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Original Article

Intratracheal Administration of Budesonide-instilled Surfactant for Prevention of Bronchopulmonary Dysplasia: A Randomized Controlled Clinical Trial

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ABSTRACT

Background: Despite numerous clinical strategies performed over the years, Bronchopulmonary dysplasia (BPD) still remains a common disease with considerable long-term adverse effects in very premature infants. This study investigated the effect of budesonide-instilled surfactant on the incidence of BPD in preterm infants.

Methods: In this clinical trial, a total of 190 neonates with a gestational age of less than 30 weeks, who were identified as candidates for surfactant therapy, were randomly assigned to two groups. The control group (S) received surfactant at a dosage of 200 mg/kg for the initial dose and 100 mg/kg for subsequent doses. In cases where it was deemed necessary (n=95), the intervention group (BS) received surfactant along with budesonide, instilled once at a dose of 0.25 mg/kg (n=95). The primary outcome was the occurrence of BPD, and the combined incidence of BPD and death Secondary outcomes encompassed other complications related to prematurity and adverse effects associated with corticosteroid use.

Results: Demographic characteristics of the neonates were comparable between the two groups. Although a slight reduction was seen in the incidence of BPD in the group receiving budesonide, BPD rates remained statistically unchanged after the intervention (48.4% in the BS group vs 50.5% in the S group, P value = 0.772). The combined outcome of BPD and death was insignificantly different between the two groups (61.1% in the BS group vs. 63.2% in the S group, P value = 0.765). The addition of budesonide resulted in an increased incidence of sepsis and pneumothorax in the control group. However, secondary outcomes such as IVH (Inra ventricular Hemorrhage), retinopathy of prematurity, necrotizing enterocolitis, patent ductus arteriosus, and hyperglycemia were unaffected. Duration of total parenteral nutrition and hospitalization time were longer in the BS group than in the S group.

Conclusion: The addition of budesonide to surfactant in very premature neonates at gestational age <30 weeks who were candidates for surfactant therapy did not prevent BPD. Conversely, it led to an increase in certain secondary morbidities such as sepsis and pneumothorax. Furthermore, it extended the duration of hospitalization.

Keywords: Bronchopulmonary dysplasia, Budesonide, Surfactant

Introduction

Years after its initial introduction by Northway et al., Bronchopulmonary dysplasia (BPD) still remains a prevalent and challenging issue in very premature infants. While advances

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in neonatal care have led to a less fatal disease, morbidities and challenges in treatment persist (1). Furthermore, even after successfully managing the acute phase of the condition, the likelihood of enduring long-term complications and subsequent re-hospitalizations remains significant (2,3).

Clinicians perform numerous strategies to prevent and/or treat BPD, of which the use of postnatal corticosteroids is in accordance with the central pathogenesis known for the disease inflammation (4). Studies have suggested that early postnatal use of systemic corticosteroids prevents BPD and facilitates extubating; however, significant adverse effects, such as cerebral palsy, gastrointestinal bleeding, hypertension, and hyperglycemia, might be pursued (5). In attempts to lower the unfavorable adverse effects and maximize direct drug effect in the lungs, inhaled corticosteroids (ICS) was proposed and examined in several trials and clinical practices (6). Although the use of ICS is associated with lower rates of BPD, results remain inconclusive (7-10).

A recent promising trend has emerged, focusing on treating patients with a combination of surfactant and budesonide. Budesonide has been proven to have strong and long-lasting local anti-inflammatory effects, (11,12) While surfactant, acting as a vehicle, delivers budesonide to distal parts of the lung. The combination administered intratracheally has been shown to improve gas exchange and oxygenation index (13-15). Despite limited research investigating the effect of the combination of surfactant and budesonide on BPD, existing literature suggests that intratracheal instillation of this combination is associated with reduced rates of BPD and decreased mortality (16-18). Furthermore, this approach might offer the advantage of avoiding the adverse effects often associated with systemic corticosteroid use (19).

Hoping to reduce the incidence of BPD in patients of the current study and in an attempt to affirm the former findings, the present research aimed to examine the effects of intratracheally administered budesonide mixed with surfactant in comparison with surfactant alone on the prevention of BPD in premature infants who were candidates for surfactant administration.

