의학석사 학위논문

Risk Factors of Refractory Respiratory Distress Syndrome among Very Low Birth Weights Infants

극소저출생체중아에서 불응성 호흡곤란증후군의 위험요인에 관한 연구

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신 정 민

Risk Factors of Refractory Respiratory Distress Syndrome among Very Low Birth Weight Infants

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이 논문을 의학석사 학위논문으로 제출함

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신정민

신정민의 의학석사 학위논문을 인준함

2023 년 1 월

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Abstract

Objective

To evaluate risk factors of refractory respiratory distress (RDS) among very low birth weight (VLBW) infants.

Method

VLBW infants who were born and registered in Korean Neonatal Network (KNN) between January 2013 and December 2020 were analyzed. Infants who died within postnatal 5 days, were not diagnosed as RDS, or were not given surfactant were excluded. Study population was divided into non-refractory RDS group in which infants were administered surfactant once, and refractory RDS group in which infants were administered surfactant 2 or more times. Adjustment of confounding factors were done by multivariable logistic regression.

Results

After adjusting with confounding factors, male sex (adjusted odds ratio (aOR = 1.169), cesarean section delivery (aOR = 1.576), presence of maternal hypertensive disorders of pregnancy (aOR = 1.538), low 5 min Apgar score (aOR = 1.237) were analyzed as risk factors of refractory RDS. Gestational age (aOR = 0.795), completion antenatal steroids administration (aOR = 0.809) and presence of chorioamnionitis (aOR = 0.792) were shown to be protective factors of refractory RDS. Overall neonatal outcomes of refractory RDS group including various respiratory morbidities were poor compared with the non-refractory RDS group.

Conclusion

Maternal hypertensive disorders of pregnancy were found to be considerable risk factors of refractory RDS in addition to previously known risk factors of RDS. Perinatal distress represented by low 5 min Apgar score was also found to be a risk factor of refractory RDS.

Keyword: preeclampsia, preterm infant, pulmonary surfactants, respiratory distress syndrome, very low birth weight infant

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Chapter 1. Introduction

1.1 Study Background

Initial respiratory status in early life is important to preterm infants which influences further clinical course and neonatal outcomes. Preterm infants with same gestational age (GA) and birth weight show different initial respiratory courses according to various perinatal factors. Infants with mild intrauterine infection or inflammation often show better respiratory state initially comparing to infants born from mothers without such conditions but deteriorate later accompanied with radiographic structural changes and increased oxygen demand[1] . Completion of antenatal steroid (ANS) administration to mothers who are at risk of preterm delivery is known to reduce the incidence of respiratory distress syndrome (RDS) [1]. Regarding association between maternal pregnancy-induced hypertension (PIH) or preeclampsia (PE) and initial respiratory state, there are still controversies. Some recent studies with large cohorts revealed maternal hypertensive disorders of pregnancy can be risk factors of RDS[2]. Severe perinatal distress or birth asphyxia and meconium aspiration are known as risk factors of RDS even for term infants[3, 4]. Male sex and cesarean section delivery before labor are also known as common risk factors of RDS revealed by previously conducted studies[5].

Currently in Republic of Korea (South Korea), poractant alfa (Curosurf®), calfactant (Infasurf®), and bovine lung-derived, semi-synthetic surfactant (Surfecten®, Newfactan®) are available in the clinical field. Poractant alfa (Curosurf®) is most commonly used throughout the nation which is extracted from lungs of pigs due to its convenience of use. Once administered, they are

divided into two different components, and hydrophilic and hydrophobic components form films on alveolar surface to prevent alveolar collapse and lower surface tension[7]. When finishing job as a surfactant protein, they are reproduced by type II pneumocytes or degraded by macrophages. Recycling efficacy is more than 90% in most of mammalians, including human preterm and term infants[8].

Theoretically, RDS should be resolved after administration of a single dose of surfactant because most surfactant proteins are uptake and recycled. Infants with RDS should show better pulmonary compliance and reduced oxygen demands after surfactant administration[8]. However in the clinical field, we experience cases of refractory RDS, which require multiple surfactant therapies and advanced ventilator support. Especially infants with birth asphyxia or meconium aspiration syndrome may show RDS even in term infants. From this, we can infer various perinatal factors can influence the responsiveness of the surfactant therapy in preterm infants with RDS.

1.2 Purpose of Research

In clinical field, clinicians meet various degrees of RDS and it would be desirable to be able to predict which patient may require multiple surfactant administration and suffer from poor initial respiratory morbidities. This prediction can help clinicians to prepare mid to long term plans for respiratory care and ventilator weaning strategies. For such a reason, this study aimed to evaluate risk factors of refractory RDS using Korean Neonatal Network (KNN) national cohort data analysis.

Chapter 2. Methods

2.1 Study Population

This study has been conducted using patient data from the KNN data registry which is prospective cohort of very low birth weight (VLBW) infants collected from 75 neonatal intensive care unit (NICU) across South Korea. The KNN registry is a part of a national health project which has been collecting clinical data of VLBW infants born in South Korea prospectively since 2013. The purpose of the KNN registry is to accumulate clinical data of VLBW infants and analyze collected data to improve neonatal outcomes. For short term outcome data collection, each participant researcher enters major neonatal morbidities and mortalities during NICU hospitalization. 1^{st} long–term follow up visit is scheduled on 18 months of corrected age to collect growth and disease data. 2^{nd} long–term follow up visit is scheduled at 36 months of corrected age to collect developmental data. Approximately 70% of VLBW infants born in South Korea have been enrolled in this national cohort registry.

