Indonesian Journal of Pharmaceutics
IdJP
ISSN : 2597-8748

Vol. 7, Issue 1, 2025 (11-24)
http://journal.unpad.ac.id/IdJP

Standardized vs. manufacturer leaflet techniques for inhalation devices: A randomized controlled trial

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Submitted: 11/02/2025, Revised: 28/04/2025, Accepted: 08/05/2025, Published: 26/07/2025

ABSTRACT

Variations in inhaler leaflet information may affect the understanding of inhalation techniques.We aimed to determine the effectiveness of standardized and package leaflets in describing correct inhaler usage and to identify any existing pitfalls. This prospective, randomized, open-labeled, blinded endpoint study with a 2 × 2 factorial design was conducted in August2019. We included 38 pharmacy students who did not use inhalers and allocated them into 4 groups: 2 groups used standardized leaflets (with 1 and 2 devices, respectively), while the other 2 groups used package leaflets (with 1 and 2 devices, respectively). The participants were instructed on the essential techniques of using each inhaler and asked to practice using the assigned leaflets until the procedures were completely learned. The primary outcome was evaluated the following day as the score rate (%) of the technique. The effectiveness of leaflets stratified by the number of devices was tested using a two-way analysis of variance with an interaction term. We compared techniques with different implementation rates between groups to identify potential pitfalls. The differences and 95% confidence interval in the score rate (%) between the groups using standardized or package leaflets were significantly different in the two-device group analysis. The implementation rate of certain instructions between the two-device groups was higher when using standardized leaflets for both devices. Standardized leaflets enhanced the

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https://doi.org/10.24198/idjp.v7i1.61601

comprehension of inhalation techniques for multiple devices due to their normalized wording. These findings may help improve package leaflets and healthcare professionals' instructions, thereby promoting appropriate inhaled medication use.

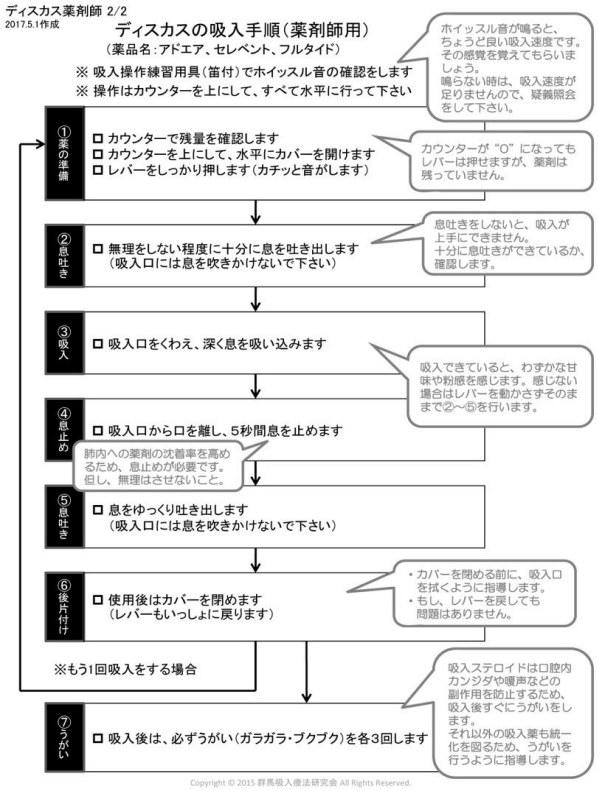
Keywords: inhalation technique, asthma, chronic obstructive pulmonary disease, standardized leaflet, score rate

1. Introduction

The use of inhaled medications has become the mainstay form of treatment for asthma and chronic obstructive pulmonary disease (COPD) [1-3]. A systematic review revealed a strong association between immature inhalation technique and poor disease outcomes [4], urging patients to learn the appropriate inhaler usage technique for achieving the desired therapeutic effect.

