Clinical outcomes of children using a metered dose inhaler with a sleeve attachment device to improve ease of use

Kassim Babu Mapondela, MD, MMed (ENT),[a] Roopam Dey, PhD,[b,c,d] and Michael Levin, MBChB, PhD[a] *Cape Town, South Africa*

Background: Activating pressurized metered dose inhalers (pMDIs) is often challenging for children. The Easy Squeezy (ES) is a novel sleeve attachment device that reduces activation force by 3 times. Although users have favored using the ES over using a pMDI alone, the clinical impact of the ES remains unknown. The aim of this study was to compare lung function and quality of life between ES users and users of a pMDI alone.
Objectives: Our aim was to measure and compare lung function of asthmatic children after they used the ES and pMDI alone.
Methods: In this crossover study we recruited 65 asthmatic children between the ages of 5 and 12 years. The participants were randomized into 2 groups. One of the groups used the ES for 6 weeks whereas the other group used a pMDI. After 6 weeks the participants crossed over to the other group. Lung function test parameters were measured after randomization and after each 6 weeks of device use. Quality of life (measured by the Patient Asthma Quality of Life Questionnaire [PAQLQ]) and Childhood Asthma Control Test were measured after each period of device use.
Results: There was no significant difference in the baseline lung function between the groups. The ES group had a significantly lower percentage difference between prebronchodilator and postbronchodilator FEV_1 values. Although no significant differences were observed in PAQLQ scores between the groups, more patients in the ES group had improvement of their PAQLQ score than did patients in the group using a pMDI alone. Total Childhood Asthma Control Test scores were significantly higher for the ES group.
Conclusions: The ES device may allow users' asthma to be better controlled than by using a pMDI alone. (J Allergy Clin Immunol Global 2023;2:100126.)

Key words: *Pressured metered dose inhaler, children, Easy Squeezy, quality of life, lung function, asthma*

Abbreviations used
C-ACT: Childhood Asthma Control Test
COVID-19: Coronavirus 2019 disease
ES: Easy Squeezy
FVC: Forced vital capacity
PAQLQ: Patient Asthma Quality of Life Questionnaire
pMDI: Pressurized metered dose inhaler

In 2019, asthma affected 262 million people, caused 455,000 deaths, and was responsible for 21.6 million disability-adjusted life years.[1,2] Higher loss in years owing to disability caused by asthma has been observed in children aged 1 year to 14 years and in low- and middle-income countries.[1]

Several management options are available to control asthma. Pressurized metered dose inhalers (pMDI) are the most commonly used treatment devices for asthma in children and adults.[3] The high activation forces required to activate pMDIs make it difficult for children to use them independently.[4] Most children need cooperation from parents or caregivers to activate metered dose inhalers.[4] This means that many children are unable to use their pMDI away from their parents, for instance, in their school or while performing independent extracurricular activities.

Recently, a sleeve attachment device, the Easy Squeezy (ES) (see Fig E1 in the Online Repository at www.jaci-global.org), was developed to reduce the force of pMDI activation.[5] This device is acceptable to pediatric pMDI users and their caregivers, who report that the device made it easier for children to activate the pMDI, that the children were more likely to take the pMDI with them to school, and that the built-in dose counter made it easier to keep count of the doses.[6] There are no studies evaluating the clinical efficacy of any lever aid device[7] such as the ES. This study aimed to assess whether use of a pMDI with the ES device affected the clinical efficacy of regular controller therapy (asthma control, lung function and quality of life) in children with moderate-to-severe asthma who were receiving inhaled corticosteroids.

METHODS

A total of 65 participants with asthma who were aged 5 to 12 years and using either inhaled corticosteroids or inhaled corticosteroid–long-acting β2 agonist combination therapy via a metered dose inhaler at a stable dose for more than 3 months before enrollment were included in this 12-week crossover study. Participants were excluded if they had coronavirus 2019 disease COVID-19–related symptoms, were experiencing or had recently (<14 days) recovered from COVID-19, had household contact

From [a]the Division of Paediatric Allergology, Department of Paediatrics and Adolescent Health, [b]the Division of Biomedical Engineering, Department of Human Biology, [c]the Division of Physiological Sciences, Department of Human Biology, and [d]the Division of Orthopaedic Surgery, Department of Surgery, Faculty of Health Sciences, University of Cape Town.

