PEN Pathway:

The Impact of Prebiotics, Zinc and Vitamin A on Diarrhea in Children

Robyn Wardlaw
FRAN 6610
December 6, 2015
Abstract

Introduction

Oral rehydration solution (ORS) is the treatment of choice for children with mild to moderate dehydration caused by acute gastroenteritis (WHO). Oral rehydration reverses the effects of dehydration, but doesn’t decrease the duration of diarrhea or amount of stool output. There is evidence that prebiotics, zinc and vitamin A may improve diarrhea duration and output. This report is a review of the research to answer the following: 1) Does ORS with prebiotics decrease the duration and stool output of diarrhea in children compared to children who receive ORS without prebiotics? 2) Does ORS with zinc cause a greater decrease in diarrhea duration and output in children compared to ORS without zinc? 3) Do children who receive combined zinc and vitamin A supplementation have decreased duration of diarrhea and stool output compared to children who receive only zinc supplementation?

Methods

Peer-reviewed randomized controlled trials and systematic reviews were found through Primo Central, Cochrane Library, Web of Science. Findings were graded using PEN’s Critical Appraisal Tool and then were combined to make PEN statements.

Results

1) Prebiotics do not show evidence of decreasing diarrhea duration or stool output.

2) Zinc supplements decrease diarrhea duration but limited evidence in ability to decrease stool output.

3) Vitamin A in combination with zinc supplement doesn’t improve diarrhea but may show some improvements in decreasing prolonged diarrhea
Conclusions

Zinc supplementation is recommended to decrease the duration of diarrhea. Currently more research is required before prebiotics and vitamin A can be recommended for decreasing effects of diarrhea.

Background

Category: Health Condition/Disease

Sub-category: Intervention

Introduction

Diarrhea is one of the greatest reasons for death in young children. It is a greater risk for children because they have a higher fluid turnover and are more likely to contract pathogens, viruses, bacteria causing diarrhea. Oral Rehydration Solution development is considered one of the greatest discoveries in medicine’s history (1). One of the first times that a standard oral rehydration solution was used for the masses was in Bangladesh in 1971. There was an outbreak of cholera among refugees in Calcutta. When given ORS the death rate dropped to 5%, compared to 50% with no ORS given (2).

The science behind oral rehydration solution is based on the sodium glucose co-transporter on the brush border of the intestinal walls. Dehydration is caused by a pathogen that halts all absorption of water. By consuming ORS with sodium and glucose available it activates the co-transport system and allows water to be moved from the intestines into the bloodstream (3).

Originally WHO made a standard ORS with osmolarity of 311 mOsm/L, however there were rare cases of hypernatremia found when this solution was used. A Cochrane study revealed that with a lower osmolarity ORS there was an improvement in response. This was evidenced by
fewer unscheduled intravenous rehydration due to oral rehydration complications, and decreased stool output (4). WHO now recommends ORS with reduced osmolarity of 245 mOsm/L with a lower concentration of salt, potassium, chloride and glucose than the original ORS.

The Canadian Pediatric Society recommendation for mild to mild to moderate dehydration is a hypotonic ORS. The treatment plan for ORS is to administer frequently in small amounts increasing as the child will drink more. Even if the child is vomiting the ORS should still be given in small amounts according to what child will tolerate. Child should be fed their normal diet as soon as possible once they reach hydration status. Refeeding the child as soon as possible has many benefits including: restarting the action of digestive enzymes, improving nutritional status, maintaining child’s weight and reducing length of diarrhea (3). Breastfeeding should be continued throughout oral rehydration treatment. Carbonated, sugar sweetened beverages and sports drinks are not recommended because of their high osmolarity yet low electrolyte content. Water is also not recommended due to risk of hyponatremia.

Contraindications for ORS are persistent vomiting, if child is unconscious, paralytic ileus or a rare disease called monosaccharide malabsorption where the intestines cannot absorb glucose or galactose, severe dehydration (lost more than 10% body weight) (3). The severity of diarrhea is divided into 3 categories: mild, moderate and severe. The clinical assessment guidelines from the Canadian Pediatric Society of these categories can be referred to in Appendix 1.

