditions involving term neonates exists. There is limited high quality randomised controlled trials (RCTs) to recommend its routine use in the above clinical condition.

Meconium aspiration syndrome (MAS) with severe respiratory failure and primary pulmonary hypertension of the new-born (PPHN) may be complicated by surfactant inactivation (12). Surfactant therapy has been shown to improve oxygenation and reduce need for extracorporeal

membranous oxygenation (ECMO) in term infant(13). Surfactant administration in meconium aspiration syndrome(MAS) has two approaches which involves bolus / slow infusion or Lavage which takes advantage of detergent-like property of pulmonary surfactant in which meconium can be solubilized and washed from the lungs (13). Congenital pneumonia has been associated with surfactant inactivation(14). Pulmonary haemorrhage has been implicated in inactivation of surfactant and administration of surfactant(SRT) may be capable of reversing this process even in the continued presence of inhibitors(15).

Most studies reviewing the role of surfactant replacement therapy (SRT) were conducted in high income countries. Hence surfactant replacement therapy (SRT) is the standard of care for neonates with respiratory distress syndrome (RDS) in these countries. In low- and middle-income countries which South Africa is part of, limited financial and physical resources is of great concern. Artificial surfactant became commercially available in South Africa in November 1991(16),at this time it was not routinely used for new-borns with RDS. It was then necessary to define specific criteria for its use(16)which were birthweight <1000g and respiratory distress in the first 12hours of life. This was also a result of limited resources and high cost of neonatal intensive care(17). In March of 1991 the delegates to the 10th conference on priorities in perinatal care in South Africa only recommended the use of surfactant for babies >1000g birthweight and only as Rescue therapy(16). Since nasal continuous positive airway pressure (NCPAP) are available, the birthweight cut-off has been dropped to <1000g.

Justification for the Study

In our NICU owing to financial constraint, infants below 850g birth weight are not routinely ventilated. Hence babies with a better prognosis are selected out and would be expected to have a favourable outcome(16),supporting a more liberal use at Charlotte Maxeke Johannesburg hospital. A practice in south Africa is the use of continuous positive airway pressure(CPAP)

as primary mode of management of respiratory distress syndrome(RDS)and surfactant replacement therapy(SRT) may be reserved for non-responders to continuous positive airway pressure(CPAP)(18).

Prophylactic use of surfactant has been shown to reduce cost by 27% per patient by reducing severity of respiratory distress syndrome(RDS) and length of stay in neonatal intensive care unit (NICU)(17).But treating large number of surfactant sufficient infants is not cost effective. The cost of surfactant in South Africa has not increased since its introduction into the country making it relatively cheaper based on the current value of the rand. The use of early rescue surfactant has shown to decrease the severity of respiratory distress syndrome and the need for mechanical ventilation. However, introducing a policy on its judicious use maybe cost saving. The aim of my study is to look at the use of surfactant at our hospital and outcome of babies that receive versus those babies who did not receive surfactant.

STUDY OBJECTIVES

- To compare and describe demographics, clinical characteristics and outcome in babies who received surfactant replacement therapy (SRT) with those who did not.
- To describe indications for use of SRT.
- To describe time of administration of SRT and number of doses in VLBW neonate.

METHODS

Respiratory distress syndrome is caused by deficiency of pulmonary surfactant which helps to reduce alveolar surface tension for adequate gas exchange.

At our unit surfactant is administered as early rescue to patients with respiratory failure at the discretion of the attending physician usually followed with continuation of NCPAP (nasal continuous positive airway pressure) ventilation. Method of surfactant administration is the INSURE (incubate-surfactant administration-extubate) technique although some use MIST (minimally invasive surfactant therapy) technique using feeding tube for administration. We don't administer prophylactic surfactant.

Study Design

This is a cross sectional descriptive study. Two groups compared.

The one group includes neonates who received surfactant and the other group are those who did not receive surfactant, which is the control group. Within each group are babies who died and those who survived.

They will be stratified by their birthweight. Those group whose birthweight falls below 1500g and the other group above 1500g.

An analysis of an existing database will be done using the REDCap system.

Intraventricular haemorrhage will be confirmed by cranial sonar.

Necrotising enterocolitis (NEC) will be graded using standard grading methods

Patent ductus arteriosus will be confirmed by echo.

Study Duration

From January 2013 to June 2016

Site of Study

Neonatal unit Charlotte Maxeke Johannesburg academic hospital.

Study Group

All neonates admitted within 72hours of birth.

Inclusion Criteria

All neonates, term and preterm (<37weeks) born at CMHAH.

