Noninvasive Respiratory Support or Intubation during Stabilization after Birth and Neonatal and Neurodevelopmental Outcomes in Infants Born Preterm at 23-25 Weeks of Gestation

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Objective To examine the association between noninvasive respiratory support (NRS) or tracheal intubation (TI) during stabilization in infants born at 23-25 weeks of gestation and severe brain injury (sBI) or death, and significant neurodevelopmental impairment (sNDI).

Study design A retrospective cohort study of infants born at $23^{\circ/7}$-$25^{6/7}$ weeks of gestation in Canada. We compared infants successfully managed with NRS or TI during 30 minutes after birth. The primary outcomes were sBI or death before discharge, and sNDI among survivors with follow-up data at 18-24 months corrected age. The associations between exposures and outcomes were assessed using logistic regression models, and propensity score-matched analyses.

Results The mean (SD) of gestational age and birth weight were 24.6 (0.6), 24.3 (0.7) weeks [$P < .01$], and 757 (173), 705 (130) grams [$P < .01$] in the NRS, and tracheal intubation (TI) groups, respectively, and 77% of infants in the NRS group were intubated by 7 days of age. sBI or death occurred in 25% (283/1118), and 36% (722/2012) of infants in the NRS and TI groups, respectively (aOR and 95% CI 0.74 [0.60, 0.91]). Among survivors with follow-up data, sNDI occurred in 17% (96/551), and 23% (218/937) of infants in the NRS and TI groups, respectively (aOR [95% CI] 0.77 [0.60, 0.99]). In the propensity score-matched analyses (NRS vs TI), results were consistent for sBI or death (OR [95% CI] 0.72 [0.60, 0.86]), but not for sNDI (OR [95% CI] 0.78 [0.58, 1.05]).

Conclusions Infants born at 23-25 weeks who were successfully managed with NRS, compared with TI, in the first 30 minutes after birth had lower odds of sBI or death before discharge, but had no significant differences in neurodevelopmental outcomes among survivors. *(J Pediatr 2025;276:114270)*.

The use of noninvasive respiratory support (NRS), particularly nasal continuous positive airway pressure (CPAP) in the delivery room instead of elective tracheal intubation (TI) and mechanical ventilation, has emerged as a gentler approach to care for preterm infants in the last 2 decades and is associated with reduced death or bronchopulmonary dysplasia (BPD).[1-3] However, many preterm infants initially managed with non-invasive techniques may ultimately be intubated and placed on mechanical ventilation.[4] Infants born at <26 weeks of gestation frequently require earlier intubation[1] and represent a uniquely high-risk group that has seen significant increases in survival over the last decades.[5,6]

Studies from both Canada and the USA showed increasing use of NRS in preterm infants.[7,8] Over a similar timeframe, survival and neurodevelopmental outcomes among extremely preterm infants have improved.[9,10] The association between early use of NRS and neurodevelopmental outcomes in preterm infants <26 weeks of gestation remains uncertain. In this study, we aimed to investigate

BPD	Bronchopulmonary dysplasia	NICU	Neonatal intensive care unit
CA	Corrected age	NRS	Noninvasive respiratory support
CNN	Canadian Neonatal Network	PMA	Postmenstrual age
CPAP	Continuous positive airway pressure	sBI	Severe brain injury
		SGA	Small for gestational age
GMFCS	Gross Motor Function Classification Scale	sNDI	Significant neurodevelopmental impairment
NDI	Neurodevelopmental impairment	TI	Tracheal intubation

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the association between the use of NRS or intubation during initial stabilization of preterm infants born at 23-25 weeks of gestation and death or severe brain injury (sBI) during neonatal intensive care unit (NICU) admission, and neurodevelopmental impairment (NDI) among survivors at 18-24 months corrected age (CA). We hypothesized that successful use of NRS during initial stabilization after birth would be associated with lower odds of sBI or death in the NICU and lower odds of NDI at 18-24 months CA among survivors.

Methods

Study Sample

This was a retrospective cohort study of preterm infants born at $23^{\circ/7}$ to $25^{6/7}$ weeks of gestation and admitted to the Canadian Neonatal Network (CNN) NICUs between January 2010 and December 2019. We excluded infants who had major congenital anomalies or chromosomal abnormalities, received palliative care at birth, and outborn infants. To reduce the risk of confounding by indication, that is, sicker infants at risk of death or brain injury would have been intubated at birth, we excluded infants who received extensive resuscitation at birth (chest compressions ≥30 seconds or receipt of intravenous or endotracheal epinephrine), and infants with Apgar scores ≤1 at 1 minute or ≤3 at 5 minutes.[11,12]

Definition of Exposure and Control Groups

The exposure group included infants who were successfully managed with NRS for at least 30 minutes after birth, regardless of later need for intubation (NRS group), and the control group included infants who had TI within 30 minutes after birth (TI group). At our network level, the immediate stabilization period is defined as the first 30 minutes after birth for standardization of data collection process.

Variable and Outcome Definitions

The CNN and Canadian Neonatal Follow Up Network data were collected by trained abstractors at each center according to standard protocol,[13] with high reliability and internal consistency.[14] Approval for data collection was granted at each center by local research ethics boards. This project was approved by the CNN and Canadian Neonatal Follow Up Network Executive Committees and the University of Calgary Conjoint Health Research Ethics Board (REB22-1534).

We reported infants' demographics, as well as pregnancy and birth information. Maternal diabetes and hypertension included gestational or pre-existing disease. Chorioamnionitis included clinical or histopathologic diagnosis. Small for gestational age (SGA) was defined as birth weight <10th percentile on the Population-Based Canadian Reference for Birth Weight for Gestational Age.[15] Score of Neonatal Acute Physiology version 2 (SNAP II) more than 20 was used to compare severity of illness.[16-18] Mechanical ventilation was defined as positive pressure ventilation through an endotracheal tube including conventional ventilation, and high-frequency ventilation. First successful extubation was defined as extubation from mechanical ventilation without reintubation for 7 days.[8] NRS was defined as positive pressure respiratory support without an endotracheal tube, and included CPAP, nasal intermittent positive pressure ventilation, and high flow nasal cannula of ≥2 L per minute. Systemic corticosteroids included receipt of hydrocortisone or dexamethasone.

