Terbutaline vs Albuterol for Out-of-hospital Respiratory Distress: Randomized, Double-blind Trial

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ABSTRACT

Objective: To determine the efficacy and safety of single doses of subcutaneous terbutaline (TERB) or nebulized albuterol (ALB) during out-of-hospital treatment for respiratory distress from asthma or chronic obstructive pulmonary disease.

Methods: Patients aged >18 years who had respiratory distress were enrolled in a double-placebo, double-blind, randomized trial. Paramedics measured respiratory severity using an empiric score [respiratory rate, wheezing, speech, and peak expiratory flow rate (PEFR)], and the patients rated their own respiratory distress using a visual analog scale (VAS). The patients received O_2 plus ALB (2.5 mg) and saline injection (n = 40) or TERB (0.25 mg) and saline aerosol (n = 43).

Results: The groups were similar with respect to age, gender, initial empiric scores (median score 9 for both groups), PEFRs (89 ± 84 L/min, mean ± SD, for ALB vs 97 ± 84 L/min for TERB), and respiratory distress VAS scores. Both groups showed significant improvement in their respiratory distress VAS scores by the time of ED arrival. The ALB group had a greater improvement in respiratory distress VAS score than did the TERB group ($p < 0.05$). Empiric scores, PEFR scores, and hospital admission frequencies were not significantly different. No complication was observed.

Conclusion: The out-of-hospital administration of either aerosolized ALB or subcutaneous TERB reduced respiratory severity. Albuterol provided greater subjective improvement in respiratory distress.

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Treatment of patients with respiratory distress from wheezing-related illness, such as asthma or chronic obstructive pulmonary disease (COPD), is a common clinical problem during out-of-hospital care.[1] Out-of-hospital care may be important in reducing asthma-related deaths, since mortality has been associated with delays in the initiation of treatment.[2] Although current initial treatment varies with different emergency medical services (EMS) systems, administration of O_2 and bronchodilator therapy are typically provided. In some EMS systems, bronchodilator therapy is limited to injections of epinephrine and terbutaline (TERB), which are painful and may have increased risks of side effects.[3]

Since pressurized gas, usually O_2, is ubiquitously available in ambulance systems, the ability to deliver aerosolized bronchodilators is possible. Aerosolized β-agonists are effective, are painless, may have fewer side effects than do traditional injected bronchodilators, and are generally preferred in many EDs for the initial management care of wheezing-related respiratory distress.[4] Open-label studies of inhaled β-agonists have demonstrated their feasibility and effectiveness in the out-of-hospital setting.[4–6] No previous study has compared traditional, injectable therapy with aerosolized treatment during out-of-hospital care of patients in respiratory distress. In this study, adult patients experiencing respiratory distress from asthma or COPD received either a single treatment of subcutaneous TERB and saline aerosol or aerosolized albuterol (ALB) and saline injection during routine out-of-hospital care. We sought to compare these therapies to determine their effects on subjective and objective indexes of respiratory distress severity.

METHODS

Study Design

This study was a prospective, double-placebo, double-blind, randomized, controlled, out-of-hospital trial of a single dose of TERB vs ALB to assess the efficacy and safety of these agents for patients aged >18 years who had respiratory distress.

Population and Study Site

The study took place in Syracuse, NY, a medium-sized city, and its surrounding region with urban, suburban, and rural populations totaling approximately 1.4 million people, and covering an area of approximately 12,000 square miles. The private ambulance system used provides 24-hour advanced life support (ALS) service with paramedic coverage. The EMS system is self-dispatched; it receives calls by direct lines and by an enhanced 911 system. The service handles, on average, 35,000 ALS calls per year. The study took place over a six-month period, ending November 1992. The study was approved by the local institutional review board for patient enrollment with initial verbal consent (see below).

Patients were included if they were >18 years of age and judged to have respiratory distress secondary to exacerbations of asthma or COPD. Patients were excluded for chest pain of presumed cardiac origin, allergies to any study medication, refusal to give informed consent, prior subcutaneous epinephrine administration, refusal of further care, the need for immediate assisted ventilation or endotracheal (ET) intubation, or incomplete data. Patients who refused the study treatment were then treated according to the regional protocols for their conditions.

