Original Research Article

Comparative studyof nebulizationwithsalbutamol vs.placebo at the acute phase ofbronchiolitis of 100 infants aged 1 to 23 months

Abstract

The efficacy of bronchodilators in the treatment of infant bronchiolitis is still controversial. As a contribution to this debate, we performed a prospective study on 100 infants, and evaluated the effect of nebulization of salbutamol in the acute phase of bronchiolitis. Our study was carried out at the pediatric pulmonology unit at the Children's Hospital, Rabat. Using arandomized selection process, 52 infant patients received salbutamol, and 48 received a placebo solution. The patients included in the study were aged 1 to 23 months andpresented with their first episode of wheezing. During patient selection, we excluded infants who were asthmatic or had other pulmonary issues prior to their bronchiolitis episode. Three nebulizations were performed for each patient, at one-hour intervals, after admission to the service. Wang's score and oxygen saturation were recorded for each patient on arrival, then at 30 minutes after each nebulization. During the treatment period (which lasts three hours), the mean Wang score decreased from 7 to 3.5, and the mean oxygen saturation increased from 92.5% to 95.6%. Statistical analysis of the data, based on a parametric statistical test of the Student type (T-test), shows that there is no significant difference between nebulization with salbutamol and those given saline placebo. The evolution of the clinical scores leads to the general conclusion that we cannot recommend using salbutamol nebulization over saline solution for the treatment of bronchiolitis.

***Keywords** : bronchiolitis, bronchodilators, nebulization, Wang score.*

Introduction

Infant bronchiolitis is an acute viral infection of the lower respiratory tract [1, 2]. It is the most common viral infection in infants and is mainly caused by the respiratory syncytial virus [3]. The condition is defined by predominantly expiratory dyspnea, and

can be associated with polypnea and signs of respiratory struggle. At auscultation, there are cracklings, sub-cracklings or sibilants, sometimes audible from a distance (wheezing) [2]. Bronchiolitis is generally preceded (48 to 72 hours before) by a picture of nasopharyngitis [1, 2].

In Morocco, bronchiolitis occurs in autumn-winter epidemics, usually starting in mid-October, peaking in December, and ending in late winter. The evolution is very variable: ranging from the mild form treated on an outpatient basis to the more serious form requiring hospitalization in the pediatric ward, or even in intensive care [2].

The treatment of bronchiolitis is currently controversial [1]: despite the number of studies reported in the literature in recent years, the therapeutic role of bronchodilators in the treatment of bronchiolitis is questioned by many practitioners. Some studies conclude that bronchodilatorshave no special clinical and functional efficacy [4]. Gadomski et al's extensive literature review [3] argued that, in order to answer completely the question of efficacy, there isa need for treatment trials using placebo controls, and for randomized controlled trials with large sample size and standardized methodology. They recommended that exclusion criteria be consistently applied to exclude infants with recurrent wheezing, asthma or other pulmonary disease. They surmised that widespread use of bronchodilators in bronchiolitis is likely due to the similarity between symptoms and signs of bronchiolitis and asthma.

Our study follows the above recommendation, and consists of a double-blind study that compares the evolution of the oxygen saturation and Wang score of 100 infants, half of whom received salbutamol nebulization, and the other half (the control group) received a placebo.

MaterialsandMethods

Inclusionand exclusion criteria

The study was carried out at the pediatric pulmonology unit at the University Hospital of Rabat, during the local bronchiolitis peak season between September and January. The inclusion criteria are:

1. Age 1 to 23 months
2. First episode of wheezing
3. Meets clinical definition of bronchiolitis

The exclusion criteria are:

1. Previous episode of wheezing
2. Pathology associated with the first episode of wheezing (sequelae of virus of infections, bronchial dilatation, heart disease, etc.)
3. Prior steroid treatment within 48 hours of admission
4. Bronchodilator treatment within 4 hours of admission
5. Respiratory rate greater than 80 cycle per minute
6. Disturbance of consciousness
7. Heart rate greater than 180 beats per minute
8. Low oxygen saturation (85% or less)

These criteria were inspired by previous studies [1,2,7-11].

