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Change in practice after the Surfactant, Positive Pressure and Oxygenation Randomised Trial

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Abstract

Objective—To test the hypothesis that the proportion of endotracheal intubation (ETI) in the delivery room (DR) decreased in Neonatal Research Network (NRN) centres after the National Institute of Child Health and Human Development NRN Surfactant, Positive Pressure, and Oxygenation Randomised Trial (SUPPORT).

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Contributors JML: designed the study, drafted the protocol and the initial manuscript, and approved the final manuscript as submitted. LPB: conceptualised and designed the study, edited the protocol and the initial manuscript, revised the manuscript and approved the final manuscript as submitted. He had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. LAW: edited the protocol, conducted the statistical analysis, edited the initial manuscript and approved the final manuscript as submitted. She had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. MGG, MHW, PJS, RH, MJ, NNF, WAC, AD, BJS and RDH: edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Competing interests None.

Patient consent Obtained.

Ethics approval The IRB of each participating centre.

Provenance and peer review Not commissioned; externally peer reviewed.

Design—Retrospective cohort study using the prospective NRN generic database.

Setting—Eleven centres that participated in the SUPPORT trial and remained part of the NRN. Preterm neonates 24^{0/7}–27^{6/7} weeks' gestational age enrolled in the SUPPORT trial were randomised to: (1) DR continuous positive airway pressure or DR ETI with early surfactant administration; and (2) oxygen saturation targets of 85–89% or 91–95%. The prior NRN feasibility trial had assessed the feasibility of randomisation to continuous positive airway pressure versus ETI.

Patients—Infants 24^{0/7}–27^{6/7} weeks' gestational age, excluding infants with syndromes or major malformations and those on comfort care only.

Main outcome measure—Proportion of DR ETI.

Results—The proportion of DR ETI decreased significantly in the group of infants from centres that had not participated in the feasibility trial (91% before vs 75% after SUPPORT, adjusted relative risk 0.86, 95% CI 0.83–0.89, $p < 0.0001$) but not in the group of infants from the other centres, where the proportion of ETI was already lower prior to initiation of the SUPPORT trial (61% before vs 58% after SUPPORT, adjusted relative risk 0.96, 95% CI 0.89 to 1.05, $p = 0.40$).

Conclusion—This study shows that DR ETI changed after SUPPORT only in NRN centres that had not participated in a similar trial.

INTRODUCTION

The Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network (NRN) Surfactant, Positive Pressure, and Oxygenation Randomised Trial (SUPPORT) was a multicentre randomised controlled trial (RCT), in which preterm infants of 24^{0/7} to 27^{6/7} weeks gestational age (GA) were randomised at birth to (1) either continuous positive airway pressure (CPAP) initiated in the delivery room (DR) and protocol-driven limited ventilation begun in the DR, or endotracheal intubation (ETI) with early surfactant administration followed by a conventional ventilation strategy, and (2) one of two oxygen saturation targets.¹² From 2005 through 2009, 1316 infants were enrolled in 20 centres.¹² The results of SUPPORT were released to NRN centres in December 2009.¹² The risk of the primary outcome of the CPAP trial (death or bronchopulmonary dysplasia (BPD) at 36 weeks postmenstrual age) was not significantly different between the CPAP and the ETI groups.¹

The NRN previously conducted another trial in five centres, to determine the feasibility of randomisation to DR CPAP versus DR ETI and the GA range that would be most appropriate for SUPPORT.³

A previous study in one NRN centre that had not participated in the feasibility trial demonstrated that the proportion of DR ETI changed among eligible but non-enrolled neonates of 24^{0/7} to 27^{6/7} weeks and non-eligible neonates of 28^{0/7} to 34^{6/7} weeks during SUPPORT and before release of its results.⁴ Thus, a centre's participation in an unblinded RCT may affect process of care of non-enrolled patients. It is not known whether prior exposure of a centre to a RCT might affect the change in process of care associated with the conduct of an unblinded RCT involving a similar intervention.

