UNIVERSITY OF THE WITWATERSRAND
SCHOOL OF CLINICAL MEDICINE
DEPARTMENT OF PAEDIATRICS AND CHILD HEALTH

SURVIVAL OF EXTREMELY LOW BIRTH WEIGHT INFANTS AT CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL

Candidate: DR KALIMBA M EDGAR
Supervisor: PROF DAYNIA E BALLOT
[2013]

[**DISSERTATION SUBMITTED IN PARTIAL FULFILLMENT OF REQUIREMENTS FOR A MASTER OF MEDICINE DEGREE IN PAEDIATRICS AND CHILD HEALTH (MMED PAED)**

DECLARATION

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

…………………………………………

The…………day of……………2013

DEDICATION

To the two people who bring so much joy and meaning to my life, Ciella and Irene.

ACKNOWLEDGEMENTS

- My greatest appreciation goes to Professor Daynia Ballot for accepting to supervise this research project and for her availability, encouragement and guidance.
- To Professor P Cooper and the Wits paediatric department for giving me the chance to train in one of the best clinical units in South Africa.
- A vote of thanks to Miss Tabither Muthoni Gitau for teaching me what I needed to know about the relevant statistics.
- My gratitude also goes to the Rwandan government for sponsoring my studies.

SURVIVAL OF EXTREMELY LOW BIRTH WEIGHT INFANTS AT CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL

Student: Edgar M KALIMBA (MD)

Student number: 395519

Supervisor: Daynia Ballot (ASSOC PROF)

ABSTRACT

Objectives: Survival of extremely low birth weight (ELBW) infants in a resource limited public hospital setting is still low in South Africa. The study aimed at establishing the determinants of survival in this weight category of neonates who, due to limited intensive care facilities, were not mechanically ventilated.

Design: A retrospective study where patient data was retrieved from the departmental computer database.

Setting: Neonatal unit at Charlotte Maxeke Johannesburg academic hospital (CMJAH).

Subjects: Neonates admitted at birth between January 2006 and December 2010 with birth weights of ≤ 900g.

Outcome measures: Survival at discharge was the major outcome. Maternal variables were: age, parity, gravidity, antenatal care, antenatal steroids, place and mode of delivery and HIV status. Neonatal variables: gestational age (GA), birth weight (BW), gender, place of birth, hypothermia, resuscitation at birth, sepsis, necrotising enterocolitis, intraventricular hemorrhage, jaundice, nasal continuous positive airway pressure (NCPAP) with or without surfactant and APGAR scores.

Results: A total of 382 neonates were included in our study. Overall survival was 26.5%. The main causes of death, as per the PPIP classification, were extreme multi-organ immaturity and respiratory distress syndrome. The main determinants of survival were BW, OR= 0.994; (95% CI 0.991-0.997) and GA, OR= 0.827; (95% CI 0.743-0.919). Overall, NCPAP use was 15.5% and was not associated with better survival.

Conclusion: Survival of ELBW infants is low. Birth weight and gestational age were the strongest predictors of survival. Effective steps are required to avoid extreme prematurity, encourage antenatal care, and avail antenatal steroids in anticipated preterm birth.

TABLE OF CONTENTS

ABBREVIATIONS

1. AGA :Appropriate for gestational age
2. ELBW :Extremely low birth weight
3. ICU : Intensive care unit
4. IVH : Intraventricular haemorrhage
5. MDG :Millenium development goals
6. NCPAP :Nasal continuous positive airway pressure
7. NEC :Necrotising enterocolitis
8. RDS :Respiratory distress syndrome
9. SGA :small for gestational age
10. InSurE : Intubation, Surfactant and Extubation
11. USA : United States of America
12. CMJAH : Charlotte Maxeke Johannesburg Academic hospital
13. CHBAH : Chris Hani Baragwanath Academic hospital

1. BACKGROUND

According to the World Health Organisation, nearly four million neonatal deaths occur worldwide every year. Most of these deaths take place in developing countries.[1]

Millennium development goal number 4 is to reduce child mortality by reducing the under-five mortality by two thirds between 1990 and 2015. More than 8 million under five children die every year, and neonatal causes are among the 6 conditions for which over 90% of these deaths are attributed.[2] As such, improved maternal and new-born care with timely management of complications will play a significant role in attaining this goal.

While under-5 mortality rates are improving in many countries worldwide, neonatal mortality rates have shown a much less progress.[3] Neonatal deaths now account for more than 42% of all under-5 deaths, up from 37% in the year 2000.[3] Complications of preterm birth are the leading direct cause of neonatal mortality accounting for an estimated 27% of the 4 million neonatal deaths every year. Hence achieving MDG 4 is strongly dependent upon progress in reducing neonatal deaths, and more precisely on achieving an improved survival rate for preterm infants.

According to UN data, the neonatal mortality rate (NMR) for Africa in the year 2009 was estimated to be 34 per 1000 live births, with the highest mortality in sub-Saharan countries. The same survey estimated South Africa's NMR at 19 for the year 2009. This is still significantly high especially in comparison with industrialised countries whose NMR averages 3-7 per 1000 live births.[4]

In South Africa, perinatal mortality and low birth weight rates have, in the past, generally been reported only for those infants weighing 1000g or more at birth because smaller infants are often regarded as miscarriages and not recorded. However, with improving maternal and neonatal care, more and more infants weighing 500g to 1000g are expected to survive.

There's no doubt that the mortality rate of very low birth weight infants is a big contributor to the overall neonatal mortality rate, both for developing and developed countries.

In one study carried out in Bangladesh, a developing country, the biggest contributor to NMR was preterm delivery, with VLBW infants making the majority of the early neonatal deaths (38%).[5] A similar observation was made in the USA in one study that showed 50% of neonatal deaths were due to very low birth weight infants.[6]

In the sixth perinatal care survey of South Africa (saving babies 2006-2007), neonatal deaths due to "immaturity related causes" accounted for the majority of deaths at 50% of all neonatal deaths.[7]

Globally, the trend of survival of extremely low birth weight infants has improved significantly over the past decade mostly through increasing availability of surfactant, provision of nasal continuous positive airway pressure (NCPAP) and mechanical ventilation and other ICU facilities where resources permit. In two studies carried out in New Zealand in 1986 and 1998-1999 respectively, rates of survival were compared and it was shown to have improved from 65% in 1986 to 81% in 1998-99 (P<0.001). It should also be noted that in the same study, use of CPAP had increased from being used in only 5% of VLBW infants in 1986 to 38% use in 1998-99.[8]

In South Africa, most previous studies generally include very low birth weight category babies. However, even with paucity of available data on survival rates of ELBW infants, an improved trend of survival has been noted. A study done at Madadeni hospital, a district hospital in northern Kwa Zulu Natal, compared survival rate in VLBW infants for the years 1993-2001 and 2002-2005 with improved survival of non-ventilated infants from 21% to 41%.[9] It should be noted that NCPAP and surfactant were not readily available at the mentioned hospital. Another recent study carried out at Tygerberg children's hospital in the Western Cape showed that intubation, surfactant and extubation (InSurE) to NCPAP of ELBW infants with RDS significantly improved survival with a 62.9 % survival at discharge.[10] This included infants who failed to cope on NCPAP and were given back up mechanical ventilation in ICU. These results were similar to the SUPPORT group study involving multiple academic centres in the USA that looked at mortality and morbidity of very low birth weight infants which showed an overall survival of 72%.[11]

However, survival of ELBW infants generally remains low in South African public hospital. In a study carried out at Chris Hani Baragwanath Hospital for the years 2000 to 2002, the survival rate of extremely low birth weight infants was shown to be 34% as compared to 84% for infants weighing more than 1000g.[12]

Charlotte Maxeke Johannesburg academic Hospital (CMJAH) is a public hospital in the heart of Johannesburg, South Africa, with a busy neonatal unit. In a previous study carried out in the same unit, survival of infants weighing less than 1001 grams at birth was found to be 34.9% at a time when nasal Continuous positive airway pressure was not yet fully introduced in the unit. [13] Given the scarcity of resources and limited ICU facilities, the unit only offers mechanical ventilation to infants born with a weight > 900g.

