Comparative efficacy of terbutaline sulphate delivered by Turbuhaler dry powder inhaler or pressurised metered dose inhaler with Nebuhaler spacer in children during an acute asthmatic episode

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Aims: To compare the efficacy of terbutaline sulphate delivered via Turbuhaler with a pressurised metered dose inhaler (pMDI) connected to Nebuhaler spacer in a population of asthmatic children presenting to emergency departments because of an acute episode of asthma.

Methods: Randomised double blind, double dummy, parallel study of acute asthma in the emergency department. A total of 112 children (6–16 years), who had a diagnosis of asthma, a baseline FEV₁ of 25–60% of predicted normal value (PNV), and the ability to perform spirometry were studied. Patients received two doses of 0.5 mg/10 kg (maximum 2.0 mg) of terbutaline sulphate at time 0 minutes and time 30 minutes. The two groups were also stratified into subgroups based on FEV₁: 25–45% and 45.1–60% PNV. FEV₁, before treatment and at two 15-minute intervals after each treatment was the main outcome measure. PIF, PEF, heart rate, \( \text{SpO}_2 \), and tremor were also measured at these times.

Results: Both the Turbuhaler and pMDI+Nebuhaler groups showed significant increases from baseline to final value in their FEV₁ results, 49% and 50% change from baseline to \( t = 60 \) minutes, respectively (\( p < 0.001 \)) using last value carried forward. No significant difference was found between the two groups for these results. Subanalysis of the stratified groups revealed similar results. In addition, no significant difference was found in the group and subgroup comparisons for heart rate, \( \text{SpO}_2 \), and tremor.

Conclusion: Results show that Turbuhaler and pMDI+Nebuhaler are similar in terms of benefit and side effects in the treatment of acute moderate to severe asthma attacks in this study population.

METHODOLOGY

Patients

Patients aged 6–16 years inclusive, with acute asthma, who presented to one of three emergency units in Canada, were recruited to the study: Hôpital Ste-Justine, Montréal, Québec (n = 102); Alberta Children’s Hospital, Calgary, Alberta (n = 7); and Misericordia Community Hospital, Edmonton, Alberta (n = 3). Inclusion criteria were a baseline forced expiratory volume in one second (FEV₁) of 25–60% of predicted normal value (PNV), baseline peak inspiratory flow (PIF) of at least 30 l/min when measured through Turbuhaler, and the ability to perform correctly both spirometry and the inhalational techniques required of Turbuhaler and pMDI+Nebuhaler. In addition, baseline resting heart rate could not exceed 160 beats/minute.

Patients were ineligible if they had used inhaled \( \beta \)₂ agonists within three hours prior to enrolment, or theophylline, ipratropium bromide, or oral \( \beta \), agonists within 12 hours. Potential patients were also excluded if they had any known contraindication to sympathomimetic amines, lactose (non-drug component of the placebo), or pMDI additives (Frem 11, 12, 114, and sorbitan trioleate).

The respective ethics committee of each participating hospital approved the study, and informed written consent was obtained from the parents. The study was performed in accordance with

Abbreviations: DPI, dry powder inhaler; FEV₁, forced expiratory volume in one second; ITT, intention to treat; PEF, peak expiratory flow; PIF, peak inspiratory flow; pMDI, pressurised metered dose inhaler; PNV, predicted normal value; \( \text{SpO}_2 \), transcutaneous oxygen saturation; \( t \), time
Turbuhaler, PEF, and safety variables (heart rate, tremor, and SpO₂) were compared between the treatment groups by an analysis of covariance (ANCOVA) with factors for treatment, stratification, and interaction effects between treatment and stratification in the preliminary model. The corresponding baseline value was used as the covariate. Where spirometry data were missing, the principle of last value carried forward was used. The interaction effect was removed from the final model because of statistical insignificance. The 95% confidence intervals for treatment differences were calculated. No analysis for centre effect was undertaken because of the small sample sizes at two of the three centres.

