

Nebulizer versus inhaler with spacer for beta-agonist treatment in acute bronchospastic disease

比較「噴霧器」與「吸入器暨分隔器」對 β -促效藥治療急性支氣管痙攣疾病之功效

GPC Lee 李秉聰, WY Sung 孫惠儀, HT Fung 馮顯達, CW Kam 甘澤華

Objectives: To compare the efficacy of nebulized wet aerosol with metered-dose inhaler with a spacer (MDIS) in the management of acute bronchospasm. **Methods:** It was a retrospective study by reviewing the clinical records of patients with acute exacerbation (chief complaint of shortness of breath) of asthma or chronic obstructive pulmonary disease (COPD) presenting to the Accident and Emergency Department (AED) of Tuen Mun Hospital from 1st to 30th November 2002 and 2003 respectively. All patients received beta-agonist by nebulizer, in the year 2002 (pre-SARS period) while all patients received treatment by MDIS in the year 2003 (post-SARS period). Treatment outcome measures included admission rate, length of hospitalisation for those admitted and AED re-attendance within 7 days for those discharged from the AED. **Results:** Altogether 821 patients were recruited in this retrospective study, 522 belonged to the nebulizer group and 299 were of the MDIS group. The two groups had similar demographic characteristics. Concerning the admission rate (47% in the nebulizer group and 41% in the MDIS group; $p=0.089$) and re-attendance rate (7% in the nebulizer group and 6% in the MDIS group; $p=0.607$), the differences were not statistically significant. For the length of hospital stay, it was shorter in the nebulizer group than the MDIS group ($3.65\pm SD 1.88$ days vs $4.10\pm SD 1.94$ days; $p=0.035$). However, the admission rate in the adult subgroup (61% in the nebulizer group and 47% in the MDIS group; $p=0.002$) was shown to be statistically significant. In multivariate analysis, usage of nebulizer, increase in respiratory rate and age were associated with a higher admission rate. Increase in SpO_2 , absence of co-morbidity and asthma patients were associated with a lower admission rate. Increase in age, respiratory rate and usage of MDIS were associated with an increase in hospital stay. Asthma was associated with a decrease in AED re-attendance rate as compared to COPD. **Conclusions:** This retrospective study showed that both nebulizer and MDIS were effective for beta-agonist therapy in acute bronchospasm in AED with respect to hospital admission rate and AED re-attendance rate, but the length of hospital stay was slightly prolonged when using MDIS. (*Hong Kong j.emerg.med.* 2005;12: 133-139)

Correspondence to:

Lee Ping Chung, Gordan, MBBS, MRCSEd
Tuen Mun Hospital, Accident & Emergency Department,
Tsing Chung Koon Road, Tuen Mun, N.T., Hong Kong
Email: gpclee@yahoo.com.hk

Sung Wai Yee, M Stat
Fung Hin Tat, FRCSEd, FHKCEM, FHKAM(Emergency Medicine)
Kam Chak Wah, MRCP(UK), FRCSEd, FHKAM(Emergency Medicine)

目的：比較「濕氣噴霧」與「量計吸入器暨分隔器」對治療急性支氣管痙攣之功效。**方法：**這是一個回顧性的研究，審查分別於 2002 年及 2003 年 11 月 1 日至 31 日期間，因哮喘或慢性阻塞性肺病急劇惡化（主要申訴為氣促）而前往屯門醫院急症室求診病者的臨床記錄。於 2002 年（非典型肺炎前）所有病者經「噴霧器」接受 β - 促效藥治療，而於 2003 年（非典型肺炎後）則所有病者使用「量計吸入器暨分隔器」治療。治療結果的量度包括入院率、留院期及急症室出院後於 7 天內的再度求診率。**結果：**是次回顧性研究共招募了 821 名病者，522 位屬噴霧器組，而 299 位為吸入器組；兩組的病人統計特徵相似。關於入院率（噴霧器組 47% 及吸入器組 41%； $p=0.089$ ）；再求診率（噴霧器組 7% 及吸入器組 6%； $p=0.607$ ），兩者的差分並沒有統計顯著性。至於留院期，噴霧器組較吸入器組為短（ $3.65\pm SD1.88$ 日對 $4.10\pm SD1.94$ 日； $p=0.035$ ）；而成人子群組的入院率（噴霧器組 61% 及吸入器組 47%； $p=0.002$ ）顯示有統計顯著性差分。以多元分析，噴霧器的使用、呼吸率的增加及年齡與較高的入院率有關聯；高血氧飽和度，沒有共存的病態及哮喘的病者則與較低入院率有關聯。高齡、呼吸率及吸入器的使用則與留院期的增加有關聯。與慢性阻塞性肺病比較，哮喘與急症室再求診率的減低有關聯。**總結：**是次回顧性的研究顯示在急症室使用「噴霧器」或「量計吸入器暨分隔器」進行 β - 促效藥治療急性支氣管痙攣，在入院率及急症室再求診率方面均有成效，但使用量計吸入器則留院期稍為延長。

