Review Article

Role of Zinc in Pediatric diseases: Evidence based Guidelines

Gedam DS

Dr D Sharad Gedam, Associate Professor in Pediatrics, L N Medical College, Bhopal, India & Editor- in- chief, IJMRR

Address for correspondence: Dr D Sharad Gedam, Email: editor.ijmrr@gmail.com

Abstract

Role of zinc in human health including growth, development, immune status and acute diarrhea is indisputable. Zinc deficiency is well known because of poor dietary habits, increased secretion and poor absorption of zinc during diarrhea. Present review will demonstrate role of zinc in various pediatric disorders and newer update. We have tried to include recent review on role of zinc in childhood diseases as per evidences available on electronic databases.

Introduction

Zinc deficiency in humans is now known to be an important malnutrition problem world-wide. It is a required for proper functioning of most human body systems. Respiratory, GIT, Immune, CNS, Skeletal and Reproductive systems are most affected in deficiency. In this review we will provide a brief discussion on evidence based role of Zinc in various childhood diseases.

Role of Zn in paediatric Diarrhea

Acute diarrhea is leading cause of under five mortality in most of developing countries including India despite the use of Oral rehydration solution. Worldwide it accounts for 1.5 billion episode and 1.5-2.5 million deaths estimated annually in children below 5 years of age[1,2]. In developing countries like India scenario is worse due to triad of Malnutrition, Infections and Poverty. Of India's more than 2.3 million annual deaths among children, about 334 000 are attributable to diarrhoeal disease[3,4,5]. It means around 1000 babies are dying every day due to diarrhea. First recommendation for Zinc use came years back in 1992 when Centre for disease control has recommended its use for Acute diarrhea[6].As per Joint statement of World health Organization (WHO), United Nations International children's Emergency Fund (UNICEF) & United States agency for International Development (USAID) has recommended Use of Zinc in children. It has been recommended that Low Osmolar Oral Rehydration Solution (Low Osmo ORS) with low glucose and salt along with Zinc reduces severity and Duration of diarrhea. It also reduces recurrence in next 2-3 months.[7]

But according to recent cocharane Review[8] which consist of 9128 children and 24 clinical trials in acute diarrhoea, there is currently not enough evidence from well conducted randomized controlled trials to be able to say whether zinc supplementation during acute diarrhoea reduces death or hospitalization (very low quality evidence).

Review also indicated that In children above than 6 months zinc supplementation can decrease the duration of diarrhea (low quality evidence) Conversely, In children aged less than six months, the available evidence

Manuscript received: 16th Aug 2013
Reviewed: 26th Aug 2013
Author Corrected: 29th Sep 2013
Accepted for Publication: 20th Oct 2013

suggests zinc supplementation may have no effect on mean diarrhoea duration (low quality evidence), and may even increase the proportion of children whose diarrhoea persists until day seven. Zinc supplementation during acute diarrhoea causes vomiting in both age groups (high quality evidence). In children with persistent diarrhoea, zinc supplementation probably shortens the duration of diarrhoea by around 16 hours (moderate quality evidence)[8]

Mechanism of action: A very recent publication has established that zinc inhibits cAMP-induced, chloride-dependent fluid secretion by inhibiting basolateral potassium (K) channels, in *in-vitro* studies with rat ileum. As this study was not performed in Zn-deficient animals, it provides evidence that Zn is probably effective in the absence of Zn deficiency [9,10]. Zinc also improves the absorption of water and electrolytes, improves regeneration of the intestinal epithelium, increases the levels of brush border enzymes, and enhances the immune response, allowing for a better clearance of the pathogens [11]

Role of Zinc in Respiatory disorder

In India, around 1.7 million children died before reaching the age of 5 years in 2010, and more than half of them (52%) died in the first month of life. The major causes of deaths were pneumonia (24%) with Diarrhea (13%)[12].

