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The role of bronchodilators in the management of bronchiolitis: a clinical trial

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Summary A randomized clinical trial was conducted on young children with bronchiolitis admitted to hospital with moderate illness to determine the efficacy of the bronchodilators Salbutamol and ipratropium bromide, either as a single drug or in combination, given as a nebulized solution, compared with a normal saline placebo. Eighty-nine patients, aged from 23 days to 11 months, were randomized into four groups, depending on administered drug or placebo, as follows: group 1—Salbutamol ($n = 20$); group 2—ipratropium bromide ($n = 23$); group 3—combined Salbutamol and Ipratropium bromide ($n = 24$); group 4—normal saline ($n = 22$). The groups were identical with respect to age, sex, family history of atopy, respiratory syncytial virus (RSV) positivity and enrolment score. They were scored using the clinical parameters of wheezing, retractions and respiratory rate at enrolment, at 30 and 60 minutes after the first nebulization, and after 60 minutes following completion of subsequent nebulization at 6, 12, 24 and 36 hours. We did not find any significant difference in the rate of improvement and the final score ($p = 0.49$) in the four groups. The same finding was also noted in children aged more than 3 months ($p = 0.35$) and in those positive for RSV infection ($p = 0.18$). The lengths of hospitalization in the four groups were also similar ($p = 0.79$). It is concluded that there is no role for the nebulized bronchodilators Salbutamol and Ipratropium bromide, either as a single agent or in combination, compared with normal saline placebo in treating young children in hospital with bronchiolitis.

Introduction

Bronchiolitis is a major cause of morbidity in young infants requiring outpatient and inpatient management. There is still great controversy regarding which symptomatic treatment would be both effective and safe in improving the clinical status or shortening the duration of hospitalization in such patients. There are numerous publications: most of them establish the ineffectiveness of bronchodilator therapy,[1–12] but some report benefit, at least in the short-term.[13–15] However, there is a widespread impression among clinicians that bronchodilators do work in at least some cases, and these drugs are in routine use in inpatients and outpatients in many hospitals, including our hospital.[16]

In most of the studies which failed to show any effect of bronchodilator drugs, patients were studied by tests of pulmonary function, which are not used in routine clinical practice in following up bronchiolitis patients. Furthermore, some of these babies needed sedation

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and were in the recovery phase of their illness, which makes interpretation of their response to treatment less straightforward. In addition, in most of the patients, a reasonable frequency of scoring was not maintained for long enough to reveal a meaningful outcome in terms of real clinical benefit and period of hospitalization. This is also true of clinical trials which show the beneficial effects of bronchodilators. The contrast between the evident effectiveness of bronchodilators in a pulmonary function test and the lack of it in the clinical trial by the same investigators was also demonstrated in the case of ipratropium bromide.[4,12] In routine hospital practice, patients with bronchiolitis are commonly assessed using clinical parameters regarding day-to-day improvement and decisions about discharge. A recent study which used clinical parameters and pulse oxymetry failed to show significant improvement in hospitalized patients with bronchiolitis who were treated with commonly used nebulized bronchodilators.[1] However, the patients had mild disease and had been receiving treatment with a Salbutamol nebulizer before admission, which led the authors to comment that only patients unresponsive to this agent might in fact have been studied. Considering these facts, we conducted a clinical trial in patients not previously on bronchodilators using a well tried clinical scoring method[13] and the commonly used bronchodilators Salbutamol, ipratropium bromide and a combination of both for a reasonably long period, and compared their efficacy with a normal saline placebo. We also chose to score the patients with sufficient frequency to detect the onset of any bronchodilator effect.

Patients and methods

Suleimania Children's Hospital is a major Ministry of Health referral centre in Riyadh City, with its population of about two million, and is the paediatric teaching hospital of King Saud University. During the period from 15 October 1992 to 30 January 1993 all children admitted with a diagnosis of bronchiolitis were screened for eligibility to enrol in the study, and those who met the following criteria were included: (i) age less than 2 years; (ii) presence of wheezing, audible and/or on auscultation; (iii) no previous history of wheezing or use of bronchodilator; (iv) no chronic pulmonary disorder such as cystic fibrosis, bronchopulmonary dysplasia, immunodeficiency, etc.; (v) no congenital heart disease; (vi) no radiological evidence of significant pulmonary consolidation; (vii) patients who were judged by the admitting resident to be not sufficiently sick to require intensive monitoring or therapy. The diagnosis of bronchiolitis was made on the basis of a history of cough and/or wheeze, tachypnoea, intercostal retractions and, on auscultation, ronchi and râles. We excluded patients with a previous history of wheezing or use of a bronchodilator in order to exclude cases of probable asthma.

