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Lung Function in Adult Patients with Cystic Fibrosis after Using the eFlow® rapid for One Year

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Abstract

Background: The new generation nebuliser PARI eFlow® rapid allows a highly efficient aerosol delivery at reduced inhalation time. However, lung function data during long-term use of this device are not available until now.

Methods: 70 clinically stable adult cystic fibrosis patients participated in this observation study. Lung function tests were performed prospectively 12 weeks after and again 9 to 12 months after switching the inhalation device from a conventional jet nebulizer to the PARI eFlow® rapid. Lung function data were collected retrospectively from the visits 1 year as well as 12 weeks prior to the switch-over. Lung function data for all time points were only available for 59 patients. Treatment time and patient's satification were recorded for both conventional and new nebuliser in all 70 patients.

Results: After 1 year of inhalation with eFlow® rapid, the mean change in FEV1% was – 1.4% (n = 59 patients). The decrease in FEV1 was smaller than the change in FEV1 after 1 year of inhalation with the conventional jet nebuliser (control period, -3.1%), although this difference was not statistically significant. The same effect was seen in MEF25[%] (-2.6% with conventional nebuliser compared to –1.6% after eFlow® rapid). Concerning the FVC, there was a greater improvement after 1 year of inhalation with the eFlow® rapid than with the jet nebuliser (+ 2.9% vs. +1.1%). For PEF%, there was an increase during the control period, whereas after inhalation with eFlow® rapid there was a decrease (+1.1% vs. –2.9%). All changes were not significantly different. The eFlow® rapid reduced total daily inhalation time by two-thirds (conventional nebuliser: 31.1 min/day; eFlow® rapid: 10.2 min/day, n = 70 patients)

Conclusion: Inhalation with the new nebuliser eFlow rapid does not alter FEV1, FVC or PEF significantly after 1 year of inhalation. The treatment time could be reduced significantly by the eFlow® rapid.

Key words: Cystic fibrosis, inhalation, nebuliser, eFlow® rapid, inhalation time, lung function

Introduction:

Cystic fibrosis is a multiorgan disease in which respiratory failure accounts for nearly 85 % of the mortality. Lung destruction is caused by obstruction of the airways due to dehydrated, thickened mucus, by resultant endobronchial infection, and an exaggerated inflammatory response leading to development of bronchiectasis and progressive obstructive pulmonary disease. Aggressive multimodal management of the cystic lung disease has resulted in great improvements in length and quality of life [1].

The delivery of aerosolized medication by nebuliser is an important part of pharmacotherapy for maintenance of lung function in cystic fibrosis [2]. The use of inhaled aerosols provides a selective treatment of the lungs as high drug concentrations can be achieved in the airways without major systemic adverse events.

Currently, the most common nebulisers are compressed air driven jet nebulisers, e.g. the advanced breath enhanced nebulisers PARI LC Plus or PARI LC Star. Recently, new technologies have emerged based on a perforated vibrating membrane. The motion of the membrane is created by an annular piezo-electric element, thus extruding liquid via the laser drilled perforated membrane and dispersing it into fine regularly sized droplets. The new electronic nebuliser Pari eFlow® rapid may represent a significant advance in aerosol delivery to the lungs, as the variation of droplet size is significantly lower ás with conventional jet nebulisers. The respirable fractions are comparable (71.3% with eFlow, 70.1% with LC Plus). With the eFlow®, treatment time can be reduced significantly from 17.4 minutes to 6.0 minutes for Tobramycin and from 4.4 minutes to 1.6 minutes for salbutamol, although in that study the inhaled volumes were not exactly the same [3]. Therefore less time burden might improve treatment adherence. However, little is known about the long-term effect of this new technology on lung function in CF patients.

After the launch of the eFlow® rapid in Germany in early 2005, most of our patients asked for a prescription for the new inhalation device during their routine visits. This study assessed long-term lung function over 12 months in those patients with cystic fibrosis whose health insurance companies permitted the prescription and therefore could use the eFlow® rapid.

