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Original Article

Exploration of the Impacts of Curosurf at 100 and 200 mg/kg Doses in Neonates with Respiratory Distress Syndrome

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ABSTRACT

Background: The use of surfactants is still considered a cornerstone in the treatment of neonatal respiratory distress syndrome (RDS). This study aimed to compare two doses of Curosurf to determine the most effective dose of this medicine with the least side effects. The study was performed as a double-blind clinical trial in the Neonatal Intensive Care Unit of Valiasr Hospital in Birjand, Iran, from June to October 2021 on 51 neonates admitted with RDS.

Methods: Neonates with RDS who met the inclusion criteria were randomly divided into two groups. Initially, they underwent nasal Continuous Positive Air Way Pressure (n-CPAP), and if failed, Curosurf was administered intratracheally at a dose of 100 or 200 mg/kg. The two groups were compared in the mean hospital stay, the need for supplemental oxygen, the need for n-CPAP, the start of complementary feeding after Curosurf injection, the relative frequency of the need for mechanical ventilation, and possible complications after the injection and re-injection of surfactant. Data were analyzed using the independent sample t-test, the Mann–Whitney U test, Chi-squared test, and Fisher's exact test at a significance level of $\alpha=0.05$.

Results: The sample size was calculated based on the existing studies considering the days of the need for oxygen therapy in the two groups with different doses of surfactant (6.4±3.5 and 8.9±2.6 days) and according to the formula for comparing the means in the two groups with 95% confidence interval and 80% power. Accordingly, 24 neonates were assigned to each group. $N=[z\ (1-\alpha/2)+z\ (1-\beta)]\ (\delta 12+\delta 22)/\ (\mu 1-\mu 2)2$. Data were analyzed at a significant level of $\alpha=0.05$. The findings indicated no significant difference between the two groups of neonates in the mean length of hospital stay, adjuvant oxygen requirement, n-CPAP requirement, time to oral feeding initiation from birth with breast milk (with breast or assistive devices) or formula, the relative frequency of the need for mechanical ventilation, and possible side effects after the injection and re-injection of surfactant.

Conclusion: In conclusion, 100 and 200 mg/kg of Curosurf appear to have the same effects and outcomes in the treatment of neonatal RDS.

Keywords: Curosurf®, Mechanical ventilation, N-CPAP, RDS, Surfactant

Introduction

Respiratory distress syndrome (RDS) is a common disease in most premature infants. Its prevalence in premature infants less than 28 weeks gestation is about 60%-80%, while in premature infants with a gestational age of 36-32 weeks, it is about 15%-30% (1). The primary cause of this disease is surfactant deficiency (decreased secretion or lack of production) (2), and its clinical symptoms include tachypnea, obvious grunting, nasal flaring, intercostal and subcostal retractions, and cyanosis. It is approved that the lack of timely treatment or inappropriate methods and doses of medication increase mortality and cause multiple complications in infants2 with RDS using nasal Continuous Positive Air Way Pressure (n-CPAP) as prophylaxis and for

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ventilatory support. In infants with RDS and n-CPAP failure, it is essential to administer surfactant into the lungs in different ways to prevent lung damage (1). The immediate effects of surfactant replacement therapy include improving the alveolar-arterial oxygen gradient, reducing respiratory support, increasing pulmonary consent, and improving the graphic appearance of the lung (1). Currently, surfactants are mostly from natural sources (such as animal sources) and sometimes industrial. Among animal surfactants, Poractant alfa (Curosurf®), Bovactant (Alveofact®), and Beractant (Survanta®) are approved for consumption in Europe despite their different side effects and high prices (3). Among the available brands in the Iranian market, Curosurf is widely used; however, the international community has not stated a recommended fixed dose for its consumption (100-200 mg/kg) (3). Furthermore, various researchers have only studied the types of surfactants and compared their prescription methodologies (4-8). Therefore, due to the possibility of various side effects and therapeutic responses in different doses and the high price of this medication, it is necessary to find the minimum dose with the least side effects and the most effective therapeutic function. Therefore, this study aimed to compare the impact and outcome of administering Curosurf surfactant at doses of 100 and 200 mg/kg in neonates with RDS.

Methods

The present study was a double-blind clinical trial since neonates' parents and the analyst were unaware of the group assigned to each person. The study was performed from June to October 2021 on premature infants with RDS admitted to the Neonatal Intensive Care Unit (NICU) of Valiasr Hospital in Birjand, Iran.

