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Original Article (Pages: 17374-17382)

Acute Effect of Inhalant Artemisia Persica Boiss on Pulmonary Function in Asthmatic Patients Aged 6-18 Years Old: A Randomized Control Trial

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Abstract

Background: Asthma is an inflammatory disease of the airways which is highly prevalent in children. Treatment of the disease is based on the relief of obstruction and inflammation of the airways. Artemisia persica Boiss. Has antioxidant and anti-inflammatory effects. The aim of this study was to investigate the acute effect of A. persica on pulmonary function in patients with asthma aged 6-18 years.

Methods: In this double-blind clinical trial, 118 asthmatic patients in the age range of 18-6 years, referred to the Spirometry Unit of Imam Ali Clinic, in Shahrekord, southwest of Iran, were randomly divided into control and intervention groups. Patients in the two groups were exposed to a placebo (distilled water) and 10 ml of inhalant A. persica 1.5% formulation for 15 minutes, respectively. Spirometry was performed before and 20 minutes after the completion of inhalation and the values were recorded. Data was analyzed by SPSS 20.

Results: Before the intervention, spirometric indices (including FEV1, FVC, FEV1/FVC, PEF25, PEF50, PEF75, and PEF2575) were not significantly different between the control and case groups. After the intervention, these indices were not significantly different between the two groups. In the group exposed to A. persica inhalation, after the intervention, spirometric indices including FEV1/FVC, PEF50, PEF75, and PEF2575 significantly decreased ($P<0.05$), while FEV1, FVC, and PEF25 indices did not change significantly after the intervention.

In the control group, FEV1/FVC, FVC, PEF25, PEF50, PEF50, PEF75 and PEF2575 significantly decreased ($P<0.05$) after the intervention, but FEV1 did not change significantly.

Conclusion: Acute inhalation of A. persica and placebo caused no improvement in spirometric indices in asthmatic patients.

Key Words: Antioxidant, Anti-inflammation, Artemisia Persica Boiss., Asthma, Spirometry.

* Please cite this article as: Panahandeh G, Rafieian-Kopaei M, Lorigooini Z, Kheiri S, Mahmoudian M. Acute Effect of Inhalant Artemisia Persica Boiss on Pulmonary Function in Asthmatic Patients Aged 6-18 Years Old: A Randomized Control Trial. Int J Pediatr 2023; 11 (02):17374-17382. DOI: **10.22038/ijp.2023.68357.5079**

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Received date: Oct.10,2022; Accepted date: Jan.30,2023

1- INTRODUCTION

Asthma is the most common chronic illness in childhood and adolescence and is increasing worldwide (1, 2). Although the disease has a low mortality rate, it is estimated that it comprises 1.1% of Disability-Adjusted Life Years (DALYs)/100,000 for all causes across the globe, and in addition to imposing stupendous direct and indirect costs, it is one of the main causes of hospitalization (3, 4). Children with asthma also experience a lower quality of life than their healthy peers (5). Shortness of breath, dyspnea, coughing, and wheezing are common complications and symptoms of the disease (6, 7), but these also include other complications such as rhinitis, infection, insomnia, and impaired social relationship and schooling (8-10). There are several treatments for this disorder, but each may lead to certain complications (11). Concerns about the side effects of asthma medications, on the other hand, may contribute to refusing treatment (12, 13). Therefore, it is important to seek out an effective herbal treatment for asthma that is available and inexpensive and has no side effects (14). However, there is little evidence for the use of complementary drugs such as herbal remedies; and this necessitates further investigations (15). Due to the inflammatory nature of asthma and its pathophysiological understanding, including airway spasms and reduced total antioxidant capacity in causing asthma attacks, one group of the plants with antioxidant, anti-inflammatory and antispasmodic effects are those of the Artemisia genus (16-19).

Artemisia is a genus of plants comprising 200-400 species belonging to the Compositae family, with clustered piles and usually bitter flowers. One of the valuable drugs of this genus is Artemisia persica (20). Therefore, in this study we aimed to evaluate the acute effect of inhaled A. persica in patients with asthma aged 6-18 years and also its acute changes using spirometry.

2- METHODS

2-1. Design and setting

This parallel clinical trial was performed on patients with asthma referred to the Spirometry Center of Imam Ali Clinic in Shahrekord, southwestern Iran, in 2018.

2-2. Sampling

The patients were selected by convenience sampling and were randomly divided into two groups.

According to the study of Ghanaie et al. (21), assuming that the rate of improvement in spectrometric indices including FEV1, FVC, FEV1/FVC, PEF25, PEF50, PEF2575, and PEF75 during the intervention was at least 30% in the case group and at least 10% in the control group, using the following formula and taking into account the 95% confidence interval and 80% power, the sample size in each group was calculated at 59, so that the total sample size was decided to be 118.

