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Research Article

Short Term Effects of Nebulized Epinephrine as a Treatment of Viral Bronchiolitis

Osama Moustafa Zayed[1]*, Badr El-deen Mohamad Mesbah[2], Hoda Ahmed Atwa[2], Nesreen Mosad Handooka[2] and Monira Taha Ismael[1]

[1]Department of Emergency Medicine, Faculty of Medicine, Suez Canal University, Ismailia, Egypt

[2]Department of Paediatrics and Neonatology, Faculty of Medicine, Suez Canal University, Ismailia, Egypt

***Corresponding Author**: Osama Moustafa Zayed, Department of Emergency Medicine, Faculty of Medicine, Suez Canal University, Ismailia, Egypt.

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Abstract

Objective: To assess short term effects of nebulized epinephrine on heart rate, clinical score and oxygen saturation.

Patients and Methods: Prospective, randomized, controlled study to determine if there is adverse effects of using nebulized epinephrine in treatment of infants suffering from bronchiolitis, 96 infant were enrolled in the study divided to 3 groups randomly, first group received nebulized hypertonic saline 3% only (placebo group), second group received nebulized hypertonic saline 3% with 1:1000 epinephrine, and third group received normal saline 0.9% with 1:1000 epinephrine. Patients' heart rate, oxygen saturation and clinical scores were recorded before treatment and after each nebulizer they received at 30, 60, 90 and 120 minutes. Comparison of the three groups was done by SPSS Kruskal Wallis test and ANOVA.

Results: We found that epinephrine didn't cause increase in heart rate compared to placebo group, change of heart rate was almost equal in the three groups with a p-value of 0.898. Change of clinical severity score and oxygen saturation was also similar in both epinephrine group and placebo group with no significant difference p-value = 0.868 and 0.452 respectively.

Conclusion: Nebulized epinephrine doesn't increase heart rate and can be used safely in treating infants with bronchiolitis.

Keywords: *Bronchiolitis; Nebulized Epinephrine*

Introduction and Rationale

Bronchiolitis is a disorder most commonly caused by viral lower respiratory tract infection (LRTI) [1]. It refers to the first episode of acute wheezing in children less than two years of age, starting as a viral upper respiratory infection (coryza, cough or fever) [2]. The most common etiology is the respiratory syncytial virus (RSV), with the highest incidence occurring from winter to spring [3]. Ninety percent of children are infected in the first 2 years of life. Bronchiolitis is characterized by acute inflammation, edema and necrosis of epithelial cells lining small airways, peribronchiolar mononuclear infiltration, increased mucus production, and bronchospasm. These changes obstruct flow in the small airways, leading to hyperinflation, atelectasis, and wheezing [1,4-6]. Signs and symptoms are typically rhinitis, tachypnea, wheezing, cough, crackles, use of accessory muscles of respiration, and/or nasal flaring. Despite 4 decades of efforts, there are no effective means to control RSV, and still the mainstay of treatment for RSV infection is supplemental oxygen and hydration. Because until now there is no definitive treatment for bronchiolitis, trials and researches on more novel therapies is being tried. A single inhalation of recombinant human deoxyribonuclease has been recently used as a mucolytic agent in RSV bronchiolitis with some success [7]. A recent meta-analysis [8] concluded that nebulization with 3 to 5 ml of adrenaline (1:1000) is a safe treatment with few side effects.

Patients and Methods

This is a prospective randomized controlled study to assess the short term effects of nebulized epinephrine in treatment of bronchiolitis.

Setting: Emergency department in Suez Canal University Hospital. The estimated sample size was 32 patients for each group calculated (29+10% drop out).

- μ1= change of clinical score using normal saline + epinephrine (5.13) [9].
- μ2= change of clinical score using 3% saline+ epinephrine (4.39) [9].

Inclusion criteria was Infants younger than 24 months with mild to moderate bronchiolitis, and exclusion criteria was Previous episode of wheezing, Chronic cardiopulmonary disease or immunodeficiency, Critical illness at presentation requiring admission to intensive care, The use of nebulized HS within the previous 12 hours, Premature birth (gestational age ± 34 weeks), Haemoglobin saturation ≥ 95%.

