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Original Research

Efficacy of a device for training metered dose inhaler breathing proficiency: a crossover, double-blind, pilot trial in healthy volunteers

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Abstract

Background: The accurate administration of inhalation medications, including metered dose inhalers (MDI), is crucial for achieving desired treatment outcomes in patients with chronic airway diseases. A simple, inexpensive, and validated device for measuring respiratory force, the NU_spiroBreathe (NUB), has been invented. Although preliminary use of NUB indicated its potential as a training tool for improving breathing proficiency among MDI users, its efficacy in this application has not yet been studied. **Objective:** This study aimed to examine the efficacy of NUB in training MDI breathing proficiency among healthy volunteers. **Methods:** A mixed-method pilot study was conducted, combining a crossover, double-blinded, placebo-controlled trial with an AI-assisted qualitative study. Healthy participants were instructed to perform oral inhalation using NUB, a placebo MDI (pMDI), and a NUB-assisted MDI (NUB-MDI) in a crossover manner. MDI breathing proficiency was assessed by measuring inhalation time (Ti) and inhalation force (Fi). Cardiopulmonary safety was evaluated using blood pressure (BP), heart rate (HR), and arterial oxygen saturation (SpO2). Participants' opinions on NUB and other interventions were collected via a self-administered questionnaire. **Results:** A total of 30 participants completed the trial. They were healthy adults with an average age of 22.05 years, predominantly females. None of them had experience with any oral inhalation medications. Compared to the pMDI, the mean Ti for both NUB and NUB-MDI were statistically higher with the mean differences of 6.73 seconds [95% confidence interval (CI) 3.22 to 10.245, $p < .001$] and 6.10 seconds [95%CI 3.00 to 9.20, $p < .001$], respectively. While no significant difference in Ti was found between NUB and NUB-MDI, the mean Fi for NUB-MDI was marginally higher than that of the NUB group (mean difference of 1.48 cmH2O, [95%CI 0.36 to 2.60, $p = .011$]). Cardiopulmonary parameters showed no statistical changes. Content analysis of participants' opinions corroborated the quantitative findings. **Conclusion:** The NUB device could serve as a useful training tool for improving MDI breathing proficiency. However, further studies in real-world clinical settings were warranted (registration number: TCTR20230401004)

Keywords: metered dose inhaler, MDI, breathing proficiency, NU_spiroBreathe

INTRODUCTION

The optimal selection and administration of inhalation medications, such as metered dose inhalers (MDI), play a pivotal role in the management of chronic airway diseases, including asthma and chronic obstructive pulmonary disease (COPD).[1, 2] Although prescribing inhalation therapies according to established treatment guidelines should enhance the efficacy and safety of therapeutic regimens, medication adherence and accurate administration with the correct technique are critical determinants for achieving desired treatment outcomes.[3] Inhalation medications are designed to deliver the active drug to pathological areas within the airway. Improper inhalation techniques can result in insufficient drug delivery to the intended sites, leading to compromised therapeutic outcomes, uncontrolled disease symptoms, frequent or persistent exacerbations, disease progression, deleterious complications, impaired quality of life (QoL), and increased healthcare costs.[4] Adverse reactions, such as oropharyngeal candidiasis and hoarseness, may also occur with a higher incidence due to drug distribution and deposition in off-target areas.[5]

Despite the availability of several auxiliary measures to support the correct MDI usage, such as spacers, placebo medication samples, demonstrations, and various educational materials, issues with the inhalation technique persist.[6, 7] While these tools are suitable for initially teaching patients to understand and become familiar with their medications, they may not effectively improve inhalation techniques or empower patients' self-efficacy. Therefore, a tool that trains the patients to correctly use their inhalation medications by objectively assessing and providing instantaneous feedback on MDI breathing proficiency is warranted. Such a tool could progressively improve inhalation technique, self-efficacy, and medication adherence. Additionally, the selection of inhalation medications guided by the tool's testing results could benefit

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prescribers.