Our interest in carrying out this study was to establish the survival rate of infants whose birth weight was ≤ 900g and were not mechanically ventilated in ICU according to the unit's ICU admission protocol.

2. METHODS

This was a retrospective study of all neonates with a birth weight of ≤ 900g admitted to the neonatal unit at CMJAH between January 2006 and December 2010. These infants were not offered mechanical ventilation as per the unit's neonatal ICU admission criteria. Infants' records were reviewed only for the period of hospitalisation until discharge. All inborn neonates were admitted directly to a transitional nursery in labour ward, so statistics included babies who died shortly after birth. Neonates delivered at primary level hospitals or clinics in the close vicinity and those who were born before arrival (BBA) were also admitted to the transitional unit and are thus a part of our statistics. Nasal Continuous Positive Airways Pressure (NCPAP) was introduced into the unit in 2006. Babies with a birth weight ≥ 750g were offered NCPAP with surfactant at the discretion of attending staff. There was no back up mechanical ventilation available for these infants.

A computer database is kept for purposes of clinical audit and information for patient follow up clinic. The following relevant data were retrieved from the database; maternal data: age, parity, gravidity, antenatal care (ANC), antenatal steroids, place and mode of delivery and HIV status. Infant data included the major outcome which was death or survival, gestational age, birth weight, gender, place of birth, hypothermia, resuscitation at birth, sepsis, necrotising enterocolitis (NEC), intraventricular haemorrhage (IVH), jaundice, NCPAP with or without surfactant and 5 minute APGAR scores. The causes of death were reviewed and classified according to the perinatal problem identification programme (PPIP) classification. (http://www.ppip.co.za) The PPIP was established in 1999 in South Africa as a national tool for perinatal death audit.

Data was entered in MS-Excel spread sheet and then imported to the statistical software SPSS version 19 (http://www.spss.com) for data analysis. Categorical data were described using frequencies and percentages, continuous data as means and standard deviations. A univariate statistical analysis was done on maternal and neonatal variables considering survival at discharge as the outcome. Categorical data were compared using Chi square analysis and continuous data were compared using unpaired t tests (as the distribution was normal). A p value of 0.05 was considered to be significant. Factors with a p value of 0.1 or less were included in the multiple logistic regression analysis.

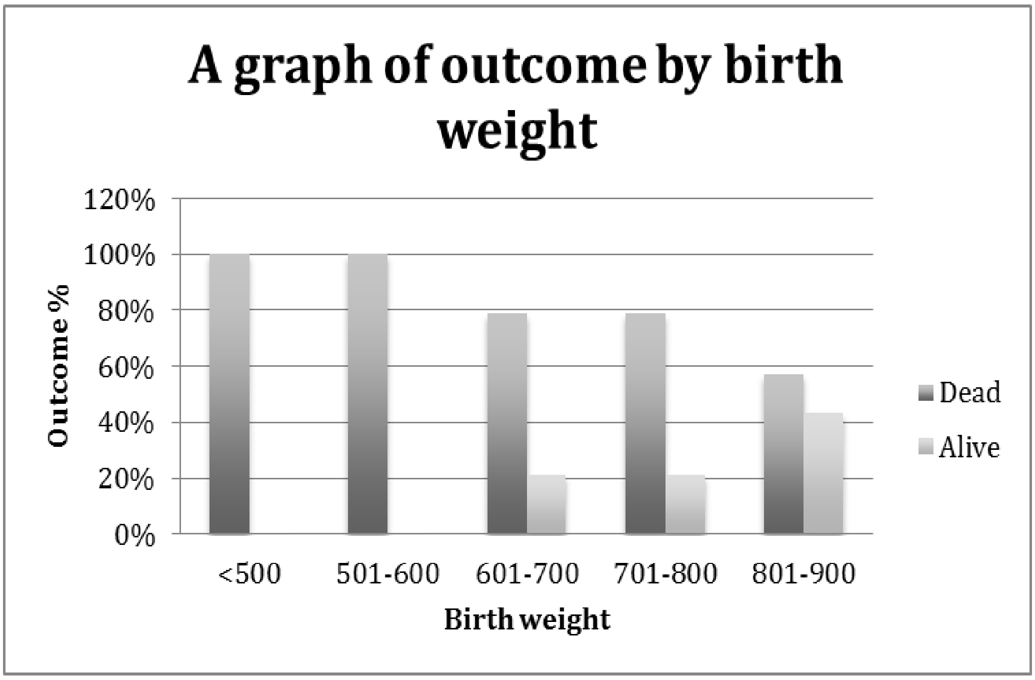
Ethics: This study was approved by the Committee for research on human subjects of the University of the Witwatersrand. (Ethics approval number M120673)

3. RESULTS

There was a total of 410 babies. Twenty nine had incomplete data and therefore were excluded from analysis. Three of these had no final outcome recorded. Of the 26 whose final outcome was recorded, gestational age, mode of delivery, HIV status, NCPAP and surfactant were some of the factors that were not available in our records. All the 29 that were excluded had birth weights greater than 600g. There were 8 survivors among this group (30.6%). We therefore had 382 babies with complete records included in our study. Female infants accounted for a slight majority at 53.5% of the total infants. Of the female babies, 64 (30.6%) survived whereas among the males, 42 (23.7%) survived. (X^2 4.38, P = 0.357). The infants' mean gestational age was 26.7 weeks (SD 2.37) and mean birth weight was 774 grams (SD 94). The mean gestational age of non survivors was 26.36 weeks (SD 2.331) as compared to survivors 27.6 weeks (SD 2.23) (P<0.001). The mean birth weight of survivors was 814 grams (SD 74) as compared to non survivors 759.8 grams (SD 97) (P< 0.001). The vast majority of infants were inborn (79.27%) with the rest of the babies either referred from the sorrounding clinics or born before arrival (BBA). There was no statistically significant difference on survival between the inborn and outborn infants. (X^2 6.95, P = 0.325)

The overall survival was 26.5% with no survivors in neonates less than 600 g birth weight (see figure 1 below). The highest survival rate was observed in babies with the highest birth weights.

Figure 1: Survival according to birth weight



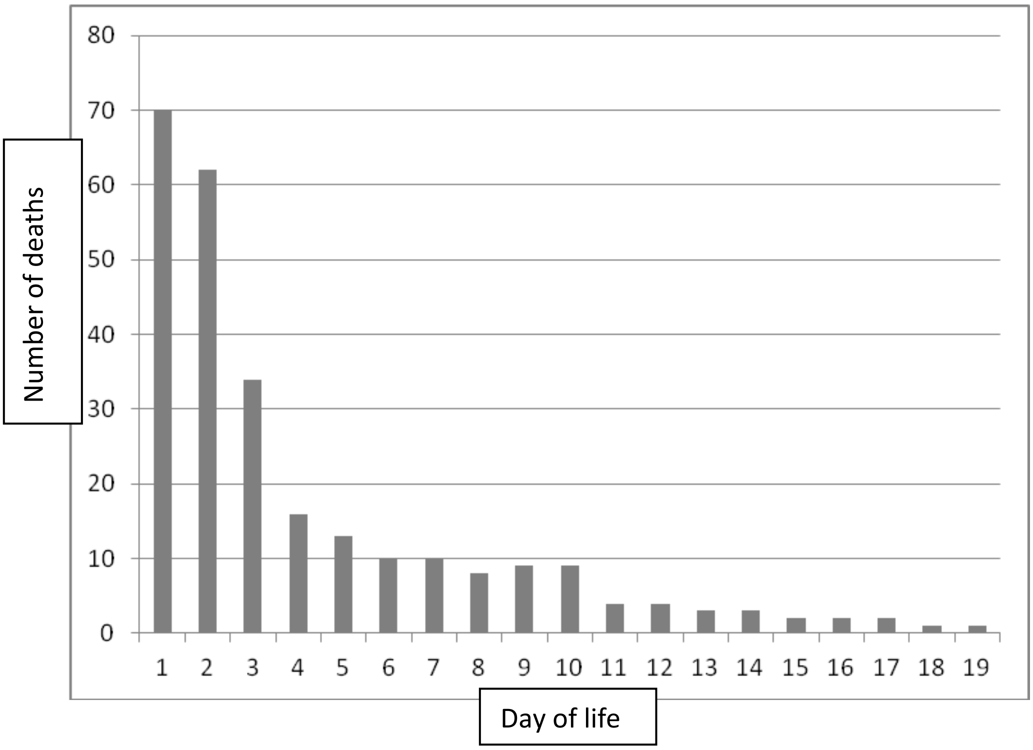
The different causes of death according to the PPIP classification are shown in Table 1. The most frequent cause of death was extreme multi-organ immaturity (63.9%) followed by respiratory distress syndrome (25.9%).

