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Tanner McCalley

Philadelphia College of Osteopathic Medicine, tannermc@pcom.edu

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Is the use of Intestinal Helminths Safe and Effective in the Treatment of Allergic Rhinitis?

Tanner McCalley PA-S

A SELECTIVE EVIDENCE BASED MEDICNE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

Health Sciences – Physician Assistant

Department of Physician Assistant Studies
Philadelphia College of Osteopathic Medicine
Philadelphia, Pennsylvania

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Abstract

Objective: The objective of this EBM review is to determine whether the use of intestinal helminths is safe and effective in the treatment of allergic rhinitis.

Study design: Review of three English language, blinded randomized controlled trials from 2009, 2010, and 2010.

Data source: Randomized, controlled, blinded trials comparing the use of intestinal helminths versus visually matched placebo as a treatment for allergic rhinitis found using PubMed and Ovid databases.

Outcomes measured: Several different systems were used to evaluate the symptoms or occurrence of AR. Bager *et al.*2010 uses symptom scores of AR scale of 0 to 3. Feary *et al.*2009 used the Juniper rhinoconjunctivitis quality of life questionnaire. Flohr *et al.*2010 used the International Study of Asthma and Allergies in Childhood (ISAAC). Mean symptom score and incidence recorded in daily diaries were used for adverse events.

Results: Bager *et al.*2010 reported a mean difference in symptom scores of AR as 0.0 a t-test produced a p-value of 0.87 with a 95% CI 0.0(-0.5, 0.4). Feary *et al.*2009 reported no difference between the treatment and control groups (MD 0.33, 95% CI -0.27 to 0.93). No serious adverse events were reported in Bager *et al.*2010 or Feary *et al.*2009. There were several gastrointestinal adverse events reported including indigestion, flatus, upper abdominal pain and diarrhea.

Flohr *et al.*2010 reported a mean difference of 1.39 between experimental and control groups 95% CI (0.89-2.15) with a P-value of 0.1. The relative risk increase of AR was 37% after treatment. Absolute risk increase of AR was 1.8%. The number needed to harm (in this case cause AR after elimination of helminthic infection) was 56 patients.

Conclusions: The efficacy of intestinal helminths as a treatment for Allergic rhinitis is inconclusive. The P-values comparing the effect of treatment to placebo were not statistically significant. The controlled administration of helminths can be considered safe since there have been no reports of severe adverse events. Mild Gastrointestinal adverse events have been reported. Flohr *et al.*2010 demonstrates possible protective actions of helminthes but more research is warranted to obtain more conclusive data.

Keywords: Allergic Rhinitis, Helminth

INTRODUCITON:

Allergic rhinitis (AR) is a heterogeneous disorder that despite its high prevalence is often undiagnosed. It is characterized by one or more symptoms including sneezing, itching, nasal congestion, and rhinorrhea which are precipitated by an allergen. An allergen is defined as an environmental substance which may produce a hypersensitivity reaction in the body but may not be intrinsically harmful.¹

This paper evaluates three double blind randomized controlled trials. Two of the articles evaluate the efficacy and safety of intestinal helminths as treatment for AR. The third trial evaluates the prevalence of AR after treatment for intestinal helminths in area endemic with intestinal helminths.

AR is a significant cause of illness and disability. In the United States of America between 40 and 50 Million people have AR.² This condition effects between 10 and 30% of adults.² AR is also a common cause of missed school days in children, approximately 40% of children miss some school each year due to allergies.² AR may also play a role in other significant diseases such as sinusitis. It is estimated that 55% of people with sinusitis have a history of AR.² Not only does this condition cause a significant amount of illness and missed school it also has a huge cost. In 2005 total expenditures to treat AR was \$11.2 billion.³ Average expenditures per person for those with an AR related expense was \$434 for those under age 18, and for those ages 18–64 was \$566.³ This condition also accounts for approximately 12 million doctor-visits per year.⁴ Those 12 million doctor-visits congest an already busy health care system and take up precious time of the health care workers and adds to the already stressed health care system.

