Inhalation effects of beclomethasone and furosemide on pulmonary function and oxygenation index of preterm newborns

Efeitos da inalação de beclometasona e furosemida sobre a função pulmonar e índice de oxigenação de recém-nascidos prematuros

Efectos de la inhalación de beclometasona y furosemida sobre la función pulmonar e índice de oxigenación de recién nacidos prematuros

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ABSTRACT | The objective of this study was to evaluate lung function and oxygenation index of preterm infants undergoing endotracheal inhaling of beclomethasone and furosemide. We studied 30 newborn preterms with gestational age ≤36 weeks, undergoing conventional mechanical ventilation for at least 12 hours. Three sequential inhalations with their medications were executed with an interval of three hours between each. We collected samples of arterial blood for gas analysis, and after endotracheal aspiration, the measurement of respiratory variables was performed in two stages, two hours before and after the last inhalation. Dynamic compliance and the oxygenation index showed no statistically significant difference between before and after the medication, however, the airway resistance group demonstrated a reduction in beclomethasone between the moments before and after the intervention (p=0.03). These results cannot imply that inhaled beclomethasone and furosemide exerted significant influence on lung function and oxygenation in the newborn infants studied.

Keywords | infant, premature; diuretics; beclomethasone; respiratory mechanics.

RESUMO | O objetivo deste estudo foi avaliar a função pulmonar e o índice de oxigenação de recém-nascidos pré-termo submetidos à inalação endotraqueal de beclometasona e furosemida. Foram avaliados 30 recém-nascidos pré-termo com idade gestacional ≤36 semanas, sob ventilação mecânica convencional por pelo menos 12 horas. Três inalações sequenciais com as respectivas medicações foram realizadas, com intervalo de três horas entre as mesmas. Foram coletadas amostras de sangue arterial para análise dos gases sanguíneos; após aspiração endotraqueal, a mensuração das variáveis respiratórias foi realizada em dois momentos, antes e após duas horas da última inalação. A complacência dinâmica, assim como o índice de oxigenação, não apresentou diferença estatística significativa entre os momentos antes e após as medicações; no entanto, a resistência de vias aéreas demonstrou redução no grupo beclometasona entre os momentos antes e após a intervenção (p=0,03). Diante desses resultados, não podemos afirmar que a beclometasona e a furosemida inalatória exercem influência significativa na função pulmonar e oxigenação dos recém-nascidos estudados.

Descritores | prematuro; diuréticos; beclometasona; mecânica respiratória.

RESUMEN | El objetivo de este estudio fue evaluar la función pulmonar e índice de oxigenación de recién nacidos de pre-término sometidos a la inhalación endotraqueal de beclometasona y furosemida. Fueron evaluados 30 recién nacidos de pre-término con edad gestacional ≤36 semanas, bajo ventilación mecánica convencional por lo menos 12 horas. Tres inhalaciones secuenciales con las respectivas medicaciones fueron realizadas, con intervalo de tres horas entre las mismas. Fueron tomadas muestras de sangre arterial para el análisis de los gases sanguíneos y después de la aspiración endotraqueal, la medición de las vías respiratorias fue realizada en dos momentos, antes y después de dos horas de la última inhalación. La compliance

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dinámica así como el índice de oxigenación, no presentaron diferencia estadísticamente significativa entre los momentos antes y después de las mediciones, sin embargo, la resistencia de las vías aéreas demostró reducción en el grupo beclometasona entre los momentos antes y después de la intervención (p=0,03). Mediante estos resultados no podemos afirmar que la beclometasona y la furosemida inhalatoria ejercen influencia significativa en la función pulmonar y oxigenación de los recién nacidos estudiados.

Palabras clave | prematuro; diurético; beclometasona; mecánica respiratoria.

INTRODUCTION

The technological and scientific advancement has been increasingly providing the strengthening of Perinatology. The greater understanding of pathophysiological mechanisms involved allowed the development of new therapeutic resources in perinatal care improvement contribution[1].

Associated with mechanical ventilation and allied to traditional forms of drug administration, parenteral and oral, the new concept of topical treatment in respiratory diseases represents a considerable advance, allowing the maximization of therapeutic effects, enabling directly the airways through endotracheal inhalation, with less risk of systemic side effects: it happens using beclomethasone and furosemide[2-4].

The glucocorticoids have multiple mechanisms of action and effects, including the inhibition of arachidonic acid metabolism and its action on the inflammatory process inhibiting diapedesis of phagocytic cells, which allows the capacity of lymphocytic cells increase and have more functions[3,5].

Inhaled furosemide has anti-inflammatory effect, that interferes with the metabolism of cytokines, but new studies are necessary[5].