The sample size calculation was based on comparison of the mean change in FEV₁ %PNV from baseline between treatments. With a two sided test at α = 0.05 and a power of 80%, 64 patients were required in each group in order to detect a clinically relevant difference of 5% in the FEV₁, with a standard deviation (SD) of 10%. Since the study was terminated prematurely because of a slow recruitment rate, a retrospective sample size calculation was performed. The actual power of the study was 75% given a total of 112 patients and SD of 10%. All randomised patients were included in the intention to treat analysis (ITT). All statistical tests were two sided and p values of <0.05 were considered statistically significant.

RESULTS

Of the 112 patients that were enrolled into the study, nine children did not complete the investigation. Six patients were from the Turbuhaler group, of which three were unwilling to continue the study and three were removed after 30 minutes when their baseline FEV₁ failed to increase by more than 10%. Their ages ranged from 6 to 10 years, and their baseline FEV₁ values were 36–60% PNV. The reasons for early withdrawal for the three patients in the Turbuhaler group were unwillingness to continue in two patients and a <10% increase in FEV₁, after 30 minutes following the first treatment in one patient. These three patients were between 10 and 13 years of age with baseline FEV₁ values 28–53% PNV. Since the ITT approach was selected for analysing the data, all data were included in the analysis.

Table 1 shows the demographic and baseline spirometric data of the 112 patients who were enrolled in the study. No significant difference was found between the two groups for any baseline variable, indicating that both groups were well matched for sex, age, height, and FEV₁. The mean baseline FEV₁ (SD) value for the Turbuhaler group was 44.8% (9.0%) PNV, and the mean baseline FEV₁ (SD) value for the pMDI+Nebulizer group was 43.4% (10.1%) PNV. Stratification of the two treatment arms into the two subgroups (FEV₁ 25–45% and 45.1–60%) resulted in comparable findings. In the FEV₁ 25–45% stratum, there were 26 patients in the Turbuhaler group (FEV₁ %PNV: 36.6 (4.9); range 26–44) and 26 patients in the pMDI+Nebulizer group (FEV₁ %PNV: 34.1 (5.1); range 26–46). In the FEV₁ 45.1–60% stratum, there were 31 patients in the Turbuhaler group (FEV₁ %PNV: 51.6 (5.0); range 43–60) and 29 in the pMDI+Nebulizer group (FEV₁ %PNV: 51.8 (4.4); range 46–60). Neither of these differences nor any other baseline measurements resulting from the stratification proved to be significantly different between the two groups.

Similar doses of terbutaline sulphate were given to both groups at the two dosing times. At the initial treatment time (t = 0), the Turbuhaler group received a mean value of 1.75 (0.33) mg (range 1.0–2.0 mg), while the pMDI+Nebulizer group received a mean value of 1.71 (0.3) mg (range 1.0–2.0 mg) of terbutaline sulphate. At the second treatment time (t = 30), the Turbuhaler group received an additional mean amount of 1.78 (0.32) mg (range 1.0–2.0 mg), and the pMDI+Nebulizer group received a mean amount of 1.69 (0.33) mg (range 1.0–2.0 mg). None of these differences were significantly different between the two groups.
treatment dose at t = 0, there was a 33% increase in the FEV1 (p < 0.001). As fig 1 shows, 30 minutes following the first after each treatment when compared with baseline values. Each group did show, however, a significant improvement baseline to final value (p > 0.05; 95% CI 4.4% to 3.5% PNV).

Comparison between the two groups showed no significant difference for the changes in FEV1, the primary variable, from baseline to final value (p > 0.05; 95% CI 4.4% to 3.5% PNV). Each group did show, however, a significant improvement after each treatment when compared with baseline values (p < 0.001). As fig 1 shows, 30 minutes following the first treatment dose at t = 0, there was a 33% increase in the FEV1, %PNV in the Turbuhaler group and a 35% increase in the pMDI+Nebuhaler group. This results in a mean absolute change of 26% and 22%, respectively. While these increases were statistically significant within each treatment stratum, no difference was observed between the Turbuhaler and the pMDI+Nebuhaler within the 25–45% stratum. Similar statistical results were found for the 45.1–60% stratum. The final mean value at t = 60 minutes was 70.8% (8.1%) PNV for the Turbuhaler group and 73.1% (8.8%) PNV for the pMDI+Nebuhaler group, which yielded a mean absolute change of 19% and 21%, respectively. Once again, although these increases proved to be statistically significant within each treatment subgroup, no difference was found between the Turbuhaler and the pMDI+Nebuhaler 45.1–60% stratum. Similar statistical results were found for PIF and PEF.

