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Comparison of Intravenous Dexamethasone and Budesonide Nebulizer in the Treatment of Infantile Respiratory Distress Syndrome; A Randomized Clinical Trial

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Abstract

Background: Respiratory distress syndrome (RDS) is one of the most common causes of mortality in preterm infants. Despite appropriate results of corticosteroids prescription for preventing RDS, early use of these medications after birth has raised concerns about short and long-term complications. Inhaler corticosteroids have lower systemic absorption and have been considered to decrease short and long term complications of systemic corticosteroids to minimum.

Objectives: In this randomized clinical trial we aimed to assess effectiveness of intravenous dexamethasone and budesonide nebulizer in treatment of infantile respiratory distress syndrome.

Methods: In this randomized clinical trial preterm infants with confirmed diagnosis of RDSwere randomly allocated to two groups; the first group received intravenous Dexamethasone (0.15 mg/kg every 12 hours) and the second group received Budesonide nebulizer (200 µg/ day) through jet nebulizer. Treatment duration, complicationsand received doses as well as response to treatment and mortality rates were recorded in a checklist.

Results: Finally 60 infants (35 female and 25 male) in Budesonide and Dexamethasone groups underwent analysis. Mean arterial oxygen saturation was 88.60±3.21 % in Budesonide and 88.13±3.73% in Dexamethasone group before intervention (p=0.606). In the fifth day of intervention it was 93.80±2.14% in Budesonide and 93.25±3.76 in Dexamethasone group (p=0.441). Prior to intervention, Budesonide group had a mean respiratory rate (RR) of 71.50±12.33 and it was 67.17±12.84 in Dexamethasone group (p=0.188). In the fifth day of intervention, infants had a mean RR of 45.66±8.87 in Budesonide and 48.21±10.11 in Dexamethasone group (p= 0.179). Mean hospitalization duration was 16.36±11.32 days in Dexamethasone and 17.40±14.39 in Budesonide group (p=0.758).

Conclusion: We concluded that there is no significant difference between intravenous Dexamethasone and Budesonide nebulizer for treatment of infantile RDS.

Keywords: Budesonide, Dexamethasone, Nebulizer, Respiratory distress syndrome, Systemic corticosteroids

1. Background

As one of the most common cause of mortality, respiratory distress syndrome (RDS), may be resulted from pulmonary or non-pulmonary disorders. Hyaline membrane disease (HMD) in preterm and meconium aspiration and transient tachypnea of neonates (TTN) in term infants are among the most prevalent reasons of neonatal distress (1,2).

Surfactant has been being used as the main treatment of RDS since 1990 and has markedly decreased RDS-related mortality (3-5).One of the important progresses in natal care is the appliance of corticosteroids in pregnant women impending to preterm delivery. Increasing trend in using corticosteroids before delivery for pulmonary maturation and triggering enzymes involved in biochemical maturation of lungs, early treatment with surfactant after birth and application of gentle mechanical ventilation for decreasing barotrauma of the lungs areconsidered as desirable results of treatment of RDS (6,7). Despite recent progresses in application of corticosteroidsfor preventing RDS and its appropriate results, early use of these medications after birth has remained controversial and raised concerns about short and long-term complications (8). The corticosteroid of choice prior to delivery is Bethamethasone and Dexamethasone is used after birth most commonly (9). Corticosteroids are effective drugs in management of neonatal pulmonary disorders and improve pulmonary function through a variety of mechanisms such as suppressing inflammatory response (10).

Dexamethasone is widely used as a systematic medication which could be used within or after first week of life. Treatment with Dexamethasone has shown favorable effects in improving pulmonary functions, especially in those dependent to mechanical ventilation (11).

Inhaler corticosteroids have lower systemic absorption and have been considered as an alternative treatment strategy for decreasing short and long term complications of systemic corticosteroids to minimum. Treatment with inhaler corticosteroids in the first two week of life of infants depend to mechanical ventilation has shown a dramatic decrease in incidence of respiratory

diseases (12).

So in the present study we aimed to compare the therapeutic effects of intravenous Dexamethasone and inhaler Budesonide in preterm infants with respiratory distress syndrome.

2. Objectives

In this randomized clinical trial we aimed to assess effectiveness of intravenous dexamethasone and budesonide nebulizer in treatment of infantile respiratory distress syndrome.