Table 1; Causes of death according to the PPIP Classification

Cause of death	Frequency	Percentage
Extreme multi-organ immaturity	179	63.90
Respiratory distress syndrome	71	25.90
Sepsis	12	4.29
NEC	5	1.79
Asphyxia	4	1.43
IVH	2	0.69
Others	7	2.00
Total	280	100

Most infants died within the first few days of life: 60% within 72 hours and 79% by the end of the first week. The median age at death was 3 days (range 0 – 69 days; (see figure 2 below)

Figure 2; The number of deaths according to day of life



Univariate analysis was done on the various patient characteristics by comparing survivors and non – survivors using cross tabulation with Chi Square analysis. The results are shown in Table 2. The most significant predictors of survival on univariate analysis were antenatal care, HIV exposure, mode of delivery, hypothermia at birth, weight for gestational age, mode of feeding and the presence of neonatal jaundice. These factors together with gestational age and birth weight were considered in the binary logistic regression model with survival as the outcome. The final results of the logistic regression are shown in Table 3 – birth weight, gestational age and neonatal jaundice were the most significant determinants of outcome.

Table 2: Univariate analysis considering survival as outcome

Factor	X^2	P value
Antenatal Care	15.83	0.003
Antenatal Steroids	5.489	0.061
5 minute Apgar	31.02	0.055
Resuscitation	10.05	0.04
Place of birth	4.645	0.59
Multiple gestation	2.88	0.41
Hypothermia at birth	14.101	0.007
Mode of delivery	17.14	0.002
HIV exposure	16.34	0.003
Gender	4.38	0.357
Weight for gestational age	8.61	0.013
NEC (Stage 2/3)	2.68	0.104
IVH	12.92	0.115
Sepsis	9.068	0.059
Type of food	90.538	<0.001
Neonatal Jaundice	33.62	<0.001
Nasal CPAP	0.602	0.74

Nasal continuous positive airway pressure (NCPAP)

For the 5 years study period, a total of 59 infants with birth weights between 750g and 900g were given NCPAP. Twenty nine of these infants were also given surfactant. The use of NCPAP in this group of patients significantly increased from less than 10% in 2007 to 37.5% in 2010. Of the 59 infants who were put onto NCPAP, 16 (27.1%) survived till discharge. Overall, NCPAP had no influence on survival. (X^2 0.602, P = 0.74) However, NCPAP was only used in the latter part of our study years and only in neonates with birth weights ≥ 750g. Considering only babies >700g in 2008- 2010, then babies > 800g who got NCPAP were significantly less likely to survive. (19% in the NCPAP group versus 27% in the non- NCPAP group; X^2 9.247, P = 0.002)

Table 3; Logistic regression analysis of variables associated with survival

Variable	B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I. for EXP(B)	
							Lower	Upper
BW	-.006	.002	14.749	1	.000	.994	.991	.997
Jaundice	1.302	.269	23.428	1	.000	3.677	2.170	6.231
GA	-.190	.054	12.280	1	.000	.827	.743	.919

4. DISCUSSION

This was the first study in our unit looking strictly at the ELBW infants, more precisely, those with birth weights less or equal 900g who never received conventional mechanical ventilation. Similar studies previously done in the same unit included the very low birth weight category. Generally, all studies in the literature looking at the ELBW babies considered weights of 500- 1000g. Our mean gestational age was 26.7 weeks with 774g as the mean birth weight. This mean birth weight was lower than that of the InSurE study (856.2g) done at Tygerberg Children's Hospital in the western cape as expected since their weight category included 900-1000g.[10]Our overall survival of 26.5% is lower than that reported in the above mentioned study which was 62.9%. However, our statistics included babies who died in labour ward shortly after birth as well as the out-born babies and these were both excluded in the InSurE study. The survival was also lower than the previous data from our unit which showed survival in the ELBW category to be 34.9%, very similar to the CHBAH study findings of 34%.[12,13] However, it should be noted that our study only considered babies up to 900g birth weight, excluding the 901 – 1000g weight babies who were included in both the above mentioned studies. This makes a significant difference because previous data from our unit demonstrated exponentially improved survival in babies above 900g, given also that they are allowed admission to ICU.

In the current study, birth weight and gestational age were the most significant predictors of survival ($P < 0.001$). This is well documented in the literature in studies done across both developed and developing countries.[10, 12, 13] This was also the same finding both in the previous study from our unit on determinants of survival in the very low birth weight group as well as in the study done at CHBAH.[12, 13] Similar findings were reported from a large cohort study that included multiple participating academic centres in the USA.[14]

On univariate analysis, birth weight with relation to gestational age was also a significant determinant of survival ($P=0.013$). Similar findings were reported in a study done in Norway that compared survival of SGA babies, defined as having a birth weight below the fifth percentile for post menstrual age, to the AGA group which showed that the former group had higher mortality and morbidity compared to the latter.[15]

Surprisingly, NCPAP did not seem to improve survival. Neonates weighing greater or equal to 750g were the ones that qualified to be put on to NCPAP according to the unit guidelines. None of the infants in our study group was given back up ventilation in ICU. However, due to the limited number of NCPAP machines, the sickest babies were the ones given NCPAP and this probably explains the increased mortality in this group.

Although antenatal steroids have been shown to improve survival mostly by reducing the severity of RDS, our results only approached statistical significance. ($P = 0.06$)

On univariate analysis, sepsis was paradoxically associated with a higher chance of survival. This finding was in contrast to a large study carried out in India looking at survival and morbidity of ELBW infants over a 6 year period where sepsis was a major contributor to mortality constituting 41% among the babies who died.[(16)] This association between sepsis and survival could be explained by the fact that most babies in our study died within the first few days of life. Those who survived longer had a higher chance of getting nosocomial sepsis.

There was a strong association between jaundice and survival ($P < 0.001$). This would be explained by the fact that up to 80% of preterm babies may have physiological jaundice peaking towards the end of the 1st week of life. Since most of our babies died in the first week of life, survivors were the babies who became jaundiced. There was association between hypothermia and death ($P = 0.007$). This association has been well demonstrated before.[17, 18]

HIV exposure in our study was a significant factor in increasing the risk of death ($P = 0.003$). However, it is also worrying that 45.9% of the mothers did not know their HIV status.

Babies born by NVD had a significantly less chance of survival compared to babies born by C/S. These findings were similar to data from a study in the USA which showed that ELBW babies born by C/S had a significantly higher chance of survival.[19]According to this study, the small babies born vaginally had more than twice the risk for developing severe IVH and poor short term outcome compared to those born by C/S.

After multiple logistic regression analysis, birth weight and gestational age were the most powerful predictors of survival. This was similar to findings in studies already mentioned above as well as the previous data from our unit.[10, 12, 13]

5. CONCLUSION

Our study shows that survival of ELBW infants in resource limited public hospital setting in South Africa is very low. Birth weight and gestational age were the strongest predictors of survival. Although our results did not show a positive impact from NCPAP and surfactant, it has been demonstrated in several studies that provision of NCPAP with surfactant to this category of infants improves outcome. Effective steps to avoid extreme prematurity and encourage ANC attendance need to be put in place. Preventing important causes of morbidity and mortality like HIV, asphyxia and hypothermia would also improve survival.

