A RANDOMIZED, CONTROLLED TRIAL OF NEBULIZED TERBUTALINE IN THE FIRST ACUTE BRONCHIOLITIS IN INFANT LESS THAN 12 MONTHS OLD

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ETUDE RANDOMISÉE EN DOUBLE AVEUGLE DE LA NÉBULISATION DE TERBUTALINE DANS LE PREMIER ÉPISODE DE BRONCHIOLITE DU NOURRISSON ÂGÉ DE MOINS DE 12 MOIS.

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RÉSUMÉ

Prérequis : L'utilisation des bronchodilatateurs dans la bronchiolite aigue du nourrisson reste un sujet de controverse.
But : Evaluer l'efficacité des nébulisations de terbutaline dans le traitement de la bronchiolite aigue sur l'amélioration du score clinique, la saturation en oxygène à l'air ambiant et la réduction de la durée d'hospitalisation
Méthode : Il s'agit d'une étude prospective randomisée en double aveugle réalisée au service de médecine infantile B de l'hôpital d'enfants de Tunis de décembre 2004 à avril 2006
Résultats : 35 enfants âgés de moins de 12 mois présentant un premier épisode de bronchiolite aigue de sévérité modérée ont été inclus dans notre étude. Chaque nourrisson a reçu des nébulisations de terbutaline ou de sérum physiologiques à l'admission (T0), à 30 min de l'admission (T30) et puis toutes les 4 heures durant la période d'hospitalisation. Nous n'avons trouvé de différence significative entre les nébulisations de terbutaline à l'état de base, après 30 min , 60 min et 120 min du début du protocole comparées aux nébulisations de sérum physiologique concernant le score de détresse respiratoire (RDAI), la saturation en oxygène, la fréquence respiratoire et la fréquence cardiaque. Nous n'avons pas également noté de différence significative concernant la durée de l'hospitalisation entre le groupe ayant reçu la terbutaline et celui ayant reçu le sérum physiologique en nébulisation.
Conclusion : La terbutaline n'apparaît pas améliorer les nourrissons âgés de moins de 12 mois présentant un premier épisode de bronchiolite aigue de sévérité modérée.

MOTS-CLÉS

Bronchiolite, bronchodilatateurs, nourrisson, terbutaline, wheezing, essai controlé, tirage au sort

SUMMARY

Background: Despite the common clinical practice, the available evidence on the efficacy of bronchodilators therapy for bronchiolitis is conflicting.
The aim of this study is to evaluate the efficacy of nebulized terbutaline in bronchiolitis as measured by improvement in clinical score, oxygen saturation or reduction in duration of hospitalization.
Methods: This prospective, double blind, placebo controlled, randomized clinical trial was performed at Children's Hospital of Tunis from December 2004 to April 2006.
A total of 35 patients less than 12 months of age with diagnosis of moderately severe bronchiolitis were enrolled and assigned to receive nebulized terbutaline or normal saline placebo at admission (T0), at 30 minutes after admission (T30) and every four hours during a study period. Outcome measurements included: Respiratory Distress Assessment Instrument (RDAI) score, respiratory rate, oxygen saturation, heart rate and the duration of hospitalization.
Results: There were no significant difference between terbutaline and placebo at baseline, T30 min, T60 min, and T120 min after start study in RDAI score, oxygen saturation in room air, rate respiratory and heart rate. There was no difference in duration of hospitalization.
Conclusion: Nebulized terbutaline therapy does not appear effective in treating moderately ill infants with the first acute bronchiolitis.

KEY-WORDS

Bronchiolitis; bronchodilator agents; infant; terbutaline; wheezing, randomized, controlled trial

العنوان : دراسة عشوائية مزدوجة الأعمى لـ " Terbulatine " في علاج إلتهاب القصيبات الهوائية عند الرضيع دون 12 شهر من العمر

الباحثون : تينسا . ف . بن رحوما . أ . جعفاري . هـ . بوستة . ك . زواري . ب . بريني . ي . كاربول . ل . سويدي . م . بوسنينا . س.