Materials and Methods

Patients:

This prospective observational study was conducted at

the Center for Adult Cystic Fibrosis Patients at the Medizinische Klinik-Innenstadt of the University of Munich. The diagnosis of cystic fibrosis was documented by two sweat tests and/or two identifiable mutations consistent with CF, accompanied by one or more clinical features consistent with CF. Inclusion criteria were for all subjects: a) permission of the healthcare insurance company to buy the new nebuliser after patient's request for a prescription during a routine visit, b)written informed consent prior to the performance of any study related procedures, c) age 18 years and older.

After the launch of the new Pari eFlow rapid®, seventy adult CF patients of our center participated in the investigation. They all were clinically stable in the opinion of their physicians. Clinically stable was defined as no clinical relevant worsening in symptoms or lung function during the 4 weeks prior to the recruitment time.

Study design:
The investigations were conducted in accordance to the criteria of the Helsinki Declaration and to the standards of Good Medical Practice

Outcome parameters:
Primary and secondary outcome measures were defined prospectively. The primary outcome was lung function data after 9-12 months use of the new nebuliser compared to lung function data obtained with the use of conventional nebuliser, secondary outcome parameter was treatment time, and satisfaction with aerosol therapy.

Methods:
Lung function parameters were assessed prospectively eight to twelve weeks after the beginning of regular use of the new inhalation device Pari eFlow rapid® and again nine to twelve months later. Lung functions tests were done during routine visits at our out-patient clinic with a standard spirometer (Viasys MasterLab, Höchberg, Germany). In order to have a control period, we assessed lung function data retrospectively for the time points eight to twelve weeks as well as 9-12 months prior to the replacement of the conventional device with the new PARI eFlow® rapid.

Patients were asked to estimate their inhalation time (except dry powder inhaler) before the switch to the eFlow® rapid and during use of the new device and to report their satisfaction with the use of the nebuliser on a scale of 0-10 (0 = not satisfied at all, 10 = very satisfied) concerning duration of inhalation time, cleaning of the device, integration into daily physiotherapy and tolerability of the device.

Statistical Analysis:
Data are expressed as mean ± SD except for the analysis of treatment satisfaction (median, range). Paired t-tests for continuous variables were two-sided. Wilcoxon-test with exact significance was used for comparison of ordinal scaled data (treatment satisfaction). P values that were less than 0.05 were considered to indicate statistical significance. Statistical analyses were performed with SPSS software (SPSS Inc., Illinois, USA).

Results

Study population:
Between March and June 2005 70 patients (36 females, 34 males, aged 18-53 years, mean age 32 years) received the new inhalation device and were therefore included in our study. 45 patients (65%) inhaled an antipseudomonal antibiotic, either tobramycin (TOBI, 300 mg tobramycin, 32 patients) or colistin (Colistin CF, 1 mega colistine, 13 patients). Five patients inhaled other tobramycin solutions (either Tobrasix®, 160 mg tobramycin or Gernebcin®, 80 mg tobramycin). 46 patients used dornase alpha (Pulmozyme®) for mucolytic therapy, 33 of these patients had a combination therapy with either tobramycin or colistin. Additionally, each patient received daily saline inhalation therapy, either with isotonic (0.9%) or hypertonic (5.85%) solution.

As the retrospective lung function data were available in only 59 patients, the statistical analysis of all lung function values does only include data of 59 patients.

Lung function (Table 1 (n = 59))
While inhaling with the conventional jet nebulisers, the mean FEV1 at the beginning of the year was 2.38 l (range 0.72-6.19 l), which is 67.2% (range 26.2-136.4%) predicted. After 9-12 months inhalation with the conventional nebuliser, FEV1 decreased by 3.1% to 2.22 l (range 0.84-6.37 l); 64.1%, p = 0.88, not significant). Eight to twelve weeks after changing to the eFlow® rapid, FEV1 remained stable (2.23 l, range 0.66-5.94l; 65.0%). Nine to twelve months after the switch-over to the new nebuliser, FEV1 was 2.24 l (range 0.71-5.97 l, 63.6%, p = 0.61, not significant). Concerning the FVC, the increase was greater after 1 year of inhalation with eFlow® rapid than with the jet nebuliser (+ 2.9% vs. +1.1%). There were no statistically significant differences in data for PEF and MEF25 (see Table 1). Concerning MEF25 as a parameter for small airway disease, during the one year period of inhalation with the conventional nebuliser we observed a decrease of 0.09 l/sec (-2.7%). MEF25 increased after 8-12 weeks of inhalation with eFlow rapid® by 0.11 l/sec (+ 6%) and then decreased again by 0.13 l/sec (-6%) after 9-12 months of inhalation with the new device. Neither the changes after 1 year of inhalation with conventional nebuliser nor the changes after the switch-over to eFlow® rapid were statistically significant.

