The Efficacy of Zinc Supplementation to Prevent Progression to Immunologic Failure among HIV- Infected Adults

A Meta-Analysis

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Abstract: - Adequate zinc is critical for immune function. HIV infection progressively destroys the immune system and increase the susceptibility to opportunistic infection. Some scientific papers have linked zinc deficiency with decrease CD4 lymphocyte. We conducted a meta-analysis to evaluate the efficacy of zinc supplementation for prevention of immunologic failure among HIV adults.

The review was conducted and reported according to the Preferred Reporting Items for systematic Reviews and Meta-analysis (PRISMA). Eligible studies regardless of their publication status were identified by searching electronic literature using PUBMED and Cochrane. We included all RCT comparing orally administered zinc with placebo. Assessment for study inclusion, data extraction and risk of bias analyses were performed in duplicate.

We included 7 trials involving 1,611 participants. Result showed a significant p value of 0.003. Out of 873 adult patients included in the study that was on zinc supplementation (experimental group), a total of 424 (48.57%) patients had progression of immunologic failure. On the other hand, out of 758 adult patients, a total of 418 (55.14%) patients that had immunologic failure on the controlled group. This showed a significant result with a p value of 0.003 and a C.I of 0.74 (0.61-0.90).

The results of our meta-analysis showed that oral zinc supplementation may prevent progression of immunologic failure among HIV infected adults. However, large high quality trials are needed before definitive recommendations for clinical practice can be made. Adverse effects were common and should be the point of future study, because a good safety and tolerance profile is essential to any supplement.

Key Words: — ***HIV infection, PUBMED, Immunologic failure, Clinical practice.***

I. INTRODUCTION

Since its first discovery in an Iranian male in 1961, zinc deficiency in human is now known to be an important malnutrition problem worldwide (1). Zinc is an essential micronutrient for human metabolism that catalyzes more than 100 enzymes, facilitates protein folding and help regulate gene expression (2). Zinc supplementation may be effective for the prevention of URTI and diarrhea. Human IV infection are important health concerns worldwide (2).

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HIV is a virus that spread through certain body fluids that attacks the body's immune system.

Overtime, HIV can destroy so many of cells such as CD4 cells that the body can't fight off infections and disease (3).

Baum et.al, recently reported a benefit of zinc supplementation without adverse effect to prevent immunological failure in HIV patient.

Literature has postulated that HIV activation is associated with long-term oxidative stress.

Scientific papers have linked zinc deficiency with decrease CD4 lymphocytes and decrease survival. Baum et al showed in 2010 and in 2013, that supplementation with anti-oxidant, vitamins and minerals was associated with longer survival and fewer immunological failure.

II. Patients And Methods

A. Search Strategy

The review was conducted and reported according to the Preferred Reporting Items for systematic Reviews and Meta-analysis (PRISMA). Eligible studies regardless of their publication status were identified by searching electronic literature using PUBMED and Cochrane. All randomized controlled trials involving the use of zinc supplementation to prevent progression to immunologic failure are published in English Language. The search was done by Keywords: HIV, Zinc supplementation, Immunologic failure and in combination. The electronically generated list of eligible studies for inclusion were hand searched to avoid missing any relevant studies.

B. Inclusion And Exclusion Criteria

Studies were selected for this metanalysis if they met the following inclusion criteria: 1. the study is a Randomized controlled clinical trial design, reported as full text and published in the English language. 2. Participants in the study include adults (over 18 years old) including those who diagnosed with HIV with ART or without ART treatment. 3. Adult patient >18 years old with confined HIV infection based on Western blotting test result. They were all reported to have CD4> 200 mm3.

The exclusion criteria were pregnancy, history of Hypersensitivity to zinc, uncontrolled virus >40 copies per ml, patient who previously received zinc supplementation.