There is plenty known about the pathophysiology of AR but the reason why the immune system reacts to these otherwise innocuous particles is still debated. AR occurs when a non-harmful substance, such as pollen, is entrapped in the nasal mucosa and digested, which releases protein allergens. The initial immune reaction occurs when mast cells laden with IgE for the particular allergen comes in contact with the released protein. The mast cells degranulate and release inflammatory cytokines and histamine. Eosinophils infiltrate the submucosa and add to the edema and damage to the mucosa with the release of major basic protein. The damage from the inflammation and edema of the nasal mucosa produce the symptoms of AR.⁵

The diagnosis and treatment of AR is very common in the western world. AR is diagnosed primarily on typical history of allergic symptoms and physical exam findings including swollen nasal membranes, enlarged turbinates, and boggy pale mucosa. A nasal smear may also show eosinophilia. But since the symptoms of AR can have multiple causes additional tests may be performed. These tests include serological testing for circulating allergen specific IgE and skin prick tests using suspected allergens.

Once the diagnosis is made, the treatment of AR may be initiated. Typical treatments include allergen avoidance, pharmacotherapy and immunotherapy. Common pharmaceuticals used for AR include antihistamines, topical nasal corticosteroid sprays, decongestants, mast cell stabilizers or leukotriene inhibitors. In some severe cases, allergen immunotherapy may be attempted. These current treatments for AR are not optimal. Allergen avoidance is usually impractical and may cause significant interference in the patient's life. Pharmacotherapy for AR can be a great expense to the patient and in many cases may be ineffective. Topical nasal decongestants are associated with Rhinitis Medicamentosa and have the potential for abuse. Allergen injection immunotherapy takes between 3-5 years with regular injections administered

by a trained health care worker. This may be inconvenient for the patient and very expensive to the health care system. The problems with the current treatment options for AR warrant the search for a new treatment.

A relatively new hypothesis has occurred after several observational studies noted AR, asthma and eczema being less common in areas with a high prevalence of helminthic infections. It was postulated that helminthic infections may be protective against these immune mediated conditions. Helminths are a type of parasitic worm which infest humans and various animals. There are several different categories of helminths including nematodes (round worms), trematodes (flukes) and cestodes (tapeworms). Helminths may gain access to their host through a few different routes including orally and percutaneously. Once they have gained access to the host they would be destroyed by the host immune system. The helminths have evolved with their hosts and adapted ways to suppress or avoid the immune response. It is theorized that a side result of this modulation of the immune system may dampen the symptoms of AR. Due to this theory the use of low burden helminthic infections has been suggested as a treatment for AR.

OBJECTIVE:

The objective of this selective EBM review is to determine whether the use of intestinal helminths is safe and effective in the treatment of allergic rhinitis.

METHODS:

Criteria for articles to be included in this EBM review include randomized controlled trials with participants which suffer from AR or have a current Intestinal helminth infection. The interventions included in the search were the administration of any helminth species administered in any dose, by any route (oral or percutaneous), for any duration of exposure, and

at any developmental stage of the organism. The comparisons used in all three RCTs were visually matched placebos.

Information utilized in this review was found using the PubMed and Ovid databases. Inclusion criteria included randomized controlled trials limited to the English language and published in peer-reviewed journals. The key words used in searches were: “intestinal helminths” and “allergic rhinitis”. Research was conducted by the author. Articles were selected based on relevance to the clinical question and on the importance of outcomes to the patient (POEMs). The inclusion criteria includes that the studies were randomized, controlled, prospective, and included patient oriented outcomes (POEMs). Exclusion criteria included trials which combined analysis of AR and asthma or focused on disease oriented outcomes (DOEs). Ultimately, three studies were found and analyzed. They included: 1) a randomized, controlled, double blind trial comparing the resolution of symptoms of AR after administration of 8 doses of 2500 live *T. suis* ova with a 21 day interval, 2) a randomized placebo controlled feasibility study measuring the resolution of AR symptoms after cutaneous administration of 10 *Necator americanus*, and 3) a randomized, placebo controlled double blind trial of Vietnamese school children located in an area endemic for intestinal helminth infections measuring the occurrence of AR symptoms after administration of mebendazole 500mg at 0,3,6 and 9 months to eradicate helminth infections. A summary of the statistics used include relative risk increase (RRI), absolute risk increase (ARI), number needed to harm (NNH), and p-values.

