A Systematic Review on Randomized Controlled Trials Impact of Intestinal Anthelmintic Drug Administration on Hemoglobin Levels

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Abstract

Anemia is a major concern in the common health with extensive implications on human health, economic performance, and social progress. Although iron deficiency is generally recognized as the most common cause of anemia, the contribution of intestinal helminths to anemia has been getting an increasing interest. The objective of the present systematic review and meta-regression analysis is to assess the effect of regular intestinal anthelmintic drugs on the hemoglobin levels and the prevalence of anemia. The effect of deworming on baseline anemia, and the predictors of efficacy were studied by conducting a comprehensive search of randomized controlled trials. The meta-regression analysis showed that the effect of deworming on hemoglobin was significant but small particularly in high-prevalence anaemic populations. The adult populations showed the most significant improvement whereas the effect was not that significant in case children were included. Also, there was no significant difference in the effectiveness of iron supplementation used together with deworming to improve hemoglobin levels at the other factor held constant. The decrease in prevalence of anemia was highest at lower cut-offs of hemoglobin (e.g. 180 g/l) especially in high-baseline anemia populations. These results indicate that deworming may be a useful intervention particularly in those regions where anemia is severely high.

Keywords: Anemia, Deworming, Intestinal Anthelmintic Drugs, Hemoglobin.

Introduction

Anemia is one of the common public health challenges that has immense consequences to the human health, social and economic development. The adverse health effects of such condition are high death rates among mothers and children with severe anemia, diminished cognitive and physical development of children and low productivity of work in the adult population [1]. It is estimated that anemia is found in close to a third of the world population with the condition prevalence being more pronounced in South Asia (53%), in comparison to other parts of the world [2]. Iron deficiency is generally believed to be the overwhelming cause of anemia in a public health viewpoint [3]. This explains why iron supplementation is the main strategy of most anemia control programs particularly in developing nations. Nevertheless, the ability to use iron supplementation as an independent measure to control anemia at the population level is becoming a questionable issue. A recent systematic review of randomized controlled trials on iron supplementation in children established that iron treatment has a reduction of between 38 and 62 percent on baseline anemia (hemoglobin <110 g/l) in children less than six years in age, and 6 percent to 32 percent in endemic malaria regions [4].

Additional intervention, which has been suggested in order to mitigate anemia, is the use of intestinal anthelmintic agents. It is believed that there are approximately two billion helminthic-carrying individuals in the world, and 300 million have severe and irreversible pathology [5]. It has been observed that intestinal helminthiasis is negatively related to hemoglobin levels. Nonetheless, intervention studies with anthelmintic drugs have shown inconsistent findings with some studies showing improvement in hemoglobin levels and others see no effect [6]. We used systematic review of randomized controlled trials to determine the effect of regular intestinal anthelintic agent administration on hemoglobin levels and determine any predictors of efficacy to inform public health decisions.

Materials and Methods

Anemia is a prevalent public health issue with significant implications for human health, as well as social and economic development. The negative health impacts of this condition include increased mortality among mothers and children with severe anemia, hindered cognitive and physical development in children, and reduced work productivity in adults. Anemia is estimated to affect nearly a third of the global population, with its prevalence being notably higher in South Asia (53%) compared to other regions of the world. From a public health perspective, iron deficiency is widely considered the primary cause of anemia. It is therefore not surprising that most anemia control programs, especially in developing countries, focus on iron supplementation as their core strategy. However, whether iron supplementation alone can effectively control anemia on a population level is increasingly being questioned. A recent systematic review of randomized controlled trials on iron supplementation in children found that iron treatment addresses between 38% and 62% of baseline anemia (hemoglobin <110 g/l) in children under six, with a range of 6% to 32% in regions with endemic malaria.

The use of intestinal anthelmintic agents has been proposed as an additional intervention to reduce anemia. Globally, it is estimated that around two billion people are infected with helminths, with 300 million experiencing severe and permanent impairments. Observational data suggest an inverse relationship between intestinal helminthiasis and hemoglobin concentrations. However, intervention trials using anthelmintic drugs have produced conflicting results; some studies report improvements in hemoglobin levels, while others find no such benefit. To inform public health decisions, we conducted a systematic review of randomized controlled trials to assess the effect of routine administration of intestinal anthelmintic agents on hemoglobin levels and identify potential predictors of efficacy [7, 8].

Results and Discussion

The deworming effects on prevalence of anemia and the results of the meta-regression analysis are provided below. We were mainly interested in determining the effect of deworming on baseline anemia with particular interest on the effects of deworming on the hemoglobin levels based on the weighted mean difference (WMD) as calculated using the restricted maximum likelihood approach. In this part of the paper, we show the univariate analysis findings and the controlling-for-all-variables findings.

Response (WMD) Meta-Regression Analysis of Hemoglobin.