إستعمال الموسعات القصبية لمعالجة التهاب القصيبات الهوائية الحاد لا تزال موضع جدل. الغرض تقييم فعالية التحرير إلى ذرات " Terbutaline " في معالجة إلتهاب القصيبات الحاد على تحسين رصيد السريرية ، تشبع الأكسجين في الهواء و الحد من طول مدة العلاج في المستشفى. الطريقة : هذه دراسة مستقبلية عشوائية مزدوجة الأعمى أجريت في قسم طب الأطفال بمستشفى الأطفال بباب سعدون بتونس من ديسمبر 2004 إلى أفريل.2006 النتائج 35 : رضيع يبلغون أقل من 12 شهر من العمر يشكون من أول حلقة للإلتهاب القصيبات الهوائية الحاد المعتدل الشدة قد أدرجو في هذه الدراسة. تلقى كل رضيع التحويل إلى ذرات " Terbutaline " أو المصل الفيزيولوجي عند القبول في المستشفى 30 (T0) دقيقة بعد القبول (T 30) ثم كل أربع ساعات خلال فترة البقاء في المستشفى .لم نجد أي فرق كبير بين التحويل إلى ذرات " Terbulatine "بعد 30 دقيقةو 60 دقيقة أو 120 دقيقة من بدأ الدراسة بالمقارنة مع تحويل الذرات المصل الفيزيولوجي على مستوى درجة الشدة التنفسية قطشوْ و تشبع الأكسجين و معدل التنفس و ضربات القلب .إننا لم نلاحظ أيضا إختلافا كبيرا بشأن طول البقاء في المستشفى بين مجموعة من تلقي "Terbutaline" و مجموعة من تلقي المصل الفيزيولوجي. الخاتمة " Terbutaline " : لم تحسن الأطفال دون 12 شهر و الذين يشكون من إلتهاب القصيبات الهوائية الحاد المعتدل

الكلمات الأساسية : إلتهاب القصيبات الهوائية،رضيع، ,Terbutaline القحيح، الموسعات القصيبية

Bronchiolitis is the most common lower respiratory track infection in infancy afflicting 11% to 12% [1,2] and hospitalizing 1% to 2% [3] of all children in their first year. Bronchiolitis associated hospitalizations have increased considerably since 1980 becoming a problem of public health in the world and in Tunisia [4]. Given the prevalence and morbidity of bronchiolitis, an effective therapy is needed. Bronchodilators have been used in the treatment of bronchiolitis since the late 1950s, and continue to be widespread use in Tunisia [5]. The use of bronchodilators to treat children with bronchiolitis remains controversial. The controversy may be result of difference in study populations, in choice of bronchodilators, in measured outcome variables between trials.

The objective of this study was to evaluate the efficacy of nebulized bronchodilators (Terbutaline) in moderate severity bronchiolitis as evidenced by improvement in oxygen saturation in room air and reduction in the RDAI score, respiratory rate and the hospital stay duration.

METHODS

Design:

This prospective, double blind, placebo-controlled, randomized clinical trial was performed at the department of pediatrics B of the Children's Hospital of Tunis (Tunisia)

Study setting:

Infants were recruited throughout two bronchiolitis seasons winters (December 2004 to March 2005 and October 2005 to April 2006) at the time of hospital admission from the emergency department.

Patients:

Eligible infants included all previously well infants aged between 3 months old and 12 months old with a clinical diagnosis of first acute viral bronchiolitis and who are hospitalized during the study period. Viral bronchiolitis is defined as an acute infection of the lower respiratory trac, preceeded by or accompanied by fever and/or rhinitis, and characterized by expiratory wheezing and increased respiratory effort. Moderate severity bronchiolitis is characterized by a score on the respiratory distress instrument (RDAI score) between 4 and 15; the RDAI score is based on two respiratory variables, wheezing and retraction. This score was chosen because of its face validity, high inter-and intrarater reliability [6] and its discriminative ability [7].

Children were excluded from the study if they had a gestational age at birth<34 weeks, or underlying chronic cardiac or pulmonary disease (eg, bronchopulmonary dysplasia, cystic fibrosis…), concurrent bronchodilator or corticosteroid, recurrent wheezing, severe respiratory distress, as evidence by apnea, heart rate> 200beats per minute, RDAI score >15, respiratory rate >80 breath/minute, profound lethargy, duration of illness exceeding 15 days.

Study design:

After an initial clinical assessment, patients were randomly assigned, by means of a computer-generated table of random numbers, to receive blinded treatment with either nebulized terbutaline (0.06 ml/kg = 0.15 mg/kg) in normal saline to make a total volume of 4 ml or saline placebo (4ml of normal saline) solution. Nebulizations were administrated for 10 minutes with small, tight-fit-ting plastic face mask with an up draft nebulizer with continuous flow of 100% oxygen at 6 to 7 L/min. Infants received another nebulization 30 min after the start of the first treatment and every 4 hours during the study period. All infants with oxygen saturation in room air of 93% or less received supplemental oxygen when not receiving nebulizations. All patients were evaluated using standardized complete respiratory history and physical examination by the medical doctor. Initial history included age, gender, duration of the illness, current medications, allergies, family history of wheezing or smoking, birth history, history of previous chronic illness, cardiac or pulmonary disease. All patients had a baseline clinical assessment consisting of the RDAI score, respiratory rate, heart rate and pulse oximetry. The assessment were made by medical doctor who is blind for the solution nebulized, when the infant was relatively calm and had breathing room air for at least 10 minutes. The clinical assessment was repeated 30, 60, 120 minutes after the start of the first treatment. An additional secondary outcome measure was hospital stay duration. Criteria of discharge from the hospital included: no need for supplemental oxygen, RDAI score less than 4 and adequate fluid intake.