An innovative inhalation training device, referred to as NU_ spiroBreathe (NUB, Thailand petty patent number 12019), has been developed. The tool quantifies respiratory quality related to oral inhalation and exhalation dynamics, encompassing respiratory force and respiratory time via the oral route.[8] The measurement accuracy, precision, and safety of the tool have been determined in controlled laboratory settings among healthy volunteers over 4-8 weeks. [9] No significant changes in hemodynamic parameters or respiratory function, as assessed by blood pressure (BP), heart rate (HR), and arterial oxygen saturation (SpO_2) monitoring, were evidenced.[9] Early findings suggested the potential of using NUB as a training tool for MDI users. This pilot study aimed to examine the efficacy of NUB in training MDI breathing proficiency in healthy volunteers.

METHODS

This was a mixed-method, pilot study combining a crossover, double-blinded clinical trial with an AI-assisted qualitative study. The trial and data collection were conducted between April and May 2024 at the Medical and Pharmacy Innovation Research Unit, Faculty of Pharmaceutical Sciences, Naresuan University, Thailand. The study protocol was registered in the Thai Clinical Trial Registry (TCTR20230401004) and received ethical approval from the ethics committee of the University (No. P3-0063/2566).

Outcomes and measurement

The primary outcomes were the differences in MDI breathing proficiency among NUB, placebo MDI (pMDI), and NUB-assisted MDI (NUB-MDI). MDI breathing proficiency was assessed in terms of inhalation time (Ti) and inhalation force (Fi). Inhalation time was defined as the longest inspiratory period the participants could achieve, reflecting the "breath in slowly" technique. Inhalation force, measurable by NUB, reflected the "breath in deeply" technique. The secondary outcomes were: 1) the cardiopulmonary safety of NUB, and 2) participants' opinions towards the devices. Cardiopulmonary safety parameters included BP, HR, and SpO_2, which were measured using calibrated stopwatches, blood pressure monitoring devices, and pulse oximeters. Participants were asked open-ended questions regarding their opinions immediately after completing all the tests.

Trial tool

NUB is a simple, inexpensive, validated device specifically designed to measure respiratory force during both inhalation and exhalation. As depicted in Figure 1, the cylindrical device has closed ends on both sides, with a screw cap at the top and a drilled bottom for the insertion of a central airway tube. This tube is connected to the mouthpiece for inhalation or exhalation. Inside the device, another one-sided, open-end, upside-down cylinder covers the central airway tube. A specific amount of water is filled in the outer cylinder. When held upright, the water levels inside the outer and inner cylinders are equal. Changes in air pressure in the inner cylinder, caused by exhalation or inhalation, result in changes in the water height in both the outer and the inner cylinders. Scales indicating the height of the filled water are labeled on the device's outer surface. This works based on the principle of static fluid pressure (P), which depends on its height (h) when density (ρ) and gravity (g) are constant ($P = \rho * g * h$). Thus, the respiratory force can be read in terms of the change in water height. The device has been validated with a digital pressure gauge meter (Testo 435-1-Multi-function climate measuring instrument) with 100% accuracy [8, 9]