3. Methods

This randomized clinical trial was conducted between September 2014 and August 2015 in Najmiyeh hospital, Tehran, Iran. The present study was registered at ethics committee of Islamic Azad University (Reference code: IR.IAU.PS.REC.1392.20) and Iranian Registry of Clinical Trials (Reference code: IRCT2016101917413N20). Figure 1 shows a flowchart of the trial. Preterm infants with diagnosis of respiratory distress syndrome (RDS) confirmed by chest radiography and a single neonatologist who were intubated and underwent mechanical ventilation for 3 to 5 days were assessed for eligibility. Patients with birth weight between 1000 and 2500 gr, gestational age of less than 36 weeks, mechanical ventilation for at least 2 days and needed oxygen saturation of more than 30% after extubation were included in the study. Infants with hemorrhagic events, congenital or chromosomal anomalies, early sepsis or death before 72 hours were excluded from the study. Demographic information as well as birthweight, prematurity complications and duration of ventilation were recorded in a predesigned checklist.

After explanation of study process for parents and signing an informed consent form patients were randomly allocated to two groups using blocks at a ratio of (1:1); the first group received intravenous Dexamethasone (0.15 mg/kg every 12 hours) and the second group received Budesonide nebulizer (200 µg/day) through jet nebulizer.Treatment duration, complicationsand number of received doses as well as response to treatment and mortality rates were recorded in a checklist.

Data was analyzed using SPSS software version 21 (SPSS Inc., Chicago, IL) for Microsoft Windows. Normal distributed variables (approved by 1-sample Kolmogorov-Smirnov test) were compared using independent sample *t* test between the groups. The chi square test was used to compare categorical variables in the 2 groups. Mean and standard deviation (SD) were used for describing categorical variables.

