

THE INFLUENCE OF THE WIDER USE OF SURFACTANT THERAPY ON NEONATAL MORTALITY AMONG BLACKS AND WHITES

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Abstract Background. Surfactant therapy reduces morbidity and mortality among premature infants with the respiratory distress syndrome (RDS). Fetal pulmonary surfactant matures more slowly in white than in black fetuses, and therefore RDS is more prevalent among whites than among blacks. We reasoned that the increased use of surfactant after its approval by the Food and Drug Administration (FDA) in 1990 might have reduced neonatal mortality more among whites than among blacks.

Methods. We merged vital-statistics information for all 1563 infants with very low birth weights (500 to 1500 g) born from 1987 through 1989 or in 1991 and 1992 to residents of St. Louis with clinical data from the four neonatal intensive care units in the St. Louis area; we then compared neonatal mortality during two periods, one before and one after the FDA's approval of surfactant for clinical use (1987 through 1989 and 1991 through 1992).

Results. The use of surfactant increased by a factor of 10 between 1987 through 1989 and 1991 through 1992. The neonatal mortality rate among all very-low-birth-weight infants decreased 17 percent, from 220.3 deaths

per 1000 very-low-birth-weight babies born alive (in 1987 through 1989) to 183.9 per 1000 (in 1991 through 1992; $P=0.07$). This decrease was due to a 41 percent reduction in the mortality rate among white newborns with very low birth weights (from 261.5 per 1000 to 155.5 per 1000; $P=0.003$). In contrast, among black infants, the mortality rate for very-low-birth-weight infants did not change significantly (195.6 per 1000 and 196.8 per 1000). The relative risk of death among black newborns with very low birth weights as compared with white newborns with similar weights was 0.7 from 1987 through 1989 and 1.3 from 1991 through 1992 ($P=0.02$). The differences in mortality were not explained by differences in access to surfactant therapy, by differences in mortality between black and white infants who received surfactant, or by differences in the use of antenatal corticosteroid therapy.

Conclusions. After surfactant therapy for RDS became generally available, neonatal mortality improved more for white than for black infants with very low birth weights. (N Engl J Med 1996;334:1635-40.)

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IN a series of randomized, placebo-controlled trials, surfactant-replacement therapy was effective in reducing pulmonary morbidity and mortality in infants with very low birth weights (500 to 1500 g) who had the respiratory distress syndrome (RDS).¹⁻⁸ After surfactant was approved for this use by the Food and Drug Administration (FDA) in August 1990, it was expected that the use of surfactant would reduce neonatal mortality in this group of infants.⁹⁻¹¹

Although neonatal mortality is significantly higher among black infants than among white infants, mortality among very-low-birth-weight infants is generally lower for blacks, in part because of the more rapid maturation of pulmonary surfactant in black fetuses.¹²⁻¹⁸ Because of this biologic difference in pulmonary development and possible socially determined differences in access to surfactant therapy, we reasoned that surfac-

tant therapy, as it moved from investigative protocols to general use, might have reduced mortality more among white neonates than among black neonates. To examine this question in a population-based study, we merged vital statistics and clinical data for all infants with very low birth weights in St. Louis, a metropolitan area where racial differences in neonatal mortality and in the proportion of newborns with very low birth weights are similar to those in the rest of the United States.^{19,20}

METHODS

We used linked data on birth and death certificates from the Missouri State Department of Health to identify all 1563 very-low-birth-weight infants (those weighing 500 to 1500 g) who were born to residents of the city and county of St. Louis from January 1, 1987, through December 31, 1989 (before the approval of surfactant), and from January 1, 1991, through December 31, 1992 (after the approval of surfactant). We identified all 315 deaths in this group. The race recorded on the birth certificate was provided by the mother at the time of birth.