Several studies have shown the usefulness of leaflets providing instructions regarding inhalation techniques. A study examined the contribution of illustrations in improving instruction comprehension and inhaler use [5], whereas another evaluated the effectiveness of leaflets with pictograms [6]. Another study investigated the benefits of simplified leaflets for following the correct technique for using a pressurized metered-dose inhaler (pMDI) in patients with asthma who have limited literacy skills [7]. Despite the availability of different types of inhalation devices currently on the market, the template of instructions for these devices, provided by pharmaceutical companies as package leaflets, is not standardized. In addition, the terminology used in the leaflets of various devices often differs, regardless of shared device parts or procedures. These complexities can confuse patients who use multiple inhalation devices. In a previous study, patients who used different types of inhalers, such as DPIs and MDIs, made more inhalation errors than those who used just one inhaler or a combination of DPIs. Consequently, the authors recommended prescribing only one type of inhaler whenever possible [8]. Owing to the diversity in inhalation devices, providing usage instructions for the correct inhalation technique remains challenging even for healthcare professionals [9, 10]. Therefore, instructional leaflets must be made easy to understand for both patients using inhalers and healthcare workers prescribing them or instructing patients intheir use.

In 2011, the Gunma Inhalation Therapy Study Group, cooperating with hospitals and community pharmacies, created original instruction leaflets with standardized wording (standardized leaflet). This leaflet outlines the inhalation procedure in seven steps: medicine preparation, exhalation, inhalation, breath-holding, exhalation, device assembly, and gargling (Fig. 1).



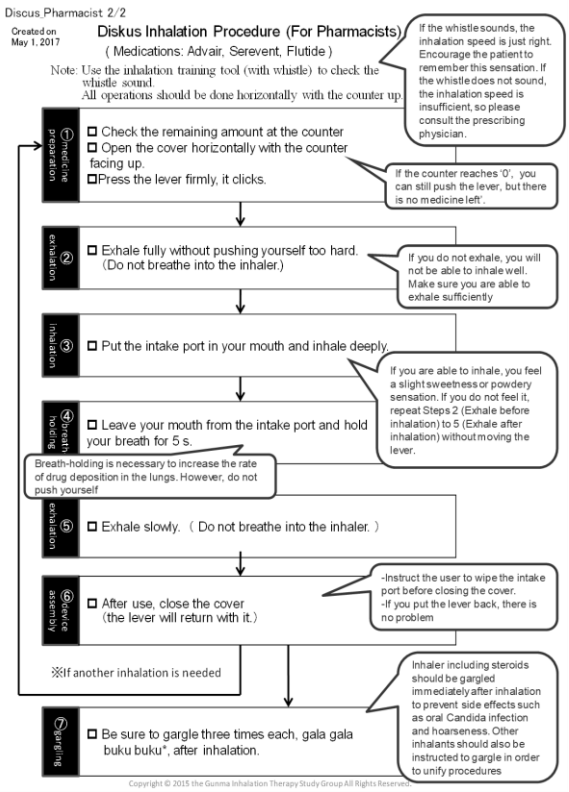
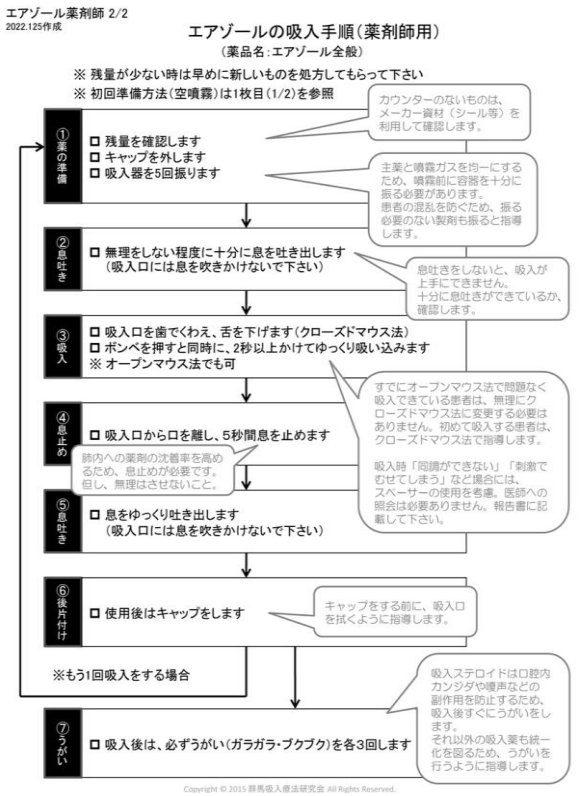