Admission within 72hours of birth

Exclusion Criteria

Major congenital abnormalities

Incomplete data

Delivery room death

Outcome

- Length of hospital stay
- Need for intermittent positive pressure ventilation (IPPV).
- Mortality
- Progression to bronchopulmonary dysplasia (BPD)

Data Collection

This will involve the use of an existing neonatal database present at CMJAH. Data is captured using (REDCap) Research Electronic Data Capture made available by University of Witwatersrand Johannesburg. The collection of the data is done by clinicians using hospital records and is verified at different stages. Consent for use of the database will be obtained.

Sample Size

There is an estimate of 1900 new-born admissions to CMJAH each year of which approximately 500 are VLBW (500g to 1500g). Approximately 60% of the babies are inborn. It is therefore anticipated that there will be 3990 neonatal records available for inclusion

Data Analysis

Standard statistical methods will be used to analyse the data. Continuous variables will be described using mean and standard deviation or median and range, depending on the distribution. Neonates will be divided into those who received surfactant and those who did not. The groups will also be stratified according to birth weight (< 1500 grams and > 1500 grams). Comparisons will be done between both groups. The student t-test will be used to compare continuous variables with normal distribution and Non-parametric tests for skewed data. Categorical variables will be described using frequency or percentage. Chi Square tests will be used to compare categorical variables using frequency or A P-value of <0.05 will be considered significant. Associations with the use of surfactant will be determined using binary logistic regression.

TIMELINES

	Sept 2016	Oct 2016	Nov 2016	Dec 2016	Jan 2017	Feb 2017	Mar 2017	April 2017	May 2017	June 2017	July 2017	August 2017
Literature review												
Preparing protocol												
Protocol assessment												
Ethics application												
Collecting data												
Data analysis												
Writing up-thesis												
Writing up-paper												

ETHICS

Informed consent will not be warranted as this is a retrospective study. The protocol for the study will be submitted to Human Research Ethical committee of the University of Witwatersrand and to the Postgraduate Committee of the University of Witwatersrand for approval.

BUDGET AND FUNDING

The cost of the study is estimated to be R 500 to cover printing and stationery. The cost will be covered by the researcher.

LIMITATIONS

It is a retrospective study so accurate data collection might be a problem.

ABBREVIATIONS

RDS Respiratory distress syndrome

MAS Meconium aspiration syndrome

BPD Bronchopulmonary dysplasia

HICs High income countries

LMICs Low- and middle-income countries

PPHN Persistent pulmonary hypertension of the new-born

CPAP Continuous positive airway pressure

NCPAP Nasal continuous positive airway pressure

CMJAH Charlotte Maxeke Johannesburg academic hospital

VLBW Very low birth weight

IPPV Intermittent positive pressure ventilation

SRT Surfactant replacement therapy

NICU Neonatal intensive care unit

ECMO Extra corporal membranous oxygenation

RCT Randomised controlled trial

Fio2 Fraction of inspired oxygen.

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DATA COLLECTION SHEET

Subject number _____

Gender _____

Gestational age _____

Birth weight _____

Maternal characteristics

Antenatal steroid Yes No

Multiple gestation Yes No

Mode of delivery Caesarean section Vaginal

Maternal comorbidity Yes No

Hypertension

Diabetes mellitus

Maternal chorioamnionitis

Neonatal Characteristics

Place of birth

Inborn Born at another hospital Born before arrival Unknown

Initial Resuscitation in delivery room Yes No

Nasal CPAP Yes No

Duration _____ days

Mechanical ventilation Yes No

Duration _____days

Died in Delivery room Yes No

Temperature in the first hour of admission to neonatal unit in degrees Celsius

Surfactant received Yes No

Time _____

Number of doses _____

Type ----------

Method of instillation INSURE MIST

Respiratory distress syndrome Yes No

Grade ----------

Congenital pneumonia Yes No

Meconium Aspiration syndrome Yes No

Initial Oxygen saturation_____%

Persistent Pulmonary Hypertension of New-born Yes No

Infant of Diabetic Mom Yes No

Retinopathy of Prematurity Yes No

Stage ----------

Intraventricular Haemorrhage Yes No

Grade ----------

Pneumothorax Yes No

Patent Ductus Arteriosus Yes No

Necrotising Enterocolitis Yes No

Stage ----------

Duration of stay in hospital _____days

Required IPPV

Duration ----------

Appendix C: Ethics Clearance

R14/49 Dr Oluwakemi Zainab Ayodele et al

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M170231

NAME: (Principal Investigator)	Dr Oluwakemi Zainab Ayodele et al
DEPARTMENT:	Paediatrics and Child Health Charlotte Maxeke Johannesburg Academic Hospital Neonatal Unit
PROJECT TITLE:	A Review of Surfactant use at Charlotte Maxeke Johannesburg Academic Hospital from 2013-2016
DATE CONSIDERED:	24/02/2017
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Prof D. Ballot
APPROVED BY:	Professor P Cleaton-Jones, Chairperson, HREC (Medical)
DATE OF APPROVAL:	03/04/2017