This study had the purpose of assessing lung function and oxygenation index of preterm newborns (PN) undergoing endotracheal inhalation of beclomethasone and furosemide, admitted in a public hospital.

METHODOLOGY

The study was approved by the Research Ethics Committee of the Federal University of mato Grosso do Sul (UFMS), Campo Grande (MS).

Were evaluated 30 PN, with gestational age (GA) ≤36 weeks)[6], at the Neonatal Intensive Care Unit (ICU) of the Hospital Universitário da UFMS (HU-UFMS) and that had to be on mechanical ventilation for at least 12 hours, with non-invasive monitoring of oxygen saturation and heart rate during all data collection. The ventilatory parameters were recorded before the intervention, and two hours after the end of the last inhalation.

After two hours of last inhalation, was held a airway aspiration, a pulmonary function evaluation of dynamic compliance (mL/cmH_2O) and of the average resistance of airways (cmH_2O/L/s), a blood collection for blood gas analysis (collection), determining the oxygenation index after the intervention, evaluation of oxygen saturation and heart rate.

The patientswere randomly selected and divided into sub-groups: control group (CG), Beclomethasone Group (BG) and Furosemide (FG).

In the CG, the PN received 3 mL of physiological saline 0.9%, by inhalation. In BG, the PN received 200 μg/mL endotracheal of glucocorticoid (Beclomethasone) by inhalation, associated to 3 mL of physiological saline. The FG of PN received, endotracheal, 1 mg/kg inhalation of furosemide in solution with 3 mL of physiological saline 0.9%. All groups received the medication three times a day, with three-hour interval between them, in just one day.

Pulmonary auscultation were performed and signs of clinical stability were displayed, right after that, were submitted to standard procedure of tracheal aspiration (Endomed®), according to the technique recommended by the service[7].

The pulmonary function was evaluated using an equipment (NMI Newport Medical Instruments, Inc., USA) coupled to a flow transducer BICORE® neonatal model Varfley. The values of the average of the last 10 respiratory cycles were observed calculated by equipment monitor.

Respiratory mechanics measurements were measured in two stages: after the suction procedure made right before the beginning of the first inhalation administered to newborn, according to the group, and after the extraction procedure conducted two hours after the last patient administered inhalation of each group.

The blood gas analysis was done by collecting arterial blood by umbilical catheter or puncture and analyzed by Radiometer/Copenhagen gasometer – ABL 5®, as sector routine. The collection was held after the first

suction and two hours after the end of the last inhalation of each group.

For the inhalation, the patients were subjected to a sequence of three inhalations for each group with the proposed drugs, at intervals of three hours between the inhalations; to do this, a micro-nebulizer NS® was coupled to the fan circuit, inspiratory branch through a adapted T tube.

Oxygen saturation and heart rate were monitored throughout the data collection period through a Pulse Oximeter Dixtal® brand, DX2010 input model, with neonatal sensor.

The oxygenation index was calculated by the formula recommended by Santos et al.[8].

The sedatives was used with the utmost caution, due to complications that it can cause. Taught, however, as it was necessary, as the industry's routine of Fentanyl or Midazolam[9].

The comparison between the newborn control groups, furosemide and beclomethasone, in reference to chronological age variable, was accomplished using non-parametric test of Kruskal-Wallis test, while the variables: age, weight, lung, airway resistance and oxygenation index was accomplished using ANOVA test of a via.

The comparison between the moments before and after the treatment, for the same variables, was accomplished using paired Student's *t*-test. The other results were presented in descriptive statistics (mean±standard deviation of average) or table. Statistical analysis was performed using SigmaStat software, version 2.0, whereas significant differences when $p \leq 0.05$[10].

RESULTS

The chronological age of the 30 PN, distributed in three groups (GC, FG and BG), was of 3.20±2.82, 2.50±0.85 and 5.60±6.82 days, respectively, demonstrating the difference between the groups (Kruskal-Wallis, p=0.31).

To the IG of newborns in the CG, FG and BG, the results were: 29.40±2.67, 30.10±3.66 and 30.30±1.89 weeks, respectively, expressing no significant difference between groups (ANOVA test of a via, p=0.76). The IG of newborns ranged between 24 and 36 weeks, with an average of 29.93±2.77 weeks. 16 were male (53.3%) and 14 (46.7%) female. The chronological age of the groups varied between 2 and 23 days, with an average age of 3.77±4.35 days (mean±standard deviation).

Five new-born male and five female were included in CG. The FG was composed of six new-born male and four female. As a result, in BG were included five newborn male and five female.