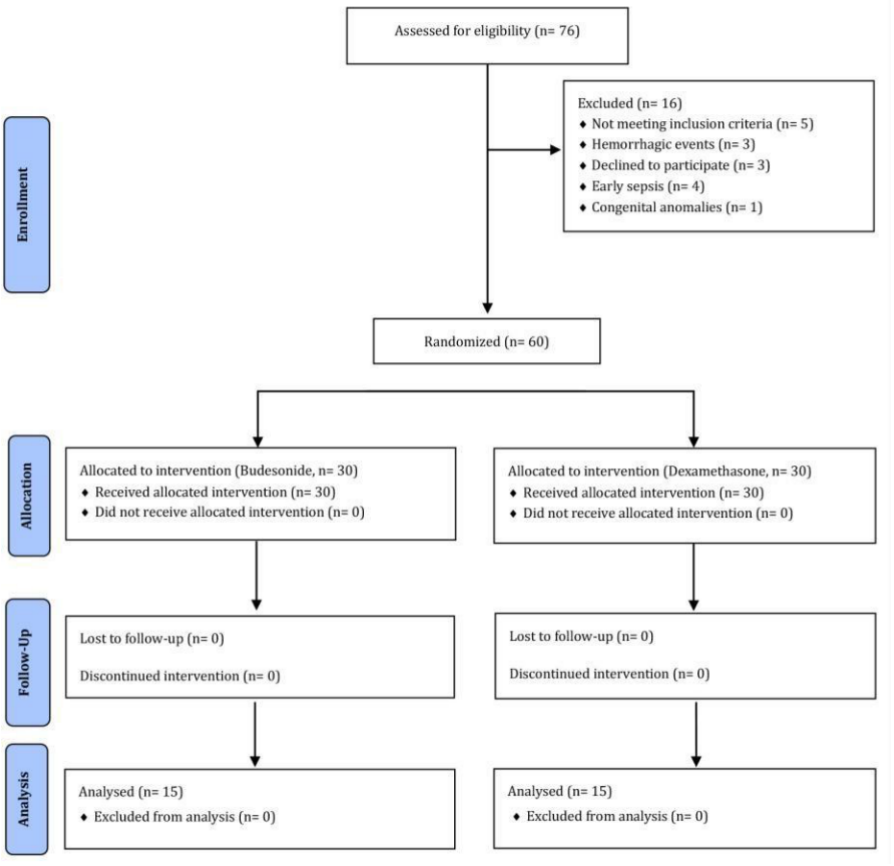

Figure 1. Study flowchart

4. Results

Finally 60 infants (35 female and 25 male) in Budesonide and Dexamethasone groups underwent analysis. Demographic information has been summarized in Table 1.In Dexamethasone group 93.3% and in Budesonide group 96.67% of infants were conceived by cesarean section. In Dexamethasone group 15 (50%) infants were female and in Budesonide group 20 (66.6%) infants were female. Two (6.67%) infants in Dexamethasone group and one (3.33%) in Budesonide group had a gestational age of less than 28 weeks. Infants in Dexamethasone group had a mean birthweight of 1465.83 ± 374.21 gr and it was 1576.67±263.97 gr in Budesonide group (p=0.190). None of the infants in both groups had a birthweight of more than 2000 gr; while 6 (20%) infants had a birthweight of less than 1000 gr in Dexamethasone group. Of the infants in Dexamethasone group 7(23.33%) and of those in Budesonide group 5 (16.66%) were under mechanical ventilation more than 3 days.All the mothers in both groups had received Antenatal corticosteroids. Placental decollement was recorded for 3(10%) of infants in Dexamethasone group and 2 (6.7%) in Budesonide group (p>0.05). Three (10%) infants in Budesonide group had premature rupture of membrane (PROM) more than 18 hours before delivery and one infant (3.33%) in Dexamethasone group had premature meconium defecation. Disease complications have been listed in Table 2. Patent ductus arteriosus (PDA) was the most prevalent complication among both groups.

Mean weight at the time of discharge was 1656.4 ±342.4 gr for infants in Dexamethasone and 1773.3±196.4 gr for infants in Budesonide group.In Dexamethasone group mean arterial oxygen pressure (PaO_2) was 68.46±23.77 mmHg before and 94.73±25.76 mmHg after intervention. Mean arterial oxygen pressure (PaO_2) was 70.06±31.44 mmHg before and 83.46±26.21 mmHg after intervention in Budesonide group. Mean duration of hospitalization was 16.36±11.32 days in Dexamethasone and 17.40±14.39 days in Budesonide group (p=0.758). No mortalities were recorded for Budesonide group; while it was 13.3% in Dexamethasone group. Treatment complications have been shown in Table 3. Milk intolerance was the most prevalent treatment complication among both groups.

Figure 2 shows arterial oxygen saturation (O_2 sat)

Table 1. Demographic characteristics of study individuals

		Budesonide (N=30)	Dexamethasone (N=30)	p Value
Male N(%)		10(33.3%)	15(50%)	>0.05
Gestational age (weeks)	<28	1(3.33%)	2(67.7%)	>0.05
	28-33	20(66.7%)	14(46.7%)	
	34-36	9(30%)	14(46.7%)	
Birthweight (gr)	<1000	6	0	0.190
		9	12	
	1500-2000	15	18	
	>2000	0	0	
Mean Apgar score		7.40±1.0	6.93±1.65	0.193
	5th minute	7.96±1.54	7.96±1.54	0.135
PROM>18 hours N(%)		3(10%)	0	>0.05
Meconium defecation N(%)		0	1(3.33%)	>0.05
Placental decollement N(%)		2(6.7%)	3(10%)	>0.05

Table 2. Incidence of disease complications among study individuals

Complication	Budesonide (N=30)	Dexamethasone (N=30)
Necrotizing Enterocolitis (NEC)	1(3.33%)	2(6.7%)
Sepsis	1(3.33%)	1(3.33%)
Intracranial Hemorrhage	1(3.33%)	1(3.33%)
Patent Ductus Arteriosus (PDA)	7(23.3%)	5(16.7%)
Pneumonia	2(6.7%)	2(6.7%)
Pneumothorax	1(3.33%)	4(13.3%)

Table 3. Incidence of treatment complications in study individuals

Complication	Budesonide (N=30)	Dexamethasone (N=30)
Hyperglycemia	1(3.33%)	1(3.33%)
Hypertension	0	0
Raised intracranial pressure	0	0
Milk intolerance	6(20%)	6(20%)
Nausea	2(6.7%)	0
Abdominal distension	2(6.7%)	2(6.7%)
Coagulopathies	0	0