Experimental Protocol

Two months prior to initiation of the study, paramedics were given in-service instruction on the study protocols, and peak expiratory flow rate (PEFR) meters (see Measurements) were placed on the ambulances. Prior to study initiation, the paramedics were instructed in and became practiced in clinical use of the PEFR meters. Upon ascertaining the patient's history and medications, and assessing the patient's condition, the paramedics delivered routine medical care. This included O_2 by mask or cannula, an IV of D_5W at a keep-vein-open rate, and cardiac monitoring.

Informed consent was obtained in a two-step process. A verbal assent was obtained by any indication of acceptance (e.g., a head nod or verbal acceptance) when the treating paramedic arrived at the patient's side and read the following: "After our evaluation, we have determined that you are having an asthma or emphysema attack. We are conducting a research trial comparing two medications commonly used to treat your condition. If you agree to participate, you will receive a breathing treatment and a shot to help your condition. If you do not wish to participate, your treatment will be the standard protocol of the EMS program. You will receive more information regarding this study when we arrive at the hospital. Do you wish to participate in the study?" Written informed consent was obtained upon arrival at the receiving ED.

Randomization of drugs was carried out at the hospital pharmacy. The pharmacy prepared identically appearing sets of vials (one containing the medication and the other the placebo). Two vials, one marked for injection and one for aerosolization, were placed in each envelope. The paramedics selected envelopes in sequence for each eligible consenting patient. The ambulance personnel and the patients were blinded to medication identity. Each patient received an aerosol followed by an injection, in rapid sequence. Hence, a

TABLE 1 Empiric Respiratory Score Components

Score	RR* (breaths/min)	Wheezing	Speech	PEFR† (L/min)
0	<20	None	Unimpaired	>350
1	20–30	End-expiration	Short phrases	250–350
2	30–40	Entire expiration	1 or 2 words	150–250
3	>40	Audible wheezing	Aphonic	0–150

*RR = respiratory rate category.
†PEFR = peak expiratory flow rate.
Empiric respiratory score = Σ all scores (RR + wheezing + speech + PEFR). Worst status (maximum score) = 12; best status (minimum score) = 0.

single dose of either 2.5 mg of ALB or 0.25 mg of TERB was administered following routine medical protocols.

Measurements

In addition to routine assessment, the patients underwent PEFR measurement (Model #43, Vitalagraph Peak Flow Meter, Kansas City, MO) by the treating paramedic. The highest of three PEFRs was taken as the actual value. An empiric respiratory score was calculated for each patient (Table 1). The components of this empiric score were arrived at by consensus of the study authors. They represented a compromise between obtainable out-of-hospital parameters and data demonstrated to indicate the severity of respiratory distress. Total empiric respiratory scores could range from 0 (dyspnea only) to 12 (maximum severity score). Patients also marked their level of respiratory distress on the data collection sheet using a horizontal 6-cm visual analog scale (VAS). Scores of 0 indicated the worst possible distress, while scores of 6 indicated no respiratory distress.

Upon arrival at the receiving ED, patients were asked by the same paramedics whether they experienced subjective improvement from the treatment. Additionally, repeat PEFR measurements, severity scores, and VAS respiratory distress scores were obtained by the paramedics. The treatment-to-ED interval was defined as the time from receiving the study medications until ED arrival. Complications were defined prospectively and the patients were monitored for dysrhythmias, vomiting, pain from injection, and headache.

Data Analysis

For analysis of the impact of out-of-hospital care including the study drugs, the ALB and TERB treatment groups were compared for median changes in empiric respiratory scores, PEFR values, respiratory rates, and patient-rated dyspnea VAS scores using the Wilcoxon signed-ranks test. The percentages of patients in the two groups who had overall subjective improvement and hospital admission were compared using chi-square. A significance level of $\alpha = 0.05$ was used throughout.

RESULTS

Ninety patients were entered into this study. Five patients were excluded for incomplete data, one for refusal of written consent and one for protocol violation. The patient who refused written consent worsened and required ED ET intubation for congestive heart failure and a COPD exacerbation. Of 83 evaluable patients, 40 were given ALB and 43 TERB. The treatment groups were similar with respect to age, gender, and initial respiratory parameters (Table 2). Diagnoses of patients could not reliably be determined because of a mixture of reactive airway diseases, including bronchitis, emphysema, asthma, and COPD. The initial measurements indicate that the study group had severe respiratory distress. The initial variables (mean ± SD) for the entire study group were a PEFR of 93 ± 82 L/min, a respiratory rate of 33 ± 6 breaths/min, and an empiric respiratory score of 8.4 ± 1.8 (maximum severity = 12).

