Comparison of Aerosol Medication Delivery Using Different Length Expiratory Reservoirs

Comparación de la entrega del medicamento en aerosol usando diferente longitud de reservorios espiratorios

COLCIENCIAS TIPO 1. ARTÍCULO ORIGINAL
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Abstract

Introduction: Many hand-held nebulizers have a T-piece that allows attachment of a mouthpiece and an optional 6-inch corrugated tube or expiratory reservoir. Although a previous study has demonstrated that a nebulizer with an expiratory reservoir tubing extension provides more inhaled medication, there is no report in the literature on the impact of using different tubing length expiratory reservoirs. *Objective*: To measure the effect of expiratory tubing of various lengths on the inhaled dose of a constant output nebulizer. *Methods*: An in vitro model was used to evaluate delivery of nebulized bronchodilator to simulated spontaneously breathing adults. A traditional constant output nebulizer was used (Airlife Misty-Neb). Three configurations were tested: (1) nebulizer with T piece adapter without an expiratory reservoir, (2) nebulizer with a 6-inch (50 mL) expiratory reservoir, and (3) nebulizer with a 12-inch (100 mL) expiratory reservoir. The amount of aerosol drug in the filter attached to the proximal end of the T-piece, between the nebulizer and the breathing simulator, was used as an indicator of the amount of drug available to the patient on each inspiration. All drug amounts were analyzed using a spectrophotometer and expressed as a percentage of the total dose. *Results*: There was no significant difference in the amount of drug measured at the inspiratory filter between the configuration without the reservoir and that with the 6-inch reservoir ($p= 0.133$). However, the 12-inch reservoir configuration was associated with a statistically significant higher inhaled drug mass than without ($p<0.001$) or with a 6-inch reservoir ($p=0.02$). *Conclusions*: Varying the length of the expiratory reservoir affects the amount of medication available to the patient. Attachment of a 12-inch reservoir to the T-piece used with small volume nebulizers may be a more efficient configuration to improve aerosolized drug amounts available for the patient.

Keywords

Aerosol medication delivery; expiratory reservoir; inhaled dose; constant output nebulizer.

Resumen

Introducción: muchos nebulizadores de mano tienen una pieza en T que permite la fijación de una boquilla y un tubo corrugado opcional de 6 pulgadas, o un deposito espiratorio. Aunque estudios anteriores han demostrado que un nebulizador con una extensión de tubo de reservorio espiratorio ofrece más medicación inhalada, no hay ningún reporte en la literatura sobre el impacto del uso diferente de la longitud de los tubos de reservorios espiratorios. Objetivo: medir el efecto del tubo espiratorio de varias longitudes sobre la dosis inhalada de un nebulizador de salida constante. Métodos: un modelo in vitro fue usado como modelo para evaluar la entrega del broncodilatador nebulizado a adultos con respiración espontáneamente simulada. Un nebulizador de salida constante fue utilizado (Airlife Misty-Neb). Tres configuraciones se probaron: (1) nebulizador con adaptador de pieza T sin un reservorio espiratorio, (2) nebulizador con reservorio espiratorio de 6 pulgadas (50ml), y (3) el nebulizador con reservorio espiratorio de 12 pulgadas (100ml). La cantidad de fármaco en aerosol en el filtro unido al extremo proximal de la pieza en T, entre el nebulizador y el simulador de la respiración, fue utilizado como un indicador de la cantidad de fármaco disponible para el paciente sobre cada inspiración. Todas las cantidades de fármaco fueron analizadas usando un espectrofotómetro y se expresaron como un porcentaje de la dosis total. Resultados: no hay diferencia significante en la cantidad de fármaco medido en el filtro inspiratorio entre la configuración sin el reservorio y que con el reservorio de 6 pulgadas ($p= 0.133$). Sin embargo, la configuración del reservorio de 12 pulgadas se asoció estadísticamente con un significante fármaco de mayor inhalación más que sin ($p <0.001$) o con un reservorio de 6 pulgadas. Conclusiones: la variación de la longitud del reservorio espiratorio afecta la cantidad de medicamento disponible para el paciente. La unión del reservorio de 12 pulgadas a la pieza T se usó con pequeños nebulizadores de volumen pueden tener una configuración más eficiente para mejorar las cantidades de fármaco en aerosol para el paciente.