6. REFERENCES

1. Lawn JE, Cousens S, Zupan J. 4 million neonatal deaths: when? Where? Why? Lancet. 2005 Mar 5-11;365(9462):891-900.
2. United Nations. Reduce child mortality. The millenium development goals report New York. 2008.
3. Lawn JE, Kerber K, Enweronu-Laryea C, Massee Bateman O. Newborn survival in low resource settings--are we delivering? BJOG. 2009 Oct;116 Suppl 1:49-59.
4. nations u. The state of the world's children. 2009.
5. Yasmin S OD, Paul E, Costello A. Neonatal mortality of low birth weight infants in Bangladesh. J Health Popul Nutr. 2010.
6. Alexander GR, Kogan M, Bader D, Carlo W, Allen M, Mor J. US birth weight/gestational age-specific neonatal mortality: 1995-1997 rates for whites, hispanics, and blacks. Pediatrics. 2003 Jan;111(1):e61-6.
7. Pattison RC. Saving babies 2006-2007: Sixth perinatal care survey of South Africa Tshepesa Press. 2009.
8. Darlow BA, Cust AE, Donoghue DA. Improved outcomes for very low birthweight infants: evidence from New Zealand national population based data. Arch Dis Child Fetal Neonatal Ed. 2003 Jan;88(1):F23-8.
9. Bondi FA, M. Improved survival of non-ventilated very low birth weight infants at Madadeni Hospital, Kwa-Zulu Natal. sajch. 2007.
10. Kirsten GF, Kirsten CL, Henning PA, Smith J, Holgate SL, Bekker A, et al. The outcome of ELBW infants treated with NCPAP and InSurE in a resource-limited institution. Pediatrics. 2012 Apr;129(4):e952-9.
11. Finer NN, Carlo WA, Walsh MC, Rich W, Gantz MG, Laptook AR, et al. Early CPAP versus surfactant in extremely preterm infants. N Engl J Med. 2010 May 27;362(21):1970-9.
12. Velaphi SC, Mokhachane M, Mphahlele RM, Beckh-Arnold E, Kuwanda ML, Cooper PA. Survival of very-low-birth-weight infants according to birth weight and gestational age in a public hospital. S Afr Med J. 2005 Jul;95(7):504-9.
13. Ballot DE, Chirwa TF, Cooper PA. Determinants of survival in very low birth weight neonates in a public sector hospital in Johannesburg. BMC Pediatr. 2010;10:30.
14. Fanaroff AA, Stoll BJ, Wright LL, Carlo WA, Ehrenkranz RA, Stark AR, et al. Trends in neonatal morbidity and mortality for very low birthweight infants. Am J Obstet Gynecol. 2007 Feb;196(2):147 e1-8.
15. Westby Wold SH, Sommerfelt K, Reigstad H, Ronnestad A, Medbo S, Farstad T, et al. Neonatal mortality and morbidity in extremely preterm small for gestational age infants: a population based study. Arch Dis Child Fetal Neonatal Ed. 2009 Sep;94(5):F363-7.
16. Narayan S, Aggarwal R, Upadhyay A, Deorari AK, Singh M, Paul VK. Survival and morbidity in extremely low birth weight (ELBW) infants. Indian Pediatr. 2003 Feb;40(2):130-5.
17. Miller SS, Lee HC, Gould JB. Hypothermia in very low birth weight infants: distribution, risk factors and outcomes. J Perinatol. 2011 Apr;31 Suppl 1:S49-56.

18. Ogunlesi TA, Ogunfowora OB, Adekanmbi FA, Fetuga BM, Olanrewaju DM. Point-of-admission hypothermia among high-risk Nigerian newborns. BMC Pediatr. 2008;8:40.
19. Deulofeut R, Sola A, Lee B, Buchter S, Rahman M, Rogido M. The impact of vaginal delivery in premature infants weighing less than 1,251 grams. Obstet Gynecol. 2005 Mar;105(3):525-31

7. APPENDIX 1.

SURVIVAL OF EXTREMELY LOW BIRTH WEIGHT INFANTS

Edgar Kalimba[1] MBBCH and Daynia Ballot[1] MBBCH; FCPaed (SA); PhD

[1]Department of Paediatrics and child health, University of the Witwatersrand / Charlotte Maxeke Johannesburg Academic Hospital.

Corresponding author: Edgar Kalimba

Department of Paediatrics and child health, University of the Witwatersrand / Charlotte Maxeke Johannesburg Academic Hospital, 7 York road, Parktown 2193, Johannesburg, South Africa.

Email address: eddiekalimba@yahoo.co.uk

ABSTRACT

Objectives: Survival of extremely low birth weight (ELBW) infants in a resource limited public hospital setting is still low in South Africa. The study aimed at establishing the determinants of survival in this weight category of neonates who, due to limited intensive care facilities, were not mechanically ventilated.

Design: A retrospective study where patient data was retrieved from the departmental computer database.

Setting: Neonatal unit at Charlotte Maxeke Johannesburg academic hospital (CMJAH).

Subjects: Neonates admitted at birth between January 2006 and December 2010 with birth weights of ≤ 900g.

Outcome measures: Survival at discharge was the major outcome. Maternal variables were: age, parity, gravidity, antenatal care, antenatal steroids, place and mode of delivery and HIV status. Neonatal variables: gestational age (GA), birth weight (BW), gender, place of birth, hypothermia, resuscitation at birth, sepsis, necrotising enterocolitis, intraventricular hemorrhage, jaundice, nasal continuous positive airway pressure (NCPAP) with or without surfactant and APGAR scores.

Results: A total of 382 neonates were included in our study. Overall survival was 26.5%. The main causes of death, as per the PPIP classification, were extreme multi-organ immaturity and respiratory distress syndrome. The main determinants of survival were BW, OR= 0.994; (95% CI 0.991-0.997) and GA, OR= 0.827; (95% CI 0.743-0.919). Overall, NCPAP use was 15.5% and was not associated with better survival.

Conclusion: Survival of ELBW infants is low. Birth weight and gestational age were the strongest predictors of survival. Effective steps are required to avoid extreme prematurity, encourage antenatal care, and avail antenatal steroids in anticipated preterm birth.

BACKGROUND

According to the United Nations, Millennium development goal four is to reduce child mortality by reducing the under-five mortality by two thirds between 1990 and 2015. More than 8 million under five years old children die every year and neonatal mortality and especially very low birth weight (VLBW) infant mortality are among the 6 conditions for which over 90% of these deaths are attributed.(1)

Survival of extremely low birth weight (ELBW) infants has markedly improved over the past decade largely due to improved care, availability of antenatal steroids, provision of surfactant and establishment of equipped intensive care units (ICU) where resources permit.(2-4) However, survival of these infants in a resource limited setting like South African public hospitals is still low.(5)

Mortality as a result of prematurity is the major contributor to the neonatal mortality rate both in developing and developed countries.(6) According to the World Health Organisation, nearly four million neonatal deaths occur worldwide every year. Most of these deaths take place in developing countries.(7)

In South Africa, perinatal mortality and low birth weight rates have, in the past, generally been reported only for those infants weighing ≥ 1000g at birth because smaller infants are often regarded as miscarriages and not recorded. However, with improving maternal and neonatal care, more infants weighing 500g to 1000g are expected to survive.

In a study carried out at Chris Hani Baragwanath academic hospital (CHBAH), a busy public hospital in Soweto Johannesburg, survival of ELBW infants was found to be 34%.(5) A similar study previously done at CMJAH found survival of ELBW infants to be 34.9%.(8) More recently, a study done in the Western Cape at the Tygerberg Children's Hospital reported survival of ELBW infants that received surfactant and nasal continuous positive airway pressure (NCPAP) to be 62.9%.(4) The infants in this study had back up mechanical ventilation provided for failed NCPAP.

