Soil Transmitted Helminth Infections and its Association with Haemoglobin Levels in India: A Meta-analysis

Microbiology Section

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ABSTRACT

Introduction: Soil Transmitted Helminth (STH) infections affect some of the poorest countries in the world. India is one of the most severely affected countries by these parasitic infections. They primarily affect children by impairing nutritional status, cognitive ability and overall development. Lower haemoglobin levels are a very common symptom associated with Helminth infections.

Aim: The present study was conducted to analyse the effect of STH infections on haemoglobin levels in India.

Materials and Methods: A systematic search of PubMed and Web of Science was carried out. We systematically reviewed the literature to identify studies reporting data on STH infection associated anaemia without any bar on language or date of publication. Full text studies reporting data on STH infection associated anaemia in humans were considered for final analysis.

Results: Careful screening resulted in 16 publications that met the eligibility criteria out of which six were case reports and ten were cross-sectional studies that reported data on helminth infections and haemoglobin levels. Odds ratio analysis of five cross-sectional reports indicated that Helminth infections are three times (OR-2.8, CI-95%, 2.4-3.4) more likely to be associated with lower haemoglobin levels as compared to uninfected population. An analysis of case reports indicated severe to moderate anaemia in all patients.

Conclusion: Helminth infections are often associated with lower haemoglobin levels resulting in lower cognitive development. We have found evidence that helminth infections are associated with lower haemoglobin levels in Indian population.

Implications of Key Findings: This study can provide a guideline to clinicians and healthcare professional in identifying a baseline for haemoglobin level associated with STH infection associated anaemia and might lead to more comprehensive analysis of reasons for anaemia, growth stunting and cognitive impairment in at risk Indian population.

Keywords: Ascariasis, Deworming, Hookworm, Iron-deficiency, Trichuriasis

INTRODUCTION

Soil Transmitted Helminth (STH) infections affect nearly 2 billion people across the world. Most of these infection are reported in children. WHO estimate puts nearly 870 million children under high-risk zones [1]. Most intense Infection has been observed in children aged 5-15 years possibly due to differential exposure to contaminated soil, lack of sanitation and an immature acquired immune response [2]. The prevalence pattern indicates that maximum cases are reported from South America, Africa and Asia [3-5]. India is the one of the largest contributor of STH infection cases with nearly 220.7 million children in need of preventive chemotherapy [6]. These infections are caused by four different species of helminths, Ascaris lumbricoides (roundworm), Trichuris trichiura (whipworm), Ancylostoma duodenale and Necator americanus (hookworm) [3]. The parasite eggs survive in warm and moist climate of tropical countries where they are deposited in soil and can infect via feco-oral transmission in case of roundworm and whipworm and by penetrating the skin of feet in case of hookworm. Prevalence of these infections is often associated with lower socio-economic status, lack of personal and community hygiene, open defecation practices and poor maternal education [7,8]. Consistent infections with any of the three parasites can lead to impaired nutritional status, school performance and irreversible cognitive deficits in the long run [9]. These infections can be treated by a single dose of either Mebendazole or Albendazole and policy makers in India have targeted the school going population by massive deworming programs [10]. WHO recommends annual deworming for areas with higher that 20% prevalence and biannual deworming for areas with higher than 50% prevalence [11]. STH infections are also associated with iron deficiency anaemia with infected individuals reporting lower haemoglobin levels as compared to uninfected individuals [12]. Hookworm infections are particularly of concern as they cause damage to the mucosa of small intestine causing 0.3-0.5 mL of blood loss every day [13]. Initial symptoms at the site of skin penetration appear as pruritic erythematous papular rash known as ground itch followed by eosinophilia and increased IgE levels. Heavy infections of hookworm are associated with abdominal pain, diarrhea, loss of appetite, weight loss, fatigue and anaemia. Roundworm and Trichuris infection results in atrophy of the intestinal villus and creation of mechanical barrier to nutrient absorption resulting in poor intake of food and malabsorption. Children with increased STH infection are shown to have lower mean haemoglobin, haematocrit and serum ferritin levels as compared to non-infected children [3,14]. Iron deficiency anaemia in children is associated with impaired psychomotor skills and reduced work capacity as adults and in pregnant women it is associated with increased maternal mortality [15]. Several studies have been published that show the effect of anti-helminthic drugs on haemoglobin levels. Two studies published by Stoltzfus RJ et al., indicate that anti-helminthic treatment can improve moderate to severe anaemia in children as young as two-year-old [16,17]. Other studies show similar effects in school going children complemented with hygiene education programs [18]. However, their role in improving anaemia during pregnancy is still debatable [19]. Given the prevalence of STH infections in India and its close association with anaemia, the aim of the present study was to comprehensively analyse the published literature on the topic and provide current information on the correlation of STH infections with anaemia in India.