Mean total inhalation time (Table 2), n = 70:
With the conventional jet nebulisers, the estimated mean total inhalation time was 31.3 min/day. With the PARI eFlow® rapid, inhalation time was significantly reduced by two-thirds to 10.2 min/d. The reduction in inhalation time was similar for all inhaled medications.

Tolerability of conventional and new device (Table 3):
All 70 patients completed the whole observation period. No patient had to be withdrawn because of severe adverse events or intolerability of the device. In contrast, patients considered the eFlow® rapid significantly superior to the conventional jet nebuliser both in

Table 1. Lung function data of the control period (jet nebuliser) and the study period (eFlow® rapid), n = 59; Values are median (range)

Control period	**Jet Nebuliser**		**Mean difference**	**P**
	T1	**T2**	**(T1 – T2)**	
FEV1 [%]	67.2 (26.2-136.4)	64.1 (27.6-130.1)	-3.1%	
FVC [%]	88.3 (43.2-145)	89.4 (44.4-142.1)	+ 1.1%	
PEF [%]	63.6 (18.6-109.7)	65.0 (23.2-108.3)	+1.4%	
MEF 25[%]	15.6 (0.0-101.3)	13.0 (3.0-89.0)	-2.6%	
Study period	**eFlow® rapid**		**Mean difference**	**P**
	T3	**T4**	**(T3 – T4)**	
FEV1 [%]	65.0 (24.0-131.0)	63.6 (222.0-131.6)	-1.4%	
FVC [%]	86.0 (42.9-151.4)	88.9 (30.9-151.0)	+2.9%	
PEF [%]	62.4 (17.1-113.2)	59.5 (13.9-122.2)	-2.9%	
MEF25 [%]	16.0 (0.0-278)	14.4 (2.8-78.2)	-1.6%	

Table 2. Comparison of treatment times with the conventional jet nebuliser and the PARI eFlow® rapid; n = 70 patients.

Nebulised medication	Jet nebuliser	eFlow® rapid
Total inhalation time (min/d)	31.3 (21.4)	10.2 (8.3)
Tobramycin (300 mg/5 ml)	24.3 (11.9)	8.4 (4.8)
Colistine (79 mg/3 ml)	18.8 (8.7)	6.4 (2.1)
Dornase alpha (2.5 mg/2.5 ml)	15.3 (8.1)	5.4 (4.2)

All data were presented as mean (SD). P < 0.01 for each row comparing jet nebuliser und eFlow® rapid

Table 3. Median Tolerabiliy, inhalation time, cleaning and integration into the conventional therapy comparing jet nebuliser and eFlow® rapid; n = 70 patients

	Jet nebuliser	eFlow®® rapid	p
Tolerability	9 (2-10)	10 (5-10)	0.021
Inhalation time	3 (1-10)	10 (3-10)	< 0.01
Cleaning	7 (1-10)	7 (1-10)	0.93
Integration	7 (1-10)	7 (1-10)	0.95

All data were presented as median (range). Both treatment devices were compared using the Wilcoxon test with exact probabilities.

terms of inhalation time and overall tolerability. The median score for the jet nebulisers were 9 points (2-10) for tolerability and 3 points (1-10) for inhalation time. For the eFlow® rapid, after 8-12 weeks of usage the scores were 10 (5-10) for tolerability and 10 (3-10) for inhalation time, respectively. These differences were statistically significant. Regarding cleaning or integration into physiotherapy, there were no significant differences between both types of inhalation device.

Discussion

The major results of this observational study of a cohort of 70 adult patients with cystic fibrosis indicate a) that the use of the new nebuliser PARI eFlow® rapid preserved lung function in 59 patients, b) that the new nebuliser was well tolerated in all 70 patients, and c) that the use of this device reduced significantly the inhalation time.