Our study was done in the neonatal unit at CMJAH, a busy public hospital in Johannesburg, South Africa. Due to limited neonatal ICU facilities, mechanical ventilation is only provided for infants with a birth weight > 900g. ELBW infants who have no access to ICU are therefore managed in a busy high care ward. The aims of this study were to review the survival of these infants and to evaluate their determinants of survival.

METHODS

This was a retrospective study of all neonates with a birth weight of ≤ 900g admitted to the neonatal unit at CMJAH between January 2006 and December 2010. These infants were not offered mechanical ventilation as per the unit's neonatal ICU admission criteria. Infants' records were reviewed only for the period of hospitalisation until discharge. All inborn neonates were admitted directly to a transitional nursery in labour ward, so statistics included babies who died shortly after birth. Neonates delivered at primary level hospitals or clinics in the close vicinity and those who were born before arrival (BBA) were also admitted to the transitional unit and are thus a part of our statistics. Nasal Continuous Positive Airways Pressure (NCPAP) was introduced into the unit in 2006. Babies with a birth weight ≥ 750g were offered NCPAP with surfactant at the discretion of attending staff. There was no back up mechanical ventilation available for these infants.

A computer database is kept for purposes of clinical audit and information for patient follow up clinic. The following relevant data were retrieved from the database; maternal data: age, parity, gravidity, antenatal care (ANC), antenatal steroids, place and mode of delivery and HIV status. Infant data included the major outcome which was death or survival, gestational age, birth weight, gender, place of birth, hypothermia, resuscitation at birth, sepsis, necrotising enterocolitis (NEC), intraventricular haemorrhage (IVH), jaundice, NCPAP ± surfactant and 5 minute APGAR scores. The causes of death were reviewed and classified according to the perinatal problem identification programme (PPIP) classification. (http://www.ppip.co.za) The PPIP was established in 1999 in South Africa as a national tool for perinatal death audit.

Data was entered in MS-Excel spread sheet and then imported to the statistical software SPSS version 19 (http://www.spss.com) for data analysis. Categorical data were described using frequencies and percentages, continuous data as means and standard deviations. A univariate statistical analysis was done on maternal and neonatal variables considering survival at discharge as the outcome. Categorical data were compared using Chi square analysis and continuous data were compared using unpaired t tests (as the distribution was normal). A p value of 0.05 was considered to be significant. Factors with a p value of 0.1 or less were included in the multiple logistic regression analysis.

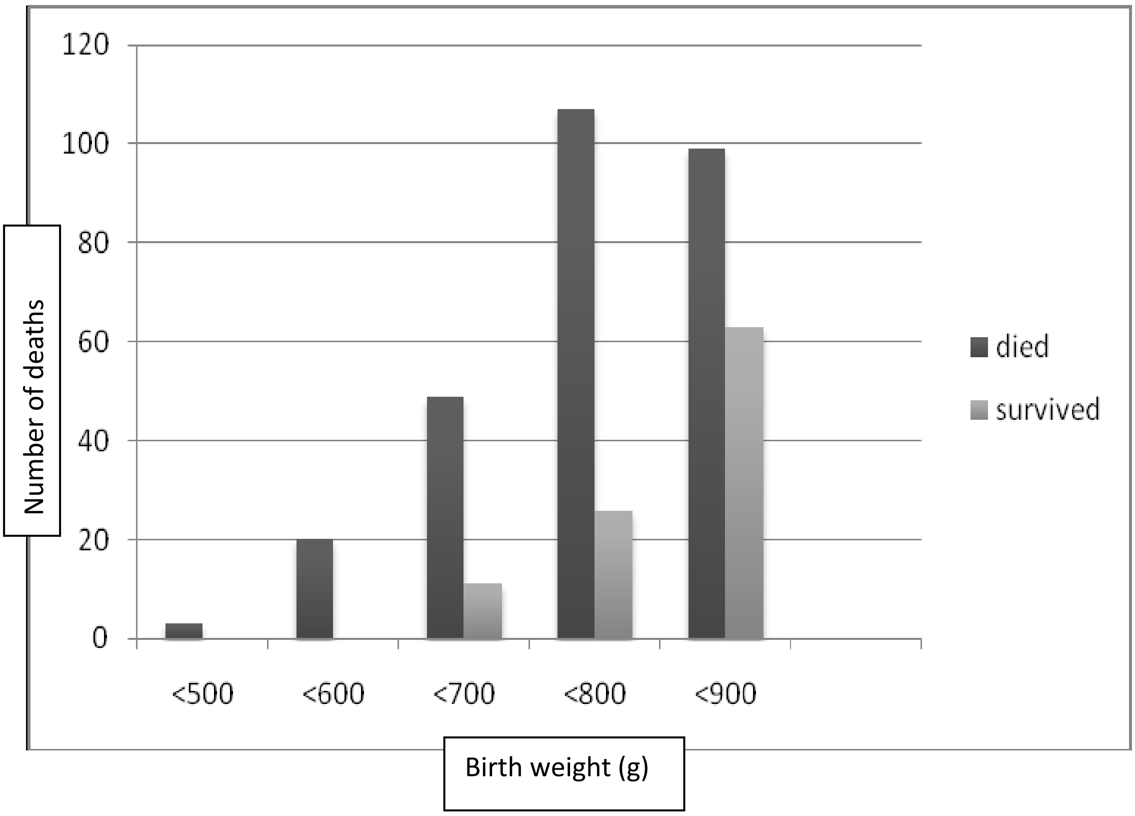
Ethics: This study was approved by the Committee for research on human subjects of the University of the Witwatersrand.

RESULTS:

There were a total of 410 babies. Twenty nine had incomplete data. Three of these had no final outcome recorded. Of the 26 whose final outcome was recorded, gestational age, mode of delivery, HIV status, NCPAP and surfactant were some of the factors that were not available in our records. All the 29 that were excluded had birth weights > 600g. There were 8 survivors among this group. (30.6%) We therefore had 382 babies with complete records included in our study. Female infants accounted for a slight majority at 53.5% of the total infants. Of the female babies 30.6% survived, whereas among the males 23.7% survived. (X^2 4.38, P = 0.357). The infants' mean gestational age was 26.7 weeks (SD 2.37) and mean birth weight was 774 grams (SD 94 grams). The mean gestational age of non survivors was 26.36 weeks (SD 2.331) as compared to survivors 27.6 weeks (SD 2.23). (P<0.001). The mean birth weight of survivors was 814 grams (SD 74) as compared to non survivors 759.8 grams (SD 97) (P< 0.001) The vast majority of infants were inborn (79.27%) with the rest of the babies either referred from the sorrounding clinics or born before arrival (BBA).

The overall survival was 26.5% with no survivors in neonates less than 600 g birth weight. (See figure 1 below) The highest survival rate was observed in babies with the highest birth weights.