We analyzed data of VLBW infants who were registered in the KNN registry and who were born between January 2013 and December 2020 with gestational age ranged from 23^{+0} weeks to 31^{+6} weeks. We narrowed the study population to those who were administered surfactant at least once under the diagnosis of RDS. Infants who were not administered surfactant even they were diagnosed as RDS or infants who were not diagnosed as RDS were excluded. Infants with major congenital anomalies and cases which are difficult to fully determine the effect of the surfactant administration because of death within 5 days of birth were also excluded from the analysis.

We divided the study population into two groups. Non-refractory RDS group was defined as a group of infants who were administered surfactant only single time for treatment of RDS. Refractory RDS group was defined as a group of infants who were administered surfactant 2 times or more.

Currently in South Korea, administration of 1st dose of exogenous surfactant is approved by the national health insurance system for infants with definite respiratory difficulty accompanied with typical radiologic findings of RDS and increased need of oxygen. Preterm infants born less than GA 30 weeks or 1,250 gm of birth weight can be administered 1st dose of surfactant as prophylaxis under the national health insurance system. Reimbursement for 2nd dose of surfactant is [v1]provided in cases administered after 6 hours of 1st dose and within postnatal 48 hours under clinician's judgement of refractoriness of severe RDS. Reimbursement for 3rd dose or more is also provided in cases administered after 6 hours of the last dose of exogenous surfactant administration with clinician's judgement[11]. Based on these current clinical settings and support of national health insurance system, we defined the refractory RDS group as cases with multiple usage of exogenous surfactant.

2.2 Definition of Variables

Definitions of perinatal and neonatal clinical data were based on KNN data registry manual. Maternal chronic hypertension was defined as hypertension developed before pregnancy or before GA 20 weeks and preeclampsia was defined as hypertension accompanied by proteinuria and edema which developed after GA 20 weeks. These two entities share many common

pathophysiology and clinical manifestations, so we grouped these two disease as a maternal hypertensive disorders of pregnancy and analyzed as single factor[9]. Similarly, maternal overt diabetes mellitus (DM), which means hyperglycemia first recognized during pregnancy but meets non-pregnancy adults standard, or gestational DM (GDM), which means any hyperglycemia first recognized during pregnancy, also share many clinical aspects, such as large for gestational age (LGA) baby delivery, postnatal hypoglycemia, and myocardial hypertrophy caused by high insulin level, so we grouped these two and analyzed together[10]. Oligohydramnios was defined in cases of amniotic fluid index (AFI) less than 5 cm, and polyhydramnios was defined when AFI exceeded 8 cm. We defined "low 5 minutes (min) Apgar score (AS)" when 5 min AS[v2] was 7 or lower which, implied possible perinatal distress or birth asphyxia and further assessments should be required[12]. Initial body temperature, initial blood gas pH, initial blood base excess were defined as the first value reported within 1 hour after NICU admission. Completion of antenatal steroid administration was defined when the administration of last dose of antenatal steroids (ANS) was completed between 24 hours and 7 days before delivery.

2.3 Statistics

Continuous variables are expressed as means ± standard deviation (SD) and categorical variables are expressed as numbers and proportions. Pearson's χ^2 test was used to analyze categorical variables between two groups. Student's t test was used to compare continuous variables between groups. For adjusting confounding factors, multivariable logistic regression was

performed. Confounding factors were determined based on the results of previously conducted studies and the results of univariate analysis. Adjusted odds ratios (aORs) and 95% confidence intervals (CIs) were calculated through multivariable logistic regression analysis. Factors with missing values exceed more than 20% were excluded from multivariable logistic regression. Confounding factors used in multivariable logistic regression were gestational age, male sex, Cesarean section delivery, in-vitro fertilization (IVF), maternal GDM or overt DM, maternal hypertension during pregnancy, presence of chorioamnionitis (CAM), completion of antenatal steroid and low 5 min Apgar score. Multivariate ANOVA has been done for comparison of continuous variables in multivariate analysis. Pearson χ^2 residual test has been done for comparison of categorical variables in multivariate analysis and P-value lower than 0.0083 (0.05/6 cells) were considered as statistically significant. Statistical analysis were conducted using SPSS software, version 26.0 (IBM, Corp., Armonk., NY). A P value of < 0.05 was considered statistically significant.

2.4 Ethical Approval and Informed Consent

The KNN registry was approved by the Institutional Review Board of Chungnam National University Sejong Hospital (IRB No. CNUSH 2020-11-006). Informed consent was obtained from the parents before participating in the KNN registry.

Chapter 3. Results

3.1 Demographics and Baseline Characteristics

Among 16,384 VLBW infants born between January 2013 and December 2020, 191 infants born before gestational age 23 weeks, 2,453 infants born after gestational age 32 weeks, 594 infants with major congenital anomalies and 644 infants who died within postnatal 5 days were excluded. After removal of common exclusive cases, 12,502 infants remained. Among them, 1,730 infants without RDS diagnosis, 212 infants who diagnosed RDS but were not administered surfactant were also excluded. A total 10,560 VLBW infants were included in final data analysis. There were 7,732 infants in non-refractory RDS group and 2,828 infants were in refractory RDS group (Figure 1).

Average gestational age of 10,560 final inclusion infants was 28^{+1} weeks and average birth weight was 1,045gm. Average maternal age was 33 years old. There were 50.6% of male sex, 78.1% of cesarean section delivery, 25.4% of IVF pregnancy, 35.7% of multiple pregnancy, 10.4% of maternal overt DM or GDM cases, 19.4% of maternal hypertensive disorders of pregnancy cases, 12.6 % of oligohydramnios cases, 1.2 % of polyhydramnios cases, 32.2% of chorioamnionitis cases, 38.8% of PPROM cases, 47.1% were completed administration of antenatal steroid (Table 1).