Figure 3 shows the relation between the bronchodilatory effects of the terbutaline sulphate delivered in dry powder and the inspiratory flow through Turbuhaler. Only the data from the Turbuhaler group are shown. No significant correlation could be found between the percent change from baseline to the final FEV1 value and the PIF measured through Turbuhaler during the first treatment dose at t = 0 (p = 0.10; r = 0.31). Similar results were found when this relation was examined using the PIF measured through Turbuhaler during the second treatment dose at t = 30. The six data points below the 10% mark on the y axis are the results of the six patients who were enrolled and randomised into the Turbuhaler group but did not complete the protocol.

The changes for heart rate from baseline to final value were statistically significant (p < 0.001) within each group, but no significant difference was found when between group comparisons were made (table 2). The greatest increase in heart rate for both groups occurred 30 minutes after the first treatment (Turbuhaler: 12% change; pMDI+Nebuhaler: 10% change) which was followed by another increase, albeit smaller, 30 minutes after the second treatment (Turbuhaler and pMDI+Nebuhaler: 7% change). No patient in either group had an increase in heart rate of more than 40% above their baseline value. The changes in SpO2 from baseline to final value were not significantly different between the two groups, and although within group comparisons were statistically significant, there was no clinical relevance to these changes.

On entry into the study, 88% of the Turbuhaler patients and 91% of the pMDI+Nebuhaler patients did not exhibit any hand tremor. At the final measurement interval of the study, after two treatment doses had been given, mild hand tremor was observed in 26% and 56% of the Turbuhaler and pMDI+Nebuhaler patients, respectively, while 61% of the Turbuhaler and 40% of the pMDI+Nebuhaler patients were
exhibiting moderate hand tremor. Statistical analysis of these differences did not show any significance for the between group comparisons, while within group comparisons did reach significance (p < 0.001). At no time during the study did any patient exhibit a severe hand tremor.

**DISCUSSION**

The results from this study have shown that in our sample population terbutaline sulphate delivered in dry powder by Turbuhaler was as efficacious as the same nominal dose of terbutaline sulphate delivered by the pMDI+Nebuhaler spacer as a first line treatment of moderate and severe acute asthma attacks in children. These findings are in agreement with previous reports that suggested that Turbuhaler was an effective method of treating children during an acute asthma exacerbation. Springer and colleagues compared 2.5 mg terbutaline sulphate delivered via Turbuhaler with 5,0 mg terbutaline sulphate given by nebulisation and found significant and comparable improvements in PEF in a sample of 12 children (aged 7–12 years) attending an emergency department for treatment of an acute asthma exacerbation. In the other paediatric study, Rufin and colleagues recruited 30 children (aged 6–14.5 years) with moderate acute asthma from an outpatient clinic. Using an open design, two groups of 15 patients each received a single dose of 0.5 mg terbutaline sulphate either via Turbuhaler or by a pMDI+Nebuhaler. This study also found significant and comparable improvements in FEV1 between the two groups up to 30 minutes following the treatment.

While the conclusions of these studies are in agreement with our study, neither study reported their statistical power. Therefore, the possibility exists that their sample sizes were too small to detect a significant treatment difference. Although the actual power of the current study was calculated to be 75% instead of the initially planned 80%, this was not a concern since the confidence interval of the treatment difference had a small range (that is, both the lower and upper limits were less than 5%). If we had chosen a value of 7% instead of 5% for the clinically relevant difference in FEV1, as significant, the power of our study would increase to 96%. In fact, a clinically relevant difference as high as 12% in the FEV1, PNV has been used previously in a comparably designed emergency department study which examined the difference between β2 agonists delivered by nebuliser and pMDI with a spacer in children with mild to severe acute asthma. In addition, we chose to compare the Turbuhaler with a metered dose inhaler and spacer because of the simplicity and ease of use of the spacer, as well as results of numerous studies, including that of Kerem and colleagues, showing the equivalency of the spacer to the wet nebuliser.

