Optimal Ventilation and Surfactant Therapy in Very-Low-Birth-Weight Infants in Resource-Restricted Regions

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Keywords

Continuous positive airway pressure · Surfactant therapy ·
Very low birth weight · Resource-restricted regions

Abstract

In resource-restricted regions, respiratory distress syndrome (RDS) data are often underreported, making the determination of effective interventions and their outcome difficult. The combination of oxygen, nasal continuous positive airway pressure (CPAP) and surfactant therapy has the potential to prevent 42% of RDS-related deaths in sub-Saharan Africa, despite the financial implications. This article provides a brief overview on the status of RDS management, mainly nasal CPAP and surfactant therapy in very-low-birth-weight infants, in resource-restricted regions of sub-Saharan Africa. Data from the public health sector, as compared to the private health sector, of the Western Cape province, South Africa, are used to illustrate what RDS management strategies are able to accomplish in a resource-restricted region. Upscaling of all components (antenatal care, antenatal corticosteroids, prevention of hypothermia and RDS management strategies) are required to decrease premature infant mortality rates in resource-restricted areas.

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Introduction

In resource-restricted regions (RRR), neonatal respiratory distress syndrome (RDS) is a leading cause of mortality among preterm infants [1]. The wide variation of reported RDS rates (1.2–76%), with RDS-related mortality rates up to 52% [2], hampers efforts to determine which interventions would improve outcomes [3]. In developed countries, RDS management includes invasive and non-invasive ventilation options, surfactant replacement therapy (SRT) and other adjunctive therapies [4]. In RRR with limited or absent ventilation facilities, management of RDS poses significant challenges.

There is a gross underutilization of effective healthcare in RRR [5]. Most sub-Saharan countries lack neonatal training and experience in ventilation. The high cost of technology and drugs, as well as a lack of neonatal training and barriers to technology adoption, prevent the upscaling of neonatal services [6]. This results in healthcare disparities, affecting access to medical care and treatment modalities and leading to poorer patient outcomes [5].

The aim of this article was to provide a brief overview of the status of RDS management, mainly nasal continuous positive airway pressure (nCPAP) and SRT in very-low-birth-weight (VLBW) infants, in RRR of sub-Saharan Africa (SSA).

Table 1. Comparison of two SRT strategies in ELBW infants in RRR

	InSurE + poractant alfa	LISA + beractant	<i>p</i> value
Subjects, <i>n</i>	97	111	
Number of surfactant doses	1.34±0.7	1±0.66	<0.001
Duration of nCPAP, days	6.8±2.8	3±8	<0.001
Duration of total respiratory support, days	9.4±3.5	1±20	<0.001
Pulmonary haemorrhage	11 (11.3)	1 (0.9)	<0.001
Pneumothorax	2 (2)	0	0.135
CPAP failure (NICU <3 days)	15 (15.4)	9 (8.1)	0.101
BPD	2 (2)	2 (1.8)	0.916
Death <3 days	18 (18.5)	25 (22.5)	0.478

Unpublished data. Values denote the mean ± SD or *n* (%). BPD, bronchopulmonary dysplasia (36 weeks corrected gestational age); ELBW, extremely low birth weight; InSurE, intubation, surfactant and rapid extubation; LISA, less invasive surfactant administration; nCPAP, nasal continuous positive airway pressure; RRR, resource-restricted regions; SRT, surfactant replacement therapy.

RDS Management in RRR of SSA

In SSA, 85% of the countries are classified as low- and middle-income economies [7]. The perinatal mortality rate is the highest in the world (approx. 35 deaths per 1,000 live births) [8], similar to other low-resource areas such as South Asia and China [9]. The increased health-care expenditure in SSA over the last decade has had a minimal impact on maternal and child health [10]. This may be due to the prioritization of public health expenditure aimed at specific diseases (e.g. HIV, malaria) with no improvement in overall healthcare [10].