Preparation of the nebulization solution

As soon as an infant is selected for inclusion in the study, an assistantnot otherwise involved in the study decides, based on a random draw, to fill a syringe with a salbutamol solution (0.03 ml/kg of the 0.5% solution) or with a placebo solution (0.03 ml/kg of 0.9% sodium chloride solution). In both cases, 0.9% sodium chloride is added to the syringe to obtain a total solution volume of 4 ml. The person who administers the solution does not know which type of solution is in the syringe until after nebulizations are performed.

Administration of the nebulization solution

The solution prepared in the syringe is administered to the patient in three nebulizations: the first at H_0, the second at $H_1 = H_0 + 60$ minutes, and the third at $H_2 = H_0 + 120$ minutes. Each nebulization is delivered for 10 minutes by means of an aerosol equipped with a facial mask and propelled by oxygen with a flow rate of 6 liters per minute. No other treatment was administered during the study; only nasopharyngeal obstruction is performed just before each nebulization. This approach is similar to what has been done in other work [1,2,7].

Follow-up

The clinical evaluation according to the Wang score[12] and oximetric score is performed on admission and 30 minutes after each nebulization (H_0 + 30 mins; H_1 + 30 mins; H_2 + 30 mins). The study included patients from each severity level defined by range of Wangscore:

- Score from 0 to 3: bronchiolitis with low or no severity
- Score 4 to 7: bronchiolitis of moderate severity
- Score 8 to 12: severe bronchiolitis

A favorable response to treatment is defined by the transition from one class of severity to another class of lesser severity [13].

Statistical Analysis

The aim of our study is to determine if there is a difference in efficacy between the two types of nebulization. We consider that a difference of 1 point in the Wang score between the two intervention groups to be clinically significant. Using the same statistical design as Khanal et al [4], we planned our study to have 100 patients. To analyze our results, we used a T-test statistical method for comparing two proportions with large independent samples (since we have more than 30 patients) [14].

To determine the effectiveness of a treatment method, the rate of change (ratio) of each monitored parameter (respiratory rate, wheezing, draft, and Wang score) is calculated between admission and discharge. For example, for placebo, the sum of the admission and discharge respiratory frequencies is 112 and 60, respectively, which corresponds to a decrease of 53.6% thanks to the treatment with placebo solution. For salbutamol nebulization, this reduction rate is 52.4%. The p-value statistic [14] corresponding to these ratios is p-value = 0.906. This value being higher than the standard value of the risk threshold = 0.05, confirming that the hypothesis that the two treatments cannot be differentiated.

Results

Patientsat admission

The characteristics of the study population at admission are reported in Table I. Of the 100 infants in the study, 61 were boys and 39 were girls, and all were 1 to 23 months of age. The randomized selection resultedin over twice as many boys as girls in the placebo group, but the number of girls and boys are the same in the salbutamol group. The other epidemiological, clinical and oxymetric parameters at admission are comparable for the two groups. The evolution of the means of the scores during the treatment are reported in Tables II and III, and in the figures below.

	Salbutamol	Placebo
Number of patients	52	48
Sex (F/M)	26/26	13/35
Age (months)	9.0±6.1	8.2±5.72
Respiratory rate	2.4±0.5	2.3±0.5
Sibilant score	2.0±0.0	2.0±0.3
Indrawing score	2.2±0.4	2.2±0.4
Wang score	7.0±1.5	6.7±1.7
Oxygen saturation (%)	92.3±2.2	92.7±2.1

Table I : Parameters atadmission (mean ± stdv)

Nebulization of salbutamol

	Admission	H0+30 mins	H0+90 mins	H0+150 mins
Respiratory rate	2.4±0.5	2,4 ± 0,5	1,8 ± 0,5	1,3 ± 0,4
Sibilant score	2.0±0.3	1,8 ± 0,4	1,2 ± 0,4	1,0 ± 0,2
Indrawing score	2.2±0.4	2,1 ± 0,4	1,5 ± 0,5	1,1 ± 0,4
Wang score	7.0±1.5	6,6 ± 1,7	4,8 ± 1,6	3,4 ± 0,9
Oxygen saturation (%)	92.3±2.2	92,8 ± 2,4	94,4 ± 1,6	95,6 ± 1,2

Table II: Evolution of the patient group nebulizedwith salbutamol (mean ± stdv)