2-3. Inclusion and exclusion criteria

Children and adolescents with asthma aged 6 to 18 years whose diagnosis had been confirmed by previous clinical and spirometric examination and response to treatment with bronchodilator, and who provided consent to participate in the study (by completing and signing a written consent form) were eligible for enrollment in the study. None of the patients were taking systemic corticosteroids; they were previously known as patients who had exacerbation of symptoms due to the discontinuation of treatment for the occurrence of viral respiratory infections. Patients in the stages of mild and moderate persistent asthma were included in the study.

The exclusion criteria were suffering from severe asthma necessitating hospital care, chronic pulmonary disease with permanent obstructive or restrictive symptoms, acute respiratory infections, other infectious diseases, or chronic diseases of other organs, as well as taking short-acting bronchodilators during the last 4 hours and LABA (long acting beta agonist) within 12 hours before the test.

Finally, 118 patients were randomly divided into case and control groups (**Fig. 1**). To observe blinding, the two groups were identified by codes one and two and patients and researchers were blind to group allocation; and the inhalations of A. persica and placebo, as well as the spirometry were performed in two separate rooms.

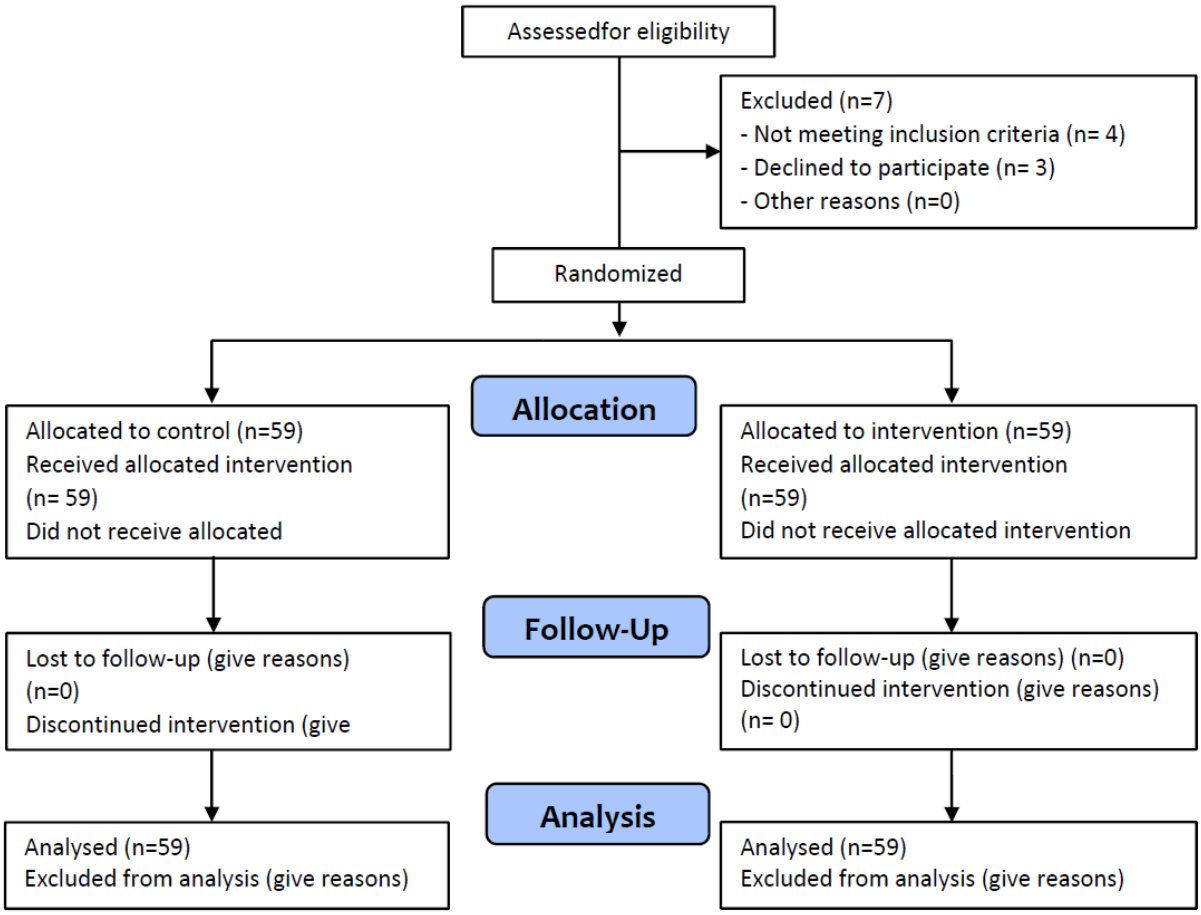

Fig. 1: CONSORT flow diagram of the study population

2-4. Drugs and treatments

Artemisia persica Boiss was collected from the Zagros Heights and after the scientific name was confirmed by the botanist, herbarium sample no. 1008 was recorded for it at the Medicinal Plants Research Center.

