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Comparison of efficacy and safety of two available natural surfactants in Iran, Curosurf and Survanta in treatment of neonatal respiratory distress syndrome: A randomized clinical trial

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ABSTRACT

Introduction: The benefit of surfactant prescription for respiratory distress syndrome (RDS) has been approved. Curosurf and Survanta are two commonly used natural surfactants in Iran. Previous studies did not report priority for one of these two drugs. The present study aimed to compare the effectiveness and safety of Curosurf and Survanta in treatment of RDS.

Methods: In this randomized clinical trial, neonates were born with RDS diagnosis in two governmental and referral hospitals of Tehran (the capital of Iran) in 2014 were randomly selected. Neonates were randomly assigned into two groups receiving 100 mg/kg Curosurf or Survanta as soon as possible after randomization. Complications, mortality and needing the second dose were compared between the two groups.

Results: A total 112 patients with the mean gestational age of 32.59 ± 3.39 weeks were evaluated (56 patients in each group). There were no significant differences regarding birth weight, gestational age, delivery method, and parity between the two groups ($P > 0.05$). The complications were occurred in 18 neonates (32.1%) of Curosurf group and 20 neonates (35.7%) of Survanta group (RR = 0.922, 95% CI = 0.617–1.379). There were no significant differences regarding complications, mortality, and needing nasal CPAP and endotracheal tube between the two groups. In the neonates with gestational age of 29–32 weeks the IVH and NEC incidence were significantly more in Curosurf group compared to Survanta group (27.8% vs 0% and 22.3% vs 0%, $P < 0.05$).

Conclusion: There was no significant difference in complications or mortality between those two groups; however Curosurf was associated with less need of ET tube (in >32 birth weeks subgroup) and NCPAP (in 29–32 birth weeks subgroup) ($p = 0.008$). Further evaluations with longer follow-up duration are needed for comparing these two surfactants.

1. Introduction

Involving approximately 60% of infants with gestational age of lower than 30 weeks and 42% of those with birthweight lower than 1500 gr, respiratory distress syndrome (RDS) or hyaline membrane disease (HMD) is the most common respiratory disease and most important cause of mortality in premature infants [1,2].

RDS has a progressive trend and its severity increases during the first two days of life which may be resulted in death due to hypoxemia and respiratory failure [3]. Various studies were conducted to determine the physiopathology of the disease and eventually the effect of surfactant in lung maturity was discovered in 1929. Successful application of surfactant in RDS was first reported in 1980 [4,5].

Respiratory protection, endotracheal mechanical ventilation (EMV) and nasal continuous positive air way pressure (N.CPAP) and surfactant prescription is the basis of management in RDS [6,7].

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Associated complications with mechanical ventilation have led to design of new strategies [7]. Early application of N.CPAP and Surfactant has been shown effective in reducing need to EMV and complications as well as improving RDS prognosis in infants [7,8]. Previous studies have reported INSURE as an effective method for reducing side effects of RDS management as well as hospitalization duration and expenses [9–11].

Thus the benefit of surfactant prescription for RDS treatment has been approved. At the present time, surfactant is available in Iran with various trading names and there are some controversies about their effectiveness. Curosurf and Survanta are two commonly used natural surfactants in Iran. Previous studies did not show significant priority for one of these two drugs. So in the present study we aimed to compare the effectiveness and safety of Curosurf versus Survanta in treatment of RDS.

2. Methods

This randomized clinical trial was approved by ethics committee of Baqiyatallah University of Medical Sciences (IR.BMSU.REC.1394.107) and was registered at Iranian Registry of Clinical Trials (IRCT) with unique ID of **IRCT2015082817413N12**.

Neonates were born with RDS diagnosis in Najmieh and Baqiyatallah hospitals, two governmental and referral hospitals from south and north areas of Tehran (the capital of Iran) in 2014 were randomly selected. The selection was done based on a randomization list among RDS neonates in 2014. Other inclusion criteria were birth weight more than 750 gr; gestational age less than 35 weeks; O_2 saturation 85%–96%; signed informed consent by parents, and age ≤6 h at the time of randomization. RDS diagnosis was based on clinical picture of infant with the onset of progressive respiratory failure shortly after birth (manifested by an increase in the work of breathing and an increase in the oxygen requirement), in conjunction with a characteristic chest radiograph (low lung volume and the classic diffuse reticulogranular ground-glass appearance with air bronchograms).