The primary outcomes were sBI or death in NICU before discharge, and significant neurodevelopmental impairment (sNDI) at 18-24 months CA among a sub-cohort of infants who survived and had follow-up data. sBI was defined as intraventricular hemorrhage grade 3 or 4, or periventricular leukomalacia.[19] sNDI was defined as any of the following: a Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III) score <70 in any domain, cerebral palsy with a Gross Motor Function Classification Scale (GMFCS) ≥3, bilateral blindness, or hearing loss requiring amplification.

NICU secondary outcomes included late onset sepsis defined as positive blood or CSF culture after 2 days of age, necrotizing enterocolitis defined as Bell's stage 2 or higher,[20] BPD defined as any supplemental oxygen or positive pressure respiratory support at 36 weeks postmenstrual age (PMA) or at the time of transfer to a lower level of care,[21] and severe retinopathy of prematurity defined as stage 3 or greater in either eye or treatment with laser or injections of anti–vascular endothelial growth factor.[22]

Follow-up secondary outcomes included the presence of NDI defined as either a Bayley-III score <85 in any domain, a Bayley-III Adaptive Behavior score <85 among children who could not be tested using standard Bayley-III, any cerebral palsy, sensorineural or mixed hearing loss, or unilateral or bilateral visual impairment. The use of aids at home at 18-24 months CA was assessed as a secondary outcome; aids included the use of an apnea monitor, pulse oximeter, supplemental oxygen, CPAP, home ventilator, gavage feeding, gastrostomy or jejunostomy, ileostomy or colostomy, tracheostomy, adapted wheelchair or stroller, braces, splints, orthoses, or a walker.

Statistical Analysis

We compared the entire cohort for the NICU outcomes and the follow-up sub-cohort for neurodevelopmental outcomes. Descriptive analyses (means [SDs], medians [IQRs], and frequency distributions) were used to describe baseline characteristics between groups. The Student t-test (for variables with normal distribution) or Wilcoxon Rank Sum test (for variables with non-normal distribution) were used to compare continuous variables as appropriate, and Chi square test was used to compare categorical variables. Multivariable analyses were conducted to compare the primary outcomes between groups using 3 models to account for potential confounders. In model 1, we adjusted for prenatal covariates that occurred before the decision or need for intubation which included maternal receipt of antenatal steroids, cesarean birth, gestational age (continuous), SGA status, sex, year of birth, and clustering within center using Generalized Estimating Equations. For models 2 and 3, we used propensity score analysis. A propensity score was estimated using a

multivariable logistic regression model with maternal receipt of antenatal steroids, cesarean birth, gestational age (continuous), SGA status, and sex. Confounders were selected based on likelihood of being associated with exposure and related to outcome.[23,24] For the model 2, we adjusted for the propensity score (used as a covariate) and for center (fixed effect). In model 3, we conducted a propensity score matching analysis. Matching was performed using the SAS macro match.sas and was based on a caliper width of 0.1-fold the SD of the logit-transformed propensity scores.[25] We did not include SNAP II score in the model given that it is calculated based on variables measured in the first 12 hours of admission, and those variables can be affected by the exposures, TI or NRS.[16] In addition, including SNAP II in the models may introduce overadjustment bias.[26] The association of the outcome with TI vs NRS groups in the matched samples was examined using logistic regression analyses using GEE with an unstructured correlation. Analysis for the NICU cohort and the follow-up sub-cohort were conducted separately to maximize the number of matched pairs in each cohort. aORs with their 95% CIs were estimated. A sensitivity analysis was conducted in the subgroup of infants with 5-minute Apgar scores >5 to exclude sicker infants who were more likely to be intubated within the first 30 minutes of age. In addition, a subgroup analysis was carried out to compare the primary outcomes between the groups in infants born at 23-24 weeks and 25 weeks of gestation. Data management and statistical analyses were performed using SAS, version 9.4 (SAS Institute Inc).

Results

There were 5746 infants admitted during our cohort timeframe. Figure 1 shows that 3130 infants were included in the NICU cohort (2012 in the TI group and 1118 in the NRS group), and 1488 in the follow-up sub-cohort (937 in the TI group and 551 in the NRS group). Figure 2 shows that the proportion of infants who were successfully managed with NRS increased over the years in each gestational age week.

NICU Cohort

Infants in the NRS group had significantly higher gestational age and birth weight; mean (SD) of gestational age and birth weight were 24.6 (0.6) weeks and 757 (173) grams, and 24.3 (0.7) weeks and 705 (130) grams, in the NRS and TI groups

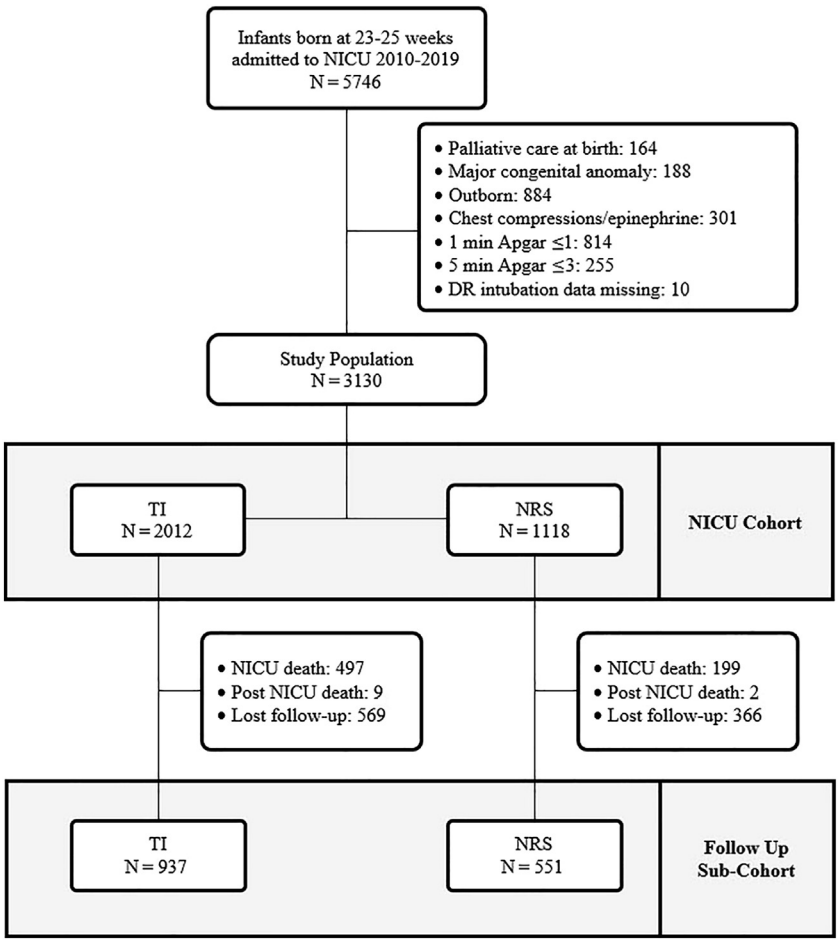

Figure 1. Patient flow diagram. *DR*, delivery room.