Table 1: Demographics of included studies

Study	Study Type	N	Age (yrs.)	Inclusion criteria	Exclusion criteria	W/D	Interventions
Bager 2010	Randomized double blind controlled clinical trial	100	18-65	Symptoms of grass pollen allergy the last 2 seasons Men or women not of childbearing potential, scoring symptoms >50mm on a 100 mm visual analogue scale during previous seasons	Significant asthma, use of systemic steroids in last 2 months, history of severe disease, anti-helminth treatment in last 2 weeks	4	8 doses of 2500 live <i>T. suis</i> ova with a 21 day interval
Feary 2009	Randomized placebo controlled feasibility study	30	>18	Current symptoms of allergic rhinoconjunctivitis	Diagnosis of asthma, other significant medical disorders, pregnant or unwilling to use contraceptives for duration of study	3	Cutaneous administration of 10 <i>Necator americanus</i>
Flohr 2010	Randomized placebo controlled double blinded trial	1,566	6-12	Vietnamese school children grades 1-8 located in four communities in the Khanh Son district in Vietnam which is endemic for intestinal helminths infections	Not completing the baseline survey or providing a stool sample after the baseline survey	79	oral dose of mebendazole 500mg at 0,3,6,and 9 months

MEASURED OUTCOMES:

The measured outcomes included were; a change in mean daily total symptom score for runny, itchy, sneezing nose; the occurrence of adverse events such as diarrhea, flatulence, and upper abdominal pain; and the incidence of rhinitis since the start of treatment with mebendazole 500mg.

RESULTS:

The data collected from the three studies was presented in either dichotomous or continuous or both forms. In the Bager *et al.*2010 study the efficacy of the treatment with 8 doses of 2500 live *T. suis* ova with a 21 day interval was measured using a daily mean symptom score of AR symptoms. The scale used was from 0 to 3, where 0 is no symptoms, 1 is mild symptoms, 2 is moderate symptoms, and 3 is severe symptoms. The symptoms rated were itchy nose, runny nose, sneezing, blocked nose, red/itchy eyes, and watery eyes. They reported no difference between the groups. The mean difference was 0.0 a t-test was performed which produced a p-value of 0.87 with a 95% CI 0.0(-0.5, 0.4)

Table 2: Efficacy of *T. suis* ova in comparison to placebo measured in mean daily symptom score

	TSO Mean (SD)	Placebo Mean (SD)	Difference in mean	P-value	95% CI
Mean daily symptom score	1.4(1.2)	1.4(1.1)	0.0	0.87	(-0.5,0.4)

In Feary *et al.*2009 the efficacy of cutaneous administration of 10 *Necator americanus* was determined using the Juniper rhinoconjunctivitis quality of life questionnaire (RQLQ) over 12 weeks. There was no statistically significant difference between the groups (mean difference

0.33, P=0.31 95% CI -0.27 to 0.93). The data was adjusted for smoking status and produced an adjusted mean difference of 0.26 a 95% CI of -0.45,0.97, and a p-value of 0.46.

Table 3: Efficacy of *N. americanus* in comparison to placebo measured with Juniper RQLQ score

	Hookworm mean (SD) n=13	Placebo mean (SD) n=14	Mean difference (95% CI)	P-value	Adjusted* mean difference (95% CI)	P-value
JuniperRQLQ score (log area under the curve)	6.01 (0.82)	5.68(0.85)	0.33 (-0.33,1.00)	P= 0.31	0.26 (-0.45,0.97)	P=0.46

*adjusted for smoking status

Adverse events were also measured in Bager *et al.*2010 and Feary *et al.*2009. There were no adverse events requiring hospitalization in Feary *et al.*2009. Bager *et al.*2010 reported any adverse event and hospitalization due to gastrointestinal events. There was no significant difference in either group. Bager *et al.*2010 reported a greater likelihood of any of the adverse event in the subjects receiving helminths. NNH was calculated for the adverse events reported in the article and demonstrated the NNH for diarrhea as 7, the NNH for upper abdominal pain and flatulence as 4.

