Original Article

Effect of oral vitamin C administration along with iron supplementation for treating anaemia among adolescent girls - Protocol for systematic review and meta-analysis

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Abstract

Background: Anemia among adolescent girls is a worldwide public health problem. Although anemia has several causes, the most common and significant is iron deficiency. Treatment of anemia with iron alone may result in reduced compliance on account of adverse effects. Various studies have revealed that use of vitamin C in addition to iron improves its absorption and reduces the ill effects of the therapy. However, a concrete evidence of adding vitamin C to iron for treating iron deficiency anemia is lacking. **Aims:** Protocol for current systematic review was prepared and registered with the aim to generate evidence on role of vitamin C in addition to iron for treatment of anemia. **Materials and Methods:** Present protocol has been prepared based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines and registered with International Prospective Register of Systematic Reviews. Data extraction will be done by the reviewers independently. Cochrane risk of bias assessment tool will be used for risk of bias assessment. **Results:** For primary outcome and each of the other outcomes pairwise random effects meta-analysis and network meta-analysis will be performed. Sensitivity analysis will be performed in case of any heterogeneity is detected to find out the difference of the effect estimation between subsets. **Conclusions:** The evidence for role of vitamin C as an adjunct in iron and folic acid for treatment of anemia in adolescent girls will be generated once the systematic review and meta-analysis is completed.

Keywords: Anemia, iron, protocol, systematic review, vitamin C

Introduction

In anemia, the hemoglobin concentration or the red blood cell count of a person is less than normal. The optimal hemoglobin concentration required to meet physiologic needs varies by age, gender, elevation of residence, smoking behaviours, and pregnancy status.[1] Anemia is thus a lower hemoglobin concentration than World Health Organization's thresholds for varying life stages and is characterized by insufficient erythropoiesis and lower oxygen-carrying capacity for red blood cells to meet physiological requirements.[2] Although anemia has several causes, the most common and significant is iron deficiency, which accounts for approximately 50% of cases.[3] Iron deficiency is defined as inadequate mobilizable iron stores caused by long-term negative iron balance and depleted ferritin and hemosiderin stores.[4] Undiagnosed or untreated iron-deficiency anemia may cause serious problems such as fatigue, headaches, restless legs syndrome, heart problems, pregnancy complications,

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and developmental delays in children. Iron-deficiency anemia can also make other chronic conditions worse or cause their treatments to work poorly. This underlines the importance of timely and adequate treatment of iron deficiency anemia by primary care providers.

World Health Organization defines adolescence as the period of life from 10 to 19 years of age. Anemia arising out of nutritional causes particularly iron deficiency anemia is a fairly common occurrence among adolescent girls. They are at higher risk of anemia due to a period of physical growth, reproductive maturation, and cognitive transformations which demands high macronutrients and micronutrients including iron. The ill effects of anemia in this age group are many making it empirical to treat adequately at primary care level by family physicians.[5]

Rationale- Among adolescent girls, anemia is not limited to any topographical region, but it is a problem faced across the world. Nutritional anemia being a common health-related issue in the current set up has been extensively studied. However, a concrete evidence of adding vitamin C to iron for treating iron deficiency anemia is lacking. This is adversely affecting the implementation of the treatment plan. With this backdrop, the current systematic review will be conducted.

Treatment of anemia with iron alone may result in reduced compliance on account of adverse effects. Studies reveal use of vitamin C in addition to iron improves its absorption and ill effects of the therapy alone. Vitamin C is the only dietary constituent other than animal tissue that has been shown to promote iron absorption.[5-7] The facilitating impact of vitamin C with food on iron status is minimal.[8] However, whether vitamin C has additional advantages, such as improving the efficacy of iron tablets and, thus, speeding up the recovery of anemia remains poorly understood. Whether iron tablets with vitamin C supplements should be suggested is still a matter of debate.[9]

With this backdrop, the present systematic review and meta-analysis was planned and the protocol for the same was prepared with the objectives to study effect of oral vitamin C administration along with iron supplementation for treating anemia among adolescent girls.