Received for publication January 20, 2023; revised April 11, 2023; accepted for publication April 19, 2023.
Available online June 12, 2023.

Corresponding author: Michael Levin, MBChB, PhD, Room 516, ICH building, Red Cross Children's Hospital, Klipfontein Road, Rondebosch 7025, South Africa. E-mail: michael.levin@uct.ac.za.

The CrossMark symbol notifies online readers when updates have been made to the article such as errata or minor corrections

2772-8293

© 2023 Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

https://doi.org/10.1016/j.jacig.2023.100126

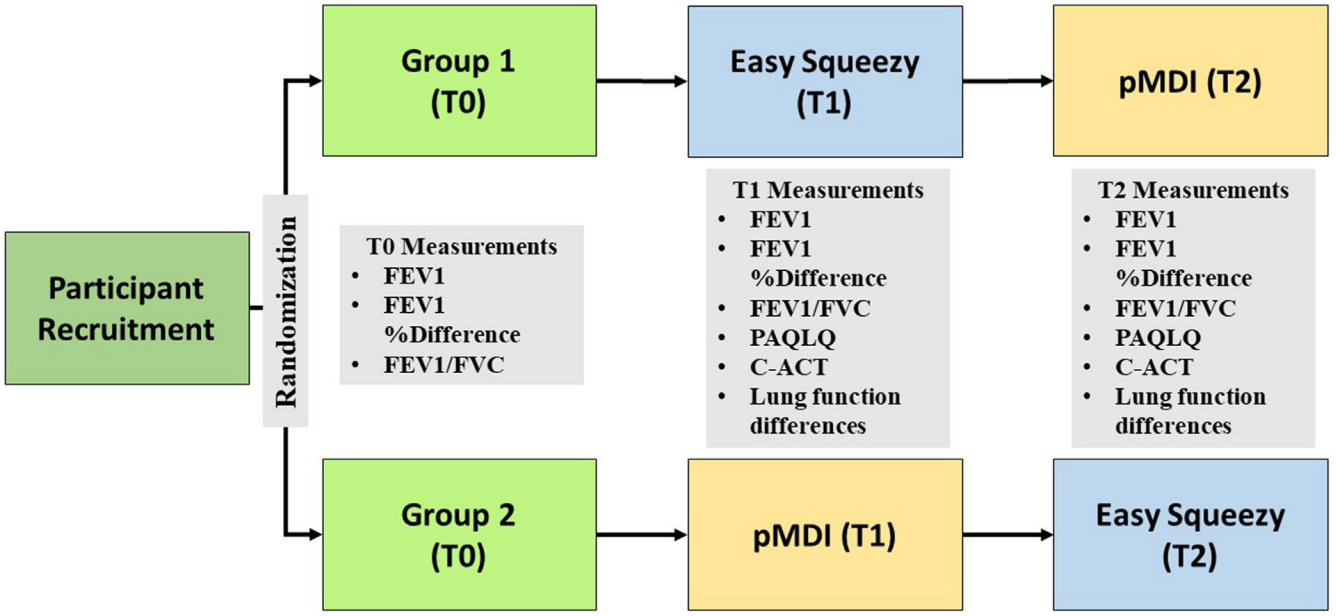

FIG 1. Schematic flowchart of participant recruitment, randomization, and crossover.

with someone who was experiencing COVID-19 or had recently recovered from COVID-19, had any physical or mental disease or injury that might reduce ability to activate a pMDI, or were unable to follow basic instructions in English. Participants were randomly assigned to the order in which they would commence the study, either continuing with use of a pMDI alone or commencing with use of a pMDI together with the ES. This study was performed with ethical approval from the University of Cape Town, South Africa (human research ethics committee reference no. 592/2021) in accordance with the Declaration of Helsinki and South African Good Clinical Practice guidelines. To calculate the sample size required to ensure no significant adverse effect of using the device, we expected that the difference in FEV_1 value–to–forced vital capacity (FVC) ratio between participants using a pMDI alone and those using a pMDI along with the ES would be less than 10%. By assuming an SD of 15, an equivalence limit of 10, a *P* value of .05, and a power of 95%, we determined that 59 participants in total would be required.

