Pulmonary Pharmacology & Therapeutics 34 (2015) 46–54

Contents lists available at ScienceDirect

Pulmonary Pharmacology & Therapeutics

journal homepage: www.elsevier.com/locate/ypupt

Effect of exogenous pulmonary surfactants on mortality rate in neonatal respiratory distress syndrome: A network meta-analysis of randomized controlled trials

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ARTICLE INFO

Article history:
Received 3 March 2015
Received in revised form
15 July 2015
Accepted 17 August 2015
Available online 18 August 2015

Keywords:
Neonatal respiratory distress syndrome
Exogenous pulmonary surfactant
Randomized controlled trials
Network meta-analysis

ABSTRACT

Background: The utilization of multiple natural and synthetic products in surfactant replacement therapies in treatment of neonatal respiratory distress syndrome (NRDS) prompted us to take a closer looks at these various therapeutic options and their efficacies. The purpose of our study was to evaluate the effects of six exogenous pulmonary surfactants (EPS) (Survanta, Alveofact, Infasurf, Curosurf, Surfaxin and Exosurf) on mortality rate in NRDS by a network meta-analysis.

Methods: An exhaustive search of electronic databases was performed in PubMed, Ovid, EBSCO, Springerlink, Wiley, Web of Science, Cochrane Library, China National Knowledge Infrastructure, Wanfang and VIP databases (last updated search in October 2014) to retrieve randomized controlled trials (RCTs) relevant to our study topic. Published clinical trials were screened based on the following inclusion criteria: (1) study design: RCTs; (2) interventions: treatment with Survanta, Alveofact, Infasurf, Curosurf, Surfaxin or Exosurf for NRDS; (3) study subject: infants with NRDS confirmed by clinical diagnosis; (4) outcome: the mortality rate of infants with NRDS. Statistical analysis was performed using Stata 12.0 software (Stata Corporation, College Station, TX, USA) and Comprehensive Meta-analysis (CMA 2.0) software.

Results: From the 1840 studies initially retrieved through database searches, a total of 17 high quality RCTs were selected for this network meta-analysis. The selected studies included a combined total of 57,223 infants with NRDS treated with various EPS (Survanta, 27,017; Alveofact, 159; Infasurf, 20,377; Curosurf, 20,911; Surfaxin, 646; Exosurf, 1640). Network meta-analysis results showed that the mortality rates in NRDS infants treated with Alveofact, Infasurf, Curosurf, Surfaxin, Exosurf were not significantly different compared to Survanta (Alveofact: OR = 1.163, 95% CI = 0.645–2.099, $P = 0.616$; Infasurf: OR = 0.985, 95% CI = 0.777–1.248, $P = 0.897$; Curosurf: OR = 0.789, 95% CI = 0.619–1.007, $P = 0.056$; Surfaxin: OR = 0.728, 95% CI = 0.477–1.112, $P = 0.142$; Exosurf: OR = 0.960, 95% CI = 0.698–1.319, $P = 0.799$). Notably, the surface under the cumulative ranking curves (SUCRA) value in Surfaxin group was significantly higher than the other five groups (Surfaxin: 80.4%; Survanta: 37.0%; Alveofact: 24.4%; Infasurf: 40.0%; Curosurf: 73.9%; Exosurf: 44.2%), suggesting that infant mortality rate in Surfaxin group was the lowest among the six EPS groups.

Conclusion: Our study demonstrated that Surfaxin could effectively reduce the mortality rate of infants with NRDS and may have a better efficacy in NRDS treatment, compared to Survanta, Alveofact, Infasurf, Curosurf and Exosurf.

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http://dx.doi.org/10.1016/j.pupt.2015.08.005
1094-5539/

1. Introduction

Respiratory distress syndrome is the most common life-threatening form of respiratory failure in neonates worldwide [1]. The incidence of neonatal respiratory distress syndrome (NRDS) is closely associated with the degree of prematurity, and approximately occurs in half of the preterm infants born before 30 weeks of gestation [2,3]. The abnormality in NRDS is primarily a deficiency in the production of pulmonary surfactants (PS), which results in poor compliance of lungs, insufficient gas exchange and a demand for high ventilatory pressures [4]. As a critical method for supplementing PS, exogenous pulmonary surfactant (EPS) therapy is routinely used in clinics for prevention and treatment of NRDS [4]. NRDS is the leading cause of the unacceptably high mortality rates in preterm infants, and multiple EPS therapies are being rapidly introduced into clinics to address the disease, and, thus, it is of urgent need to compare the efficacies of current EPS therapies for NRDS [5].