Fig. 1 (a)



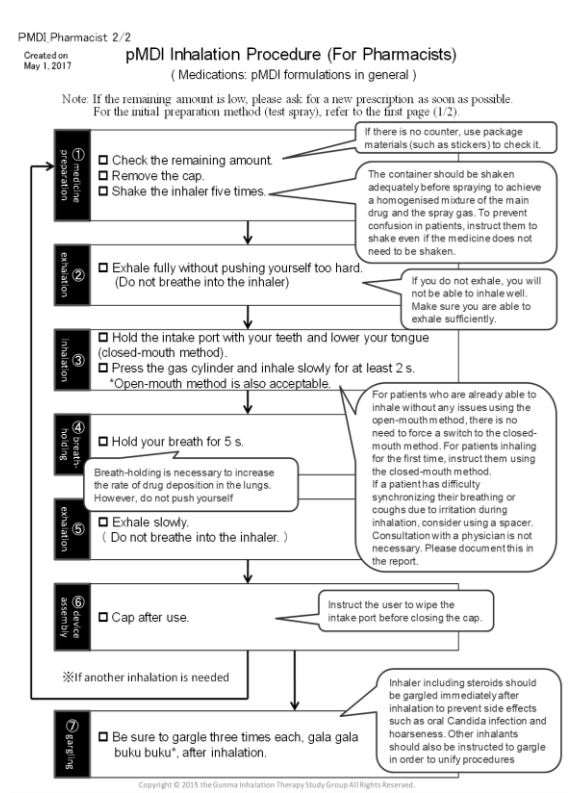


Fig. 1 (b)

Fig. 1 Standardised leaflets for (a) dry powder inhaler (Diskus®) and (b) pressurized metered-dose inhaler (Meptin Air®)

In this leaflet, the terminology and description are standardized and unified across various inhalers to the greatest extent possible. These unified expressions, which include factors such as inhalation speed for a pMDI [11], duration of breath-holding [12], and gargling method and frequency [13], were derived from the findings of previous studies. We hypothesize that our standardized procedures could enhance inhalation techniques, particularly for patients who use multiple inhalation devices. However, the necessity and significance of using a standardized leaflet for acquiring information about an inhalation device usage technique have not been previously demonstrated.

We conducted a randomized controlled trial (RCT) with a 2 × 2 factorial design to determine the effectiveness of standardized and package leaflets in explaining the correct usage of an inhaler and to identify any existing pitfalls.

2. Methods

2.1 Study design

This prospective, randomized, open-labeled, blinded endpoint study had a 2 × 2 factorial design and was conducted over two consecutive days in August 2019.

2.2 Participants

Pharmacy students in their first to fourth years who had not attended a practical lecture on inhalation techniques were included as adults with a general understanding but without inhalation technique skills. Students using inhalers were excluded from the study. Prospective participants received an explanation of the study through written documents and made the voluntary decision to participate in the research. Those who wished to participate provided written informed consent. Participant recruitment for the trial was conducted from approximately one month to one week before the trial commenced.

2.2.1 Randomization

The participants were randomly assigned to four groups according to a computer-generated random sequence table: group A (one device with a standardized leaflet), group B (two devices with a standardized leaflet), group C (one device with a package leaflet), and group D (two devices with a package leaflet for each device). A statistician created an allocation table using a computer-generated random number sequence. Prior to the day of the study, another researcher assigned groups to a list of participants that was sorted by student ID number after stratifying for prior inhaler use. Participants were informed of their allocation group on the day of the study. Two types of inhalation devices were used: dry-powder inhaler (DPI) and pMDI, with Diskus® (GSK plc., London, UK) as DPI and Meptin Air® (Otsuka Pharmaceutical Company, Tokyo, Japan) as pMDI. DPI was used in the one-device groups (groups A and C), whereas both DPI and pMDI were used in the two-device groups (groups B and D). The standardized leaflet was used for the intervention groups, whereas the package leaflet, with check boxes added for evaluating points, was used for the control group.