On the day of inclusion, prebronchodilator and postbronchodilator lung function tests were performed to obtain the prebronchodilator FEV_1 value, the prebronchodilator FEV_1/FVC ratio, and the percentage difference between prebronchodilator and postbronchodilator FEV_1 values. The participants who were randomized to group 1 continued to use the pMDI inhaler for the next 6 weeks, whereas the participants in group 2 used the ES to activate their pMDI for the next 6 weeks. After randomization, the investigator trained the participants in use of both a pMDI alone and a pMDI with the ES, witnessed the children's use of the devices independently, and recorded the method with which the device was actuated (1 finger or the whole hand). After 6 weeks (T1), the lung function tests were repeated, quality of life was assessed by using the Pediatric Asthma Quality of Life Questionnaire (PAQLQ),[8,9] and asthma control was assessed by using the Childhood Asthma Control Test (C-ACT).[10,11] Participants then crossed over to use the other device, and after another 6 weeks (T2), the same investigations were repeated (Fig 1). Apart from changes in treatment required for a severe exacerbation, no changes in asthma treatment were permitted between randomization and conclusion of the study.

Analysis

Distribution of the data was checked by using the Shapiro-Wilk test. The data did not follow a normal distribution. Baseline lung function data were compared between group 1 and group 2 at randomization. PAQLQ score, C-ACT score, and lung function data were compared at the end of the study, when the participant had used each of the devices for 6 weeks. Use of the ES with a pMDI and use of a pMDI alone were compared with each other, regardless of time point (use of the ES with a pMDI at T1 + use of the ES with a pMDI at T2 vs use of a pMDI at T1 + a pMDI T2 [Fig 1]). In addition, the difference in lung function test parameters from the previous measurement was calculated, grouped according to whether the measurements were made after use of the pMDI ([group 1 T2 – T1] + [group 2T1 – T0]) or ES alone (group 1, T1 – T0 + group 2, T2 – T1), and compared between the groups (Fig 1). Mann-Whitney *U* tests were performed to find significant differences, with a *P* value less than .05 serving as the criterion for statistical significance. The proportion of subjects with the minimal important difference in total PAQLQ score[8,9] was calculated and reported in terms of percentages.

RESULTS

Ultimately, 55 participants completed the study (after 10 participants were randomized but did not attend their first follow-up visit). Of the participants lost to follow-up, 7 were assigned to group 1 (commenced with use of a pMDI alone) and 3 were assigned to group 2 (commenced with use of the ES device with a pMDI). The average age of our cohort was 7.2 ± 1.5 years. Their height, weight, and body mass index were 25.7 ± 9.3 kg, 1.2 ± 0.1 m, and 16.6 ± 2.9 kg/m^2, respectively The majority of our participants (64%) were males and went to school (93%). All

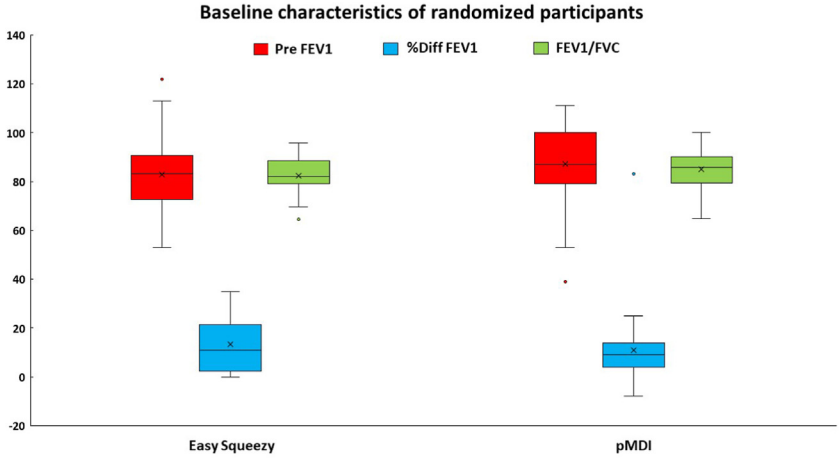

FIG 2. Outcomes of the lung function tests for recruited participants on the day of randomization. *Diff,* Difference; *Pre,* prebronchodilator.