III. Data Extraction And Validity Assessment

The literature search, data extraction, and quality assessment were independently undertaken by two authors (AMQ and AC) using a standardized approach. Any inconsistencies were settled by arbitration with the primary author (AMQ) until a consensus was reached. Assessment of validity of the included studies were performed using the quality scale for metanalytic reviews provided by our recent training (SLMC) by the two mentioned investigators. The risk of bias tool encompasses 8 domains which included allocation concealment, physician caring for the patient blinded regarding the treatment, intention to treat analysis conducted and person making an outcome assessment blinded regarding treatment, groups being compared balanced in terms of known determinants outcome, groups treated equally in terms of other medication received, frequency of follow up and general quality of care, dropout rates between the groups comparable and outcome detection methods used in similar in both groups.

A checklist was generated (Appendices) and studies were given an assessment of “yes”, “no”, or “NS”. Table 1.2 shows a summary of the risk of bias. Most studies were rated as having low risk of bias.

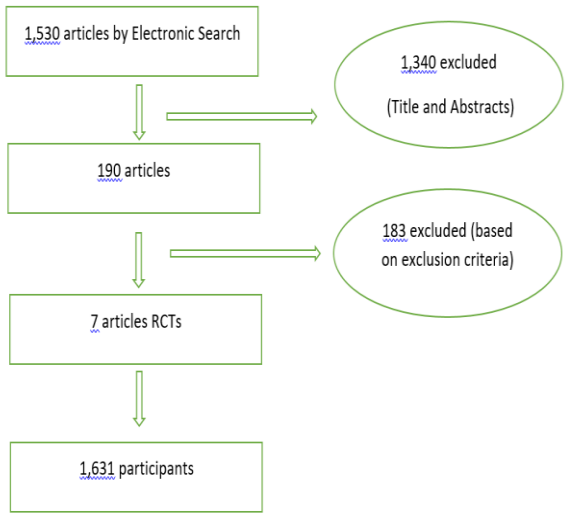


Fig.1. Flow chart of study selection

IV. Study Selections

We identified more than 1,530 articles during our initial electronic search, of which 1340 were excluded following an initial review (title and abstract). We retrieved the full text for the remaining 190 articles, and 7 randomized controlled trials were found to meet all of the inclusion criteria in which the investigators involved a total of 1,631 randomized patients who underwent zinc supplementation of more than 6 months. (Figure 1.1)

Table.1. Characteristics of included studies

Reference	Location	Year of Publication	Design	Population	Treatment Duration
Green et al	Singapore	2005	Double blinded RCT	130	28 th days and 6 months

Carcamo et al	Washington CA	2006	Double blinded RCT	159	14 days and 6 months
Baum et al	California, USA	2010	Double blinded RCT	234	6 and 18 months
Asdamongkol et al	Thailand	2013	Prospective RCT	62	6 and 12 months
Heidy et al	Columbia	2013	Double blinded RCT	80	6 months
Gnatienko et al	Russia	2018	Double blinded RCT	254	6 and 18 months
Hadadi et al	Iran	2019	Double blinded RCT	146	3,6,9 months

Table.2. Risk of bias of included studies

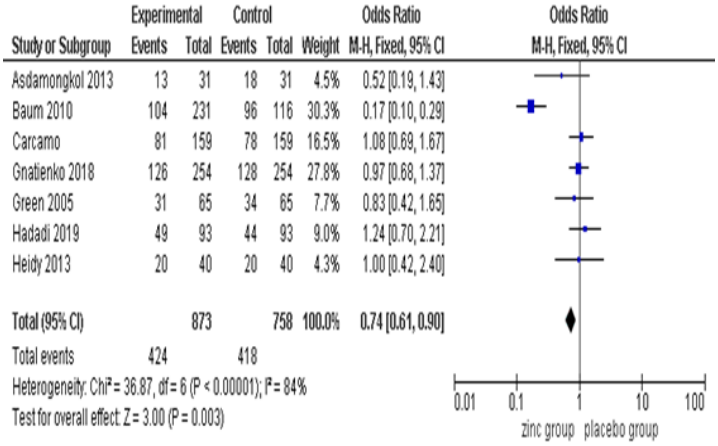
	SUBTLE BIAS				FRANK BIAS	
References	**Allocation concealment**	**Blinding of participants and health professionals**	**Blinding of outcome assessors**	**Intent to treat analysis**	**Proper description of losses to follow up and dropout rates**	**Selective outcome reporting**
Baum et al	Y	Y	Y	Y	Y	Y
Asdamongkol et.al.	N	Y	Y	Y	Y	Y
Heidy et.al.	Y	Y	Y	Y	Y	Y
Green et.al.	Y	Y	Y	Y	N	Y
Gnatienko et. al.	Y	Y	Y	Y	Y	N
Carcamo et. al.	N	Y	Y	Y	Y	N
Hadadi et.al.	Y	Y	Y	Y	Y	Y