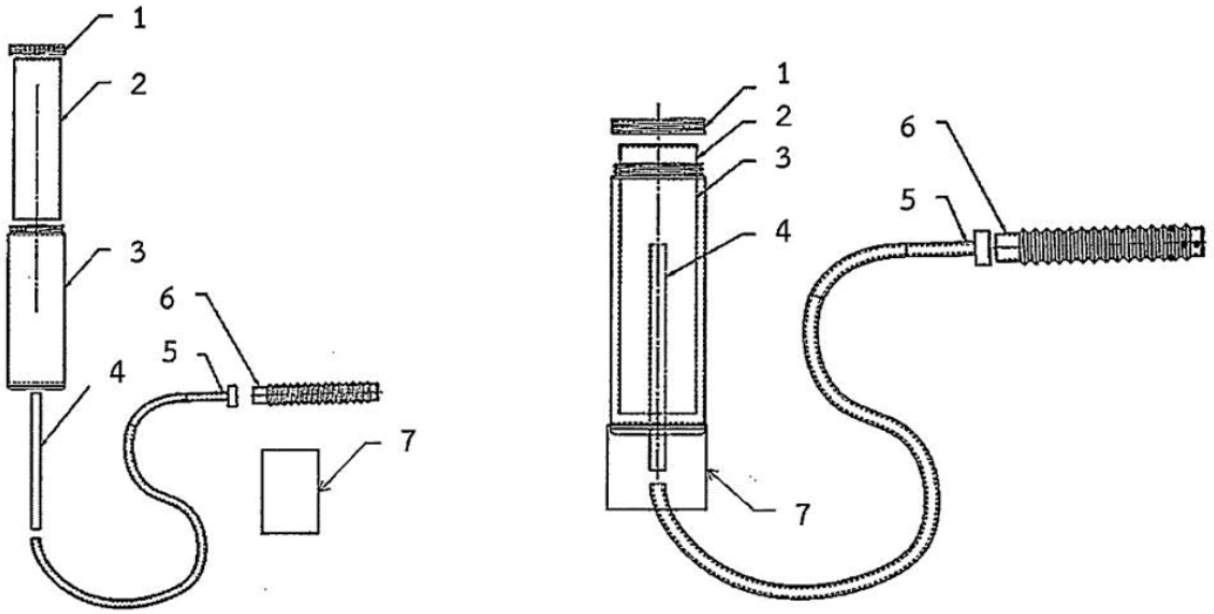

Figure 1. The NU_spiroBreathe (NUB) device
The indicating numbers are as follows: 1 = screw cap, 2 = inner cylinder, 3 = outer cylinder, 4 = central airway tube, 5 = breathing tube, 6 = mouthpiece, and 7 = supporting base.

Trial population & protocol

Participants were randomly recruited at Naresuan University. Before enrollment, each participant was thoroughly informed of the study protocol and provided their written informed consent voluntarily. The inclusion criteria were healthy university students aged 18 years or above. Students were excluded if they 1) had been diagnosed with chronic airway diseases, 2) had ongoing acute airway diseases, 3) had experience with inhalation medications, or 4) had known hypersensitivity reactions to plastic. According to Hertzog et al., and Whitehead et al., a total sample size of 30 participants was chosen for this pilot cross-over study. [10, 11] The enrolled participants were verbally explained the trial protocol and demonstrated the proper inhalation technique (breathing in deeply and slowly through the mouth) via videotape. They were then asked to perform oral inhalation using NUB, pMDI, and NUB-MDI in a cross-over manner. Each device was placed at three separate stations, concealed in black opaque boxes to ensure participants were unaware of the device at each station. Six possible sequences of the stations were randomly assigned to the participants by SW and SI, using a lottery ticket method, to eliminate the potential influence of different sequences of the devices. Participants were instructed to sit in a comfortable chair for 5 minutes between each device as a washout period. Before and after each station, BP, HR, and SpO_2 were measured. These cardiopulmonary parameters were used for the secondary outcome evaluation and to reduce potential biases caused by excitement or fatigue. After completing the third station, participants answered questions: "How do you feel about your inhalation when using each device?" and "How do you feel after using each device?" in Thai using a self-administered survey form. The trial protocol flow diagram is presented in Figure 2.

Data analysis

Quantitative data analysis was performed by PP and KY by using IBM® SPSS® statistics version 29. Both PP and KY were blinded to the devices used in each data set to maintain the double-blinding of the trial. Demographic data and cardiopulmonary parameters were presented as mean with standard deviation (SD). Comparisons of inhalation time, inhalation force, and cardiopulmonary parameters among stations were performed using repeated-measure analysis of variance (RM-ANOVA) or paired T-tests. Statistical significance was set at $p < 0.05$. The opinions of participants on the open-ended questions were translated and initially analyzed using OpenAI's ChatGPT version 4 with the following prompts: Prompt 1) "These texts are opinions regarding three inhalation devices; please translate the entire text into English," and Prompt 2) "Please identify emerging themes and perform content analysis comparing these three groups". PP and KY reviewed and edited the content as needed to ensure a literal translation without altering the essential meaning of the content.

