A PROSPECTIVE RANDOMIZED, DOUBLE BLIND, PLACEBO - CONTROLLED TRIAL OF A SINGLE DOSE OF SURFACTANT AS RESCUE THERAPY FOR INFANTS LESS THAN 1000grams WHO ARE NOT VENTILATED.

Kleopatra Savva

Johannesburg, 2000

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Kleopatra Savva

A Dissertation submitted to the Faculty of Health Sciences , University of the Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree
of
Master of Medicine in Paediatrics

Johannesburg, 2000

DECLARATION

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

Dr Kleopatra Savva

K. Savva

15th of July 2000.

To my beloved parents
Christodoula and George

PRESENTATIONS

PRELIMINARY RESULTS OF THE RESEARCH MATERIAL OF THIS REPORT HAVE BEEN PRESENTED AT THE FOLLOWING:

1. The **Abbott Neonatal Meeting**, in George, South Africa on the 3rd of September 1999.

2. The **Annual Research Day**, Paediatric Department of the Witwatersrand University, in Johannesburg on the 18th September 1999.

THE FINAL RESULTS OF THE RESEARCH MATERIAL HAVE BEEN PRESENTED AT:
The **MilliPaed** Congress 2000 in Sun City on the 21st May 2000.

ABSTRACT

Objective:

To test if a single dose of artificial surfactant given as rescue therapy to extremely low birth weight (ELBW) infants (i.e. those with birth weight <1000g) with hyaline membrane disease who are not ventilated, will improve their survival.

Design:

Prospective, randomized, double-blind, placebo-controlled study.

Setting:

The neonatal units of three hospitals attached to the Department of Paediatrics of the University of the Witwatersrand (Coronation, Johannesburg and Baragwanath Hospitals). Due to limited resources, all these hospitals have adopted the policy of not ventilating infants weighing less than 1000g at birth.

Patients:

Premature infants appropriate for gestational age weighing 900 to 999 g with respiratory distress requiring ≥40 % inspired oxygen to maintain arterial oxygen saturation were enrolled within 12 hours of birth.

Interventions:

Infants were randomly assigned to receive either a single intra-tracheal dose of the synthetic surfactant (Exosurf® neonatal) or air-placebo as rescue therapy.

Main Outcome Measure:

The primary outcome measure was survival to one week of age.

Secondary Outcome Measures:

Oxygen requirements, hospital stay and survival to hospital discharge.

Results:

During the period from the February 1999 to the January 2000, 50 patients had been enrolled in the study (females=25, males=25, Exosurf group=23, placebo group=27). For various reasons, 42 potential cases were missed during the above period of time. The mean gestational age was 27.9 ± 1.4 weeks (range 25-30) for the treatment and 28.2 ± 1.5 (range 25-30) weeks for the placebo group(t = 0.647 ;P> 0.05). The mean birth weight was 947.1 ± 29.8g for those on treatment and 937.6 ±33.2g for those on the placebo (t-1.056; P>0.05). **Primary outcome**: The early neonatal mortality was 56% (70% in the treatment group and 44% in the placebo group, x^2 =3.12; P= 0.077,odds ratio (OR)=0.35). **Secondary outcomes:** The overall mortality to discharge was 66% (surfactant 74% , placebo 59%, x^2 =1.16; P= 0.28, OR=0.51). *The overall mortality amongst the missed cases was* 79%(the difference was not significant compared to the surfactant and placebo groups: x^2 = 0.232; P =0.63, OR=1.36 and x^2 = 2.94; P =0.089, OR=2.65 respectively) . The mean hospital stay of the patients surviving to discharge, was 57.9 ± 4.7days in the placebo group and 54.2 ± 4.0 days in the treatment group(t- 1.64;P>0.05). Four cases required subsequent admission to the intensive care unit at a later stage when their weight was

above 1000g. All four cases were in the placebo group(Fisher`s exact test; P=0.115, OR=0.00). There were no differences as regards to broncho pulmonary dysplasia ( 1 case in the treatment vs 4 cases in the placebo group, Fisher`s exact test; P= 0.36, OR=0.26) and the requirements for supplemental oxygen between the two groups (14.8 ± 17.8 vs 21.3 ± 22.5days respectively, t-0.60;P >0.05).

Conclusion:

The above results do not show any significant difference in early neonatal mortality between the two groups. Surfactant-treated infants, showed a trend towards requiring less supplemental oxygen and being discharged home earlier but conclusions can not be drawn as the sample size of survivors was too small.

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LIST OF ABBREVIATIONS

AGA: appropriate for gestational age
BA: birth asphyxia
CPAP: continuous positive airway pressure
CXR: chest X-ray
DIC: disseminated intra vascular coagulation
DPPC: Dipalmitoyl phosphatidyl choline
EEG: electroencephalogram
ELBW: extremely low birth weight
HMD: hyaline membrane disease
IUGR: intrauterine growth retardation
IVH: intraventricular haemorrhage
LBW: low birth weight
NEC: necrotizing enterocolitis
NICU: neonatal intensive care unit
PDA: patent ductus arteriosus
PPV: positive pressure ventilation
RDS: respiratory distress syndrome
RR: respiratory rate
SGA: small for gestational age
SP-A: surfactant protein A
SP-B: surfactant protein B
SP-C: surfactant protein C
SP-D: surfactant protein D
SRT: surfactant replacement therapy

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APPENDIX INDEX

CHAPTER 1: INTRODUCTION

1.1 SURFACTANT : A LITERATURE REVIEW

1.1.1 COMPOSITION AND PHYSIOLOGY OF SURFACTANT PRODUCTION

In the year 1959, lung extracts from babies with hyaline membrane disease (HMD) were found to be surfactant deficient , thus establishing the final link between surfactant deficiency and HMD.[1]

We now know that the surfactant complex is composed of at least six phospholipids and four apoproteins.[2,3] Dipalmitoyl phosphatidyl choline (DPPC or lecithin) represents the largest volume(70-80%) of phospholipids, with 5-10% being phosphatidyl-glycerol and 10% phosphatidyl inositol, phosphatidylserine and phosphatidylethanolamine.[2] Another 10% is composed of other lipids such as cholesterol and sphingomyelin, whose concentration remains unchanged throughout gestation, whereas DPPC (lecithin) increases with gestation. Therefore, measuring lecithin to sphingomyelin (L/S) reflects lung maturity.

Five to ten percent of surfactant weight is made up by the 4 apoproteins. Surfactant protein- A (SP-A) plays a role in recycling of phospholipids, in determining the structure of tubular myelin and in regulating the synthesis, uptake and secretion of surfactant. It also enhances SP-B and SP-C function and may play a role in lung immune function. Surfactant proteins -B and -C

(SP-B and SP-C) increase the spreading of surfactant phospholipids onto an aqueous surface, and surfactant protein-D (SP-D) plays a role in the immune function of the lung.[2]

Most of the surfactant components are synthesized in the Golgi apparatus of the type II alveolar cell. Alveolar type II cells are differentiated from the columnar epithelium during the canalicular phase of development.[2,3] They become prominent at about 24 week`s gestation. The characteristic feature of the alveolar type II cell is the lamellar body which is the storage vesicle of surfactant. The lamella consists of a limiting membrane surrounding about 20-70 close-packed phospholipid bilayers. Once secreted by exocytosis , the vesicles unwind to form a bipolar monolayer of phospholipid . This is in dynamic equilibrium with a second structure, tubular myelin, which seems to represent an alveolar storage form of surfactant.[2,3] Alveolar surfactant is reabsorbed and resecreted many times. Exogenous surfactant does not inhibit this reprocessing.[2,3] Once secreted, surfactant lowers surface tension of the alveoli by forming an insoluble surface film, thus preventing atelectasis (Laplace equation). This results in a reduction of the work of breathing.[2]

1.1.2 COMPOSITION AND COMPARISON OF EXOGENOUS SURFACTANTS

There are two types of exogenous surfactant used for the treatment of HMD at present: the natural surfactants which are bovine (or porcine) lung mince extracts (Survanta®, Surfacten®, Curosurf®, Infasurf® and Alveofact®) or

human amniotic fluid extract, and the synthetic group of expanding compounds (Pneumactant® and Exosurf®) (see table 1.1). Exosurf® is composed of DPPC (lowers surface tension) and 9 % hexadecanol (accelerates absorption) and 6 % tyloxapol (facilitates dispersion), while Pneumactant is composed of DPPC and phosphatidyl glycerol in 7:3 ratio.[3,4]