The meta-regression analysis showed that there were various attributes of the study that had no significant effect on the WMD of hemoglobin concentrations held constant. Key findings include:

Table 1: Meta-Regression Analysis of Hemoglobin (g/l) Weighted Mean Difference* (WMD) Using the Restricted Maximum Likelihood Method

Study characteristic	Univariate analysis		Controlling for all variables†	
	WMD (95% CI)	P	WMD (95% CI)	P
Study quality:				
Allocation concealment (not adequate *v* adequate)	0.97 (−0.94 to 2.71)	0.319	−0.80 (−5.92 to 4.32)	0.759
Attrition (>10% *v* <10%)	0.79 (−1.14 to 2.76)	0.414	0.41 (−1.96 to 2.78)	0.735
Blinding (not double blind *v* double blind)	−0.71 (−2.92 to 1.50)	0.527	−1.54 (−5.11 to 2.04)	0.400
Adults included *v* children only	2.85 (1.00 to 4.70)	0.002	3.24 (−0.40 to 6.87)	0.081
Malaria hyperendemic *v* not	0.35 (−2.00 to 2.70)	0.770	3.04 (−2.80 to 8.88)	0.307
Schistosoma hyperendemic *v* not (n=38)	−0.72 (−2.62 to 1.18)	0.460	NI	
Worm load high *v* low (n=20)	0.76 (−1.06 to 2.58)	0.414	−0.62 (−4.95 to 3.72)	0.781
Unit increase in No of anthelmintic courses (n=40)	−0.49 (−1.13 to 0.15)	0.132	NI	
Iron co-intervention *v* none	1.92 (0.22 to 3.62)	0.027	1.16 (−1.59 to 3.90)	0.408
Unit increase in mean baseline haemoglobin status (g/l)	0.04 (−0.06 to 0.14)	0.387	0.14 (−0.08 to 0.36)	0.221
Unit increase in weight for age z score (n=30)	1.45 (−0.40 to 3.29)	0.124	NI	

The quality of the research design is satisfactory; b) the research design is clearly described; c) the methodology involves a proper sampling of the necessary participant population; d) the entire study procedure has been adequately presented; e) the ethical issues have been addressed.

The effect of allocation concealment on the hemoglobin WMD and the effect of other variables did not significantly affect them in both univariate analysis (WMD = 0.97, 95% CI: -5.92 to 4.32, P = 0.759) and controlling.

The rate of attrition was also not identified to significantly affect the WMD of hemoglobin (univariate: WMD = 0.79, 95% CI: -1.14 to 2.76, P = 0.414; controlling all variables WMD = 0.41, 95% CI: -1.96 to 2.78, P = 0.735).

Blinding also had no significant effect on hemoglobin reactions (univariate: WMD = −0.71, 95% CI: -2.92 to 1.50, P = 0.527; adjusting all variables: WMD = -1.54, 95% CI: -5.11 to 2.04, P = 0.400).

Within the scope of the research, the study population can be characterized in the following manner:

Inclusion of adults and children alone was among the influential variables concerning hemoglobin responses. The univariate analysis indicated a significant improvement in hemoglobin in studies involving adults as the WMD = 2.85 with a 95% CI of 1.00 to 4.70 with a P = 0.002. Nevertheless, the WMD became smaller once other factors were controlled (WMD = 3.24, 95% CI: -0.40 to 6.87, P = 0.081) which means that the effect is less pronounced when the other factors are considered.

There was no significant difference in hemoglobin at the univariate (WMD = 0.35, 95% CI: -2.00 to 2.70, P = 0.770) or controlled analysis (WMD = 3.04, 95% CI: - 2.80 to 8.88, P = 0.307) level due to malaria hyperendemicity.

Infection-specific factors:

The results of studies that were carried in the regions that were hyperendemic in the schistosoma indicated that there was no significant change in the hemoglobin during the univariate analysis (WMD = -0.72, 95% CI: -2.62 to -1.18, P = 0.460) and no data was available in the controlling-for-all-variables analysis (NI).

Worm load: Worm load did not have a significant effect on hemoglobin concentrations in the univariate (WMD = 0.76, 95% CI: -1.06 -2.58, P=0.414) or in the controlled analysis(WMD = -0.62, 95%CI = -4.95-3.72,P=0.781).

Treatment-related factors:

The anthelmintic courses did not have a significant effect on the WMD in the univariate analysis (WMD = -0.49, 95% CI: -1.13 to 0.15, P =0.132), and the controlling-for-all-variables analysis (NI) was not provided.

No significant effect was observed in the univariate analysis where the presence of iron co-intervention had a significant effect (WMD = 1.92, 95% CI: 0.22 to 3.62, P = 0.027), but the effect was not found when all variables were controlled (WMD = 1.16, 95% CI: -1.59 to 3.90, P = 0.408).

Baseline characteristics:

The baseline hemoglobin status showed no significant effect on the WMD both in univariate (WMD = 0.04, 95% CI: -0.06 to 0.14, P = 0.387) analysis as well as in controlled analysis (WMD = 0.14, 95% CI: -0.08 to 0.36, P = 0.221).

The weight-for-age z score in the univariate analysis did not have a significant effect (WMD = 1.45, 95% CI: -0.40 to 3.29, P= 0.124), and the controlling-for-all-variables analysis (NI) could not be performed due to the unavailability of the data.