RESULTS

Characteristics of the trial participants

Thirty participants completed the trial. They were healthy adults, predominantly female, with no known major health concerns or active, ongoing airway diseases. Their body mass indexes, chest circumference, and cardiopulmonary parameters were within normal ranges, as shown in Table 1.

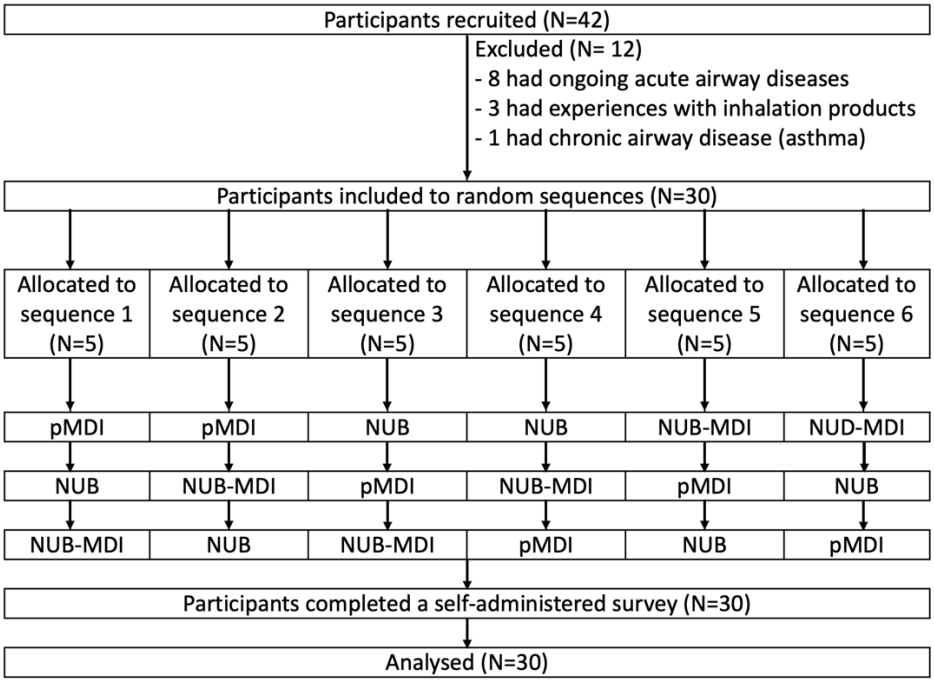

Figure 2. Trial protocol flow diagram
Abbreviations: pMDI, placebo metered-dose inhaler; NUB, NU_spiroBreathe; NUB-MDI, NUB-assisted MDI.

Table 1: Characteristics of the trial participants.		
Variables	**Mean**	**SD**
Age (years)	22.05	1.11
Female (n; %)	21 (70%)	
Body mass index (BMI; kg/m^2)	24.70	5.09
Chest circumference (cm)	91.66	9.92
Systolic blood pressure (SBP; mmHg)	107.89	0.77
Diastolic blood pressure (DBP; mmHg)	62.63	0.82
Heart rate (HR; bpm)	80.81	0.61
Blood oxygen saturation (SpO_2; %)	97.12	0.23

All participants reported having no experience with any oral inhalation medications.

Comparisons of MDI breathing proficiency

The mean inhalation time for the pMDI was considerably lower than for NUB and NUB-MDI, with statistically significant differences ($p < .001$ for both comparisons). However, no significant difference in inhalation time was observed between NUB and NUB-MDI, as shown in Table 2 and Figure 3. The mean inhalation force for NUB-MDI was marginally higher than the NUB group, with statistical significance ($p = .011$) (Figure 4).

Cardiopulmonary safety

No significant differences in SBP, DBP, HR, and SpO_2 were observed among pre- or post-procedures for the three devices (Table 3). These tests ensured that the participants' respiratory statuses remained stable during the trial. Furthermore, the findings indicate NUB is safe when used alone or in combination with MDI, as respiratory and hemodynamic parameters were unaffected.