The presence of surfactant apoproteins, especially SP-B, appears to be important for in vitro functioning of surfactant. Studies comparing different types of in vitro surfactant show that the natural ones are superior to the synthetic products (which lack apoproteins), and that the lung-wash preparations function better than the lung-mince surfactants products.[3] Meta-analysis of clinical trials comparing natural and synthetic surfactants have also shown that natural surfactants are associated with less oxygen requirements, fewer pulmonary air leaks and lower mortality.[3,5] These differences though are not as dramatic in vivo as they are in vitro. It is thus suggested that artificial surfactants may be combined with endogenous apoproteins, or that they are incorporated into recycling pathways.[3]

1.1.3 TIMING AND DELIVERY METHODS OF SURFACTANT ADMINISTRATION

Clinical trials have shown that administration of surfactant immediately after birth ("prophylaxis") is more beneficial than waiting until the development of HMD ("rescue").[3] The prophylaxis group required less supplemental

Table 1.1 Surfactant preparations

Surfactant Generic name	Trade name	Preparation
Beractant	Survanta®	Bovine lung mince extract with added DPPC*, tripalmitin and palmitic acid. SP-B§, SF-C†
Surfactant-TA	Surfacten®	Bovine lung mince extract with added DPPC ,tripalmitolglycerol and palmitic acid SP-B, SP-C
Porcine surfactant	Curosuf®	Porcine lung mince; chloroform-methanol extract; liquid -gel chromatography SP-B, SP-C
Calf lung surfactant extract (CLSE)	Infasurf ®	Bovine lung wash; chloroform-methanol extract SP-B, SP-C
SF-RI 1	Alveofact®	Bovine lung wash; chloroform-methanol extract SP-B, SP-C
Human amniotic fluid extract		human surfactant with SP-A/, SP-B, SP-C
Artificial lung expanding Pneumactant compound(ALEC)		DPPC and phosphatidylglycerol in 7:3 ratio
Colfosceril palmitate ,hexadecanol, tyloxapol(CPHT)	Exosurf®	DPPC with 9% hexadecanol and 6% tyloxapol

*DPPC = dipalmitoylphosphatidylcholine. SP-B§ = surfactant apoprotein B, SP-C† = surfactant apoprotein C, SP-A/ = surfactant apoprotein A

oxygen and in some studies was associated with a decreased mortality rate and fewer pulmonary air leaks. The cost-benefit ratio is better in babies less than 30 to31 week's gestation who have higher incidence of HMD as opposed to more mature babies. Therefore, it is currently recommended that babies below or up to 30 to 31 week's gestation receive surfactant as prophylaxis, and within the first 10 minutes after birth, although resuscitation measures are provided first if needed.[3] Most neonatologists would recommend that babies above 30 to 31 week's gestation receive surfactant as rescue therapy.[3] Evidence also indicates that earlier administration of a first rescue dose is more beneficial than delayed therapy.[3,6] It has also been shown that, even in the absence of surfactant administration in babies with a birth weight of 501 to 1500g, immediate ,elective intubation after birth is beneficial and safe, compared to selective intubation later on, even if this is only for a very brief period of time.[7] It has been shown that the five-minute apgar score was higher, the prevalence of metabolic acidosis was decreased within four hours of birth, the ventilatory requirements were diminished and the survival of these (electively intubated at birth) babies improved by 26 %. Although not statistically significant, there was lower incidence of pneumothorax, necrotizing enterocolitis (NEC) and pulmonary haemorrhage in the treatment group. Furthermore, in one study, intubation solely for surfactant administration (with removal of the endotracheal tube soon after the surfactant had been administered and placement of the babies on continuous positive airway pressure (CPAP)) resulted in decreased oxygen requirements and hospital stay.[3,8]

1.1.4 DOSAGE AND RETREATMENT REGIMENS

Preterm babies with HMD are surfactant deficient. The estimated surfactant pool in these babies is as low as 5 mg phospholipid per kg of body weight, versus 100 mg per kg in the normal term baby.[3] Most manufactures recommend doses of 100mg of phospholipid per kg of body weight[3], suspended in 3 to 5 ml of saline per kg (recommended dose of Exosurf® is 5 ml per kilogram body weight which provides 67.5 mg of DPPC per kilogram). The OSIRIS trial with synthetic surfactant [3,6] showed no advantage of 4 vs 2 doses. On the other hand other studies have shown improvement in oxygenation[9,10] and reduction in mortality[9] with multiple doses of surfactant. Studies are ongoing to attempt to define better retreatment criteria.[3]

1.1.5 DELIVERY TECHNIQUES OF EXOGENOUS SURFACTANT

Previously, surfactant administration was done slowly by infusion pump or aerosol. Those techniques have been abandoned, as they resulted in less homogenous distribution of surfactant. Nowadays it is recommended that surfactant be administrated as a bolus in multiple aliquots over a brief period of time (few seconds to few minutes).[4,11]The manufacturers recommend that, natural surfactants like Survanta® and Infasurf® are administered through a catheter inserted into the endotracheal tube (which should be placed with the tip in the midtrachea). During administration, the assisted ventilation is temporarily discontinued. Exosurf® is administered via a side port connected to the endotracheal tube which allows for assisted ventilation to be continued. Changing the patient's position does not improve the distribution

of surfactant in the lobes of the lung.[11]

Acute complications of surfactant administration include oxygen desaturation, bradycardia (from airway obstruction by the liquid volume or from vagal stimulation), electroencephalogram (EEG) changes and hypotension.[3,11]

1.1.6 EFFICACY AND SAFETY OF EXOGENOUS SURFACTANT

It is now clear that both rescue and prophylactic use of artificial surfactant improves survival[3,4,6,12,13,15-18] and respiratory status[3,4,12,13-20]. While it decreases air leak,[13,15-17,19] it has not increased the incidence of intraventricular haemorrhage(IVH),[12,13,16-17,18,20] ,necrotizing enterocolitis (NEC),[13,16,17] sepsis[13,16-17,20] and pulmonary haemorrhage. [13,15-16,18-20] . Although the risk for patent ductus arteriosus (PDA) is not increased when comparing surfactant treated versus placebo infants,[13,16-18,20] meta-analysis of surfactant trials[18] suggest that prophylactic use of both natural and synthetic surfactant increases the risk for PDA as compared to rescue therapy. Meta-analyses of published placebo-controlled studies have shown no change in the incidence of broncho pulmonary dysplasia (BPD) after the use of surfactant.[17,19,20,21] None of the studies reported a significant occurrence of feared complications (e. g. , complications of endotracheal intubation or evidence of asphyxia) from delays in resuscitation that might be caused by administering the surfactant immediately after birth.[3] One year follow up of the survivors showed that surfactant treated patients had a neurological outcome that was at least as good as that of the placebo treated patients.[12,23-24]The same is true

for the results at one year, comparing those babies treated prophylactically with patients who received rescue therapy.[24]

1.1.7 USE OF ASFC IN SOUTH AFRICA

Exogenous surfactant has been available commercially for the management of HMD since 1987.[12] In South Africa, it only became generally available in November 1991.[25] In this country, health services are provided, either by the state-funded public hospitals (which supply health care to about 80% of the population), or by the private sector. The high cost of artificial surfactant, and the limited financial and physical resources available in the public sector, has resulted in academic neonatologists establishing strict criteria for ventilation of neonates with HMD, as well as for those receiving surfactant replacement therapy.[25,26] The Conference on Priorities in Perinatal Care in South Africa in March 1991 recommended that surfactant replacement therapy (SRT) be given to those babies with birth weight >1000 g as rescue therapy.[25,27]

1.1.8 COST OF ASFC PRODUCTS

Surfactant replacement therapy is an expensive treatment. During the study period (years 1998-1999) the price of the natural surfactant survanta® was R1600 per 8.0 ml vial(state hospitals), as compared to Exosurf® whose price was R1200 per 8.0 ml vial.

1.2 THE EXTREMELY LOW BIRTH WEIGHT (ELBW) INFANT

1.2.1 DEFINITION , INCIDENCE AND MORTALITY IN SOUTH AFRICA

The extremely low birth weight (ELBW) infant is defined as the one weighing less than 1000 grams at birth. There is a strong correlation between birth weight and improved survival. It has been shown that approximately 80 % of ELBW babies who die do so within the first three days of birth.[28] Once they survive to day four , birth weight is no longer a factor affecting survival.