Keywords: Asthma, chronic obstructive pulmonary disease, metered dose inhalers, nebulizers and vaporizers, spacer

關鍵詞：哮喘、慢性阻塞性肺病、量計吸入器、噴霧器及氣化器、分隔器

Introduction

Acute exacerbation of asthma or chronic obstructive pulmonary disease (COPD) is a common complaint of those attending accident and emergency departments (AED). In the past, most doctors in Hong Kong hospitals employed nebulizer therapy for relieving the bronchospasm. However, in the year 2003, we learned that nebulizer drug therapy could spread the fatal coronavirus of the severe acute respiratory syndrome (SARS) to people nearby. It was time for us to think whether nebulizer was really necessary for treating bronchospastic patients and whether there was any equally effective and safe alternative treatment.

Metered-dose inhaler with a spacer (MDIS) is a well-known method of delivering bronchodilator and steroid medication to patients with bronchospastic disease. The lung deposition of β_2 -agonist from a MDI varies between 5.7% and 23.8% of the dose expelled with each actuation.¹ The lung deposition of a drug by using wet nebulizer is between 2.7% and 9.9%.^{2,3} When a spacer is added to a MDI, drug deposition in the lower airways increases with a corresponding 10-fold decrease in oropharyngeal deposition.⁴⁻⁶ The combination is

particularly valuable in patients who have poor timing and cannot adequately coordinate inhalation from a MDI with the actuation of the device. Colacone and colleagues showed a relative potency of 6:1 in favour of MDIS to nebulizer in achieving equivalent bronchodilatation.⁷ Silkstone and colleagues found that five 100 mcg doses inhaled from a MDIS delivered more to the lungs and less to the systemic circulation than either the same doses from a MDI alone or five times the dose given via a jet nebulizer.⁸

In Tuen Mun Hospital (TMH), we changed our practice in delivering bronchodilator after the SARS attack in the year 2003. We put away all the nebulizer machines and replaced them by MDIS. We found that the hospital admission rate and patient response to treatment were similar after this change. As a result, a retrospective study was carried out to find out whether these two treatment modalities were equally effective in treating patients with acute bronchospasm.

Patients and methods

Our study was carried out in the Tuen Mun Hospital of Hong Kong. We reviewed all the AED records of

patients attending during the period of 1st to 30th November, 2002 and 2003 respectively. In November 2002, all patients with acute bronchospasm received nebulizer treatment but in November 2003 all received MDIS treatment instead.

The inclusion criteria included all patients above one year old attending the TMH AED in the above periods with a history of either asthma or COPD and presenting with shortness of breath (SOB) as the chief complaint. Beta₂-agonist was given by either nebulizer or MDIS. The exclusion criteria included those patients presenting with SOB due to other causes such as heart failure or pneumonia, with serious attacks requiring either invasive or non-invasive positive pressure ventilation, developing complications such as pneumothorax, having serious co-morbidities like stroke, heart or renal failure, respiratory conditions other than asthma or COPD, social problems causing prolonged hospital stay, or discharged against medical advice.

We identified all the appropriate AED records, and then analysed the demographic data, disease presentation, physical examination, treatment methods and disposal of the patients. For those patients who were admitted, we checked their discharge summary. For those who were discharged from the AED, we checked the computer to see if they re-attended to TMH AED within 7 days.

Results were expressed as mean (\pm SD). Chi-square test was used to assess the hospital admission rate, re-attendance rate, sex, history of significant co-morbidity and proportion of asthma to COPD. The unpaired

Student's t-test was used to calculate the length of hospital stay, age, respiratory rate, SpO₂ and pulse rate. Multivariate analysis was also carried out. Logistic regression was used in the admission and re-attendance rates, and multiple regression was used in the length of hospital stay.

Results

Altogether 821 patients were recruited in this retrospective study, 522 patients belonged to the nebulizer group and 299 patients were of the MDIS group. Table 1 shows the demographic characteristics of the patients.