TABLE I. Lung function test outcomes of all participants

Indicator, median (IQR)	Baseline value	pMDI alone	ES with pMDI
Prebronchodilator FEV_1 value	85.0 (17.0)	89.0 (18.0)	96.0 (17.0)
FEV_1 value difference (reversibility)	9.0 (14.0)	10.0 (14.0)	4.0 (9.0)*
FEV_1/FVC ratio	84.4 (9.4)	84.2 (11.1)	85.4 (8.3)

*Statistically significant ($P < .05$) difference between values with a pMDI alone and the Easy Squeezy used with a pMDI.

of the participants had had asthma for an average of 4.5 ± 2.0 years, had experience using a pMDI for 4.4 ± 2.0 years, and had been using their pMDI through a spacer.

Of those participants who completed the study, 24 were in group 1 and 31 were in group 2. The baseline characteristics of the 2 groups of those who completed the study (Fig 2) had no statistically significant differences in prebronchodilator FEV_1 value (82.9 ± 16.4 vs 87.2 ± 15.8), percentage difference between prebronchodilator and postbronchodilator FEV_1 value (13.6 ± 11.5 vs 11.0 ± 15.4), or prebronchodilator FEV_1/FVC ratio (82.3 ± 7.6 vs 85.0 ± 9.4).

The outcomes of the lung function test, for the whole cohort, are reported in Table I. There were no significant differences between FEV_1 value and FEV_1/FVC ratio when participants used the ES together with a pMDI and when they used a pMDI alone. The difference in FEV_1 values between the 2 groups was just 2.5%, indicating clinical equivalence. However, the bronchodilator reversibility (postbronchodilator – prebronchodilator FEV_1 value) was significantly lower ($P < .05$) in the ES group than in the pMDI group (Fig 3). The differences in lung function parameters from previous measurement (Fig 4) with the ES together with a pMDI (FEV_1 value, 9.1 ± 15.7; difference in FEV_1 value, –6.5 ± 15.7; FEV_1/FVC ratio 2.5 ± 7.5) were found to be significantly better than with the pMDI alone (FEV_1 value, –3.5 ± 14.6; difference between FEV_1 values, 3.4±13.8; FEV_1/FVC ratio, –2.6 ± 7.4).

Our cohort members could not activate the pMDI by using their index finger and thumb. Most of the cohort members (40%) could activate the pMDI only when using their thumb and 2 fingers, and 25% of them could not activate the pMDI at all. In contrast, 98% of the cohort could activate the pMDI by squeezing the bunny ears of the ES with 1 hand (see Fig E2 in the Online Repository at www.jaci-global.org).

Median (interquartile range) PAQLQ scores (see Table E1 in the Online Repository at www.jaci-global.org) were not statistically significant between the ES group and the pMDI group (see Fig E3 in the Online Repository at www.jaci-global.org). PAQLQ scores increased by more than the minimal important difference in 15% of the ES group compared to 0% of the participants using pMDI alone.

The median C-ACT scores (Table II) were significantly higher after use of the ES with a pMDI than when a pMDI was used alone (Fig 5). In our cohort, 21 participants had a C-ACT score less than 20; of these 21 participants, 15 were in pMDI group and only 6 were in the ES group. In 31% of our cohort (17 of 55), the total C-ACT score was of at least 3 points higher (the minimally clinically significant value) with use of the ES with a pMDI than when a pMDI was used alone (see Fig E4 in the Online Repository at www.jaci-global.org), with this difference reversed in the case of only 1 participant. No participants experienced loss of control severe enough to warrant emergency treatment or a change in controller medication.