Zinc supplementation in young children demonstrated inconsistent results. One study in developing countries demonstrated that zinc supplementation reduces risk of Pnemonia[13]. Another clinical trial from Bangladesh suggested that it reduces duration of hospital stay, Hypoxia, Tachypnia and rapid recovery is possible[14]. However some double blind trials from developing countries suggested no beneficial effect of zinc supplementation in severe pneumonia either in duration of hospital stay or duration of pneumonia recovery[15]. Another meta analysis has demonstrated No significant difference between the two groups for common parameters (duration of resolution of hypoxia, chest indrawing or tachypnoea, change of antibiotics and treatment failure rates)[16]. As per evidences available Zinc supplementation is not indicated for severe pneumonia[17-20].

Role of Zinc in asthma

Acute severe asthma is associated with low level of Zinc but recovery from asthma is not associated with zinc level. Routine supplementation of zinc is not advised in asthma[21].

URI

Zinc administered within 24 hours of onset of symptoms reduces the duration of common cold symptoms in healthy people but some caution is needed due to the heterogeneity of the data. As the zinc lozenges formulation has been widely studied and there is a significant reduction in the duration of cold at a dose of ≥ 75 mg/day, for those considering using zinc it would be best to use it at this dose throughout the cold. Regarding prophylactic zinc supplementation, currently no firm recommendation can be made because of insufficient data. When using zinc lozenges (not as syrup or tablets) the likely benefit has to be balanced against side effects, notably a bad taste and nausea[22]

In another clinical trials Zinc bis-glycinate given in a dose of 15 mg once a day for 3 months failed to reduce the incidence of the common cold in 8 to 13-year-old school children, but decreased the number of days on which children suffered from cough, rhinorrhoea and the likelihood of having two or more symptoms of the common cold[23].

Zinc in Neonatal Health

Twice daily administration of oral zinc in a dose of 10 mg/day does not reduce the incidence of hyperbilirubinemia in at-risk term and late-preterm neonates during first wk of age[24]. Another study demonstrated Zinc status was poor in many infants at birth irrespective of BW. Zinc status worsened significantly during early infancy, with infants with BW <2,000 g having the lowest zinc levels[25]. Supplementation with multivitamin drops doesn't affect zinc level. One study does not report decrease in mortality rates, duration of

hospital stay and requirement of higher lines of antibiotic therapy following zinc supplementation in neonatal sepsis[26].

Another study by Christian P et al demonstrated that antenatal micronutrient supplements including Zinc were not associated with improved symptoms of neonatal morbidity in the first 10 days of life or at 6 weeks of age[27]. In a review[28] of Nutritional need of surgical Neonate it was stated that Zinc supplementation must begin at initiation of Parental Nutrition of surgical neonate (PN). All other trace elements can be added to PN 2 to 4 weeks after initiation. Although it is not clear that nutritional supplementation is associated with rapid recovery & less morbidity or not.

Zinc in Sepsis

Zinc supplementation is associated with immune modulation in infection related diseases like Sickle cell anemia, Human immunodeficiency virus infection, Down's Syndrome. Zinc supplementation has shown to restore lymphocyte production, NK cell function, wound healing and resistance to infection[29]. One animal study on mice has shown significant better survival with prophylactic zinc supplementation[30]. Although at present evidences are not available for routine supplementation of zinc in sepsis.

Zinc in Dengue

One study[31] demonstrated that lower zinc level during illness was associated with higher grade of Dengue severity and more liver cell injury demonstrated by higher liver enzyme level (SGPT & SGOT). Although at present evidences are not available for routine supplementation of zinc in Dengue.