Regarding basic demographic features of preterm infant, infants in refractory RDS group showed lower GA (28^{+0} weeks vs 27^{+1} weeks, $P < 0.001$), lower birth weight (1,045 gm vs 961 gm, $P < 0.001$) and showed high incidence of male sex (50.4% vs 53.6%, $P = 0.003$) and cesarean section delivery (71.9% vs 38.0%, $P < 0.001$).

Regarding maternal factors, refractory RDS group showed IVF pregnancy (24.7% vs 27.2%, $P = 0.010$), maternal GDM or overt DM (1.9% vs 23.7%, $P = 0.016$), maternal hypertensive disorders of pregnancy (17.8% vs 21.7%, $P < 0.001$), polyhydramnios (1.0% vs 1.7%, $P = 0.011$) and completion of antenatal steroid administration (47.2% vs 41.4%, $P < 0.001$). By contrast, incidence of chorioamnionitis was lower in refractory RDS group (38.9% vs 36.4%, $P = 0.030$).

Regarding infant factors, refractory RDS group showed high incidence of low 5 min AS score (36.2% vs 46.1%, $P < 0.001$), lower initial BT (36.2 ℃ vs 36.1 ℃, $P < 0.001$). Refractory RDS group showed lower initial pH (7.27 vs 7.26, $P < 0.001$) and base excess (−4.95 vs −5.90, $P < 0.001$), which mean high incidence of initial metabolic acidosis. Low 5 min Apgar score, low initial BT and initial metabolic acidosis can be represented by perinatal distress. Time to administration of 1st surfactant from birth was shorter in refractory RDS group (52 min vs 34 min, $P < 0.001$) (Table 2).

3.2 Risk Factors of Refractory RDS

Multivariable analysis was done by adjusted with confounding factors revealed by univariate analysis which are gestational age (per week), male sex, Cesarean section delivery, IVF pregnancy, maternal overt DM or GDM, maternal hypertensive disorders of pregnancy, presence of chorioamnionitis, completion of antenatal steroid administration and low 5 min Apgar score. There were few cases of small for gestational age and birth weight showed high proportionality and multicollinearity so that birth weight is eliminated from multivariable analysis. Initial pH and blood gas base excess, time to 1st surfactant

administration were also excluded from adjusting factors due to high missing values exceeding 20 % of total cases.

After adjusted by confounding factors, male sex (aOR = 1.169, P = 0.002), Cesarean section delivery (aOR = 1.576, P < 0.001), maternal hypertensive disorders of pregnancy (aOR = 1.538, P < 0.001), low 5 min Apgar score (aOR = 1.237, P < 0.001) increase the risk of refractory RDS. Whereas GA (aOR = 0.795, P < 0.001), presence of CAM (aOR = 0.792, P < 0.001), and completion of ANS (aOR = 0.809, P < 0.001) were shown to reduce the risk of refractory RDS (Table 3). IVF pregnancy, overt DM or GDM were removed by multivariable logistic regression process.

3.3 Neonatal Outcomes

After adjusting confounding factors which can influence the neonatal outcomes revealed by previously conducted studies and univariate analysis, refractory RDS group showed significantly high incidence of pulmonary morbidities, hemodynamically significant patent ductus arteriosus, and neurologic outcomes. Refractory RDS group also needed significantly longer respiratory support for both invasive and non-invasive ventilator methods.

Regarding neonatal outcomes, except treated retinopathy of prematurity (ROP), infants in refractory RDS group showed poor outcomes in overall neonatal morbidities. Refractory RDS group showed higher incidence of respiratory morbidities, including air leak (4.0% vs 10.4%, P < 0.001, aOR = 1.824), pulmonary hemorrhage (4.7% vs 11.6%, P < 0.001, aOR = 1.599), pulmonary hypertension (7.9% vs 18.2%, P < 0.001), moderate to severe bronchopulmonary dysplasia (BPD) (36.2% vs 54.4%, P < 0.001, aOR = 1.197),

severe BPD or death before postmenstrual age (PMA) 36 weeks (30.0% vs 45.4%, $P < 0.001$). Incidence of systemic corticosteroid treatment for BPD (30.0% vs 45.4%, $P < 0.001$), treated patent ductus arteriosus (PDA) (42.7% vs 52.2%, $P < 0.001$, aOR = 1.173), surgically treated PDA (19.5% vs 30.4%, $P < 0.001$, aOR = 1.173) and neurologic morbidities, including intraventricular hemorrhage (IVH) grade 3 (18.4% vs 32.7%, P < 0.001, aOR = 1.398) or more and periventricular leukomalacia (PVL) (9.1% vs 11.9%, $P < 0.001$), were also higher in refractory RDS group. Infants in refractory RDS group needed longer duration of invasive (17.4 days vs 27.5 days, $P < 0.001$, aOR = 1.003) and non-invasive mechanical ventilation (23.4 days vs 25.8 days, $P < 0.001$, aOR = 1.004) and hospitalization (76.7 days vs 84.0 days, $P < 0.001$). Infants in refractory RDS group also needed more medical support (16.5% vs 18.4%, $P < 0.001$) including home oxygen saturation monitor, home oxygen supplement and gavage tube feeding, when discharged from NICU (Table 4). Factors without adjusted odds ratio are statistically significant in univariate analysis but removed during multivariable logistic regression analysis. [v3]