Table 4: Adverse events oral administration of 2500 *T. suis* ova

Adverse event	RRI	ARI	NNH
Diarrhea	0.46	0.15	7
Upper abdominal pain	8.25	0.33	4
Flatulence	1.5	0.26	4

Feary *et al.*2009 also measured the occurrence of adverse events using a mean daily score (scale 1-10) over a total 12 week period. They calculated statistical significance of adverse events using the Mann-Whitney U-test. Indigestion was the only statistically significant adverse

event which had a mean difference in medians of 0.11 and a calculated P-value of 0.2. Other adverse events were reported but were not statistically significant.

Table 5: Adverse events reported with administration of *N. americanus*

Mean daily score (scale 1-10) over total 12 week period				
Median (range)				
symptoms	Hookworm group	Placebo group	Difference in medians	P-value
Diarrhea	0.12 (0-3.37)	0.11 (0-3.88)	0.01	0.59
Abdominal pain	0.24 (0-3.81)	0.02 (0-3.00)	0.22	0.06
Flatulence	0.28 (0-1.76)	0.13 (0-2.62)	0.15	0.36
Indigestion	0.11 (0-2.39)	0 (0-0.87)	0.11	0.02

In Flohr *et al.* 2010 the intervention was the administration of mebendazole 500mg at 0, 3, 6 and 9 months to eradicate current helminth infections. They then had the parents of the Vietnamese school children answer questions from the International Study of Asthma and Allergies in Childhood (ISAAC) Phase Two questionnaires translated into Vietnamese. The parents answered the question if their child has experienced rhinitis since the start of treatment. 6.7% of those in the anti-helminthic treatment reported rhinitis while only 4.9% of placebo group reported the finding. This produced a mean difference of 1.39 with a 95% CI (0.89-2.15) and a P-value of 0.1. Using this information it was calculated that the relative risk increase of AR was 37% after treatment. Absolute risk increase or AR was 1.8%. The number needed to harm (in this case cause AR after elimination of helminthic infection) was 56 patients.

DISCUSSION:

Bager *et al.* 2010 reported no statistically significant difference in the mean daily symptom score between placebo and intervention, which signifies no therapeutic effect on rhinitis. . The efficacy of this treatment had a P value of .87 meaning the evidence cannot disprove that the results were not due to chance. Additionally for every four patients taking the

intervention one additional would also experience GI adverse events. There were several limiting factors to this experiment. The experiment was only done over one grass pollen season and compared selected patients based on their scoring of symptoms over the last 2 grass pollen seasons. Grass pollen severity can vary with differences in weather from season to season so some patients that had grass pollen allergy the last 2 years may not have the same severity of symptoms in the year of the trial lowering their average daily score.

Feary *et al.* 2009 shows that there is no significant benefit to administering intestinal helminths in the treatment of allergic rhinitis. The P-values was listed as 0.46 which indicates that this data could have either been random or as an effect of treatment. The adverse effects had a range of p values. Indigestion was the only symptom which was statistically significant with a P-value of 0.02. The article discusses egg count in the experimental group's stool, which demonstrated only 9 of the 13 in the experimental group had confirmed helminth infections. The remaining 4 had a rise in eosinophil count which was suggestive of established adult infestation of the bowel but not definite. It is possible that those 4 unconfirmed infections could have skewed their outcomes of the trial.

In Flohr *et al.* 2010 the results of the clinical trial even though not statistically significant demonstrate that for every 56 patients treated with anthelmintic treatment 1 more would experience symptoms of rhinitis. This demonstrates that there is limited protection provided from rhinitis by intestinal helminths. There are several factors that might have affected the outcome of the research including parents administering supplemental anthelmintic treatment and not honestly reporting its use. The parents also filled out the questionnaire which may have skewed the data since they were not the subjects of the experiment and they have missed the symptoms of AR in the children.

CONCLUSION:

From the research performed and obtained results, there is insufficient evidence to support the use of intestinal helminths as an effective treatment of AR. The controlled administration of helminths does appear to be safe with reports of no severe adverse events. There does appear to be a moderate amount of GI adverse events most significantly indigestion. According to Flohr *et al.* 2010 there does appear to be a slight protective element provided by the helminths against AR, even though not statistically significant, but further research with stricter guidelines and reporting would be needed for a more definitive answer. More preclinical research is required with specific helminth therapy including specific dosing, administration technique, and reporting of symptoms before a large scale clinical trial should be undertaken. The results of the preclinical trials would need to demonstrate a more statistically significant efficacy for the larger clinical trial to be initiated.

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