This study was approved by the Human Ethics committee of the Charles Nicolle's hospital, because we have not a Human Ethics committee in our hospital and the Tunisian legislation provides that in such cases it is allowed to submit the study to the human Ethics committee of the institution closest. We did not seek signed informed consent because nebulized terbutaline is routinely and widespread used in the management practise of acute bronchiolitis by paediatricians in Tunisia in outpatients and inpatients without side effects observed. However, there is not available evidence on the efficacy of this therapy for bronchiolitis in the literature.

Statistical analysis:

The following data were analyzed using SPSS/PC V 11.5 soft ware.

For descriptive statistics we calculated proportions for qualitative variables and means with standards derivation and IC 95% for quantitative variables.

We used parametric t-test or non parametric Mann and Withney test for comparison of two means from independent groups. We used Wilcoxon test for comparison of two means from dependant groups. We used X2 or Ficher's exact test for comparison of two proportions from independent groups. We used rank correlation coefficient of Spearman (Rho) to test correlation between quantitative variables (eg, RDAI score and time). A value of P≤ 0.05 was taken as indicating statistical significance.

RESULTS

36 infants were randomized to the study protocol. One patient was withdrawn by the pediatric inpatient team because of worsening clinical status during the first 24 hours. He was

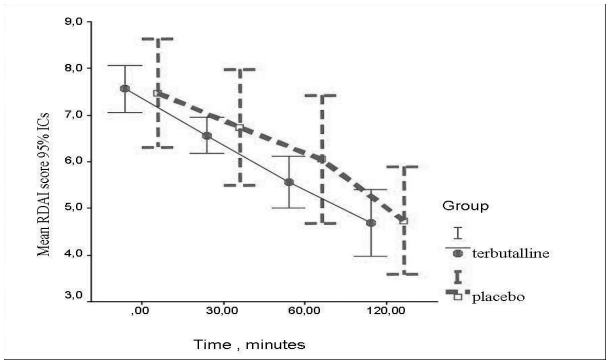
transferred to intensive care department. This patient had been randomized to receive placebo. He was excluded from the statistical analysis. Ninteen infants received placebo and 16 infants received terbutaline. The two groups were similar for all baseline variables (Table I).

Table 1 : Patient characteristics at entry into study

variables	Terbutaline	Placebo	P
Number of patients	16	19	0.371
Male patients (%)	62.5	47.4	0.443
Exposure to smokers (%)	60	43.7	0.253
Family history of asthma (%)	37.5	7.7	0.369
Age (months)	6.6±2.02	5.9±2.3	0.723
Heart rate(beats/min)	136.7±15.6	134.6±18.09	0.382
Respiratory rate(breath/min)	63.5±14.2	59.5±12.7	0.275
Oxygen saturation in room air (%)	95.8±1.58	96.5±1.8	0.884
RDAI Score	7.5±0.96	7.4±2.4	

There was no significant difference in mean RDAI score between terbutaline and placebo at any time point (T0, T30, T60, T120) (Table II); RDAI score decreased significantly with time across study population (p<0.001 in group placebo, P= 0.001 in group terbutaline) (Figure 1).

Figure 1 : Mean RDAI score by time



There was no significant difference in mean of oxygen saturation in room air between terbutaline and placebo at any time point (T0, T30, T60, T120) (Table II); oxygen saturation in room air increased significantly with time in group placebo (P =0.023); in group terbutaline oxygen saturation increased but not significantly (p=0.13)(Figure 2).

There was no significant difference in mean of respiratory rate between terbutaline and placebo at any time point (T0, T30, T60, T120) (Table II); respiratory rate decreased significantly with time across study population (P= 0.003 in group placebo, P= 0.049 in group terbutaline) (Figure3).