The objective of this study was to determine if the proportion of DR ETI (a process of care) decreased after SUPPORT in participating centres. We hypothesised that after SUPPORT there would be a decrease in DR ETI in preterm infants 24^{0/7} to 27^{6/7} weeks GA. We hypothesised that the degree of change in proportion of DR ETI in each centre after SUPPORT would depend on the proportion before the trial. We also hypothesised that the change in DR ETI after SUPPORT would be less at centres that had participated in the feasibility trial than at the other centres.

METHODS

Study design

This was a retrospective birth cohort analysis with before/after design. We extracted data from the National Institute of Child Health and Human Development Generic Database (GDB) (a registry of very low birthweight infants admitted to NRN centres) in one cohort of patients born before SUPPORT and in a second cohort born after release of the results of SUPPORT to NRN centres. The GDB collects detailed maternal pregnancy/delivery data and baseline, treatment and outcome data on infants using standardised protocols and forms. Data are collected to death, discharge or 120 days 'status', whichever comes first, and limited additional data are collected on infants who remain in the hospital at 120 days. We included the 11 centres that participated in SUPPORT and were part of the NRN during the entire study period (2003–2012). Of these centres, three had participated in the feasibility trial.

Study population

The first cohort includes patients born during a period preceding SUPPORT (1 January 2003–31 December 2004). The second cohort includes preterm patients born after release of the results of SUPPORT to NRN centres (1 January 2010–31 December 2012).

Eligibility and exclusion criteria

Criteria were similar to those used in SUPPORT.¹² Specifically, eligible infants were 24^{0/7} to 27^{6/7} weeks GA at birth by best obstetrical estimate, delivered at a NRN centre participating in SUPPORT. Exclusion criteria were: known malformations, and respiratory support (first cohort) or medical therapy (second cohort) withheld or withdrawn at any time prior to death <12 h. The last criterion was different from SUPPORT, where patients were included if a decision had been made to provide full resuscitation.

Baseline variables

Neonatal and maternal characteristics included birth weight, GA, gender, race/ethnicity, prenatal steroid use, mode of delivery, multiple birth, prolonged rupture of membranes, maternal hypertension, diabetes or antibiotic use before delivery.

Outcome variables

The primary outcome variable was a practice variable, DR ETI, which was defined as ETI for ventilation (excluding intubation done for suctioning or to give surfactant and immediately removed).

Secondary outcomes of prime interest included (1) the composite of death or BPD (oxygen use at 36 weeks postmenstrual age, as defined in SUPPORT), (2) the composite of severe retinopathy of prematurity (ROP) (defined as ROP surgery, retinal detachment or treatment with a drug antivascular endothelial growth factor) or death before discharge and (3) death before discharge. The definitions of BPD and ROP for this study were those used in the GDB; however in SUPPORT primary outcomes also included the physiological definition of BPD, and severe ROP was determined using examinations continued until the outcome of SUPPORT was reached or resolution occurred.¹²

Additional outcomes are described in table 3 and in the online supplementary appendix. Outcome variables were selected a priori, except the proportion of babies who were never intubated (see online supplementary appendix).

Statistical analysis

Variables of interest were compared by study group using χ^2 tests for categorical variables, Wilcoxon tests for Apgar scores and skewed continuous variables, and Student t tests for all other continuous variables. Robust Poisson regression models were used for dichotomous outcomes to obtain adjusted relative risks and 95% CIs. General linear models were used for continuous outcomes to obtain differences in adjusted means and 95% CI. All models included an indicator for study group (post-SUPPORT vs pre-SUPPORT), NRN centre, and prespecified prenatal covariates shown to affect outcomes in very preterm infants⁵ (GA, antenatal corticosteroids, gender, singleton vs multiple, birth weight by 100 g increment) as well as additional covariates that were significantly different by study group ($p < 0.10$) in the unadjusted tests, and that preceded the outcome. The models for the primary and secondary outcomes, with the exception of BPD, included additional variables that preceded birth (race/ethnicity, caesarean section, rupture of membranes > 24 h, maternal hypertension, maternal diabetes and NRN centre), but not postnatal variables to which some infants may not have been exposed before the outcome took place. The model for BPD contained the same variables that preceded birth as well as DR ETI, surfactant, fractional inspired oxygen (FiO_2) at 24 h, patent ductus arteriosus ligation, patent ductus arteriosus indomethacin treatment and late onset sepsis.^{6–15} To assess whether the change in proportion of DR ETI varied across the subgroups of infants in centres who did and did not participate in the feasibility trial we used stratified χ^2 tests and also included an indicator for these subgroups and its interaction with the pre-SUPPORT versus post-SUPPORT indicators in the DR ETI model. Since we did not adjust p values for multiple comparisons, all secondary and tertiary analyses should be considered as exploratory. A Spearman correlation was used with aggregate centre data to assess whether the change in proportion of DR ETI from the first cohort to the second cohort was higher in centres with higher proportion of DR ETI during the first period.