Pari eFlow® rapid is a lightweight, portable electronic aerosol platform that utilizes advanced technology to ensure the efficiency of medication delivery within reduced treatment times. In spite of the common application of aerosolized medications in the therapy of cystic fibrosis and the increasing demand for the next generation nebuliser PARI eFlow® rapid, there are no prospective randomized comparisons of the two nebuliser devices. There is, however, rapidly growing evidence that the new generation of nebulisers are as effective as the standard jet nebuliser [4]. E. g., in a 7 week cross-over study Militz et al. observed a better FEV1% with an increased volume of sodium chloride inhalation solution (14.8 ml vs. 5.8 ml) using PARI eFlow® rapid [5]. Within the limits of an observational study, we found no significant differences in mean FEV1 in 59 patients changing from conventional jet nebulisers to PARI eFlow® rapid. There seems to be a small advantage in favour of the eFlow® rapid, as the loss in FEV1% after 1 year of inhalation with a conventional nebuliser was –3.1% compared to -1.4% after one year of inhalation with the eFlow rapid®, and the increase in FVC was slightly higher after the inhalation with the eFlow® rapid, but again these differences were statistically not significant. Furthermore, several other factors (e.g. number of exacerbations) which might have an impact on FEV1% have not been considered.

The comparability in terms of effect on lung function is consistent with the in vitro comparability of aerosol delivery characteristics from inhaled medica-

tions administered either by PARI eFlow® rapid or PARI LC PLUS [6]. The delivered and respirable doses of tobramycin were found to be comparable with both nebulisers in a prospective, randomized (cross-over design) bio-equivalence study [6]. In another study Scherer et al. [7] showed, that the eFlow® rapid delivers dornase alfa more rapidly and efficiently that jet nebulizers, and does not affect the physiochemical properties of the drug. They also showed that the droplet size distribution of the eFlow® rapid is narrower than the droplet distribution of jet nebulizers. Geidel et al. investigated patients with cystic fibrosis and found no effect of body position (either vertical or horizontal) on serum tobramycin concentration [8]. Two pharmacokinetic studies compared serum and sputum tobramycin levels after inhalation of tobramycin solution for inhalation either with PARI LC Plus or PARI eFlow® rapid for 15 days. In the first study by Tavakkol et al. [4] the serum tobramycin AUC after 15 days of inhalation was comparable in both devices, whereas the sputum concentration of tobramycin was higher in the PARI eFlow® group. This might lead to an even improved therapeutic ratio. Furthermore, they found a reduction in treatment time which is comparable to our study (17.7 min with LC Plus, 7.3 min with eFlow® rapid). In the second study conducted in France [9] systemic tobramycin exposure in serum with eFlow® rapid was broadly similar to that observed from LC Plus, particularly at day 15 (steady state). They observed higher tobramycin sputum concentrations, although in both groups sputum concentrations were highly variable. In this study inhalation time was reduced by one half with eFlow® rapid (7.4 ± 1.7 min for 5 ml TOBI) compared to the Pari LC Plus (17.6 ± 4.0 min for 5 ml TOBI).

In Canada, a deposition study was done by Coates et al. comparing two different formulations of tobramycin in children [10]. They demonstrated an equivalent dose delivery when applying 300 mg tobramycin in 5 ml saline via PARI LC Plus compared to 300 mg tobramycin in 3 ml saline via eFlow® rapid.

In all 70 patients of our study, satisfaction with the use of one inhalation device was greater with the eFlow® rapid than with the PARI LC plus. One outstanding feature of the electronic nebuliser is the much shorter treatment time due to the high aerosol output rate, another feature is the more quiet operation. Similarly, in the study by Militz et al. (5) eFlow® rapid was rated significantly better than the conventional device (using German school marks). In a French study adherence to eFlow® was assessed using the CFQ14 questionnaire in 17 patients. In 8 patients adherence significantly increased while inhalation time decreased. An increase in quality of life was also observed (11) Whether the increase in mobility due to long battery life (for up to 8 inhalations) adds to improved adherence remains to be studied.

Conclusion

The use of the new inhalation device eFlow® rapid over one year does not alter significantly FEV1 and FVC compared to one year of inhalation with a conventional nebuliser, although concerning the changes in FEV1 there seems to be a small favour for the eFlow® rapid. Treatment time was significantly less than with conventional nebulisers, therefore our patients preferred the new device.

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