The Hospital Scientific Committee approved the project and informed consent by the parents was obtained. All study patients were admitted to the Respiratory Care Unit (RCU) and to two other general wards under physicians who were not involved in the study. The resident on duty in the emergency room referred patients eligible for enrolment to the admitting wards. After their arrival, the head nurse or charge nurse called one of the investigators (either DC or SC) who took the history, performed the physical examination and scored the patient, which was the enrolment score at 0 hours. Then the nurse randomly selected one of the four following modes of therapy, using coded envelopes: 1. Salbutamol respiratory solution (Ventolin, 5 mg/ml, Allen & Hanbury Ltd, England), 0.15 mg/kg (0.03 ml/kg); 2. ipratropium bromide (Altrovent, 0.025% solution, Boehringer Ingelheim), 12.5 μg/kg; 3. a combination of both the above drugs at doses given; 4. normal saline, 0.3 ml/kg. All these medications were mixed with two ml normal saline and delivered by 100% oxygen at a rate of 6–7 litres/minute, using 64095 Ped Aerosol Mist Nebulizer, B&M Medical nebulizer system. The medications or the placebo were administered 6-hourly for 36 hours. After the enrolment score at 0 hours, all the patients were scored at 30 and 60 minutes

TABLE I. Modified respiratory distress assessment instrument

	0	1	2	3	4	Points
Wheezing:						
Expiratory	None	End	1/2	3/4	All	4
Inspiratory	None	Partial	All			2
Location	None	< 2 of 4 lung fields	< 3 of 4 lung fields			2
Retraction						
Supraclavicular	None	Mild	Moderate	Marked		3
Intercostal	None	Mild	Moderate	Marked		3
Subcostal	None	Mild	Moderate	Marked		3
Resp. rate	20–25	26–35	36–45	> 45		3
Total						

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after the first nebulization, and after 60 minutes following completion of subsequent nebulization at 6, 12, 24 and 36 hours. The investigator knew which drug had been used after 36 hours, i.e. after the seventh scoring, after which all patients, for ethical reasons, were switched to a Salbutamol nebulizer solution, 0.15 mg/kg 6-hourly mixed with 2 ml normal saline, delivered by the same method.

Discharge of patients was at the discretion of the treating physician. Nasopharyngeal aspirates were collected on the morning following admission and sent to the laboratory in viral culture media for culture and also for immunofluorescence study. We used the modified Respiratory Distress Assessment Instrument (RDAI) (Table I) which uses the clinical parameters of intercostal retractions and wheezing in addition to respiratory rate. These three parameters were assessed in a total score of 20 points. We did not analyze the blood gases routinely, but according to the severity of the case.

All patients were given a score on enrolment and subsequently after medication at 6 am, 12 noon, 6 pm and midnight so that for any patient admitted between these times scoring began at the next 6-hourly set time. If the admitting physician felt that the child required urgent attention and medication before the investigator could score the patient, treatment was started immediately and the patient was excluded from the study. We considered a score of 0–7 indicated mild illness, 8–14 moderate illness and 15–20 a severe illness.

Statistical analysis

SPSSPC V4 was used for statistical analysis. The χ^2 and Fisher's exact tests were used to compare the four intervention groups where analysis of variance was used to compare the age and length of stay between the groups. The clinical score at enrolment and the change in score after treatment compared with that at 0 hours which were not normally distributed were analyzed using the Kruskal-Wallis analysis.

Results

During the period of study, 278 children were admitted with a diagnosis of bronchiolitis. Of that number, 102 were considered eligible for inclusion in the study according to the eligibility criteria previously stated. Thirteen children were subsequently excluded because 12 of them developed pulmonary consolidation and were put on antibiotics by the treating physician and in one deterioration of the clinical status required transfer to the intensive care unit. A total of 89 patients therefore completed the study.

The demographic criteria of the patients

TABLE II. Characteristics of the four groups

Groups	1 (Salbutamol)	2 (Ipratropium bromide)	3 (Salbutamol + Ipratropium bromide)	4 Normal Saline
Number of patients	20	23	24	22
Sex—Male/female	14/6	16/7	18/6	17/5
Age:				
Mean (SD) (mths)	3.88 (2.3)	4.16 (2.4)	3.64 (1.8)	3.72 (2.27)
No. of patients >3 months	11	11	11	12
Saudis	17	18	21	19
Positive consanguinity	9	13	9	12
Family history of atopy	9	12	10	9
RSV positivity	12/16	15/18	14/21	11/19
Median enrolment score (quartiles)	10.5 (10–12.75)	12 (10–12)	11 (10–12.75)	10 (9–12.25)

regarding numbers, age, sex, family history of atopy, positive RSV results, either by culture or immunofluorescence, nationality, parental consanguinity and initial scores were not significantly different in all the four groups (Table II). There was a high rate of consanguinity, which is usual in Saudi Arabia. Nasopharyngeal aspirates from all 89 patients were examined; 52 patients proved to be RSV-positive, either by culture or immunofluorescence, 22 were negative and in the remaining 15 aspirated material was inadequate. No other viral agents were identified, although we also looked for parainfluenza, influenza and adenovirus. So we had an RSV-positive result in 70.2%, which is comparable with results in other studies.[11,14]