Sample size analysis

In 1993–1997 the intubation rate among extremely low birthweight infants in the NRN was 80%. Based on available GDB data when the study was designed, a first 2-year cohort and a second 3-year cohort were expected to yield approximately 2400 neonates each. This sample size was sufficient for detecting a reduction in ETI from 80% to 60% with a type I error less than 5% and a power greater than 99%.

Approvals

The institutional review board of each participating centre has approved the GDB and SUPPORT. The protocol was approved by the NRN GDB and steering committees.

RESULTS

Maternal and neonatal characteristics

The study population included 3849 inborn infants: 1617 infants in the pre-SUPPORT group and 2232 infants in the post-SUPPORT group (figure 1). The baseline maternal and neonatal characteristics of the pre-SUPPORT and post-SUPPORT groups are shown in table 1.

Primary outcome

Using aggregate centre data, figure 2 shows the proportion of infants intubated in the DR during the first and second study periods in all centres in the study. The correlation between the proportion of DR ETI during the first period and the change in proportion of DR ETI from the first period to the second period was not significant (Spearman correlation coefficient -0.44 , $p=0.18$). The three centres with the lowest baseline proportion were those that had participated in the feasibility trial.

In the model for DR ETI the interaction term between the pre-SUPPORT versus the post-SUPPORT indicators and the indicator for the subgroups of centres that did and did not participate in the feasibility trial was statistically significant ($p=0.01$). This indicates that the change in proportion of DR ETI was different in the two subgroups, thus results for DR ETI are presented within subgroup (table 2). The proportion of DR ETI did not decrease significantly after SUPPORT among infants from centres that had participated in the feasibility trial but decreased significantly among infants from the other centres.

Other outcomes

The adjusted risks of BPD or death, severe ROP or death, severe ROP, and death or mechanical ventilation at day 7 of life were significantly lower in the post-SUPPORT group (table 3). Several processes of care and outcomes changed after SUPPORT (see online supplementary appendix). The proportion of babies who were never intubated increased from 5.6% before SUPPORT to 11.4% after SUPPORT ($p<0.001$).

DISCUSSION

Among infants 24^{0/7} weeks to 27^{6/7} weeks GA born in 11 centres participating in SUPPORT, the proportion of infants with DR ETI significantly decreased after SUPPORT

at centres that had not participated in the feasibility trial, but not at the three centres that had participated in the feasibility trial, and thus had experience with unblinded randomisation to CPAP versus ETI in the DR. In one of these three centres, the proportion of ETI had already decreased in 2000, after prospective introduction of routine, early, bubble nasal CPAP.¹⁶

The strengths of this study include the large sample size; the use of a prospective data base of inborn patients; the use of multivariate analysis; inclusion and exclusion criteria that were similar to those in SUPPORT; inclusion of centres with or without prior participation in a similar trial; and inclusion of centres that remained in the NRN, thereby limiting bias due to large interinstitutional differences.

Limitations of this study include the observational before/after study design; the high percentage of exclusions; lack of information on DR CPAP, oxygen saturation and individual decisions about DR ETI; and lack of information on policies and practice guidelines in NRN centres. We decided against conducting a survey of clinical practices because information in queries is usually obtained from a single individual and may not be reflective of all practitioners at individual sites. The study lacked serial data and data from centres that did not participate in SUPPORT, thereby preventing analysis of secular trends and of the exact time when DR ETI changed in each centre. Nevertheless, in another study the proportion of DR ETI in one NRN centre decreased in non-enrolled patients during SUPPORT and before its publication, in the absence of any changes in DR policy or practice guidelines.⁴ In that centre, DR ETI decreased by 22% during/after SUPPORT. In contrast, DR ETI decreased by only 1.6% in another large contemporaneous cohort of infants participating in the Vermont Oxford Network.⁴

This study did not address how generalisable the study results might be to other centres. Centres participating in SUPPORT might have developed experience with T-piece connectors and with tight oxygen monitoring during SUPPORT. Further studies are needed to investigate how participating in a RCT might affect individual decisions about process of care. A trial in which centres are randomly allocated to participation in an unblinded RCT would allow to test whether such participation may affect process of care and outcomes in enrolled and non-enrolled patients during and after conducting a RCT.