Nebulization of the placebo solution

	Admission	H0+30 mins	H0+90 mins	H0+150 mins
Respiratory rate	2,3 ± 0,5	2,3 ± 0,5	1,7 ± 0,5	1,3 ± 0,5
Sibilant score	2,0 ± 0,3	1,8 ± 0,5	1,3 ± 0,4	1,0 ± 0,3
Indrawing score	2,2 ± 0,4	2,1 ± 0,4	1,4 ± 0,5	1,1 ± 0,3
Wang score	6,7 ± 1,7	6,5 ± 1,5	4,6 ± 1,1	3,4 ± 0,8
Oxygen saturation (%)	92,7 ± 2,1	93,0 ± 2,1	94,7 ± 1,7	95,8 ± 1,2

TableIII: Evolution of the patient group nebulized with placebo (mean ± stdv)

FIG 1 : RESPIRATORY RATE

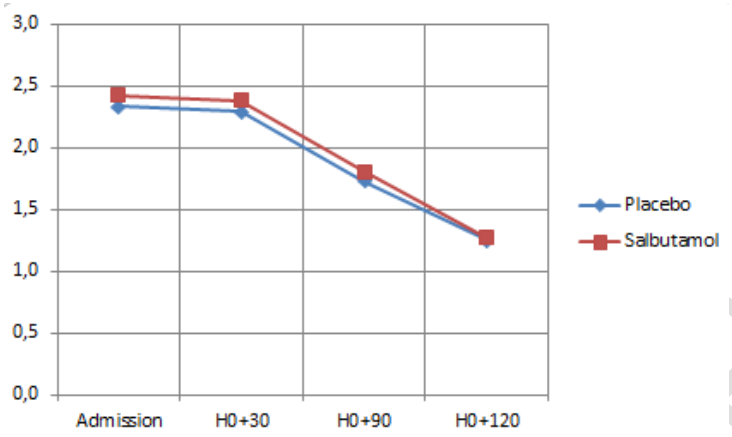


FIG 2 : SIBILANTSCORE

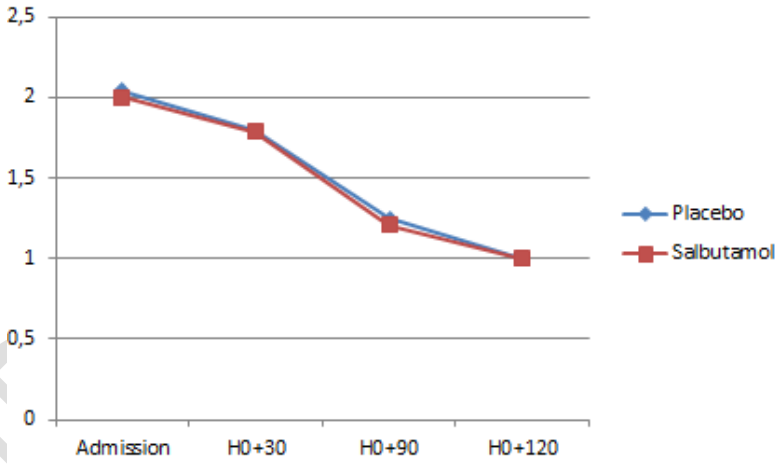


FIG 3 : INDRAWINGSCORE

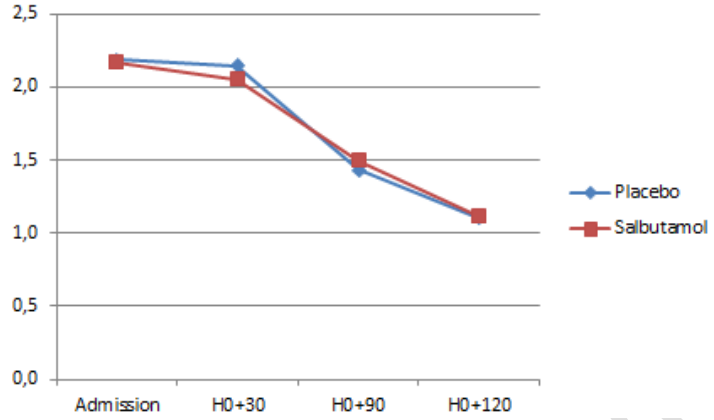


FIG 4 : OXYGEN SATURATION (%)