Materials and Methods

The present protocol has been prepared based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[10] It has been registered with International Prospective Register of Systematic Reviews vide registration number CRD42021287012. For the present review, only peer-reviewed published studies will be considered irrespective of their sample size and geographical setting.

Data management and selection process- For the present review, only peer-reviewed published studies will be considered. However, the reviewers will not include data from dissertations, scientific papers, and abstracts from conferences and grey literature.

In the initial scrutiny, pertinent research articles on the topic will be considered based on the titles and abstracts. Further full texts of the shortlisted articles will be appraised for their quality assessment and relevance.

Details on eligibility criteria for inclusion and exclusion of studies are depicted in Table 1.

For conducting the present review, studies will be included irrespective of their sample size and geographical setting. The studies will be finally included for the review after independent evaluation by two of the reviewers. In case of a scenario with differences of opinions regarding selection of studies, the matter will be settled by discussion and consultation with the third reviewer. This procedure will be followed to ascertain that biases in selection of studies are minimal. Data extraction will be done by the two reviewers independently.

Types of study to be included

Case-control studies, cohort studies, and randomized controlled trials that are peer-reviewed and for which full text is available online will be included for the present systematic review.

Information sources

The search will be performed by reviewer 1 and 2. The differences will be resolved by discussion with reviewer 3 and 4. Literature search will be conducted in PubMed Central, EMBASE, The Cochrane Library, Science Direct, Up To Date, Web of Science, and Scopus. In addition to the electronic search, the studies cited by the included studies and the studies included in the previous meta-analysis related to the subject will also be searched. Standard Preferred Reporting Items for Systematic Reviews and Meta- Analyses guidelines will be followed for including studies. Initially, the reviewer will screen the abstracts to shortlist the relevant studies which will be eventually followed by scrutiny of full texts of selected articles.

Table 1: Eligibility criteria for selection of studies

Inclusion criteria	Exclusion criteria
Studies for which full texts are available.	Studies conducted during the COVID-19 pandemic period
Studies published before December 2021	Studies whose publication language is other than English
Case control studies, cohort studies, and randomized controlled trials published in peer-reviewed journals	Gray literature, congress, conference, symposium, abstracts, and reports published in meeting booklets and theses
Studies published in English language	Studies in which the intervention was applied for less than 2 weeks
Studies in which the treatment was given for at least 2 weeks	

Data collection and extraction

Study characteristics (author, year, and country of the study), characteristics of adolescent girls (such as age, socioeconomic status, etc.), and primary and/or secondary outcome measurements will be collected and extracted to an Excel spreadsheet. Data extraction will be done by the two reviewers independently.

Data items

Participants/population

Studies covering adolescent age groups girls of and irrespective of their menstrual status will be included for this systematic review. Selection criteria that will be applied for the study participants in the included articles are shown in Table 2.

Intervention(s), exposure(s)

Studies will be included which assess the effect of vitamin C administration (as an intervention or exposure) in treatment of anemia among adolescent girls. In the present review, the interventions will be examined in three groups.

1. Only vitamin C administration for treatment of anemia-
   Studies that estimate effect of vitamin C as the mainstay of treatment for anemia in the adolescent girls will be included.
2. Vitamin C administration along with iron for treatment of anemia-
   Studies that are based on treatment of anemia with vitamin C in addition to iron supplementation will be included.
3. Other dietary supplementation in addition to vitamin C administration along with iron for treatment of anemia-

This will include the studies which examine effect of multiple treatment modalities such as dietary supplementation of iron, vitamin D, and B12 in addition to vitamin C along with iron.

Comparator(s)/control

The comparator groups in which vitamin C supplementation in any form was not given and/or placebo was given will be considered as a control group.