DISCUSSION

Patients find it difficult to adhere to inhaled medications.[12] Adherence rates to asthma medication range from 22% to 78%.[13] Poor adherence has also been reported in children,[14] with their adherence rates ranging from 28% to 67%.[15]

Poor adherence to inhaled asthma medication reduces patients' quality of life and lung function.[16] Reduced adherence can be intentional or nonintentional.[17] Nonintentional lack of adherence may be caused by social barriers, including inability to access medication or inability to use the medication that has been acquired. Physical inability to operate a pMDI can also become a

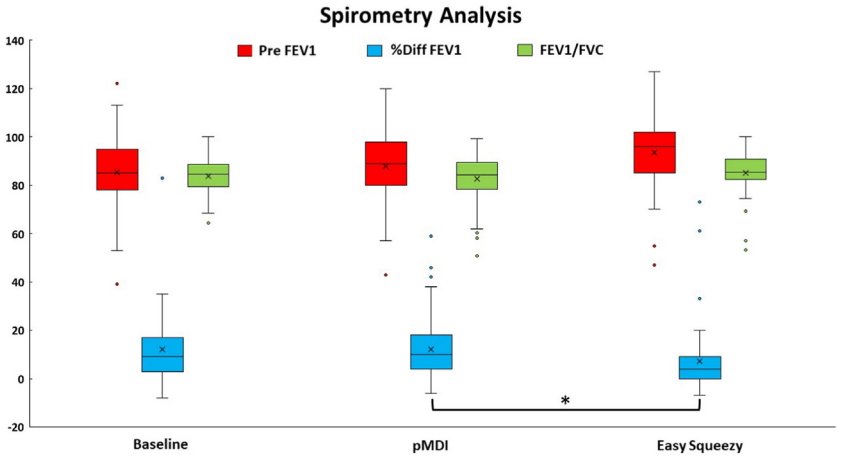

FIG 3. Lung function test results after 6 weeks of using the pMDI alone and ES device with a pMDI. Asterisk suggests statistical significance. *Diff,* Difference; *Pre,* prebronchodilator.

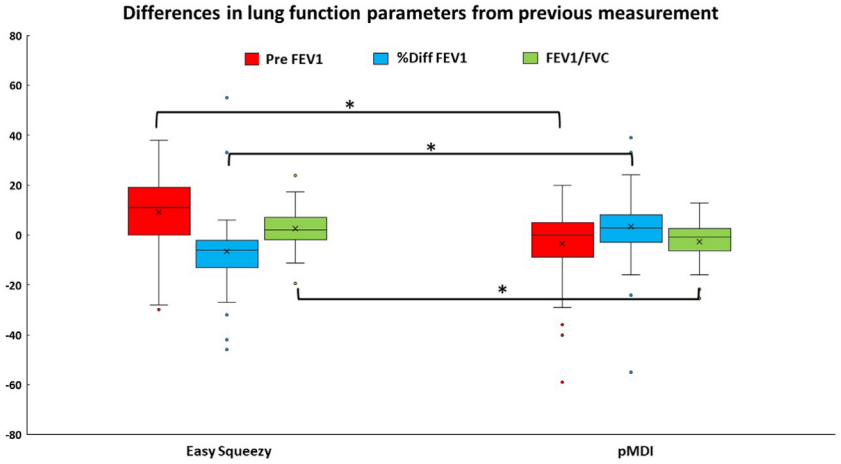

FIG 4. Differences in lung function test parameters due to use of a pMDI and the ES together with a pMDI, as measured from their previous time point. Asterisk indicates statistical significance. *Diff,* Difference; *Pre,* prebronchodilator.

barrier for children[18] and the elderly population.[19] The activation force required to operate a pMDI could be a limiting factor in these 2 population groups.[4,19] In various studies, the proportion of participants who could not use pMDIs varies from 12% to 89%, with an average incidence of misuse of 38%.[20]

Inability to use inhalers causes lack of control.[20,21] The role of difficulty in use of a pMDI as a cause of nonadherence has not been well studied,[22-24] but it has been reported as being among the secondary reasons for nonadherence.[25] Lack of adherence in children has been reported as a cause of poor control and death.[26] Children using an inhaler on their own, without help from an adult, is correlated with better technique.[27] This may imply that fostering patient autonomy is an important aspect of asthma care.