CONCLUSION

The proportion of a process of care, DR ETI, decreased significantly after SUPPORT at centres that had not previously participated in a similar trial but not at other centres. This study suggests that participation of a centre in randomised trials may affect process of care of non-enrolled patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Appendix

Collaborators Data collected at participating sites of the NICHD Neonatal Research Network (NRN) were transmitted to RTI International, the data coordinating centre (DCC) for the network, which stored, managed and analysed the data for this study. One behalf of the NRN, AD (DCC Principal Investigator), LAW and MGG (DCC Statisticians) had full access to all of the data in the study, and with the NRN Center Principal Investigators, take responsibility for the integrity of the data and accuracy of the data analysis. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. We are indebted to our medical and nursing colleagues and the infants and their parents who agreed to take part in this study. The eleven NRN centres that remained in the NICHD NRN during the duration of this study included: Brown University; Case Western Reserve University; Cincinnati Children's Hospital Medical Center; Duke University; Emory University; Indiana University; Stanford University; University of Alabama at Birmingham; University of Texas Health Science Center at Houston; University of Texas Southwestern Medical Center; Wayne State University. Preliminary data were presented as a poster. JML, LPB, LAW, on behalf of the NICHD NRN. Changes in therapy and outcomes associated with the SUPPORT Trial. Poster presentation at the Paediatric Academy Society Meeting, Washington DC, May 5, 2013. E-PAS2013:2924.474.

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What is already known on this topic

A centre's participation in an unblinded randomised trial may affect the process of care of non-enrolled patients during the trial and before the release of its results.

What this study adds

- ▶ The proportion of delivery room intubations (a process of care) decreased after the SUPPORT trial at centres that had not participated previously in a related trial, but not at other centres.
- ▶ This study provides additional evidence suggesting that participation of a centre in unblinded randomised trials may affect the process of care of non-enrolled patients.

Figure 1.

Flow diagram representing all infants in the Generic Database during the two study periods and those included in the study.

Figure 2.

Per cent delivery room intubations in pre/post-SUPPORT periods for the eleven Neonatal Research Network (NRN) centres included in this study.

Table 1

Maternal and neonatal characteristics*

Characteristic	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p Value [†]
Birth weight (grams)	825 (191)	818 (194)	0.32
GA (weeks)	25.7 (1.1)	25.7 (1.1)	0.93
Male	858/1617 (53.1)	1126/2232 (50.5)	0.11
Race/ethnicity:			
Non-Hispanic black	727/1617 (45.0)	965/2192 (44.0)	0.02
Non-Hispanic white	603/1617 (37.3)	808/2192 (36.9)	
Hispanic	241/1617 (14.9)	314/2192 (14.3)	
Other	46/1617 (2.8)	105/2192 (4.8)	
Antenatal steroids:			
Betamethasone [‡]	953/1614 (59.1)	1980/2229 (88.8)	<0.0001
Dexamethasone	383/1614 (23.7)	18/2229 (0.8)	
None	278/1614 (17.2)	231/2229 (10.4)	
Multiple birth	370/1617 (22.9)	540/2228 (24.2)	0.33
Mode of delivery: caesarean section	1004/1617 (62.1)	1476/2228 (66.3)	0.008
Prolonged rupture of membranes: (>24 h)	436/1586 (27.5)	520/2161 (24.1)	0.017
Maternal hypertension	322/1617 (19.9)	610/2230 (27.4)	<0.0001
Maternal diabetes	42/1617 (2.6)	120/2231 (5.4)	<0.0001
Maternal antibiotics	1198/1615 (74.2)	1618/2228 (72.6)	0.28

GA, gestational age.