Participants' opinions towards NUB and other interventions

Content analysis revealed four common themes corresponding to the survey questions: 1) inhalation time, 2) inhalation force, 3) depth of inhalation, and 4) post-procedure changes or feelings. Perceived inhalation time, inhalation force, and depth of inhalation were higher when using NUB or NUB-MDI. These findings were aligned with quantitative data, confirming the initial hypothesis that NUB could be used as a training tool for MDI breathing proficiency (Table 4).

DISCUSSION

This preliminary study aimed to evaluate the efficacy of the innovative inhalation training device, NU_spiroBreathe (NUB), among healthy volunteers. The device is non-toxic, safe, simple, economical, and validated for measuring respiratory force.[9] It is anticipated to be a useful training tool for improving MDI breathing proficiency, a critical component of care for patients with chronic airway diseases.[12-14] In this study, inhalation time and inhalation force were used as indicators for MDI breathing proficiency. The results showed that inhalation times when using NUB and NUB-MDI were significantly longer than with pMDI, indicating an improved "breath in slowly" technique. Inhalation forces when using NUB or NUB-MDI were approximately 10 cmH_2O, an optimal threshold for an adequate delivered dose for inhalation medication.[15] These findings suggested that training with NUB could enhance MDI breathing proficiency (slowly and deeply, as evidenced by increased inhalation time and inhalation force, respectively). The content analysis of participants' opinions also indicated that NUB and NUB-MDI led to prolonged and deeper inhalations. Cardiopulmonary parameters remained stable throughout the trial, further supporting the safety and potential benefits of NUB for MDI proficiency training.

Selecting appropriate inhalation devices based on individual pulmonary function is vital for achieving desired treatment outcomes.[1, 13, 16] MDIs are suitable for patients with a wide range of inhalation forces, as drug delivery is controlled by patient triggering. On the contrary, dry powder inhalers (DPI) require stronger and deeper inspiratory efforts for de-aggregation and delivery of the active drug, making them suitable for patients with intact or adequate inhalation forces.[17] The inhalation force measured by NUB could guide the selection of appropriate inhalation devices, similar to the use of commercial inspiratory flow meters like In-Check® DIAL.[18] Therefore, rational device selection, correct breathing technique, improved medication adherence, and enhanced treatment effectiveness are anticipated with NUB, as evidenced in trials with In-Check® DIAL.[7, 18, 19]

Table 2: Comparisons of MDI breathing proficiency					
Variable		**pMDI**	**NUB**	**NUB-MDI**	**P-value***
Inhalation time (seconds)	Mean	7.0	13.73	13.10	< .001
	SD	7.39	5.00	6.90	
	Mean difference	pMDI vs NUB: 6.73 [95%CI 3.22 to 10.245]			< .001
		pMDI vs NUB-MDI: 6.10 [95%CI 3.00 to 9.20]			< .001
		NUB vs NUB-MDI: -.633 [95%CI -2.90 to 1.64]			1.000
Inhalation force (cmH_2O)	Mean	-	9.69	11.18	.011
	SD	-	4.12	4.04	
	Mean difference	NUB vs NUB-MDI: 1.48 [95%CI 0.36 to 2.60]			

Abbreviations: pMDI, placebo metered-dose inhaler; NUB, NU_spiroBreathe; NUB-MDI, NUB-assisted MDI; cmH_2O, centimeters of water. * tested by repeated-measure analysis of variance (RM-ANOVA) or paired T-tests.