We investigated surfactant use within the four intensive care nurseries in St. Louis where surfactant was administered. We used the clinical data bases from these nurseries to identify all very-low-birth-weight infants with RDS and those who received surfactant during the two study periods. Synthetic and bovine surfactant preparations were used both to prevent RDS and to treat infants with RDS.¹⁻⁸ We did not record the specific type of surfactant, the infant's age at the time of administration, or the number of doses received. During the three years before the FDA's approval of surfactant, clinical investigations at each of the four institutions accounted for a small number of surfactant recipients. All the neonatologists at all the tertiary care units we studied used similar guidelines for the administration of surfactant, which corresponded to those outlined in the clinical trials of surfactant replacement.¹⁻⁸ RDS was defined by characteristic findings on chest ra-

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diography and by the need for supplemental oxygen therapy.²¹ All very-low-birth-weight infants identified in the birth-certificate files were successfully linked with the clinical data bases by means of the infant's name, the hospital of birth, the birth date, and the birth weight.

We also reviewed the obstetrical records of 1171 of the 1329 women who delivered very-low-birth-weight babies at the tertiary care centers, in order to determine the frequency of antenatal corticosteroid therapy during the two study periods. A full course of corticosteroids was defined as two doses given at least 24 hours before delivery.²² We assumed that the 234 women who gave birth outside the tertiary care system did not receive any corticosteroids before delivery. There were no differences in the proportions of black and white infants between the 1171 very-low-birth-weight infants whose mothers' records were reviewed and the 392 whose records were not available for review.

To examine patterns of surfactant use in the different racial groups, we used logistic-regression models that included the baby's gestational age, birth weight, race, and sex; whether antenatal corticosteroid therapy was administered; and whether there was a diagnosis of RDS. Birth weight and gestational age were treated as continuous variables in these models. Mortality rates were calculated as crude rates and reported for each 1000 live births of very-low-birth weight infants.

For the analyses in this study, respiratory causes of death were defined according to the following codes from the *International Classification of Diseases, 9th Revision, Clinical Modification* (ICD-9-CM)²³: 769, 770.2, 770.3, 770.4, 770.7, and 770.8, representing RDS, pulmonary interstitial emphysema, pulmonary hemorrhage, primary atelectasis, bronchopulmonary dysplasia, and other respiratory disorders, respectively. We excluded infants with the codes 765.0 and 765.1, denoting extreme prematurity and "other preterm infants."

Statistical Analysis System software (SAS Institute, Cary, N.C.) was used at the Washington University Pediatric Computing Facility and the Harvard Institute for Reproductive and Child Health to perform statistical calculations. Comparisons between racial groups and between study periods were made with the Mantel-Haenszel estimate of relative risk and the Cochran-Mantel-Haenszel method of chi-square analysis to calculate two-tailed P values. The Breslow-Day test for the homogeneity of odds ratios was used to evaluate changes in the degree of difference between the races in neonatal mortality from the earlier to the later period.²⁴ The study protocol was approved by the institutional review board of each hospital.

RESULTS

Demographic Characteristics of the Study Population

According to the linked data from birth and death certificates, 1563 (1.4 percent) of the 111,464 children born to residents of the city and county of St. Louis during the two study periods had birth weights between 500 and 1500 g. The rate of very low birth weight in-

creased from 1.3 percent in 1987 through 1989 to 1.5 percent in 1991 through 1992 (P=0.003). Though there were differences among the institutions in the proportions of black and white babies born, the distribution of race and sex among very-low-birth-weight infants did not change significantly during the study. Forty-eight percent of the infants in the study group were girls. There were 16 infants who were not black or white or whose birth certificates were missing data on race. These 16 infants were not included in the analysis. The median birth weights and estimated gestational ages did not differ significantly between black and white infants and did not change significantly between 1987 through 1989 and 1991 through 1992.

The frequency of other conditions known to influence the birth and death rates of very-low-birth-weight infants, including maternal smoking, multiple gestation, and congenital anomalies, did not differ significantly between the two study periods (data not shown). The use of alcohol, reported by the mothers, was not recorded before 1989, and thus comparisons with respect to this factor were not possible. Fewer mothers of very-low-birth-weight infants received prenatal care in the later study period than in the earlier one (P=0.07).