In this study we compared the clinical performance of a novel sleeve attachment device, the ES, with the pMDI over a 6-week period. When compared with use of a pMDI alone, use of the ES together with a pMDI enabled pediatric patients to activate their pMDIs with ease. Use of the ES decreased reversibility, indicating improvements in bronchial hyperreactivity. Use of the ES was associated with improvements in prebronchodilator FEV_1 value and FEV_1/FVC ratio compared with the prior lung function measurement. This may have contributed toward the improved asthma control in participants after they used the ES. Although total PAQLQ scores between the ES and pMDI groups were not significantly different, more patients in the ES group than in the group using a pMDI alone had improvement in their PAQLQ score exceeding the minimally important difference.

Our study had a few limitations. First, our cohort was younger than the cohorts in most of the studies in the literature. This meant that we could neither compare our results with those in the literature efficiently nor extrapolate our findings to all ages. Studies have shown that advancing age also causes inability to use pMDIs, with the factor best correlated with advanced age being late actuation or inability to activate the device,[28] indicating that muscle strength or hand mobility may also play a role in use of a pMDI by elderly patients.[19] Second, all of our participants were familiar with pMDI use. If anything, this would mean that they are able to use the device better than patients unfamiliar with a pMDI, as studies have shown that a new device is associated with less ability to use it.[29] We observed that the participants

TABLE II. C-ACT scores for our cohort

C-ACT questions	Score for a pMDI used alone, median (SD)	Score for n ES used with a pMDI, median (SD)
Q1. How does your asthma make you feel today?	3.0 (1.0)	3.0 (1.0)*
Q2. How much does your asthma bother you when you run, exercise, or play sports?	2.0 (1.0)	2.0 (1.0)*
Q3. Do you cough because of your asthma?	2.0 (0)	2.0 (1.0)
Q4. Do you wake up during the night because of your asthma?	3.0 (1.0)	3.0 (1.0)
Q5. During the past 4 weeks, how many days did your child have any daytime asthma symptoms?	4.0 (2.0)	4.0 (1.0)*
Q6. During the past 4 weeks, how many days did your child wheeze during the day because of asthma?	4.0 (2.0)	5.0 (1.0)
Q7. During the past 4 weeks, how many days did your child wake up during the night because of asthma?	4.0 (1.0)	5.0 (1.0)
Total score	22.0 (6.0)	24.0 (5.0)*

*Statistically significant ($P < .05$).

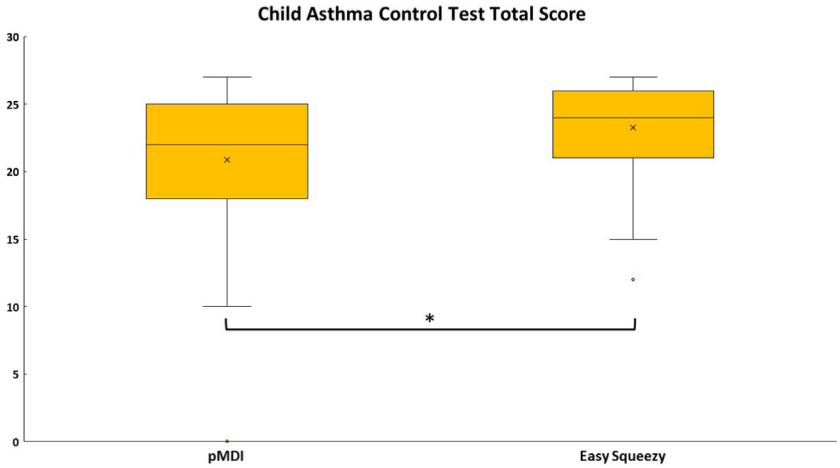

FIG 5. Total C-ACT score for our cohort members after they had used a pMDI alone and ES with a pMDI. Asterisk indicates statistical significance.