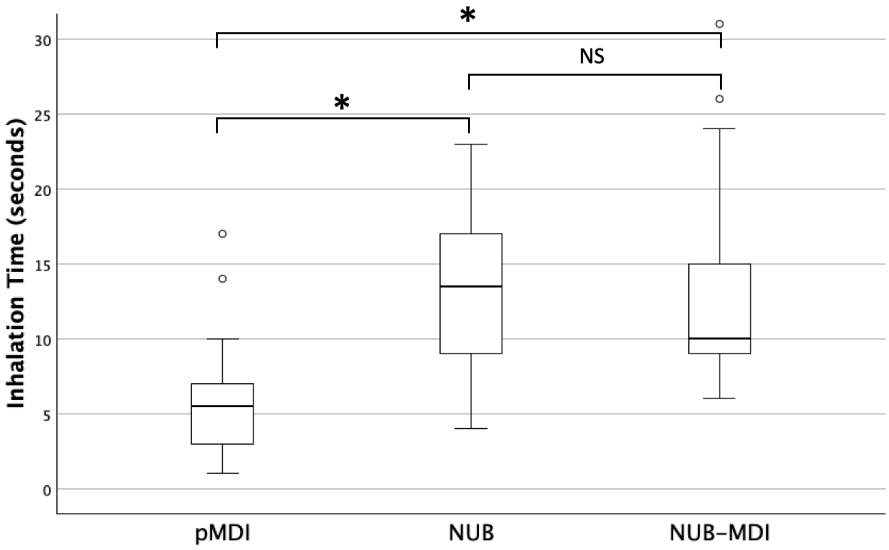

Figure 3. Inhalation time (seconds)
Abbreviations: pMDI, placebo metered-dose inhaler; NUB, NU_spiroBreathe; NUB-MDI, NUB-assisted MDI. * indicates statistical significance, NS indicates non-statistical significance, tested by paired T-tests.

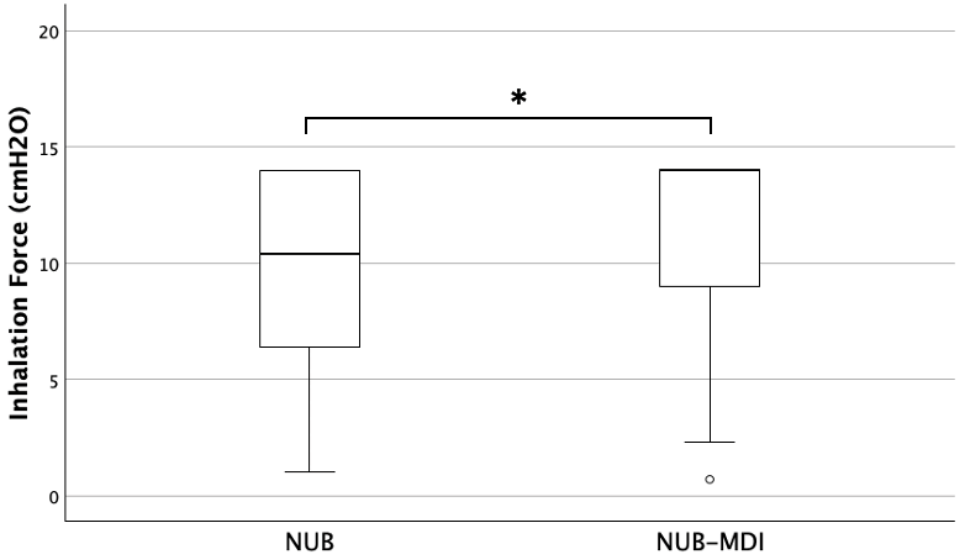

Figure 4. Inhalation force (Fi, cmH2O)
Abbreviations: NUB, NU_spiroBreathe; NUB-MDI, NUB-assisted MDI. * indicates statistical significance, tested by paired T-tests.