Prenatal Care and Antenatal Corticosteroids

Lack of prenatal care is known to increase neonatal mortality and morbidity [11]. In RRR, antenatal care varies widely, with only one-third of women in SSA receiving the recommended 4 antenatal visits [12]. Numerous issues affect a mother's ability to attend antenatal care [13]. Antenatal corticosteroids (ACS) improve outcomes among newborns [14]. However, their advantages in RRR, where overall newborn care is inadequate, need to be confirmed [15].

Nasal Continuous Positive Airway Pressure

In developed countries, nCPAP is the standard respiratory support for RDS [4], leading to decreased invasive

Table 2. Comparison of porcine versus bovine SRT (via InSurE) in VLBW infants in RRR

	Beractant	Poractant alfa	<i>p</i> value
Subjects, <i>n</i>	108	100	
Repeat surfactant doses	20 (18.5)	26 (26)	0.185
Pneumothorax	2 (1.8)	1 (1)	0.607
O ₂ at 28 days	38 (35.2)	26 (26)	0.230
O ₂ at 36 weeks CGA	3 (2.8)	8 (8)	0.220
Mortality	36 (32.7)	31 (31)	0.822
Combined BPD/death	38 (35.2)	36 (36)	0.902

Adapted from Boshoff-Coyles et al. [27]. Values are presented as *n* (%). BPD, bronchopulmonary dysplasia (36 weeks CGA); CGA, corrected gestational age; O₂, oxygen; RRR, resource-restricted regions; SRT, surfactant replacement therapy; VLBW, very low birth weight.

ventilation requirement and mortality [16]. In RRR, nCPAP has been shown to decrease mortality with no significant increase in pneumothoraces, CPAP failure or cost [17]. Most RRR studies have utilized bubble CPAP, with few data available regarding the use of flow driver systems. This may be due to financial constraints, lack of piped gas or availability of research grants [18]. It has been hypothesized that providing a wider availability of oxygen and CPAP in RRR, with an appropriate supportive infrastructure, would dramatically decrease neonatal mortality [1]. Despite its cost-effectiveness [19], CPAP introduction into RRR remains challenging, requiring not only financial input but also human resources, training and monitoring [2].

Surfactant Replacement Therapy

SRT is the core of RDS management [4]. In RRR, SRT with nCPAP is safe and efficacious [20] and decreases mortality by 25% [21]. SRT, via less invasive methods, is widely used on a global scale. In developed countries, less invasive surfactant administration (LISA), compared to intubation, surfactant and rapid extubation (InSurE), decreases the need and duration of mechanical ventilation and the duration of nCPAP and oxygen [22]. In RRR, nCPAP, with InSurE within 1 h of birth, improves the survival of extremely-low-birth-weight (ELBW) infants [23]. SRT without intubation, compared to InSurE, reduces the need for mechanical ventilation within 72 h of life [24]. LISA + beractant decreased the need for SRT re-dosing and nCPAP duration, compared to InSurE + poractant alfa in an RRR, with no differences in mortality or bronchopulmonary dysplasia rates (Table 1) [25].

Table 3. Hospital-level MANDATE model of intervention penetration, utilization and efficacy for RDS management in sub-Saharan Africa

Intervention	WHO recommendation	WHO strength of recommendation	Penetration, %	Utilization, %	Efficacy, %
Antenatal steroids	For women at risk of preterm birth (24–34 weeks' gestation), under specific conditions	Strong	50	25	50
CPAP	CPAP is recommended for treating preterm newborns with RDS	Strong	20	70	50
SRT	SRT is recommended for intubated and ventilated newborns with RDS	Conditional (facilities with intubation, ventilator care, blood gas analysis, newborn nursing care and monitoring)	5	75	35

Adapted from Griffin et al. [28]. CPAP, continuous positive airway pressure; MANDATE, Maternal and Neonatal Directed Assessment of Technology; SRT, surfactant replacement therapy; WHO, World Health Organisation.

In RRR, the choice of surfactant is often based on pharmaceutical and financial accessibility. The type of surfactant used in RDS may be immaterial, with similar clinical outcomes and financial implications [26]. A comparison of beractant with poractant alfa, combined with nCPAP, in an RRR showed no differences in a combined outcome of death/bronchopulmonary dysplasia or other short-term outcomes [27] (Table 2).

