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Effects of nebulizer fill volume on the efficacy and safety of the bronchodilator

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ABSTRACT

This study aimed to demonstrate the effect of adding saline to the respirable-solution of salbutamol placed in a nebulization chamber on the clinical status of the ventilated patient.

A total of 160 (80 female) asthmatic subjects were randomly divided into 8 groups (gp1-gp8). They received 0.5 ml salbutamol respirable-solution (5000 μg\ml), 0.5 ml salbutamol respirable-solution + 1 ml saline, 0.5 ml salbutamol respirable-solution + 2 ml saline, 0.5 ml salbutamol respirable-solution + 3 ml saline, 1 ml salbutamol respirable-solution, 1 ml salbutamol respirable-solution + 1 ml saline, 1 ml salbutamol respirable-solution + 2 ml saline and 1 ml salbutamol respirable-solution + 3 ml saline respectively using jet-nebulizer. Forced expiratory volume in 1 s as a percentage of predicted (FEV_1%), oxygen-saturation, pulse-rate, and respiratory-rate were measured before and 10–20 min after the nebulization of the salbutamol.

0.5 ml salbutamol respirable-solution had no significant improvement in FEV_1%. However, 1 ml had a significant improvement in FEV_1% ($p < 0.001$). Increasing fill volume increased the FEV_1% significantly ($p < 0.001$). No significant difference in FEV_1% when saline increased from 2 ml to 3 ml. There was no significant difference in oxygen-saturation before and after the administration of salbutamol. Pulse-rate increased significantly ($p < 0.01$) at higher fill-volumes especially in group 6–8. A few subjects complained of palpitation and headache at the end of nebulization.

Increasing fill-volume with jet-nebulizer enhanced the bronchodilator effect of salbutamol and plateau occurs after 2 ml added saline.

1. Introduction

Aerosol therapy is the backbone for the management of obstructive lung diseases [1]. Bronchodilators and inhaled corticosteroids are the main drugs used in this form. The inhalable formulations like the respirable solution, pressurized metered-dose inhalers (pMDIs) and dry powder inhalers (DPIs) are the commonly available forms to be used [2]. Respirable solution is one of the most commonly used forms for aerosol delivery because it is simple, cheap and cost-effective compared to other forms [3]. Also, other forms of aerosol delivery require additional accessory devices and patient counseling [4–11].

The main drawback of aerosol therapy using a nebulizer is the low amount of the drug delivered and deposited into the lung that could be affected ever by the interface [12]. Around 10% of the respirable solution could be delivered to the lung after the end of nebulization [13]. This problem is related to many factors like aerosol particle size, gas density, operating mode of the nebulizer, gas flow and nebulizer type. The most common type of nebulizer is the jet nebulizer because of its low cost however it is less effective in delivering aerosol compared to ultrasonic and vibrating mesh nebulizers [14–27]. There are many types of jet nebulizers, all of them work with the same mechanism but they differ in their designs. Different nebulizer designs could result in different dead volumes for each type [28,29]. Vibrating mesh nebulizer is the most effective one but it is very expensive compared to the traditional jet nebulizer [30]. Jet nebulizers consist of an air compressor (produce gas) and a nebulizer chamber connected by a flexible tube. The respirable solution is converted to aerosol droplets by the effect of gas pressure. In a previous study adding more diluent volume to the

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bronchodilators in the nebulizer chamber resulted in delivering higher amounts of the drug [13,30,31]. This was explained by the large dead volume (amount of drug remained in the nebulizer chamber at the end of nebulization) of the jet nebulizer [32,33]. These previous studies discussed the clinical pharmacokinetic aspect of delivering bronchodilators but it did not measure the clinical impact and the adverse effects of that intervention on the patient, and that gap was the main reason for the current study. These previous studies stated that the delivered amounts of salbutamol increased significantly by increasing nebulizer fill volume [13,30,31]. Clinical impact of respirable bronchodilators could be measured by spirometry which indicates the lung function before and after administration of bronchodilators [34]. Reversibility of bronchoconstriction after inhalation of the drug can be used as an indicator of the improvement of the clinical status of the patient [34]. Also, the optimum volume of the diluent with different drug doses should be determined. However, bronchodilators have a positive effect on asthmatic patients but also they cause some adverse effects such as increased heart rate, a sensation of palpitation and headache that could be assessed by counseling the patient and measuring heart rate. So in the current study, the clinical impact and the effect of different fill volumes and drug doses were examined to indicate the recommended fill volume for each dose according to spirometry. Also common adverse effects of salbutamol like increasing heart rate, palpitation and headache examined and recorded.