Table 3 Cardiopulmonary safety

Variables		SBP (mmHg, mean [SD])	DBP (mmHg, mean [SD])	HR (bpm, mean [SD])	SpO_2 (%, mean [SD])
pMDI	Before	107.00 [11.31]	62.03 [8.62]	80.27 [9.67]	97.43 [0.97]
	After	108.73 [9.65]	62.80 [10.90]	80.17 [9.94]	97.00 [1.70]
NUB	Before	108.33 [11.89]	63.57 [9.12]	81.47 [10.93]	97.07 [1.23]
	After	110.03 [10.98]	62.63 [8.14]	80.87 [11.03]	97.67 [0.88]
NUB-MDI	Before	108.33 [11.51]	62.30 [8.59]	80.70 [10.51]	97.00 [1.89]
	After	111.433 [10.32]	62.03 [9.48]	80.37 [9.84]	97.53 [0.78]
P-value*		0.134	0.957	0.800	0.099

Abbreviations: pMDI, placebo metered-dose inhaler; NUB, NU_spiroBreathe; NUB-MDI, NUB-assisted MDI; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; SpO_2, arterial oxygen saturation; mmHg, millimeters of mercury; bpm, beats per minute. * tested by repeated-measure analysis of variance

Table 4 Opinions towards NUB and other interventions	
Themes	Opinions and example quotations
#1: Inhalation time	100% (12/12) participants reported shorter inhalation time when compared with other devices. On the contrary, 100% (7/7) and 75% (6/8) of them reported longer inhalation time when using NUB and NUB-MDI, respectively. • "It flows very fast, I cannot inhale slowly as directed" [pMDI, subject #13] • "I can inhale deeper and longer than other devices" [NUB-MDI, subject#4]
#2: Inhalation force	77.8% (14/18) feel they did not need additional inhalation force when using MDI, but majority of them used additional force when using NUB or NUB-MDI (65%; 15/23 and 57.14%; 12/21, respectively). • "It is easier to inhale than testing devices in other stations" [pMDI, subject #12] • "I use more breathing force and feel that my lungs are expand per the incoming air" [NUB, subject #26]
#3: depth of inhalation	When using NUB or NUB-MDI, 100% (7/7 and 9/9) reported their inhalation were deeper than usual. Depth inhalation had been observed only 16% (1/6) when using MDI. • "I cannot inhale deeply. It like air come-in and out quickly" [pMDI, subject 17] • "Since it has airflow resistance, I can maintain my inhalation as long and deep as suggested" [NUB, subject #24] • "It is harder to inhale by this device, but I can inhale longer and forceful. I feel more air get into my lungs with this device" [NUB-MDI, subject #13]
#4: post-procedure changes or feeling	Almost participants reported no changes or abnormal feelings following inhalation through the devices (80% of MDI, 63.33% of NUB, and 66.67% of NUB-MDI). The rests of them feel tried or discomfortable. However, these feeling were transient and mild. Two participants reported improved inhalation technique following NUB or NUB-MDI. • "I feel a bit discomfort like after drinking water from a too small straw " [NUB, subject #18] • "I've just found out how to take a deep breathe. I think I can have deeper breathing-in" [NUB-MDI, subject #24]

Abbreviations: pMDI, placebo metered-dose inhaler; NUB, NU_spiroBreathe; NUB-MDI, NUB-assisted MDI

This study has strengths and limitations worth noting. The major strengths include the double-blind, crossover design and the combination of objective outcome measurement with qualitative data analysis. However, the current study is a pilot with a small sample size, limited to healthy adult volunteers without experience with oral inhalation devices. Therefore, the generalizability of the findings to broader populations, such as patients with chronic airway diseases, children, or the elderly, is limited, necessitating further studies.

CONCLUSION

This study demonstrated that higher inhalation force and longer inhalation time were observed both objectively and subjectively when using NU_spiroBreathe (NUB), with or without MDI. These findings highlight that the appropriate inhalation technique for MDI can be improved with NUB. No abnormal cardiopulmonary safety indicators were found, supporting the safety of NUB. Therefore, NUB has the potential to be an effective training tool for enhancing MDI breathing proficiency.

AUTHORS' CONTRIBUTIONS

PP: Conceptualization, data curation, formal analysis, investigation, methodology, project administration, resources, visualization, writing-original draft, review & editing. SW and SI: Investigation, visualization, review & editing. KY: Conceptualization, data curation, formal analysis, methodology, visualization, writing-original draft, review & editing.

CONFLICT OF INTEREST

None.

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