MATERIALS AND METHODS

Search Strategy

We did a literature search based on PRISMA guidelines to identify all relevant literature pertaining to anaemia due to helminth infections in India. We systematically search PubMed and Web of Science with the following search terms anywhere in the article: (helminth or hookworm) AND (anemia or anaemia or hemoglobin or haemoglobin) AND India. We searched the databases without any bar on language, date or nature of study from inception upto December 2017. To identify additional studies, reference list of publications were carefully screened.

Eligibility Criteria

Studies that were published from inception upto December 2017 in English language were considered. Initial assessment was based on review of title and abstract of all studies. Full texts of potentially relevant studies were further analysed for soil transmitted helminth related anaemia. Cross-sectional studies and case reports with full text availability and reporting data about STH related anaemia were included in the study. We excluded studies carried out in animals, reviews and studies reporting anaemia due to other parasitic infections.

Data Extraction

The data extracted from the selected publications included first author, date of publication, date of survey, place where the study was carried out, sample size and age, type of diagnostic test performed, study design, percentage anaemic and haemoglobin levels. All the data was entered in excel file and double-checked.

Meta-Analysis

Odds ratio with 95% Confidence Interval (CI) was used as a measure of association for STH infection related anaemia. Odds ratio is considered in this study, since it can inform about the probability of anaemia among patients due to STH infection as a causative factor. The values of odds ratio were calculated from the data extracted from the included studies comparing the frequency of anaemia cases in STH infected patients verses non infected cases; and also by comparing the frequency of non anaemia cases having STH infection with non anaemia cases without STH infection. More value of odds ratio represents more probability of anaemia induced by STH infection. Raw data for anaemia in STH infected and uninfected patients were extracted from tables, figures, texts or summary data from the selected articles. Odds ratio was calculated using online resources (https://www.medcalc.org/calc/odds_ratio.php).

RESULTS

Initial search of the databases with keywords resulted in 352 references [Table/Fig-1]. A total of 97 studies were identified for screening after removal of duplicates. After initial reviewing of title and abstract 54 studies were identified for full text screening out of which 38 studies were excluded with reason (Reviews-11, Non-Human Studies-10, articles inaccessible-8, Other helminth infections-5, No correlation between anaemia and STH-2, anaemia not reported-1, Anaemia reported in Tuberculosis-1). Sixteen potentially relevant studies were identified that reported STH infections along with anaemia or haemoglobin levels from India [20-35]. Out of these references 10 were community based cross-sectional studies and 6 were case reports [Table/Fig-2,3]. Five cross-sectional studies were included in the final qualitative synthesis [Table/Fig-4].



S. No.	Author	Date of publication	Age	Method of parasite detection	Parasite detected	Ν	Infected	Infected			Uninfected		Haemoglobin
								Anaemic	Non anaemic	Uninfected	Anaemic	Non anaemic	levels (g/dl) Mean/Median*
1	Srinivasan V et al., [20]	1987	5-59	Microscopy	HW	1113	1040	894	146	73	49	24	10.3
2	Rao VG et al., [21]	2003	Adolescents	Microscopy	HW	783	466	410	56	317	235	82	9.19
3	Wani SA et al., [22]	2008	5-15 yrs	Microscopy	AL, TT	382	299	NR	NR	83	NR	NR	10.54
4	Tengse VG et al., [23]	2011	10-20 yrs	Microscopy	AL, TT, HW	122	45	35	10	77	NR	NR	10.95*
5	Sharma SK et al., [24]	2012	Adolescent female	Microscopy	AL, TT, HW	2499	424	NR	NR	2075	NR	NR	11.02
6	Shrinivas K et al., [25]	2014	18-35 yrs Pregnant female	Microscopy	AL, HW	500	62	55	7	438	245	193	9.5
7	Ramyasree A et al., [26]	2015	1-90 yrs	Microscopy	AL, HW	238	34	NR	NR	204	NR	NR	13.7
8	Ajwani KD et al., [27]	1974	0-10 yrs	Microscopy	AL, TT, HW	3200	435	318	117	2765	NR	NR	8.5*
9	Kumar V et al., [28]	2003	6-10 yrs girls	NR	AL, TT, HW	716	511	334	177	205	101	104	8.2
10	Nallam NR et al., [29]	1998	7-13 yrs	Microscopy	AL, TT, HW	217	177	157	20	40	32	8	9.7