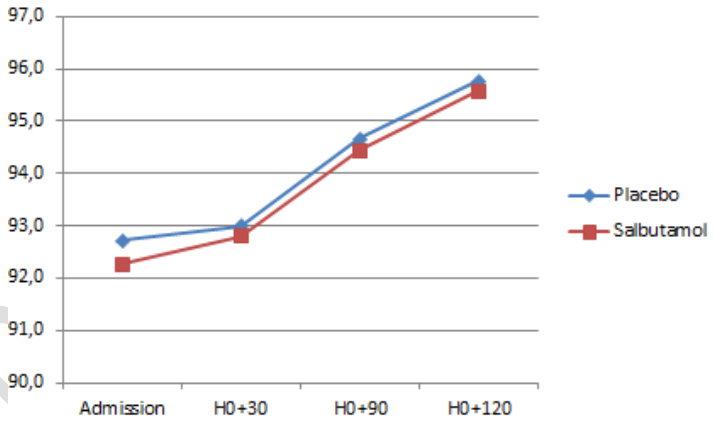
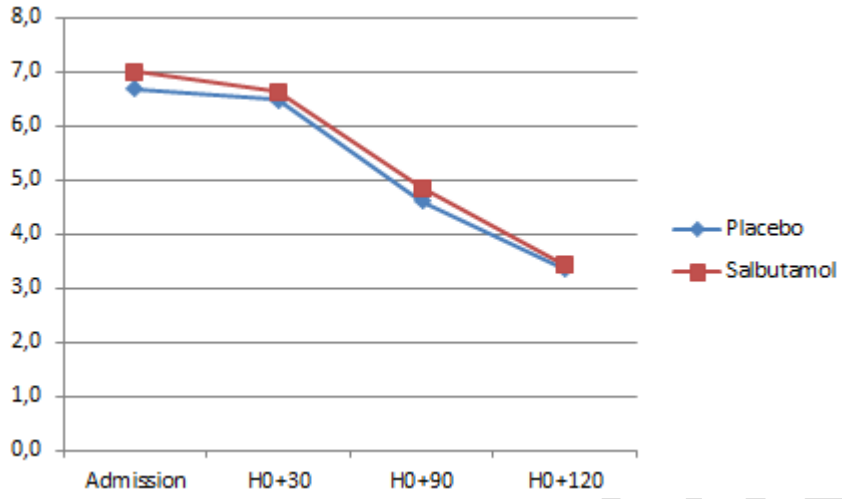


FIG 5 : WANG SCORE



Discussion

Bronchiolitis is an acute, highly communicable lower respiratory tract infection characterized by cough, runny nose, fever, expiratory wheezing, grunting, fast breathing, retractions, and air trapping. Children with bronchiolitis have wheezing that is clinically similar to asthma, but there are some key differences. First, the pathophysiology of bronchiolitis is such that the airways are obstructed rather than contracted. Second, while children with asthma have recurrent wheezing, infants with bronchiolitis have wheezing for the first time.

Bronchodilators, which are known to reversebronchoconstrictioninducedbyasthma, have not proven to be as effective for infants with bronchiolitis. Bronchodilators such as albuterol or salbutamol have not improved oxygen saturation or any the Wang Score parameters [4, 12]. This could be because the pulmonary beta-agonist receptor sites of infants appear inadequate, and because the potential effectiveness of β2- adrenergic agonists is limited by the smooth muscles of their bronchiolar walls.Given the adverse side effects and the expense associated with these treatments, bronchodilators are not effective in the routine management of bronchiolitis.As asthmatic children are known to respond to bronchodilators, their exclusion from our study prevented a false increase in the apparent level of efficacy of bronchodilators in patients with bronchiolitis.

This is confirmed by the results of our study. Visually, the graphs shown in the Results section, as well as the p-values shown in Table IV, show that salbutamol nebulization has no significant advantage over placeboin improving oxygen saturation or Wang's score. For both groups, there is gradual improvement in all scores and the effect seemed to be more pronounced after the second session of nebulization at 30 min. But there is no significant difference in the mean change in each score between the two groups.