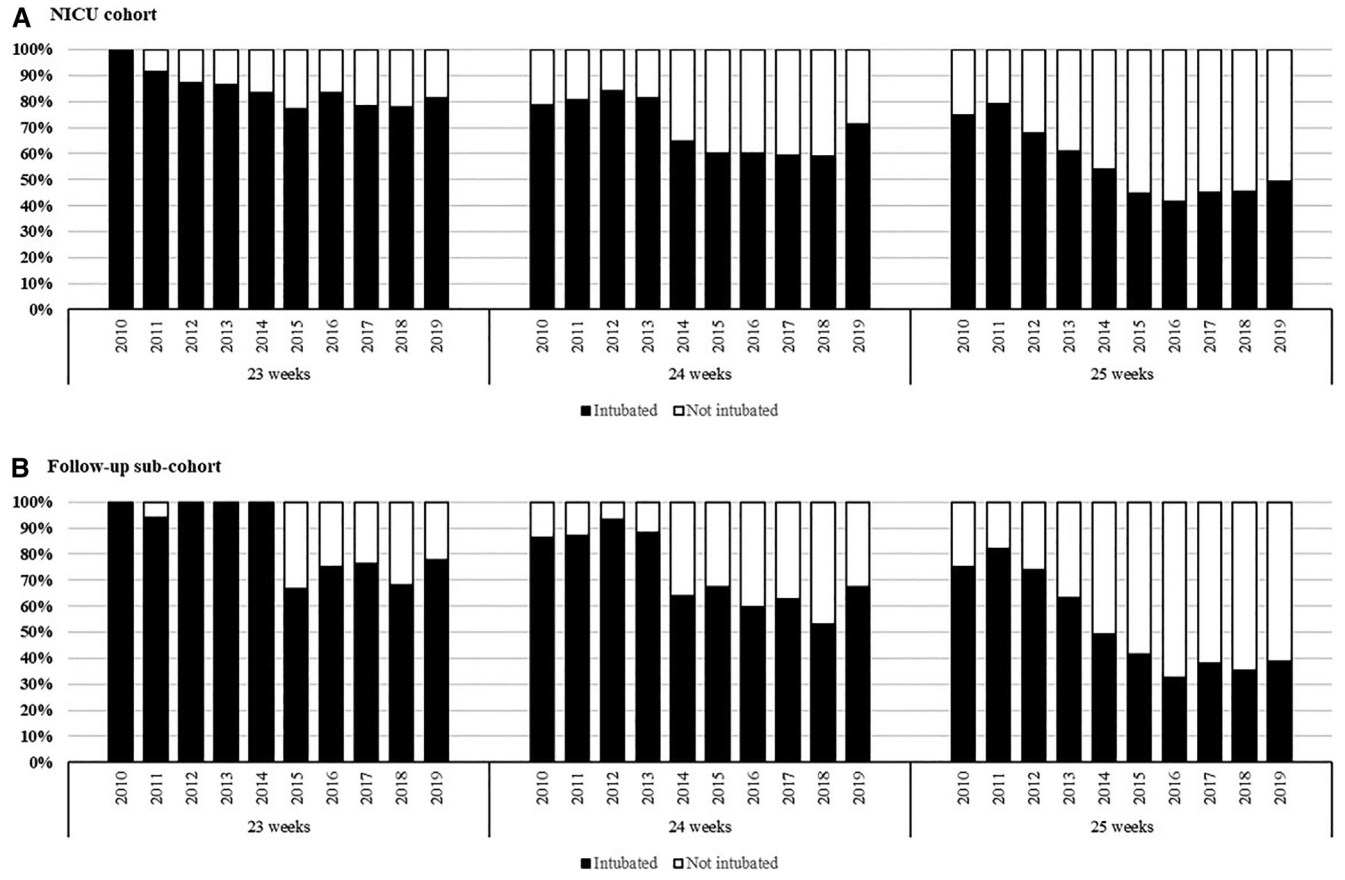

Figure 2. Intubation during first 30 min of birth in the study cohort. DR, delivery room.

respectively. The NRS group had significantly higher rates of caesarean birth, antenatal steroids, magnesium sulphate, and deferred cord clamping, and they had lower SNAP-II scores (Table I). The primary outcome of death or sBI was significantly less frequent in the NRS group (Table II). All secondary outcomes were significantly less frequent in the NRS group, except for NEC and spontaneous intestinal perforation. Approximately 77% of infants in the NRS group were intubated within 7 days of birth. Infants in the NRS group had significantly shorter mechanical ventilation days with no significant difference in subsequent NRS or oxygen days between the groups.

Follow-up Sub-cohort

Among infants who were discharged alive from the NICU, 2 died from the NRS group and 9 from the TI group prior to 18-24 months CA. Follow up rate among survivors was 60.1 and 62.2% in the NRS and TI groups, respectively. Table III shows a comparison between infants seen vs missed at follow-up. Infants assessed at 18-24 months CA had significantly lower birth weight, lower sBI and BPD rates, and were more likely to have been exposed to antenatal steroids and undergone surgical ligation of the patent ductus arteriosus. The baseline characteristics and NICU outcomes in NRS and TI groups among those seen at follow-up are presented in Tables II and III. The rate of sNDI was significantly lower in the NRS group. Rates of Bayley-III Cognitive Composite Score <85 and the use of aids at home were lower in the NRS group. Other secondary outcomes were not significantly different (Table IV).