The univariate result of the study is shown in Table 2. Concerning the hospital admission rate (47% in the nebulizer group and 41% in the MDIS group; $p=0.089$) and AED re-attendance rate (7% in the nebulizer group and 6% in the MDIS group; $p=0.607$), the differences were not statistically significant. In the length of hospital stay, it was shorter in the nebulizer group than in the MDIS group ($3.65\pm$ SD 1.88 vs $4.10\pm$ SD 1.94 days; $p=0.035$).

When the patients were subdivided into adult (18 years old and above) and paediatric (under 18 years old) age groups and analysed separately, the results are shown in Tables 3, 4 & 5. There were altogether 565 adult (346 patients in the nebulizer group and 219 patients in the MDIS group) and 256 paediatric patients (176 patients in the nebulizer group and 80 patients in the MDIS group). Only the hospital admission rate for adult (61% in nebulizer group and 47% in MDIS

Table 1. Demographic characteristics of the patients

	Nebulizer group	MDIS group	p-value
Age	41.82 \pm 30.06 yr	45.21 \pm 28.95 yr	0.115
Sex	M=63%, F=37%	M=67%, F=33%	0.187
Respiratory rate	26.52 \pm 5.10/min	25.62 \pm 4.66/min	0.018
Pulse rate	105.85 \pm 22.53/min	103.93 \pm 21.43/min	0.232
SpO ₂	96.07 \pm 2.64%	95.56 \pm 2.87%	0.010
Significant co-morbidity	Yes=11%, No=89%	Yes=14%, No=86%	0.310
Asthma/COPD	Asthma=60%, COPD=40%	Asthma=55%, COPD=45%	0.115

Table 2. Outcome of the two groups of patients after treatment

	Nebulizer group	MDIS group	p-value
Hospital admission rate	47%	41%	0.089
Length of hospital stay	3.65±1.88 days	4.10±1.94 days	0.035
AED re-attendance rate	7%	6%	0.607

Table 3. Demographic characteristics of the adult subgroup (>=18 years old)

	Nebulizer group	MDIS group	p-value
Age	59.45±20.78 yr	58.91±20.87 yr	0.765
Sex	M=66%, F=34%	M=70%, F=30%	0.294
Respiratory rate	25.98±4.52/min	25.52±4.63/min	0.273
Pulse rate	98.13±17.48/min	99.40±19.05/min	0.418
SpO ₂	96.34±2.70%	95.63±3.01%	0.003
Significant co-morbidity	Yes=17%, No=83%	Yes=18%, No=82%	0.817
Asthma/COPD	Asthma=40%, COPD=60%	Asthma=38%, COPD=62%	0.638

Table 4. Demographic characteristics of the paediatric subgroup (<18 years old)

	Nebulizer group	MDIS group	p-value
Age	7.16±4.18 yr	7.73±4.12 yr	0.319
Sex	M=57%, F=43%	M=53%, F=47%	0.633
Respiratory rate	27.62±5.97/min	25.89±4.76/min	0.038
Pulse rate	121.04±23.64/min	116.23±22.76/min	0.128
SpO ₂	95.54±2.43%	95.37±2.45%	0.614
Significant co-morbidity	Yes=0%, No=100%	Yes=2%, No=98%	0.097
Asthma/COPD	Asthma=100%	Asthma=100%	

Table 5. Outcome of adult and paediatric patients in the two treatment arms

	Nebulizer group	MDIS group	p-value
Hospital admission rate (adult)	61%	47%	0.002
Hospital admission rate (paediatric)	19%	23%	0.558
Length of hospital stay (adult)	3.81±1.92 days	4.27±2.01 days	0.051
Length of hospital stay (paediatric)	2.68±1.25 days	3.11±1.08 days	0.217
AED re-attendance rate (adult)	10%	8%	0.488
AED re-attendance rate (paediatric)	4%	2%	0.458

group; $p=0.002$) was statistically significant. All the other outcomes for adult and paediatric patients were not statistically significant.

In multivariate analysis, all variables as listed in Table 1 were used for analysis. The accuracy of logistic

regression was 77.14% and 93.83% in patient disposal and AED re-attendance respectively. R-square in multiple regression for length of hospital stay was 0.102. All statistically significant results are presented in Tables 6, 7 & 8. Increase in SpO₂, absence of co-morbidity and asthma patients were associated with a lower

Table 6. Patient disposal (admission compared to discharge)

Variable	Odds ratio	95% C.I.
Respiratory rate	1.1122	1.0678 - 1.1583
SpO ₂	0.8975	0.8326 - 0.9676
Co-morbidity (absence)	0.3067	0.1483 - 0.6346
Age	1.0336	1.0219 - 1.0454
Diagnosis (asthma vs COAD)	0.5222	0.2810 - 0.9705
Treatment (nebulizer vs MDIS)	1.8744	1.2622 - 2.7835