found using a ES with a pMDI to be easier than using a pMDI alone. This might mean that our cohort's previous knowledge of pMDI use did not impair their ability to use the ES. Third, our participants had relatively better PAQLQ scores than those reported in the literature,[30] probably because PAQLQ score has been measured predominantly in patients with poor asthma control rather than in a group such as ours, which had stable, well-controlled asthma. This, along with a sample size powered to ascertain differences in lung function testing, may have influenced our ability to show differences in changes in quality of life between groups. We addressed this concern by additionally looking at the proportion of patients with an increased PAQLQ score of more than the minimally important difference of 0.5 in the 2 groups. A larger sample size of approximately 2000 participants would be required to demonstrate differences in quality of life by using median PAQLQ scores. Lastly, we were unable to blind our participants, as they had to actively use the inhaler device.

One of the strengths of our study was that our participants were used as their own control. This reduced interparticipant bias. We had the same clinician throughout the study and single (blinded) impartial lung function measurement. This meant that there was no clinician variability and that the medications prescribed were the same for both arms of the study. We analyzed our data at every time point of data collection, as well as the difference from the previous time point. The baseline lung function test results were the same in group 1 and group 2. This provided us with multiple measures of the actual effect that each device had on the lung function of each of the participants.

Conclusion

The ability to use an inhaler and ability to use it with the best possible technique are important components of asthma management. These data suggest that young children, and possibly other individuals with limited hand strength or mobility, could benefit from using an assistive device such as the ES, which can also facilitate improved lung function test results and asthma control. The ES aids in achieving better asthma control and improved lung functioning.

DISCLOSURE STATEMENT

Disclosure of potential conflict of interest: R. Dey consults for Impulse Biomedical Pty Ltd. M. Levin consults for Impulse Biomedical Pty Ltd. K. B. Mapondela declares no relevant conflict of interest.

Clinical implications: Using a pMDI with the novel sleeve attachment device Easy Squeezy aids in significant improvement in asthma control and lung function, compared to the use of pMDI alone, in children between the age of 5 to 12 years.