Multivariable Analysis Using Regression Models and Propensity Score Matching

The NRS group had significantly lower aORs for the primary outcome of sBI or death in NICU before discharge in the 2 regression models, which is primarily attributable to the lower odds of sBI. There were 1108 infants in each group matched for propensity score analysis. The NRS group had a lower OR of sBI or death (Table V). The NRS group had significantly lower aORs for the primary outcome of sNDI in model 1 but not in model 2. There were 546 infants in each group of the follow-up sub-cohort matched for propensity score analysis. There was no statistically significant difference in the OR between the groups for the primary outcome of sNDI or any secondary outcome (Table V). In the sensitivity analyses that included infants with 5-minute Apgar score >5, the NRS group had lower aORs of the primary outcome of sBI or death in models 1 and 2, but not in the propensity score

Table I. Baseline characteristics

Maternal and neonatal variables	NICU cohort			Follow-up sub-cohort		
	TI (n = 2012)	NRS (n = 1118)	*P* value	TI (n = 937)	NRS (n = 551)	*P* value
Gestational age	24.3 (0.7)	24.6 (0.6)	<.01	24.4 (0.7)	24.6 (0.6)	<.01
23 wks	351 (17.5)	71 (6.3)	<.01	116 (12.4)	25 (4.5)	<.01
24 wks	751 (37.3)	334 (29.9)		361 (38.5)	146 (26.5)	
25 wks	910 (45.2)	713 (63.8)		460 (49.1)	380 (69.0)	
Birth weight	705 (130)	757 (173)	<.01	718 (126)	759 (130)	<.01
<500 g	112 (5.6)	30 (2.7)	<.01	39 (4.2)	8 (1.5)	<.01
500-749 g	1207 (60.0)	535 (47.9)		545 (58.2)	262 (47.6)	
≥750 g	693 (34.4)	553 (49.5)		353 (37.7)	281 (51.0)	
SGA (<10th centile)	157 (7.8)	67 (6.0)	.06	54 (5.8)	27 (4.9)	.47
Female sex	958 (47.7)	568 (50.8)	.09	477 (51.0)	291 (52.8)	.50
Multiple pregnancy	550 (27.3)	284 (25.4)	.24	243 (25.9)	135 (24.5)	.54
Antenatal steroids (complete)	1418 (71.1)	888 (80.1)	<.01	717 (76.9)	457 (83.6)	<.01
Antenatal steroids (any)	1856 (93.1)	1066 (96.1)	<.01	889 (95.3)	535 (97.8)	.01
Maternal diabetes	126 (6.5)	81 (7.8)	.17	66 (7.2)	29 (5.8)	.29
Maternal hypertension	207 (10.4)	139 (12.6)	.06	96 (10.3)	60 (11.0)	.68
Caesarean birth	1026 (51.1)	613 (55.0)	.03	499 (53.3)	308 (56.0)	.32
Rupture of membranes >24 hr	551 (28.0)	292 (26.9)	.50	280 (30.3)	140 (26.0)	.08
Magnesium sulphate	1154 (58.5)	733 (68.1)	<.01	481 (52.4)	354 (65.9)	<.01
DCC ≥30 sec	503 (25.3)	404 (36.7)	<.01	197 (21.3)	206 (37.7)	<.01
Apgar Score at 5 min	7 (6-8)	8 (6-8)	<.01	7 (6-8)	8 (7-9)	<.01
Admission temperature	36.7 (0.8)	36.6 (0.8)	.05	36.7 (0.7)	36.6 (0.9)	.01
SNAP II >20	980 (51.1)	378 (36.8)	<.01	406 (45.0)	168 (33.4)	<.01

DCC, deferred cord clamping; *SGA*, small for gestational age; *SNAP II*, Score of Neonatal Acute Physiology version 2.
Results are presented as mean (SD), median (IQR), or n (%).

matching (Table V). There was no statistically significant difference in sNDI or any other follow up outcome between the NRS and TI groups in follow-up sub-cohort (Table V).

Sub-group Analysis

Table VI shows the primary outcomes for NRS and TI groups in the subgroup analysis. In infants born at 23-24 weeks, the aOR of the primary outcome of sBI or death was significantly lower in the NRS group in model 2, but not in model 1 or the propensity score matched analysis. Interestingly, the aOR of sBI was significantly lower in the NRS group in all models. There was no statistically significant difference between the groups in the primary outcome of sNDI. In infants born at 25 weeks, the aOR of the primary outcomes of sBI or death, and sNDI were significantly lower in the NRS group in all models. Table VII shows the primary outcomes for NRS and TI groups at each gestational age week. All outcomes occurred in lower frequency in the NRS group but were not statistically significant. Adjustment for confounders was not performed given the small numbers at 23 weeks' gestation sub-group

Discussion

In this retrospective Canadian national cohort study, we found that successful use of NRS, compared with tracheal intubation, in the first 30 minutes after birth in infants born at 23-25 weeks of gestation was associated with significantly lower odds of sBI or death in the NICU before discharge; however, the difference in sNDI at 18-24 months CA among survivors with follow-up data was not statistically significant.

Some studies demonstrated that using NRS during the initial stabilization is associated with favorable outcomes. A 2013 meta-analysis of 4 randomized controlled trials showed that nasal CPAP in the delivery room, compared with intubation, in preterm infants <30 weeks of gestation was associated with increased survival without BPD at 36 weeks PMA with a number needed to benefit of 25.[1] However, none of the trials included infants born at 23 weeks, one trial included infants born at 24 weeks, and the authors did not present a subgroup analysis for infants born at <26 weeks of gestation. In a retrospective study, Debay et al showed that intubation in the delivery room was associated with higher odds of death or sBI compared with no intubation or intubation in the NICU among infants born at 23-32 weeks GA[27] That study included only 191 infants born at <29 weeks without a subgroup analysis for infants <26 weeks. In a retrospective study comparing NRS vs intubation in the first 10 minutes after birth in 230 infants born at 22-23 weeks of gestation, Shukla et al reported that NRS was associated with higher aOR of severe IVH or death by 36 weeks PMA.[28] This is contrary to our findings of lower odds of sBI or death in the NRS group after adjustment for potential confounders. In our subgroup analysis of infants born at 23-24 weeks which included 1507 infants, the aOR of sBI or death was lower in the NRS group but was not statistically significant. This discrepancy might be explained by the difference in populations considered by the 2 studies. Shukla et al included infants of younger gestational age and lower birth weight and did not exclude patients who likely required intubation for indications such as extensive resuscitation or low Apgar scores. They defined successful NRS at