3.4 Features According to the Number of Surfactant Administration

Comparing subgroups divided by the number of surfactant administration, GA and birth weight were lowest in the 3 or more surfactant group. There were more male infants in 2 surfactant and 3 or more surfactant group comparing to 1 surfactant group. The incidence of maternal hypertensive disorders of pregnancy was higher according to the increase of the number of surfactant

administration and showed the highest incidence in 3 or more surfactant group. The incidence of the presence of CAM was lowest in the 2 surfactant group but there were no constant tendency according to the number of surfactant administration. The 1 surfactant group showed highest incidence of ANS completion and statistically significant comparing to 2 surfactant group, but was not statistically significant comparing to 3 or more surfactant group. The incidence of low 5 min AS was remarkably low in 1 surfactant group comparing to other groups. Initial body temperature, the value of initial blood gas base excess was lower in 2 surfactant group and 3 or more surfactant group comparing to 1 surfactant group but the degree of difference was minor. Time to 1st surfactant administration was shorter in 2 surfactant and 3 or more surfactant group comparing to 1 surfactant group (Table 5).

Table 1. Demographics and baseline characteristics of final inclusion cases.

	Total (N=10,560)
Gestational age (weeks)	28^{+1} ($\pm$ 2^{+1})[v4]
Birth weight (gm)	1,054($\pm$ 274)
Male	6,329 (50.6%)
Cesarean section delivery	9,766 (78.1%)
Maternal Age	33.0 ($\pm$ 4.1)
IVF pregnancy	3,171 (25.4%)
Multiple pregnancy	4,463 (35.7%)
Overt DM or GDM	1,303 (10.4%)
Maternal hypertensive disorders of pregnancy	2,425 (19.4%)
Oligohydramnios	1,576 (12.6%)
Polyhydramnios	147 (1.2%)
CAM	4,029 (32.8%)
PPROM	4,849 (38.8%)
Completion of ANS	5,887 (47.1%)

IVF: In-vitro fertilization
GDM: Gestational diabetes mellitus
CAM: Chorioamnionitis
PPROM: Preterm premature rupture of membrane
ANS: Antenatal steroid

Table 2. Demographics and baseline characteristics between non-refractory RDS and refractory RDS group.

		Non-Refractory RDS (n=7,732)	Refractory RDS (n=2,828)	*P*-value
Basic Features	Gestational age (weeks)	28^{+0} ($\pm$ 2^{+1}) [v5]	27^{+1} ($\pm$ 2^{+1})	<0.001
	Birth weight (gm)	1,045 ($\pm$ 270)	961 ($\pm$ 268)	<0.001
	Male	3,895 (50.4%)	1,516 (53.6%)	0.003
	Cesarean section delivery	5,992 (71.9%)	2,346 (83.0%)	<0.001
Maternal Factors	Maternal Age	33.2 ($\pm$ 4.3)	33.3 ($\pm$ 4.4)	0.345
	IVF pregnancy	1,911 (24.7%)	769 (27.2%)	0.010
	Multiple pregnancy	2,669 (34.5%)	1,032 (36.5%)	0.060
	Overt DM or GDM	839 (01.9%)	261 (23.7%)	0.016
	Maternal hypertensive disorders of pregnancy	1,379 (17.8%)	615 (21.7%)	<0.001
	Oligohydramnios	984 (12.7%)	347 (12.3%)	0.532
	Polyhydramnios	81 (1.0%)	47 (1.7%)	0.011
	Chorioamnionitis	2,555 (38.9%)	861 (36.4%)	0.030
	PPROM	3,027 (39.4%)	1,055 (37.7%)	0.101
	Completion of ANS	3,648 (47.2%)	1,172 (41.4%)	<0.001
Infants Factors	Small for gestational age	506 (6.4%)	178 (6.3%)	0.891
	Large for gestational age	1623 (21.0%)	490 (17.2%)	0.735
	Low 5 min AS	2,783 (36.2%)	1297 (46.1%)	<0.001
	Initial body temperature (℃)	36.2 ($\pm$0.6)	36.1 ($\pm$ 0.7)	<0.001
	Initial base excess (BE)	$-$4.95 ($\pm$ 4.00)	$-$5.90 ($\pm$ 4.47)	<0.001
	Initial pH	7.27 ($\pm$ 0.11)	7.26 ($\pm$ 0.13)	<0.001
	Time to 1st surfactant administration (min)	0:52 ($\pm$ 0:02)	0:34 ($\pm$ 0:01)	<0.001

IVF: In-vitro fertilization
GDM: Gestational diabetes mellitus
PPROM: Preterm premature rupture of membrane
ANS: Antenatal steroid
AS: Apgar score

Table 3. Adjusted odds ratio of refractory RDS group comparing to non-refractory RDS group.

		aOR (95% CI)	*P*-value
Risk Factors	Male	1.169 [1.060, 1.290]	0.002
	Cesarean section delivery	1.576 [1.380, 1.801]	<0.001
	Maternal hypertensive disorders of pregnancy	1.538 [1.352, 1.749]	<0.001
	Low 5min Apgar score	1.237 [1.117, 1.370]	<0.001
Protective Factors	Gestational age (per week)	0.795 [0.774, 0.815]	<0.001
	Chorioamnionitis	0.792 [0.710, 0.882]	<0.001
	Completion of ANS	0.809 [0.733, 0.893]	<0.001

ANS: Antenatal steroid

Table 4. Major neonatal outcomes between non-refractory RDS group and refractory RDS group and its adjusted odds ratio.