The plant was extracted by maceration after drying and pulverizing by 70% ethanol. After 72 hours, the extract was concentrated by rotary apparatus under vacuum. 1% was prepared for incense. After the final drying of the extract in a 37 ° C incubator, the extract was prepared from a 1.5% drug form extract (21).

2-5. Intervention

For all participants, the initial examination was performed and other causes of dyspnea were ruled out, and finally the diagnosis of asthma was made based on clinical symptoms and spirometric indices (22). The patients underwent spirometry after group allocation and before intervention, and Forced Expiratory Volume in 1 second (FEV1), Forced Vital Capacity (FVC), FEV1/FVC, and Peak Expiratory Flow at 25-75% (PEF 25-75%), PEF 25%, and PEF 75% were recorded. Patients in the two groups of intervention and control were then exposed to 10 ml of 1.5% A. persica inhalation and placebo inhalation for 15 minutes, respectively.

The inhalation in both A. persica and placebo groups was similar in appearance and spirometry was performed 20 minutes later again and their spirometric values were recorded after re-intervention. Subjects with at least 10% improvement in the above-mentioned values in spirometry were considered as responding to treatment (17).

In the present study SPIROLAB MIR spirometry device (no. A23-0J. 03844) and standard methods were used. Finally, the information obtained from the medical history, examination and spirometry was recorded in the checklist especially designed for this purpose.

2-6. Data analysis

The data were entered into SPSS version 20. Because spirometric indices were measured in percentages and therefore were ordinal, the median and interquartile range were used to describe them.

Mann-Whitney test was used for comparing the two groups and Wilcoxon signed-rank test was used to compare before and after the test.

3- RESULTS

A total of 118 children and adolescents participated in this clinical trial (59 in the control group and 59 in the intervention group). The age of the participants in the control group ranged from 7 to 16 (mean: 10.07±2.08) years and in the intervention group from 7 to 16 (mean: 9.21±2.02) years (P=0.23).

Overall, 81 (68.64%) patients were male and 37 (31.35%) ones were female, with no statistically significant difference between the two groups (P=0.55) (**Table 1**).

Table-1: Gender distribution of the participants

Variable		Placebo		A. persica	
		Number	Percent	Number	Percent
Sex	Male	39	66.1	42	71.2
	Female	20	33.9	17	28.8
Total		59	100	59	100

The spirometric indices were compared between the two groups, and the rate of changes in these indices before and after the intervention were also investigated (**Table 2)**.

According to the results of this table spirometric indices (including FEV1, FVC, FEV1/FVC, PEF25, PEF50, PEF75, PEF2575) were not significantly different between the control and intervention groups, before and after the intervention (P>0.05).

In the group exposed to A. persica inhalation, before and after the intervention, spirometric indices including FEV1/FVC, PEF50, PEF75, and PEF2575 significantly decreased (P<0.05),

indicating an adverse effect of A. persica inhalation on these indices.

In the intervention group, the FEV1, FVC, and PEF25 indices did not change significantly after the intervention (P>0.05).

In the control group after intervention, FEV1/FVC, FVC, PEF25, PEF50, PEF50, PEF75 and PEF2575 significantly decreased (P<0.05), but FEV1 after intervention did not change significantly (P>0.05).

Table-2: Comparison of the results regarding spirometric indices between the intervention and control groups before and after the intervention

Spirometric indices	Stage	Placebo	Iranian Artemisia	P-value
		Median	Median	
FEV1	Before	(82-108) 97	(82-106) 94	0.794
	After	(84-104) 96	(80-105) 95	0.435
	P-value	0.46	0.182	-
	Changes	(-3 (-5)) 0	(-3 (-5)) -1	0.759
FVC	Before	(91-118) 105	(89-114) 102	0.659
	After	(95-119) 104	(93-117) 103	0.583
	P-value	0.025*	0.216	-
	Changes	(-4 (-2)) 1	(-5 (-5)) 2	0.871
FEV1%	Before	(74-84) 80	(76-83) 79	0.534
	After	(72-83) 78	(74-81) 78	0.94
	P-value	0.002*	0.004*	-
	Changes	((-2 (-5)) -3	(-1(-4)) -1	0.679
PEF25	Before	(59-83) 81	(63-95) 79	0.968
	After	(61-89) 76	(62-92) 75	0.936
	P-value	0.027*	0.135	-
	Changes	(-4 (-12)) -2	(-6(-8)) -3	0.755
PEF50	Before	(59-90) 77	(59-83) 73	0.367
	After	(54-85) 72	(58-79) 70	0.639
	P-value	0.001*	0.01*	-
	Changes	(-4 (-11)) -5	(-3 (-8)) -4	0.550
PEF75	Before	(44-83) 62	(45-72) 58	0.317
	After	(43-78) 59	(43-64) 54	0.167
	P-value	0.03*	0.007*	-
	Changes	(7-(-15)) -4	(-8 (-15)) -7	0.671
PEF2575	Before	(57-91) 77	(60-87) 74	0.464
	After	(56-88) 69	(56-79) 68	0.324
	P-value	0.007*	0.004*	-
	Changes	(6-(-11)) -4	(-3 (-13)) -4	0.634