In Southern Africa, ELBW rate is estimated to be 0,7% of the total number of births.[27] Available statistics report that the total number of births in South Africa in 1995 was 809 439 . Therefore the total number of ELBW babies was 5666, and of these, 60% would require neonatal intensive care unit (NICU) admission. In this country, weight-specific survival rates from birth to discharge in state hospital NICUs vary between 32% to 66% for ELBW infants weighing between 750 and 1000g.[27] If all the babies who required ventilation could be admitted into NICU (and received SRT), and 66% survived as mentioned above, then the provision of intensive care would have saved 1 infant for every 7 infants treated.[27]

Locally, available statistics from Coronation hospital show that the current neonatal mortality (deaths in the first twenty eight days of life) of ELBW babies who are denied NICU care, is 59 % with the early neonatal mortality (deaths up to day 7) being 48 %. At Baragwanath hospital during the years

1995/96 Cooper et al[29] reported a neonatal mortality of 68% for those with birth weight less than 1000g.

1.2.2 HYALINE MEMBRANE DISEASE (HMD) AND THE ELBW BABY

Hyaline membrane disease is an acute respiratory illness, most commonly of preterm babies. Clinically it is characterized by respiratory rates of 60 per minute or more, dyspnoea defined as intercostal and subcostal indrawing and expiratory grunt.

The etiology of HMD is immaturity of lungs and the surfactant producing system. It is thus a common disease in babies < 30 week`s gestation, and those babies < 28 week`s gestation are invariably affected.[11] Factors associated with prematurity which predispose and / or contribute to development of HMD are as follows: 1) poorly developed alveoli 2)increased connective tissue 3)increased protein leak (the presence of proteins in alveoli inactivates surfactant) and 4)increased risk of birth asphyxia, hypothermia, hypotension and hypoxia, which impair surfactant synthesis and / or secretion.[11] HMD presents within 4-6 hours of birth and it progressively worsens over the next 12-24 hours as the small quantities of surfactant available at birth are rapidly used up or inhibited by proteins, acidosis and hypoxia.

1.2.2.1 INCIDENCE OF HMD

The incidence of HMD varies from study to study, and is affected by ethnicity , gender, inheritability and maternal health. [illegible] ine growth

retardation (IUGR) and multiple pregnancies may also affect surfactant production.

In Sweden,[11] during the period from November `76 to October `77, there was an incidence of 0.33% of HMD, while in Nottingham[11] during the period from April `83 to March`84, the incidence reported was 0,96%. In the USA , during the period from 1986 to 1987, HMD incidence in all live born babies was reported to be 1,72%.[11] In South Africa, no such data are available.

1.2.2.2 FACTORS AFFECTING THE RISK FOR HMD

HMD is twice as common in males as in females.[11] In Blacks the incidence of HMD less than in Caucasians.[11,30-32] In one study only 40% of black babies of 32 week`s gestation or less develop HMD, as compared to 75% observed in white babies matched for gestational age and birth weight.[30] In South Africa, a study done by Cooper PA et al[31], compared the prevalence of HMD between black and white low birth weight (LBW) infants 1000 to 1749g birth weight, of 29 to 34 week`s gestation at Johannesburg and Baragwanath hospitals. Black infants had a significantly lower prevalence of HMD (36.2% vs 62.5%).

Other factors, such as poorly controlled maternal diabetes have been documented to inhibit surfactant production.[11,33-34] IUGR was previously believed to protect against HMD, but recent studies suggest that it does not protect against severe HMD.[35-36] In twins, it was previously believed that the second twin was more predisposed to severe HMD,[37] but recent studies

have shown that twins have the same risk of developing HMD as singletons.[11,38] Inheritance seems to play a role in the development of HMD, with the relative risk of HMD in a subsequent preterm infant being 3.3.[39] Surfactant protein B deficiency is a rare lethal condition with an autosomal recessive mode of inheritance.[11]

Maternal alcohol and heroin use, as well as smoking during pregnancy have been shown to result in advanced maturation of the lungs. In these cases, the risk of developing HMD is decreased.[11] These maternal habits have other deleterious and often disastrous consequences. Prenatal steroid use has been well documented to decrease the incidence and the severity of HMD.[11,40] This is the result of induction of surfactant producing enzymes, of induction of the genes producing SP -proteins A, B, C and D and of improvement of the quality of the surfactant produced.

1.2.3 CURRENT PRACTICE IN STATE- FUNDED PUBLIC HOSPITALS FOR ELBW INFANTS WITH HMD

Currently, in most state-run hospitals in South Africa, babies <1000 g at birth are denied NICU admission (therefore, they are denied PPV and SRT). The only exceptions are those babies who are born as a result of in vitro fertilization, or where mothers were treated aggressively during pregnancy for medical conditions such as diabetes, rhesus disease and renal failure. This practice is based on the recommendations layed down by the Conference on Priorities in Perinatal Care in South Africa in March 1991, due to limited

resources available to the state -funded public hospitals.[25,27] As a result, of the 5666 ELBW infants born annually in South Africa (as mentioned in section 1.2.1) it is expected that 2244 will die within the first 3 days of life, due to the fact that they are currently denied NICU care and SRT. In the private sector, there is no birth weight cut -off point for ventilation, and surfactant is presumably used in neonates across the full weight spectrum.[25,27]

All studies reviewed in the literature referred to premature babies who were either on the ventilator at the time of the enrollment to the study, or who would be admitted in the NICU following surfactant administration , and ventilated and /or offered CPAP if needed. Targeting those 2244 babies born and destined to die annually in South Africa based on the current practices, we **hypothesized that giving a single dose of artificial surfactant as a rescue treatment to ELBW babies, may improve their survival beyond the critical first week of life.**

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CHAPTER 2 : THE STUDY

2.1 AIMS OF THE STUDY

The main purpose of the study was to test if a single dose of artificial surfactant given as rescue therapy to extremely low birth weight (ELBW) infants (i.e. those with birth weight < 1000g) with hyaline membrane disease who are not ventilated, will improve their survival.

The main outcome measure was **survival to one week of age**. Secondary outcome measures that we looked at included **oxygen requirements, hospital stay and survival to hospital discharge.**

2.2 MATERIAL AND METHODS

2.2.1 SETTING

The study patients were enrolled from the neonatal units of the three hospitals attached to the Department of Paediatrics of the University of the Witwatersrand (Coronation, Johannesburg and C. H. Baragwanath hospitals). These hospitals, due to limited resources, have adopted the policy not to ventilate infants weighing less than 1000g at birth.

2.2.2 SUBJECTS

The following inclusion /exclusion criteria were used:

INCLUSION CRITERIA

- Birth weight: 900 to 999g (as birth weight is the most obvious predictor of outcome in extremely low birth weight babies, a narrow weight range was chosen to minimise the effect of this variable).

- Appropriate for gestational age (AGA) by the " new" Ballard score[41]: it was not always possible for the registrar on call to perform the score;at times the paediatric medical officer performed this task. To avoid bias the investigators were not allowed to score the patients. Infants were classified as appropriate on the basis of a birth weight ≥ the 10th and ≤90th percentile on the growth curve[42] (see appendix D).
- Respiratory distress: - Respiratory rate (RR)≥ 60 breaths / minute

  PLUS - Intercostal and subcostal recession

- Oxygen requirements: in < 40% head box inspired oxygen the patient`s oxygen saturation was ≤ than 90%
- Age at enrollment: first 12 hours of age.

EXCLUSION CRITERIA

- Small for gestational age (SGA). Infant were classified as small on the basis of a birth weight below the 10th centile on the growth curve[42] (see appendix D)
- Major congenital anomalies
- Hydrops fetalis
- Evidence of symptomatic congenital infections
- Age at the time of enrolment > 12 hours
- Cases where the decision to ventilate artificially was made by the attending physician
- Parental refusal.

Chest X-Ray (CXR) findings were not used as an entry criterion to the study because of the poor early correlation with HMD severity[43] and for practical reasons (some babies only had CXRs done after surfactant /placebo administration). At all three hospitals it is not uncommon for long delays to occur before CXRs are obtained. All initial CXRs were reviewed at the end of the study by a senior neonatologist who remained blinded to whether the patient received surfactant or placebo.

The presence of respiratory distress (RDS) was based on clinical criteria. Special investigations such as arterio-alveolar oxygen tension ratios and arterial blood gases analysis are not routinely performed on these babies and thus were not used for study purposes.