	Non-Refractory RDS (n=7,732)	Refractory RDS (n=2,828)	*P*-value	aOR (95% CI)
Air leak	309 (4.0%)	293 (10.4%)	<0.001	1.824 [1.424, 2.335]
Pulmonary hemorrhage	366 (4.7%)	328 (11.6%)	<0.001	1.599 [1.268, 2.016]
Pulmonary hypertension	611 (7.9%)	514 (18.2%)	<0.001	
Moderate to severe BPD	2,574 (36.2%)	1,272 (54.4%)	<0.001	1.194 [1.131, 1.583]
Severe BPD or death before PMA 36 weeks	2,314 (30.0%)	1,365 (45.4%)	<0.001	
Systemic corticosteroid treatment for BPD	1,087 (14.1%)	575 (20.3%)	<0.001	
Treated PDA	3,301 (42.7%)	1,475 (52.2%)	<0.001	1.363 [1.174, 1.583]
Surgically treated PDA	951 (19.5%)	577 (30.4%)	<0.001	1.173 [1.010, 1.365]
IVH Grade 3 or more	1,419 (18.4%)	925 (32.7%)	<0.001	1.398 [1.211, 1.614]
Periventricular leukomalacia	704 (9.1%)	336 (11.9%)	<0.001	
Culture proven sepsis	1,814 (23.5%)	829 (29.3%)	<0.001	
NEC stage 2 or more	587 (7.6%)	311 (11.0%)	<0.001	
Treated ROP	4,689 (60.6%)	1,725 (61.0%)	0.742	0.901 [0.798, 1.017]
Invasive ventilator duration (days)	17.4 (± 26.7)	27.5 (± 33.8)	<0.001	1.003 [1.001, 1.005]
Non-invasive ventilator duration (days)	23.4 (± 21.4)	25.8 (± 25.8)	<0.001	1.004 [1.001, 1.007]
O2 support duration (days)	7.9 (± 12.2)	8.9 (± 15.5)	<0.001	

Discharge with support	1,274 (16.5%)	520 (18.4%)	0.021	0.876 [0.757, 1.014]
Admission duration (days)	76.67 (± 38.2)	83.98 (± 50.6)	<0.001	

BPD: Bronchopulmonary dysplasia
PMA: Postmenstrual age
PDA: Patent ductus arteriosus
IVH: Intraventricular hemorrhage
NEC: Necrotizing enterocolitis
ROP: Retinopathy of prematurity
PMA: Postmenstrual age

Table 5. Demographics and baseline characteristics according to the number of surfactant administration.

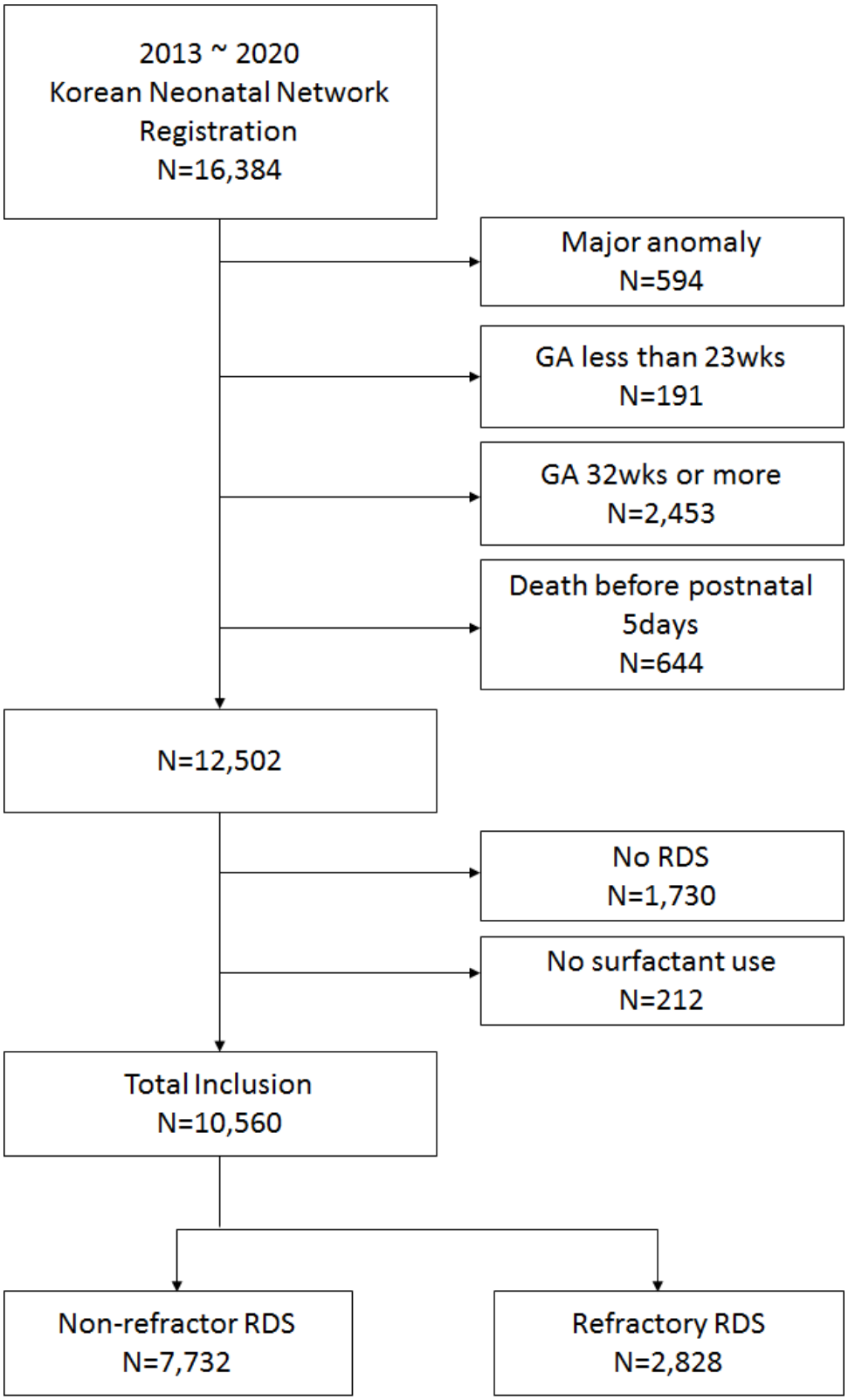
	1 Surfactant (n=7,960)	2 Surfactant (n=2,234)	3 or more Surfactant (n=609)	*P*-value
Gestational age (weeks)	28+0 (± 2^{+1})	27+2 (± 2^{+1}) ¶	26+5 (± 2^{+1}) ¶,†	<0.001
Birth weight (gm)	1,047 (± 227)	978 (± 269) ¶	898 (± 254) ¶,†	<0.001
Male	4,007 (50.3%)	1,196 (53.5%)*	329 (54.0%)*	0.010
Cesarean section delivery	6,168 (77.5%)*	1,862 (83.3%)*	497 (81.6%)*	<0.001
Maternal Age	33.2 (± 4.3)	33.3 (± 4.3)	33.6 (± 4.4)	0.154
In-vitro fertilization	1,952 (24.5%)	611 (27.4%)	160 (26.3%)	0.020
Multiple pregnancy	2,737 (34.4%)	840 (37.6%)*	196 (32.2%)	0.006
Overt DM or GDM	857 (10.8%)	206 (9.2%)	56 (9.2%)	0.066
Maternal hypertensive disorders of pregnancy	1,427 (17.9%)*	474 (21.2%)*	144 (23.6%)*	<0.001
Chorioamnionitis	2,626 (38.8%)	661 (35.2%)*	202 (40.1%)	0.011