Data collection

Every infant was assessed by history and clinical examination for; History including: name, age, gender, present complaint, past medical history of wheezes, prematurity, immunodeficiency, cardiopulmonary disease or previous admission to the intensive care unit or the use of nebulized HS within the previous 12 hours. Examination including; General examination, pulse, respiratory rate, heart rate, general condition, cyanosis, grunting and nasal flaring; Chest examination, for working accessory muscles (intercostal and/or subcostal retraction and auscultatory findings such as wheezes or crackles; Haemoglobin saturation with oxygen measured by oximetry was recorded on admission and before discharge from the emergency department, and daily in infants who were hospitalized. Participants received inhalation of one of the following; 4 ml of 3% saline solution (group 1), epinephrine, 1 mg, in 4 mL of 0.9% saline solution (group 2), epinephrine, 1 mg, in 4 mL of 3% saline solution (group 3). A recent meta-analysis [8] concluded that nebulization with 3 to 5 ml of adrenaline (1:1000) is a safe treatment with few side effects. Therapy was repeated maximum 4 doses over 2 hours 30 minutes apart. Patients were assessed every 30 minutes up to 120 minutes. Clinical severity scores were assessed and recorded after each dose until discharge upon improvement or inpatient admission. Failure of treatment was considered if deterioration of clinical severity score was recorded. Nebulized medication was delivered to a settled infant from a standard oxygen-driven hospital nebulizer through a tight-fitting facemask, or head box, whichever was better tolerated by the infant.

Types of outcome measures

Primary outcome: Change of heart rate.

Secondary outcomes: Clinical severity scores; Haemoglobin saturation (oximetry), A clinical severity score described by Wang., *et al.* [10] was used in this study. This scoring system assigns a number from 0 to 3 to each variable, with increased severity receiving a higher score, Data collected were managed by statistical package SPSS (statistical package for social sciences) SPSS for windows base system user guide 10.1 Chicago, SPSS INC., 2001. Kruskal wallis test and ANOVA were used as a test of significance of statistical analysis. Tables and graphs were used to illustrate the collected data together with the statistical analysis of data.

Results

A total of 96 infants were enrolled in this study, 32 in each of the study groups, with male predominance in the 3 groups, the mean age was 4 - 4.5 months, studied patients were of average weight and built. Figure 1 shows male to female ratio in study population, 77% are males and 23% are females.

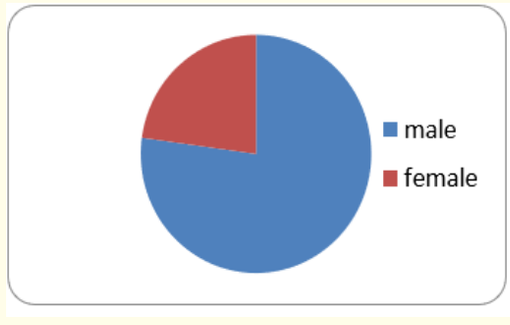

Figure 1: *Frequency of males and females in all study population.*

Figure 2 shows frequency of age groups in all study population. Most of the study population lied between 3 - 4 months of age.

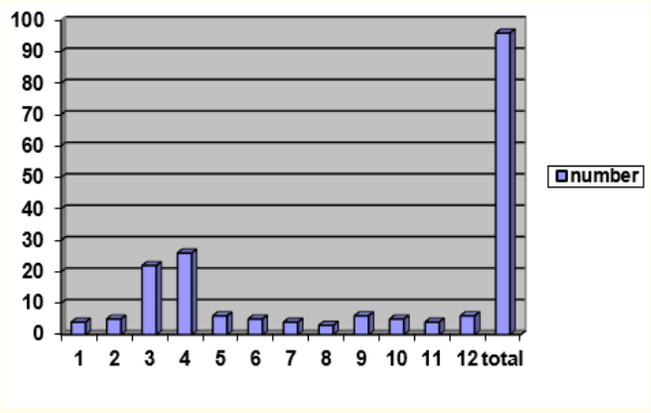

Figure 2: *Frequency of age by month.*

Table 1 shows primary outcome, there was no significant difference in the change of heart rate in the three study groups.

Outcome / Group	Hypertonic saline 3%	Hypertonic 3% + Epinephrine	Normal saline 0.9%+ epinephrine	p-value
Change of heart rate	18.87 ± 8.16	20.53 ± 18.46	20.94 ± 17.45	. 0.898

Table 1: *Primary outcome.*

*Kruskal Wallis test * significant at 0.05*

Table 2 shows the secondary outcomes of the study; there was significant difference in the change of clinical score before and after treatment between the three study groups in favor of the first group; there was no significant difference in the change of oxygen saturation before and after treatment.