The lack of correlation between the percent increase in FEV1, from baseline to final value and the measured inspiratory flow through Turbuhaler (fig 3) suggests that the bronchodilatory effects achieved with the DPI were independent of inspiratory flow above our minimum requirement of 30 l/min. Similar observations were reported by Pedersen and colleagues. Their investigation examined the bronchodilatory effects of a submaximal dose of terbutaline sulphate delivered via Turbuhaler while varying inspiratory flows between 13 and 60 l/min in a sample of 14 children (aged 7–15 years) with stable chronic asthma. They found the increase in FEV1 after treatment was comparable for patients with mean inspiratory flows of 31–60 l/min. However, when the inspiratory flow was decreased to 22 l/min, the treatment effect was reduced by approximately 67%. In addition, a further decrease in inspiratory flow to 13 l/min resulted in a 33% treatment effect. Based on their findings, we chose a minimum inspiratory flow through Turbuhaler of 30 l/min as an inclusion criterion, and it would appear that our results in an unstable acute asthmatic state are in agreement with their results in a stable chronic asthmatic state.

In our study, we did not find inspiratory flow to be a limiting factor in either patient attrition or recruitment. Once enrolled, no patient was withdrawn from the study because of their inability to continue to generate throughout the course of the protocol the minimally required inspiratory flow through Turbuhaler. This was observed in children as young as 6 years and in children with a baseline FEV1, as low as 25%. In addition, apart from the 112 patients enrolled, only five patients (4%), aged 6–13 years, whose baseline FEV1% PNV was 25–60%, were not enrolled when they failed to achieve a Turbuhaler PIF of at least 30 l/min; values were 24–28 l/min. In this very small group, this was a result of either limited ability to perform the technique or actual flow limitation, and does not necessarily mean they would not have improved using this technique. This small number of subjects not studied should not detract from the major findings of this study. Of interest, studies investigating Turbuhaler in adults also found that only 2–4% of their sample were unable to generate 30 l/min, and none of them were lower than 25 l/min. Although these patients were not

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The change from baseline to last value within each group was p<0.05. The differences between groups were not significant. SpO2 and heart rate results are expressed as mean (2 SEM).
enrolled in either their studies or in our study, it is quite probable that a beneficial response from the treatment would have been observed based on the findings from Pedersen and colleagues which showed that a significant bronchodilatation could still be achieved with Turbuhaler inspiratory flows of 22 l/min.

The similar bronchodilatory improvements accounted for by the changes in FEV₁, not only were observed between the two groups, but also were comparable within the strata subgroups. The results of stratification of the sample into severe (25–45% FEV₁, PNV) and moderate (45.1–60% FEV₁, PNV) indicated that the bronchodilatory benefits were not related to degree of severity. Indeed, the mean absolute changes within each stratum were similar. However, when calculated on a relative basis, improvements in the severe stratum were greater than those changes calculated for the moderate stratum. One possible explanation for this observation could be that the severe patients had a greater potential to improve based on their lower initial value. The profile of our sample population could also account for the variation in bronchodilatory response. The duration of the asthmatic episode previously prescribed, type and dose of medication, and effective treatment delivery modalities were uncontrolled factors, which could have accounted for the degree of response to our treatment. Our patients were selected essentially on degree of severity, capabilities, and previous medication restrictions.

The calculated dose of terbutaline sulphate used for each patient was the same for the two delivery methods, and based on the FEV₁ results, provided similar bronchodilatory effects. On this topic the literature is equivocal. Previous cumulative dose response adult and children studies, as well as investigations comparing predetermined equivalent doses at various time intervals have found no significant difference in efficacy between Turbuhaler and pMDI. On the other hand, other well designed studies have shown a higher dose-potency in efficacy between Turbuhaler and pMDI. Our findings suggest that the Turbuhaler (DPI) is an effective alternative modality for the first line treatment of an acute asthmatic episode in children.

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