PPROM	3,108 (39.3%)	830 (3.4%)	227 (38.0%)	0.239
Completion of ANS	3,770 (47.4%)*	992 (41.3%)*	258 (42.4%)	<0.001
Low 5 min Apgar score	2,845 (35.9%)*	1027 (46.1%)*	276 (45.6%)*	<0.001
Initial body temperature (℃)	36.2 (± 0.6)	36.1 (± 0.6)¶	36.1 (± 0.7)¶	<0.001
Initial base excess	−4.93 (± 4.09)	−5.81 (± 4.37)¶	−6.23(± 4.82)¶	<0.001
Initial pH	7.27 (± 0.11)	7.26 (± 0.13) ¶	7.26 (± 0.13)	<0.001
Time to 1st surfactant administration (min)	0:52 (± 2:00)	0:36 (± 1:37)¶	0:28 (± 1:14)¶	<0.001

* compared to other cells. $P < 0.0083$ (0.05/6 cells)
¶ compared to 1 surfactant group (P<0.001).
† compared to 2 surfactant group (P<0.001)..

GDM: Gestational diabetes mellitus
PPROM: Preterm premature rupture of membrane
ANS: Antenatal steroid

Figure 1. Study population



Chapter 4. Discussion

Through this study, low gestational age, low birth weight, male sex, cesarean section delivery, maternal hypertensive disorders of pregnancy and low 5 min Apgar score were analyzed as risk factors of refractory RDS which were not resolved with single dose of surfactant administration. Presence of chorioamnionitis and completion of antenatal corticosteroid administration were analyzed as protective factors of refractory RDS. Most risk factors and protective factors of refractory RDS were overlapped with already known risk and protective factors of RDS including low gestational age, low birth weight, male sex, cesarean section delivery, presence of chorioamnionitis and administration of antenatal steroids. From this study, maternal hypertensive disorders of pregnancy was found to be an important risk factor of refractory RDS. Perinatal distress or birth asphyxia representing low 5 min Apgar score is also known as a risk factor of RDS. It is remarkable that perinatal distress is analyzed as a risk factor of refractory RDS regarding surfactant metabolism mechanism. Some factors are correctable which make perinatal distressful condition worse including cold delivery site environment and prolonged moving distance from delivery site to NICU. Clinicians should pay attention to these correctable factors for prevent refractory or severe RDS because perinatal distress encompassing initial metabolic acidosis and hypothermia revealed as a risk factor of refractory RDS and some factors can correctable by quality improvement activities.

In this study, we limited the study subjects to VLBW infants with RDS with surfactant treatment. This differs from previously conducted studies in the

definition of RDS which is commonly defined as respiratory difficulty with increased oxygen demands accompanied by typical ground glass opacity in radiologic exam. In South Korea, under national health insurance system, most of medical costs incurred from premature baby care in NICU are covered by national health insurance system and baby' s parents pay little portion of total hospital expenses[11]. Furthermore the cost of surfactant is provided by the national health insurance system based on the clinical decision of the physician and costs are provided for multiple administration[11]. This point reflects that the number of surfactant use is proportion to the severity of RDS in preterm infants[6]. Traditionally RDS is known to be originated from the deficiency of surfactant in preterm infants due to immature endogenous surfactant synthesis. Thus theoretically, single dose of surfactant administration should resolve RDS. However some preterm infants show refractory RDS and need multiple surfactant administration which exceed physiologic surfactant pool size[6,8]. This suggests that RDS is not only due to simple deficiency of endogenous surfactant but also may attribute to disruption of the overall processes of endogenous surfactant synthesis, transportation, secretion and recycling. Our study revealed that low gestational age, low birth weight, male sex, cesarean section delivery, maternal hypertensive disorders of pregnancy, low 5 min Apgar score increase the risk of refractory RDS, and we can infer that these factors influence not only to the synthesis but to overall process of surfactant metabolism. Gestational age and birth weight are commonly known as risk factors for overall preterm morbidities[7]. In this study, gestational age and birth weight also have been revealed as risk factors of refractory RDS. As we defined refractory RDS according to needs of multiple surfactant administration which exceed normal

surfactant pool[6,8], low gestational age and birth weight influence not only to the surfactant production bus also to other surfactant metabolism process such as transportation, secretion and recycling process possibly due to immaturity of pneumocytes[14]. Maternal hypertensive disorders of pregnancy including preeclampsia has been identified as a risk factor of refractory RDS in this study and the incidence of maternal hypertensive disorders of pregnancy increases according to the number of surfactant administrations increases and showed highest incidence in surfactant 3 or more group.