Outcome / Group	Hypertonic 3%	Hypertonic+ epinephrine	Normal+ epi-nephrine	p-value
Change of clinical score after 90 minutes	5.22 ± 2.1	5.06 ± 1.33	3.78 ± 1.94	.027*
Change of O_2 sat	0.44 ± 0.43	0.30 ± .43	0.36 ± 0.50	0.362

Table 2: *Secondary outcomes.*

*Kruskal Wallis test * significant at 0.05*

Discussion

In our study the male to female ratio was 3.3, male percentage 77% and females 23%. Similar to our study male percentage was higher in many studies; Grewal., *et al.* [9] had a male percentage of 60.9%, Kuzik., *et al.* [11] had a male percentage of 61%, and Ansari., *et al.* [12] which had a male percentage of 64% while Ralston., *et al.* had a male percentage of 51.5% [13]. Opposite to our results some studies found higher female percentage in their study like Mandelberg who had male percentage of 34% and Sarrel., *et al*. who had a male percentage of 16.7% [14,15]. Distribution of patients in age groups showed that most of the patients were less than 6 months 68% with the peak at 3 - 4 months. Mean age 4.5 ± 2 months similar to study by Grewal., *et al*. [9] which had patients mean age of 4 - 5 months, and similar to a study by Kuzik., *et al*. [11] which had patients age of 4.4 ± 3.7, and also similar to Ansari., *et al.* [12] which had patient's mean of age

ranging from 3.30 ± 2.43 to 4.02 ± 2.56 and Ralston., *et al.* [13] 5.2 ± 3.9 months, Mandelberg., *et al.* 3 ± 1.2 months [14]. Unlike Sarrel., *et al*. 12.7 ± 0.9 months [15]. In our study, there was no significant difference between change of heart rate before and after treatment in the three study groups. Change in heart rate was 18.87, 20.53 and 20.94 in the first, second and third groups respectively with a p-value of 0.898. Similar to our results, Menon., *et al*, Bertrand., *et al*, Hariprakash., *et al*. and Fitzgerald., *et al.* found no significant increase in heart rate in patients treated with nebulized epinephrine compared to placebo or another bronchodilator [16-19]. Unlike our results, Abul-Ainine and Luyt and Wainwright., *et al*. found a significant increase in heart rate after treatment with nebulized epinephrine an increase of 7 - 21 beats per minute with a significance level ≤ 0.05 [20,21]. On the other hand, Waisman., *et al*. found a decrease in heart rate after treatment with nebulized racemic epinephrine compared to placebo [22]. In our study there was no significant differences in the change of clinical score after treatment between the first group (hypertonic saline 3% only) and the second group (hypertonic saline 3% plus epinephrine), but there was significant differences between both those groups and the third group (normal saline 0.9% plus epinephrine), which indicates that epinephrine had no significant rule in the treatment of bronchiolitis in the emergency department. After 90 minutes of treatment, the change of the mean clinical score in the first group was 5.22, in the second group was 5.06 and in the third group was 3.78 with a statistically significant difference (p = .027). Similar to results of Grewal., *et al*. [9] who recorded 4.93 points difference (6.13 to 2.64) in the hypertonic saline group and 5.13 points (3.71 to 6.55) in the normal saline group with no statistically significant difference (p= 0.73) after giving two doses over 120 minutes. Our results proved significant difference between the groups probably because we had a larger sample size we had and the more frequent use of nebulizer sessions (4 sessions half an hour apart, compared to two sessions one hour apart by Grewal., *et al* [9]. Sarrel., *et al.* [15] also found a highly statistically significant difference (p < 0.005) between the mean clinical score in the 2 groups of their study (normal saline + terbutaline and hypertonic saline + terbutalin), after 1 day of treatment in the outpatient department, and (p < 0.01) after 2 days of treatment. Madelberg., *et al*. and Tal., *et al.* [14,23] found borderline statistically significant difference after 3 days inpatient treatment (p = 0.05). Zhang., *et al*. found a statistically significant difference between the clinical score after 1 day (p = 0.02) and highly statistically significant after 2 days of treatment (p = 0.003) [24]. Similar to our results; Ralston., *et al*. proved that hypertonic saline 3% alone is an effective treatment of bronchiolitis in the inpatient department after treating 68 patients with hypertonic saline 3% only without adjuvant and they reported only 1% percentage of side effects (moderate coughing) [13]. Kuzik., *et al*, Mandelberg., *et al*. and Sarrel., *et al.* reported no side effects of the hypertonic saline with additional bronchodilators in the inpatient [11,14,15]. Wainwright., *et al*, Hariprakash., *et al*. and Bul-Ainine., *et al*. also proved that epinephrine didn't have additional effect on both clinical score and length of hospital stay compared to their placebo group which was normal saline 0.9% only [18,20,21]. On the other hand, Grewal., *et al*. reported that racemic epinephrine had a positive effect on bronchiolitis with additional effect of hypertonic saline [9].

Conclusion

Nebulized epinephrine doesn't increase heart rate and has no positive effect on clinical severity score and oxygen saturation in treatment of bronchiolitis.

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