The weight of the PN of CG, FG and BG was 1,448.50±404.75, 1,562.00±828.07 and 1,562.00±828.07 g, respectively. There was no difference between groups (ANOVA test of a via, p=0.68).

The study was concluded with all children, since there were no episodes of instability that could lead to the suspension of the intervention. The distribution of pathologies observed in three groups is presented in Table 1. Concerning to respiratory variables and dynamic compliance oxygenation index, there were no significant statistical differences between the moments before and after the administration of corticosteroids beclomethasone inhalation (Table 2). The average airway resistance was significantly lower in the BG after the intervention (Student´s paired *t*-test, p0 .03) (Figure 1).

DISCUSSION

Most of the PN is in a period where the anatomical structures are rudimentary and not effective to perform gas exchange[11].

The differences between the values obtained in three groups regarding to chronological age, IG and gender were not significant, ensuring the sample homogeneity. These data is important due to morphological and structural immaturity of lungs, aspects that vary according to the chronological and gestational age.

Among the patients, Respiratory Distress Syndrome (RDS) was observed in 22 of the 30 infants. As for the genre, the population was homogeneous.

The corticosteroids are commonly used to treat severe bronchial asthma by decreasing the hospitalization and having a significant influence on pulmonary function. The prescription is more systemic, despite side effects[12].

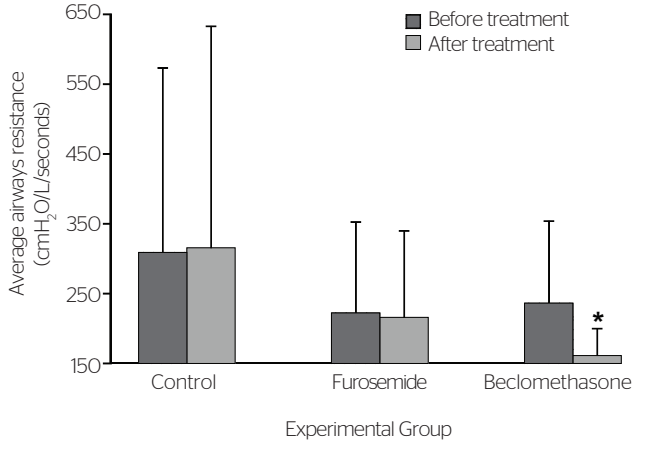
In this study, the beclomethasone inhalation did not show any difference in dynamic compliance before or after application. But in a study where they used budesonide and nedocromil, was observed a improvement in pulmonary function with budesonide inhalation in asthma. But in the long term it is not known whether inhaled use can present the same side effects of systemics[13].

Table 1. Prematurity-related pathologies in the sample

Pathologies	Groups						Total	
	Control		Furosemide		Beclomethasone			
Sample	n	%	n	%	n	%	n	%
Neonatal infection	8	80.0	7	70.0	6	60.0	21	70.0
Respiratory distress syndrome	5	50.0	8	80.0	9	90.0	22	73.3
Prematurity	10	100.0	10	100.0	10	100.0	30	100.0

Table 2. Results regarding pulmonary compliance, and airway resistance to oxygenation index (gross values and gain), observed before and after treatment, to each of the experimental groups

Measurement moment	Treatment			p-value (between groups)
	Saline	Furosemide	Beclomethasone	
Pulmonary dynamic compliance (mL/cmH_2O)				
Before	0.71±0.41	0.60±0.28	0.54±0.30	0.52
After	0.71±0.48	0.53±0.20	0.67±0.29	0.48
p-value (between moments)	0.99	0.40	0.18	
Gain	0.00±0.40	-0.07±0.26	0.14±0.30	0.36
Average airway resistance (cmH_2O/L/second)				
Before	309.11±264.02	222.20±130.28	236.20±117.60	0.53
After	315.71±317.02	216.10±123.85	161.45±38.27	0.23
p-value (between moments)	0.84	0.71	0.03	
Gain	+6.60±102.36	-6.10±50.07	-74.75±88.87	0.08
Oxygenation índex (%)				
Before	4.60±4.19	6.02±4.80	3.92±2.57	0.49
After	6.28±6.66	5.61±5.08	4.79±3.14	0.81
p-value (between moments)	0.17	0.42	0.47	
Gain	1.68±3.58	-0.41±1.53	0.87±3.64	0.33



*Significant difference regarding the time before treatment with beclomethasone (Student paired *t* test, p=0.03).

Figure 1. Average airways resistance, before and after treatment, between the experimental groups (control, furosemide and beclomethasone)

Side effects have not been observed; however, it is believed that the time was not long enough for the assessment of the appearance or absence of side effects.