* Presented as mean (SD) for continuous variables, and n (%) for categorical variables.

[†] The p values shown are from Student t tests for continuous variables and χ^2 tests for categorical variables.[‡] Includes 24 infants whose mothers received a combination of betamethasone and dexamethasone.

Table 2

Primary outcome

Outcome intubated in delivery room [*]	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p Value [†]	Adjusted RR [‡] (95% CI)	Adjusted p value [§]
Subjects from centres in feasibility trial	326/532 (61%)	454/789 (58%)	0.18	0.96 (0.89–1.05)	0.40
Subjects from centres not in feasibility trial	987/1085 (91%)	1085/1443 (75%)	<0.0001	0.86 (0.83–0.89)	<0.0001

^{*} Results are shown for groups defined by combining subjects from centres that had or had not participated in the feasibility trial.

[†] Unadjusted results presented as n/N (%), p value from χ^2 tests.

[‡] Adjusted RRs (post-SUPPORT vs pre-SUPPORT) from robust Poisson model taking into account gestational age, birth weight (by 100 g increment), antenatal corticosteroids, gender, singleton vs multiple, race/ethnicity, caesarean section, rupture of membranes >24 h, maternal hypertension, maternal diabetes, and Neonatal Research Network centre.

[§] Adjusted p values from robust Poisson model.

CI, confidence interval; RR, relative risk; SUPPORT, Surfactant, Positive Pressure, and Oxygenation Randomised Trial.

Table 3

Secondary outcomes^{*}

Outcome	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p Value [†]	Difference in means [‡] (95% CI)	Adjusted RR [‡] (95% CI)	Adjusted p value [‡]
BPD or death at 36 weeks	970/1617 (60.0)	1199/2213 (54.2)	0.0003	–	0.94 (0.89 to 0.99)	0.03
Severe ROP or death	515/1581 (32.6)	559/2165 (25.8)	<0.0001	–	0.85 (0.77 to 0.95)	0.003
Death before discharge	358/1614 (22.2)	393/2196 (17.9)	0.001	–	0.93 (0.81 to 1.1)	0.26
BPD (36 weeks)	664/1311 (50.7)	855/1869 (45.8)	0.0064	–	1.02 (0.95 to 1.1)	0.55
Severe ROP [§]	174/1294 (13.5)	181/1875 (9.7)	0.0009	–	0.66 (0.53 to 0.82)	0.0002
Death by 36 weeks	306/1617 (18.9)	344/2222 (15.5)	0.0050	–	0.96 (0.83 to 1.1)	0.59
Death or mechanical ventilation on day 7	741/1613 (45.9)	875/2211 (39.6)	<0.0001	–	0.90 (0.83 to 0.97)	0.004
Days on ventilator (survivors) [¶]	22.3 (24.4), 13	17.8 (21.3), 9.0	<0.0001	–4.2 (–5.7 to –2.7)		<0.0001

^{*} Presented as mean (SD), median for days on ventilator and n (%) for categorical variables.

[†] Unadjusted p values from χ^2 tests, or Wilcoxon tests, as appropriate.

[‡] Adjusted values (Post-SUPPORT vs Pre-SUPPORT) from robust Poisson models (categorical variables) or general linear models (continuous variables). All models include gestational age, birth weight (by 100 g increment), antenatal corticosteroids, gender, singleton versus multiple, race/ethnicity, caesarean section, rupture of membranes >24 h, maternal hypertension, maternal diabetes and NRN centre. The model for BPD also includes intubation in the DR, surfactant, FiO₂ at 24 h, PDA ligation, PDA indomethacin treatment and late onset sepsis.

[§] For infants who had a ROP exam with complete information.

[¶] Survivors to discharge, transfer or 120 days, whichever came first, maximum is 120 days.

BPD, bronchopulmonary dysplasia; CI, confidence interval; DR, delivery room; FiO₂, fractional inspired oxygen; NRN, Neonatal Research Network; PDA, patent ductus arteriosus; ROP, retinopathy of prematurity; RR, relative risk; SUPPORT, Surfactant, Positive Pressure, and Oxygenation Randomised Trial.