No patients in either treatment group experienced clinically significant adverse side effects (tachycardia, flushing, tremor) (Table II). The mean time for discharge was 3.3 days in terbutaline group compared to 2.57 day in placebo group; there was no significant difference in the median time for discharge in two groups (p= 0.253)

Table 2 : Outcome variables

	Terbutaline	Placebo	P
DRAI score (median)			
Baseline	7.4± 2.4	7.5±0.9	0.88
At 30 min	6.73±2.5	6.5±0.7	0.78
At 60 min	6.05±2.8	5.5±1	0.52
At 120 min	4.7±2.4	4.6±1.3	0.94
Respiratory rate (breath/min)			
Baseline	59.5±12.7	63.5±14.2	0.38
At 30 min	54.2±13.4	59.8±15.5	0.26
At 60 min	54.3±13.5	56.1±13.3	0.7
At 120 min	50.8±12.8	50±9.6	0.83
Oxygen saturation (%)			
Baseline	96.5±1.8	95.8±1.5	0.27
At 30 min	96.1±2.1	95.5±1.8	0.39
At 60 min	96.8±1.9	96±2.04	0.26
At 120 min	97.2±1.5	97±1.3	0.67
Heart rate (beats/min)			
Baseline	134.6±18.	136.7±15.6	0.72
At 30 min	132.6±15.5	133.2±19.6	0.91
At 60 min	136.4±23.1	136.7±16.4	0.96
At 120 min	125.05±36.0	132.5±10.9	0.48

Figure 2 : Mean oxygen saturation by time

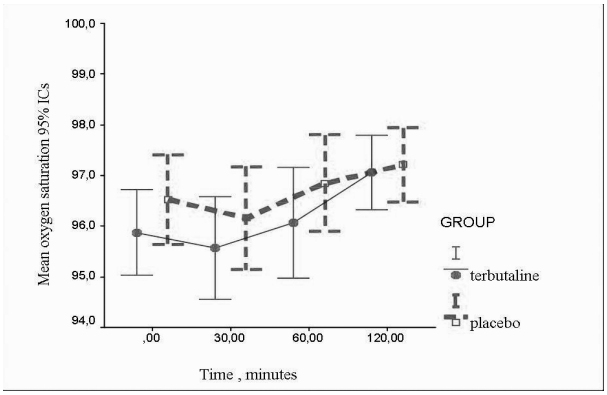
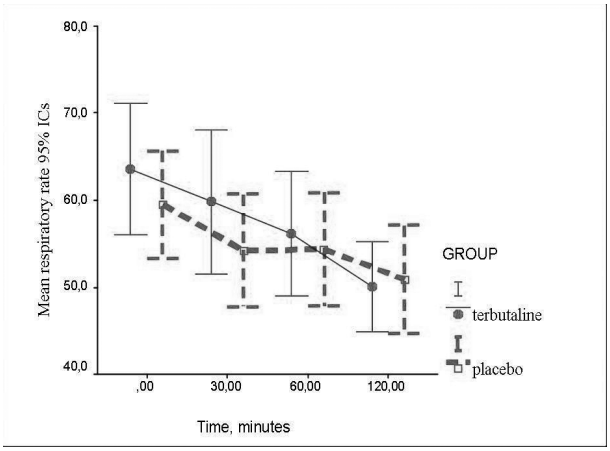


Figure 3 : Mean respiratory rate by time



DISCUSSION

The analysis of the outcome measures in this randomized trials show no clear benefit to nebulized terbutaline treatment in hospitalized patients with moderate severity bronchiolitis, as evidenced by improvement in oxygen saturation in room air, DRAI score, respiratory rate at any time point or duration of hospital stay. Both treatment groups demonstrated clinical improvement in score RDAI, oxygen saturation, respiratory rate over the hospital course.

We believe that the lack of benefit from bronchodilators is related to the unique pathologic features of viral bronchiolitis and the anatomic features of the young infant. The extent of bronchiolar epithelial regeneration is likely limiting factors that influence recovery from the illness.

Dobson et al [8] conducted a prospective, double blind, placebo controlled randomized clinical trial to determine whether the use of albuterol by nebulization enhances physiologic or clinical recovery in hospitalized infants with moderate bronchiolitis. These authors concluded that there was no significant difference in mean oxygen saturation in room air between albuterol and placebo at baseline, 24 hours, or maximum oxygen saturation achieved during hospitalization. Both groups showed significant improvement in oxygen saturation over time, but there was no significant difference in improvement between the groups. This data were closest to our findings.

