

Executive Summary

Selective versus prophylactic use of surfactant in preterm infants

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Background

Pulmonary surfactants improve dyspnea, and they are administered to preterm infants to prevent and treat respiratory distress syndrome. The use of pulmonary surfactants can be broadly classified into two categories: prophylactic surfactant use and selective surfactant use. Currently, the national health insurance system covers one round of prophylactic administration of pulmonary surfactants to preterm infants with a birth weight of less than 1,250 g or those born earlier than 30 weeks gestational age within two hours of birth (Transition to the benefit bracket, January 2011).

However, a recent multicenter clinical trial reported that performing both early initiation of continuous positive airway pressure (CPAP) and selective surfactant administration on (extremely) preterm infants anticipated to have infant respiratory distress syndrome (RDS) has superior benefits over

prophylactic surfactant administration. Selective surfactant use not only prevented unnecessary endotracheal intubation and surfactant administration but also lowered mortality and chronic pulmonary disease. Further, European Consensus Guidelines (2013 update) recommend that early rescue surfactant, as opposed to prophylactic use of surfactant, should be standard.

In South Korea, appropriate prenatal and postnatal management for preterm birth is performed. In addition to current management, further review about surfactant treatment for preterm infants who are subject to reimbursement prophylactic use of surfactants is needed in consideration of prenatal management (e.g., steroid use), delivery environment (presence of medical staff, facility, and equipment 재진able of resuscitation and stabilization in the delivery room), and patient's state immediately after birth (need for endotracheal intubation, infection).

Purpose

This study aims to compare selective and prophylactic surfactant administration in terms of their clinical effects, such as clinical progress and mortality, in preterm infants who often have RDS based on a systematic review and data from the Korean Neonatal Network (KNN).

Methods

1) Systematic review

A systematic review was conducted to examine the clinical effects of selective and prophylactic surfactant use on preterm infants. The search was made in three foreign databases (Medline, EMBASE, Cochrane library) and five Korean databases (KoreaMed, KMBASE, RISS, KISS, NDSL) as well as manually. No particular requirements were set for the year of publication and language. Articles were selected independently by two investigators according to the pre-established inclusion and exclusion criteria, and the final selections were made upon agreement between the two investigators. Risk of bias for the

selected articles was assessed using the Cochrane RoB tool with baseline characteristic imbalance and confounding variables added, and meta-analysis was performed when quantitative synthesis was possible.

2) KNN data analysis

To compare the clinical effects of selective and prophylactic use of surfactants on preterm infants, the KNN registry data were used to establish a retrospective cohort. The subjects were set to preterm infants with a high risk of RDS who were born earlier than 30 weeks gestational age or with a birth weight of less than 1,250 g registered in KNN between January 2013 and December 2015.

The intervention group defined as selective treatment group, and the control group defined as prophylactic treatment group. The clinical definition of prophylactic surfactant treatment was surfactant treatment performed for prophylactic purposes in all preterm infants with a high risk of RDS regardless of the onset of symptoms. The clinical definition of selective surfactant treatment was surfactant treatment selectively performed only on preterm infants who developed the symptoms of RDS.

The primary outcome indices were: 1) death before hospital discharge, 2) neonatal death, 3) bronchopulmonary dysplasia (BPD) among survivors or those who died before hospital discharge, and 4) BPD among survivors or neonatal death. The secondary outcome indices were: sepsis, patent ductus arteriosus, air leak, intraventricular hemorrhage, intraventricular hemorrhage \geq stage 3, peri-ventricular leukomalacia, pulmonary hypertension, retinopathy of prematurity (ROP), surgery for ROP, necrotizing enterocolitis, and massive pulmonary hemorrhage.

Subgroup analysis was performed in terms of gestational age, birth weight, combination of gestational age and birth weight, prenatal steroid use, and combination of gestational age and prenatal steroid use.

Stratification-matching was performed to eliminate the bias of outcome variables resulting from any differences of baseline characteristics between the

selective and prophylactic treatment groups. Characteristics were stratified based on prenatal steroid use, gestational age, and birth weight. Then, 1:1 propensity scores matching was performed using a logistic regression including gender, Apgar score, mode of delivery, premature rupture of membranes, chorioamnionitis, and resuscitation. The pre- and post-matching results were presented for all major analytical results. Conditional logistic regression was performed to estimate odds ratios, which were presented with 95% confidence interval (CI) and p-value.