Palabras clave

Administración o entrega de medicamento en aerosol; reservorio espiratorio; dosis inhalada; nebulizador de salida constante.

I. INTRODUCTION

Gas-powered nebulizers are a popular means of delivering aerosolized medication to the airway. Many hand-held nebulizers that provide constant aerosol generation during inspiration and expiration have a T-piece that fits on top of the unit to allow attachment of a mouthpiece. Such nebulizers have been termed *constant output* nebulizers [1]. Since drug delivery with these types of nebulizers is reduced during the noninspiratory phase of the respiratory cycle, a number of strategies have been used. Addition of a reservoir device to aerosol devices has resulted in a more efficient configuration to improve aerosolized drug amounts available for the patient [2,3]. An optional 6-inch corrugated tube extension or reservoir with an internal volume of about 50 mL can be placed either between the T-piece and the mouthpiece (inspiratory reservoir) or at the distal end of the T (expiratory reservoir). It has become standard practice to use the 6-inch reservoir tubing at the expiratory end of the T-piece. A logical extension of this aerosol conservation concept is the use of a reservoir bag to store aerosol between breaths. This has been shown to increase inhaled dose approximately 28% when compared to a standard nebulizer with mouthpiece[4]. However, these devices increase cost and have not yet replaced the conventional T-piece with corrugated tubing extension.

A previous in vitro study demonstrated that a T-nebulizer with an expiratory corrugated tubing extension provides more medication than either a T-nebulizer with an inspiratory reservoir or one without a reservoir [5]. However, that study quantified the amount of inhaled drug dose using measurement of weight, or gravimetric analysis. This method of measuring aerosolized drug delivery from a nebulizer can significantly over-estimate the emitted dose [6,7].

The choice of a 6-inch expiratory reservoir, with an approximate 50 mL volume, appears to be somewhat arbitrary and has not been based on measures of optimal aerosol delivery. We could find no report in the literature on the impact of using different length expiratory reservoirs on the amount of drug available for inhalation. We hypothesize that varying the length of the expiratory reservoir may considerably affect the amount of medication available to the patient. Therefore, the purpose of this study was to measure the effect of various expiratory tubing lengths on the inhaled dose of a constant output nebulizer.

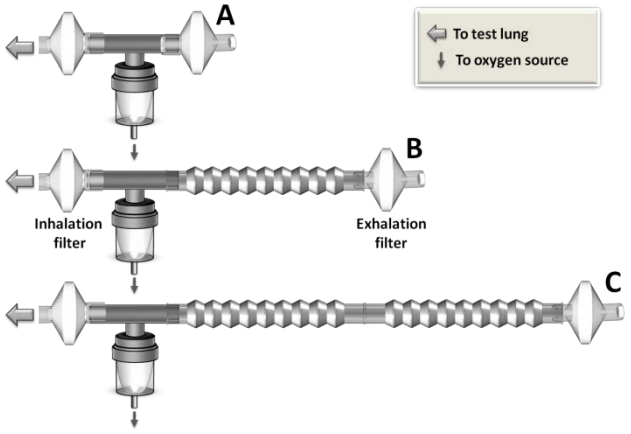
II. METHODS

A. Bench Model

An adult TTL Model 2601I dual chambered test lung (Michigan Instruments, Grand Rapids, MI) was used to simulate a normal adult breathing pattern [8]. A Puritan Bennett MA-2 ventilator was used to power one side of the test lung and the other side of the test lung served as the breathing simulator (in the inspiratory and expiratory phases). Nebulizer mouthpieces were removed and the inspiratory side of the T-piece was connected to a two-way, nonconductive anesthesia filter (model number 1T0241, Baxter Healthcare, Deerfield, IL), which was then connected to the test lung inlet to simulate the patient's mouth. The adult lung was powered by the MA-2 at a suitable volume, rate, and flow to create an inspiratory tidal volume of 600 ml at a respiratory rate of 12 breaths per minute. The inspiratory to expiratory ratio was set at 1:3. The tidal volume was read from the displacement line marker on the adult test lung, and was verified using a Novametrix "Vent Check" (Novametrix, Inc., Wallingford, CT).