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

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary in Room 301, Third Floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand. 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 resubmit the application to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in February and will therefore be due in the month of February each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature Date

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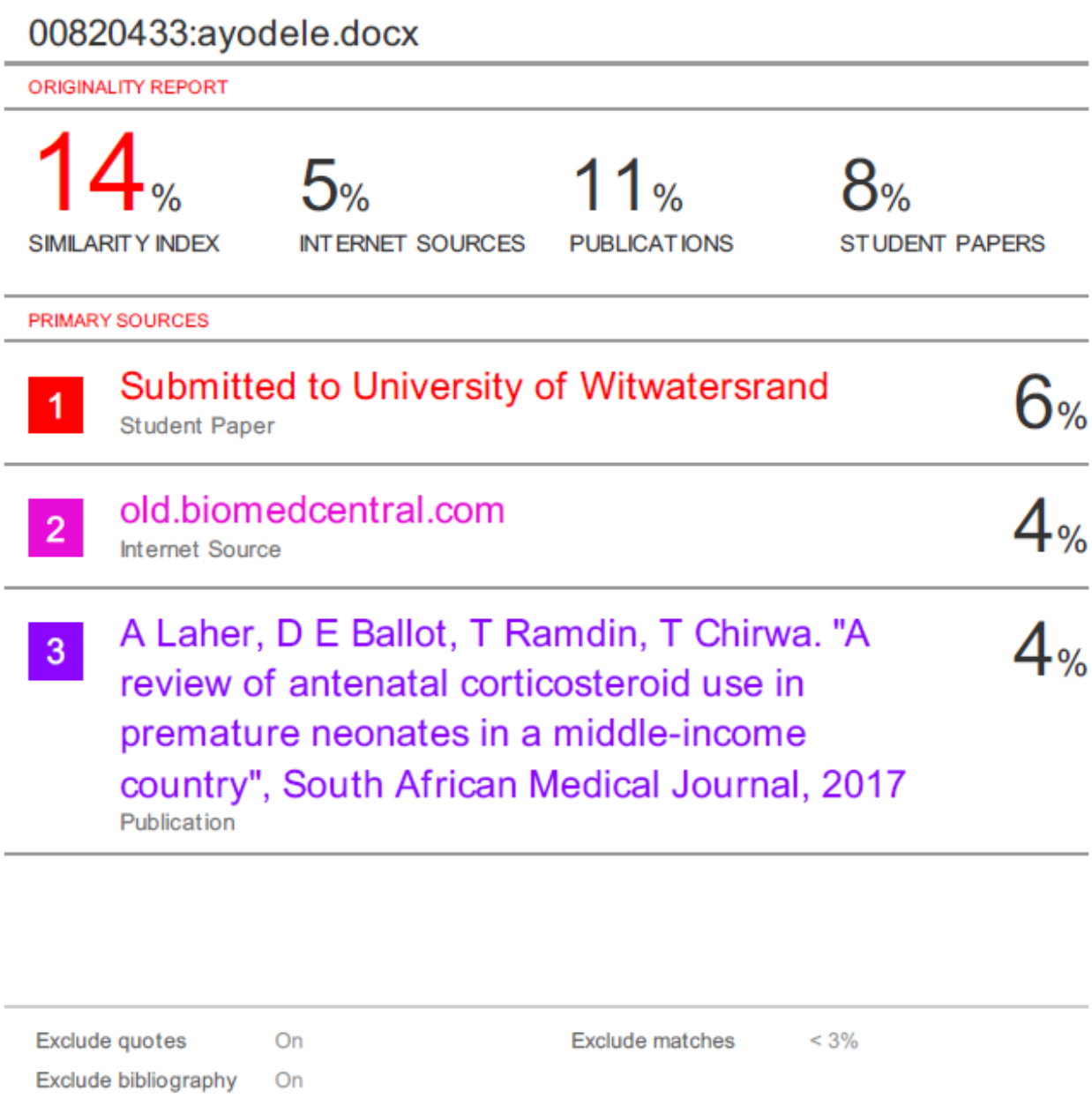

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