Figure 1: Survival according to birth weight



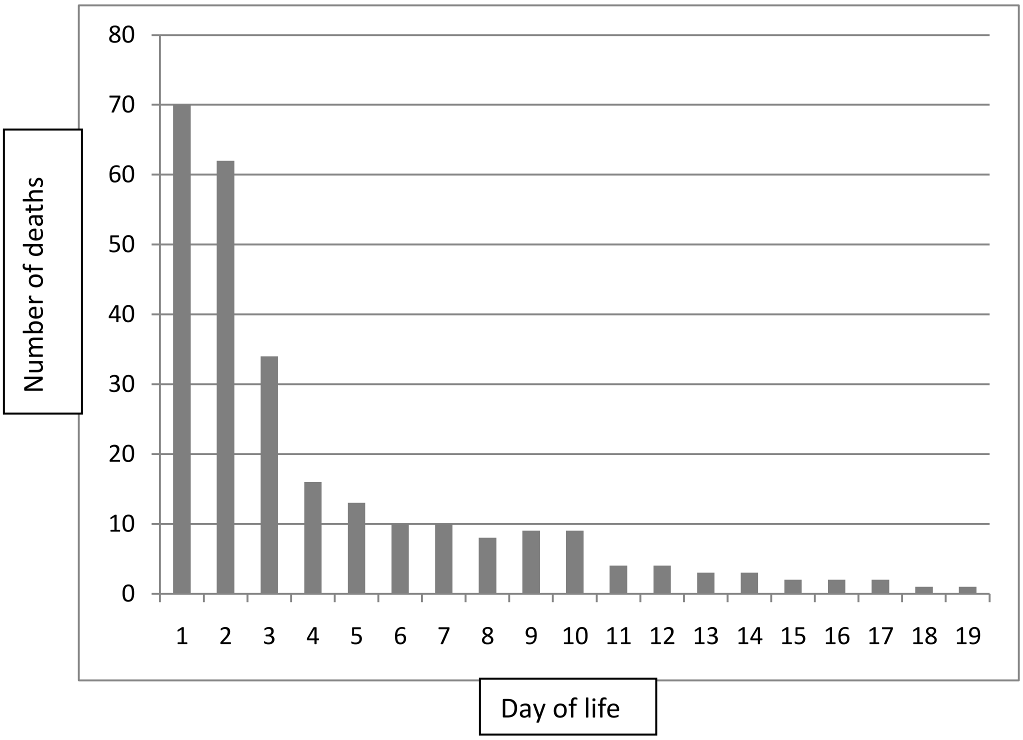
The different causes of death according to the PPIP classification are shown in Table 1 below. The most frequent cause of death was extreme multi-organ immaturity(63.9%) followed by respiratory distress syndrome (25.9%).

Table 1; Causes of death according to the PPIP Classification

Cause of death	Frequency	Percentage
Extreme multi-organ immaturity	179	63.9
Respiratory distress syndrome	71	25.9
Sepsis	12	4.29
Necrotising enterocolitis	5	1.79
Asphyxia	4	1.43
Intraventricular hemorrhage	2	0.71
Others	7	2.52
Total	280	100

Most infants died within the first few days of life: 60% within 72 hours and 79% by the end of the first week. The median age at death was 3 days (range 0 – 69 days; See figure 2 below)

Figure 2; The number of deaths according to day of life



Univariate analysis was done on the various patient characteristics by comparing survivors and non – survivors using cross tabulation with Chi Square analysis. The results are shown in Table 2. The most significant predictors of survival on univariate analysis were antenatal care, HIV exposure, mode of delivery, hypothermia at birth, weight for gestational age, mode of feeding and the presence of neonatal jaundice. These factors together with gestational age and birth weight were considered in the binary logistic regression model with survival as the outcome. The final results of the logistic regression are shown in Table 3 – birth weight, gestational age and neonatal jaundice were the most significant determinants of outcome.

Table 2: Univariate analysis considering survival as outcome

Factor	X^2	P value
Antenatal Care	15.83	0.003
Antenatal Steroids	5.489	0.061
5 minute Apgar	31.02	0.055
Resuscitation	10.05	0.04
Place of birth	4.645	0.59
Multiple gestation	2.88	0.41
Hypothermia at birth	14.101	0.007
Mode of delivery	17.14	0.002
HIV exposure	16.34	0.003
Gender	4.38	0.357
Weight for gestational age	8.61	0.013
NEC (Stage 2/3)	2.68	0.104
IVH	12.92	0.115
Sepsis	9.068	0.059
Type of food	90.538	<0.001
Neonatal Jaundice	33.62	<0.001
Nasal CPAP	0.602	0.74

Nasal continuous positive airway pressure (NCPAP)

For the 5 years study period, a total of 59 infants with birth weights between 750g and 900g were given NCPAP. Twenty nine of these infants were also given surfactant. The use of NCPAP in this group of patients significantly increased from less than 10% in 2007 to 37.5% in 2010. Of the 59 infants who were put onto NCPAP, 16 (27.1%) survived till discharge. Overall, NCPAP had no influence on

survival. (X^2 0.602, P = 0.74) However, NCPAP was only used in the latter part of our study years and only in neonates with birth weights ≥ 750g. Considering only babies >700g in 2008- 2010, then babies > 800g who got NCPAP were significantly less likely to survive. (19% in the NCPAP group versus 27% in the non- NCPAP group; $X^2$9.247, P = 0.002)

Table 3; Logistic regression analysis of variables associated with survival

Variable	B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I. for EXP(B)	
							Lower	Upper
BW	-.006	.002	14.749	1	.000	.994	.991	.997
Jaundice	1.302	.269	23.428	1	.000	3.677	2.170	6.231
GA	-.190	.054	12.280	1	.000	.827	.743	.919

DISCUSSION:

This was the first study in our unit looking strictly at the ELBW infants, more precisely, those with birth weights ≤ 900g who never received conventional mechanical ventilation. Similar studies previously done in the same unit included the very low birth weight category. Generally, all studies in the literature looking at the ELBW babies considered weights of 500- 1000g. Our mean gestational age was 26.7 weeks with 774g as the mean birth weight. This mean birth weight was lower than that of the InSurE study (856.2g) done at Tygerberg Children's Hospital in the western cape as expected since their weight category included 900-1000g.[(4)]Our overall survival of 26.5% is lower than that reported in the above mentioned study which was 62.9%. However, our statistics included babies who died in labour ward shortly after birth as well as the out-born babies and these were both excluded in the InSurE study. The survival was also lower than the previous data from our unit which showed survival in the ELBW category to be 34.9%, very similar to the CHBAH study findings of 34%.[5, 8]However, it should be noted that our study only considered babies up to 900g birth weight, excluding the 901 – 1000g weight babies who were included in both the above mentioned studies. This makes a significant difference because previous data from our unit demonstrated exponentially improved survival in babies above 900g, given also that they are allowed admission to ICU.

In the current study, birth weight and gestational age were the most significant predictors of survival. ($P < 0.001$) This is well documented in the literature in studies done across both developed and developing countries.[4, 5, 8] This was also the same finding both in the previous study from our unit on determinants of survival in the very low birth weight group as well as in the study done at CHBAH.[5, 8] Similar findings were reported from a large cohort study that included multiple participating academic centres in the USA.[9]

On univariate analysis, birth weight with relation to gestational age was also a significant determinant of survival. ($P=0.013$) Similar findings were reported in a study done in Norway that compared survival of SGA babies, defined as having a birth weight below the fifth percentile for post menstrual age, to the AGA group which showed that the former group had higher mortality and morbidity compared to the latter.[10]

Surprisingly, NCPAP did not seem to improve survival. Neonates weighing ≥ 750g were the ones that qualified to be put on to NCPAP according to the unit guidelines. None of the infants in our study group was given back up ventilation in ICU. However, due to the limited number of NCPAP machines, the sickest babies were the ones given NCPAP and this probably explains the increased mortality in this group.

Although antenatal steroids have been shown to improve survival mostly by reducing the severity of RDS, our results only approached statistical significance. ($P = 0.06$) There was association with improved outcome in the InSurE study where 76% of the mothers had received steroids with improved survival of babies at day 3 and day 7 of life.[4]

On univariate analysis, sepsis was paradoxically associated with a higher chance of survival. This finding was in contrast to a large study carried out in India looking at survival and morbidity of ELBW infants over a 6 year period where sepsis was a major contributor to mortality constituting 41% among the babies who died.[11] This association between sepsis and survival could be explained by the fact that most babies in our study died within the first few days of life. Those who survived longer had a higher chance of getting nosocomial sepsis.

There was a strong association between jaundice and survival. ($P < 0.001$) This would be explained by the fact that up to 80% of preterm babies may have physiological jaundice peaking towards the end of the 1st week of life. Since most of our babies died in the first week of life, survivors were the babies who became jaundiced. There was association between hypothermia and death. ($P = 0.007$) This association has been well demonstrated before.[12, 13]

HIV exposure in our study was a significant factor in increasing the risk of death. ($P = 0.003$) However, it is also worrying that 45.9% of the mothers did not know their HIV status.