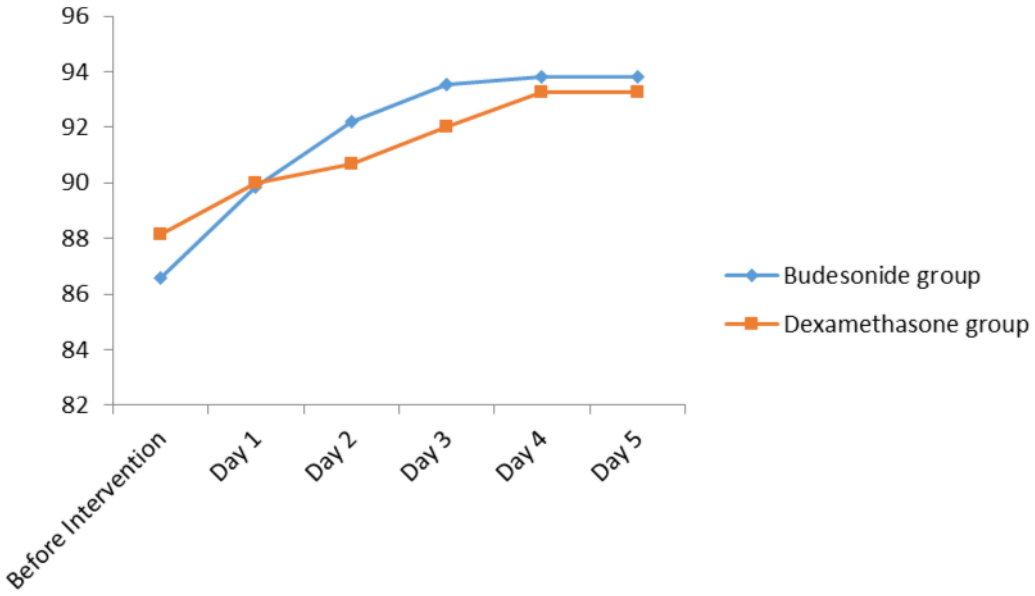

Figure 2. Trend of Mean Arterial Oxygen Saturation (%) during intervention

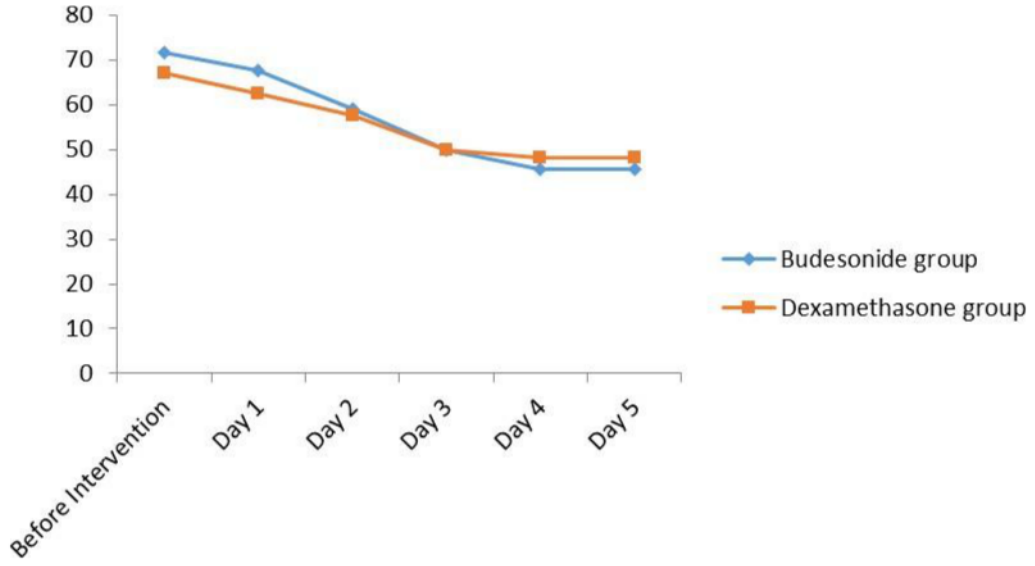

Figure 3. Trend of Respiratory Rate during intervention

trend during treatment. Mean arterial oxygen saturation was 88.60±3.21 % in Budesonide and 88.13±3.73% in Dexamethasone group before intervention (p=0.606). In the fifth day of intervention it was 93.80±2.14% in Budesonide and 93.25±3.76 in Dexamethasone group (p=0.441). Trend of respiratory rate has been shown in Figure 3. Prior to intervention, infants in Budesonide group had a mean respiratory rate (RR) of 71.50±12.33 and it was 67.17±12.84 in Dexamethasone group infants (p=0.188). In the fifth day of intervention, infants had a mean RR of 45.66±8.87 in Budesonide and 48.21±10.11 in Dexamethasone group (p= 0.179). Oxygen density needed was 90.67±17.21% in Budesonide group and 83.33±24.68% in Dexamethasone group before intervention (p=0.187). In the fifth day of intervention it was 11.67±23.21% in Budesonide and 17.54±30.26% in Dexamethasone group (p=0.409). Before intervention, 8(26.6%) infants in Budesonide and 13 (43.3%) infants in Dexamethasone group needed to be re-intubated (p=0.412). In the fifth day of intervention2(6.7%) infants in Budesonide and 2

(7.1%) infants in Dexamethasone group needed to be re-intubated (p>0.1).