Surfactant administration should not be a single procedure but rather a component of a complex holistic care bundle supporting the neonate's capacity to adapt to extrauterine life [28].

Bundles of Care for RDS Management

Maternal and Neonatal Directed Assessment of Technology (MANDATE) examination of WHO-recommended interventions for preterm birth showed that combining interventions had the greatest potential to decrease preterm mortality [29]. A combination of oxygen and nCPAP was hypothesized to prevent 42% of RDS-related deaths in SSA [29]. However, the availability, at a hospital level, of these interventions is variable (Table 3). The EPICE study showed that combining administration of antenatal steroids, in-hospital delivery, prevention of hypothermia and early SRT or nCPAP could decrease preterm mortality by 18% [30].

Financial Implications of RDS Management in RRR

RDS management (oxygen, ventilation and surfactant) constitutes 19% of medical costs [31]. The cost-effectiveness of ACS, oxygen, SRT and nCPAP/ventilation has been well documented in developed countries. De-

spite the overall expense of neonatal care, it remains cost-effective in terms of quality-adjusted life years per survivor [32].

With approximately 12 million preterm births in Asia and SSA [33], neonatal care constitutes a tremendous financial burden. In RRR, ACS [34] and nCPAP [35], as part of a neonatal care bundle, are cost-effective. From RRR, SRT cost-effectiveness data are lacking [20]. It is possible that ACS, nCPAP and SRT, even in RRR, would be able to provide both healthier infants and economically viable adults. Widespread implementation of evidence-based, cost-effective treatment strategies may decrease costs in RRR [32].

RDS Management in the Western Cape Province, South Africa

South Africa is considered an upper-middle-income country by the World Bank. However, the health sector in South Africa mirrors the country's complexity. The public health sector provides medical services to the majority of South Africans (84%). It has significant resource restrictions, including a low human resource ratio, financial constraints and an ageing infrastructure. The private, for-profit health sector has near-unrestricted resources, similar to those of developed countries, providing medical services to 16% of the population [36].

During the last decade, the neonatal mortality rate (NMR) in South Africa has remained at 11–12 deaths per 1,000 live births [37]. The NMR accounts for 44% of the infant mortality rate and 32% of the under-5-year-of-age

Table 4. Demographics and in-hospital outcomes of VLBW infants in RRH versus URH in the Western Cape province, South Africa, 2016–2018

	URH	RRH	<i>p</i> value
<i>Demographics</i>			
Total VLBW infants (2016–2018)	218	3,960	
Annual VLBW infant admissions	24±10	660±179	
Inborn	203 (93.1)	3,585 (90.5)	0.200
Male	121 (55.5)	1,919 (48.5)	0.045
Prenatal care	214 (98.2)	3,456 (87.3)	<0.001
Birth weight			
<750 g	48 (22.0)	307 (7.8)	<0.001
751–1,000 g	61 (28.0)	994 (25.1)	0.338
1,001–1,250 g	40 (18.3)	1,334 (33.7)	<0.001
1,251–1,500 g	69 (31.7)	1,347 (34.0)	0.486
Antenatal steroids	160 (73.4)	3,063 (77.3)	0.183
Delivery by caesarean section	187 (85.8)	2,591 (65.4)	<0.001
SGA at birth	56 (25.7)	1,139 (28.8)	0.324
Maternal hypertension	54 (24.8)	1,946 (49.1)	<0.001
<i>In-hospital neonatal outcomes</i>			
Survival	184 (84.4)	2,789 (70.4)	<0.001
Mortality <12 h	12 (5.5)	703 (17.8)	<0.001
Pneumothorax	0 (0.0)	32 (0.8)	0.185
CLD at 36 weeks CGA	12 (5.5)	72 (1.8)	<0.001
Steroids for CLD	44 (20.2)	40 (1.0)	<0.001
Late-onset sepsis	9 (4.1)	387 (9.8)	<0.001
NEC	1 (0.5)	216 (5.5)	<0.001
Cranial ultrasound			
Examination performed	196 (89.9)	3,064 (77.4)	<0.001
Severe IVH	5 (2.3)	153 (3.9)	0.23
Retinopathy of prematurity			
Examination performed	156 (71.6)	1,373 (34.7)	<0.001
Severe ROP	1 (0.5)	44 (1.1)	0.401