Methods

The present study was a randomized, controlled clinical trial. Patients were selected from Neonatal Intensive Care Unit (NICU) wards of Alzahra and Beheshti hospitals, tertiary referral centers affiliated with Isfahan University of Medical Sciences, Isfahan, Iran. Beginning in March 2020 and ending in October 2021, all premature infants admitted to NICU with a gestational age (GA)<30 weeks that were candidates for surfactant administration were enrolled in this study. Surfactant was administered to patients requiring positive airway pressure ventilation (NCPAP) with FiO2≥30% to maintain oxygen saturation levels equal to or above 91%. Infants with major congenital anomalies, asphyxia, and sepsis prior to the study were excluded.

To investigate the effect of budesonide-instilled surfactant on the incidence of BPD, two study groups were formed, the intervention group receiving budesonide + surfactant (BS) and the control group of infants receiving only the surfactant treatment (S). Neonates were randomly assigned to one of the study groups. Due to the gradual enrollment of patients into this study, randomized assignment was performed using envelopes containing names of the therapy group using permuted block randomization of size 6. A sealed envelope was randomly selected to assign the patient to one of the two groups, namely BS (budesonide + surfactant) or S (surfactant). In the BS group, after implication of inclusion and exclusion criteria, infants received exogenous surfactant (Curosorf, Chiesi Farmaceutici, Parma, Italy) and budesonide solution (Pulmicort nebulizing suspension, Astra Zeneca, Lund, Sweden) within the first 36 hours of birth. Each infant received budesonide once at the dose of 0.25 mg/kg (0.5 cc/kg). However, in the S group, after the implication of inclusion and exclusion criteria, infants received exogenous surfactant only. The initial surfactant dose was 200 mg/kg for for both groups and 100 mg/kg for subsequent doses, if required. The dose of budesonide and its ratio to surfactant were calculated according to previous studies (20,21). Budesonide and surfactant were administered through endotracheal tube into the trachea in both groups.

The primary outcome of this study was the incidence of BPD and the combined outcome of BPD and death. The diagnosis of BPD is first based on treatment with more than 21% oxygen for at least 28 cumulative days after birth. As outlined in the NHLBI workshop guidelines, the severity of Bronchopulmonary dysplasia (BPD) is categorized into subgroups based on the fraction of inspired oxygen (FiO2) requirement at 36

weeks post-menstrual age (PMA). The subgroups are mild BPD (breathing room air at 36 weeks PMA/ discharge), moderate BPD (requiring < 30% oxygen at 36 weeks PMA/ discharge), severe BPD (requiring ≥ 30% oxygen with or without positive pressure at 36 weeks PMA/ discharge) (22). Secondary outcomes related to prematurity or corticosteroid treatment included total hospitalization days, death rate, and other complications such as sepsis, candidiasis, pneumothorax, hyperglycemia, patent ductus arteriosus (PDA), necrotizing enterocolitis (NEC) intraventricular hemorrhage (IVH), retinopathy of prematurity (ROP).

Sepsis and candidiasis were proven by culture and lab results. Pneumothorax, IVH, and NEC were diagnosed by reviewing radiologic findings by expert radiologists. The ROP would be diagnosed by indirect ophthalmoscopy. Finally, hemody-namically significant PDA was proved via echocardiograms by expert pediatric cardiologists.

Statistical analysis

Sample size in the current study was determined by considering type one error rate of 5%, statistical power of 80%, a presumed prevalence rate of 50% for chronic lung disease in neonates and the risk ratio of 0.48 as the expected effect size from applying treatments (BS in comparison with S) on the incidence of BPD as study main outcome lead to 95 patients in each study groups. The presentation of data in the study included numerical variables reported as mean ± standard deviation (SD) and categorical variables reported as frequency (percentage). Non-normal numerical data were reported as median (interquartile range [IQR: first quartile and third quartile]). Normality of continuous variables was evaluated by using Kolmogorov-Smirnov test and Q-Q plot. Non-normally distributed data were subjected to logarithmic transformation. Continuous data with normal distribution were compared between the two groups using independent samples t-test, while abnormal data were compared employing the Mann-Whitney U test. The Chi-square or Fisher's exact tests were performed to compare categorical data. The effects of intervention on categorical outcomes were quantified by using odds ratio (OR) and 95% confidence interval (95%CI) for OR by applying logistic regression. All analysis was performed by Statistical Package for the Social Science (SPSS) version 26 (IBM Inc., Chicago, IL, USA).