The sample size was based on Wang and Wang (11) on the days of the need for oxygen therapy in the two groups with different doses of surfactant (6.4±3.5 and 8.9±2.6 days) and according to the formula for comparing the means in the two groups with 95% confidence interval and 80% power. Accordingly, 24 neonates were assigned to each group. $N=[z\ (1-\alpha/2)+z\ (1-\beta)]\ (\delta 12+\delta 22)/(\mu 1-\mu 2)2$. The researcher randomly selected the infants, but only those with written consent and eligible to enter the study were chosen and given a secret code. After that, they were referred to the resident physician in the NICU to receive the relevant intervention according to the random allocation code.

The study population included 61 premature infants at baseline. The inclusion criterion was the diagnosis of RDS based on clinical and radiographic evidence and laboratory results. After receiving n-CPAP and showing no response to the treatment, they were treated with surfactant. On the other hand, the exclusion criteria were congenital heart and lung abnormalities, infection or shock, cardiac massage in the delivery room, pneumonia at birth, pulmonary hemorrhage before injection, asphyxia, and parental dissatisfaction. The study protocol was approved by the Ethics Committee of Birjand University of Medical Sciences (code: IR.BUMS.REC.1399.421) and the Iranian Registry of Clinical Trials (code: IRCT20210102049921N1). After obtaining written consent from parents, the infants entered the first stage of the study. In total, 51 infants with RDS diagnoses who needed to receive surfactants were randomly assigned to one of the two groups receiving 100 or 200 mg/kg surfactants. The restriction randomization method was used to assign randomization using Permuted block randomization based on blocks of eight patients.

The steps of selecting and assigning patients are shown in Figure 1.

The surfactant used in this study was Poractant alfa under the brand name of Curosurf® (Chiesi Farmaceutici, Italy). The recommended dose for the first injection was 100-200 mg/kg based on world-renowned sources. While infants were receiving oxygen with n-CPAP, Curosurf was injected intratracheally by Minimally Invasive Surfactant Therapy or Less Invasive Surfactant Administration (LISA) methods. In these methods, the material enters the trachea with narrow catheters (LISAcath) instead of intubation. Moreover, 16G angiocath, suction catheters, umbilical artery catheters, or feeding tubes can be used instead of this catheter (9). The researchers also used feeding tubes 5Fr. The second Curosurf (100 mg/kg) was injected into infants whose clinical symptoms, including intravenous blood gases (VBG), fractional inspired oxygen (FiO2), saturation of peripheral oxygen (SPO2) and chest X-ray control, did not improve within the next 6 h. Data were analyzed by the SPSS software (version 22). Since the distribution of the study variables (hospital days, duration of supplementary oxygen requirement, and other variables) was not normal, the Mann-Whitney U test was applied to compare the means between the two groups. Additionally, the Chi-squared test and Fisher's exact test were used for comparing qualitative variables. The significance level was $\alpha=0.05$.