Mortality

The neonatal mortality rate (defined as the rate of death within 28 days of birth) for all babies born to residents of the city and county of St. Louis did not differ significantly between the two periods we studied (Table 1). However, the relative risk of neonatal death for black infants as compared with white infants increased from 2.4 during the first period to 2.9 during the second (P=0.04). The birth-weight distribution of newborns who died also did not change significantly. Infants with birth weights of 500 to 1500 g accounted for 43 percent of all neonatal deaths in 1987 through 1989 and for 41 percent in 1991 through 1992.

The neonatal mortality rate among very-low-birth-weight infants of all races decreased by 16 percent from the first to the second study period, from 220.3 deaths per 1000 live-born, very-low-birth-weight infants

Table 1. Total Births, Neonatal Deaths, and Births of Infants with Very Low Birth Weights during the Two Study Periods, According to Race.*

RACE	TOTAL BIRTHS		NEONATAL DEATHS			BIRTHS OF VLBW INFANTS		
	1987-1989	1991-1992	1987-1989	1991-1992	P VALUE†	1987-1989	1991-1992	P VALUE‡
	no. (mortality rate per 1000 live births)					no. (% of total births)		
Black	23,044	17,544	242 (10.5)	194 (11.1)	0.59	542	442	0.27
White	43,483	26,378	196 (4.5)	107 (4.1)	0.38	325	238	0.07
Total	66,617	44,847	444 (6.7)	305 (6.8)	0.82	877 (1.3)	686 (1.5)	0.003
P value‡	—	—	<0.001	<0.001	—	<0.001	<0.001	—
Relative risk (95% CI)§	—	—	2.4 (2.0-2.8)	2.9 (2.3-3.6)	0.04	—	—	—

*VLBW denotes very low birth weight, defined as 500 to 1500 g, and CI confidence interval. Infants who were not known to be black or white have been included in the totals.

†For the comparison between 1991-1992 and 1987-1989.

‡For the comparison between blacks and whites.

§For blacks as compared with whites.

to 183.9 per 1000 ($P=0.07$). This reduction in neonatal mortality was due entirely to a reduction in deaths among white infants with very low birth weights. The mortality rate among white very-low-birth-weight neonates decreased by 41 percent ($P=0.003$), whereas that among black neonates with similar weights did not change significantly between the two time periods (195.6 per 1000 vs. 196.8 per 1000) (Fig. 1 and Table 2). The mortality rate among white newborns with birth weights from 500 to 999 g decreased from 477.6 per 1000 to 333.3 per 1000, a decline of 30 percent ($P=0.03$), whereas that among black newborns of the same weight declined by only 5 percent ($P=0.66$). Although the rate of death for white infants weighing 1000 to 1500 g declined by 68 percent ($P=0.01$), that for black infants rose, but not significantly ($P=0.68$). These disparate trends did, however, reverse the relative risk of death among black as compared with white very-low-birth-weight neonates from 0.7 during the first period studied to 1.3 during the second ($P=0.02$).

The post-neonatal death rate (the rate of death between 28 days and 1 year of age) among all very-low-birth-weight infants who survived the neonatal period also decreased in the two years after surfactant became generally available, from 7 percent to 4 percent ($P=0.03$). The post-neonatal death rate for white infants decreased from 5 percent to 1.5 percent ($P=0.03$), whereas that for black infants was similar in the two study periods (7 percent and 5 percent; $P=0.19$).

RDS, Surfactant Therapy, and Antenatal Corticosteroid Therapy

The reduction in the rate of death among white very-low-birth-weight infants was due to a major decrease in mortality among newborns with a diagnosis of RDS (Fig. 1). Indeed, 66 percent of the overall decline in mortality was due to improved survival of white neonates with RDS. Although the incidence of RDS among whites remained stable during the two periods (approximately 70 percent of white very-low-birth-weight newborns had RDS), mortality among these neonates fell from 228.5 per 1000 to 125.7 per 1000 ($P=0.008$) (Table 3). For black neonates, the incidence of RDS rose slightly, from 60 percent to 65 percent of those with very low birth weights ($P=0.07$), whereas mortality fell by only 11 percent ($P=0.50$). The proportion of deaths among very-low-birth-weight infants that were due to respiratory causes decreased from 48 percent to 32 percent for white infants ($P=0.11$) and from 42 percent to 38 percent for black infants ($P=0.67$).