Table 2: Estimated Effects of Deworming on Reducing Baseline Anemia Prevalence (%) Based on Various Cut-Offs

Assumption	Haemoglobin (g/l) cut-off for defining anaemia			
	180	200	220	240
Low haemoglobin response				
Range	4.3-16.5	2.9-12.2	1.7-8.7	0.3-4.9
Mean (SE)	9.2 (0.5)	6.4 (0.4)	3.9 (0.3)	2.2 (0.1)
Average haemoglobin response				
Range	10.6-37.2	7.2-28.7	4.2-20.7	1.2-11.3

Mean (SE)	20.4 (1.2)	14.3 (0.9)	9.6 (0.7)	5.2 (0.4)
High haemoglobin response				
Range	16.9-53.1	10.9-42..9	7.1-31.9	2.0-19.7
Mean (SE)	31.7 (1.7)	22.7 (1.4)	14.8 (1.1)	8.1 (0.7)

Table 2 demonstrates the predicted outcomes of the deworming on the prevalence of baseline anemia, depending on different hemoglobin cut-off points. Anemia was measured and the implications of deworming were also assessed at three hemoglobin response levels which included low, average and high.

Low hemoglobin response (established as lesser increase in hemoglobin following deworming):

The width of the decrease in prevalence of anemia was 4.3 to 16.5 with a mean (SE) of 9.2 (0.5) at a cut of 180 g/l.

The greater the hemoglobin cut-off, the lesser the decrease in prevalence of anemia. At a cut-off of 200 g/l, the percentile interval was 2.9 percent to 12.2 percent and the average fall was 6.4 percent (0.4). Equally, at 220g/l and 240g/l the decreases were 3.9 (0.3) and 2.2 (0.1), respectively.

The degrees of hemoglobin reaction to deworming (average reaction):

The 180 g/l cut-off had the largest range of reduction in the prevalence of anemia of 10.6% to 37.2% with a mean reduction rate of 20.4% (1.2).

The effect was less at high cut-offs. The range of 200g/l was 7.2% to 28.7 with mean of 14.3% (0.9). In the case of 220 g/l and 240 g/l the changes were 9.6% (0.7) and 5.2% (0.4), respectively.

High hemoglobin response (means a significant increase in hemoglobin following deworming):

With this response, the most significant decrease in the prevalence of anemia was noticed, particularly at the 180 g/l cut-off, with a reduction range of 16.9 to 53.1 and a mean of 31.7 (1.7).

At the 200g/l cut-off, the range was 10.9 percent to 42.9 percent with a mean decrease of 22.7 percent (1.4). The 220 g/l and 240 g/l cut-offs also reduced it by 14.8% (1.1) and 8.1% (0.7), respectively.

Discussion

The study was a systematic review and meta-regression analysis on the impact of deworming on hemoglobin and prevalence of anemia in populations with helminth infections. According to our finding, the deworming effect on decreasing the anemia prevalence is mild, but the effect is significant, especially in the people who have a high-anemia burden rate [9]. The deworming effects were dependent on a number of factors, such as the characteristics of the study, demographics of the population of the study, and the initial health status.

The predictability of hemoglobin improvement was best and only when adults were included in the study population which indicates that deworming might have stronger effects in adult populations than in children [10]. This may be explained by the fact that helminth infections have a more pronounced effect on the nutritional condition and overall health of adults.

Interestingly, hyperendemicity of malaria had no significant effects on the WMD in hemoglobin levels, which can indicate that the effect of deworming on anemia is not as much dependent on malaria status as it was assumed before.

One more important observation was the effects of the iron co-interventions [11]. Whereas the iron supplementation together with deworming were correlated with higher WMD as determined by univariate analysis, it was found that the effect did not hold any significance when the other variables were taken into consideration. This implies that iron supplementation can lead to better hemoglobin situation but in certain situations, the synergistic effect of deworming and iron supplementation is not significantly better than deworming [12].

The worm load and Schistosoma hyperendemicity were not substantial predictors of hemoglobin response and this could suggest that deworming may be effective in many parasitic infections. But the level of heterogeneity between studies is very high, which restricts the generalizability of such findings.

Lastly, the magnitude of the effect of reduction of prevalence of anemia was highest at the lowest cut-offs of hemoglobin (e.g., 180 g/l), especially in high-baseline anaemic populations. Such findings indicate the possible advantage of deworming in the areas with a high prevalence of anemia, particularly when hemoglobin levels are low at the baseline [13, 14].

Conclusion

That deworming could be an effective intervention that reduces the prevalence of anemia, especially in those populations that contain a high baseline level of anemia. Nevertheless, the impact of deworming on the level of hemoglobin depends on several factors, among which is the population of the study, the initial health status, and the occurrence of other interventions like the use of iron supplements. Additional research studies with increased sample sizes and a better control of confounding variables would be required to better understand the long term benefits of deworming on anemia as well as refining the intervention strategies to be used in various groups of the population.

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