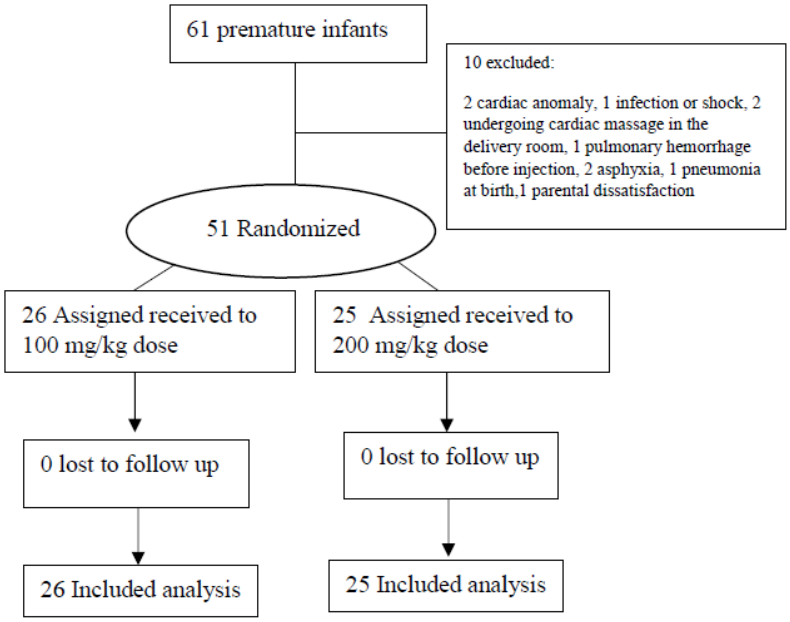

Figure 1. Steps of selecting and assigning participants

Results

This study included 51 neonates with a mean weight of 1607.94±528.81 g, with 26 in the 100 mg/kg surfactant dose group and 25 in the 200 mg/kg surfactant dose group. The mean gestational age was about 32 weeks. Table 1 shows the results of comparing the characteristics of neonates (the mean weight, Apgar, gestational age, maternal age, singleton, cesarean section, maternal smoking, and opium use by the mother) in the two groups. As can be seen, there was no statistically significant difference between the two groups (P<0.05).

The mean days of infants' hospitalization were 15.76±14.30 days. The minimum and maximum length of hospitalization were 3.5 and 82 days, respectively. It was observed that the days of hospitalization in the group receiving 100 mg/kg of surfactant were more than that in the 200 mg/kg group, though the difference was not statistically significant (P=0.83) (Table 2). Furthermore, the duration of auxiliary oxygen requirement and the duration of n-CPAP requirement after surfactant injection were not significantly different in the study groups (Table 2). It should be added that no statistically significant differences were observed in the duration of oral feeding (h) after the surfactant was administered in the two intervention groups (P=0.30) (Table 2).

Table 1. Comparison of the characteristics of infants and mothers in the studied groups

Characteristic	100 mg/kg dose group		200 mg/kg dose group		*Statistically significant
	mean±SD		mean±SD		
Weight (g)	1595.96±555.65		1620.40±510.53		0.87
Apgar minute one	7.2±1.6		7.3±1.8		0.79
Gestational age (w)	31.92±2.99		31.96±2.65		0.96
Gravidity	2.6±1.4		2.5±1.1		0.63
Mother age (y)	29.2±5.8		28.4±5.8		0.52
	N (%)		N (%)		**
	Yes	No	Yes	No	
Singleton	21 (80.8)	5 (19.2)	17 (68)	8 (32)	0.28
Cesarean section	20 (76.9)	6 (23.1)	17 (68)	8 (32)	0.46
Maternal smoking	1 (3.8)	25 (96.2)	0 (0)	25 (100)	1
Mother opium addiction	2 (7.7)	24 (92.3)	3 (12)	22 (88)	0.66

*Independent sample t-test
**Chi-squared test and Fisher's exact test

Table 2. Comparison of the outcomes in the studied groups

Outcome	100 mg/kg dose group Median (25th and 75th percentile)	200 mg/kg dose group Median (25th and 75th percentile)	*Statistically significant
Duration of hospitalization (day)	13.5 (8.25-18.25)	11 (9.25-16)	0.83
Duration of auxiliary oxygen requirement (h)	6 (5.5-41.5)	8 (6-39)	0.70
Duration of n-CPAP requirement (h)	36 (24-108)	48 (13-102)	0.22
Duration of oral feeding (h)	30 (16-42)	38 (22-51)	0.30

*Mann-Whitney U test
n-CPAP: nasal Continuous Positive Air Way Pressure

The findings showed that 19 infants (37.3%) needed mechanical ventilation after surfactant injection, which was higher in the group receiving 100 mg/kg of surfactant. However, this difference was not statistically significant (P=0.85) (Table 3).

Complications following surfactant injection include pulmonary hemorrhage, pneumothorax, intracerebral hemorrhage, pneumonia, and sepsis. After surfactant injection, pulmonary hemorrhage was observed in one infant in the 100 mg/kg group. The number of cases requiring the second dose of surfactant injection was not different in the study groups (Table 3). Mortality in the 100 mg/kg surfactant dose group was 3.8%, while there was no complication (including pneumothorax, pulmonary hemorrhage, cerebral hemorrhage, pneumonia, and sepsis) in the 200 mg/kg dose group (Table 3).