2. Method

A total of 160 (80 female) mild to moderate asthmatic subjects were recruited in the study. The study was conducted in Beni-Suef university hospital and Beni-Suef chest hospital after the study protocol was approved by the "Research Ethical Committee" of Faculty of Pharmacy, Beni-Suef University (REC-H-PhBSU-19008) and following the Declaration of Helsinki. All subjects gave signed informed consent. The patients were divided randomly (Simple randomization) into eight groups each contain 20 (10 female) asthmatic subjects. Group 1 received 0.5 ml salbutamol respirable solution (Farcolin respirator solution, 5000 μg/ml; Pharco Pharmaceuticals, Egypt) by jet nebulizer (Dolphin medical, turkey), Group 2 received 0.5 ml salbutamol respirable solution + 1 ml saline, Group 3 received 0.5 ml salbutamol respirable solution + 2 ml saline, Group 4 received 0.5 ml salbutamol respirable solution + 3 ml saline, Group 5 received 1 ml salbutamol respirable solution, Group 6 received 1 ml salbutamol respirable solution + 1 ml saline, Group 7 received 1 ml salbutamol respirable solution + 2 ml saline and Group 8 received 1 ml salbutamol respirable solution + 3 ml saline.

For each group forced expiratory volume in 1 s (FEV_1%) percent of predicted was measured by spirometer (One Flow, Clement Clarke International, UK) before receiving the drug by the jet nebulizer and 15 min after the end of nebulization. Subjects were told not to receive drugs like theophylline, long-acting beta-2 agonist, short-acting beta-2 agonist or short-acting anticholinergics before the intervention time by 24hrs, 12hs, 6hrs, and 8hrs respectively not to interfere with the spirometry measurements. In addition to spirometry, all subjects were asked about the improvement in their symptoms (lung tightness and ability to breathe smoothly) and the adverse effects of the therapy (palpitation and headache). Pulse rate and oxygen saturation were measured before and after 10–20 min from the end of nebulization for each group using oximeter (Zacurate Pro Series 500DL Fingertip Pulse Oximeter, Zacurate, Stanford, USA).

2.1. Statistical analysis

All data are expressed as mean ± SD. The statistical analysis of the current study was performed using SPSS V21.0 (SPSS Inc., Chicago, USA). One way analysis of variance (ANOVA) test was used to compare the results with the least significant difference (LSD) as post hoc. Values considered significant at p-value ($P < 0.05$).

Table 1
Mean ± SD for age, weight, and height of all subjects.

Group	age	weight	height
Group 1	45 ± 6.8	74 ± 12.9	166 ± 14.4
Group 2	52 ± 9.3	79 ± 7.4	159 ± 8.2
Group 3	55 ± 5.3	80 ± 4.9	169 ± 9.2
Group 4	48 ± 3.2	76 ± 6.3	158 ± 8.7
Group 5	43 ± 4.9	81 ± 3.9	161 ± 9.1
Group 6	58 ± 6.2	87 ± 4.9	170 ± 8.5
Group 7	47 ± 8.3	83 ± 6.1	164 ± 9.2
Group 8	59 ± 3.3	77 ± 5.7	173 ± 9.7

3. Results

Subjects' demographic data were expressed as mean ± SD age, weight, and height and these data were expressed in Table 1.

Mean ± SD of delta FEV_1% (after-before), time of nebulization, pulse rate and oxygen saturation are shown in Fig. 1 and Table 2.

The nebulizer fill volume of 0.5 ml salbutamol respirable solution did not result in any effect on FEV_1%. Adding 1 ml of saline to 0.5 ml salbutamol resulted in significant ($p < 0.01$) improvement in FEV_1% (Fig. 1), this significant improvement was noted also by adding 2 ml and 3 ml of saline. Improvement in FEV_1% was not significant when saline volume increased from 2 ml to 3 ml. However, when placing a 1 ml salbutamol respirable solution in the nebulization chamber, it had a significant improvement in FEV_1% ($p < 0.001$). Adding 1 ml of saline to 1 ml salbutamol respirable solution resulted in significant ($p < 0.01$) improvement in FEV_1% (Fig. 1), this significant improvement was noted also by adding 2 ml and 3 ml of saline. A significant ($p < 0.01$) difference was observed in FEV_1% between 1 ml saline and 2 ml, while there was no significance between 2 ml and 3 ml saline. Also, there was no significant difference in FEV_1% improvement between 0.5 ml salbutamol respirable solution + 3 ml saline and 1 ml salbutamol respirable solution.