5. Discussion

We found that infants in both Dexamethasone and Budesonide groups showed a significant response to treatment in terms of respiratory rate, arterial Oxygen saturation and oxygen dependency after extubation. Treatment goal is a respiratory rate of less than 60 which was achieved in both groups in the present study. The favorable treatment condition for oxygen dependency is the decrease in density of required oxygen after extubation which was seen in both Dexamethasone and Budesonide groups of infants. We could maintain oxygen saturation (based on pulse-oxymetry) between 90% to 92 % in preterm infants less than 1250 gr and upmost 95 % in preterm infants more than 32 weeks of gestational age in both groups which is the treatment goal. We also realized that treatment in both groups resulted in a significantly lower rate of chest retraction and need for re-intubation. Also both groups showed a decrease in mortality and oxygen dependency.

It has been proved that incidence of respiratory distress syndrome (RDS) is inversely related to gestational age (13). In the present study more than 60% of infants had gestational age of less than 34 weeks which shows higher prevalence of RDS in lower gestational ages.

In agreement with Halliday et al. study, there was no significant difference for disease complications between two groups in our study (14). Also patent ductus arteriosus (PDA) was significantly more common in Budesonide group in comparison with Dexamethasone which was previously concluded by Halliday et al. in a similar study (15). No significant difference was seen between two groups in terms of treatment complications. In contrary with our study, Halliday et al. in a systematic review on early treatment of RDS with Dexamethasone (0.25 mg/kg every 12 hours) mentioned that despite remarkable benefits in extubating infants, incidence of short-term complications such as hemorrhage, hypertrophic cardiomyopathy, high blood pressure and high blood glucose were increased by systemic corticosteroids (16). Since the treatment doses administered in the present study, in both Dexamethasone and Budesonide groups, were in the minimum range of common doses and according to the short treatment duration (3 to 5 days) after extubation, incidence of adverse effects were significantly low and management of respiratory distress was acceptable.

In a similar study Henry et al. evaluated the effect of early (less than 7 days) and late (more than 15 days) administration of intravenous Dexamethasone and Budesonide. There was a significant response to treatment and decrease in mortality and oxygen dependency in early prescription of low dose Dexamethasone and late administration of higher dose of Budesonide. Generally, infants who had received early treatment with Dexamethasone had a better survival without respiratory disorders in comparison with those who had received late Budesonide treatment. Also treatment with Dexamethasone was associated with lower incidence of patent ductus arteriosus (PDA). However the superiority of each treatment remained controversial (17). In another study by Doyle et al., prescription of the lowest possible dose of Dexamethasone was evaluated. The results showed facilitation in extubation, shorter intubation duration and improvement in respiratory condition in ventilator-dependent infants (18). In a review article, Shah et al. evaluated effect of systemic and inhaler corticosteroids and reported no superiority for none of the treatments (9).

There was no significant superiority for systemic or inhaler corticosteroids in treatment of RDS in the present study; however Budesonide nebulizer had a slightly better effect on treatment parameters such as respiratory rate, oxygen dependency and arterial oxygen saturation which seems to be related to more accurate delivery of drugs to lungs. Dexamethasone had a better effect on decreasing intercostal retraction and need for reintubation which is related to systemic nature of the drug.

6. Conclusion

In conclusion we found that there is no significant difference between intravenous Dexamethasone and Budesonide nebulizer for treatment of infantile respiratory distress syndrome; however there was a significant response to treatment in both groups. Considering the appropriate signs of response to treatment and lack of notable adverse effects, short-time prescription of these drugs is recommended.

We suggest further studies with larger sample volume and more follow up durations for better addressing the efficacy and possible long-term adverse effects of these medications. Future researches should also assess effective doses and appropriate path of inhaler drugs delivery.

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Conflicts of interest

We have no conflicts of interest in terms of the present manuscript.

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