The changes in the clinical score were calculated from the differences between the scores at 30 and 60 minutes, at 6, 12, 24 and 36 hours, and the enrolment score at 0 hours. There was no significant difference in the median change of score between the four groups of patients ($p = 0.49$) (Table III). This lack of difference was observed both in the rate of improvement at different scoring intervals and in the final difference in score. But there was a gradual improvement in the scores in all the four groups over 36 hours, again without a significant difference between the groups, probably an effect of the natural history of the disease.

When we analyzed patients older than 3 months we again failed to note any significant difference in the median score between the four groups ($p = 0.35$) (Table IV). The same results were observed in the patients positive for RSV infection ($p = 0.18$). Nor was the period of hospitalization significantly different in the four groups ($F = 0.34$, $p = 0.79$) (Table V). We noted that the most marked improvement occurred after the first nebulization following enrolment at 30 minutes and that it was similar in all four groups ($p = 0.23$). Although an improvement at the same rate was not noted in the subsequent scoring, there was a gradual improvement in the score till the last score at 36 hours.

Discussion

While bronchiolitis is a major cause of illness and hospitalization in young infants, the efficacy of bronchodilator agents in relieving symptoms and shortening the duration of hospitalization has been debated for more than 2 decades.[7,17,18] In the absence of any solid clinical and laboratory evidence supporting the usefulness of these drugs, bronchodilators such as B-2 agonist and ipratropium bromide are still commonly prescribed for both outpatients and inpatients.[16] It has been noted that a significant proportion of patients with bronchiolitis continue to wheeze for a long time

TABLE III. Median change in the clinical score of different treatment groups

Time of assessment	Group 1 ($n = 20$) Median (quartiles)	Group 2 ($n = 23$) Median (quartiles)	Group 3 ($n = 24$) Median (quartiles)	Group 4 ($n = 22$) Median (quartiles)	p
30 min	3 (1.25–4.75)	2 (1–3)	2 (1–3)	2 (1–3)	0.23
60 min	2.5 (1–4)	3 (1–4)	2.5 (1.25–3.75)	2.5 (1–4)	0.93
6 hrs	2.5 (1–4.75)	2 (2–5)	3 (1–5)	2.5 (2–3.25)	0.92
12 hrs	3.5 (2–6)	2 (2–4)	4 (2–4.75)	2.5 (1.75–4.25)	0.54
24 hrs	2.5 (1.25–4.5)	4 (1–6)	4 (2–4.75)	2.5 (1.75–4)	0.58
36 hrs	4.5 (3–6)	5 (2–7)	4 (2.25–5.75)	3 (1.75–5)	0.49

Group 1—Salbutamol; group 2—Ipratropium bromide; group 3—Combined Salbutamol and ipratropium bromide; group 4—Normal saline.

after an initial attack, that the wheezing may also be intermittent,[19,20] and that on long-term follow-up over 10 years some of these patients had asthmatic symptoms.[19] These findings have led some observers to believe that a bronchodilator would work in some of these patients. But, on the other hand, the cause of the symptoms and signs in bronchiolitis is mainly acute inflammation of the bronchiolar epithelium with widespread small airway obstruction, which does not make the prospect of a response to bronchodilator drugs[21] particularly promising. There is also evidence that upper airway obstruction plays a major part in the symptomatology of bronchiolitis.[21] An ideal easy pulmonary function test for routine use which will assess accurately lower and upper airway obstruction has still not been developed. Techniques for measuring airway obstruction, and its relief or otherwise following the use of bronchodilators, especially in sedated patients in the recovery phase, may not always reflect adequately the actual clinical picture of an acutely ill patient, and has been criticised.[22–25] But it is clinical judgment which is used in the day-to-day monitoring of patients and in making decisions regarding discharge from hospital. Silverman noted the lack of an appropriately designed clinical trial using a drug and a placebo for a significantly long time and in multiple doses.[21] Most studies assessing the effects of bronchodilators used either a single dose or multiple doses over a relatively short period of time.[12,14,15] One study demonstrated improvement, after treatment with a Salbutamol nebulizer, at 30 minutes, but the improvement failed to continue to 60 minutes.[14]

After considering all these facts, we decided to embark upon this study, using clinical criteria and a well established scoring system, measuring the response to bronchodilators and placebo with sufficient frequency in relation to the duration of treatment. Although a total of 278 patients were admitted with a diagnosis of bronchiolitis, in accordance with our strict selection criteria only 102 were eligible for study. The selection criteria were defined with the aim of excluding other possible causes of wheezing such as bronchial asthma, chronic pulmonary disease such as cystic fibrosis, bronchopulmonary dysplasia, pulmonary manifestations of immunodeficiency, and congenital heart disease. Patients with radiological evidence of pulmonary consolidation were excluded as they required antibiotics, and acutely ill patients were also excluded because they required in-