Unpublished data. Values denote *n* (%). CGA, corrected gestational age; CLD, chronic lung disease; IVH, intraventricular haemorrhage; NEC, necrotizing enterocolitis; RRH, restricted-resource hospitals; ROP, retinopathy of prematurity; SGA, small for gestational age (<10th centile); URH, unrestricted-resource hospitals; VLBW, very low birth weight.

mortality rate. In 2016 the early and late NMRs were 10.2 and 2.4 per 1,000 live births, respectively. Complications of prematurity accounted for 47.9% of the deaths [38].

Public health sector infrastructure and human resource issues remain responsible for many neonatal deaths: delays in referral to secondary-/tertiary-level care (8%), inadequate neonatal unit/nursery facilities (14.7%), lack of transport (11.9%), unavailability of neonatal intensive care unit (NICU) cots with ventilator capacity (8.9%), and insufficiently trained personnel on duty (10.6%) [39]. Few data are available from the private health sector. The public health sector of the Western Cape (WC) province is serviced by 28 restricted-resource hospitals (RRH). The WC has approximately 100,000

births per annum with a VLBW rate of 14.5% [39]. NICUs are centralized to 2 academic hospitals in Cape Town. These 2 hospitals are the referral centres for high-risk pregnancies as well as deliveries <32 weeks' gestational age. Other provincial hospitals have a variety of level 1 and 2 neonatal care facilities. All infants, including ELBW infants, are cared for in high-care nurseries with flow driver nCPAP, LISA/InSurE SRT and aggressive enteral (breastmilk) nutrition. The 2 tertiary RRH have a combined total of 16 NICU beds, reserved for neonates requiring invasive ventilation and surgery.

Since 2000 the 2 academic neonatal units have actively implemented a non-invasive ventilation strategy for all preterm babies. In 2014, due to resource constraints, the

Fig. 1. Comparison of respiratory management strategies in resource-restricted versus -unrestricted hospitals, per birth weight category. CPAP, continuous positive airway pressure; SRT, surfactant replacement therapy; vent., ventilation.

WC public health sector initiated a periviability management protocol which restricts invasive ventilation for infants ≤ 26 weeks and/or < 750 g and ELBW infants born outside of tertiary facilities [40].

The private health sector of the WC is serviced by 24 unrestricted-resource hospitals (URH). Neonatal care at these hospitals follows international standards, with ELBW and VLBW infants cared for in NICU rather than in high-care facilities. Between 2016 and 2018, a total of 3,960 VLBW babies were treated at the 2 tertiary RRH, compared to 218 babies in 3 participating URH. More neonatal beds were available in URH than in RRH, i.e. 18 versus 16 general neonatal beds per 1,000 births, and 6 versus 2 NICU beds per 1,000 births, in URH and RRH, respectively. Although prenatal care was provided more often in URH, ACS administration was similar. Overall survival was higher in URH than in RRH, with significantly more early neonatal deaths (< 12 h of age) in RRH than in URH. Sepsis and necrotizing enterocolitis were more common in RRH than in URH. Significantly fewer preterm neonates underwent routine screening (cranial ultrasound and retinopathy of prematurity) in RRH than in URH (Table 4).

SRT and invasive ventilation were more often used in URH than in RRH. Resource utilization (CPAP, SRT and mechanical ventilation) differed between RRH and URH, depending on the birth weight. RRH were more aggressive than URH with the use of CPAP, for most weight

categories (Fig. 1). The difference in resource utilization, especially for infants < 750 g, may be due to the periviability management protocol in RRH.

Pneumothoraces were infrequent in both URH and RRH. The low chronic lung disease incidence in RRH may be attributable to the periviability protocol, with survival of 55% in this category (< 750 g). However, the chronic lung disease incidence is also low in URH, possibly suggesting that the non-invasive respiratory approach of RDS management practised by both resource sectors may be beneficial. Similar respiratory outcomes with nCPAP and SRT have been shown at other academic hospitals in South Africa [41]. However, no data are available from the other 7 South African provinces. The mortality of ELBW and VLBW infants outside the WC and Gauteng provinces is high and varies widely [38].