Eight trials of each of three system configurations were performed. Configurations were the following: (A) without an expiratory reservoir, (B) with a 6-inch (50 mL) expiratory reservoir, and (C) with a 12-inch (100 mL) expiratory reservoir. Each set of nebulizer and the T-piece was numbered with a permanent marker. The nebulizer setup was placed horizontally to prevent condensation and wash-through of aerosol drug to the collecting filter. No tapping, repositioning or shaking of the nebulizer was performed during the study (see Figure 1) [9].

Figure 1. Bench model of the three configurations tested. A: without a reservoir; B: with a six-inch reservoir; and C: with a 12-inch reservoir



The nebulizer brand tested was the Airlife Misty-Neb. (Allegiance Healthcare Corp., McGaw Park, IL) used to represent an example of traditional constant output nebulizer. Each device nebulized a unit-dose of albuterol sulfate solution, 2.5-mg base equivalent (Proventil, Schering, Kenilworth, New Jersey), with a 3 mL total fill volume. No additional diluents were added to any nebulizer. All nebulizer samples were powered by 50-psi oxygen at 8 L/min for 5 minutes using a Fisher interval timer.

The same nebulizer was used for each of the three configurations to reduce error from nebulizer variability. The order in which the configurations were tested for each nebulizer was rotated to eliminate any order bias in the dose measurement. Between each measurement the nebulizer and connectors were rinsed with distilled water and dried. A total of 24 trials were performed.

B. Measures

In each nebulizer trial the inhaled dose, exhaled dose and the residual drug in the nebulizer apparatus (T-piece and reservoir tubing) were collected and measured. The amount of aerosol drug in the filter was used as an indicator of the amount of drug available to the patient on each inspiration. A filter was also placed on the outlet of the expiratory side of the T-piece or tubing to collect exhaled drug on each configuration. The drug remaining in the nebulizer apparatus was collected by washing the components with a 0.1 normal hydrochloric acid solution (J.T. Baker, Phillipsburg, NJ). Each nebulizer was weighed empty, after filling, and at the end of nebulization, to calculate the dead volume as described previously by Coates et al.,[9] Drug concentration determined by spectrophotometry, and drug mass were then calculated and expressed as a percentage of the nominal dose. Based upon previous measures a negligible amount of drug is left in the unit dose vial, and this was not analyzed in the present study.

All drug amounts were analyzed using a spectrophotometer (Beckman Instruments, Inc., Fullerton, CA) at a wavelength of 276 nm. Collecting filters were washed for one minute with gentle agitation. The sample solutions were drawn up from the filter with a glass pipette. The spectrophotometer was calibrated prior to each trial using a holmium oxide filter to determine wavelength accuracy, and set to zero using the solvent alone. A regression curve and prediction equation was developed from serial dilutions of a known albuterol sulfate solution (Sigma, St. Louis, MO). Concentrations of sample solutions, and thereby drug amounts of albuterol, were calculated from this known concentration/absorbance relationship[10]

C. Data Analysis

A one-way analysis of variance (ANOVA) was performed for the three configurations, with an alpha level of 0.05. Follow-up comparisons between configurations were performed using Bonferroni posthoc t tests.

III. RESULTS

Table 1 lists the mean ± SD values for total drug mass in the inhalation and exhalation filters, and the nebulizer apparatus as a percentage of nominal dose for each type of configuration.