2.3 STUDY DESIGN

2.3.1 RANDOMIZATION METHOD

Variable balanced randomization blocks were utilized. The investigators were unaware of the actual randomization sequence. Each one of 60 opaque brown envelopes used contained a command either to use surfactant or air-placebo. The randomization process was done separately for males and females to ensure that equal numbers of the two sexes would be enrolled. In cases of multiple pregnancies, the first to be randomized was twin (or triplet) I, followed by twin (or triplet) II etc.

Once subjects were noted to fulfill all criteria for the study, each patient's details (name, surname, hospital number and hospital name) were recorded in a register before the randomization envelope was opened to ensure that the

randomization sequence could not be changed. A separate list, containing the details of all potential cases who were missed was also kept.

2.3.2 DOUBLE BLIND CHARACTER OF THE STUDY

Three investigators (neonatologists) located at Coronation hospital were involved in enrolling the patients into the study. These investigators were not involved in the day-to-day management of the patients they enrolled. They ensured that the administration of the surfactant /placebo was carried out unobserved by the care-givers of the patient (nursing and medical staff) who were thus blinded to treatment received by the individual patient.

2.3.3 ADMINISTRATION OF THE PLACEBO / ARTIFICIAL SURFACTANT

This was done in isolation with the patient`s saturation monitored and, if possible, on a cardiac monitor. If an assistant was needed for intubating the patient, we made sure that the assisting nurse/doctor was not allocated to work in the neonatal unit. Once it was found that the patient fulfilled all the entry criteria then he / she was placed in a 100% head box oxygen for 5 minutes. During that time the patient`s details were entered in a register (there were two separate lists numbered 1 to 25 ,one for males and one for females). Then the next available numbered randomization envelope (from the appropriate sex group) was opened to reveal whether the patient was to receive surfactant or air-placebo. Next, a 5-ml syringe with either 5.0 ml air or surfactant was filled and the patient was intubated with a size 2.5 endo

tracheal tube either orally or nasally. The side port for the use of injecting the surfactant/placebo was connected and the 5.0 ml of the medicine (or the 5.0 ml of air) were injected over the next 5 minutes, in small aliquots, while the patient received positive pressure ventilation(PPV) manually. Post administration of the surfactant/placebo the patient received 5 more minutes of PPV. Then, the baby was extubated into 100% head box oxygen (if an oxygen blender was not available the patient was placed in 15 litres/ minute of inspired oxygen). During the above procedure records were kept of the apneic episodes, lowest oxygen saturation, lowest heart rate observed as well as the patient`s respiratory rate before and during intubation and after extubation( see sample sheets, appendix A ). Once the procedure was completed the patient`s care was handed back to the ward physician.

2.4 DATA COLLECTION

Maternal characteristics, the patient`s details and information regarding the cardio respiratory status of the patient during the administration of surfactant/placebo were recorded on specific charts(see sample sheets appendix A). Thereafter the patients were followed up until the discharge / death day specifically monitored for their oxygen requirements, subsequent NICU admissions, the development of PDA, IVH and NEC (see sample sheets appendix A).

Cranial ultrasounds were done by the attending physicians in time intervals that followed the established protocol of each centre. Papile`s classification was used[44] for grading intraventricular haemorrhage. Chest X-rays (CXR)

were done when possible. Some patients who died shortly after birth had neither CXR, nor cranial sonars done. All initial CXRs were kept to be reviewed at the end of the study by a senior neonatologist blinded to the treatment received by each baby. The X-ray appearances were graded I-IV, using the criteria suggested by Tudor et al. [45,46] All data was entered onto "Statistica" computer program for subsequent analysis.

2.5 SAMPLE SIZE CALCULATION

In calculating the sample size, a difference in mortality of 10% between the two groups was considered to be clinically significant. Assuming a mortality rate ranging between 20 to 80% ,a minimum sample size of 18 patients in each group was required for statistical significance at a 5% level of significance and a power of 90%.

2.6 STATISTICAL ANALYSIS

Statistical significance testing for the mortality rate in the two groups was done using the chi-square test and for the means between groups using the unpaired t-test. Fischer's exact test was used when any cell of the expected values was < 5. A p-value of <0.05 was considered to be statistically significant.

2.7 ETHICAL CLEARANCE

Ethical clearance for the study was obtained from the Committee for Research on Human Subjects of the University of the Witwatersrand

(reference number: E 990111). Written consent was required for all patients enrolled to the study. For patients whose parents were non-literate, the parent's finger print was used instead of their signature along with the witness's signature. It was requested by the Committee that an interim analysis was done at some stage and if the results were indicative of significant differences between the two groups the trial would be stopped.

2.8 FUNDS

This was an investigator initiated study. The artificial surfactant (Exosurf® neonatal) was provided free of charge by Glaxo-Wellcome company. The only extra cost incurred by the hospital was that of one disposable endotracheal tube per patient.

2.9 DURATION OF THE STUDY

The study was started in February 1999 and it was expected to be completed by October 1999. However, more time was needed for enrolling the total number of patients required and thus it was only completed in January 2000.

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CHAPTER 3 : RESULTS

3.1 SUBJECTS

During the period from February 1999 to January 2000, 50 babies were enrolled into the study (of whom 25 were males and 25 females). Twenty seven babies were in the placebo group and 23 in the surfactant group. Twenty -nine babies were enrolled from C. H. Baragwanath, 13 from Johannesburg and 8 from Coronation hospitals. The mean gestational age was 27.9± 1.4 weeks (range 25 to 30) for the surfactant treated group and 28.2 ± 1.5 weeks (range 25 to 30) for the placebo group. The above difference was not statistically significant (t-0.647, P>0.05). The two groups were comparable as regards their birth weight (mean birth weight 947.1 ± 29.8g in the surfactant treated group and 937.6 ± 33.2g in the placebo group, t-1.056; P>0.05). The mean age at enrollment was 4.9 ± 2.8 and 4.9 ± 3.1 hours respectively. The 5- minute Apgar score was below 4 in 2 babies in the surfactant group; there was no case with 5-minute Apgar score less than 4 in the placebo group. The Apgar score was unavailable in 5 cases in the surfactant group and in 8 cases in the placebo group(see table 3.1).

Case number 17 in the female group (surfactant group) had to be excluded after randomization when it was realised that the patient's gestational age had been incorrectly entered in the patient notes. In this group of females randomization process was extended to number 26. To ensure against all eventualities, we initially planned 30 randomization envelopes for each group

although we aimed for only 25 patients in each group.

Table 3.1 **Patient characteristics and P values in Surfactant and Placebo treated babies as well as those of the cases missed.**

Characteristics	Surfactant (n=23)	Placebo (n=27)	P-value	Missed (n=42)
Males (%)	12 (52)	13 (48)	–	16 (38)
Females (%)	11 (48)	14 (52)	–	26 (62)
Gestational age, weeks (mean±STD)	27.9(±1.4)	28.2(±1.5)*	P >0,05	27.3 *(±1.4) (23/42)
Birth weight , grams (mean±STD)	947.1(±29.8)§	937.6(±33.2)	P >0,05	926.8 §(±28.9)
Age at enrollment, hours (mean±STD)	4.9(± 2.8)	4.9(±3.2)	--	–
Apgar < 4			–	–
At 5-minutes	2	0	--	--
Unknown	5	8		

*** There was no statistically significant difference in gestational age (GA) between surfactant and missed cases group(t-1.74 ; P >0.05). The patients in the missed group were younger than those in the placebo group and the difference was statistically significant (t-2.52; 0.02 > P >0.01). § The same patients were lighter than those in the treatment group and the difference was statistically significant (t-2.68; 0.01> P >0.005). The cases in the placebo group were heavier than those in the missed group but the difference was not statistically significant(t-1.43;P> 0.05).**

3.1.1 PROTOCOL VIOLATIONS

3.1.1.1 WRITTEN CONSENT PROTOCOL VIOLATIONS

Verbal consent was obtained telephonically from the parent in one case(female number 7) with the intention of having the consent form signed the next day as the baby was transferred to labour ward at Baragwanath hospital and the mother remained in South Rand hospital. Unfortunately the baby died the same night and we lost contact with the mother thereafter. Verbal consent was also obtained from the mother in male case number 2 in Johannesburg hospital with the plan to formally sign the consent form the next day. That mother has since disappeared and neither our staff nor the police could find her. Despite this, both cases were included in the final analysis of the study.