As expected, only a small proportion (5 percent) of all very-low-birth-weight infants with a diagnosis of RDS received surfactant therapy during the first period (1987 through 1989), as compared with 56 percent of all such infants in 1991 through 1992. In 1991 through 1992, white very-low-birth-weight infants were more likely to receive surfactant therapy than their black counterparts (63 percent vs. 52 percent, respectively; $P=0.04$). There were no differences among the medical

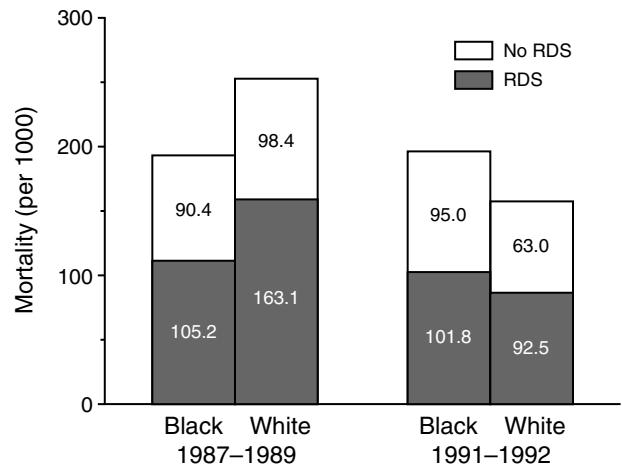


Figure 1. Crude Neonatal Mortality Rates per 1000 Very-Low-Birth-Weight Infants Born Alive in 1987 through 1989 and 1991 through 1992, According to Race and the Presence or Absence of the Respiratory Distress Syndrome (RDS).

The neonatal mortality rate for all very-low-birth-weight infants in 1987 through 1989 was significantly greater among white than among black infants (relative risk for blacks as compared with whites, 0.7; 95 percent confidence interval, 0.6 to 1.0; $P=0.02$); the rate for whites decreased significantly in 1991 through 1992 (relative risk as compared with 1987 through 1989, 0.6; 95 percent confidence interval, 0.4 to 0.8; $P=0.003$). The neonatal mortality rate for black infants did not change from 1987 through 1989 to 1991 through 1992 ($P=0.96$), and it was similar to that among whites in 1991 through 1992 ($P=0.19$). The neonatal mortality rate among white very-low-birth-weight infants with RDS decreased between 1987 through 1989 and 1991 through 1992 (relative risk in 1991 through 1992 as compared with 1987 through 1989, 0.6; 95 percent confidence interval, 0.3 to 0.9; $P=0.008$), but the rate among black infants with RDS did not change significantly ($P=0.50$).

institutions in the rate of administration of surfactant to infants with RDS.

The rate of administration of antenatal corticosteroids increased from 14 percent to 28 percent between 1987 through 1989 and 1991 through 1992 (Table 3). The rate of administration of antenatal corticosteroid therapy to black women in the later period was 1.6 times that in the earlier period (22 percent vs. 14 percent of patients whose records were reviewed; 95 percent confidence interval, 1.2 to 2.2; $P=0.003$), whereas the rate for white women increased to 2.6 times that in the earlier period (36 percent vs. 14 percent; 95 percent confidence interval, 1.9 to 3.6; $P=0.001$). In 1991 through 1992, black women were 50 percent as likely to receive antenatal corticosteroids as white women, even after adjustment for gestational age ($P<0.001$) (Table 3).