*Significance level: P<0.05

4- DISCUSSION

The present study was conducted due to the inconsistencies in the literature regarding the efficacy of Artemisia as well as differences in the use of the extract or essential oil of this plant.

According to the results, no significant difference in spirometric indices was

observed between the two groups before and after the intervention. After intervention compared to baseline, FEV1/FVC, PEF50, PEF75 and PEF2575 indices significantly decreased in the intervention groups. The mentioned indicators showed a significant change in the stages before and after the intervention in the control group. In addition, FVC and PEF25 indices significantly decreased in the control group but not in the intervention group. These findings indicate that the use of inhalant A. persica has no beneficial effect on the improvement of spirometric indices.

The results of the present study were inconsistent with those of Ghanaie et al. They observed that Artemisia spp. improved the FEV1 in 10% of the placebo group and 50% of the intervention group, and also improved the FEV1/FVC in 50% of the placebo group and 50% of the intervention group (21). This discrepancy may be related to the differences in the study populations so that the cited study was done on adults and in the present study, only children were included. Therefore, it seems that the treatment response is different in the two groups. In addition, the reassessment interval in this study was 20 minutes and in the study of Ghanaie et al., it was 50 minutes. Various other studies of different species of Artemisia, whether with humans or with animals, have shown promising results regarding reduction in asthma symptoms and attacks.

For example, Artemisia pallens, Artemisia argyi, and Artemisia princeps have been reported to exhibit anti-inflammatory and subsequently anti-asthmatic properties by modulating the levels of factors such as IgE, IL's, TGF-β, TNF-α, Nrf-2 and matrix metalloproteinase (MMP) in rats (23-27). In a study by Kim et al., which examined the effect of Artemisia asiatica extract on allergic asthma in rats, the extract was found to reduce the inflammatory process in these animals by regulating the MAP kinases/ NF-KappaB pathway (28). Another study showed that L. Artemisia annua relaxed the smooth muscle in the airways of the rat, thus revealing anti-asthmatic properties (29). Yet another study, by Khan et al., revealed that Artemisia vulgaris exhibited antispasmodic and bronchodilator properties. These effects are produced by blocking muscarinic receptors and preventing calcium influx into the muscles (30).

In this regard, similar results were obtained in the study by Shah et al. (31). These inconsistencies between the results of the present study and other studies may be attributed to the time and frequency of plant consumption.

Artemisia may also have side effects. Studies have shown that Artemisia pollen extracts can enhance allergic responses in animal models and urban environments, which requires further research and study in this field (32-34).

4-1. Limitations of the study

One of the limitations of the present study was the use of spirometry only 20 minutes after inhalation (acute effect). In a number of studies, the bronchodilator effects of medicinal plants have been observed after 30-60 minutes.

Another limitation of this study along with other studies on herbal extracts is the variability of the constituents of herbal extracts in different studies as well as the extracts obtained at different times and places. It has been reported that the biological effects of plant extracts and the amount of their active ingredients are affected by certain factors such as season of growth, location of collection, time of collection, and method of extraction (35). In this respect, it seems that the identification and study of the active ingredients of the plant resolves this limitation.

Yet another limitation of this study was the use of the extract of A. persica. It is suggested that in other studies, other formulations such as the extract of the plant be used due to their volatile, non-polar compounds.

5- CONCLUSION

According to the results of the present study, spirometric indices were not significantly different between the intervention group (A. persica) and placebo (distilled water) 20 minutes after the intervention. Inhaling A. persica for 15 minutes had no beneficial effect on spirometry findings at 20 minutes post-intervention. Placebo (distilled water) also had an adverse effect on spirometric indices.

6- ETHICAL CONSIDERATION

The present study was approved by the Ethics Committee of Shahrekord University of Medical Sciences (ethics code: IR.SKUMS.REC.1396.59). It should be noted that written consent for participation in the study was obtained from the parents of the patients.

7- ACKNOWLEDGMENTS

This article was derived from a research project approved by the Research and Technology Deputy of Shahrekord University of Medical Sciences (approval no. 2529).

8- CONFLICT OF INTEREST

None.

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