3.1.1.2 RESPIRATORY RATE VIOLATIONS

Four cases of hypoxic babies who were demonstrating periodic breathing as a result of exhaustion and who did not demonstrate sustained tachypnoea ≥60 breaths / minute were still included in the study. These 4 cases were all females (cases 14 and 20 in the placebo group who had with RR 46 and 52/ minute respectively ; cases 7 and 16 in the surfactant group with RR 40 and 52/ minute respectively). Cases 7,14 and 16 died within 0.5 , 0.3 and 3.3 days respectively. Case number 20 survived to discharge. After reviewing their CXRs, cases 16 and 20 had HMD III and I respectively . CXRs were not done on cases 7 and 14.

3.2 POTENTIAL CASES MISSED OR EXCLUDED

During the 12 month period that the study took place there were 42 potential cases who were missed or excluded. One parent was unavailable for consent, 2 patients were older than 12 hours of age at the time the investigator was

informed, and in 8 cases the patient died before or on the investigator's arrival at the scene. Errors in classifying or weighing the babies resulted in 2 exclusions. In 14 cases the investigators were not informed of the birth of these babies by the labour ward staff. The group of females was completed in September while the group of males was only completed in January 2000. During the time from September 1999 to January 2000 there were 15 further female babies born who met the inclusion criteria. Their data was kept for comparison bringing the total number of potential cases not enrolled to 42 as mentioned above. This explains the finding that there were in total 26 females versus 16 males in this group of missed cases. The mean gestational age in this group was 27.3 ± 1.4 weeks(range 24 to 29) which was comparable to that in the surfactant group (t-1.74 ; P >0.05) but these babies were younger by one week compared to the placebo group. This difference was statistically significant (t-2.524; 0.02>P>0.01). The mean birth weight was 926.8 ± 28.9g which was comparable to that in the placebo group (t-1.43; P>0.05) but it was statistically, significantly lighter than that of those babies in the surfactant group (t-2.68;0.01> P> 0.005, see table 3.1).

3.3 MATERNAL CHARACTERISTICS

Maternal characteristics of the patients enrolled to the study are shown in table 3.2. The characteristics of the missed cases group are listed in a separate column. The proportion of booked patients (i.e. those who received antenatal care) was 65% in the surfactant, 83% in the placebo and 68% in the missed cases group. Statistically there was no significant difference in the above groups

(surfactant vs placebo: x^2=1.91;P=0.17,OR=0.37 , surfactant vs missed :x^2=0.68; P=0.41,OR=0.62 and placebo vs missed x^2=1.62;P=0.20, OR=0.42). Fifty three percent of the surfactant group received prenatal steroids compared to 45% of the placebo group . The above difference was not statistically significant (x^2 = 0.21;P=0.65,OR=1.33). The age distribution was similar in the two groups with the majority of mothers being in the 20 to 35 year age group. In 28 (67 %)cases in the missed cases group information concerning age was not available.

Table 3.2 Maternal characteristics and P values of Surfactant (n=23) and Placebo (n=27) treated babies.

Characteristics	Surfactant (n=23)	Placebo (n=27)	P-value	Missed (n=42)
Age Group				
< 20 year old	2	2	–	1
20-35 year old	18	21	–	12
> 35 year old	1	2	–	1
Unknown (%)	2	2	–	28(67)
Booked (%)	13 (65)	20 (83)	P=0.17	19*(68)
Unknown	3 (13)	3 (11)	–	14 (33)
Prenatal steroids				
Received	10 (53)	10 (45)	P=0.65	?
Unknown	4	5	–	

*There was no difference between surfactant (or placebo) and missed cases group as regards the booking status (P=0.41 and P=0.20 respectively).

3.4 PRIMARY OUTCOME MEASURE : SURVIVAL TO ONE WEEK OF AGE AND EARLY NEONATAL MORTALITY.

Sixteen out of 23 (70%) patients died in the first seven days of life in the surfactant group versus 12 out of 27 (44%) patients in the placebo group(x^2 =3.12; P= 0.077, OR=0.35, see table 3.3). In the interim analysis done for the first 28 cases enrolled, the early neonatal mortality was very similar(6/14 (43%) died in the treatment group and 7/14(50%) in the placebo group;x^2 = 0.143; P>0.5).

Table 3.3 Comparison of primary outcome measures and corresponding P values in surfactant (n=23) , Placebo (n=27) treated babies and potential missed cases (n=42).

Outcome measures	Surfactant No (%)	Placebo No (%)	P-value	Missed No (%)
Mortality				
Early neonatal*	16 (70)	12[4] (44)	P =0.077	27/39[4] (69)
Overall	17 (74)	16 (59)	P =0.281	27/34[5] (79)

***Deaths occurring in the first 7 days of life.**

[4] The early neonatal mortality was statistically significantly higher in the missed cases group vs placebo (x^2=3.99; P=0.046,OR=0.36)

[5] Total number of patients who survived to discharged amongst this group n=7

The early neonatal mortality amongst the missed cases group was 69%(27 /39 patients; no data available for 3 patients). This figure was statistically higher than that of the placebo but was similar to that of the surfactant group ($x^2 = 3.99$; P=0.046,OR=0.36 and $x^2 = 0.001$;P=0.978 OR=0.98 respectively).

3.5 SECONDARY OUTCOME MEASURES

The overall mortality was very high in all three groups and the differences between groups did not reach statistically significant levels (see table 3.3). Seventeen out of 23(74%) patients died in the surfactant treated group vs 16 out of 27(59%) patients in the placebo group(x^2=1.16; P=0.281,OR=0.51). The overall mortality was 27 out of 34 (79%) patients in the missed cases group (no information being available in 8 patients in the last group). Comparing the latter group's overall mortality to that of surfactant and placebo ,the difference was not significant (x^2= 0.23; P=0.631,OR=1.36 and x^2=2.89; P=0.089,OR=2.65 respectively). One patient in the placebo group died due to perforated necrotizing enterocolitis, two patients due to sepsis and disseminated intra vascular coagulation (DIC) and for 13 the certified diagnosis was apnea and RDS. The cause of death in the treatment group as recorded by the attending physician was sepsis in 2 cases, sepsis and DIC in another 2 and apnea/RDS in the remaining 12.

The mean hospital stay of the survivors was 54.2 ± 4.0 days(range 11 days) in the surfactant group and 57.9 ± 4.7 days (range 14 days) in the placebo

group (t-1.64; P> 0.05, see table 3.4). Oxygen requirements were decreased but, not significantly so, in the surfactant group (14.8 ±17.8 vs 21.3±22.5 days, t-0.60;P> 0.05).

Chronic lung disease (C.L.D.= oxygen dependancy ≥28 days) was diagnosed in only one patient in the surfactant group and in 4 patients in the placebo group(Fisher's exact test; P = 0.357,OR=0.26).

Table 3.4 Comparison of secondary outcome measures and corresponding P values in Surfactant and Placebo treated babies.

Outcome measures	Surfactant (n=23)	Placebo (n = 27)	P-value
Hospital stay of survivors (mean(days)±STD)	54.2(± 4.0)	57.9(±4.7)	P>0.05
Oxygen Requirements of survivors (mean(days)±STD)	14.8 (±17.8)	21.3(±22.5)	P>0.05
C.L.D.*	1	4	P=0.357
NICU**admissions	0	4	P =0.115

*** C.L.D -chronic lung disease defined as oxygen dependancy beyond 28 after birth. **NICU: Neonatal intensive care unit.**

None of the surfactant treated babies required subsequent NICU admission while 4 patients in the placebo group did so (Fisher's exact test; P = 0.115; OR=0.00). These babies required NICU admission at a time when their weight was above one kilogram or they were older than two weeks old. One

case was diagnosed as having nosocomial sepsis and suspected NEC (female, case number 3). Another one (female, case number 6) was admitted in NICU with fungal sepsis and hypotension. A third case (male, case number 1) was admitted in NICU with sepsis and cardiac failure due to a patent ductus arteriosus and anaemia. The last case which required NICU admission was male, case number 19, who needed ventilation for apnea relateu to anaemia.