Ethical approval

The ethics committee of Isfahan University of Medical Sciences reviewed and approved this study (IR.MUI.MED.REC.1398,507), and it was registered in the Iranian Registry of Clinical Trials (IRCT) (IRCT20171030037093N38). Informed written and verbal consent was obtained from parents or legal guardians of the patients included.

Results

A total of 349 neonates were screened in this study. Among them, 115 patients did not meet the inclusion criteria for various reasons. Specifically, 18 neonates had congenital cardiopulmonary anomalies at birth, 26 had gastrointestinal abnormalities, 28 did not require surfactant treatment, and 43 were beyond 36 hours of age at the time of drug administration. Among the remaining 234 eligible infants, 10 were excluded due to parental reluctance to participate, while 11 infants were referred to other medical centers and were consequently excluded from the study. An additional 14 patients were lost to premature death within the first 72 hours, and 9 were excluded due to the presence of other congenital anomalies. Finally, 190 infants underwent randomization in two groups with 95 infants assigned to each group (Figure 1). Mean gestational age (GA) and birth weight (BW) in the BS and S groups were 28.94 ± 1.57 and 29.015 ± 1.57 weeks (P value= 0.741) and 1134.97 ± 237.61 and 1190 ± 289.33 grams, respectively, (P value = 0.149). As the patients were randomized into two groups, no significant difference was recognized in other demographic characteristics (Table 1).

According to Table 2, the incidence of BPD was not significantly different between the two groups. However, a slight decrease was observed in the BS group (48.4% in the BS group vs 50.5% in the S group, P value = 0.772, OR = 0.955 [0.71-1.27]). The combined outcome of BPD and death was also not statistically different between the case and control groups (61.1% in the BS group vs 63.2% in the S group, P value = 0.765, OR = 1.094 [0.608-1.96]). It was found that some secondary outcomes had a higher rate of occurrence in the intervention group. For instance, the incidence of sepsis and pneumothorax were higher in the BS group (sepsis: 32.8% and 10%; P value <0.001, OR = 3.28 [1.61-6.67]) and pneumothorax: 9.5% and 0; P value = 0.02 in BS and S groups, respectively). Duration of total parenteral nutrition (TPN) and