Zinc in ADHD

Attention Deficit hyperactivity disorder is common behaviour problem in children with multifactorial etiology. One double blind randomized trial demonstrated beneficial effect of Zinc supplementation when given with Methylphenidate[32]. More evidence based studies needed to confirm role of zinc in ADHD. Some study[33] stated significantly low level of zinc when compare with normal child. Another study also suggested improvement in symptoms with zinc supplementation in ADHD patients[34]. Less conclusive evidence exists for the effectiveness of zinc alone or in general community samples. Recommendations for further research in this area are provided[35]

Zinc in Autism

Autism spectrum disorders (ASDs) are a group of behavioural disorder that can cause significant social & communication challenges. Few studies demonstrated low zinc level in children suffering from autism[36]. Result of other studies are not conclusive[37,38].

Zinc in oral Health

According to one randomized trial zinc deficiency is associated with higher caries prevelance and poor gingival health compared to zinc sufficient patient[39].

Zinc in Wilsons Disease

Zinc is approved by US Food and Drug Administration (USFDA) in 1997 for treatment of Wilsons Disease for life long treatment. Recent review also supports this recommendation. Although higher serum zinc level and urinary excretion was observed but only with few gastrointestinal side effects[40].

Zinc in Malignancy

According to one Double blind controlled trial it has become evident that supplementary zinc exerts a positive effect on nutritional status as positive weight gain. Moreover, the number of infection episodes was significantly reduced; possibly because of the immune stimuli in patients with acute leukemia on chemotherapy. To conclude zinc supplementation can prevent some of the chemotherapy adverse effects in children with leukemia, improving their quality of life[41].

Conclusion

Zinc deficiency is common in developing counties because of their dietary habits and poor quality of food. Role of zinc is crucial in severe diarrhea. It reduces duration of recovery and malnutrition in diarrheal episode. Althoug Cochrane review does not support zinc supplementation in diarrhea[8].

As per evidences available zinc supplementation is not indicated for severe pneumonia. In wilson's disease in role of zinc supplementation is well established. In other pediatric problem like Asthma, URI, Neonatal disorder, ADHD, Autism & Sepsis enough evidences are not available to support routine zinc supplementation.

References

1. Black RE, Morris SS, Bryce J. Where and why are 10 million children dying every year? Lancet2003;361:2226-33

2. Kosek M, Bern C, Guerrant RL. The global burden of diarrheal disease as estimated from studies published between 1992 and 2000. Bull world health organ 2003;81:197-204

3. Black RE, Cousins S, Johnson HL, Johnson HL, Lawn JE, Rudan I, et al., et al. Global, regional, and national causes of child mortality in 2008: a systematic analysis. *Lancet* 2010; 375: 1969-87 doi: 10.1016/S0140-6736(10)60549-1

4. Million Death Study Collaborators, Bassani DG, Kumar R, Awasthi S, Morris SK, Paul VK. Causes of neonatal and child mortality in India: a nationally representative mortality survey. *Lancet* 2010; 376: 1853-60 doi:10.1016/S0140-6736(10)61461-4

5. Parashar UD, Burton A, Lanata C, Boschi-Pinto C, Shibuya K, Steele D, Birmingham M, Glass RI..
Global mortality associated with rotavirus disease among children in 2004. *J Infect Dis* 2009; 200: S9-15 doi: 10.1086/605025

6. King CK, Glass R, Bresee JS, Duggan C, Centers for Disease Control and Prevention. Managing acute gastroenteritis among children: oral rehydration, maintenance, and nutritional therapy. MMWR Recomm Rep.2003;52:1-16.

7. WHO/UNICEF joint statement- Clinical management of Acute Diarrhea. WHO/FCH/CAH/ 04.07.2004 May.

8. Lazzerini M, Ronfani L. Oral zinc for treating diarrhoea in children. Cochrane Database Syst Rev. 2012 Jun 13;6:CD005436. doi: 10.1002/14651858.CD005436.pub3.

9. Hoque KM, Rajendran VM, Binder HJ. Zinc inhibits cAMP-stimulated Cl secretion via basolateral K-channel blockade in rat ileum. Am J Physiol. 2005;288:G956–63.