2.2.2 Intervention and outcome

The study was conducted over 2 days at the Takasaki University of Health and Welfare (Takasaki, Gunma Prefecture, Japan). On day 1, proper device usage was explained in a group training format using leaflets assigned to each group. Subsequently, the participants practiced inhalation techniques individually,

followed by the assessment of their skills. If participants did not use the correct technique, they reviewed the leaflet and repeated the practice and assessment until they achieved proficiency for all evaluation criteria. The next day, following similar evaluation criteria, the appropriateness of inhalation techniques was assessed. Notably, on day 2, the grouping of participants was not disclosed to the evaluators, ensuring that the assessment was conducted under blinded conditions.

The primary endpoint was the scoring rate for the practical test of inhalation techniques. The scoring rate (%), calculated as the ratio of the number of items that could be performed with an appropriate technique to the total number of evaluation items (Table 1 and 2), was used as the primary evaluation metric.

Table 1. Differences in the implementation rates (%) for each item and evaluation point in DPI leaflets

	Evaluation item	Description in the standardized leaflet Groups A and B	Description in the package leaflet Groups C and D	Implementation rate (%)				Difference	
				A	B	C	D	A–C	B–D
1	Check the remaining amount at the counter	Check the remaining amount at the counter. "If the counter reaches "0," you can still push the lever, but there is no medicine left."	The counter indicates the number of medications remaining. Do not use it when the display shows "0."	90.9	100	90.9	87.5	0	12.5
2	Open the cover	Open the cover horizontally with the counter facing up.	Open the cover until you hear a "click" sound. Hold the cover with one hand, place the thumb of your other hand on the grip, and turn the grip until it stops (you will hear a click).	100	100	100	100	0	0
3	Press the lever firmly, and it clicks	Press the lever firmly, and it clicks.	Press the lever until you hear a "click" sound. Hold the mouthpiece (intake port) toward you and push the lever down to the grip (you will hear a click). #Do not operate the lever unless you are inhaling the medicine.	100	100	100	100	0	0
4	Exhale fully without pushing yourself too hard	Exhale fully without pushing yourself too hard. "If you do not exhale, you will not be able to inhale well. Make sure you are able to exhale sufficiently."	Exhale, (then put the mouthpiece [intake port] in your mouth, inhale hard and deep, "Soooo"). Exhale fully without pushing yourself too hard.	93.4	100	100	75.0	−6.6	25.0
5	Do not breathe into the inhaler	Do not breathe into the inhaler.	#Do not blow into the mouthpiece (intake port).	100	100	100	75.0	0	25.0

6	Keep the inhaler horizontal with the counter up (from when you press the lever to when you inhale)	#All operations should be done horizontally with the counter up. (Note: The instruction to hold the device horizontally is also described in the second procedure.)	Hold your inhaler flat, (Note: Continuation of the description of the step after exhaling to prepare for inhalation and just before inhalation)	100	100	100	75.0	0	25.0
7	Put the intake port in your mouth and inhale deeply	Put the intake port in your mouth and inhale deeply. "If you are able to inhale, you feel a slight sweetness or powdery sensation. If you do not feel it, perform steps (2) to (5) without moving the lever. (Note: 2: exhale before inhalation; 5: exhale after inhalation)."	Put the mouthpiece (intake port) in your mouth, and inhale deeply and strongly, "Soooo."	100	87.5	72.7	50.0	27.3	37.5
8	Leave your mouth from the intake port and hold your breath	Leave your mouth from the intake port and hold your breath for 5 s. "Breath-holding is necessary to increase the rate of drug deposition in the lungs. However, do not push yourself."	Leave the mouthpiece (intake port) from your mouth, and hold your breath for about 3–4 s.	100	100	100	100	0	0
9	For 3–4 s	Hold your breath for 5 s.	Hold your breath for 3–4 s.	100	100	100	100	0	0
10	Exhale slowly	Exhale slowly.	Then exhale slowly and gently, and return to your normal breathing.	100	100	100	87.5	0	12.5
11	Do not breathe into the intake port	(Do not breathe into the intake port.)	#Do not blow into the mouthpiece (intake port).	100	100	100	100	0	0
12	After use, close the cover until you hear a click	After use, close the cover (the lever will return with it) "Instruct the user to wipe the intake port before closing the cover. If you put the lever back, there is no problem."	Place your thumb on the grip, and turn it back to the point where it clicks to close the cover (the lever will return to its original position as well).	100	100	100	100	0	0
13	Gargle after inhalation	Be sure to gargle three times each, "Galagala, buku buku," after inhalation. "Inhalers that include steroids should be gargled immediately after inhalation to prevent side effects, such as oral *Candida* infection and hoarseness. Gargling should also be recommended for other inhalants in order to unify the procedures."	After inhalation, be sure to gargle to wash away any remaining medicine in the throat and mouth.	54.5	75.0	72.7	87.5	−18.2	−12.5