Table 7. Length of hospital stay

Variable	B	Significance
Constant	-0.277	0.695
Age	0.021	0.000
Respiratory rate	0.047	0.019
Treatment (1=nebulizer, 2=MDIS)	0.452	0.036

Table 8. AED re-attendance

Variable	Odds ratio	95% C.I.
Diagnosis (asthma vs COAD)	0.1532	0.0665 - 0.3532

admission rate. Increase in respiratory rate and age were associated with a higher admission rate. However, usage of nebulizer was also associated with an increase in admission rate (Table 6). Concerning length of hospital stay, increase in age, respiratory rate and usage of MDIS were associated with an increase in hospital stay (Table 7). In AED re-attendance rate, only asthma was associated with a decrease in re-attendance rate as compared to COPD.

Discussion

The results of this study showed that MDIS was at least as effective as nebulizer in the treatment of acute bronchospasm in terms of hospital admission rate and AED re-attendance rate, although the length of hospital stay was slightly prolonged in the MDIS group.

In the past, bronchodilatation achieved by nebulization was considered to be greater than MDIS. As a result,

the nebulizer was the treatment of choice for AED and in-hospital wards for acute exacerbation of asthma and COPD. However, recent studies have suggested that there is no significant difference between these two forms of treatment in both asthmatic⁹⁻¹² and COPD patients.⁹ Some studies even showed that the MDIS might be superior to the nebulizer in the management of paediatric asthmatic patients.^{12,13} It was a common belief that patients with a severe attack of acute bronchospasm had difficulty in inhaling medication from the MDIS. However, studies on patients with FEV₁ <30% predicted showed that the MDIS was equally effective as the nebulizer in relieving bronchospasm.¹⁰

In this retrospective study, all suitable patients attending TMH AED in the periods of 1st to 30th of November 2002 and 2003 were recruited. This period was chosen because in the year 2002, which was the pre-SARS period, nebulizer therapy was widely used in AED and in-hospital management of acute bronchospasm. After the attack of SARS from March

to June 2003, we identified that nebulizer might be one of the culprits in spreading the fatal coronavirus. Then, our practice was changed from nebulizer to MDIS therapy. After a few months' use of MDIS, medical staff and patients became familiar with this new treatment modality. As a result, we chose patients attending in November 2002 and 2003 as the subjects in this study.

In the interpretation of univariate results, we found that the difference in hospital admission rate of all patients in the two treatment arms was not statistically significant, nor was the AED re-attendance rate. It showed that we had not discharged inappropriately more patients in the MDIS group who actually required in-patient management than in the nebulizer group. When the patients were subdivided into two groups according to their age, we found that in the paediatric age group the difference in all the three outcomes were not statistically significant. Concerning the adult age group, we found that the hospital admission rate was statistically significantly lower in the MDIS group.

From univariate and multivariate analyses, we found that nebulizer usage was associated with a higher admission rate, and this was not the usual finding in other studies. My postulation is that patient had changed their attitude and became reluctant to be admitted to the hospital in the post-SARS period because they knew that hospital was a place that they might acquire nosocomial infection. Besides, nebulizer therapy was no longer offered in the ward for relieving bronchospasm, so they might prefer to continue the medical therapy at home if they got significant improvement after the initial treatment in the AED. On the other hand, medical and nursing staff had been providing more patient education after the change in the bronchodilator delivery method. Counselling and instruction in asthma self-management are generally regarded as being cost-effective adjuncts to asthma therapy, with multiple studies showing asthma education leading to decreased AED visits, hospital admissions and cost.¹⁴⁻¹⁶

A meta-analysis done by Turner and colleagues showed that bronchodilator delivery by means of MDIS or wet nebulizer was equivalent in the acute treatment of adults with airflow obstruction caused by asthma or COPD.⁹ In the Cochrane database of systematic reviews done by Cates and colleagues, they found that in asthmatic patients the relative risk of hospital admission did not differ on the basis of delivery methods in adults or in children. There were no significant differences demonstrated between MDIS and wet nebulizer bronchodilator therapy in acute asthmatic attacks as regard to improvement in lung function, change in respiratory rate, development of tremor and the number of patients requiring steroids. MDIS had additional advantages in children in reducing side effects such as tachycardia and in reducing the length of stay in the emergency department, but no significant differences were found in adults. In four studies in adults that included analysis of changes in lung function in the most severely affected patients ($FEV_1 < 30\%$ predicted), the weighted mean differences in the FEV_1 between the two delivery methods were not significant statistically.^{10,11}