King et al [9] conducted a systematic review of the effectiveness of commonly ,-agonist bronchodilators for bronchiolitis in infant and children. They included 13 studies of various bronchodilators agents. Eleven used salbutamol or albuterol in at least one treatment arm compared with saline placebo, nebulized saline placebo or unspecified placebo control. Outcomes studied were largely surrogate measures, such as change in clinical severity score, and were primarily short term in nature. Differences in agents, dose, delivery system, sitting and outcomes limit overall comparisons. Seven trials examined a primary outcome measure related to need for or length of hospitalization. None reported significance differences between groups. Three studies demonstrated improvement in various types of clinical measures in the short term (30 to 60 minutes after treatment) for patients receiving nebulized bronchodilators therapy and one demonstrated worse score.

A critical review and meta-analysis of randomized controlled trials of inhalated ,2-agonists conducted by Flores et al [10] concluded that evidence for efficacy was inadequate given the short- term nature of outcome (emergency department studies) and the inability to compare outcome in studies of hospitalized patient.

A Cochrane review conducted by Gadomski et al [11] included twenty-two clinical randomized placebo-controlled trials of treatment with bronchodilators in bronchiolitis (1428 infants). Studies of epinephrine in bronchiolitis were excluded. In eight trials of 468 infants, there was no improvement in clinical score for 43% for those treated with bronchodilators compared to 57% of those treated with placebo (OR for non improvement 0.45, 95% CI 0.15 to 1.29). There was a statistically significant but clinically modest improvement in the overall average clinical score (standardized mean difference (SMD) – 0.48, 95% CI -0.62 to -0.33); however there was no statistically significant improvement in oxygenation overall (weighted mean difference (WMD) – 0.57, 95% CI -0.1.17 to -0.3) and the duration of hospitalization was not reduced among bronchodilator recipients (WMD 0.02 days, 95% CI -0.32 to 0.36). This comparison may be biased for showing difference because some studies included patients with recurrent wheezing and the inclusion of asthmatic children, who are known to respond to bronchodilators, will falsely increase the apparent level of efficacy in patients with bronchiolitis. More over studies in this metanalysis included children in the 0-24 months et in the 0-36 months age category and it is possible that older infants might be more likely to have viral induced bronchospasm amenable to bronchodilator therapy; there will falsely increase the apparent level of efficacy in patients with bronchiolitis.

For these raisons we had chosen in this randomized trial, patients who had the first episode of bronchiolitis and were aged less than 12 months old. The only limitation in our study may be the sample size which is not large.

CONCLUSION

In summary nebulized terbutaline therapy dose not appear to enhance recovery in this group of hospitalized infant with acute bronchiolitis. Treatment with nebulized bronchodilators represents a significant health care cost. For these reasons its routine use for bronchiolitis in the hospital setting is not supported.

RÉFÉRENCES

1. Denny FW, Clyde WA. Acute lower respiratory tract infections in non hospitalized children. J. Pediatr. 1986; 108: 635-646.
2. Henderson FW, Clyde WA, Collier et al. The etiologic and epidemiologic spectrum of bronchiolitis in pediatric practice. J. Pediatr. 1979; 5:183-190.
3. Martin AJ, Gardner PS, Mc Quillin J. Epidemiology of respiratory viral infections among paediatric inpatients over a six year period in North East England. Lancet. 1978; 2:1035-1038.
4. Glezen WP, Taber LH, Frank AL, Kasel JA. Risk of primary infection and reinfection with respiratory syncytial virus. Am. J. Dis. Child. 1986; 140: 543-546
5. Menif K, Kechaou W, Bouziri A et al. Current management of acute bronchiolitis in Tunisia. Tunis. Med. 2007;85: 65-8.
6. Menon K, Sutcliff T, Klassen TP. A randomized trial comparing the efficacy of epinephrine with salbutamol in the treatment of acute bronchiolitis. J. Pediatr. 1995; 126:1004-1007.
7. Klassen TP, Rowe PC, Sutclifft T, Ropp LJ, Mc Dowel IW, Li MM. Randomized trial of salbutamol in acute bronchiolitis. J. Pediatr. 1991;118:807-11.
8. Dobson JV, Groff S, McMahon SR, Stemmlar MM, Brallier SL, Bay C. The use of albuterol in hospitalized infants with bronchiolitis. Pediatrics. 1998; 101:361-368
9. King V, Viswanathan M, Bordely C et al. Pharmacologic treatment of bronchiolitis in infants and children. Arch. Pediatr. Adolesc. Med. 2004; 158:127-137.
10. Flores G, Horwitz R. Efficacy of ,2-agonists in bronchiolitis: A reappraisal and meta-analysis. Pediatrics. 1997; 100: 233-239.
11. Gadomski AM , Bhasale AL. Bronchodilators for bronchiolitis. Cochrane Database of Syst Rev 2006, Issue 3. Art. No.: CD001266. DOI: 10.1002/14651858.CD001266.pub2.