Paramètre	Ratio		Z	p-value
	Placebo	Salbutamol		
Respiratory rate	53,57%	52.38%	0,119	0,906
Sibilant score	48,98%	50,00%	0,102	0,919
Indrawing score	50,48%	51,33%	0,085	0,933
Wang score	50,16%	48,90%	0,125	0,901
Oxygen saturation (%)	96,82%	96.54%	0,080	0,937

Table IV: Change in each monitored parameter between admission and discharge and corresponding p-values.

Conclusion

Our study was designed to minimize the biases and limitations described in Gadomski et al's extensive literature review [3]. The sample size was significant (100 infants), and the strict inclusion and exclusion criteria were used to minimize possible confounding effects. Blinding was maintained each patient from admission to release.

The resultsshow that salbutamol nebulization is not more effective than saline solutions in the routine management of bronchiolitis. This conclusion is consistent with the results of other studies [3, 12]. The use of bronchodilators in the management of the first bronchiolitis cannot be not recommended.

Ethical approval

Ethical approvalhas been taken from ethics commette to carry out the study

Consent

Informed written consent was taken from all respondents

References

1. Chevallier B, P Aegerter, S Parat, E Bidat, C Renaud, B Lagardère. Comparative study of salbutamol nebulizations against placebo in the acute phase of bronchiolitis in 33 infants from 1 to 6 months. Archives of Pediatrics, Volume 2, Issue 1,

Pages 11-17

2 M.Verstraete et al. Management of acute bronchiolitis in infants under 1 year old: updating and medical consensus in university hospitals in the Great West (HUGO)

3 Chéron, G., G. Patteau, and V. Nouyrigat. "Infant bronchiolitis." EMC-Emergency Medicine (2009): 1-7..

4 Khanal A., Sharma A., Basnet S., Sharma P.R., and GamiF.C .. Nebulized hypertonic saline (3%) among children with mild to moderately severe bronchiolitis-a double blind randomized controlled trial. BMC pediatrics 15.1 (2015): 115

5 Gadomski AM, Scribani MB. Bronchodilators for bronchiolitis. Cochrane Database of Systematic Reviews 2014, Issue 6. Art. No .: CD001266. DOI: 10.1002 / 14651858.CD001266.pub4

6 Pailhouse et al. Acute infant bronchiolitis: national survey of pediatric emergency departments. Archives of Pediatrics 2015; 22: 373-379

7 Labbe A. Treatment of acute bronchiolitis in infants. Place of bronchodilators and corticoids. Archives of Pediatrics, Volume 3, Issue 4, April 1996, Pages 383-389

8 Fily A. Place of bronchodilators in the treatment of acute bronchiolitis in infants. Archives of Pediatrics, Volume 8, Supplement 1, January 2001, Pages 149-156

9 Sebban S. Influence of respiratory physiotherapy on the decision to hospitalize infants under one year of age suffering from bronchiolitis in pediatric emergencies. Physiotherapy, the Review, Volume 17, Issue 183, March 2017, Pages 3-8

10 Sardet A. et al. Bronchiolitis and bronchodilators. Medicine and Infectious Diseases, Volume 23, Supplement 5, November 1993, Pages 880-882

11 Gajdos et al. Acute bronchiolitis in infants Are treatments really necessary? Current state and prospects. Archives of Pediatrics, Volume 21, Issue 5, Supplement 1, May 2014, Pages 232-233

12 Wang EE, Milner R, Allen U, Maj H. Bronchodilators for treatment of mild bronchiolitis: a factorial randomized trial. Arch Dis Child. 1992; 67: 289–93

514/5000

13 Chin HJ, Seng QB. Reliability and Validity of the Respiratory Score in the Assessment of Acute Bronchiolitis. The Malaysian Journal of Medical Sciences?: MJMS. 2004;11(2):34-40.

14 http://cerim.univ-lille2.fr/fileadmin/user_upload/statistiques/michael_genin/Cours/Tests_statistiques/Tests_parametriques_printable.pdf

15 Friedman, Jeremy N., et al. "Bronchiolitis: recommendations for diagnosis, monitoring and management of children one to 24 months of age." Paediatrics& child health 19.9 (2014): 485-491.