The HHAPI-NeSS strategy is being implemented in South Africa with the aim of reducing neonatal deaths [38]. This strategy utilizes a package of care aimed at decreasing prematurity-related deaths: (1) ensuring that corticosteroids are given to every woman in preterm labour; (2) ensuring that antibiotics are given for preterm rupture of membranes; (3) ensuring that appropriate hospitals are skilled in the use of nCPAP; and (4) ensuring that all mothers of immature infants have easy access to kangaroo mother care.

The roll-out of nCPAP has been identified by PRICE-LESS SA (Priority Cost-Effective Lessons for System

Strengthening in South Africa) as being one of the interventions that would enable South Africa to meet the WHO's Sustainable Development Goal 3 by 2030. The Perinatal Problem Identification Program (South Africa's public health sector perinatal mortality auditing tool) data have shown a 20% overall reduction in absolute deaths coded for RDS [38]. Although it is difficult to attribute the decreased mortality to nCPAP use only, similar trends have been observed in district hospitals where nCPAP has been rolled out [38].

Conclusion

A balanced, evidence-based approach is necessary when any therapy or strategy is introduced. Unanswered questions remain in the management of RDS in developed countries: which surfactant administration technique is superior; which oxygen thresholds for SRT at different gestational ages should be followed; what is the best device/catheter for SRT? However, the reality in RRR is that thousands of preterm infants are still dying due to untreated RDS. It is important to understand that in RRR, the health of individuals, including preterm infants, is a complex social construct. Improved outcomes may not be amenable to increased expenditure on technology-based medical care [39]. Due to profound economic disparities, there is a lack of social justice and equitable healthcare in RRR. Salvageable babies, with treatable conditions such as RDS, are denied evidence-based life-sustaining therapies either due to inaccessibility to technology or parental financial constraints [40]. Significant differences between SSA countries, as well as within countries, need to be considered in health planning and prioritization [41].

Upscaling of all components (antenatal care, ACS, prevention of hypothermia and RDS management strategies) are required to decrease premature infant mortality [29]. No single modality will be able to improve neonatal outcomes in RRR. Despite the well-described advantages of early nCPAP, there are numerous barriers to its implementation in RRR (equipment and consumable costs, electricity, oxygen and air supply, as well as the availability of skilled personnel). Training should be an ongoing endeavour and requires policymaker buy-in. Novel implementation strategies, cognisant of the different societal problems in RRR, are urgently required.

SRT, despite its financial implications, has the potential to dramatically improve the outcome of RDS in RRR. However, the same barriers apply as with nCPAP. More

research is also required as to how to improve SRT administration, combined with nCPAP, in RRR.

In RRR, few data regarding neurodevelopmental outcomes are available. RDS management, as part of a holistic preterm infant care bundle, should aim to increase neurodevelopmentally intact survival, in order to produce economically viable adults. It is crucial to select infants who would benefit whilst limiting potentially devastating complications (morbidity-free survival). Tools such as the periviability document, which limits ventilation for the most vulnerable, can help achieve this.

Despite the global crisis in the health workforce and the maldistribution of doctors to the private health sector, it is important to upskill all levels of medical personnel [42]. Empowering community health workers in RRR has the potential to further reduce neonatal and thus child mortality [43].

Recommendation

In RRR, nCPAP should be used as the primary mode of RDS management, with SRT reserved for non-responders or high-risk infants [21]. There is a dire need to upscale nCPAP, SRT and antenatal care services in RRR to reduce preterm mortality. More research is required to determine which combination of modalities will decrease mortality and produce economically viable infants in RRR.

Acknowledgements

We wish to acknowledge Mike Harrison, Division of Neonatology, Department of Paediatrics and Child Health, University of Cape Town, South Africa.

Disclosure Statement

None of the authors have any disclosures to make.

Funding Sources

No funding was received.

Author Contributions

All authors contributed to conception, writing, editing and the final manuscript.

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