14	"Gala gala, buku buku (kuchu kuchu)"*	"Gala gala, buku buku."	"Gala gala (throat), kuchu kuchu (inside the mouth)."	45.5	75.0	72.7	87.5	−27.2	−12.5

Table 2 Differences in the implementation rates (%) for each item and evaluation point in pMDI leaflets

	Evaluation item	Description of the standardized leaflet Group B	Description of the manufacturer leaflet Group D	Implementation rate (%)		Difference
				B	D	B–D
1	Check the remaining amount	Check the remaining amount. "If there is no counter, use package materials (such as stickers) to check it."	When using a new inhaler device for the first time, the counter indicates "102." Shake the inhaler well, and spray it twice until it reaches "100" before use.	100	75.0	25.0
2	Remove the cap	Remove the cap.	Remove the cap.	100	100	0
3	Shake the inhaler	Shake the inhaler five times. "The container should be shaken adequately before spraying to achieve a homogenized mixture of the main drug and the spray gas. To prevent confusion in patients, instruct them to shake even if the medicine does not need to be shaken."	Shake the container well a few (several) times. #Is the push button in the up position?	100	50.0	50.0
4	Shake at least two times	Five times.	A few (several) times.	100	50.0	50.0
11	Hold your breath for at least 5 s	5 s.	A few (several) seconds.	100	100	0
12	Leave your mouth from the input port and exhale slowly	Exhale slowly (Do not breathe into the input port).	Exhale slowly.	100	87.5	12.5
13	Cap after use	Cap after use.	Put the cap on after use.	100	100	0
14	Gargle after inhalation	Be sure to gargle three times each, "Gala gala, buku buku," after inhalation.	Try to gargle after inhalation.	75.0	87.5	−12.5
15		"Gala gala, buku buku."	Not available.	—	—	

2.2.3 Sample size

We could not pre-calculate the sample size because of insufficient published data. The target number of cases was set at 25 for each group, totaling 100 cases, which was determined by the feasible number of participants. Owing to the unforeseen effect of the COVID-19 pandemic, the study deviated from the original design. However, this unexpected change led to the discovery of a statistically significant difference. Consequently, we decided to conclude the study at this stage and publish the findings.

2.3 Statistical analysis

The scoring rates (%) were compared among the groups. A two-way analysis of variance (ANOVA) was used to examine the effect of leaflets and the number of inhalation devices on the scoring rate (%). Statistical significance was set at $p < 0.05$. All analyses were performed using IBM SPSS Statistics for Windows, version 26 (IBM, NY, USA).

3. Results

Forty-two participants were enrolled in the study, of whom four (one from group B and three from group D) did not attend the trial and were, therefore, excluded. Finally, 38 students participated in the study, with 11 placed in group A, 8 in group B, 11 in group C, and 8 in group D (Table 3).