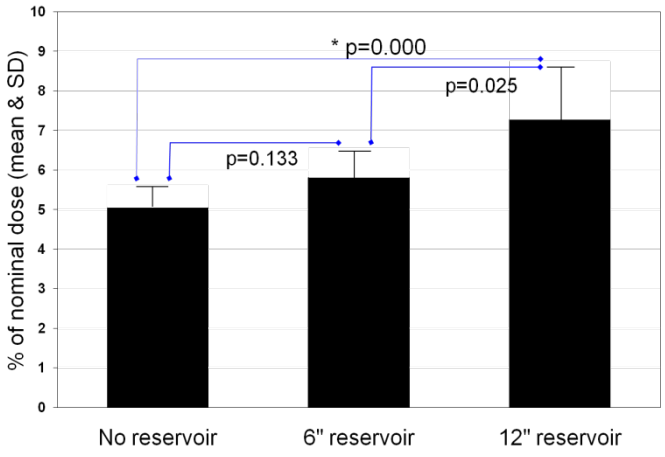
Table 1. Drug mass on the inhalation filter, nebulizer apparatus, and drug mass on the exhalation filter, expressed as a percentage of the beginning nominal dose

Destination	Configuration (reservoir)					
	No reservoir		6-inch res.		12-inch res.	
	Mean	SD	Mean	SD	Mean	SD
Inhalation filter (measured)	5.05	0.57	5.81	0.76	7.28	1.47
Nebulizer apparatus loss (measured)	86.31	1.47	87.43	1.63	87.69	3.12
Exhalation filter (measured)	8.58	1.09	6.86	1.01	5.06	1.61

On average, total drug recovered was 3.16 ± 0.02 mg, which is close to the nominal drug dose of 3.0 mg of albuterol sulfate, or 2.5 mg equivalent albuterol base.

Analysis of variance for configuration showed that the overall main effect for inhaled drug mass between groups was significant ($p < 0.001$). The posthoc comparisons showed no difference between no reservoir and the 6-inch extension tubing ($p = 0.133$); however, there were significant differences between no reservoir and the 12-inch one ($p < 0.001$) and between 6-inch and 12-inch extension tube ($p = .025$). (Figure 2)

Figure 2. Amount of drug measured at the inspiratory filter expressed as percentage of the 2.5 mg albuterol base nominal dose



* significant difference ($p<0.05$)

IV. Discussion

Although in vitro results generally give higher absolute amounts of drug delivery compared to in vivo, proportional differences between configurations for delivery methods remain accurate. The predictive validity of this type of in vitro bench test of aerosol delivery has been established by O'Riordan et al.,[10] The efficiency of the T-nebulizers has been considered to be suboptimal[11, 12, 13, 14, 15]; however, administration of aerosols with a T-piece has been found to result in a higher inhaled drug mass than a face mask [16,17]. Kradjan had reported that nebulizers attached to a T-piece vent more of the drug away from the patient's mouth since the end of the T-piece not connected to the mouthpiece constitutes the path of least resistance for the aerosol particles[18]. Visual observation of our model confirms previous reports that more of the mist vents out through the expiratory side of the T-piece than through the mouthpiece [17]. Therefore, addition of an expiratory reservoir explains the significant difference in emitted dose versus the no reservoir configuration by capturing a large percentage of the otherwise wasted aerosol.

The present study examined the inhaled drug dose from three system configurations using a T-piece without expiratory reservoir and with two different lengths of expiratory reservoir. Our study showed an overall inhaled drug mass of 6.04% ± 0.9%, and apparatus losses of 87.4% ± 2.07% using the Misty-Neb in simulated breathing. Although we have reported similar inhaled drug mass and apparatus loss [19], these results are not consistent with previous studies. Lewis and Fleming evaluated total drug disposition with a conventional constant-output nebulizer (Inspiron Mini-Neb) in human subjects with normal breathing patterns and found a 14% inhaled drug mass, 20% exhaled drug mass, and 66% lost in the apparatus [20]. Kradjan and Lakshminarayan found that between 41% and 66% of the original amount was left in five brands of constant-output jet nebulizers attached to T-pieces with a mouth piece.[17] While their average nebulization time for the same volume of drug (3 ml) was between 6 and 13 minutes, we limited nebulization time to 5 minutes in order to compare our results head-to-head with the study by Pisut and also to avoid the artifact introduced by repositioning, tapping, and even vigorous shaking of the nebulizer usually performed during studies where nebulizers are run to dryness.[19] These techniques allow less of the medication to remain in the nebulizer apparatus. While inhaled drug mass and drug lost in the apparatus in our report differed considerably from these studies, it is questionable if these differences would have been present had we used a similar time of nebulization.