Table II. NICU outcomes and management

Outcomes and management variables	NICU cohort			Follow-up sub-cohort		
	TI (n = 2012)	NRS (n = 1118)	*P* value	TI (n = 937)	NRS (n = 551)	*P* value
sBI or death in NICU	722 (35.9)	283 (25.3)	<.01	-	-	-
Death in NICU	497 (24.7)	199 (17.8)	<.01	-	-	-
sBI	396 (20.6)	146 (13.5)	<.01	129 (13.8)	42 (7.7)	<.01
PDA, medical treatment	1022 (50.8)	510 (45.6)	.01	523 (55.9)	275 (49.9)	.03
PDA, surgical treatment	300 (14.9)	133 (11.9)	.02	193 (20.6)	80 (14.5)	<.01
Late onset sepsis	743 (36.9)	359 (32.1)	.01	361 (38.5)	179 (32.5)	.02
NEC	226 (11.3)	120 (10.7)	.66	95 (10.2)	49 (8.9)	.43
Surgical NEC	93 (4.6)	50 (4.5)	.84	40 (4.3)	17 (3.1)	.25
SIP	84 (4.2)	51 (4.6)	.61	31 (3.3)	22 (4.0)	.48
Severe ROP	506 (25.2)	235 (21.0)	.01	300 (32.2)	124 (22.5)	<.01
BPD	1158 (75.2)	620 (66.5)	<.01	671 (71.6)	366 (66.4)	.04
Timing of first intubation:						
PND 0-1	-	687 (61.5)	-	-	332 (60.2)	-
PND 2-7	-	171 (15.3)	-	-	89 (16.2)	-
PND 8-14	-	68 (6.1)	-	-	36 (6.5)	-
PND >14	-	56 (5.0)	-	-	30 (5.4)	-
Never intubated/ventilated	-	136 (12.2)	-	-	64 (11.6)	-
Days of mechanical ventilation	25 (8-42)	20 (6-37)	<.01	30 (14-44)	21 (8-36)	<.01
Days of NRS	47 (33-62)	47 (33-61)	.59	47 (36-62)	50 (38-64)	.02
Days of oxygen therapy	65 (25-102)	60 (27-98)	.38	79 (54-112)	72 (44-104)	<.01
Age at first successful extubation	10 (2-31)	24 (9-42)	.02	13 (2-42)	26 (12-44)	.10
Pneumothorax	172 (8.6)	65 (5.8)	.01	59 (6.3)	16 (2.9)	<.01
Systemic corticosteroids for BPD	595 (29.6)	349 (31.2)	.34	353 (37.7)	208 (37.8)	.98
Any systemic corticosteroids	1026 (51.0)	534 (47.8)	.08	499 (53.3)	277 (50.3)	.27
Discharge home or transfer to level 2 center on oxygen	395 (19.6)	157 (14.0)	<.01	280 (29.9)	97 (17.6)	<.01

BPD, bronchopulmonary dysplasia; *IVH*, intraventricular hemorrhage; *NEC*, necrotizing enterocolitis; *PDA*, patent ductus arteriosus; *PND*, postnatal day (day of birth is PND 0), *ROP*, retinopathy of prematurity; *sBI*, severe brain injury; *SIP*, spontaneous intestinal perforation.
Results are presented as n (%) or median (IQR).

Table III. Comparison between infants seen vs lost to follow-up at 18-24 months corrected age

Patient variables	Seen at follow-up (n = 1488)	Lost to follow-up (n = 935)	*P* value
Gestational age	24.5 (0.7)	24.5 (0.7)	.96
23 weeks	141 (9.5)	95 (10.2)	.75
24 weeks	507 (34.1)	307 (32.8)	
25 weeks	840 (56.5)	533 (57.0)	
Birth weight	733 (129)	751 (178)	.01
<500 g	47 (3.2)	27 (2.9)	.15
500-749 g	807 (54.2)	472 (50.5)	
≥750 g	346 (42.6)	436 (46.6)	
Female sex	768 (51.7)	447 (47.8)	.06
Multiple pregnancy	378 (25.4)	224 (24.0)	.42
Antenatal steroids (complete)	1174 (79.3)	686 (74.2)	<.01
Antenatal steroids (any)	1424 (96.2)	873 (94.4)	.03
SNAP II >20	574 (40.9)	379 (43.3)	.25
sBI	171 (11.6)	134 (14.6)	.03
PDA, medical treatment	798 (53.7)	477 (51.0)	.20
PDA, surgical treatment	273 (18.4)	125 (13.4)	<.01
Late onset sepsis	540 (36.3)	321 (34.3)	.33
BPD	1037 (69.7)	690 (74.0)	.02
NEC	144 (9.7)	79 (8.5)	.31
Surgical NEC	57 (3.8)	32 (3.4)	.60
SIP	53 (3.6)	23 (2.5)	.13
Severe ROP	424 (28.6)	295 (31.6)	.11

BPD, bronchopulmonary dysplasia; *NEC*, necrotizing enterocolitis; *PDA*, patent ductus arteriosus; *ROP*, retinopathy of prematurity; *sBI*, severe brain injury; *SIP*, spontaneous intestinal perforation; *SNAP II*, score for neonatal acute physiology version 2.
Results are presented as mean (SD) or n (%).