REFERENCES

1. Abbafati C, Abbas KM, Abbasi-Kangevari M, Abd-Allah F, Abdelalim A, Abdollahi A, et al. Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet 2020;396:1204-22.
2. Chronic respiratory diseases: asthma. World Health Organization. 2020. Updated 2021. Available at: https://www.who.int/news-room/questions-and-answers/item/chronic-respiratory-diseases-asthma. Accessed May 30, 2021.
3. Braido F, Chrystyn H, Baiardini I, Bosnic-Anticevich S, van der Molen T, Dandurand RJ, et al. "Trying, but failing"—the role of inhaler technique and mode of delivery in respiratory medication adherence. J Allergy Clin Immunol Pract 2016;4:823-32.
4. Ciciliani AM, Langguth P, Wachtel H. Handling forces for the use of different inhaler devices. Int J Pharm 2019;560:315-21.
5. Beukes GL, Levin M, Sivarasu S. The paediatric metered dosage inhaler (pMDI) sleeve attachment. Paper presented at the 2017 Design of Medical Devices Conferences. April 10-13, 2017. Minneapolis, MN.
6. Mapondela KB, Dey R, Levin M. Usability study of a sleeve attachment device for enhancing ease of use of metered dose inhalers in children. South African Med J 2022;112:842-9.
7. Nakada H, Aomori T, Mochizuki M. Effect of a lever aid on hand strength required for using a handheld inhaler correctly. Int J Pharm 2021;596:120249.
8. Juniper EF, Guyatt GH, Ferrie PJ, Griffith LE. Measuring quality of life in asthma. Am Rev Respir Dis 1993;147:832-8.
9. Juniper EF, Guyatt GH, Feeny DH, Ferrie PJ, Griffith LE, Townsend M. Measuring quality of life in children with asthma. Qual Life Res 1996;5:35-46.
10. Liu AH, Zeiger R, Sorkness C, Mahr T, Ostrom N, Burgess S, et al. Development and cross-sectional validation of the Childhood Asthma Control Test. J Allergy Clin Immunol 2007;119:817-25.
11. Bime C, Gerald JK, Wei CY, Holbrook JT, Teague WG, Wise RA, et al. Measurement characteristics of the childhood Asthma-Control Test and a shortened, child-only version. Prim Care Respir Med 2016;26:16075.
12. Imamura Y, Kawayama T, Kinoshita T, Sakazaki Y, Yoshida M, Takahashi K, et al. Poor pharmacological adherence to inhaled medicines compared with oral medicines in Japanese patients with asthma and chronic obstructive pulmonary disease. Allergol Int 2017;66:482-4.
13. George M, Bender B. New insights to improve treatment adherence in asthma and COPD. Patient Prefer Adherence 2019;13:1325-34.
14. AlOlayan AM, Alhammad MA, Almutairi AA, Alshamari MT, Albuhairi S. Adherence to asthma controller therapy among children in Majmaah City, Saudi Arabia. Cureus 2021;13:e14633.
15. Boutopoulou B, Koumpagioti D, Matziou V, Priftis KN, Douros K. Interventions on adherence to treatment in children with severe asthma: a systematic review. Front Pediatr 2018;6:232.
16. Gamble J, Stevenson M, McClean E, Heaney LG. The prevalence of nonadherence in difficult asthma. Am J Respir Crit Care Med 2009;180:817-22.
17. Lehane E, McCarthy G. Intentional and unintentional medication non-adherence: a comprehensive framework for clinical research and practice? A discussion paper. Int J Nurs Stud 2007;44:1468-77.
18. Chen SH, Yin TJC, Huang JL. An exploration of the skills needed for inhalation therapy in schoolchildren with asthma in Taiwan. Ann Allergy Asthma Immunol 2002;89:311-5.
19. Hirose M, Kondo R, Horiguchi T. Use of assist devices to actuate pressurized metered-dose inhalers in elderly patients with asthma. Pulm Ther 2021;7:145.
20. McFadden ER. Improper patient techniques with metered dose inhalers: clinical consequences and solutions to misuse. J Allergy Clin Immunol 1995;96:278-83.
21. Levy ML, Hardwell A, McKnight E, Holmes J. Asthma patients' inability to use a pressurised metered-dose inhaler (pMDI) correctly correlates with poor asthma control as defined by the global initiative for asthma (GINA) strategy: a retrospective analysis. Prim Care Respir J 2013;22:406-11.
22. Lindsay JT, Heaney LG. Nonadherence in difficult asthma - facts, myths, and a time to act. Patient Prefer Adherence 2013;7:329.
23. Ayele AA, Tegegn HG. Non adherence to inhalational medications and associated factors among patients with asthma in a referral hospital in Ethiopia, using validated tool TAI. Asthma Res Pract 2017;3:7.
24. Aberhe W, Hailay A, Zereabruk K, Mebrahtom G, Haile T. Non-adherence to inhaled medications among adult asthmatic patients in Ethiopia: a systematic review and meta-analysis. Asthma Res Pract 2020;6:1-8.
25. Jamal S, Menon B, Yousoof M, Vardhan H. Reason for non-compliance to inhaled medications among adult patients of asthma and COPD attending outpatient department in a tertiary care hospital. Eur Respir J 2016;48:PA852.
26. Pearce CJ, Fleming L. Adherence to medication in children and adolescents with asthma: methods for monitoring and intervention. Expert Rev Clin Immunol 2018;14:1055-63.
27. Gillette C, Rockich-Winston N, Kuhn JBA, Flesher S, Shepherd M. Inhaler technique in children with asthma: a systematic review. Acad Pediatr 2016;16:605-15.
28. Barbara S, Kritikos V, Anticevich SB. Inhaler technique: does age matter? A systematic review. Eur Respir Rev 2017;26:170025.
29. Hagmolen of ten Have W, van De Berg NJ, Bindels PJE, van Aalderen WMC, van der Palen J. Assessment of inhalation technique in children in general practice: increased risk of incorrect performance with new device. J Asthma 2008;45:67-71.
30. Karandeniz P, Ozdogan S, Emecen DA, Oncul U. Asthma control test and pediatric asthma quality of life questionnaire association in children with poor asthma control. Turk J Pediatr 2016;58:464-72.