In the only similar study of expiratory reservoir tubing we found in the literature, Pisut examined the effect of reservoir extension tubing on inhaled mass by comparing an expiratory, inspiratory and no reservoir. Inhaled drug was calculated by measuring different weights of aerosol in the patient filters, also known as gravimetric analysis. In Pisut's bench model, a tidal volume of 600 mL at a rate of 10 breaths/min was used to simulate spontaneous breathing. An Airline 2010 nebulizer attached to a T-piece was used to nebulize a unit dose (2.5 ml) of metaproterenol sulfate powered at a rate of 7 L/min for a total of 5 minutes. He found a significantly greater amount of medication delivered (20% higher) by weight than the no-reservoir combination ($p < 0.05$), which is similar to the 20.3% increase in inhaled drug mass we found with the 6-inch configuration. However, the addition of a 12-inch reservoir to resulted in a 30.6% increase in the inhaled drug mass as compared to the no-reservoir configuration. Nevertheless, these percentages were associated with an absolute inhaled drug mass difference of 0.056 mg between configurations. The clinical impact of this difference and the potential for additional adverse events can only be answered in the clinical setting.

The greatest aerosol recovery was with the expiratory reservoir and the least with the inspiratory reservoir[5]. While

the gravimetric analysis used by Pisut remains the simplest technique to assess the final assessment of a nebulizer delivery, it could overestimate the emitted dose as much as 1.8 times probably due to the loss of solvent during nebulization[6]. As a result, his results cannot fully compare to ours. Nevertheless, a recent study by Vecellio et al.,[21] reported that a residual gravimetric method, when validated for a particular agent, could be an accurate way of measuring aerosol output when compared to spectrophotometric measurement or high performance liquid chromatography.

There are several limitations to the present study. It has been noted that the effectiveness of the expiratory reservoir may be lost once patients remove the mouthpiece from their mouth between inspirations [3]. The steady-state nature of our in vitro model does not represent and measure the effect of the variations of human breathing pattern often seen in clinical practice. Patients with asthma typically have a prolonged expiratory time where a large percentage of the medication is lost to ambient. A model of simulated spontaneous breathing of asthmatic patients could have been more clinically applicable to unveil the true potential of an expiratory reservoir to increase the amount of drug available to the patient. It is theoretically possible that some aerosol collected on the exhalation filter prevented those particles from being deposited as part of the inhaled drug mass. Moreover, the nebulization time used in our study is short of the traditional *clinical time* that could potentially add to the inhaled drug available to patients. Although measurement of fine particle fractions has been reported for the Misty-Neb [22], we did not measure particle size distributions in the bench model used, which seriously limits the prediction of the type of changes in particle size that may occur as the aerosol is stored in the extension tubing.

It is quite possible that a 50 mL or 100 mL reservoir may not greatly impact the amount of CO_2 rebreathing in adults. However, it should be considered in the clinical setting, in particular for those patients already hypercapnic or at higher risk for CO_2 rebreathing. A significantly higher dose of albuterol may also be associated with higher risk of side effects. Therefore, implementation of this practice needs to be considered with caution since dose titration may be necessary for some patients.

V. CONCLUSIONS

Our study suggests that varying the length of the expiratory reservoir considerably affects the amount of medication available to the patient. Attachment of a 12-inch reservoir to the T-piece used with small volume nebulizers may provide significantly higher aerosolized medications. However, pulmonary mechanics before and after aerosol delivery with these configurations as well as quantification of carbon dioxide rebreathing should be evaluated before the results of this study are extrapolated to clinical practice.

VI. REFERENCES

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