There was no significant difference in oxygen saturation before and after nebulization of different doses of salbutamol with all fill volumes used during the study. Regarding the pulse rate of the subject, it increased significantly ($p < 0.01$) at higher fill volumes especially in group 6–8.

The time of nebulization increased significantly ($p < 0.01$) in all groups with saline.

All subjects in group 1 reported no improvement in chest tightness after nebulizing 0.5 ml salbutamol respirable solution, besides, they indicated that the bronchoconstriction was increased. By increasing the saline volume the comfort of subjects was also increased and it was expressed by their improved symptoms like less wheezing and easy to breathe.

4. Discussion

Lack of improvement after nebulization of 0.5 ml salbutamol respirable solution and the significant improvement to the same amount of the drug by adding saline indicated the importance and the critical role of controlling the volume within the nebulization chamber of the jet nebulizer.

The importance of increasing the delivered amount of nebulized drugs to the lung is not only limited to increasing the efficacy of the therapy but also, decreasing the cost of the treatment, especially with expensive medications. Also, systemic exposure to the inhaled drug will be decreased by increasing the amount of drugs that successfully delivered to the lung, hence the adverse effects will be decreased as well [35,36].

The same bronchodilator effect demonstrated by an increase in

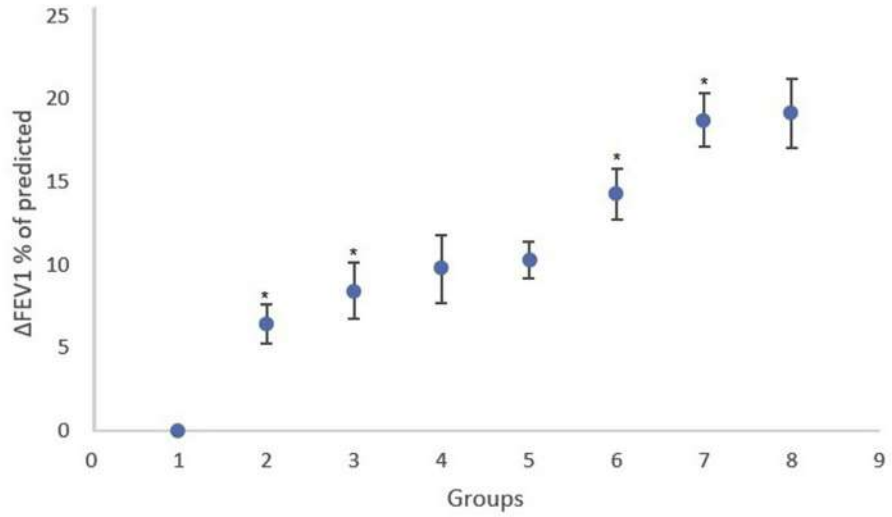

Fig. 1. Delta forced expiratory volume in 1 s percent of predicted.

Table 2
Mean ± SD for Oxygen saturation, Pulse rate, time of nebulization and ΔFEV1% of predicted for all subjects before and after nebulization of salbutamol, also percent of subjects complained from adverse effects.