□ Results

- A systematic literature review showed that prophylactic surfactant use as a treatment for RDS significantly reduced all types of death and neonatal death. However, subgroup analysis showed that the statistical significance of lowering death in the prophylactic treatment group was lost in the following cases: 1) according to the advances of NICU care (analysis of studies published after 2001), 2) in more mature preterm infants (analysis of infants born after 30weeks gestational age), 3) according to prenatal steroid use (analysis of cases involving more than 50% completion of prenatal steroid therapy), and 4) positive pressure ventilation using CPAP immediately after birth (analysis of cases in which CPAP was used to assist breathing).
- Analysis using a logistic regression model for death before hospital discharge showed that the selective treatment group had a significantly higher odds ratio than that of the prophylactic treatment group.
- In the subgroup analysis, there were no significant differences between the two groups in all primary outcome variables, including death before discharge, neonatal death, and BPD among survivors, in infants born after 30 weeks gestational age.
- There were no significant differences in all outcome indices between the prophylactic and selective treatment groups among infants born after 30 weeks gestational age with a birth weight below 1,250 g.
- There were no significant differences in all outcome indices between the prophylactic and selective treatment groups among infants born after 30 weeks gestational age with completion of prenatal steroid therapy.

1) Systematic review

A systematic literature review was performed to compare the clinical effects of prophylactic and selective use of surfactants on RDS of preterm infants. A total of 16 articles were included in the final analysis after literature search and selection process. One of them was a Korean study while 15 were foreign studies. Twelve were randomized controlled studies,

while four were non-randomized controlled studies.

Selective treatment referred to surfactant administration after definitive diagnosis of RDS, and prophylactic treatment referred to surfactant administration within two hours of birth or immediately after birth without the diagnosis of RDS. Prenatal steroid use exceeded 50% in three studies, and CPAP, which is a recent treatment method, was performed in addition to selective surfactant treatment in five studies. Studies that performed prenatal steroid therapy and used latest treatment methods, such as CPAP, were mostly published after the year of 2000.

Meta-analysis revealed that death from all causes was significantly lower in the prophylactic treatment group, but in the subgroup analysis, the two groups showed no significant differences in death rate for studies published after 2001, cases involving preterm infants born after 30 weeks gestational age, cases involving more than 50% use of prenatal steroids, and cases involving the use of CPAP to assist breathing.

The prophylactic treatment group also had a significantly lower neonatal death rate, but the statistical significance was lost in subgroup analysis for studies published after 2001, cases involving more than 30 weeks gestational age, and cases involving the use of CPAP to assist breathing. There were no significant differences between the selective and prophylactic treatment groups in death rate before discharge.

There were also no significant differences between the selective and prophylactic treatment groups in the incidence of BPD (use oxygen for more than 28 days after birth) and chronic pulmonary disease (use supplementary oxygen at postmenstrual age 36 weeks).

Although the combined index for BPD or neonatal death was significantly lower in the prophylactic treatment group, but the statistical significance was lost in subgroup analysis for studies published after 2001, cases involving preterm infants born after 30 weeks gestational age, cases involving more than 50% of prenatal steroid use, and cases involving use of CPAP to assist breathing.

There were no significant differences between the selective and prophylactic treatment groups in air leak, pulmonary hemorrhage, patent ductus arteriosus, pulmonary hypertension, sepsis, necrotizing enterocolitis, intraventricular hemorrhage, periventricular leukodystrophy, retinopathy of prematurity (ROP), and pneumonia.

Three follow-up studies were included in this analysis. The follow-up periods were one year for one study and two years for another study, and the last study followed-up until school age (4.5-8 years of age). The one-year follow-up study compared growth, neurologic outcomes, and development outcomes and found similar results in both groups. The two-year follow-up study examined the incidence of ROP, and there were no significant differences in the number of patients with the worst stage of acute ROP between the two groups. The study that followed-up on the subjects until school age reported pulmonary and neurologic development outcomes. Pulmonary function was abnormal in 78% and 75% of prophylactic and selective treatment groups, respectively. About 11% and 9.3% of prophylactic and selective groups, respectively, had cerebral palsy, and 18% and 20%, respectively, had a mean cognitive function index of below 70, showing similar outcomes between the two groups.

2) KNN analysis

From the 2013-2015 KNN infant data, infants born with a birth weight of below 1,250 g or born earlier than 30 weeks gestational age were selected, resulting in 1,286 infants in the selective treatment group and 3,167 infants in the prophylactic treatment group. Stratification-matching was performed using propensity scores calculated in consideration of the baseline characteristics of these 4,453 infants. A total of 1,027 infants in each group were matched, showing a matching rate of 80%.

After matching, the number of infants who died before discharge was 138 (13.4%) in the selective treatment group and 106 (10.3%) in the prophylactic treatment group. In the multivariate conditional logistic