Described as above, current dose of surfactant given to preterm infants with RDS is exceed surfactant pool size of healthy term infants[6,8]. Some preterm infants need multiple surfactant administration because of refractory RDS which is not resolved by single dose of surfactant. This study was planned based on these theoretical points. However decision of multiple surfactant administration is totally depends on clinician's opinion and there is no clear standard for multiple surfactant administration. Also each NICU has their own policies for surfactant administration. These facts made non-linear relation between the number of surfactant administration and severity of RDS. Although multiple surfactant administration can reflect the severity of RDS in some extent, the fact that the number of surfactant administration is not proportionated to the severity of RDS and differences of policies among NICUs are not reflected on this study are the limitation of this study.

Maternal hypertensive disorders of pregnancy, including preeclampsia, is one of the major causes of preterm delivery along with intrauterine inflammation. Exact pathophysiology of maternal hypertensive disorders of pregnancy, including preeclampsia, is not known clearly. Immunologic and vascular

dysregulation caused by maternal hypertension are thought to be key mechanism affecting spiral artery development and placentation[15]. Poor placentation leads to placenta insufficiency and result in fetal intrauterine growth retardation (IUGR) and preterm delivery. Maternal hypertension during pregnancy can be divided into several subcategories which are chronic hypertension, preeclampsia and superimposed preeclampsia[16]. These subgroups of maternal hypertensive disorders of pregnancy share many aspects of pathophysiology and neonatal clinical manifestations[9]. However the relationships between maternal hypertension during pregnancy and neonatal RDS is not certain for now. According to previous studies, maternal hypertension regarded as a protective factors of RDS[17]. The idea of acceleration of organ maturation caused by chronic intrauterine stress was theoretical background of previously conducted studies[17]. On the other side several recent studies with large cohort have reported that maternal hypertension can be the risk factor of RDS. Yu-Hua Wen et al.[2] reported that maternal hypertension during pregnancy is the risk factor of RDS which needs surfactant treatment. This study was conducted with VLBW infants registered in Premature Baby Foundation in Taiwan cohort population similar with this study. These different conclusions regarding maternal hypertension during pregnancy and neonatal respiratory morbidities might originate from accessibility to usage of exogenous surfactant therapy, advances in obstetric care of hypertensive mother during pregnancy and changes in trends of neonatal respiratory care. Another cohort study conducted in Netherlands targeted to late preterm infant, gestational age between 34 and 37 weeks, showed little relevance between the incidence of RDS and maternal hypertensive disorders of pregnancy[18].

One major cause of placental dysfunction or insufficiency due to maternal hypertension during pregnancy has been thought to be derived from increased soluble fms-like tyrosine kinase-1 (sFLT-1)[19]. Increased sFLT-1 lowers the concentration of circulation free vascular endothelin growth factor (VEGF) family and results in abnormal spiral artery formation in placenta[20, 21]. Also VEGF family is also known to affect lung maturation process in fetus. Preeclampsia is known to be developed lately in pregnancy, mainly after GA 34 weeks, and earlier development of preeclampsia or maternal chronic hypertension increase the incidence of neonatal morbidities[22]. Considering previous studies conducted with late preterm infants showed no differences in the incidence of RDS and other neonatal respiratory morbidities, the duration of exposure to low VEGF family might affect to the degree of fetal lung maturation and microscopically maturation of pneumocytes. It can be assumed that the longer exposure to low VEGF level due to early onset of maternal hypertension during pregnancy, the worse fetal lung maturation and pneumocytes function. Abnormal pneumocytes function affect the overall process of endogenous surfactant synthesis, transportation, secretion and recycling and these malfunctioning influence to the severity of RDS in VLWBI or very low gestational age infants. Further studies should be performed to identify when is the key period of fetal lung maturation regarding maternal hypertension during pregnancy and what are key molecules and what we can do to these preterm infants.

The refractory RDS group showed low 5 min Apgar score which suggesting perinatal distress or birth asphyxia. Although initial low pH, base excess and low body temperature were excluded due to high missing value,

these factors are also indicating initial distressful condition. Initial pH, base excess and initial body temperature were also significantly lower in refractory RDS group in univariate analysis. These findings can be considered as a distress full condition before or during delivery. Prolonged stay in delivery room due to resuscitation and also makes hypothermia and advanced metabolic acidosis. Low 5 min AS, low initial body temperature, low initial blood gas pH and base excess all represent perinatal distress of asphyxia which is challenging initial situation for both infants and clinicians. Surfactant metabolism is consist with multiple steps including synthesis, transportation, secretion and recycling by pneumocytes. These complex processes are easily affected by environmental conditions such as pH, temperature, perfusion and oxygen level. In laboratory condition, acidic environment can denature protein structure so that disrupt endogenous surfactant synthesis[24]. Also hyperthermia or hypothermia affect to overall process of surfactant protein metabolism result in refractory RDS. It is also known that birth asphyxia which result in hypoxemia, metabolic acidosis and hypothermia is one of the risk factors of term asphyxia infants[23]. It is consistent with initial pH, base excess and body temperature were significantly lower in refractory RDS group. Most situation regarding perinatal distress or birth asphyxia cannot be avoidable nor predictable. However condition after birth, environment of delivery room and NICU environment can be correctable. We consider body temperature, blood gas pH and base excess should be regarded significantly even there were small difference in statistical results because this study is conducted with large cohort date. Further studies regarding molecular mechanisms of surfactant metabolism affected by cellular and environment should be performed.