group	Oxygen saturation		Pulse rate		Adverse effects complain	ΔFEV1% of predicted	Time of nebulization (min)
	before	after	before	after			
Gp1	96.9 ± 2.3	96.2 ± 1.9	86.6 ± 4.8	86.1 ± 7.2		–	0.2 ± 0.03
Gp2	94.2 ± 1.8	92.7 ± 3.1	88.4 ± 5.9	89.9 ± 6.4		6.5 ± 1.2[a]	4.3 ± 0.1[a]
Gp3	97.5 ± 1.2	96.8 ± 1.7	90.1 ± 2.6	93.2 ± 3.3		8.4 ± 1.7[a]	8.9 ± 0.5[a]
Gp4	94.7 ± 2.4	94.5 ± 2.7	89.6 ± 5.1	94.3 ± 4.7		9.8 ± 2	11.8 ± 0.6[a]
Gp5	96.4 ± 2.5	95.7 ± 3.4	85.5 ± 3.7	90.7 ± 4.9	10%	10.3 ± 1	3.5 ± 0.1
Gp6	93.5 ± 1.3	92.1 ± 3.8	85.3 ± 2.4	93.4 ± 3.8	15%	14.3 ± 1.5[a]	6.4 ± 0.3[a]
Gp7	94.7 ± 1.6	95.1 ± 1.3	88.9 ± 4.1	98.1 ± 5.5	20%	18.7 ± 1.6[a]	10.1 ± 0.2[a]
Gp8	96.1 ± 2.8	96.7 ± 1.9	83.4 ± 5.3	97.9 ± 4.3	20%	19.1 ± 2.	13.2 ± 0.4[a]

[a] Significant difference from previous groups.

FEV_1% was nearly achieved using different doses of salbutamol, since the effect on FEV_1% by adding 3 ml saline to 0.5 ml salbutamol respirable solution was not significantly different from that achieved by nebulization of 1 ml salbutamol respirable solution. This result could be explained by the delivering effect of the added diluent that carried more salbutamol to the lung [13,30,31]. Increasing the amount of saline added to salbutamol within the nebulization chamber increased the improvement in lung function expressed in the increase in FEV_1% significantly but also the time of nebulization was increased [13]. Adding saline more than 2 ml resulted in a non-significant effect compared to adding 2 ml, while it was significant compared to drug alone or drug plus 1 ml saline. So it could not be considered as a role for all nebulized medications because other drugs could express a significant efficacy by adding 3 ml or more of the diluent. In-vitro and ex-vivo studies showed a significant increase in the delivered amount of the inhalable drug using 4 ml of saline [13,30,31].

Also, it was noted that increasing the time of nebulization made some subjects breath uncomfortably during the nebulization time. However, at the end of nebulization subjects that received higher saline volume stated that they could breathe more easily and the sense of chest tightness was decreased or removed. This could be because saline has a mucolytic effect in the management of obstructive lung diseases. This effect could enhance the quality of the breath by clearing the respiratory airways and allowing more space for air exchange but it has no bronchodilator effect [37].

A few numbers of subjects (10%) complained of slight palpitations or headache at the end of nebulization of 1 ml salbutamol respirable solution with and without saline [38], but the complaint increased (up to 20%) with increasing saline volume, also pulse rate increased significantly ($p < 0.01$) at higher fill volumes especially in group 6–8. This could be because of the increase in the amount of salbutamol that had been delivered to the patient. There was no significant change in oxygen saturation before and after nebulization of salbutamol in all fill volumes used during the study and could be related to the low dose of the drug [39]. Hence, adding saline to the bronchodilator had a significant therapeutic effect compared with the same amount of bronchodilator without saline. These results are limited to jet nebulizers because other types like vibrating mesh nebulizers seem not to be affected by increasing saline volume [13,30].

Adding saline to the bronchodilators has a limit because adding large amounts of saline did not result in a significant increase in the bronchodilation effect, however, it is not a general role for other types of medications.

4.1. Limitations

The current study focused on the effect of the fill volume of jet nebulizers only on the aerosol efficacy, other types of nebulizers should be assessed for increasing the fill volume.

Other medications rather than the bronchodilators need to be studied to determine the optimum fill volume for the best therapeutic effect.

Reversibility of bronchoconstriction differ from disease to another, so it should be assessed for each disease separately.

Other diluents like water should be assessed to determine its effect on aerosol efficacy.

5. Conclusion

Adding saline to salbutamol respirable solution in the nebulization chamber resulted in significant improvement in lung function with a few side effects. Adding saline more than 2 ml has no additional bronchodilator effect. Increasing nebulizer fill volume did not improve the oxygen saturation of respiratory rates of the subjects.

Salbutamol 0.5 ml without saline had not bronchodilator effect and it should not be recommended to be used with a jet nebulizer without saline addition.

CRediT authorship contribution statement

Amr A. shokry: Writing - original draft. **Haitham Saeed:** Writing - original draft. **Hoda Rabea:** Conceptualization. **Nada S. Abdelwahab:** Conceptualization. **Mohamed H. Meabed:** Conceptualization. **Mohamed E.A. Abdelrahim:** Conceptualization.

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