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Original Article

Low-dose *l*-isoproterenol versus salbutamol in hospitalized pediatric patients with severe acute exacerbation of asthma: A double-blind, randomized controlled trial

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CI	confidence interval
MPIS	modified pulmonary index score
PGA	physicians' global assessment
SABA	short-acting β_2 -agonists
SD	standard deviation

ABSTRACT

Background: Although the guidelines in most countries do not recommend continuous inhalation of *l*-isoproterenol to treat pediatric patients with acute severe exacerbation of asthma, lower dose of *l*-isoproterenol has been widely used in Japan. To determine whether the efficacy of low-dose *l*-isoproterenol was superior to that of salbutamol, we conducted a double-blind, randomized controlled trial. **Methods:** Hospitalized patients aged 1–17 years were eligible if they had severe asthma exacerbation defined by the modified pulmonary index score (MPIS). Patients were randomly assigned (1:1) to receive inhalation of *l*-isoproterenol (10 μ g/kg/h) or salbutamol (500 μ g/kg/h) for 12 hours via a large-volume nebulizer with oxygen. The primary outcome was the change in MPIS from baseline to 3 hours after starting inhalation. Trial registration number UMIN000001991.

Results: From December 2009 to October 2013, 83 patients (42 in the *l*-isoproterenol group and 41 in the salbutamol group) were enrolled into the study. Of these, one patient in the *l*-isoproterenol group did not receive the study drug and was excluded from the analysis. Compared with salbutamol, *l*-isoproterenol reduced MPIS more rapidly. Mean (SD) changes in MPIS at 3 hours were -2.9 (2.5) in the *l*-isoproterenol group and -0.9 (2.3) in the salbutamol group (difference -2.0 , 95% confidence interval -3.1 to -0.9 ; $P < 0.001$). Adverse events occurred in 1 (2%) and 11 (27%) patients in the *l*-isoproterenol and salbutamol groups, respectively ($P = 0.003$). Hypokalemia and tachycardia occurred only in the salbutamol group. **Conclusions:** Low-dose *l*-isoproterenol has a more rapid effect with fewer adverse events than salbutamol.

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Introduction

Asthma is one of the most common non-communicable disease in children,¹ and acute exacerbation is one of the key features of asthma. For example, 36% of pediatric patients reported an

unscheduled urgent care visit, and 18% reported one or more emergency room visits because of asthma during the period of 12 months.² Although admissions for pediatric asthma exacerbation are decreasing in Japan,³ those are stable or still increasing in the other countries.^{4,5}

Short-acting β_2 -agonists (SABA) are used as the mainstay of the treatment for acute exacerbation of asthma,⁶ and their continuous inhalation using a nebulizer is a preferred option in treating children with acute severe asthma exacerbation.^{7–9} Among the available SABA, salbutamol is the most widely used drug, and a previous systematic review has shown that continuous inhalation of salbutamol is superior to its repeated intermittent inhalations.¹⁰ As a result, current clinical guidelines recommend continuous nebulization of salbutamol to treat patients with acute severe exacerbation of asthma in the emergency department or hospital.^{11,12} However, salbutamol, even in high doses, is ineffective in about one third of patients and troublesome side effects are frequently reported.^{13–15} Therefore, effective β -agonists with fewer side effects are required.

In Japan, continuous inhalation of *l*-isoproterenol, a nonselective β -agonist, is a recommended treatment for pediatric patients with acute severe exacerbation.¹⁶ Since Iikura and co-workers demonstrated the efficacy of the above inhalation therapy in children with severe asthma exacerbation, it has been widely used in Japan.¹⁷ And Japanese guideline for pediatric asthma recommends the inhalation therapy without enough evidences. Although the use of *l*-isoproterenol is not recommended in most countries because of safety concerns,¹⁸ its dose (2000 μ g/mL for metered-dose inhalers) is too high. In Japan, lower doses of up to 16 μ g/mL have been used for continuous inhalation without major safety concerns.¹⁷ It can bring about potent bronchodilating effect even in the low doses because the intrinsic β -agonist efficacy of *l*-isoproterenol is 20 times higher than that of salbutamol.¹⁹ Continuous inhalation of *l*-isoproterenol may have another advantage over salbutamol. It rapidly decreases heart rate, which is one of the key physical measures to assess the severity of asthma in children.²⁰ In contrast, no remarkable decrease in heart rates has been observed even 72 hours after starting salbutamol continuous inhalation.⁷

On the basis of these findings, we conducted a randomized controlled trial to determine whether the efficacy of low-dose *l*-isoproterenol was superior to that of salbutamol in treating pediatric patients with acute severe exacerbation of asthma.

Methods

Design and ethics

This multicenter, randomized, double-blind, parallel-group trial was conducted at 21 hospitals in Japan in accordance with the Declaration of Helsinki. The study protocol and its revision were approved by the institutional review board of each participating center. Patients' guardians provided written informed consent. Adolescent patients also provided written informed consent and younger patients provided written informed assent. This study is registered with the University Hospital Medical Information Network clinical trials registry, number UMIN00001991.

Participants

Hospitalized pediatric patients aged between 2 and 17 years were eligible for the study if they met either of the following criteria: modified pulmonary index score (MPIS) ≥ 10 points for those who received intermittent inhalations of SABA at least twice within 2 hours; or MPIS ≥ 15 points for those who received SABA less than twice. The MPIS consisted of the following 6 items: 1)

oxygen saturation on room air, 2) accessory muscle use, 3) inspiratory-to-expiratory flow ratio, 4) degree of wheezing, 5) heart rate, and 6) respiratory rate.²¹ For each of these items, a score of 0–3 is assigned according to the severity. The range of total score is 0–18, with higher total scores indicating more severe conditions.

After 4 patients were enrolled into the study, the protocol was revised to change the inclusion criteria. Thereafter, patients aged 1 year or those with MPIS of 9 points after intermittent inhalations of SABA at least twice were also eligible in addition to the patients mentioned above. These changes were made to improve the accrual rate. A diagnosis of infantile asthma aged <2 years was made if the subject had had at least 3 episodes of marked expiratory wheezing according to Japanese pediatric guideline for the treatment and management of asthma.¹⁶ Additionally, this diagnosis of asthma in young children is more likely if they have wheezing in the absence of respiratory infection or they have other allergic diathesis, which is described also in international guidelines of asthma.^{6,22} Throughout the study, we excluded patients whose body temperature was 38.5 °C or higher, those who had received antipyretics within 6 hours, and those who had wheezing not caused by asthma.

Randomization and blinding

Patients were randomly assigned in a 1:1 ratio to receive *l*-isoproterenol or salbutamol using a minimization method with the stratification factors of MPIS at enrolment (9–11 vs. 12–18 points), age (1–5 years vs. 6 years or older), and institution. Allocation sequence was created using the computer by the data center (Non-profit Organisation Japan Clinical Research Support Unit, Tokyo, Japan). When a patient was considered to be eligible for the study, the investigator contacted the data center through the website. The data center confirmed the eligibility and notified the number of the study drug to be administered.

Study drug was prepared for each patient in a sequentially numbered box containing either of the following combinations with the use of double-dummy method: *l*-isoproterenol plus matching placebo to salbutamol; or salbutamol plus matching placebo to *l*-isoproterenol. Each of active drugs and its matching placebo were contained in the same box. In this box, *l*-isoproterenol or its placebo was labelled as “Drug A” whereas salbutamol or its placebo was labelled as “Drug B”. Allocated treatment was blinded to patients, investigators, and other study personnel throughout the study. The data center was not involved in the patient enrolment.

Procedures

After hospitalization, patients received methylprednisolone 1 mg/kg intravenously. Thereafter, patients received continuous inhalation of *l*-isoproterenol (1 mL/kg [$= 10 \mu$ g/kg/h], maximum 40 mL) or salbutamol (1.5 mL/kg [$= 500 \mu$ g/kg/h], maximum 30 mL) for 12 hours using a large-volume nebulizer (Inspiron®, Japan Medicalnext Co., Ltd., Osaka, Japan) with an oxygen density of 70% and flow rate of 8 L/min. This means that the solution of both treatments was supplied by 33 mL/h. The investigators calculated and measured the dose (i.e., volume) of each study drug according to the patient's weight. Measured doses of drugs A and B were mixed and diluted with saline to achieve a total volume of 500 mL. Diluted solution was administered through the facemask connected to the nebulizer. The solution was replaced at 6 hours after starting inhalation, and methylprednisolone 1 mg/kg was administered intravenously at the same time (max 70 mg).

Outcomes

The primary outcome was the change in MPIS from baseline to 3 hours after starting inhalation. Before starting the study, all investigators completed the training using the digital learning software for MPIS. This software consisted of recorded auscultation sounds, video images, and computer graphics of the asthma exacerbation with varying severity. The investigators evaluated their skills with 10 test cases after training. MPIS are sufficiently reliable to assess pediatric patients with acute asthma, including those aged 5 years or younger.²³

The secondary outcomes included the change in MPIS at 12 hours, changes in heart rates and respiratory rates at 3 hours, and the physicians' global assessment (PGA). PGA was graded at 3 and 12 hours as "exacerbated," "no change," "slightly improved," "improved," and "markedly improved".

Adverse events were followed until 24 hours after the end of inhalation and were classified according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0. In addition, serum levels of potassium, troponin T, creatine kinase, and brain natriuretic peptide were measured before and after treatment.

Plasma levels of R- and S-salbutamol, as well as those of *l*-isoproterenol were measured at baseline and posttreatment by using liquid chromatography/tandem mass spectrometry (QTRAP[®] 5500, AB SCIEX, USA). The minimum concentration that can be measured was 0.025 ng/mL for *l*-isoproterenol and 0.01 ng/mL for R- and S-salbutamol.

Statistical analysis

In clinical practice, changes in MPIS from baseline to 3 hours after starting continuous inhalation of *l*-isoproterenol or salbutamol were -2 to -5 points with the standard deviation (SD) of about 1. Thus, a sample size of 102 patients (51 in each group) was determined to provide at least 70% power to detect the difference of 0.5 point between the treatment groups.

For the primary analysis, mean changes in MPIS at 3 hours were compared between the treatment groups using *t*-tests. The secondary outcomes were also compared using *t*-tests except for PGA. PGAs at 3 and 12 hours were compared using the Mantel–Haenszel chi-squared test. Proportions of patients who reported any adverse event were compared using Fisher's exact tests. All analyses included patients who received the study drug. Data were analyzed using SAS software version 9.4 (SAS institute, Cary, NC). All reported *P* values are 2 sided without adjustment for multiplicity.

We conducted a pre-specified interim analysis twice. The first analysis was performed for safety precautions when 30% of expected samples ($n = 30$) were enrolled, and the second one was performed for efficacy when 60% of expected samples ($n = 60$) were enrolled. The significance levels were set at 0.003, which is equivalent to 3 SDs of the differences of the changes in MPIS at 3 hours between the groups, and 0.047 for the interim and final analyses to retain overall type I error of 0.050. Results of the interim analysis were assessed by the independent data monitoring committee, and the committee recommended to continue the study.

Results

Study profile and baseline characteristics

From 24 Dec 2009 to 24 Oct 2013, 83 patients (42 in the *l*-isoproterenol group and 41 in the salbutamol group) were enrolled into the study (Fig. 1). Of these, 1 patient in the *l*-isoproterenol group did not receive the study drug because the symptom was

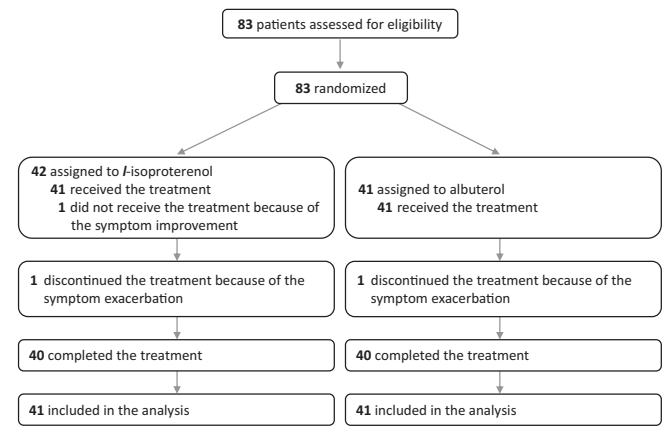


Fig. 1. Patient flow diagram.

improved. This patient was excluded from the final analysis. Out of 82 patients who received the study drug, 1 patient in each treatment group discontinued the study owing to the exacerbation of respiratory symptoms. Remaining 80 patients (40 in each group) completed the study. Although the values for some components of MPIS at 3 hours were missing in 1 patient in each group, these missing data were not replaced by the imputed values.

The demographic and baseline characteristics were well balanced between the treatment groups (Table 1). Mean (SD) ages were 4.5 (2.6) years in the *l*-isoproterenol group and 4.4 (3.1) years in the salbutamol group, and the mean MPISs at enrolment were 12.2 (2.5) in the *l*-isoproterenol group and 12.2 (2.2) in the salbutamol group. Baseline MPIS before starting the study treatment were also similar between the treatment groups.

Efficacy outcomes

Compared with salbutamol, *l*-isoproterenol reduced MPIS more rapidly (Table 2). Mean (SD) changes in MPIS at 3 hours were -2.9 (2.5) in the *l*-isoproterenol group and -0.9 (2.3) in the salbutamol group (difference -2.0 , 95% confidence interval [CI] -3.1 to -0.9 ; $P < 0.001$). However, the changes at 12 hours were not significantly different between the *l*-isoproterenol and salbutamol groups with the mean (SD) changes of -4.1 (3.1) and -3.1 (2.7), respectively (difference -1.0 , 95% CI -2.3 to 0.3 ; $P = 0.13$). Among the

Table 1

Demographic and baseline characteristics of the patients included in the final analysis.

	<i>l</i> -Isoproterenol (n = 41)	Salbutamol (n = 41)
Male sex (n, %)	26 (63%)	18 (44%)
Age (years, Mean [SD])	4.5 (2.6)	4.4 (3.1)
Age (years, n [%])		
<3	9 (22%)	9 (22%)
3 ≤ <6 years	22 (54%)	22 (54%)
6 ≤	10 (24%)	10 (24%)
Body temperature (°C, Mean [SD])	37.0 (0.7)	37.1 (0.6)
Body temperature ≥ 38.0 °C (n, %)	3 (7%)	3 (7%)
Systolic blood pressure (mm Hg, Mean [SD])	107.3 (9.7)	110.9 (11.6)
Diastolic blood pressure (mm Hg, Mean [SD])	67.3 (8.4)	66.0 (9.7)
MPIS at enrolment, Mean (SD)	12.2 (2.5)	12.2 (2.2)
MPIS before starting treatment, Mean (SD)	11.3 (2.7)	10.9 (2.4)
Heart rate (beats/min, Mean [SD])	143.3 (17.8)	141.4 (20.4)
Respiratory rate (breaths/min, Mean [SD])	45.8 (12.8)	45.4 (14.4)
Number of Patients who received pretreatment (%)		
Systemic glucocorticoids	41 (100%)	41 (100%)
Inhaled short-acting β ₂ -agonists	38 (93%)	36 (88%)

Data at enrolment are shown, except for modified pulmonary index score (MPIS) in which both data at enrolment and before starting treatment are shown.

Table 2
Changes in the modified pulmonary index score.

Modified pulmonary index score	<i>l</i> -Isoproterenol (n = 41)	Salbutamol (n = 41)	Difference (95% CI)	P value
Total score				
Baseline	11.3 (2.7)	10.9 (2.4)		
3 hours after starting treatment	8.4 (3.3)	10.1 (2.5)		
Changes from baseline	−2.9 (2.5)	−0.9 (2.3)	−2.0 (−3.1 to −0.9)	<0.001
12 hours after starting treatment	7.2 (3.5)	7.9 (2.7)		
Changes from baseline	−4.1 (3.1)	−3.1 (2.7)	−1.0 (−2.3 to 0.3)	0.13
Component of the modified pulmonary index score				
SpO ₂ score				
Baseline	1.7 (1.0)	1.5 (1.1)		
3 hours after starting treatment	1.5 (0.9)	1.5 (1.0)		
Changes from baseline	−0.2 (1.0)	0.1 (1.1)	−0.2 (−0.6 to 0.3)	0.48
Accessory muscle score				
Baseline	2.0 (0.7)	2.0 (0.7)		
3 hours after starting treatment	1.5 (0.7)	1.6 (0.8)		
Changes from baseline	−0.5 (0.6)	−0.4 (0.7)	−0.1 (−0.4 to 0.2)	0.68
IE ratio score				
Baseline	2.0 (0.6)	2.0 (0.7)		
3 hours after starting treatment	1.5 (0.6)	1.6 (0.6)		
Changes from baseline	−0.5 (0.5)	−0.3 (0.7)	−0.1 (−0.4 to 0.2)	0.44
Wheezing score				
Baseline	2.2 (0.6)	2.2 (0.8)		
3 hours after starting treatment	1.8 (0.9)	1.9 (0.7)		
Changes from baseline	−0.5 (0.7)	−0.3 (0.7)	−0.1 (−0.4 to 0.2)	0.40
Heart rate score				
Baseline	2.0 (0.8)	2.0 (0.8)		
3 hours after starting treatment	1.2 (0.9)	2.3 (0.7)		
Changes from baseline	−0.9 (1.0)	0.4 (0.8)	−1.2 (−1.6 to −0.8)	<0.001
Respiratory rate score				
Baseline	1.4 (0.9)	1.3 (0.7)		
3 hours after starting treatment	0.9 (0.8)	1.2 (0.7)		
Changes from baseline	−0.5 (1.0)	−0.1 (0.6)	−0.4 (−0.8 to −0.1)	0.02

Data are summarized as mean (SD).

SpO₂, percutaneous oxygen saturation; IE, inspiratory-to-expiratory flow.

components of MPIS, mean decrease in heart rate score was significantly larger in the *l*-isoproterenol than in the salbutamol group (difference −1.2, 95% CI −1.6 to −0.8; $P < 0.001$). Mean decrease in respiratory rate score was also significantly larger in the *l*-isoproterenol (difference −0.4, 95% CI −0.8 to −0.1; $P = 0.02$).

Table 3 shows the changes in heart and respiratory rates. At 3 hours after starting treatment, the decrease in heart rates was significantly larger in the *l*-isoproterenol group than in the salbutamol group (difference −20.3; 95% CI, −26.2 to −14.4; $P < 0.001$) whereas the decrease in respiratory rates was not significantly different between the treatment groups (difference −9.3; 95% CI, −19.4 to 0.8; $P = 0.07$).

According to the PGA, more patients in the *l*-isoproterenol group improved their symptoms at 3 hours compared with those in the salbutamol group ($P = 0.02$; Table 4). PGA at 12 hours was also in favour of *l*-isoproterenol, but the difference between the treatment groups was not statistically significant ($P = 0.68$).

Safety outcomes

Adverse events are summarized in Table 5. Only 1 patient (2%) had an adverse event (Grade 1 tachypnea) in the *l*-isoproterenol

group, whereas 11 patients (27%) reported at least 1 adverse event in the salbutamol group ($P = 0.003$). Adverse events such as hypokalemia, tachycardia, and elevated serum creatine kinase levels were observed only in the salbutamol group.

As shown in Table 6, mean serum potassium level increased in the *l*-isoproterenol group, whereas it decreased in the salbutamol group. As a result, mean (SD) potassium level at 12 hours was significantly lower in the salbutamol group than in the *l*-isoproterenol group (difference −0.53 mEq/L; 95% CI, −0.78 to −0.27; $P < 0.001$). Serum levels of troponin T were measured in 74 patients (38 in the *l*-isoproterenol group and 36 in the salbutamol group) at 12 hours. Of these, 1 patient in the salbutamol group had an abnormal value of 0.125 ng/mL. Similar proportions of patients had abnormal value of brain natriuretic peptide (57% [21 out of 37 patients] and 57% [20 out of 35 patients], respectively).

Pharmacokinetics

In the *l*-isoproterenol group, plasma drug levels were below the limit of detection (<0.025 ng/mL) at 12 hours in all patients (Table 7). In the salbutamol group, mean (SD) plasma levels of R-salbutamol were 0.46 (1.53) ng/mL before starting treatment and

Table 3
Changes in the heart and respiratory rates from the baseline until 3 hours after starting the study treatment.

	<i>l</i> -Isoproterenol (n = 41)	Salbutamol (n = 41)	Difference (95% CI)	P value
Heart rate				
Baseline (beats/min)	136.3 (20.8)	136.9 (20.9)		
Change (%)	−12.8 (13.8)	7.5 (13.1)	−20.3 (−26.2 to −14.4)	<0.001
Respiratory rate				
Baseline (breaths/min)	41.6 (11.6)	40.1 (10.3)		
Change (%)	−11.6 (24.4)	−2.4 (21.5)	−9.3 (−19.4 to 0.8)	0.07

Data are summarized as mean (SD).

Table 4

Changes of physicians' global assessment.

PGA	<i>l</i> -Isoproterenol (n = 41)	Salbutamol (n = 41)	P value
3 hours after starting treatment			0.02
Markedly improved	3/41 (7%)	0/41 (0%)	
Improved	10/41 (24%)	7/41 (17%)	
Slightly improved	17/41 (42%)	15/41 (37%)	
No change	11/41 (27%)	18/41 (44%)	
Exacerbated	0/41 (0%)	1/41 (2%)	
12 hours after starting treatment			0.68
Markedly improved	4/40 (10%)	3/40 (8%)	
Improved	16/40 (40%)	15/40 (38%)	
Slightly improved	15/40 (38%)	17/40 (43%)	
No change	5/40 (13%)	5/40 (13%)	
Exacerbated	0/40 (0%)	0/40 (0%)	

Data are summarized as n (%).

Table 5

Adverse events reported until 24 hours after the end of inhalation of the study drug.

	<i>l</i> -Isoproterenol (n = 41)	Salbutamol (n = 41)	P value
Patients with ≥ 1 adverse events	1 (2%)	11 (27%)	0.003
Number of adverse events	1	16	
Number of patients with each adverse event			
Tachypnea	Grade 1 1	0	
Tachycardia	Grade 1 0	5	
Tremor	Grade 1 0	1	
Fever	Grade 1 0	2	
Hypertension	Grade 1 0	2	
Hypokalemia	Grade 1 0	2	
	Grade 3 0	1	
Elevated serum CK levels	Grade 1 0	2	
	Grade 2 0	1	

Severity of adverse events was classified according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0.
CK, creatine kinase.

4.65 (3.22) ng/mL at 12 hours, and those of S-salbutamol were 1.43 (3.11) and 17.48 (12.91) ng/mL, respectively.

Discussion

In our study, low-dose *l*-isoproterenol rapidly improved MPIS in hospitalized pediatric patients with acute severe exacerbation of asthma compared with salbutamol. Decrease in MPIS at 3 hours was significantly larger in the *l*-isoproterenol group than in the salbutamol group. Acute severe exacerbations of asthma increase the risk of life-threatening respiratory failure.²⁴ Thus, rapidly improving its symptoms and signs is the most important strategy in treating patients in the emergency department and hospital settings.²⁵

Decrease in MPIS in the *l*-isoproterenol group was mainly derived from the decrease in heart and respiratory rate scores. Because *l*-isoproterenol is a nonselective β -agonist, it stimulates $\beta 1$

receptor and has the possibility to increase heart rates. However, its $\beta 1$ stimulating effect might be minimal, because it does not enter the blood stream when lower doses are administered. This hypothesis is supported by our results showing that the plasma levels were below the limit of detection. In addition, *l*-isoproterenol has high intrinsic $\beta 2$ -agonist efficacy,¹⁹ which provides a potent bronchodilating effect even in lower doses. As a result, low-dose *l*-isoproterenol might dilate the airway smooth muscle and decrease heart and respiratory rates without affecting the cardiovascular system. The reason why only the decrease in heart and respiratory rate scores were significant among the 6 items consisting of MPIS is presumed that it was difficult to show remarkable changes within 3 hours after the start of treatment for the subjective 3 items involving accessory muscle use, inspiratory-to-expiratory flow ratio, and degree of wheezing. Oxygen saturation on room air showed a tendency of improvement in the *l*-isoproterenol group by post hoc analysis, which was +0.7 (3.5) % in the *l*-isoproterenol group and -0.4 (3.7) % in the salbutamol group (difference 1.1, 95% CI -0.5 to 2.7; $P = 0.159$).

In the safety assessment, continuous inhalation of low-dose *l*-isoproterenol was associated with significantly fewer adverse events. Elevated serum creatine kinase levels, hypokalemia, and tachycardia were observed only in the salbutamol group. Elevation in creatine kinase levels requires cardiac monitoring, and continuous salbutamol nebulization elevates levels of creatine kinase and creatine kinase/muscle brain fraction.⁷ Hypokalemia induces muscle cramps or abnormal heart rhythms, and inhaled salbutamol decreases serum potassium in a dose-dependent manner.²⁶ Our results confirmed these safety concerns associated with salbutamol. Although the mean potassium level increased in the *l*-isoproterenol group, this result can be explained by the fact that most patients inhaled salbutamol before the study treatment. Fowler *et al.* reported the linear relationship between the plasma levels of salbutamol and the decrease in potassium levels.²⁷ Therefore, potassium levels might increase according to the decrease in salbutamol levels during the treatment with *l*-isoproterenol.

The favourable safety results in the *l*-isoproterenol group can be explained in part by the difference in plasma drug levels between the treatment groups. Although *l*-isoproterenol is known to induce adverse effects on circulatory system,²⁸ it is rapidly metabolised with a half-life of 1–7 minutes in pediatric patients.²⁹ In contrast, half-life of salbutamol is longer than that of *l*-isoproterenol, and the mean plasma levels of R- and S-salbutamol in our study were comparable to the peak levels achieved by oral administration of salbutamol 4 mg in adults.³⁰

To date, few randomized controlled trials assessed the efficacy and safety of continuous inhalation of *l*-isoproterenol. Although we searched MEDLINE, Embase, and the Cochrane Library for reports published in English or Japanese, we could not identify such trials. In this context, we found the benefits of low-dose *l*-isoproterenol. Because of safety concerns for *l*-isoproterenol, current guidelines recommend using only selective $\beta 2$ -agonists for the treatment of

Table 6

Changes in the serum levels of potassium.

	<i>l</i> -Isoproterenol (n = 41)	Salbutamol (n = 41)	Difference (95% CI)	P value
Potassium (mEq/L)				
Baseline	4.24 (0.34)	4.20 (0.36)		
12 hours [†]	4.52 (0.30)	3.94 (0.56)		
Changes from baseline	0.26 (0.43)	-0.27 (0.65)	-0.53 (-0.78 to -0.27)	<0.001
Abnormal value [‡]	0 (0%)	1 (3%)		

Data of potassium levels are summarized as mean (SD) except for the abnormal values.

[†] 12 hours after starting the study treatment.

[‡] Number (%) of patients with abnormal laboratory value.

Table 7
Changes in the plasma drug levels.

Plasma concentration (ng/mL)		l-Isoproterenol		Salbutamol		P value
		n	mean (SD)	n	mean (SD)	
l-isoproterenol	Pre	40	<0.025	41	<0.025	—
	12 hours [†]	40	<0.025	39	<0.025	—
R-salbutamol	Pre	40	0.29 (0.39)	41	0.46 (1.53)	0.52
	12 hours [†]	40	0.01 (0.02)	39	4.65 (3.22)	<0.001
S-salbutamol	Pre	40	0.92 (1.19)	41	1.43 (3.11)	0.88
	12 hours [†]	40	0.10 (0.14)	39	17.48 (12.91)	<0.001

[†] 12 hours after starting the study treatment.

acute severe exacerbation of asthma.^{11,12} However, this recommendation is based on the high doses of l-isoproterenol used in most Western countries, such as 2000 µg/mL for metered-dose inhalers. In our study, 10 µg/kg/h of l-isoproterenol and 500 µg/kg/h of salbutamol were administered. The dose of salbutamol is recommended in the Western guideline,¹² and the dose–response relationships had been assumed to be similar between isoproterenol and salbutamol. According to this assumption, 500 µg/kg/h of isoproterenol might be administered in Western countries if isoproterenol were available at present. In fact, however, far lower dose is appropriate for the treatment of acute asthma exacerbations.

Our study has some limitations. First, we should have used levsalbutamol, (R)-enantiomer of salbutamol, as a reference drug because previous reports suggest the superiority of levsalbutamol over salbutamol.^{31,32} However, other reports do not indicate the superiority in patients with acute asthma,^{33,34} and levsalbutamol is not approved in Japan. Second, the follow-up period of adverse events was not long enough to detect serious events such as cardiac toxicity or asthma death. However, continuous inhalation of low-dose l-isoproterenol has been widely used in Japan without safety concerns.³ Thus, we consider that its safety profile is acceptable.

Conclusions

Continuous inhalation of low-dose l-isoproterenol is superior to that of salbutamol in treating pediatric patients with acute severe exacerbations of asthma in the emergency department and hospital settings. It has a more rapid effect with fewer adverse events than salbutamol.

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Conflict of interest

TK received research grants from GlaxoSmithKline and Kowa Company during the conduct of the study. The rest of the authors have no conflict of interest.

Authors' contributions

TK conceptualized, designed the study, drafted the manuscript and had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. TF conceptualized, designed the study and critically reviewed the manuscript. TM designed the study and critically reviewed the manuscript. KA collected data and revised the manuscript. YOhy conceptualized the study and critically reviewed the manuscript. YA, KH, MM and TI recruited the research subjects and critically reviewed the manuscript. MSO designed the study, analyzed the data, and critically reviewed the manuscript. MS designed the study and critically reviewed the manuscript. YOha designed the study and reviewed the results and manuscript. HN designed the study, supervised data collection and critically reviewed the manuscript.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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