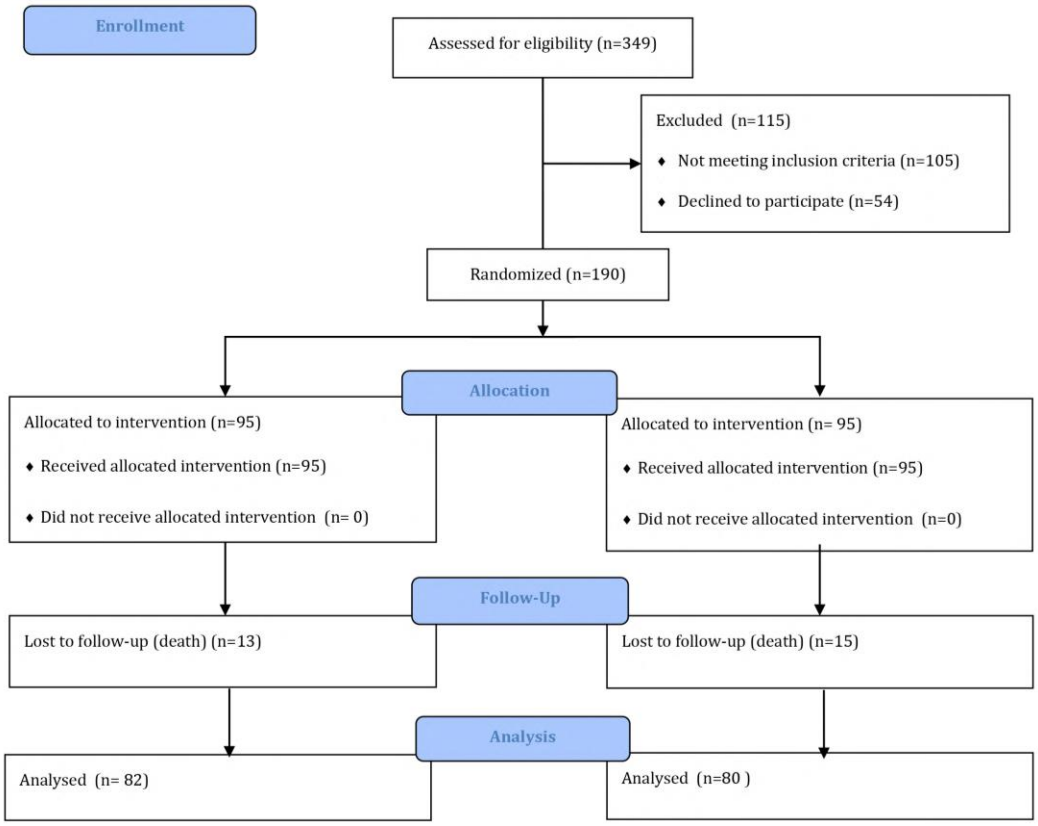

Figure 1. flow diagram of patients' recruitment and follow up

Table 1. Demographic and basic clinical characteristics of participants

		Intervention (BS) (N=95)	Control(S)(N=95)	P value*
Maternal age(year)		31.204±6.45	30.95±5.41	0.758
Gestational age(GA)(weeks)		28.94±1.57	29.015±1.57	0.741
Birth weight(gram)		1134.97±237.61	1190±289.33	0.149
Maternal race	Iranian	89(93.7%)	90(95.7)	0.606
	Afghan	3(3.2%)	3(3.2%)	
	Arab	3(3.2%)	1(1.1)	
Antibiotic use		56(59.6)	46(48.4)	0.124
Prenatal steroid use		68(73.1)	52(54.7)	0.09
Twins		36(37.9)	35(36.8)	0.881
Normal vaginal delivery		21(22.1)	18(18.9)	0.59
Maternal addiction		1(1.1)	1(1.1)	>0.99
Diabetic mother		23(24.2)	14(14.7)	0.099
Maternal renal disease		7(7.4)	2(2.1)	0.088
Maternal rheumatoid disease		2(2.1)	4(4.2)	0.4
Rupture of membrane	Hour	4 (2-11)	4(3-8)	0.428
Amniotic fluid	Oligohydramnios	24(25.5)	22(23.2)	0.287
	Polyhydramnios	9(9.6)	4(4.2)	
	Normal volume	61(64.9)	69(72.6)	
Maternal infectious disease		13(13.8)	7(7.4)	0.149
Difficult delivery		23(24.7)	33(34.7)	0.134
Asphyxia		22(23.4)	30(31.9)	0.192
Breech position		14(15.1)	10(10.5)	0.606
Sex				
Male		52(55.9)	57(60)	0.57
Female		41(44.1)	38(40)	

*Resulted from chi-squared or Fisher exact test for categorical variables, and independent samples t-test for normal and Mann-Whitney U test for non-normal continuous variables.

hospitalization time were longer in the BS group than, compared to the S group (17 ± 7.09, 12.26 ± 4.28 P value = 0.03 and 40.35 ± 18.66, 35.24 ± 14.78 P value = 0.046, OR = 5.11 ± 2.54, respectively). The incidence rates of the other neonatal outcomes, such as IVH, ROP, PDA, and NEC were not statistically different between the two groups.

Table 2. Comparison of clinical outcomes in case (BS) and control(S) groups.

Clinical outcome	Treatment groups	N(%)/ Mean±SD/ (Median(Q1-Q3)	OR (95% CI for OR)	P*
BPD	BS S	46(48.4) 48(50.5)	0.955(0.71-1.27)	0.772
IVH	BS S	56(58.9) 45(47.4)	1.24(0.95-1.63)	0.11
PDA	BS S	38(40.4) 47(49.5)	0.81(0.59-1.12)	0.135
Sepsis	BS S	22(32.8) 9(10)	3.28(1.61-6.67)	<0.001
NEC	BS S	20(22.2) 20(22)	1.01(0.58-1.47)	0.96
ROP	BS S	37(39.4) 41(43.2)	0.912(0.649-1.283)	0.596
No. of surfactant therapy	BS. S	2.92±2.7 2.92±3.08	0.89(0.56-1.04)	0.99
Intubation	BS S	20 (22.7) 16(17.8)	1.36(0.652-2.838)	0.41
NIV	BS S	18(18.9) 16(16.8)	1.12(0.452-1.12)	0.43
Hyperglycemia	BS S	11(11.43) 13(13.68)	0755(0546-1.122)	0.512
Candidiasis	BS S	6(6.31) 4(4.21)	0.552(0.432-1.23)	0.758
Pneumothorax	BS S	9(9.5) 0	N.C	0.02
Treated for RDS	BS S	18(18.9) 21(22.1)	0.331(0.208-1.108)	0.112
Death	BS S	13(13.7) 15(15.8)	0.867(0.436-1.72)	0.682
BPD+death	BS S	58(61.1) 60(63.2)	1.094(0.608-1.96)	0.765
Duration of hospitalization	BS. S	40.35±18.66 35.24±14.78	-	0.046
Weight (30 day)	BS. S	1458.62±363.13 1556.7±356.85	-	0.129
Weight at discharge	BS. S	1872.89±425.02 1763±481.16	-	0.119
Age at discharge from NICU	BS S	34.10±14.66 29.18±12.74	-	0.058
Full fed	BS. S	19(14-25) 14(9.75-19.25)	-	0.083
TPN finished	BS S	17±7.09 12.26±4.28	-	0.03