Table 3. Comparison of the need for mechanical ventilation, surfactant re-injection, complications, and mortality in the study groups

Outcome	100 mg/kg dose group	200 mg/kg dose group
	N (%)	N (%)
Need for mechanical ventilation	10 (38.5)	9 (36)
Complications	0 (0)	1 (4)
Re-injection	1 (3.8)	1 (4)
Mortality	1 (3.8)	0 (0)

Discussion

In this comparative study, no significant difference was observed in the efficacy of 100 and 200 mg/kg of Curosurf surfactant in the treatment of neonates with RDS admitted to the NICU of Valiasr Hospital in Birjand, Iran. There were no statistically significant differences between the two study groups in the mean lengths of hospitalization following Curosurf injection, the relative frequency of the need for mechanical ventilation after surfactant administration, the mean duration of indirect oxygen supplementation after Curosurf injection, the mean duration of n-CPAP after Curosurf injection, the relative frequency of side effects after Curosurf injection, the mean duration of oral feeding after surfactant administration, the number of cases requiring re-administration of the second dose of surfactant, and mortality. Although several studies have been performed on comparing the effectiveness, side effects, clinical benefits, and the methods of prescribing different types of natural surfactants (4-8), few studies have been conducted on independently comparing doses of Curosurf. Before 2019, all valid protocols in the world regarding the permissible dose of Curosurf injection in the first injection emphasized a 200 mg/kg dose. However, since 2019, the European consensus guidelines on the management of RDS have allowed doses between 100 and 200 mg/kg.3 In the same year, the UK national consensus allowed both doses, though stating that 200 mg/kg was associated with a better prognosis (10).

In the study by Wang and Wang (11), 54 infants with RDS were divided into three groups: severe, moderate, and mild. Based on the degree of hypoxemia during hospitalization, and prescription doses above 150 mg/kg and below 150 mg/kg were used. This study showed that in infants with severe RDS, receiving a high dose of Curosurf was associated with a shorter hospital stay (P<0.05). The severity of the disease and hypoxia were not classified in the present study; however, there was no statistically significant difference in the mean length of hospital stay between the two groups. Several studies revealed no difference between 200 mg/kg and 100 doses of surfactant in the need for mechanical ventilation after receiving surfactant (12,4). This is consistent with the present study findings, although 10 infants in the 100 mg/kg dose group and 9 in the 200 mg/kg dose group were mechanically ventilated. Olejnic et al. (13) showed that the need for long-term mechanical ventilation did not vary significantly at different doses of

Curosurf, while in the study by Wang and Wang, the need for mechanical ventilation was lower at higher doses than that at lower doses in severe cases (11).

In a study on the mean duration of indirect oxygen supplementation after Curosurf injection, Chao and Grobelna4 illustrated that there is no difference between 200 and 100 mg/kg, which is compatible with the current results. Furthermore, Wang and Wang (11) expressed that in severe and moderate cases of the disease, the duration of supplemental oxygen requirement at a dose of 200 mg/kg was shorter, compared to that in lower doses. On the other hand, in mild cases of the disease, the results were in line with the obtained findings in the present study. The mean duration of n-CPAP requirement after Curosurf injection did not differ between the two groups, although the need for n-CPAP was about 7 h less in the 100 mg/kg group. Furthermore, Olejnic et al. (13) obtained similar findings representing that the need for supplemental oxygen in different methods was similar in different doses, except for less need during the first three days at a dose of 200 mg/kg Curosurf. They also witnessed no side effects after Curosurf injection, except for one case in the 100 mg/kg group, and no statistically significant difference between the two groups.

It is noticeable that many studies confirm the present findings (4, 11, 14). However, in a meta-analysis study by Singh et al. (12), it was found that mortality was significantly reduced in the group using swine surfactant or Curosurf at a dose of 200 mg/kg, compared to the group receiving 100 mg/kg. It was also represented that the number of cases requiring the re-administration of the second dose of surfactant was not different between the two groups. This was compatible with the results obtained by Ramanathan et al.14 and the current findings. In the meta-analysis study by Singh et al. (12), it was observed that the need for the second dose was less at the dose of 200 mg/kg than the dose of 100 mg/kg. The duration of oral feeding after surfactant administration was not significantly different between the two groups (approximately 36 min).

In this study, the initial consequences of hospitalization time, the relative need for mechanical ventilation, common complications after surfactant administration (pulmonary hemorrhage, cerebral hemorrhage, pneumonia, and necrotizing enterocolitis), the duration of the need for indirect assistance, the time of starting oral feeding, the need for feeding (n-CPAP) after surfactant, and the need for surfactant re-administration were compared between the two study groups. This study only focused on hospitalized infants until discharge and did not examine secondary outcomes.