The empiric respiratory scores in both treatment groups were significantly improved when compared with the patients' initial scores. When analyzed within groups, there was significant improvement from baseline in the median empiric respiratory scores for both the ALB (-2, $p < 0.05$) and the TERB (-1, $p < 0.05$) groups. The mean percentage improvement (from baseline) in empiric respiratory score for the TERB group (18 ± 22%) was not significantly different from that for the ALB group (27 ± 22%) upon ED arrival. The ALB group

TABLE 2 Patient Characteristics and Initial Respiratory Scoring for the Albuterol and Terbutaline Treatment Groups

	Albuterol (n = 40)		Terbutaline (n = 43)		p-value
Age (yr)*	60	(29 to 69)	58	(36 to 71)	NS
Gender—female (%)	51		49		NS
Empiric respiratory score*	9	(7.5 to 9.0)	9	(7.0 to 10.0)	NS
Respiratory rate (breaths/min)*	35	(29 to 36)	32	(28 to 38)	NS
Dyspnea VAS† (cm)*	1.1	(0.6 to 1.6)	1.0	(0.4 to 1.8)	NS
PEFR‡ (L/min)*	75	(30 to 123)	75	(43 to 145)	NS
Interval from treatment to ED (min)*	20	(15 to 27)	20	(16 to 29)	NS

*Values are mean (interquartile range).
†VAS = visual analog scale score for dyspnea.
‡PEFR = peak expiratory flow rate.

experienced a significantly greater reduction in respiratory rates (−6 vs −4; $p < 0.05$) and had a larger proportion reporting overall subjective improvement (83% vs 52%; $p < 0.05$) than did the TERB group. There also was greater improvement in patient-rated dyspnea VAS scores in the ALB group (1.9 vs 1.1; $p < 0.05$) compared with the TERB group. Although empiric respiratory scores were more improved in the ALB group, they did not achieve statistical significance compared with the TERB group. Despite improvements in the severity of respiratory distress, large individual differences created substantial variance. However, no patient other than the excluded patient described above experienced any worsening of the empiric respiratory score or the PEFR value.

The groups had similar changes in PEFR values (Table 3). Also, the two treatment groups had similar hospital admission rates (ALB 40%, TERB 44%). Other than the patient refusing to enter the study, no patient required ED intubation and no side effect related to the study medications was noted in either treatment group.

TABLE 3 Change in Respiratory Severity Measures after Out-of-hospital Treatment for the Albuterol and Terbutaline Treatment Groups*

	Albuterol		Terbutaline		p-value
Empiric respiratory score change	−2	(−1 to −3)	−1	(0 to −2)	NS
Respiratory rate change (breaths/min)	−6	(−2 to −9)	−4	(0 to −6)	<0.05
PEFR† change (L/min)	15	(0 to 70)	0	(0 to 40)	NS
Dyspnea VAS‡ (cm)	1.9	(1.2 to 3.0)	1.1	(0 to 2.4)	<0.05
Overall subjective improvement (%)	83		52		<0.05

*ED arrival values minus initial out-of-hospital values given as either median (interquartile range) or percentage.
†PEFR = peak expiratory flow rate.
‡VAS = visual analog scale score for dyspnea.

DISCUSSION

Prompt and appropriate treatment is critical for patients suffering from respiratory distress secondary to asthma or COPD.[3] Although outcome studies of the out-of-hospital treatment for these conditions are limited, several studies conclude that early out-of-hospital treatment may benefit these patients[4–6] and may decrease morbidity and mortality.[6–8] The current study demonstrates that a single dose of aerosolized ALB or subcutaneous TERB resulted in significant improvements in our empiric respiratory score during treatment of out-of-hospital patients for exacerbations of COPD or asthma. In addition, patients receiving ALB showed significantly greater improvement than did those receiving TERB in patient-rated respiratory distress (dyspnea VAS) and overall subjective improvement.

Inhaled β-agonists have become the first line of treatment for exacerbations of asthma and COPD in the ED.[6,9–12] Although published studies have compared subcutaneous epinephrine and TERB,[13] nebulized TERB and subcutaneous epinephrine,[14] and inhaled TERB and ALB,[15,16] we could find no study comparing the efficacies of subcutaneous TERB and aerosolized ALB in a controlled, randomized fashion.

Emergency medical services system changes in treatment protocol should be based on documented improvement in patient care and outcome as demonstrated by proper research.[17] Few studies have documented the effect of out-of-hospital medications on patient outcome.[18,19] Our study demonstrates improved efficacy of ALB over TERB for some measurements during routine out-of-hospital care. The study also shows the value of out-of-hospital treatment for wheezing-related illness in adults.