Initial CXRs were done in 14/ 23 cases in the surfactant group and in 19 / 27 cases in the placebo group. These were all reviewed by a single neonatologist who was blind to the treatment allocation of the patients with the following outcome: of 33 initial CXRs available for review;5 were of poor ,5 of satisfactory and 23 of good quality, technically. In only 1 case diagnosis could not be made because of the poor quality of the CXR. Twenty-eight out of 33 (85 %) CXRs were compatible radiologically with HMD (14 cases belonged to the treatment group and 14 in the placebo). Looking at severity of HMD, 11 cases (39 %) were mild cases (radiologically classified as grades I and II) and 17 (61 %) were severe ones (grades III and IV). The mortality of the group with mild disease was compared to the mortality documented amongst the severe HMD cases. The difference approached significance (3/11 in the mild vs 11/17 in the severe cases, $x^2 = 3.61$; P=0.057, OR=0.20). In the treatment group 9/14 (64 %) had severe disease and the mortality was 7/9 (78 %). In the placebo group, 8/14(57%) cases were radiologically diagnosed as severe HMD and of these

4/8 (50%) died . The above difference was not significant (Fisher's exact test, P= 0.335, OR=3.50).

On admission, blood cultures were done in only 33 cases and 4 were positive(1/15 in the treatment and 3/18 in the placebo group, Fisher's exact test ;P= 0.61, OR=0.36). Subsequent blood cultures were done in 19 patients and of those 5 were positive (1/5 in the treatment and 4/14 in the placebo group; Fisher's exact test; P=1.00, OR=0.63).

Intraventricular haemorrhage (IVH) occurred in 3/9 (33%) infants in the treatment and 8/14(57%) babies in the placebo group(cranial sonars were done on 9/23 cases in the treatment and on 14/27 cases in the placebo group). The difference was statistically not significant (Fisher's exact test; P =0.40, OR=0.38). There were no cases of IVH grade III or IV. There was one case of peri ventricular leukomalacia in the treatment group.

As regards other secondary outcome measures there were 2 cases with PDA in the placebo group and 2 cases of DIC secondary to sepsis in the treatment group: one case died soon after birth (male, case number 11) and the second one on day 4 of life (male, case number 18). The incidence of NEC was significantly higher in the placebo group (8 vs 0 cases, Fisher's exact test; P = 0.017, OR=0.00). Of these 8 cases, 5 were suspected of having NEC (stage I) and in 3 this was confirmed radiologically (stages II-III).

Table 3.5 Comparison of other secondary outcome measures and corresponding P values in Surfactant (n=23) and Placebo (n=27) treated babies.

Outcome measures	Surfactant No (%)	Placebo No (%)	P-value
Pneumothorax (initial CXRs)	0/14(0)	0/19(0)	--
Intra ventricular Haemorrhage			
Total	3/9 (33)	8/14 (57)	P=0.40
Grades III-IV	0/9 (0)	0/14 (0)	--
PVL	1/9 (11)	0/14 (0)	--
Persistent Ductus Arteriosus	0	2	--
Pulmonary Haemorrhage / ± DIC	2	0	--
Necrotizing Enterocolitis	0	8	P =0.017

3.6 SAFETY MEASURES

As seen in table 3.6 the administration of surfactant was not associated with any adverse effects: the apnea episodes ,the respiratory rate , the desaturation events and the bradycardia episodes were similar in the two groups.

Table 3.6.Comparison of cardiorespiratory status at the time of surfactant administration and corresponding P values in surfactant (n=23) and Placebo (n=27) treated babies.

	Surfactant No (%)	Placebo No (%)	P value
Apnea			
Pre-intubation	2	1	–
During	0	0	–
Post-extubation	7 (30)	8 (30)	>0.5
Respiratory rate (breaths/min)(mean±STD)	71(±15.5)	66(±11.9)	>0.1
Pre-intubation	68(±11.6)	66(±10.2)	>0.5
During	59(±19.2)	57(±21.4)	>0.5
Post-extubation			
Lowest oxygen saturation (mean±STD)	80(±18.2)	88(±20.1)	>0.1
Pre-intubation	82(±15.9)	83(±12.0)	>0.5
During	77(±19.0)	73(±22.7)	>0.2
Post-extubation			
Lowest heart rate (breaths/min)(mean±STD)			
Pre-intubation	117(±33.3)	124(±23.4)	>0.05
During	131(±22.5)	109(±34.4)	>0.2
Post-extubation	130(±27.4)	119(±33.4)	>0.5

3.7 CONCLUSION

The above results suggest that as regards the **primary outcome** the artificial **surfactant**(Exosurf® neonatal) given as a **rescue, single intra tracheal dose** in **unventilated** ELBW babies between **900 to 999g did not improve the early neonatal survival.** Surfactant treated babies showed a **trend** towards

requiring less supplemental oxygen and **being discharged home earlier** but the difference **did not reach statistical significance.**

There was **no difference in the overall survival to discharge between the 2 groups. Mortality is strongly associated with gender**. Males have higher mortality than females(76% vs 56%, $x^2 = 2.18$; P=0.14,OR =0.40) even though in this study has not reach statistical significance levels. Surfactant administration was **not associated** with any **adverse reactions.**

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CHAPTER 4 : DISCUSSION AND CONCLUSIONS

4.1 DISCUSSION

This study showed **no benefit** in the administration of a **single rescue dose of artificial surfactant for non-ventilated ELBW** infants with HMD in terms of the primary endpoint of the study, namely improved early neonatal survival. A major question raised by the study is whether in fact administration of surfactant in unventilated ELBW infants may have resulted in an increase in mortality. Surfactant treated babies had an early neonatal mortality, as high as 70%, which was similar to the mortality (69%) of those babies receiving no intervention (neither placebo nor surfactant) in the labour ward . The overall mortalities were also similar (74% in the surfactant group and 79% in those without intervention, see table3.3). This finding alone suggests that surfactant administration was not the causative factor for such high mortality in this particular group of ELBW infants. In another developing country, Pakistan, Bhutta et al,[47]reported a similarly high mortality of 68% in babies ≤ 1000g birth weight with HMD. Locally, a previous study done in 1990 in Baragwanath hospital studying the effect of early postnatal steroids in ELBW infants showed a 63% mortality in the non study group, and a 58% mortality in the study patients.[48] The important message here is that in developing countries such as South Africa, the mortality of ELBW infants remains extremely high compared to the mortality seen in developed countries, where it is currently reported to be less than 40%.[49] The fact that ELBW babies are denied NICU care and the less than ideal level of antenatal care experienced by our population are major

causative factors of this extremely high mortality. Only 52 out of 72 (72 %) patients with known booking status received antenatal care in this study. Prenatal steroids were used in only 20 out of 41 cases (50% , see table 3.2)

Th: 25% difference in early neonatal mortality reported between the placebo and the group with no intervention (see table 3.3) was significant. The beneficial effect of immediate intubation after birth has been shown in a previous study.[7] It has been shown that the neonatal survival of electively intubated at birth babies improved by 26 % compared to the survival of those selectively intubated later on. This was almost identical to the 25% difference we found in the current study. In the above study although postneonatal mortality was mentioned, there was no reference specifically to the survival rate until discharge while the current study showed no significant difference in the survival to discharge.

Our study, shows that males with HMD had higher mortality than females (76% vs 56%). This trend was, though, not statistically significant. Gender associated mortality and HMD is well documented.[11,50] It is believed that androgens play a role in the del. ed maturation of the L/S ratio.[11] Males develop more severe HMD, and are more likely to die from it.[11,48] In Perelman's study,[50] the difference between sexes was greatest in the birth weight categories between 1001 to 1500g.

rfactant treated babies showed a trend toward requiring less supplemental

oxygen, and being discharged earlier from the hospital. Of interest was the finding that none of the patients in the treatment group required subsequent NICU admission while 4 patients in the placebo group did ultimately needed to be ventilated. The above differences were not significant, perhaps due to the small sample size. It remains unclear why placebo treatment babies should increase the need for later ventilation (after the early neonatal period).

Another interesting finding was that no case of NEC occurred in the treatment group while 8 cases had been diagnosed in the placebo group. This difference was statistically significant. The two groups may however, have not been homogeneous as regards to birth asphyxia (BA), in which case, patients with more severe BA might have been allocated to the placebo group. Birth asphyxia is a well known factor associated with NEC.[51]

It is obvious that the study suffers from a number of limitations. The small sample size of the survivors limited statistical analysis of the secondary outcome measures. The issue of birth asphyxia is an important one. On entry to the study BA was evaluated only from records of Apgar scores, but it is well accepted that Apgar scoring alone has limited use in predicting morbidity in the low birth weight infant.[52,53,54] Notwithstanding the above,1- and 5- minute Apgar scores did not differ between the two groups. It is possible that the two groups were not comparable in regards with BA status and this may have affected morbidity and mortality.