10 minutes compared with 30 minutes in our study, possibly resulting in inclusion of sicker infants in the NRS group in Shukla's study. The findings of our study support the hypothesis that successful use of NRS to stabilize "less sick" infants born at 23-25 weeks is feasible and is associated with significantly lower odds of sBI or death, without increase in other morbidities. Although 77% of infants in the NRS group were intubated within 7 days of birth, there might be a benefit

Table IV. Neurodevelopmental outcomes

Outcome variables	TI (n = 937)	NRS (n = 551)	*P* value
Significant NDI	218 (23.3)	96 (17.4)	.01
Any NDI	481 (51.3)	260 (47.2)	.12
Any CP	72 (7.8)	35 (6.4)	.30
CP with GMFCS level ≥ III	31 (3.4)	10 (1.8)	.08
Bayley-III Motor Composite Score <70	68 (8.7)	29 (6.3)	.13
Bayley-III Cognitive Composite Score <70	43 (5.2)	14 (2.9)	.05
Bayley-III Language Composite Score <70	136 (17.3)	63 (13.8)	.10
Bayley-III Motor Composite Score <85	225 (28.7)	112 (24.1)	.08
Bayley-III Cognitive Composite Score <85	176 (21.3)	78 (16.2)	.02
Bayley-III Language Composite Score <85	326 (41.5)	183 (40.0)	.62
Hearing loss requiring hearing aid or cochlear implant	29 (3.2)	10 (1.9)	.13
Sensorineural/mixed hearing loss	69 (7.7)	33 (6.2)	.30
Bilateral visual impairment	17 (2.0)	5 (0.9)	.14
Any visual impairment	18 (2.1)	7 (1.3)	.31
Use of aids at home after discharge	117 (12.5)	40 (7.3)	<.01

GMFCS, gross motor function classification scale; *NDI*, neurodevelopmental impairment.
Results are presented as n (%).

Table V. Multivariable analysis for the study cohort and sensitivity analysis including infants with 5-minute Apgar score >5

	Multivariable analysis				Propensity score matched		
Outcome variables	**TI n (%)**	**NRS n (%)**	**Model 1 aOR (95% CI)**	**Model 2 aOR (95% CI)**	**TI n (%)**	**NRS n (%)**	**OR (95% CI)**
NICU cohort							
Number of infants	2012	1118			1108	1108	
sBI or death in NICU	722 (35.9)	283 (25.3)	0.74 (0.60, 0.91)	0.66 (0.55, 0.79)	353 (31.9)	279 (25.2)	0.72 (0.60, 0.86)
Death	497 (24.7)	199 (17.8)	0.89 (0.71, 1.11)	0.75 (0.61, 0.92)	225 (20.3)	196 (17.7)	0.84 (0.69, 1.03)
sBI	396 (20.6)	146 (13.5)	0.69 (0.53, 0.90)	0.63 (0.50, 0.80)	201 (18.8)	144 (13.4)	0.67 (0.53, 0.84)
Follow-up sub-cohort							
Number of infants	937	551			546	546	
Significant NDI	218 (23.3)	96 (17.4)	0.77 (0.60, 0.99)	0.75 (0.56, 1.01)	116 (21.3)	95 (17.4)	0.78 (0.58, 1.05)
Any NDI	481 (51.3)	260 (47.2)	0.95 (0.76, 1.20)	0.87 (0.68, 1.09)	261 (47.8)	257 (47.1)	0.97 (0.77, 1.22)
Any CP	72 (7.8)	35 (6.4)	0.96 (0.53, 1.75)	1.05 (0.65, 1.68)	31 (5.8)	35 (6.4)	1.12 (0.68, 1.86)
CP with GMFCS level ≥ III	31 (3.4)	10 (1.8)	*	0.71 (0.32, 1.60)	14 (2.6)	10 (1.8)	0.70 (0.31, 1.60)
NICU cohort sensitivity analysis							
Number of infants	1575	1036			1010	1010	
sBI or death in NICU	523 (33.2)	251 (24.2)	0.77 (0.60, 0.99)	0.70 (0.57, 0.85)	277 (27.4)	242 (24.0)	0.83 (0.69, 1.01)
Death	356 (22.6)	172 (16.6)	0.90 (0.72, 1.12)	0.77 (0.61, 0.97)	163 (16.1)	165 (16.3)	1.01 (0.81, 1.27)
sBI	292 (19.3)	134 (13.3)	0.74 (0.53, 1.03)	0.67 (0.52, 0.86)	170 (17.3)	129 (13.1)	0.72 (0.56, 0.92)
Follow-up sub-cohort sensitivity analysis							
Number of infants	757	523			508	508	
Significant NDI	171 (22.6)	90 (17.2)	0.78 (0.57, 1.09)	0.77 (0.55, 1.06)	106 (20.9)	88 (17.3)	0.79 (0.58, 1.09)
Any NDI	384 (50.7)	245 (46.9)	0.94 (0.74, 1.21)	0.85 (0.66, 1.10)	250 (49.2)	238 (46.9)	0.91 (0.71, 1.16)
Any CP	56 (7.6)	33 (6.3)	1.04 (0.58, 1.88)	1.05 (0.63, 1.74)	35 (7.0)	32 (6.3)	0.90 (0.55, 1.46)
CP with GMFCS level ≥ III	24 (3.2)	9 (1.7)		0.72 (0.30, 1.73)	15 (3.0)	9 (1.8)	0.58 (0.26, 1.31)

GMFCS, gross motor function classification scale; *NDI*, neurodevelopmental impairment.
Model 1: adjusted for prenatal covariates that occurred prior to the decision for intubation including maternal receipt of antenatal steroids, cesarean birth, gestational age (continuous), SGA status, sex, year of birth, and clustering within each center. Model 2: adjusted for the propensity score (used as a covariate) and for center (fixed effect). Propensity score included maternal receipt of antenatal steroids, cesarean birth, gestational age (continuous), SGA status, and sex.
*Model did not converge.

of avoiding intubation during the immediate transition after birth in spontaneously breathing infants who can be successfully managed with NRS. Intubation attempts during early stabilization may result in physiological instability with bradycardia and desaturation which can be avoided by stabilizing these infants with NRS and carrying out intubation, if indicated, in a controlled environment in the NICU with premedications. Identifying the appropriate candidates for