10. Hoque KM, Binder HJ. Zinc in the Treatment of Acute Diarrhea: Current Status and Assessment.Gastroenterology. 2006;130:2201–05.

11. Zinc supplementation helps diarrhea symptoms. [last cited on 2010 Feb 6]. Available from:http://www.newsmedical.net / news / 2008 / 02 / 04 / 34888.aspx .

12.http://www.who.int/gho/child_health/mortality/mortality_causes_text/en cited on 30th september, 2013

13. Aggarwal R, Sentz J, Miller MA. Role of zinc administration in prevention of childhood diarrhea and respiratory illnesses: a meta-analysis. Pediatrics. 2007 Jun;119(6):1120-30

14. Brooks WA, Yunus M, Santosham M, Wahed MA, Nahar K, Yeasmin S, Black RE. Zinc for severe pneumonia in very young children: double-blind placebo-controlled trial. Lancet. 2004 May 22;363(9422):1683-8.

15. Shah GS, Dutta AK, Shah D, Mishra OP. Role of zinc in severe pneumonia: a randomized double bind placebo controlled study. Ital J Pediatr. 2012 Aug 2;38:36

16. Das RR, Singh M, Shafiq N. Short-term therapeutic role of zinc in children < 5 years of age hospitalised for severe acute lower respiratory tract infection. Paediatr Respir Rev. 2012 Sep;13(3):184-91

17. Bansal A, Parmar VR, Basu S, Kaur J, Jain S, Saha A, Chawla D. Zinc supplementation in severe acute lower respiratory tract infection in children: a triple-blind randomized placebo controlled trial. Indian J Pediatr. 2011 Jan;78(1):33-7

18. Mahalanabis D, Lahiri M, Paul D. et al. Randomised double-blind, placebo-controlled trialof the efficacy of treatment with zinc or vitamin A in infants and young childrenwith severe acute lower respiratory infection. Am J Clin Nutr. 2004;79:430–6.

19. Bose A, Coles CL, Gunavathi JH. et al. Efficacy of zinc in the treatment of severe pneumonia in hospitalized children <2 yr old. Am J Clin Nutr. 2006;83:1089–96.

20. Valentiner-Branth P, Shrestha PS, Chandyo RK, randomized controlled trial of the effect of zinc as adjuvant therapy in children 2–35 mo of age with severe or non-severe pneumonia in Bhaktpur, Nepal. Am J Clin Nutr. 2010 Jun;91(6):1667-74

21. Khanbabaee G, Omidian A, Imanzadeh F, Adibeshgh F, Ashayeripanah M, Rezaei N. Serum level of zinc in asthmatic patients: A case-control study. Allergol Immunopathol (Madr). 2013 Jan 8. pii: S0301-0546(12)00265-0. doi: 10.1016/j.aller.2012.07.008.

22. Singh M, Das RR. Zinc for the common cold. Cochrane Database Syst Rev. 2013 Jun 18;6:CD001364. doi: 10.1002/14651858.CD001364.

23. Rerksuppaphol S, Rerksuppaphol L. A randomized controlled trial of chelated zinc for prevention of the common cold in Thai school children. Paediatr Int Child Health. 2013 Aug;33(3):145-50.

24. Rana N, Mishra S, Bhatnagar S, Paul V, Deorari AK, Agarwal R. Efficacy of zinc in reducing hyperbilirubinemia among at-risk neonates: a randomized, double-blind, placebo-controlled trial. Indian J Pediatr. 2011 Sep;78(9):1073-8

25. Agarwal R, Virmani D, Jaipal M, Gupta S, Sankar MJ, Bhatia S, Agarwal A, Devgan V, Deorari A, Paul VK, Toteja GS; Investigators of the LBW Micronutrient Study Group. Poor zinc status in early infancy among both low and normal birth weight infants and their mothers in Delhi. Neonatology. 2013;103(1):54-9