The majority of current EPS therapies for clinical management of NRDS use surfaxin, curosurf, exosurf, infasurf, survanta or alveofact. Recent evidence suggests that natural surfactants offer several advantages over synthetic surfactants such as, faster weaning of supplemental oxygen and mean airway pressure, reduced duration of mechanical ventilation, and decreased rate of mortality [6]. On the other hand, counter arguments exist in favor of synthetic surfactant formulations, such as lower cost and resistance to inactivation in the body [7]. In light of the opposing arguments, an understanding of the overall rank of the efficacies of current EPS therapies is important in choosing the optimal clinical intervention approach to treat NRDS. Unfortunately, currently randomized trials, that compared the efficacy of EPS, are equivocal or were terminated early owing to insufficient patient enrollment [8,9]. In order to directly address this issue, we performed a network meta-analysis, simultaneously comparing a set of interventions for a specific disease by a common comparator intervention, using data from published studies of randomized controlled trials (RCTs), to rank the effectiveness of six current most common EPS therapies for NRDS [10,11].

2. Materials and methods

2.1. Search strategy

This systematic review was performed on the basis of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [12]. We comprehensively searched PubMed, Ovid, EBSCO, Springerlink, Wiley, Web of Science, Cochrane Library, China National Knowledge Infrastructure, Wanfang and VIP databases (last updated search in October 2014) using the key terms “neonatal respiratory distress syndrome” and “exogenous pulmonary surfactant” from title and abstract. The reference lists of the included studies were reviewed as a supplement. No language limits were applied to literature search. Authors of included trials were contacted by email for any unpublished and undergoing similar trials, and literature searching was in combination with published systematic reviews or meta-analysis.

2.2. Eligibility and exclusion criteria

In the meta-analysis, published clinical trials were screened based on the following inclusion criteria: (1) study design: RCTs; (2) RCT: two-arm or three-arm trials (3) interventions: treatment with Survanta, Alveofact, Infasurf, Curosurf, Surfaxin or Exosurf for NRDS; (4) study subject: infants (23–36 weeks) with NRDS confirmed by clinical diagnosis [4]; (5) outcome: the mortality rate of infants with NRDS; (6) publication year range: 1995–2013 year; (7) follow-up duration: 36 weeks. In cases of overlap reports, we included only the latest results. Studies were excluded if (1) the treatment was with a combination of drugs or treatments mixed with non-drug interventions (2) they contained insufficient data that means data was associated with study theme, but without end outcomes, even contact with the author.

2.3. Data extraction and quality assessment

Relevant information, including the first author, publication year, country, language, disease, age, gender, and number of cases, doses of each EPS, were systematically extracted, with particular focus on the treatment strategy. The primary endpoint was the mortality rate of infants with NRDS. All data from eligible trials were extracted by two investigators independently, using a standard form. Any disagreements were resolved by discussion with a third investigator. The corresponding investigators of included trials were contacted through emails obtain missing outcome data which also could be obtained from published systematic reviews or meta-analysis. Methodological quality of the RCTs included in this study was evaluated by two or more investigators using the Cochrane Collaboration's tool for assessing risk of bias [13]. The risk of bias covers six domains, including random sequence generation, allocation concealment, blinding of participants or blinding outcome assessment, incomplete outcome data, selective reporting and other bias. The detailed assessment criteria were: (1) whether allocation sequence is generated properly; (2) whether the method used to conceal the allocation sequence is appropriate; (3) whether the intended blinding was effective; (4) whether the incomplete outcome data are dealt with appropriately; (5) state how selective outcome reporting was examined and what was found; (6) whether any other important concerns about bias is covered in the other domains in the tool. Trials with high or unclear risk of bias for any one of the first three components were considered as trials with high risk of bias. Otherwise, they were regarded as trials with low risk of bias.

2.4. Statistical analysis

Statistical analysis was conducted using STATA statistical software (Version 12.0, Stata Corporation, College Station, TX, USA) and Comprehensive Meta-analysis (CMA 2.0) software. Odds ratio (OR) with 95% confidence intervals (95% CI) was calculated by applying fixed effects model or random effects model to evaluate the effects of intervention group and control group on the mortality rate of infants with NRDS. The pooled ORs were assessed using the Z test [14]. To account for heterogeneity between studies, the Cochran's Q-statistic was employed ($P < 0.05$ was considered significant). The heterogeneity was further assessed with the I^2 statistic and a value of more than 50% was considered as statistically significant heterogeneity. Random effects model was applied when significant heterogeneity existed ($P < 0.05$ or I^2 test exhibited > 50%), otherwise, fixed-effects model was utilized [15]. Random-effects meta-regression was applied to evaluate clinical and methodological heterogeneity within the treatment network. Network meta-analysis synthesizes data from a network of clinical trials containing more than two interventions. The integration of direct head-to-head evidence (from studies directly comparing interventions) with indirect evidence (information about two treatments derived via a common comparator) enhances the precision in the evaluation and produces a relative ranking of all interventions for the studied outcome [16]. The heterogeneity in each closed loop was estimated by utilizing inconsistency factor (IF). If the 95% confidence intervals (95% CI) of IF values are not truncated at zero, it