To determine whether differences in access to neonatal intensive care altered the outcomes of the 162 very-low-birth-weight infants born outside of the four tertiary care facilities during 1989, 1991, and 1992 (the years for which transfer data were available), the outcomes of these infants were analyzed separately. Within this group, 106 infants were transferred to a tertiary care facility. The 18 infants who died without transfer to a tertiary care facility died from conditions unlikely to be

Table 2. Birth-Weight Categories for Births and Neonatal Deaths among Very-Low-Birth-Weight Infants, According to Race and Study Period.*

RACE AND BIRTH WEIGHT	1987-1989			1991-1992			% CHANGE IN MORTALITY	P VALUE
			MORTALITY RATE (PER 1000)			MORTALITY RATE (PER 1000)		
	BIRTHS	DEATHS		BIRTHS	DEATHS			
	<i>no. (%)</i>			<i>no. (%)</i>				
Black								
500-999 g	241 (44.5)	93 (87.7)	385.9	205 (46.4)	75 (86.2)	365.9	-5	
1000-1500 g	301 (55.5)	13 (12.3)	43.2	237 (53.6)	12 (13.8)	50.6	17	
Total	542 (100)	106 (100)	195.6†	442 (100)	87 (100)	196.8‡	0.6	0.96
White								
500-999 g	134 (41.2)	64 (75.3)	477.6	96 (40.3)	32 (86.5)	333.3	-30	
1000-1500 g	191 (58.8)	21 (24.7)	110.0	142 (59.7)	5 (13.5)	35.2	-68	
Total	325 (100)	85 (100)	261.5†	238 (100)	37 (100)	155.5‡	-41	0.003
Total								
500-999 g	375 (43.3)	157 (82.2)	418.7	301 (44.3)	107 (86.3)	355.5	-15	
1000-1500 g	492 (56.7)	34 (17.8)	69.1	379 (55.7)	17 (13.7)	44.9	-35	
Total	867 (100)	191 (100)	220.3	680 (100)	124 (100)	182.4	-17	0.07

*Totals include black and white infants only.

†Relative risk of death for black as compared with white infants, 0.7 (95 percent confidence interval, 0.6 to 1.0); P=0.02.

‡Relative risk of death for black as compared with white infants, 1.3 (95 percent confidence interval, 0.9 to 1.8); P=0.19.

successfully treated with neonatal intensive care or surfactant (extreme prematurity [n=15], cytogenetic abnormalities [n=1], or congenital anomalies [n=2]).

Although black infants were less likely to have received surfactant or antenatal corticosteroid therapy than white infants in 1991 through 1992, black infants were also less likely to have had RDS. After adjustment for the presence or absence of RDS, birth weight, gestational age, and sex in a logistic-regression model, racial differences in the rate of administration of surfactant in 1991 through 1992 were no longer significant; black infants with RDS were just as likely to receive surfactant as white infants with RDS (odds ratio, 0.9; 95 percent confidence interval, 0.5 to 1.2). Once surfactant was administered, there was no significant difference between the races in neonatal mortality; 20 percent of white infants and 23 percent of black infants who received surfactant died (P=0.48). Although the rates of administration of both surfactant and antenatal corticosteroids increased between the two periods, only 28 percent of the infants born in the later period whose records were reviewed were born to women who had received corticosteroids. Of all infants who received

surfactant in 1991 through 1992, only 26 percent were born to women who received corticosteroids.

Comparison of the mortality rates in 1991 through 1992 for infants who received surfactant and those who did not suggested that the use of surfactant was associated with higher mortality (relative risk, 1.4; 95 percent confidence interval, 1.0 to 2.0; P=0.04). However, the infants given surfactant had lower birth weights and lower gestational ages than infants who did not receive surfactant. Thus, the administration of surfactant was associated with more severe clinical presentation. Because RDS was more prevalent among white than among black very-low-birth-weight infants, and because surfactant decreases morbidity and mortality due to RDS, the effects of surfactant were more apparent in white infants, and the changes in overall neonatal mortality that resulted from the use of surfactant differed between blacks and whites.