S. No.	Author Year of Publication		Age	Age Method of parasite detection		Haemoglobin levels (g/dL)			
1	Suthar PP et al., [30] 2015		10 y	Ultrasound	AL	8			
2	Zanwar VG et al., [31]	2016	7 y female	Colonoscopy	Π	3.8			
3	Achanta CR, [32]	2016	65 y male	Endoscopy	HW	8.2			
4	Sharma V et al., [33]	2017	25 y male	Endoscopy	HW	7.7			
5	Sharma V et al., [33]	2017	19 y male	Endoscopy	HW	5			
6	Sharma V et al., [33]	2017	62 y female	Endoscopy	HW	6			
7	Thomas V et al., [34]	2006	35 y male	Colonoscopy	HW	8.2			
8	Agarwal P et al., [35]	2012	6 y female	Microscopy	HW	8.8			
	[Table/Fig-3]: General characteristic of case reports considered for data extraction. AL-Ascaris lumbricoides: IT-Trichuris trichiura: HW-Hookworm								

S. No.	A settle and	N	Infected	Infected		Uninfected	Uninfected		Haemoglobin levels (g/dL)	Odds ratio 95% CI
5. NO.	Author			Anaemic	Non anaemic		Anaemic	Non anaemic		
1	Srinivasan V et al., [20]	1113	1040	894	146	73	49	24	10.3	2.992 (1.8, 5.03)
2	Rao VG et al., [21]	783	466	410	56	317	235	82	9.19	2.55 (1.8, 3.72)
3	Shrinivas K et al., [25]	500	62	55	7	438	245	193	9.5	6.2 (2.8, 13.9)
4	Kumar V et al., [28]	716	511	334	177	205	101	104	8.2	1.94 (1.4, 2.7)
5	Nallam NR et al., [29]	217	177	157	20	40	32	8	9.7	1.3 (0.5, 3)
Total		3329	2256	1850	406	1073	662	411		2.8 (2.4, 3.4)
Table/Fig-41: Studies considered for meta analysis.										

Case Reports

The six case reports reported the data from eight individuals, four male, three females and one whose gender wasn't mentioned, with ages ranging from 7-65 years. Abdominal discomfort, melena, weakness and fatigue were common symptoms reported by the patients. The diagnosis of helminth infection was made by endoscopy in four cases, two cases were diagnosed by colonoscopy and one case each was diagnosed by ultrasound and microscopy. Hookworm was the predominant STH found with six cases reporting the parasite. *A. lumbricoides* and *T. trichiura* was reported by one individual each. All of the cases reported severe to moderate anaemia with very low levels of haemoglobin ranging from 3.8-8.8 g/dL [Table/Fig-3,5]. Lowest level of anaemia was found in a seven-year-old girl with Trichuris dysentery syndrome and reported haemoglobin level of 3.8 g/dL.



Cross-sectional Studies

Ten cross-sectional studies, reported the data for STH infections and haemoglobin both. Three studies reported the data from children, one study reported the data for female child, two studies reported the data from adolescents, another study reported the data from adolescent female only, two studies reported the data from all age groups, and one study reported the data from pregnant females only. Microscopy was the preferred method of parasite detection. Five studies reported all three STH in the same population; three studies reported either *A. lumbricoides* and hookworm or *A. lumbricoides* and *T. trichiura* in the same populations, while two studies reported hookworm infection only. The percent of infections ranged from 12-93%. Nine studies reported moderate to severe anaemia and low haemoglobin levels which correlates with STH infection [Table/ Fig-2,6]. One study reported low haemoglobin levels however they did not found a correlation between STH infection and anaemia in infected verses non infected samples.



Meta-Analysis

Only five studies had reported data regarding the anaemia levels in infected and uninfected population. These five studies were included in meta-analysis. A total of 3329 patients provided the data on the association between STH infection and anaemia. Higher STH infection was correlated with threefold higher anaemia in patients (OR-2.8 2.4-3.4) [Table/Fig-4,7]. Out of the 10 cross-sectional studies five studies (Wani SA et al., Tengse VG et.al., Sharma SK et al., Ramyasree A et al., and Ajwani KD et al.,) provided no information about anaemia in non-infected population hence they were excluded from the final meta-analysis [22-24,26,27].