Babies born by NVD had a significantly less chance of survival compared to babies born by C/S. These findings were similar to data from a study in the USA which showed that ELBW babies born by C/S had a significantly higher chance of survival.[14]According to this study, the small babies born vaginally had more than twice the risk for developing severe intraventricular haemorrhage and poor short term outcome compared to those born by C/S.

After multiple logistic regression analysis, birth weight and gestational age were the most powerful predictors of survival. This was similar to findings in studies already mentioned above as well as the previous data from our unit.[4, 5, 8]

CONCLUSION

Our study shows that survival of ELBW infants in resource limited public hospital setting in South Africa is very low. Birth weight and gestational age were the strongest predictors of survival. Although our results did not show a positive impact from NCPAP and surfactant, it has been demonstrated in several studies that provision of NCPAP with surfactant to this category of infants improves outcome. Effective steps to avoid extreme prematurity and encourage ANC attendance need to be put in place. Preventing important causes of morbidity and mortality like HIV, asphyxia and hypothermia would also improve survival.

REFERENCES

1. UNITED NATIONS . Reduce child mortality. The millenium development goals report New York. 2008.
2. Wilson-Costello D. Is there evidence that long-term outcomes have improved with intensive care? Semin Fetal Neonatal Med. 2007 Oct;12(5):344-54.
3. Lorenz JM. Survival of the extremely preterm infant in North America in the 1990s. Clin Perinatol. 2000 Jun;27(2):255-62.
4. Kirsten GF, Kirsten CL, Henning PA, Smith J, Holgate SL, Bekker A, et al. The outcome of ELBW infants treated with NCPAP and InSurE in a resource-limited institution. Pediatrics. 2012 Apr;129(4):e952-9.
5. Velaphi SC, Mokhachane M, Mphahlele RM, Beckh-Arnold E, Kuwanda ML, Cooper PA. Survival of very-low-birth-weight infants according to birth weight and gestational age in a public hospital. S Afr Med J. 2005 Jul;95(7):504-9.
6. Pattison RC. Saving babies 2006-2007: Sixth perinatal care survey of South Africa Tshepesa Press. 2009.
7. Lawn JE, Cousens S, Zupan J. 4 million neonatal deaths: when? Where? Why? Lancet. 2005 Mar 5-11;365(9462):891-900.
8. Ballot DE, Chirwa TF, Cooper PA. Determinants of survival in very low birth weight neonates in a public sector hospital in Johannesburg. BMC Pediatr. 2010;10:30.
9. Fanaroff AA, Stoll BJ, Wright LL, Carlo WA, Ehrenkranz RA, Stark AR, et al. Trends in neonatal morbidity and mortality for very low birthweight infants. Am J Obstet Gynecol. 2007 Feb;196(2):147 e1-8.
10. Westby Wold SH, Sommerfelt K, Reigstad H, Ronnestad A, Medbo S, Farstad T, et al. Neonatal mortality and morbidity in extremely preterm small for gestational age infants: a population based study. Arch Dis Child Fetal Neonatal Ed. 2009 Sep;94(5):F363-7.
11. Narayan S, Aggarwal R, Upadhyay A, Deorari AK, Singh M, Paul VK. Survival and morbidity in extremely low birth weight (ELBW) infants. Indian Pediatr. 2003 Feb;40(2):130-5.
12. Miller SS, Lee HC, Gould JB. Hypothermia in very low birth weight infants: distribution, risk factors and outcomes. J Perinatol. 2011 Apr;31 Suppl 1:S49-56.
13. Ogunlesi TA, Ogunfowora OB, Adekanmbi FA, Fetuga BM, Olanrewaju DM. Point-of-admission hypothermia among high-risk Nigerian newborns. BMC Pediatr. 2008;8:40.
14. Deulofeut R, Sola A, Lee B, Buchter S, Rahman M, Rogido M. The impact of vaginal delivery in premature infants weighing less than 1,251 grams. Obstet Gynecol. 2005 Mar;105(3):525-31.

APPENDIX 2. DISSERTATION PROPOSAL

SURVIVAL OF EXTREMELY LOW BIRTH WEIGHT INFANTS AT CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL

UNIVERSITY OF THE WITWATERSRAND

DEPARTMENT OF PAEDIATRICS

STUDENT: EDGAR M KALIMBA (MBCHB)

STUDENT NUMBER: 395519

SUPERVISOR: PROF D E BALLOT

GLOSSARY

CMJAH Charlotte Maxeke Johannesburg academic hospital

ELBW Extremely low birth weight

ICU Intensive care unit

MDGs Millennium development goals

NCPAP Nasal continuous positive airway pressure

NMR Neonatal mortality rate

VLBW Very low birth weight

SURVIVAL OF EXTREMELY LOW BIRTH WEIGHT INFANTS AT CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL

BACKGROUND

According to the World Health Organisation, nearly four million neonatal deaths occur worldwide every year. Most of these deaths take place in developing countries. [1]

Millennium development goal number 4 is to reduce child mortality by reducing the under five mortality by two thirds between 1990 and 2015. More than 8 million under five children die every year, and neonatal causes are among the 6 conditions for which over 90% of these deaths are attributed. [2] As such, improved maternal and newborn care with timely management of complications will play a significant role in attaining this goal.

While under-5 mortality rates are improving in many countries worldwide, neonatal mortality rates have shown a much less progress. [3] Neonatal deaths now account for more than 42% of all under-5 deaths, up from 37% in the year 2000 when MDGs were set. [3] Complications of preterm birth are the leading direct cause of neonatal mortality accounting for an estimated 27% of the 4 million neonatal deaths every year. Hence achieving MDG 4 is strongly influenced by progress in reducing neonatal deaths, and since preterm birth is the single largest contributor to these deaths, progress is dependent on achieving a better survival rate for preterm infants.

According to UN data, the neonatal mortality rate in Africa for the year 2009 was estimated to be 34 per 1000 live births, with the highest mortality in sub-Saharan countries. The same survey estimated South Africa's NMR at 19 per 1000 live births for the year 2009. This is still significantly high especially in comparison with industrialised countries whose NMR averages 3-7 per 1000 live births. [4]

In South Africa, peri-natal mortality and low birth weight rates have, in the past, generally been reported only for those infants weighing 1000g or more at birth because smaller infants are often regarded as miscarriages and not recorded. However, with improving maternal and neonatal care, more and more infants weighing 500g to 1000g are expected to survive.

There's no doubt that the mortality rate of very low birth weight infants is a big contributor to the overall neonatal mortality rate, both for developing and developed countries.

In one study carried out in Bangladesh, a developing country, the biggest contributor to NMR was preterm delivery, with VLBW infants making the majority of the early neonatal deaths (38%). [5] A similar observation was made in the USA in one study whereby it was showed 50% of neonatal deaths to be contributed by very low birth weight infants. [6]

In the sixth peri natal care survey of South Africa (saving babies 2006-2007), neonatal deaths due to “immaturity related causes” account for the majority of deaths at 50% of all neonatal deaths.[7]

Globally, the trend of survival of extremely low birth weight infants has improved significantly over the past decade mostly due to provision of surfactant, NCPAP and mechanical ventilation for ELBW infants. In two studies carried out in New Zealand in 1986 and 1998-1999 respectively, rates of survival were compared and it was shown to have improved from 65% in 1986 to 81% in 1998-99. ($P<0.001$) It should also be noted that in the same study, use of CPAP had increased from being used in only 5% of VLBW infants in 1986 to 38% use in 1998-99. [8]

In South Africa, even with paucity of available data on survival rates of ELBW infants, an improved trend of survival has been noted. A study done at Madadeni hospital, a district hospital in northern Kwa Zulu Natal, compared survival rate in VLBW infants for the years 1993-2001 and 2002-2005 with improved survival of non ventilated infants from 21% to 41%. [9] It should be noted that NCPAP and surfactant were not readily available at the mentioned hospital.