DISCUSSION

We assessed the effect of surfactant therapy on neonatal mortality in the city and county of St. Louis. As in previous reports from single or multiple neonatal in-

Table 3. Frequency of the Respiratory Distress Syndrome (RDS), Corticosteroid Therapy, and Surfactant Administration.*

RACE	1987-1989				1991-1992				% CHANGE IN MORTALITY	P VALUE†				
	SURFACTANT THERAPY‡		% WITH RDS§	MORTALITY RATE (PER 1000)	SURFACTANT THERAPY‡		% WITH RDS§	MORTALITY RATE (PER 1000)						
	yes	no			yes	no								
	<i>no. of infants</i>				<i>no. of infants</i>									
Black	10	313	52	331	59.6	176.5	149	139	71	251	65.2	156.3	-11	0.50
White	16	216	37	226	71.4	228.5	111	64	74	129	73.5	125.7	-45	0.008
P value¶	—		0.85	<0.001	0.13	0.01	<0.001	0.03	0.37					

*Mortality rates are per 1000 infants with RDS.

†For the comparison between periods.

‡Includes only the infants with RDS.

§Percentage of very-low-birth-weight infants.

¶For the comparison between blacks and whites.

tensive care facilities, we found a decrease in neonatal mortality among very-low-birth-weight infants in association with the increased use of surfactant.^{1-8,25-27} However, this general improvement in neonatal mortality was not uniformly distributed among racial groups. White infants with very low birth weights benefited to a greater extent than did their black counterparts. This differential effect exacerbated the racial disparity in neonatal mortality at the same time that overall neonatal mortality fell.

Although racial differences in surfactant use might occur if referral to tertiary care facilities were heavily stratified according to race, the differences we found were likely to be due to clinically determined differences in the need for surfactant. In a retrospective study such as this one, we could not assess the severity of RDS in a standard manner. However, once RDS, birth weight, gestational age, and sex were accounted for by means of logistic regression, the rates of surfactant administration were similar for the two races. In addition, the rate of administration of surfactant to very-low-birth-weight infants in St. Louis in 1991 through 1992 (when surfactant was given to 38 percent of all such neonates and 56 percent of those with RDS) is similar to the 40 to 56 percent rates of administration of surfactant to very-low-birth-weight infants in two other large studies based in neonatal intensive care units.^{25,26} The reasons for the greater use of antenatal corticosteroid therapy in white than in black women are more difficult to assess. They may include differences in clinical practice, differences in access to or use of prenatal care, differences in access to obstetrical facilities providing care to high-risk women, or differences in the progression of labor at presentation.

Neonatal mortality decreased more among whites than among blacks after surfactant became generally available. Our findings suggest that this occurred because a significantly larger portion of neonatal mortality in whites was associated with RDS and, in particular, occurred in birth-weight categories likely to benefit from surfactant replacement. It thus appears that surfactant-replacement therapy was able to prevent a larger portion of neonatal mortality among white than among black infants. These findings, however, should be interpreted with caution.

Newborns with RDS die for many reasons; differences in the incidence of associated disorders and complications may have an important role in differences in mortality. Interventions that target RDS may also unmask biologic differences between black and white newborns in conditions that are not responsive to surfactant.

Use of surfactant increased over the study period; changes also occurred in obstetrical practices and neonatal intensive care, including the increased use of antenatal corticosteroid therapy, a trend that was more pronounced in the care of white women than in that of black women. It is therefore difficult to disentangle the relative contributions of surfactant replacement and cor-

ticosteroid therapy to the observed changes in neonatal mortality. Antenatal corticosteroid therapy can affect the incidence and severity of RDS.^{22,28,29} However, the rate of RDS did not change between the two study periods. Moreover, though corticosteroid use rose, only 28 percent of the infants born in the later period whose records were reviewed had mothers who received corticosteroids, and only 26 percent of the neonates who received surfactant had mothers who received corticosteroids.

Our findings serve as a useful reminder that the introduction of new, efficacious therapies may not be associated with greater social equity in health-related outcomes. When a treatment has demonstrated efficacy, differences in the distribution of the problem for which the intervention was developed, as well as possible differences in access to care, can exacerbate preexisting disparities in morbidity or mortality. Although continued improvement in the care provided to all critically ill newborns is essential, the achievement of similar survival rates for black and white infants will depend on more fundamental strategies to prevent prematurity and low birth weight and to reduce the extent of socioeconomic inequality in the United States.

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