Our study had a number of limitations. Since it was a retrospective study, patient randomisation into the two treatment arms was not possible, and the measurements were not taken in the same period. Concerning the demographic characteristics of the two groups of patients, they were not statistically significantly different in terms of age, sex, pulse rate, history of significant co-morbidity, or proportion of asthma to COPD patients. Concerning the respiratory rate ($26.52 \pm 5.10/\text{min}$ in the nebulizer group vs $25.62 \pm 4.66/\text{min}$ in the MDIS group; $p=0.018$) and SpO_2 ($96.07 \pm 2.64\%$ in the nebulizer group vs $95.56 \pm 2.87\%$ in the MDIS group; $p=0.010$), they were statistically significantly different but the difference was only minimal that might not be clinically significant. Other indicators of disease severity like peak flow rate and arterial blood gas would certainly be very useful but they were not included in this study because they were not routinely done in our AED and so data was not available. Besides, the dosage of salbutamol therapy

was not standardised in either the nebulizer or MDIS group of patients. It was determined by the age of the patient, the severity of the attack and the clinical judgement of the attending physician. Due to the limitations in this study, a randomised controlled study is suggested so as to get a higher level of evidence to support our continuation of the widespread use of MDIS therapy in the treatment of acute bronchospastic diseases.

References

1. Dolovich M. Lung dose, distribution, and clinical response to therapeutic aerosols. *Aerosol Sci Tech* 1993; 18:230-40.
2. Johnson MA, Newman SP, Bloom R, Talaee N, Clarke SW. Delivery of albuterol and ipratropium bromide from two nebulizer systems in chronic stable asthma. Efficacy and pulmonary deposition. *Chest* 1989;96(1): 6-10.
3. Zainudin BM, Biddiscombe M, Tolfree SE, Short M, Spiro SG. Comparison of bronchodilator responses and deposition patterns of salbutamol inhaled from a pressurised metered dose inhaler, as a dry powder, and as a nebulised solution. *Thorax* 1990;45(6):469-73.
4. Newman SP, Millar AB, Lennard-Jones TR, Moren F, Clarke SW. Improvement of pressurised aerosol deposition with Nebuhaler spacer device. *Thorax* 1984; 39(12):935-41.
5. Newman SP, Pavia D, Moren F, Sheahan NF, Clarke SW. Deposition of pressurised aerosols in the human respiratory tract. *Thorax* 1981;36(1):52-5.
6. Newhouse MT, Dolovich MB. Control of asthma by aerosols. *N Engl J Med* 1986;315(14):870-4.
7. Colacone A, Afilalo M, Wolkove N, Kreisman H. A comparison of albuterol administered by metered dose inhaler (and holding chamber) or wet nebulizer in acute asthma. *Chest* 1993;104(3):835-41.
8. Silkstone VL, Corlett SA, Chrystyn H. Relative lung and total systemic bioavailability following inhalation from a metered dose inhaler compared with a metered dose inhaler attached to a large volume plastic spacer and a jet nebuliser. *Eur J Clin Pharmacol* 2002;57(11): 781-6.
9. Turner MO, Patel A, Ginsburg S, FitzGerald JM. Bronchodilator delivery in acute airflow obstruction. A meta-analysis. *Arch Intern Med* 1997;157(15):1736-44.
10. Cates C. Spacers and nebulisers for the delivery of beta-agonists in non-life-threatening acute asthma. *Respir Med* 2003;97(7):762-9.
11. Cates CC, Bara A, Crilly JA, Rowe BH. Holding chambers versus nebulisers for beta-agonist treatment of acute asthma. *Cochrane Database Syst Rev* 2003; (3):CD000052.
12. Lin YZ, Hsieh KH. Metered dose inhaler and nebuliser in acute asthma. *Arch Dis Child* 1995;72(3):214-8.
13. Fuglsang G, Pedersen S. Comparison of Nebuhaler and nebulizer treatment of acute severe asthma in children. *Eur J Respir Dis* 1986;69(2):109-13.
14. Bolton MB, Tilley BC, Kuder J, Reeves T, Schultz LR. The cost and effectiveness of an education program for adults who have asthma. *J Gen Intern Med* 1991;6(5): 401-7.
15. Yoon R, McKenzie DK, Bauman A, Miles DA. Controlled trial evaluation of an asthma education programme for adults. *Thorax* 1993;48(11):1110-6.
16. Ignacio-Garcia JM, Gonzalez-Santos P. Asthma self-management education program by home monitoring of peak expiratory flow. *Am J Respir Crit Care Med* 1995;151(2 Pt 1):353-9.