However, survival generally remains low in ELBW infants. In a study carried out at Chris Hani Baragwanath Hospital for the years 2000 to 2002, the survival rate of extremely low birth weight infants was shown to be 34% as compared to 84% for infants weighing more than 1000g. [10]

It is still evident, therefore, that the overall survival rate of extremely low birth weight infants in the public hospital setting in South Africa is still low, with improved survival only seen with increase in gestational age and birth weight.

The medical field has continued to embrace great advances in technology and this has inevitably had a positive impact in providing better care and giving a chance to patients where previously prognosis of certain conditions was considered to be poor. Neonatology has certainly not stayed behind in these advances, and particularly with regard to survival of extremely low birth weight infants.

Charlotte Maxeke Johannesburg academic Hospital (CMJAH) is a public hospital in the heart of Johannesburg, South Africa, with a busy neonatal unit. In a previous study carried out in the same unit, survival of infants weighing less than 1001 grams at birth was found to be 34.9% [11] at a time when nasal Continuous positive airway pressure was not yet fully introduced in the unit. Given the scarcity of resources and limited intensive care unit facilities in the public hospital setting, the unit only offers mechanical ventilation to infants born with a weight greater or equal to 900g.

Our interest in carrying out this study lies in establishing the survival rate of infants whose birth weight was less than 900g and were not ventilated in ICU according to the unit criteria for mechanical ventilation. It will also help us to compare current survival rate with provision of nasal CPAP and surfactant offered to infants weighing 750g and above, with previous data from the same unit.

JUSTIFICATION OF THE STUDY

With advances in obstetric care, it is expected and has indeed been shown that more extremely low birth weight infants will survive. Given the fact that the mortality rate of low birth weight infants, and particularly very low birth weight and extremely low birth weight infants contribute significantly to the neonatal mortality rate and ultimately to the under five mortality rate, this study will contribute by provision of data that is essential in forward planning, especially by prioritising budgeting and facilities, staffing and training with the aim of improving outcome of extremely low birth weight infants in the public health care setting and reducing the neonatal mortality rate in South Africa.

RESEARCH OBJECTIVES

1. To determine the survival rate of extremely low birth weight infants who do not qualify for mechanical ventilation in Intensive Care Unit according to the neonatal unit criteria for CMJAH.
2. To establish if there has been significant change in survival of ELBW infants with introduction of NCPAP given with surfactant to infants weighing more than 750 g at birth.

METHODOLOGY

Study design

This is a cross sectional retrospective study where by we will do a record review of all neonates with a birth weight < 900g.

Study population

Newborn infants with a birth weight less than 900g admitted to the neonatal unit at CMJAH from 1st January 2006 to 30th June 2011.

Study sample

Inclusion and exclusion criteria:

All newborn infants weighing < 900g at birth will be included. All inborn neonates were admitted directly to a transitional nursery in labour ward, so statistics include babies who died shortly after birth. Neonates delivered at primary level hospitals or clinics in the close vicinity and those who were born before arrival (BBA) were also admitted to the unit and will thus be part of our statistics.

Infants who had a birth weight of 900g or more, or who were mechanically ventilated in ICU will not be included.

Measurements

Relevant data will be retrieved from patient files with our variables as follows:

Maternal information: age, parity, gravidity, antenatal care, antenatal steroids, place and mode of delivery and HIV status.

Infant data: gestational age (Ballard scores), birth weight and APGAR scores.

DATA PROCESSING AND ANALYSIS

Data entry

Information from the patients' files will be captured in a Microsoft Excel spreadsheet for data cleaning and coding purposes

Data cleaning and coding

Data cleaning will involve double checking the data entry for missing values, extreme values and determining internal consistency. Data coding will then be done for data analysis purposes.

Data analysis

Data in Ms-Excel spreadsheet will then be imported to statistical software (STATA version 10) for analysis purposes.

Descriptive analysis: A descriptive level outcome variable (survival of the neonate) which is a categorical variable will be described by determining the frequency and percentage. Whereas continuous variables like gestational age and birth weight, their means and standard deviations will be computed and presented on a frequency table.

Inferential analysis: A chi-square test will be done to compare survival among neonates that received NCPAP and surfactant to those that didn't from previous data.

LIMITATIONS OF THE STUDY

The retrospective design of our study is such that we will only rely on the available data in hospital records and might therefore not get all the information we desire.

The study will not be able to establish infants who survived until discharge from hospital but died post discharge.

ETHICS

This study proposal will be submitted to the ethics committee on human research for the University of the Witwatersrand for approval before start of the study. Data for this study will only be used for the purpose of this study and all the details will be confidential. To ensure confidentiality and anonymity of the participants, code names will be used during data processing and reporting. As this is a case review, there is no risk to the study participants. Consent will be obtained from the CMJAH's chief executive office.

FINANCE

An application will be made to the University of the Witwatersrand research fund to cover the research/ study costs.

Estimated costs:

- Stationary, photocopying and binding costs R1000
- Transport: from CHBH to CMJAH ; 20KM for 10 trips R2000

Approximate total cost R3000

SCHEDULE

	Aug	Sept	Oct	Nov	Dec	Jan	
Research protocol							
Assessment & Ethics application							
Data collection							
Data analysis							
Writing up							

REFERENCES

1. Lawn JE, Cousens S, Zupan J: 4 million neonatal deaths: when? Where? Why? Lancet 2005, 365(9462):891-900

2. United Nations: Reduce Child Mortality. The Millennium Development

   Goals Report New York 2008:21-3.

3. Lawn JE, Kerber K, Enweronu-Laryea C, Massee Bateman O: Newborn survival in low resource settings--are we delivering? BJOG 2009, 116(Suppl 1):49-59

4. The state of the world's children, 2009: UNdata, available at http://data.un.org/Data.aspx?d=SOWC&f=inID%3A145

5. Yasmin S, Osrin D, Paul E, Costello A: Neonatal mortality of low-birth-weight infants in Bangladesh. J Health Popul Nutr. 2010 August; 28(4): 375–382.

6. Alexander GR, Kogan M, Bader D, Carlo W, Allen M, Mor J. US birth weight/gestational age-specific neonatal mortality: 1995-1997 rates for whites, Hispanics, and blacks. Pediatrics. 2003 Jan; 111(1):e61-6.

7. Pattinson RC (Ed): Saving babies 2006 - 2007: Sixth perinatal care survey of South Africa Tshepesa Press, Pretoria; 2009.

8. Darlow BA, Cust AE, Donoghue DA: Improved outcomes for very low birth weight infants: evidence from New Zealand national population based data. Arch Dis Child Fetal Neonatal Ed. 2003 Jan;88(1):F23-8

9. Bondi FS, Adhikari M: Improved survival of non ventilated very low birth weight infants at Madadeni hospital, Kwa-Zulu Natal. SAJCH vol 1 No 1 2007

10. Velaphi SC, Mokhachane M, Mphahlele RM, Beckh-Arnold E, Kuwanda ML, Cooper PA: Survival of very-low-birth-weight infants according to birth weight and gestational age in a public hospital. S Afr Med J. 2005 Jul; 95(7):504-9.

11. Ballot DE, Chirwa TF, Cooper PA: Determinants of survival in very low birth weight infants in a public sector hospital in Johannesburg. BMC Pediatrics 2010

APPENDIX 3. ETHICS APPROVAL CERTIFICATE

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG
Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Dr Edgar M Kalimba

CLEARANCE CERTIFICATE	M120673
PROJECT	Survival of Extremely Low Birth Weight Infants
INVESTIGATORS	Dr Edgar M Kalimba.
DEPARTMENT	Department of Paediatrics & Child Health
DATE CONSIDERED	29/06/2012
DECISION OF THE COMMITTEE*	Approved unconditionally

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE 29/06/2012 CHAIRPERSON ....
(Professor PE Cleaton-Jones)

*Guidelines for written 'informed consent' attached where applicable
cc: Supervisor : Prof D Ballot

DECLARATION OF INVESTIGATOR(S)
To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10004, 10th Floor, Senate House, University.
I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. **I agree to a completion of a yearly progress report.**

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES...