Clinical Trial/Experimental Study

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Exercise training as an adjunctive therapy to montelukast in children with mild asthma

A randomized controlled trial

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Abstract

Background: This study investigated the effectiveness and safety of exercise training (ET) as an adjunctive therapy to montelukast for children with mild asthma (MA).

Methods: A total of 72 children, ages 4 to 12 years with MA were randomly assigned to a treatment group or a control group at a ratio of 1:1. The subjects in the treatment group received ET plus montelukast, while the participants in the control group received montelukast alone. The primary endpoint was lung function, as measured by forced expiratory volume in 1 second (FEV_1) and ratio between FEV_1 and forced vital capacity (FEV_1/FVC). The secondary endpoints included the symptom improvements, as measured by clinical assessment score, and quality of life (QoL), as assessed with Paediatric Allergic Disease Quality of Life Questionnaire (PADQLQ) scores. In addition, adverse events were also assessed during the period of this study. All outcomes were measured at baseline, at the end of 6-week treatment and 2-week follow-up after the treatment.

Results: After 6-week treatment and 2-week follow-up, although ET plus montelukast did not show better effectiveness in improving lung function, as evaluated by the FEV_1 ($P > .05$) and FEV_1/FVC ($P > .05$) than montelukast alone, significant relief in clinical symptoms ($P < .01$), and improvement in QoL ($P < .01$) have achieved. Additionally, both groups had similar safety profile.

Conclusion: The results of this study showed that ET as an adjunctive therapy to montelukast may benefit for children with MA. Further studies are still needed to warrant the results of this study.

Abbreviations: ET = exercise training, FEV_1 = forced expiratory volume in 1 second, FEV_1/FVC = ratio between FEV_1 and forced vital capacity, ITT = intent-to-treat, MA = mild asthma, PADQLQ = Paediatric Allergic Disease Quality of Life Questionnaire scores, QoL = quality of life, RCT = randomized controlled trial.

Keywords: asthma, effectiveness, exercise training, montelukast

1. Introduction

Asthma is one of the most common disorders of respiratory system diseases.[1–4] It has been estimated that this disorder affects 9% to 20% children and 1% to 3% adults in the United State.[5–6] In China, the prevalence of asthma is estimated to be about 5%.[7–8] Additionally, the number of patients diagnosed with asthma is increasing around the world, especially among the children population.[9–16] Thus, it is very important to treat and to prevent this disorder.

Current managements for asthma mainly use medication, such as glucocorticoids, antihistamine drugs, β2 agonists, and leukotriene receptor antagonists.[17–20] However, they often have limited efficacy.[21] In addition, those medications often accompanied a variety of adverse events, especially for children with asthma.[22–24] Thus, more management options with fewer adverse events are urgently needed to treat and to prevent children with asthma. Alternative therapy is one of most important candidates to treat such condition, such as exercise training (ET). However, limited data is available to support ET for the management of asthma in children.[25] In this study, we tested the hypothesis that the effectiveness and safety of ET as an adjunctive therapy to montelukast would be better than the montelukast alone for the treatment of children with mild asthma (MA) ages 4 to 12 years old.

2. Methods

2.1. Ethical approval

This study was approved by the Medical Ethical Committee of Yan'an People's Hospital.

2.2. Sample size

The sample size of this study was 60 participants, 30 children in each group with 12% difference of FEV_1 between 2 groups and α=0.05, β=0.1, according to the previous alternative study.[26] The desired sample size for this study is set to 72 subjects, 36 patients each group with assumed dropout rates of 20%.

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The authors have no conflicts of interest to disclose.

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2.3. Design

This study was designed as a 2 arms randomized controlled trial (RCT). It was conducted from January 2017 to June 2018 at Yan'an People's Hospital. Totally, 72 children with MA were recruited in this study. After screen, they were randomly allocated into a treatment group (n = 36, received ET plus montelukast) and a control group (n = 36, received montelukast alone). The lung function, clinical symptoms, and quality of life (QoL) were measured to assess its efficacy. All endpoints were measured at baseline, at the end of 6-week treatment, and 2-week follow-up after the treatment.

2.4. Randomization, allocation, and blinding

A total of 72 children with MA were equally and randomly allocated to the treatment group or the control group at a ratio of 1:1 by using a block randomization procedure. The random number was performed by using IBM SPSS Statistics 17.0 (IBM Corp., Armonk, NY). The randomization information was kept in opaque sealed envelopes. The outcome assessors and data analysts were masked to the study allocation.

2.5. Inclusion and exclusion criteria

2.5.1. Inclusion criteria. The both boys and girls were considered to be included if they were ages between 4 and 12 years old. All of them were diagnosed confirm as MA (symptoms occurred less than once weekly). In addition, the legal guardians of each child signed the informed written consent before the study.

2.5.2. Exclusion criteria. The children with MA were excluded if they had a history of exercise induced asthma; received any kinds of medications that help to relive MA 1-month before the study or during the study period; other severe diseases such as cancers, heart failure, and respiratory infections.

2.6. Intervention

All children in both groups received chewable montelukast (4 mg daily) tablet in the evening at bedtime, once daily, for a total of 6 weeks. Additionally, children in the treatment group also received ET program by a certified 5-year experienced training instructor. It included 40 min long aerobic circuit training class. Each child received ET 3 times weekly for a total of 6 weeks.

2.7. Endpoint assessments

The primary endpoint of lung function was measured by forced expiratory volume in 1 second (FEV_1)[27] and ratio between FEV_1 and forced vital capacity (FEV_1/FVC).[28] The secondary endpoint of clinical symptoms was assessed by clinical assessment score, and quality of life (QoL) was evaluated with Paediatric Allergic Disease Quality of Life Questionnaire (PADQLQ) scores.[29] The PADQLQ scale consists 26 items, the scores of each item range from 0, not bothered, to 6, extremely bothered. The higher score indicates the worse QoL. Moreover, any adverse events were also recorded during the study period.

The spirometry was utilized to measure FEV_1 and FEV_1/FVC by using PiKo-1 (ATS and EU electronic peak flow monitor, Ferraris Respiratory Europe Ltd., Westford SG13 7NW, UK) software. It was conducted by an experienced physician who had attended the training class before the study. All outcomes were measured at baseline, at the end of 6-week treatment, and 2-week follow-up after the treatment.

2.8. Statistical analysis

All characteristic data and endpoint values were analyzed by using IBM SPSS Statistics 17.0 (IBM Corp., Armonk, NY) by using intent-to-treat (ITT) analysis. The categorical data was applied by using Chi-squared test, while the continuous data was operated by using *t* test or Mann-Whitney *U* test to analyze the differences between 2 groups. The statistical significance was defined as $P < .05$ (2-tailed).

3. Results

A total of 105 eligible children with MA entered the study (Fig. 1). Of them, 27 did not meet the criteria, and were excluded. In addition, 6 of them rejected to participate in this study. Thus, a total of 72 children with MA were included in this study, and were equally allocated into the treatment group and the control group. Although 4 and 7 patients respectively withdraw at the end of 6-week treatment and 2-week follow-up respectively, all of them entered the final analysis by using ITT analysis (Fig. 1).

The comparisons of patient characteristics between 2 groups are summarized in Table 1. The comparisons of 2 groups did not differ significantly in all characteristics and clinical variables in this study, such as age, sex, race, asthma history, disease duration, and endpoints at baseline.

At the end of 6-week treatment, patients who received ET plus montelukast exerted better effectiveness in clinical symptoms relief ($P < .01$, Table 2) and QoL improvement ($P < .01$, Table 2), although the lung function did not show promising effective results with FEV_1 ($P = .80$, Table 3) and FEV_1/FVC ($P = .44$, Table 3), compared with patients who received montelukast alone. This trend kept steady throughout the period of 2-week follow-up with clinical symptoms relief ($P < .01$, Table 2), QoL improvement ($P < .01$, Table 2), and lung function, as assessed with FEV_1 ($P = .70$, Table 3) and FEV_1/FVC ($P = .41$, Table 3) between 2 groups.

All adverse events recorded in this study were mild (Table 4). No adverse events related to the ET occurred in the treatment group. No serious adverse event, as well as the treatment related death was recorded during the study period in either group. No significant differences regarding all adverse events were detected between 2 groups (Table 4).

4. Discussion

Although several previous studies have reported that montelukast monotherapy has been utilized to treat children with asthma,[30–33] its efficacy is still limited and also has a variety of adverse events. Thus, in order to improve its efficacy, alternative add-on therapy should be added to manage such disorder.

A previous published study has addressed the effect of ET plus montelukast for the treatment of children with EA.[25] Its results demonstrated that ET could decrease bronchial responsiveness to methacholine. It suggested that the combination of ET and montelukast provided beneficial action in children with MA. However, that study focused only on Italy children, and also had a relative small sample size, and did not evaluate the clinical symptoms and QoL in children with MA.