TABLE IV. Median change in the clinical score of different treatment groups (only children > 3 months were included)

Time after the 0 score	Group 1 ($n = 9$) Median (quartiles)	Group 2 ($n = 12$) Median (quartiles)	Group 3 ($n = 13$) Median (quartiles)	Group 4 ($n = 10$) Median (quartiles)	p
30 min	3 (1–3.5)	2 (2–3)	2 (1–3)	3 (0.75–3.25)	0.5
60 min	1 (0.5–4)	3 (1.5–4)	2 (0–3)	3.5 (1.75–6)	0.12
6 hrs	2 (0–5.5)	2 (2–4)	2 (0.5–4)	2.5 (2–4.5)	0.76
12 hrs	4 (1.5–8.5)	2 (2–3.75)	4 (1.5–4)	3 (2–4.75)	0.73
24 hrs	3 (1.5–5)	4 (1.22–6)	4 (3–5)	4 (2–4.25)	0.64
36 hrs	5 (3–7)	4 (2–5.75)	4 (2–7)	3.5 (3–8)	0.35

Group 1—Salbutamol; group 2—Ipratropium bromide; group 3—Combined Salbutamol and ipratropium bromide; group 4—Normal saline.

tensive monitoring as well as therapy other than bronchodilators. We also excluded those who had received bronchodilators prior to admission because their inclusion might have influenced the outcome of the study. Thus, many patients were excluded because they had received bronchodilators, which is the usual practice in the study hospital. Of the 102 patients, 13 were subsequently excluded because 12 of them were treated for pneumonia which developed after they had been recruited into the study and one required transfer to the intensive care unit. So a total of 89 patients completed the study. We failed to detect any efficacy of the bronchodilators Salbutamol, ipratropium bromide or their combination when compared with normal saline placebo in treating young children with bronchiolitis in terms of improvement of their median clinical scores. When we compared the subgroup of children aged more than 3 months our findings were similar.

TABLE V. Average length of hospital stay of the treatment group (in days)

Group	Mean (SD)
1. Salbutamol	4.5 (1.3)
2. Ipratropium bromide	4.4 (1.4)
3. Salbutamol + Ipratropium bromide	4.6 (1.4)
4. Normal saline	4.3 (1.1)
Total	4.3 (1.3)

Analysis of variance: $F = 0.3445$; $p = 0.79$.

With regard to RSV positivity, either in culture and/or immunofluorescence, again all the four groups showed no significant difference in improvement in median clinical scores. The bronchodilator therapy had no effect on the duration of hospitalization in these groups. The demographic characteristics of our patients were similar in all the four groups. The mean age of our patients was lower than that in other studies, owing mainly to the enrolment criteria by which we excluded previous wheezers or recipients of bronchodilators. It also reflects our policy of admission of acutely ill younger patients to our hospital.

When we observed the pattern of improvement in all the groups over the 36-hour period, we found that there was an improvement of two to three points in the score of all four groups after the first nebulization, i.e. after the enrolment score at 0 hours, but that this rate of improvement did not continue in subsequent scoring. However, there was a gradual

improvement in score over the 36-hour period which was not as marked as the first response, i.e. three to five points improvement between 0 and 36 hours compared with two to three points between 0 and 30 minutes. All these findings were similar in all the four groups. It is possible that the improvement in score was in fact due to inhalation of the oxygen used to deliver the drugs rather than the effect of any particular agent, and that the gradual increase in improvement was an additional effect of the natural history of the disease on the scoring. The studies showing deterioration of oxygen saturation after bronchodilator therapy used chloral hydrate as sedation.[10,11] This may cause respiratory depression and lower oxygen saturation in infants whose baseline oxygen saturation is less than 94%.[24] Recent studies have shown that Salbutamol does not cause a decrease in oxygen saturation;[1,14] another shows improvement of oxygen saturation after nebulized Salbutamol.[15] All used oxygen as a vehicle to deliver drugs. As we did not measure the blood gas routinely, we cannot confirm but can postulate that there was an improvement in clinical scoring when the oxygen treatment was used as a vehicle for the drugs. Thus, the improvement noted after a single nebulization of a bronchodilator drug using oxygen as a vehicle may give a false impression of the efficacy of the drug.

We conclude that the bronchodilators Salbutamol and ipratropium bromide are no more effective, when used alone or in combination, than a normal saline placebo in treating hospitalized young infants with bronchiolitis. There is no difference in efficacy in patients older than 3 months of age or in patients positive for RSV. The use of bronchodilators does not significantly reduce the duration of hospitalization more than a placebo.

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