Resulted from chi-squared or Fisher exact test for categorical variables, and independent samples t-test for normal and Mann-Whitney U test for non-normal continuous variables. OR (95%CI for OR) were obtained from logistic regression. NC:not computable

Discussion

This study was designed to provide a better understanding of the effect of instilled budesonide plus surfactant on the incidence of BPD in very preterm neonates. Based on previous literature, it was hypothesized that adding this corticosteroid to surfactant would reduce BPD rates alongside other prematurity complications (16,17). However, the findings revealed that the incidence of BPD remained unchanged with budesonide treatment, although a negligible decline was seen in the incidence of BPD in the BS group, and the combined outcome of BPD and death was comparable in the two groups. The present results are consistent with the work of Moschino et al., who conducted a retrospective study involving 68 neonates weighing <1500grams with severe respiratory distress syndrome (RDS). In their study, they discovered that adding intratracheal budesonide to surfactant would not affect the rates of BPD, death, and BPD or death at 36 weeks PMA (23). However, their study showed no risk for the combined treatment, whereas the present findings suggest that complications, such as sepsis and pneumothorax tend to be higher in the group of neonates who received budesonide. In a trial conducted by Heo et al. on infants with the same characteristics as the former study, adding budesonide to surfactant did not help reduce BPD rates (24). In a study by Yeh et al., adding budesonide to surfactant in very preterm infants significantly improved the combined outcome of BPD and death (25). A follow-up study also demonstrated that children treated with early postnatal inhaled budesonide were comparable to children in the placebo group in general health and neurodevelopmental outcomes (19). Trying to further assess their finding, in a clinical trial carried out on 265 neonates, Yeh et al. concluded that treating their patients with budesonide-instilled surfactant could reduce the incidence of BPD or death and did not lead to immediate or long-term side effects (20). A recent trial by Gharebaghi et al. demonstrated that neonates treated with budesonide and surfactant not only had lower rates of BPD but also benefitted from less respiratory support and shorter length of hospitalization. In contrast, the present study indicated that neonates in the intervention group had a longer hospitalization time and longer duration of TPN. This discrepancy may potentially be attributed to systemic corticosteroids used in their study to help extubate neonates (26). It is notable that in a large observational study, Kothe et al. treated every infant eligible for surfactant therapy with budesonide, and compared the results with a historical cohort, in settings similar to the current study. Similar to the present study, the rates of BPD or death did not change between the two groups in their study. However, they reported that adding budesonide reduced the severity of BPD, and pulmonary outcomes tended to be better, as fewer infants required mechanical ventilation and more infants were extubated faster in the group receiving budesonide. These contrasting findings call upon further studies to to thoroughly investigate whether the utilization of inhaled corticosteroids, while possibly not significantly altering BPD rates, could potentially contribute to a reduction in the severity of the disease in neonates and consequently decrease the outcomes associated with severe BPD (27).

Conclusion

The obtained results of the current study indicated that adding budesonide to surfactant via intratracheal instillation in premature infants who were candidates for surfactant therapy could not reduce the rates of BPD. Moreover, it did not make a significant difference in the combined outcome of BPD and death. The findings suggest that the addition of budesonide may also increase complications, such as sepsis and pneumothorax and prolonged hospitalization time. Future literature concerning this matter will hopefully light up the path for clinicians.

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Conflicts of interest

The authors declare no conflict of interest.

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