The results of the present study are partly consistent with the previous study.[25] In the present study, the findings showed that

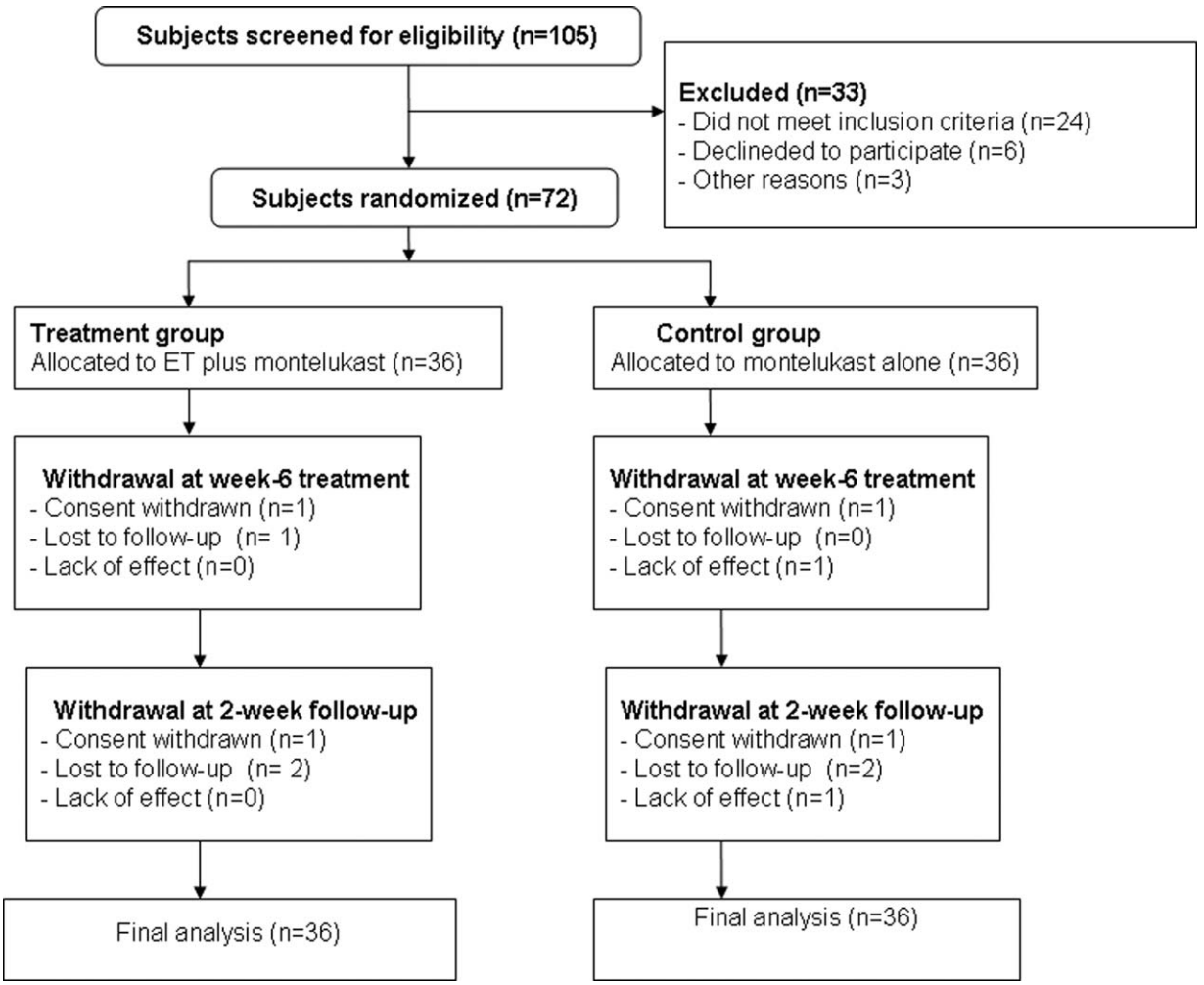

Figure 1. Flowchart of patient selection during the study.

Table 1

Comparison of baseline characteristics.