Furthermore, in accessing HMD the criteria were clinically defined without the assessment of either routine arterial blood gases or routine radiological assessment. This followed the clinical practice protocols usually offered to these babies in the early neonatal period but may have resulted in non homogeneous distribution of HMD cases between the two groups. For practical reasons we could not assign specific investigator to do the Ballard score on all the babies. Allowing the score to be done by the paediatric registrar, or if not available, the paediatric medical officer on duty, the scoring of the babies was not standardised. We do believe, though, that the differences in regards to medical care in the three neonatal units did not differ significantly, as the management protocols for the ELBW babies are very similar.

4.2 CONCLUSIONS

The results of the current study suggest that administration of a **single rescue dose of artificial surfactant without mechanical ventilatory support does not improve the outcome of ELBW infants with HMD.** It is difficult and perhaps naive to attempt to tease-out individual components of care which contribute to better outcomes in the very small premature infant but it is useful to know that an expensive medication on its own and specifically without the other trappings of neonatal intensive care does not result in better early neonatal survival.

Extremely low birth weight infants with HMD at our hospitals (C. H.

Baragwanath, Johannesburg and Coronation hospitals) have a **similar** mortality compared to the mortality reported in other **developing countries** and a much **higher mortality than that currently documented in developed countries.**

Regarding the **secondary outcomes** (oxygen requirements, subsequent NICU admissions and length of hospital stay) the **trends seen are in favour of the treatment group.** With the small numbers of survivors in this study, definite conclusions cannot be drawn.

Gender associated mortality places the **male infants at higher risk of developing and dying from HMD.**

4.3 RECOMMENDATIONS

The challenge of lowering the extremely high mortality in ELBW infants documented in our setting needs to be urgently addressed. As with the early postnatal steroid administration,[48] use of surfactant rescue therapy without ventilatory support is of no benefit.

Since it is unlikely that facilities in our NICUs will be expanded in the foreseeable future to allow for ventilation of ELBW infants, ultimately the most practical solution at present would lie in measures to reduce the rate of premature births. Better antenatal care and measures to ensure that the patients requiring prenatal steroids receive it, should be a priority.

With regard to ethical issues, it seems that there are two opposing views. The first, shares the concerns of Smith et al[27] expressed in an SAMJ Forum debate "Born too soon, too small, to die- a plea for a fair innings" where they advocate that perhaps it is more fair if service was provided on the "first come first served" basis with no cut-off on weight or gestational age. The second line of thought is the one suggested by PA Cooper [55] which refers to the principles of distributive justice and utilitarian maxim of triage. In the same editorial it is mentioned that the "ventilator time" required to produce 1 survivor weighing less than 1000g at birth could result in 2 survivors with birth weight 1000 - 1500g, 4 survivors of 1500 - 2000g and 10 survivors with birth weight greater than 2000g. People sharing this line of thought believe that it would be inappropriate to utilise scarce resources for infants with either poor prognosis for survival or with a very high risk for long term severe handicap such as the ELBW infants.

Perhaps, allowing access to NICU to all babies (irrespective of GA and birth weight) and reviewing their prognosis within the following 48 to 72 hours would be more appropriate. However decisions to withdraw care are difficult at this stage. My personal belief is that these decisions should be made by a team dedicated to dealing with these issues. Such a team should consist of senior neonatologists, parents, community members with authority and experts in both ethical and financial issues.

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APPENDIX- A

MATERNAL INFORMATION SHEET:

DATE OF ENROLLMENT	
HOSPITAL NUMBER	
INITIALS ONLY	
AGE	
PARITA	
GRAVIDA	
ADDRESS	
BOOKED	
UNBOOKED	
UNKNOWN	

	NVD	C/S EMER	C/S ELECT	BBA	ASSISTED
MODE OF DELIVERY					

	Ht	ECLAMPSIA	MULT PREG	IDDM	PROM	HIV	PLACENTA PREVIA	CORD PROLAPSE
OBSTETRIC PROBLEMS								

	NO	YES, DOSES
PRENATAL STEROIDS		

	POSITIVE	NEGATIVE	UNKNOWN
WR			

	YES	NO
SMOKING		
ALCOHOL		

PATIENT INFORMATION SHEET: DAY O - ON ADMISSION:

SEX	

CASE NUMBER (1-50)	EXOSURF	PLACEBO

AGE (HOURS) AT ENROLLMENT	
PATIENT'S INITIALS ONLY + HOSPITAL NUMBER	
DATE OF BIRTH	
TIME OF BIRTH	
BALLARD SCORE	

BIRTH WEIGHT	LENGTH	HEAD CIRCUMFERENCE

	I-MINUTE	5-MINUTES	10- MINUTES
APGAR SCORE			

	PRE-ADMINISTRATION	DURING	POST-ADMINISTRATION
RESPIRATORY RATE			
RECESSIONS			
FiO2 %			
O2 SATURATION {LOWEST}			
HEART RATE {MINIMUM}			

PATIENT INFORMATION SHEET DAY 1-7 :

	DAY 1	DAY 2	DAY 3	DAY 4	DAY 5	DAY 6	DAY 7
FiO2%							
APNEA							
RECESSIONS							
BRADYS <80							
RESP RATE							
SATURATION RANGE							
CXR							
CRANIAL U/S							

PATIENT INFORMATION SHEET ON DISCHARGE:

DATE OF DISCHARGE	DATE OF DEATH	HOSPITAL STAY(DAYS)
D/C WEIGHT	D/C LENGTH	D/C HEAD CIRCUMFERENCE

FiO2 MAXIMUM	O2 DAYS

HMD	CONGENITAL PNEUMONIA	TTN	PULMONARY HEMORRHAG	PNEUMOTHORAX	OTHER

CARDIOVASCULAR:

PDA	OTHER CHD	OTHER

GIT:

G/E	NEC	OTHER

RENAL:

PRERENAL DYSFUNCTION	RENAL FAILURE	OTHER

HAEMATOLOGICAL:

Hb	WCC	PLATELETS	NNJ	PHOTO	EXCHANGE T/F	PEAK BILI	COOMPS,GROUP

EPISODES OF INFECTION:

	SUSPECTED	PROVEN	BLOOD CULTURE	ORGANISM	CULT OTHER SIDES
SEPSIS					
UTI					
RESPIRATORY					
OTHER					

APPENDIX-B

EXOSURF STUDY:

PARENTAL CONSENT: TO BE TAKEN BEFORE DELIVERY OR AS SOON AS POSSIBLE AFTER DELIVERY

Dear parent,

Your baby is expected to be/ has been born premature. Small premature babies often suffer from poor lung development. Because of this, they may need medical assistance such as oxygen, support by the machine for breathing(the so called ventilator) and over and above these they may need a medicine called SURFACTANT. However, in our group of hospitals we are not able to give babies whose weight is below 1000gms at birth, mechanical ventilation or surfactant.

We are performing a scientific study to see whether the administration of a single dose of surfactant, into the baby's lungs in the neonatal ward, without the use of the machine for breathing(ventilator), will improve the survival of very low birth weight babies.

If you agree to let your baby participate in the study and if the baby has premature lung disease and needs oxygen, we will place a tube into the windpipe and inject a small quantity of surfactant in those babies allocated to the treatment group. Afterwards, we will remove the tube. Half the number of babies participating will be randomly chosen to receive air instead of surfactant. This group of babies is called the controlled group. Your baby may or may not belong to either the control or the treatment groups. Participation in the study may or may not be of benefit to your baby.

SURFACTANT is NOT a new medication and its safety has been established.

PLEASE NOTE: If you choose NOT to participate in the study, we will NOT hold this against you or your baby. Your baby will receive the same care as those participating in the study and all those babies treated in our ward. You are FREE to withdraw your baby from the study at any time without explanation and this will NOT affect your baby's care.

In the case of participating in the study we will ensure that confidentiality

will be maintained: although some records will be used for data, no patient names or identification numbers will be mentioned in any reports.