V. Statistical Analysis

Statistical analysis was performed using Review Manager (RevMan) Version 5.3 freeware program developed by the Cochrane Collaboration. For this meta-analysis, we allocated the results of each randomized controlled trial as dichotomous frequency data. The relative risks (RRs) and 95% confidence intervals (CIs) of the individual trials were calculated from the event numbers extracted from each trial before data pooling. The homogeneity among studies were examined using chi square test. A Forrest plot was generated by combining the OR of included studies using a random effects model.

VI. Results

Result showed a significant p value of 0.003. Out of 873 adult patients included in the study that was on zinc supplementation (experimental group), a total of 424 (48.8%) patients had progression of immunologic failure. On the other hand, out of 758 adult patients, a total of 418 (48.9) patients that had immunologic failure on the controlled group. This showed a significant result with a p value of 0.003 and a C.I of 0.74 (0.61-0.90).



VII. Discussions

Several studies have shown that zinc supplementation has significantly prevent the progression of immunologic failure among HIV infected adults by preventing the decline of CD4 count. This constitutes the therapeutic dilemma and has prompted investigator to investigate if Zinc supplementation can specifically be used in preventing the progression of immunologic failure among HIV infected adult.

In 2010 Baum et al, investigated their participants who had low plasma zinc levels. HIV viral load, complete blood counts and blood chemistry including parameters of renal and liver function were monitored at baseline and every 6 months and 18 months. This study demonstrated that long term zinc supplementation delayed immunological failure and decreased diarrhea over time. After 3 years, another study was published; Asdamongkol et al where plasma zinc levels were measured after 6 months of zinc supplementation. In this study, they concluded that the CD4+ cell count significantly increased after zinc supplementation in patients with low plasma zinc levels. On the same year, another study conducted on Mendellin Columbia, they were able to select an HIV confirmed participants and evaluated after 12 weeks. They concluded that patients who receive zinc sulfate supplement could increase the CD4 lymphocyte significantly. In the study of Green et al., Gnatienko et al., Carcamo et al., and Hadadi et al, these study conluded a negative result, that supplemental zinc had no significant effect on the duration or remission of immunologic failure among HIV infected adults. Possible explanations were postulated during analysis of these different conclusions. One possible explanation is that the schedule of follow up and reassessment are different in each study. The longer the supplementation such as in study of Baum et al, the more positive outcome.

In this meta-analysis, we found out that zinc supplementation have significant effect on preventing immunologic failure among HIV infected adults.

VIII. Conclusion

In conclusions, there is currently sufficient evidence to advocate the use of zinc supplementation to prevent immunologic failure among HIV infected adults. In the presence of significant evidence in this study, Zinc supplementation can be recommended as a supplement to prevent immunologic failure.

IX. Recommendations

A more precise and descriptive, clinical trials may be needed to determine the true effect of zinc supplementation among HIV infected adults. Future randomized clinical trials with supplementation for a longer period while assessing the viral load can help better evaluate the potential benefits of zinc supplementation among HIV infected adults. Adverse effects were common and should be the point of future study, because a good safety and tolerance profile is essential to any supplement.

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