Characteristics	Treatment group (n = 36)	Control group (n = 36)	*P*
Age, y: mean (±SD)	6.9 (2.3)	7.1 (2.7)	.74
Sex, n (%)			
Boy	22 (61.1)	20 (55.6)	.63
Girl	14 (38.9)	16 (44.4)	–
Race, Asian (Chinese), n (%)			
Han ethnicity	33 (91.7)	31 (86.1)	.46
Hui ethnicity	3 (8.3)	5 (13.9)	–
Asthma history, n (%)	34 (94.4)	32 (88.9)	.40
Family history of asthma, n (%)	29 (80.6)	26 (72.2)	.41
Cough duration (week), mean (±SD)	0.7 (0.2)	0.6 (0.4)	.18
Clinical assessment score, mean (±SD)			
Wheeze	0.89 (0.51)	0.92 (0.58)	.82
Activity	0.91 (0.44)	0.94 (0.50)	.79
Cough	0.87 (0.41)	0.84 (0.47)	.77
Sleep	0.85 (0.39)	0.88 (0.43)	.76
FEV_1 (% predicted)	89.7 (3.3)	90.7 (2.9)	.17
FEV_1 /FVC (%)	80.1 (1.4)	80.7 (1.5)	.08
PADQLQ	0.94 (0.12)	0.99 (0.14)	.10

FEV_1/FVC = ratio between FEV_1 and forced vital capacity, FEV_1 = forced expiratory volume in 1 second, PADQLQ = Paediatric Allergic Disease Quality of Life Questionnaire scores, SD = standard deviation.

Table 2

Comparison of secondary endpoints at the end of 6-week treatment and 2-week follow-up.

	6-week treatment			2-week follow-up		
Secondary endpoints	**Treatment group (n = 36)**	**Control group (n = 36)**	***P***	**Treatment group (n = 36)**	**Control group (n = 36)**	***P***
Clinical assessment score						
Wheeze	0.48 (0.27)	0.59 (0.30)	<.01	0.50 (0.26)	0.63 (0.29)	<.01
Activity	0.53 (0.25)	0.65 (0.29)	<.01	0. 52 (0.28)	0.66 (0.30)	<.01
Cough	0.45 (0.26)	0.57 (0.21)	<.01	0.47 (0.29)	0.60 (0.24)	<.01
Sleep	0.40 (0.23)	0.55 (0.27)	<.01	0.42 (0.26)	0.56 (0.21)	<.01
PADQLQ	0.51 (0.14)	0.68 (0.17)	<.01	0.53 (0.14)	0. 65 (0.16)	<.01

Data are present as mean ± standard difference; PADQLQ = Paediatric Allergic Disease Quality of Life Questionnaire scores.

Table 3

Comparison of primary endpoint at the end of 6-week treatment and 2-week follow-up.

	6-week treatment			2-week follow-up		
Primary endpoint	**Treatment group (n = 36)**	**Control group (n = 36)**	***P***	**Treatment group (n = 36)**	**Control group (n = 36)**	***P***
FEV_1 (% predicted)	91.2 (3.5)	91.4 (3.3)	.80	91.4 (3.2)	91.7 (3.4)	.70
FEV_1/FVC (%)	80.6 (1.6)	80.3 (1.7)	.44	80.8 (1.5)	80.5 (1.6)	.41

Data are present as mean ± standard difference; FEV_1 = forced expiratory volume in 1 second, FEV_1/FVC = ratio between FEV_1 and forced vital capacity.

ET as an adjunctive therapy to the montelukast can significantly relieve the clinical symptoms and also can improve the QoL in patients with EA, except no significant differences in lung function were found between 2 groups. It may be because the duration of this study was not long enough to present the positive results for this therapy with only 6 weeks treatment. The results of this study indicated that ET as an adjunctive therapy to the montelukast may still benefit for children with MA.

The present study has several drawbacks. First, the sample size was still quite small in this study, which may impact its results. Second, the duration of this study may be insufficient to show the better promising efficacy for ET plus montelukast. Thus, future studies should extend their treatment duration to further warrant the results of this study. Third, although this study is a RCT study, the investigators and patients were not blinded, except the outcome assessors and data analyst, which may impact the patient selection in this study. The further studies should avoid these drawbacks.

5. Conclusion

The findings of this study showed that ET as an adjunctive therapy to the montelukast may benefit for children with EA after 6-week treatment. More studies with longer treatment duration are still needed to warrant the results of the present study.

Table 4

Comparison of adverse events between 2 groups.

Safety	**Treatment group (n = 36)**	**Control group (n = 36)**	***P***
Anorexia	3 (8.3)	5 (13.9)	.46
Headache	4 (11.1)	3 (8.3)	.69
Insomnia	1 (2.8)	2 (5.6)	.56
Anxiety	2 (5.6)	3 (8.3)	.65
Nausea	2 (5.6)	4 (11.1)	.40

Data are present as mean ± standard deviation.

Author contributions

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Visualization: Yan-feng Zhang, Lin-dong Yang.
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