No matter what your decision is, we would like to thank you for your time !
If you decided to participate in the study, please sign below:

PARENTAL NAME and SURNAME in capitals: ----------

PARENTAL SIGNATURE: - ----------
WITNESS: - ----------

DATE : ----------

*** IF YOU HAVE ANY FURTHER QUESTIONS / QUERIES
PLEASE FEEL FREE TO CONTACT THE DOCTOR IN CHARGE:

Dr K. SAVVA
Coronation Hospital
Tel: 011-4709000 bleep: 7260
Ext :9146/3
Cell:082-4401876

RANDOMIZATION LISTS

EXOSURF STUDY:

FEMALES : 1-25

CASE NO	INITIALS	HOSPITAL NUMBER	DATE ENTERED	HOSPITAL
1	B/T Patricia Tshapa	799143 MP	2/3/99	BARAG
2	B/T SHAMBILE GLORIA NZAMA	2487187	7/3/99	SHB
3	B/T Gladys Molokwane	80376	20/3/99	Cove
4	B/T Estelina Daniels	80397	02/4/99	Covo
5	B/T Maydeline Sleppers	802053 MP	16/4/99	Bave
6	B/T FINDI MASHILOANE	802613 MP	18/4/99	Bava
7	B/T Mthembu	No No given died in L.W	23/4/99	Bava (From S Raud)
8	~~B/T Baloyi~~		~~23/4/99~~	~~Bave~~ ⇒ Boy: delivered in ward 1st.
9	B/T F. Mofolo	803643 MP	30/4/99	Bave
10	~~B/T E. Pascoe~~	~~804327 MP~~	~~7/5/99~~	Bave
11	B/T S. Shilenge	804327 MP	7/5/99	Bave
12	B/T. E Mawa	804340 MP	8/5/99	Bave
13	B/T. N. Ndlovu	2504085	17/5/99	SHB
14	B/T N. Chapi	805575	27/5/99	Bave
15	B/T ZITA SONIA	?	01/06/99	SHB
16	B/T Buldewa Mydi	807998MP	19/6/99	Bave
17	BT MOALI MAZZONE	810161 MP	14/7/99	BARA
18	B/T A. Bockholuwe	810194NP	17/7/99	Bave
19	B/T T. Shabalala	810631NP	19/7/99	Bave
20	B/T M Mbovane	?	21/7/99	SHB
21	B/T D Seekoe	103072	30/7/99	Covo
22	B/T L. Mokhele (II)	?	03/8/99	SHB
23	B/T L. Mokhele (III)	?	03/08/99	SHB
24	B/T S Matsuketwa	?	15/08/99	Covo
25	B/T A. Kock	813092NP	23/08/99	Bave
C	B/T E. Senaoe	2529693	05/09/99	SHB
26	Twin I B/T E. Senaoe Twin II	2529694	05/09/99	SHB

At ward admission

EXOSURF STUDY:

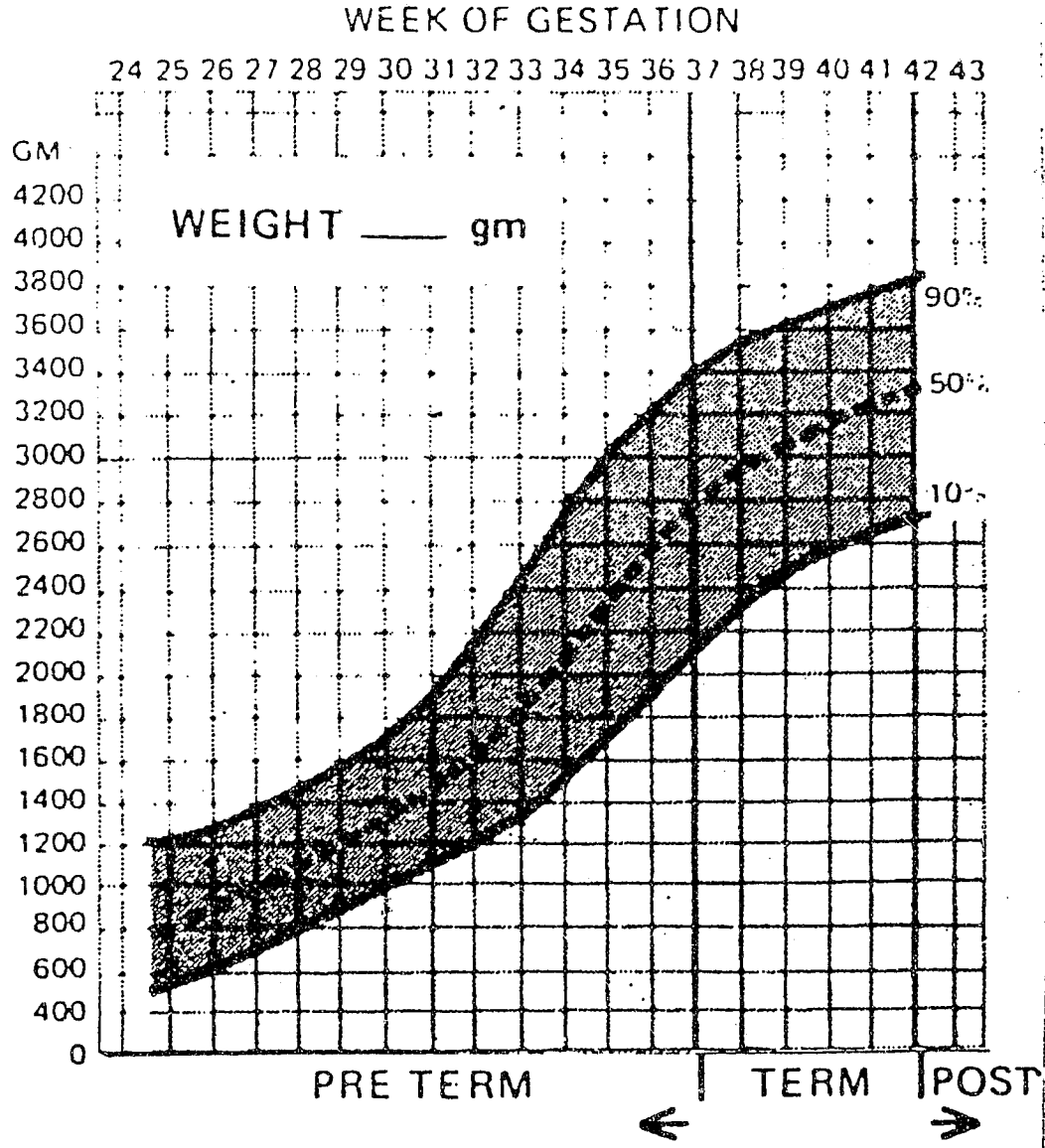
MALES : 1-25

CASE NO	INITIALS	HOSPITAL NUMBER	DATE ENTERED	HOSPITAL
1	B/T T. Nobanda	800906MP	23/3/99	Bara
2	B/T. [redacted] Shezi	2492248	27/3/99	JHB
3	B/T L.S	802044MP	14/4/99	Bara
4	B/T E. Bahul	802650MP	23/4/99	Bara
5	B/T S. Mtshaeni	?	28/4/99	Bara
6	B/T V. Gcabinde	803670MP	4/5/99	Bara
7	B/T. N. Mangaphu	804318MP	6/5/99	Bara
8	B/T K. Moyo	2501830	7/5/99	JHB
9	B/T N. Metebese	807035MP	6/6/99	Bara
10	B/T E. Mpofu	808584MP	01/07/99	Bara
11	B/T D. Shiba	809349MP	4/7/99	Bara
12	B/T L. Chotae	809367	6/7/99	Bara
13	B/T C. Msoli	810657	23/07/99	Bara
14	B/T M. Mayoni	106117	16/08/99	Coro
15	B/T C. Buys	106137	25/08/99	Coro
16	B/T B. Mshangase	813654	30/08/99	Bara
17	B/T C. Eduardo	815947MP	25/9/99	Bara
18	B/T. C. Botes	2538086	10/10/99	JHB
19	B/T. L. Ngema	?	22/10/99	JHB
20	B/T. C. Motaleng	?	24/11/99	Coro
21	B/T. S. Madisa	?	01/12/99	Bara
22	B/T. Celle	2554878	15/12/99	JHB
23	B/T A. Mashaba	150100	15/01/2000	Coro
24	B/T Imedi	825156	23/1/2000	Bara
25	B/T Imedi	825157	23/1/2000	Bara

APPENDIX-D

GROWTH CURVE[42]

(From a form developed by Jacob L. Kay)


WEEK OF GESTATION
24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43
GM
4200
4000
3800
3600
3400
3200
3000
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
0
WEIGHT ____ gm
90%
50%
10%
PRE TERM
TERM
POST

APPENDIX-E

CHEST X-RAY ANALYSIS DATA

29	G		✓					Biggest Lead
30	G			✓				
31	OIL			✓				
32	G			✓				
33	G						✓	

29	G		✓					Biggest Lead
30	G			✓				
31	OK			✓				
32	G			✓				
33	G						✓	