Despite the limitations due to the prevalence of COVID-19 disease at the time of the study, the findings show that there is no difference between 100 and 200 mg/kg of Curosurf surfactant. In addition, because of the expensive price of this surfactant, it can be a step toward reducing the cost of family treatment and helping the country's economy.

Conclusion

In general, based on clinical and statistical information, it seems that using a high dose (200 mg/kg) of Curosurf, compared to a low dose (100 mg/kg), does not have a specific clinical preference. Although some differences have been observed, they were not significant or effective.

Acknowledgments

None.

Conflicts of interest

The authors declare no conflict of interest.

Authors' contributions

All the authors, Dr. Gholamreza Faal, Dr. Reza Poorhoseiny, and Dr. Bita Bijari, actively participated and contributed to the design and implementation of this study, analysis of the results, and writing of the manuscript.

References

1. Kliegman RM, ST Geme JW, Blum NJ, Shah SS, Tasker RC, Wilson KM. Textbook of Pediatrics. 21th ed. Philadelphia: Elsevier; 2020.
2. Martin RJ, Fanaroff AA, Walsh MC. Fanaroff and Martin's neonatal-perinatal medicine diseases of the Fetus and Infant. 11th ed. Philadelphia: Elsevier; 2020.
3. Sweet DG, Carnielli V, Greisen G, Hallman M, Ozek E, Te Pas A, et al. European consensus guidelines on the management of respiratory distress syndrome - 2019 Update. Neonatology. 2019; 115(4):432-50.
4. Chao YC, Grobelna A. Curosurf (Poractant alfa) for the treatment of infants at risk for or experiencing respiratory distress syndrome: A review of clinical effectiveness, cost-effectiveness, and guidelines [Internet]. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2018.
5. Mirzarahimi M, Barak M. Comparison efficacy of Curosurf and Survanta in preterm infants with respiratory distress syndrome. Pak J Pharm Sci. 2018; 31(2):469-472.
6. Mussavi M, Mirnia K, Asadollahi K. Comparison of

the efficacy of three natural surfactants (curosurf, survanta, and alveofact) in the treatment of respiratory distress syndrome among neonates: a randomized controlled trial. Iran J Pediatr. 2016; 26(5):1-10.
7. Najafian B, Karimi-Sari H, Khosravi MH, Nikjoo N, Amin S, Shohrati M. 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. Contemp Clin Trials Commun. 2016; (3):55-59.
8. Şimşek GK, Kutman HGK, Canpolat FE, Oğuz SS. Effect of two different early rescue surfactant treatments on mortality in preterm infants with respiratory distress syndrome. Clin Respir J. 2019; 14(3):285-90.
9. Herting E, Hartel C, Gopel W. Less invasive surfactant administration (LISA): Chances and limitations. BMJ. 2019; 104(6):655-659.
10. Banerjee S, Fernandez R, Fox GF, Goss KCW, Mactier H, Reynolds P, et al. Surfactant replacement therapy for respiratory distress syndrome in preterm infants: United Kingdom National Consensus. Pediatr Res. 2019; 86:12-14.
11. Wang N, Wang L. Pharmacoeconomic evaluation of different doses of Curosurf for treating neonatal acute respiratory distress syndrome. Pak J Pharm Sci. 2020; 33(3):1139-46.
12. Singh N, Hawley KL, Viswanathan K. Efficacy of porcine versus bovine surfactants for preterm newborns with respiratory distress syndrome: systematic review and meta-analysis. Pediatrics. 2011; 128(6): 1588-95.
13. Królak-Olejnik B, Hozejowski R, Szczapa T. Dose Effect of Poractant Alfa in Neonatal RDS: Analysis of Combined Data from Three Prospective Studies. Front Pediatr. 2020; 8:1-8.
14. Ramanathan R, Rasmussen MR, Gerstmann DR, Finer N, Sekar Kandthe, North American Study Group. A Randomized, Multicenter Masked Comparison Trial of Poractant Alfa (Curosurf) versus Beractant (Survanta) in the Treatment of Respiratory Distress Syndrome in Preterm Infants. Am J Perinatol. 2004; 21:109-19.