Table 3. Characteristics of the participants

	Group A n = 11 n (%)	Group B n = 8 n (%)	Group C n = 11 n (%)	Group D n = 8 n (%)
Sex				
Women	10 (90.9)	5 (62.5)	10 (90.9)	5 (62.5)
School year				
First	4 (36.4)	3 (37.5)	3 (27.3)	2 (25.0)
Second	4 (36.4)	3 (25.0)	5 (45.5)	5 (62.5)
Third	2 (18.2)	2 (25.0)	2 (18.2)	1 (12.5)
Fourth	1 (9.1)	1 (12.5)	1 (9.1)	0 (0)
History of inhaler treatment	8 (72.7)	5 (62.5)	7 (63.6)	6 (75.0)

The score rates for groups A, B, C, and D were 91.9%, 94.9% (mean of two devices), 93.5%, and 83.2% (mean of two devices), respectively (Fig. 2).

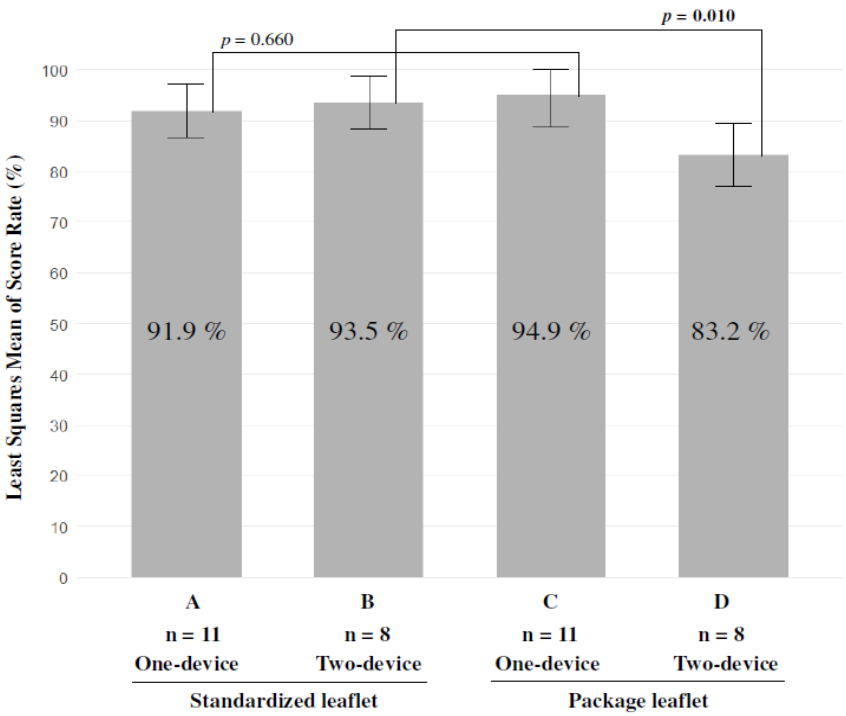


Fig. 2 Score rate (%) for each group

Bars indicate least squares means with standard errors. P values indicate differences in the score rate (%) between the two leaflet types for each number of devices (one or two), based on two-way ANOVA including an interaction term.

The two-way ANOVA, which included leaflet type and number of devices as main effects, showed that the p-values for the main effects of leaflet type and number of devices were 0.161 and 0.202, respectively. In contrast, the p-value for the interaction term was 0.024, indicating a significant difference in score rate (%) between the leaflet groups under the two-device condition (Fig. 3).

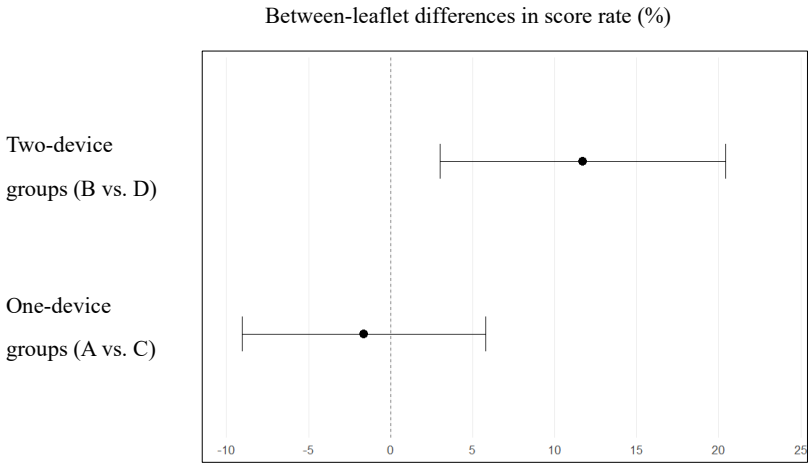


Fig. 3 Two-way ANOVA for the score rate (n = 38)