Table 2: Selection criteria for participants in included studies

Inclusion Criteria	Exclusion Criteria
Adolescent girls with anemia	Having known menstrual disorders
No known medical illness	Patients of bleeding disorders
Not on any medication that may affect the hemoglobin levels	Known hematological diseases (sickle cell diseases, thalassemia, etc.)
No ovarian disease	Using drugs that can affect hemoglobin levels
No uterine disease	Chronic kidney diseases as cause of anemia
Adolescent girls who have consumed vitamin C for at least 2 weeks	Pregnant

Outcomes and prioritization

Main outcome(s)

The hemoglobin level measured by any of the standard recommended method will be the primary outcome.

Additional outcome(s)

Red blood cell count, serum ferritin levels, and Total Iron Binding Capacity which have been measured after the intervention.

Risk of bias in individual studies

Cochrane risk of bias assessment tool will be used for risk of bias assessment which contains the following items: adequate sequence generation, allocation concealment, blinding, incomplete outcome data, and selective outcome reporting and other bias.

Results

Strategy for data synthesis

For primary outcome and each of the other outcomes pairwise random effects meta-analysis and network meta-analysis will be performed. The postintervention measures of the outcomes will be assessed while pooling the relative effect of each intervention. Conchran's Q test and I^2 statistics will be used to reveal the heterogeneity between the included trials. Forest plots will be generated to show the study-specific effect sizes with 95% confidence intervals and funnel plots will be generated to detect any small study effect or publication bias.

Network meta-analysis will be performed using a frequentist approach. The effects of direct and indirect comparisons will be estimated with random effects network meta-analysis. The structure of networks for each outcome will be showed with network plots. The transitivity assumption will be checked by controlling the effect modifiers and the consistency assumption will be checked statistically by both global and loop-specific approaches. League tables will be drawn to show the relative treatment effects and the Surface under the Cumulative Ranking values will be calculated to rank the interventions according to their effectiveness.

Analysis of subgroups or subsets

Sensitivity analysis will be performed in case of any heterogeneity is detected to find out the difference of the effect estimation between subsets.

Discussion

The proposed systematic review and meta-analysis is an attempt to investigate role of vitamin C in treatment of iron deficiency anemia. The evidence generated by gathering and summarizing information from the present review will aid the treatment providers at all levels including family physicians to emphasize on administration of vitamin C in addition to traditional only iron therapy. Further ahead in a long run it will guide

future researchers to carry out detailed research for a better understanding of role and utility of vitamin C in the treatment of iron deficiency anemia.

Anemia at adolescent age can in a long run result in multiple problems such as poor performance in academics and co-curricular activities, poor memory retention, reduced attention span and increased school dropout, reduced immunity with increased susceptibility to infections, lowered stamina for physical activities, and complicated pregnancy and motherhood.[11-14] Anemia in adolescence has serious implications for a wide range of outcomes, and nearly all of the functional consequences of iron deficiency are strongly related to the severity of anemia.[15,16]

Treatment of anemia due to iron deficiency is essentially done by oral iron therapy alone by most of the primary care providers. Vitamin C is considered to be improve iron absorption from the gut.[6,17,18]

All this would directly and indirectly impact the growth of the nation as well as the economy and thus it is imperative to treat the condition by making judicious use of all available amenities. This highlights importance of the topic and hence the current systematic review is proposed.

A critical assessment and evaluation of the research studies on this topic will help generate a pooled evidence on efficacy of vitamin C in addition to oral iron therapy for treatment of iron deficiency anemia in routine practice by primary care providers and family physicians.

Ethics and dissemination

This is a systematic review and meta-analysis as only a secondary analysis of data already available in scientific databases will be conducted. For that reason, ethical approval is not required. The results of this review will be submitted for peer-reviewed publication and will be presented at relevant conferences.

Conclusions

Anemia in adolescent girls is an important global public health problem. The evidence for role of vitamin C as an adjunct in iron and folic acid for the treatment of anemia in adolescent girls will be generated once the systematic review and meta-analysis is completed. This will go a long way in formulating policies at national level to deal with this ever burgeoning problem.

Abbreviation	Definition
RBC	Red Blood Cells
PRISMA-P	Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol
TIBC	Total Iron Binding Capacity

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Conflicts of interest

There are no conflicts of interest.

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