DISCUSSION

STH infections constitute significant disease burden in developing parts of the world. Children below the age of 18 are the most affected demographic. Ascaris and Trichuris gain access to human host by ingestion of eggs while hookworm larvae infects human by



skin penetration. Once inside the human host they develop into full adult worms. Hookworm parasitizes the upper part of small intestine, Ascaris worms parasitizes small intestine and Whipworm parasitizes the large intestine. Heavy worm infection can cause pain and abdominal distension. They may also lead to malabsorption of vitamin A and other micronutrients. STH infections contribute to anaemia through blood loss and micronutrient deficiency. Hookworm infections particularly, cause blood loss due to its penetration and attachment of mucosa and submucosa and once the blood loss exceed the nutritional reserve of host it leads to iron-deficiency anaemia. The infection can be treated with a single doze of Albendazole and Mebendazole, which inhibit parasite microtubule polymerisation. The global strategy for control of STH infection is based on regular anthelminthic treatment, sanitation and personal hygiene and health education [3,36]. In a previously published study we have looked at the prevalence of STH infections in India by systematically reviewing the published literature and found nearly 30% of India's population living with more than 50% prevalence [37]. In the current study we have tried to assess the prevalence of anaemia due to STH infections in India based on published literature.

A systematic literature search identified 10 cross-sectional studies and 6 case reports that reported anaemia in STH infected patients. The case reports noted severe STH infection with patients reporting to clinic only after symptoms of gastric pain, melena and fatigue. These are extreme cases with patients reporting in most cases severe hookworm infection, which could be visualised via endoscopy. In four of these cases patients reported severe anaemia and in other four they reported moderate anaemia. In all of these cases anaemia was corrected with Albendazole/Mebendazole therapy indicating damaging effects of STH infections on haemoglobin levels and overall health of the patients. One of the case reports reported the data in a seven-year-old girl presented with Trichuris dysentery syndrome and haemoglobin levels of 3.8 g/dL, indicating that heavy infection with T. trichiura could also lead to anaemia. Another five cross-sectional studies establish a correlation between STH infections and anaemia. In all of these studies mild to moderate anaemia was reported with haemoglobin level ranging from 8.2-11.02 g/dL. However, none of these studies have reported any data about therapeutic approaches and post-therapy haemoglobin levels. An odds ratio analysis of five studies for which complete data on anaemic and non-anaemic population in infected verses uninfected population was available, indicated that STH infected individuals are three times more likely to develop anaemia as compared to uninfected individuals. Ajwani KD et al., and Kumar V et al., also reported severe anaemia in some of the STH infected cases they observed, with haemoglobin levels below 8 g/dL [27,28].

Literature search and data extraction is prone to bias, to this effect we have comprehensively searched the databases with broad

search queries, nonetheless two relevant studies from Assam and West Bengal were unavailable due to lack of full text availability. Furthermore, association of STH infection with anaemia is widely reported phenomenon, however there aren't many studies reporting statistical correlation of STH infection with anaemia. In the crosssectional studies considered for this meta analysis, none reported the data on socioeconomic status, risk factors, therapeutic approaches or post treatment haemoglobin levels. The aetiology of anaemia could be multifactorial with poor nutrition, STH infections, gender, and socioeconomic status being some of the causes of anaemia. Establishing a statistical correlation with all of these factors will be helpful in tackling the problem.

LIMITATION

The study had certain limitations. Socio-economic status, risk factors, therapeutic approaches and post-therapy haemoglobin levels were not reported in any of the studies. Further cross-sectional studies and controlled trials should be conducted considering the mentioned parameters.

CONCLUSION

In the present study we have attempted to analyse the effects of STH infections on anaemia. An analysis of five cross-sectional studies indicates that STH infection is three times more likely to be associated with anaemia as compared to non anaemic individuals. Also, in cases of severe infections as reported by several case reports haemoglobin levels may drop down to abnormally low levels that can be life threatening. The growth stunting and cognitive impairment associated with STH infection is well documented and so does the effect of anti-helminthic drugs in alleviating this problem. This study can provide insights to public health officials and clinicians in establishing a baseline of haemoglobin levels to identify STH associated anaemia and therefore help in establishing robust deworming, iron supplementation and hygiene education programs.

Availability of data and materials: The datasets analysed during the current study is available from the corresponding author on reasonable request.

Authors' contributions: NS and MF extracted the data. NS and MF analysed the data. NS wrote the manuscript. All the authors read and approved the final manuscript.

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