Table VI. Subgroup analysis by gestational age week

	Multivariable analysis				Propensity score matched		
Outcome variables	**TI n (%)**	**NRS n (%)**	**Model 1 aOR (95% CI)**	**Model 2 aOR (95% CI)**	**TI n (%)**	**NRS n (%)**	**Or (95% CI)**
NICU cohort (23-24 wks)							
Number of infants	1102	405			400	400	
sBI or Death in NICU	465 (42.2)	139 (34.3)	0.83 (0.62, 1.11)	0.73 (0.56, 0.95)	146 (36.5)	136 (34.0)	0.90 (0.68, 1.18)
Death	343 (31.1)	108 (26.7)	0.99 (0.74, 1.31)	0.84 (0.63, 1.12)	94 (23.5)	105 (26.3)	1.16 (0.85, 1.57)
sBI	251 (24.1)	63 (16.2)	0.66 (0.50, 0.87)	0.62 (0.44, 0.86)	89 (23.3)	62 (16.2)	0.64 (0.45, 0.90)
Follow-up sub-cohort (23-24 weeks)							
Number of infants	477	171			170	170	
Significant NDI	121 (25.4)	35 (20.5)	0.82 (0.57, 1.17)	0.79 (0.49, 1.26)	37 (21.2)	35 (20.6)	0.93 (0.56, 1.56)
Any NDI	270 (56.6)	86 (50.3)	0.82 (0.61, 1.09)	0.73 (0.49, 1.07)	89 (52.4)	86 (50.6)	0.93 (0.63, 1.38)
Any CP	46 (9.9)	13 (7.6)	0.81 (0.42, 1.54)	0.90 (0.43, 1.86)	8 (4.8)	13 (7.7)	1.64 (0.67, 3.98)
CP with GMFCS level ≥ III	21 (4.5)	4 (2.3)	*	0.56 (0.17, 1.91)	5 (3.0)	4 (2.4)	0.78 (0.24, 2.55)
NICU cohort (25 wks)							
Number of infants	910	713			708	708	
sBI or Death in NICU	257 (28.2)	144 (20.2)	0.64 (0.47, 0.88)	0.58 (0.45, 0.75)	183 (25.9)	143 (20.2)	0.73 (0.57, 0.92)
Death	154 (16.9)	91 (12.8)	0.76 (0.55, 1.05)	0.63 (0.46, 0.87)	106 (15.0)	91 (12.9)	0.84 (0.62, 1.13)
sBI	145 (16.5)	83 (11.9)	0.72 (0.48, 1.07)	0.63 (0.46, 0.87)	108 (15.7)	82 (11.9)	0.72 (0.53, 0.97)
Follow-up sub-cohort (25 wks)							
Number of infants	460	380			376	376	
Significant NDI	97 (21.1)	61 (16.1)	0.72 (0.53, 0.97)	0.66 (0.44, 0.98)	81 (21.5)	60 (16.0)	0.69 (0.49, 0.98)
Any NDI	211 (45.9)	174 (45.8)	1.04 (0.77, 1.41)	0.94 (0.70, 1.27)	170 (45.2)	171 (45.5)	1.01 (0.77, 1.34)
Any CP	26 (5.7)	22 (5.8)	*	1.06 (0.54, 2.05)	23 (6.2)	22 (5.9)	0.95 (0.52, 1.72)
CP with GMFCS level ≥ III	10 (2.2)	6 (1.6)	*	0.59 (0.18, 1.97)	8 (2.2)	6 (1.6)	0.74 (0.25, 2.18)

GMFCS, gross motor function classification scale; *NDI*, neurodevelopmental impairment.
Model 1: adjusted for prenatal covariates that occurred prior to the decision for intubation including maternal receipt of antenatal steroids, cesarean birth, gestational age (continuous), SGA status, sex, year of birth, and clustering within each center. Model 2: adjusted for the propensity score (used as a covariate) and for center (fixed effect). Propensity score included maternal receipt of antenatal steroids, cesarean birth, gestational age (continuous), SGA status, and sex.
*Model did not converge.

Table VII. Comparison between included and excluded infants

Patient variables	NICU cohort			Follow-up sub-cohort		
	Included (n = 3130)	Excluded (n = 1380)	*P* value	Included (n = 1488)	Excluded (n = 554)	*P* value
Received NRS, n (%)	1118 (35.7)	156 (11.5)	<.0001	551 (37.0)	63 (11.6)	<.0001
Received TI, n (%)	2012 (64.3)	1206 (88.5)		937 (63.0)	479 (88.4)	
Gestational age, mean (SD)	24.4 (0.7)	24.1 (0.8)	<.0001	24.5 (0.7)	24.3 (0.7)	<.0001
23 weeks, n (%)	422 (13.5)	323 (23.4)	<.0001	141 (9.5)	90 (16.3)	<.0001
24 weeks, n (%)	1085 (34.7)	542 (39.3)		507 (34.1)	213 (38.5)	
25 weeks, n (%)	1623 (51.9)	515 (37.3)		840 (56.5)	251 (45.3)	
Birth weight, mean (SD)	723.87 (148.87)	685.94 (132.05)	<.0001	733.44 (128.93)	709.51 (128.31)	.0002
SGA (<10th centile), n (%)	224 (7.2)	126 (9.2)	.02	81 (5.5)	37 (6.7)	.28
Female sex, n (%)	1526 (48.8)	599 (43.6)	.001	768 (51.7)	248 (45.0)	.008
Multiple pregnancy, n (%)	834 (26.7)	338 (24.5)	.13	378 (25.4)	129 (23.3)	.32
Antenatal steroids (complete), n (%)	2306 (74.3)	837 (61.7)	<.0001	1174 (79.3)	377 (69.6)	<.0001
Antenatal steroids (any), n (%)	2922 (94.2)	1201 (88.5)	<.0001	1424 (96.2)	495 (91.3)	<.0001
Caesarean birth, n (%)	1639 (52.5)	717 (52)	.82	807 (54.3)	326 (59.2)	.0499
Rupture of membranes > 24 hr, n (%)	843 (27.6)	422 (31.5)	.009	420 (28.7)	189 (35.2)	.005
Magnesium sulphate, n (%)	1887 (61.9)	738 (55.6)	<.0001	835 (57.4)	302 (57.1)	.91
DCC ≥30 sec, n (%)	907 (29.4)	240 (17.6)	<.0001	403 (27.4)	100 (18.4)	<.0001
Apgar Score at 5 min, median (IQR)	7 (6, 8)	3 (2, 5)	<.0001	7 (6, 8)	3 (2, 5)	<.0001
SNAP II > 20, n (%)	1358 (46.1)	861 (68.6)	<.0001	574 (40.9)	328 (63.1)	<.0001
sBI or Death in NICU, n (%)	1005 (32.1)	671 (48.6)	<.0001	-	-	-
sBI, n (%)	542 (17.3)	294 (23.6)	<.0001	-	-	-
Death in NICU, n (%)	696 (22.2)	526 (38.1)	<.0001	-	-	-
Death after NICU discharge, n (%)	11 (0.4)	2 (0.1)	.37*	-	-	-
Lost follow up, n (%)	935 (29.9)	298 (21.6)	<.0001	-	-	-
Significant NDI, n (%)	-	-	-	314 (21.1)	148 (26.7)	.007

The "Excluded" groups include infants received extensive resuscitation at birth (chest compressions ≥30 seconds or receipt of intravenous or endotracheal epinephrine), infants with Apgar scores ≤1 at 1 minute or ≤3 at 5 minutes, and infants with missing delivery room intubation data, but does not include those who received palliative care at birth, major congenital anomalies, or outborn infants.
*Fisher's exact test was used to obtain the *P*-value due to the small sample size in one cell or multiple cells.

stabilization using NRS vs TI remains challenging, and identifying the optimal strategy of NRS in these vulnerable infants is an area for research and quality improvement.