Our EMS system was faced with requests from both out-of-hospital providers and ED physicians to replace TERB injection with ALB nebulization. The results of this study were a catalyst for changing out-of-hospital protocols and undertaking the significant task and expense of in-service training and medication replacement in our large EMS region, as required when switching to aerosolized ALB. Though there was not a significant difference between the groups in empiric respiratory score and PEFR, we believe the subjective improvement noted with ALB coupled with the recommendation that inhaled bronchodilators be used[3] justified the recommendation to replace TERB with ALB.

Obtaining informed consent in out-of-hospital research and from patients who have conditions necessitating emergent treatment remains a difficult task for researchers. We could not subject patients in respiratory distress to a long and detailed written consent form. We used a two-step consent process described by Grim et al.[20] Informed consent in this study was appropriate and cautious compared with that in a placebo-controlled trial because the eligible patients always received an active medication.[21]

LIMITATIONS AND FUTURE QUESTIONS

Our study was limited by the lack of a placebo-control group. A third treatment control group receiving only placebo would have eliminated potential evaluation biases and would have the added advantage of assessing outcome for patients treated with only O_2 and monitoring. We are aware of only one study that used a control

group receiving only basic life support (BLS).[4] Emerman et al. included a control group when assessing the efficacy of nebulized isoetharine because their EMS system had both ALS and BLS ambulances. Patients who were assessed and treated by BLS crews served as the control group. With our system providing only ALS care and because our EMS system promotes early diagnosis and treatment of these conditions, we could not ethically have a control group with no ALS treatment.

We did not track patients who presented with and were treated for asthma or COPD but not entered into this protocol. Although frequent verbal reminders were provided to the paramedics during the study period, the most common reason found for not enrolling patients in this study was that the paramedic chose not to enroll eligible patients. Other than the one patient excluded for written consent refusal, ED records were not reviewed to attempt to confirm accuracy of initial paramedic patient assessment.

Our empiric respiratory score was a compilation of scores previously used in the literature.[22,23] A compromise between parameters readily obtainable in the out-of-hospital setting and those parameters that have been previously demonstrated to indicate the severity of respiratory distress due to wheezing-related illness were weighted based on both published criteria and the study authors' impressions. No attempt was made to validate the score prior to the study. We could have improved the validity and utility of our study by performing a prestudy validation of the empiric respiratory score. One approach would have been to demonstrate a relationship between need for intensive care admission, need for hospital admission, need for additional steroid therapy, and/or length of hospital stay with the presenting (and/or ED) empiric respiratory score for patients treated with standard therapy. Further, some assessment of the inter- and intraobserver variabilities of scoring should be determined. Nonetheless, the variables used in the empiric respiratory score are used routinely by emergency physicians in assessing patients for improvement and need for hospitalization.[24–26]

No attempt was made during the study to differentiate patients as to the degree of reversible obstruction present. The reason for this is twofold: first, many patients carried several diagnoses relative to their pulmonary diseases. Second, the initial out-of-hospital treatments for acute exacerbations of both asthma and COPD for these conditions are nearly identical. Since the obstructive component of many pulmonary diseases increases with advancing age, it is important to note that the mean ages of the treatment groups were not significantly different.

Our study is one of a few prospective, double-placebo, double-blind, randomized out-of-hospital studies. This study supports clinical benefit from the out-of-hospital management of respiratory distress. Further studies on the out-of-hospital treatment for these conditions could be undertaken with the goal of comparing other agents or routes of delivery. For example, should BLS units administer β-agonists by mini-dose inhaler (with or without a spacer device) or should β-agonist therapy be limited to ALS providers?

Clinical outcome studies are increasingly important to demonstrate the effectiveness of EMS interventions. It is important to address subjective improvement in conditions causing patient distress such as pain or respiratory distress.[27] Patient distress levels secondary to certain conditions, though not as easily measured as mortality or hospital admission rates, do represent important outcome measurements.

CONCLUSIONS

A single, out-of-hospital dose of aerosolized ALB or subcutaneous TERB provides significant subjective improvement upon ED arrival for patients with exacerbations of COPD or asthma. Patients receiving ALB experienced a greater improvement in patient dyspnea VAS measures and in proportion with an overall subjective improvement when compared with those receiving TERB.

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