26. Mehta K, Bhatta NK, Majhi S, Shrivastava MK, Singh RR. Oral zinc supplementation for reducing mortality in probable neonatal sepsis: a double blind randomized placebo controlled trial. Indian Pediatr. 2013 Apr;50(4):390-3

27. Christian P, Darmstadt GL, Wu L, Khatry SK, Leclerq SC, Katz J, West KP Jr, Adhikari RK. The effect of maternal micronutrient supplementation on early neonatal morbidity in rural Nepal: a randomised, controlled, community trial. Arch Dis Child. 2008 A;93(8):660-4

28. Burjonrappa SC, Miller M. Role of trace elements in parenteral nutrition support of the surgical neonate. J Pediatr Surg. 2012 Apr;47(4):760-71

29. Shankar AH, Prasad AS. Zinc and immune function: the biological basis of altered resistance to infection. Am J Clin Nutr. 1998; 68:447S–463S

30. Jeffrey E. Nowak, Kelli Harmon, Charles C. Caldwell, and Hector R. Wong. Prophylactic zinc supplementation reduces bacterial load and improves survival in a murine model of sepsis. Pediatr Crit Care Med. 2012 September ; 13(5): e323–e329

31. Laoprasopwattana K, Tangcheewawatthanakul C, Tunyapanit W, Sangthong R. Is zinc concentration in toxic phase plasma related to dengue severity and level of transaminases? PLoS Negl Trop Dis. 2013 Jun 20;7(6):e2287

32. Zamora J, Velásquez A, Troncoso L, Barra P, Guajardo K, Castillo-Duran C. Zinc in the therapy of the attention-deficit/hyperactivity disorder in children. A preliminar randomized controlled trial. Arch Latinoam Nutr. 2011 Sep;61(3):242-6

33. Mahmoud MM, El-Mazary AA, Maher RM, Saber MM. Zinc, ferritin, magnesium and copper in a group of Egyptian children with attention deficit hyperactive disorder. Ital J Pediatr. 2011 Dec 29;37:60

34. Dodig-Curković K, Dovhanj J, Curković M, Dodig-Radić J, Degmecić D. The role of zinc in the treatment of hyperactivity disorder in children. Acta croatia 2009 Oct;63(4):307-13

35. DiGirolamo AM, Ramirez-Zea M. Role of zinc in maternal and child mental health. Am J Clin Nutr. 2009 Mar;89(3):940S-945S

36. Bjorklund G. The role of zinc and copper in autism spectrum disorders. Acta Neurobiol Exp (Wars). 2013;73(2):225-36.

37. Blaurock-Busch E, Amin OR, Dessoki HH, Rabah T. Toxic Metals and Essential Elements in Hair and Severity of Symptoms among Children with Autism. Maedica (Buchar). 2012 Jan;7(1):38-48

38. Lakshmi Priya MD, Geetha A. Level of trace elements (copper, zinc, magnesium and selenium) and toxic elements (lead and mercury) in the hair and nail of children with autism. Biol Trace Elem Res. 2011 Aug;142(2):148-58

39. Atasoy HB, Ulusoy ZI. The relationship between zinc deficiency and children's oral health. Pediatr Dent. 2012 Sep-Oct;34(5):383-6

40. Hong Chang, Aijing Xu, Zhihong Chen, Ying Zhang, Fei Tian, Tang Li. Long-term effects of a combination of D-penicillamine and zinc salts in the treatment of Wilson's disease in children. SExp Ther Med. 2013 April; 5(4): 1129–1132

41. Consolo LZ, Melnikov P, Cônsolo FZ, Nascimento VA, Pontes JC. Zinc supplementation in children and adolescents with acute leukemia. Eur J Clin Nutr. 2013 Oct;67(10):1056-9

.....

How to cite this article?

Gedam DS. Role of Zinc in Pediatric diseases: Evidence based Guidelines. *Int J Med Res Rev* 2013;1(4):203- 208. doi: 10.17511/ijmrr.2013.i04.13

.....