Estimated differences in the score rate between the standardized and package leaflets are shown for each device condition. Positive values indicate that the standardized leaflet use (groups A and B) led to higher scores than the package leaflet use (groups C and D). Dots represent least squares mean differences with 95% confidence intervals, based on a two-way ANOVA including an interaction termThe difference in the score rates of the standardized and package leaflets groups was -1.6 (95% confidence interval: -9.0–5.8) for the one-device groups (A vs. C, p = 0.651) and 11.7 (2.1–21.4, p = 0.021) for the two-device groups (B vs. D ; Table 4). We also observed that the interaction between factors, namely the number of devices and types of leaflets, was significant (Table 4).

Table 4. Mean difference in score rate with 95% confidence intervals for each group

	Group A n = 11 n (%)	**Group B n = 8 n (%)**	**Group C n = 11 n (%)**	**Group D n = 8 n (%)**
Sex				
Women	10 (90.9)	5 (62.5)	10 (90.9)	5 (62.5)
School year				
First	4 (36.4)	3 (37.5)	3 (27.3)	2 (25.0)
Second	4 (36.4)	3 (25.0)	5 (45.5)	5 (62.5)
Third	2 (18.2)	2 (25.0)	2 (18.2)	1 (12.5)
Fourth	1 (9.1)	1 (12.5)	1 (9.1)	0 (0)
History of inhaler treatment	8 (72.7)	5 (62.5)	7 (63.6)	6 (75.0)

We compared the scores for each technique to identify the pitfalls of each leaflet (Table 1 and 2). We compared the learning rates of techniques between the two-device groups and found that the rate of implementation of procedures with common descriptions for DPI and pMDI (procedures 1, 4, 5, and 10 in Table 1 and procedures 1, 5, 6, and 12 in Table 2) in group B, which was assigned the standardized leaflets, tended to be higher than that in group D, which was assigned the package leaflets. The instructions with the largest differences in the rate of implementation (%) were "Put the intake port in your mouth and inhale deeply" (87.5 in the standardized leaflet; 50.0 in the package leaflet) for DPI, and "Shake the inhaler" and "Shake at least two times" (100.0 in the standardized leaflet; 50.0 in the package leaflet) and "Inhale for at least 2 s" (62.5 in the standardized leaflet; 12.5 in the package one) for pMDI. In contrast, despite the common description, the groups that used the standardized leaflets showed a low implementation rate for the "Gargle after inhalation" instruction for DPI and pMDI.

4. Discussion

In this RCT, we examined the differences in learning efficiency between individuals using standardized and package leaflets. In the groups using two different devices, the scoring rate in the group using the standardized leaflets (group B) was significantly higher than that in the group using the package leaflets (group D). This difference could be attributed to user confusion owing to different descriptions of the same operation in each package leaflet. Previous studies have suggested that patients who used more than one inhaler device made frequent mistakes in usage technique [14, 15]. In another study, among patients with COPD who were prescribed multiple devices with similar inhalation techniques, the exacerbation rates were lower than in those who were prescribed devices requiring different procedures [16].

When comparing the step-by-step adherence among the groups using multiple devices, errors in the pMDI technique associated with steps such as "Not shaking the device," "No exhalation before inhalation," and "No slow and deep inspiration" were more frequent in participants using the package leaflets than in those using the standardized leaflets. This observation was similar to the finding of a previous study on patients with asthma and COPD receiving instructions for the first time [17]. Errors in using Diskus® associated with steps such as "Exhaling into the device" and "No deep breath" were also higher in the package leaflet group in this study compared with those of users in previous studies [15, 18]. An observational study found the "no exhalation before inhalation" step to be a common error among Diskus® users [19], consistent with our findings in the package leaflet group using multiple devices. Accordingly, we assumed that the standardized leaflet, which was partly written using commonly used expressions and names for device parts, might have helped the participants, particularly those using multiple devices in the present study, to learn the inhalation techniques.