Neonates with congenital heart diseases and other life threatening congenital anomalies, respiratory failure due to other causes except RDS, 5 min Apgar score ≤3, proven fetal lung maturity profile from amniocentesis, prior treatment with exogenous surfactant, prolonged (≥3 weeks) rupture of membranes, untreated hypotension, or hypoglycemia, use of high-frequency ventilation prior to first dose of surfactant, and severe grades of intraventricular hemorrhage (grades III or IV) by cranial ultrasound prior to surfactant were excluded from study. The study flowchart is shown in Fig. 1.

Neonates were randomly assigned into two groups. Randomization was stratified by birth weight with two birth weight strata (below 1250 gr and more than 1250 gr). A randomization list was generated from 1 to 112 by SPSS software and neonates were randomly assigned into each intervention group by their numbers. The block randomization technique with 1:1 ratio was used to achieve balanced group sizes.

2.1. Intervention

After intubation the group one infants were received 100 mg/kg Curosurf and group two infants were received 100 mg/kg Survanta as soon as possible after randomization. Infants were extubated after surfactant injection and nasal continuous positive airway pressure (CPAP) set at 4 cm H_2O pressure. The nasal CPAP were discontinued if the symptoms resolve and in case of FIO_2 < 0–40, PEEP <5 cm H_2O, and in the arterial blood gases $PaCO_2$ < 60 mmHg, PaO_2 > 50 mmHg, and PH > 7.25. In case of oxygen saturation by pulse oximetry less than 85%, PaCO2 > 60 mmHg, PaO_2 < 50 mmHg, and PH < 7.2 the PEEP was increased to 6 cm H_2O and in case of resistant oxygen saturation less than 85% the intubation was done and continued by mechanical ventilation. Additional dose of surfactant was given in 12–24 h if the infant continued to require mechanical ventilation and an FIO_2 of 0.30 or greater to maintain an oxygen saturation by pulse oximetry greater than 85%.

2.2. Evaluations and measurements

Gestational age was measured by mean of two first trimester Crown Rump Length measurements at the first antenatal visit.

The Apgar score was calculated using heart rate, respiratory effort, muscle tone, reflex irritability, and color given values of 0, 1, or 2 [12]. The diagnosis of sepsis was based on positive blood culture and pneumonia was approved by chest radiography, seeing bilateral alveolar densities with air bronvhograms or irregular patchy infiltrates. Cranial ultrasonography was also used for diagnosis of intraventricular hemorrhage (IVH).

2.3. Statistical analysis

Data were analyzed by statistical package for social sciences (SPSS) version 21 (SPSS Inc. Chicago, IL) for windows. Study infants described using mean descriptive statistics, standard deviation, and frequency then two groups compared by independent sample *t*-test or its nonparametric equivalent (Mann-Whitney, if indicated) for quantitative variables, then Chi-square or Fisher exact (if indicated) tests used for qualitative variables. The *P*-values that were less than 0.05 were considered statistically significant.

3. Results

A total 112 patients with the mean gestational age of 32.59 ± 3.39 weeks and birth weight of 1911.3 ± 786.5 gr were evaluated (56 patients in each group). There were no significant differences regarding birth weight, gestational age, delivery method, and parity between the two groups (P > 0.05, Table 1). Also there were no significant differences in mother's diabetes, steroid injection, IUGR, placental abruption, PROM, first and 5 min Apgar, and needing CPR between the two groups (P > 0.05, Table 1). The mother's hypertension was significantly more in Curosurf group in comparison of Survanta group (16.1% vs. 3.6%, P = 0.026). Mothers/neonates-related risk factors are shown in Table 1.

Time of surfactant injection was 8.04 ± 10.6 h in Curosurf group and 8.35 ± 9.76 h in Survanta group (P = 0.874). There were also no significant difference in needing the second surfactant dose between the two groups (OR = 2.179, 95% CI = 0.90–5.28). The mean hospital stay was 16.57 ± 11.43 days in Curosurf group and 15.36 ± 14.39 days in Survanta group (P = 0.622, Table 2).

3.1. Complications

Thirty eight neonates were complicated, the complications were occurred in 18 neonates (32.1%) of Curosurf group and 20 neonates (35.7%) of Survanta group (RR = 0.922, 95% CI = 0.617–1.379).

The sepsis was occurred in 7 neonates, pneumonia 16 neonates, IVH in 11 neonates, pulmonary hemorrhage in 9 neonates, NEC in 8 neonates, pneumothorax in 7 neonates, and ROP in 4 neonates. There were no significant differences regarding complications between the two groups (Table 3).

Twenty one patients had gestational age of below 28 weeks (6 neonates in Curosurf and 15 neonates in Survanta groups). There were no significant differences regarding complications between the two groups in below 28 weeks neonates; sepsis (16.7% vs 26.7%, P = 0.672), pneumonia (16.7% vs 13.3%, P = 0.844), IVH (16.7% vs