Early surfactant prophylaxis has been emerged as a concept which preterm infants have smaller surfactant pool size and function of pneumocytes are immature so that pulmonary epithelial cells can be injured more easily during ventilation[24]. According to randomized controlled trials conducted in late 1990's, early prophylactic surfactant administration reduced pulmonary morbidities and associated neonatal conditions[24]. However, studies recently conducted studies revealed that early surfactant prophylaxis without continuous positive airway pressure (CPAP) support increased intubation frequency and prolonged mechanical ventilation duration[25]. There were also no effective improvement of neonatal outcomes in early surfactant prophylaxis group. Other study conducted with South Korea also concluded that early surfactant prophylaxis did not improve neonatal outcomes[26]. In this study, time to 1st surfactant administration from birth was significantly short in refractory RDS group comparing to non-refractory RDS group in univariate analysis. Although this factor was not included in multivariable analysis due to high missing values, the difference between 2 groups were 18 min (52 min vs 34 min) and it was statistically significant. Considering overall neonatal outcomes were poor in refractory RDS group including pulmonary outcomes, it is assumed that early surfactant administration alone cannot improve neonatal outcomes. It is important that decision of surfactant administration should not be standardized simply depends on gestational age or birth weight but should consider current respiratory status, radiologic findings and all other factors affecting neonatal morbidities.

Chapter 5. Conclusion

In addition to known risk factors of RDS revealed by previously conducted studies, including male sex, cesarean section delivery, low gestational age and birth weight, maternal hypertensive disorders of pregnancy can be considered as a risk factors of refractory RDS. Maternal hypertensive disorders of pregnancy seemed to affect overall process of endogenous surfactant synthesis and recycling of exogenously administered surfactant. Further study regarding exact pathophysiologic relationship between surfactant metabolism and maternal hypertensive disorders of pregnancy should be performed.

Perinatal distress or birth asphyxia was also revealed as a risk factor of refractory RDS which affect surfactant metabolism process. There were some correctable factors associated with perinatal distress or birth asphyxia including delivery site environment, clinicians should pay attention about quality improvement activities and environmental changes.

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요약 (국문 초록)

목적

조산아들에게서 초기 호흡기 상태는 치료 경과에도 영향을 미치며 장기적으로 성장 발달에도 영향을 미치게 된다. 같은 재태 연령, 출생 체중을 가진 조산아들이더라도 조산과 연관된 여러 주산기 요인들에 따라 서로 다른 초기 호흡기 질환의 중등도를 보인다. 본 연구를 통하여 Korean Neonatal Network (KNN)에 등록된 조산아들 중 출생 초기 2 회 이상 폐표면활성제를 투여해야 했던 조산아들과 1 회만 투여하였던 조산아들을 비교하여 출생 초기 호흡기 경과의 중증도에 영향을 미치는 위험 요인들을 알아보고자 한다.

방법

2013 년 1 월부터 2020 년 12 월 사이에 KNN 에 등록 된 재태 연령 23 이상, 32 주 미만의 조산아들 중 호흡곤란증후군으로 폐표면활성제를 1 회 이상 투여하였던 경우를 대상으로 하였다. 폐표면활성제를 1 회만 투여 받았던 비 불응성 호흡곤란증후군 군과 2 회 이상 필요하였던 불응성 호흡곤란증후군 군으로 나누어 불응성 호흡곤란중후군의 위험 요인과 조산아 유병율을 비교해 보고, logistic regression 을 통하여 odds ratio 를 구한다.

결과

총 10,560 명의 대상자 중 비 불응성 호흡곤란증후군 군이 7,732 명 (73.2%), 불응성 호흡곤란 증후군 군이 2,828 명 (26.8%) 이었다. 단변량 분석을 통해 확인 된 교란 변수들로 보정하였을 때 남아 (aOR = 1.237), 제왕절개 분만 (aOR = 1.576), 산모의 임신 연관 고혈압성 질환 (aOR = 1.538) 그리고 낮은 5 분 아프가 점수 (aOR = 1.237) 이 불응성 호흡곤란 증후군 군의 위험요인으로 확인되었다. 재태 연령 (aOR = 0.795), 산전 스테로이드 투여의 완료 (aOR = 0.809), 융모양막염의 존재 (aOR = 0.792) 들은 불응성 호흡곤란 증후군 군의 위험을 낮추는 것으로 확인되었다. 산전 요인들로 보정하였을 때 전반적은 신생아 유병율 및 질환 이환율은 불응성 호흡곤란 증후군 군에서 불량하였다.

결론

기존에 호흡곤란증후군의 위험 인자로 알려진 재태 연령, 출생 체중, 성별과 더불어 산모의 임산 연관 고혈압성 질환은 호흡곤란 증후군의 위험요인이며, 초기 호흡기 상태를 악화시키는 요인이다. 낮은 5 분 아프가 점수로 대변되는 주신가 곤란 또는 분만 가사 또한 불응성 호흡곤란 증후군의 위험요인이다.