In the global COPD guidelines, inhaled bronchodilators (muscarinic antagonists or beta2- agonists) are the recommended initial treatment for patients and are also used as reliever inhalers for treating worsening symptoms [3]. For patients with asthma, initial treatment includes inhaled corticosteroid (ICS)-formoterol, ICS- short-acting beta2- agonist (SABA), and long-acting beta2-agonists (LABA), whereas exacerbations are treated using

ICS-formoterol or SABA inhalers [1, 2]. Therefore, patients with comorbidities must use multiple devices appropriately to manage their symptoms. As COPD is more prevalent and severe in older patients, their treatment regimens must be carefully selected [20]. Additionally, older individuals may experience more problems in handling the devices. Therefore, simple standardized leaflets may be helpful for older patients.

When using only one device, the package leaflet is considered to be sufficiently effective as a resource for acquiring knowledge about proper inhalation techniques. The rates of implementation of gargling and rinsing were negative in the groups that used standardized leaflets; however, the illustration of a gargling person might have highlighted this procedure to the participants using the package leaflets [5].

Items with good implementation rates in the standardized leaflet can be categorized into "1. Common processes but with different explanations" and "2. Insufficient explanations." Accordingly, improving the package leaflet for class 2 items is expected to enhance treatment outcomes, whereas standardization is considered to be the only solution for class 1 items. Furthermore, when standardizing the procedural manual, aligning the categorization of inhalation procedures facilitates the comparison of differences. Using specific and concrete expressions is considered to make it easier for individuals to remember and practice the procedures.

The present study had few limitations. First, to accurately assess the effect of "leaflet formatting on inhalation technique knowledge acquisition," it was necessary to recruit a population of adults with similar levels of comprehension. In this study, pharmacy students were selected for this purpose because they had comparable comprehension skills, were likely to require knowledge of inhalation techniques in the future, and were readily accessible from our research environment. However, the study participants were young adults with a general level of understanding, which may differ from that of actual patients. While standardized leaflets may have facilitated comprehension by using precise numbers compared with ambiguous expressions in package leaflets, all participants in this study were able to hold their breath for at least 5 s, unlike patients in previous studies [4, 17, 19]. Additionally, tasks such as holding the breath for a few seconds before use and checking the device's residual volume were performed at a significantly higher rate in this study than in previous studies [15, 18]. Second, although instructions are typically provided during outpatient visits, with an assessment period ranging from a few days to weeks, this study evaluated proficiency the day after training to accurately assess differences in proficiency. While this study could evaluate the effect of leaflet differences on technique acquisition, appropriate inhalation techniques may be potentially forgotten before the next instruction session, which was not addressed in this study. As instilling the habit of proper inhalation techniques likely requires reinforcement, future research should adapt illustrations to standardized leaflets and evaluate their effect on habituating proper inhalation techniques. Therefore, assessing the effectiveness of using standardized leaflets adapted with illustrations in clinical studies is necessary in the future.

5. Conclusion

The standardized leaflet may have enhanced inhalation technique learning

for multiple devices because of its normalized and common wording. In addition, it might have promoted a reliable understanding of inhaler operations through its specific, evidence-based wording. Overall, our findings suggest that standardized leaflets can help to reduce error rates in inhalation techniques and improve patient compliance. In future applications, using a standardized leaflet with normalized and common wording could improve compliance with appropriate inhalation techniques among multiple device users.

6 Acknowledgments

The authors thank the members of the Gunma Inhalation Therapy Study Group for developing the standardized leaflet and promoting its use in the community. The authors would also like to extend their gratitude to GlaxoSmithKline and Otsuka Pharmaceutical Company for providing Diskus® and Meptin Air®, respectively, for training. This work was supported by a research budget from Takasaki University of Health and Welfare.
The authors declare that they have no conflicts of interest.

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