Several studies investigated the association between management during initial stabilization and neurodevelopmental outcomes. Vaucher et al reported the neurodevelopmental outcomes of the Surfactant, Positive Pressure, and Oxygenation Randomized Trial and reported no significant difference in the composite outcome of death or neurodevelopmental impairment at 18-22 months CA between infants born at 24-27 weeks and randomized to CPAP or intubation and early surfactant.[29] In a single center retrospective cohort study from the Netherlands comparing infants born at <30 weeks of gestation in 2004-2005 and those born in 2010-2011 after introducing restricted ventilation and delivery room CPAP strategies, Vliegenthart et al reported that restricted ventilation was associated with reduced adjusted odds of death or NDI at 24 months.[30] However, the majority of infants included in the study were born at ≥25 weeks of gestation. In a study from Japan, Tamai and colleagues found that delivery room intubation, compared with "no intubation," in preterm infants born at 24-27 weeks of gestation was associated with a higher risk of NDI.[31] The follow up rate in that study was 26%, including 64 and 95 infants born at 24 and 25 weeks, respectively. In addition, they reported higher delivery room intubation rate compared with our study; 93% and 92% compared with 69% and 56%, at 24 and 25 weeks, respectively. In Shukla's study mentioned above, there was no statistically significant difference in moderate to severe disability or death at 22-30 months of age among infants born at 22-23 weeks and managed with NRS or intubation in the first 10 minutes after birth.[28] Our study identified significantly lower aOR of sNDI in the NRS group in model 1 of the multivariable analysis but not in model 2 or the propensity score matching analysis. The aOR of sNDI was significantly lower in the NRS group in infants born at 25 weeks but not in the subgroup of infants born at 23-24 weeks. The findings of our study do not support the hypothesis that using NRS to stabilize infants born at 23-25 weeks is associated lower odds of neurodevelopmental impairment, particularly, in those born at 23-24 weeks.

Our study has several strengths; first, we had a large sample size that is nationally representative of all tertiary NICUs in Canada. Second, we attempted to minimize the effect of confounding by indication using strict inclusion criteria by excluding infants who likely required intubation for clinical indications such as extensive resuscitation, outborn infants, and those with Apgar scores ≤1 at 1 minute, and ≤3 at 5 minutes as these infants had the highest risk of mortality and brain injury.[11,12] Third, we believe the statistical methods used in our study provided the best available evidence using registry data as conducting a randomized clinical trial in preterm infants <26 weeks of gestation has several challenges.[32]

Caution should still be exercised in generalizing the results of our study and we must acknowledge its limitations. First, the study included data gathered over a 10-year period, during which the use of NRS has increased over time. This change in practice did not occur simultaneously in the participating centers. In addition, we are unable to account for all other changes in practice over time despite adjusting

for year of birth. Second, despite our attempts to control for confounders, residual confounding by indication remains given the limited data on the intention of initial respiratory support strategy after birth, which may have been influenced by patient factors, practitioner preferences, local guidelines, and temporal changes in practice. In addition, our data did not include the number of intubation attempts or the experience or skill level of the practitioners present at resuscitation. The ability to stabilize these infants using NRS in the first 30 minutes of age may reflect a lesser severity of illness, rather than superiority of NRS compared with TI. Third, the number of infants born at 23 weeks in our cohort is small, which limits the generalizability in this gestational age. Forth, the follow-up rate in our cohort was suboptimal which may be attributable to various patient and system factors.

In conclusion, successful management with non-invasive respiratory support, compared with tracheal intubation, during stabilization in the first 30 minutes after birth in infants born at 23-25 weeks of gestation was associated with lower odds of sBI or death in the NICU. Among survivors with follow-up data, noninvasive respiratory support was not associated with decreased odds of significant neurodevelopmental impairment at 18-24 months CA. Prospective studies that document the indications for tracheal intubation and the details of respiratory support strategies during stabilization will provide valuable information to identify infants who may benefit from noninvasive respiratory support or tracheal intubation during this critical period. ■

CRediT Authorship Contribution Statement

Rachel Lipp: Writing – review & editing, Writing – original draft, Methodology, Funding acquisition, Conceptualization. **Marc Beltempo:** Writing – review & editing, Supervision, Resources, Methodology, Formal analysis, Data curation, Conceptualization. **Abhay Lodha:** Writing – review & editing, Methodology, Investigation, Conceptualization. **Dany Weisz:** Writing – review & editing, Methodology, Investigation, Formal analysis. **Julie McKanna:** Writing – review & editing, Methodology. **Ian Matthews:** Writing – review & editing, Methodology. **M. Florencia Ricci:** Writing – review & editing, Methodology, Investigation, Data curation. **Matthew Hicks:** Writing – review & editing, Methodology, Investigation, Data curation. **Amina Benlamri:** Writing – review & editing, Methodology, Data curation. **Amit Mukerji:** Writing – review & editing, Methodology, Data curation. **Ruben Alvaro:** Writing – review & editing, Methodology, Data curation. **Eugene Ng:** Writing – review & editing, Methodology, Data curation. **Thuy Mai Luu:** Writing – review & editing, Resources, Methodology, Investigation, Data curation, Conceptualization. **Prakesh S. Shah:** Writing – review & editing, Supervision, Resources, Methodology, Formal analysis, Data curation, Conceptualization. **Ayman Abou Mehrem:** Writing – review & editing, Writing – original draft, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of Competing Interest

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Appendix

List of the Canadian Neonatal Network, Canadian Preterm Birth Network, and Canadian Neonatal Follow Up Network Site Investigators

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