The effect of corticosteroids administered via inhalation and in PN ventilated, there wasn´t any difference between the groups for lung and airway resistance. The authors suggest caution to assure that the corticosteroids improve lung function[14].

The finds in this study about the dynamic Lung in BG were 0.54±0.30 to 0.67±0.29, and are in accordance with the results of other authors[15,16].

The European Association of Perinatal Medicine, the American Academy of Pediatrics and the Canadian Pediatric Society reported its concern regarding the use of corticosteroids in neonatology, not recommending the routine use of systemic dexamethasone for the prevention and treatment of chronic lung disease, alerting that the use of corticosteroids should be limited to exceptional clinical circumstances. This recommendation, according to the associations, was based on the complications that may occur in the short and long term, especially cerebral aggression. It is assumed that the use of topical corticosteroids through respiratory tract can result in beneficial effects on the respiratory system with less adverse effects[17].

As for the resistance of airways (RVA), there was a significant difference, resulting a reduction of this variable after administration of beclomethasone inhaled when compared with the other groups. It is known that the RVA, in newborns with normal lung, ranges from 25 to 50 cmH_2O/L/s, without significant change in newborns

with SDR; however, when undergoing tracheal intubation, it can range from 50 to 100 $cmH_2O/L/s$[18].

The presence of mucus in the airways and tracheal cannula may contribute to the increased resistance[8]. This study was made in order to remove the secretion in tracheal cannula and in the airways, once the newborns were aspirated minutes before measuring the variables, according to established protocol. This procedure, that preceded the new variable measurement, was made before the newborn receive the medication for inhalation and two hours after the last inhalation, .

However, this finding leads us to believe that the decrease in airway resistance observed in this group was really a consequence of the medication action in the respiratory system. It is known that corticosteroids administered by inhalation have effects on the pulmonary function of premature newborns, artificially ventilated, due to its anti-inflammatory power and because it improves pulmonary compliance and promotes an early extubation[3].

It was observed that budesonia and beclomethasone decreased the need for oxygen in PN under ventilation, but not decreased the ventilation time and oxygen needs[19]. Another study obtained similar results[20].

Prabhu et al.[21] conducted a study to compare the effects of a single dose of furosemide (1 mg/kg) administered by inhalation and intravenous lung mechanisms in premature infants with chronic lung disease. They concluded that inhaled furosemide increased tidal volume in 31 and dynamic compliance in 34 after 2 hours, while none of these changes could be observed after administration of furosemide intravenously; they also reported that they did not found yet any change of airway resistance in both groups.

Inhalation and intravenous furosemide in PN with chronic lung disease did not alter pulmonary function[21]; despite the existing differences in measured doses and intervals in this study, the results were similar.

Prabhu et al.[21] observed in their study that a single dose of furosemide in fraction of inhaled 1mg/kg provided an improvement of lung function for up to 6 hours after administration. However, when administered in larger quantity — 2 mg/kg inhalation — the respiratory system action was damaged. This leads us to believe that the pulmonary effects after nebulization with furosemide and diuretic function are independen, regarding the local drug function.

Furosemide at a dose of 1 mg/kg, administered with a frequency of more than twice a day to PN in the neonatal period, parenteral or inhalational ≥2 mg/kg, can lead to toxicity; in addition, the half life of furosemide in PN is longer than in adults or older children, although the distribution volume is similar[8].

In a review, the authors concluded that PN under three weeks with chronic lung disease who receive a single dose of furosemide (1 mg/kg) inhalation feature shows improvement in pulmonary mechanics; however, due to lack of studies proving its effects and long-term signals, it is recommended that some issues should be analyzed before the imposition of diuretic therapy: analysis of the factors that are likely to affect responses to furosemide inhalation; and research of the administration effects of this drug by inhalation as regards to dependency and mortality[22,23].

The control group results was similar to other groups results, but with the airway aspiration procedure, we noted changes in mucus rheology after inhalation with saline, causing a bigger secretion offset with lower density, showing that this is a good practice when combined with other therapies, since it is known that the presence of endotracheal tube, as well as the time of mechanical ventilation and sedation, changes the ciliary mucus clearence, predisposing to secretion and infections accumulation, mainly in PN.

With our results, we cannot say that the furosemide inhalation interferes with lung function; however, other studies are necessary, with different doses and intervals.

In this study, with the decrease of the RVA, despite the effect of physiotherapy by secretions removal, we believe in anti-inflammatory effect of beclomethasone, since the same effect was not observed by the furosemide inhalation.

Considering the results presented in this study, we suggest caution to implement this practice during premature newborns treatment, until we have more decisive scientific evidence.

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