Prebiotics

Prebiotics are substances that can’t be digested by the gastrointestinal system but are fermented by the microflora in the colon and benefit the health of the host. Currently only two carbohydrates fit this description: inulin and galactooligosaccharides (5).
In the colon the microflora break down the undigested prebiotics into short chain fatty acids, these help with absorption of salt and water. It is theorized that including prebiotics in ORS would decrease stool volume and the length of diarrhea by increasing colonic fermentation (6). However, this is not fully supported as it conflicts with evidence that prebiotics have a laxative effect, therefore increasing stool output (5).

There are possible side effects of prebiotics, including: gas, diarrhea, gastrointestinal inflammation. Pain was observed when prebiotic supplements were given to sensitive patients with IBS or maladapted intestinal flora. This could be a reason why limited research on successful prebiotic therapy usage (5).

Zinc

Zinc is an essential mineral found in many foods including: oysters, red meat, poultry, fortified breakfast cereals, beans and legumes and dairy products (7). Phytates are the storage form of phosphorus in plants and are antioxidants, but they bind to zinc preventing zinc absorption. Zinc deficiency is more common in populations where diet is mostly plant based. Zinc is more bioavailable from animal products. Zinc deficiency in North America is rare due to regulated fortification. Symptoms of zinc deficiency are diverse because zinc is involved in many different metabolic processes (7). Zinc is involved in many bodily processes including: immune processes, enzyme catabolism, protein synthesis, cell differentiation, immunity. Intake of zinc is essential, from either food or supplement sources, because the body doesn’t have a specific storage mechanism for zinc.

Cells with a high turnover, such as the gastrointestinal system are most affected by zinc deficiency (7). It is still unknown the exact mechanism of zinc and how it affects diarrhea. Deficiency of zinc is correlated with gastrointestinal infection, negative effects on
gastrointestinal function (8). Zinc plays a role in immune function which could affect diarrhea prevalence due to ability to fight pathogens depending on zinc status. Zinc affects the absorption of water and electrolyte absorption through the intestinal wall (9). Loss of zinc through diarrheal fluid losses perpetuate the problem of zinc deficiency (10). Intake of zinc greater than 100-300 mg can lead to decreased iron and copper absorption and decreased immune function (11).

**Vitamin A**

Vitamin A is an essential nutrient. The body does not make it and must be consumed through diet or supplements. There are two forms of vitamin A: provitamin A carotenoids and preformed vitamin A. Provitamin A carotenoids are found in fruits and vegetables, but can often not provide enough vitamin A because it is converted to retinol, the alcohol form of vitamin A, in the intestines at a rate of 12:1. Preformed vitamin A is from animal sources such as liver and eggs and is already in the form of retinol and therefore more efficiently absorbed into the body. Supplements are most often made from preformed vitamin A (12).

Thirty-three percent of children under the age of 5 living in developing countries are at risk of vitamin A deficiency. Vitamin A deficiency makes children more vulnerable to many health problems, including diarrhea (12). Vitamin A plays a role in immunity and is often referred to as the infection fighting vitamin. In a Cochrane Review Vitamin A supplementation reduced the risk of death by 24%, particularly from measles and diarrhea. This review of 17 studies showed that vitamin A supplementation reduced childhood diarrhea by 0.29 episodes of diarrhea per year.

Deficiencies of other nutrients affect the bioavailability of vitamin A, particularly zinc. Zinc is involved in many processes of vitamin A, for example: zinc regulates the transport of vitamin A in protein synthesis and retinol dehydrogenase enzyme relies on zinc to convert retinol
to retinal (13). Often children present both zinc and vitamin A deficiency, therefore it is theorized that zinc and vitamin A supplementation could have a beneficial effect on child health and disease prevention. In the case of this review, diarrhea duration and stool output is of specific concern. Toxicity from consuming food sources of vitamin A is rare, but can occur if large amounts of vitamin A supplements are taken continually for a long time. Side effects can include headaches, liver damage, vomiting, negative effect on bones. A large single dose can also cause side effects of bulging fontanelle in infants under 1 year of age, headaches and diarrhea (12).

Currently Oral Rehydration Solution by WHO contains carbohydrate, sodium, potassium and chloride. There is currently no requirement for ORS to contain prebiotics, zinc or vitamin A.

**Knowledge Pathway**

**Practice Question 1**

Does ORS with prebiotics decrease the duration and stool output of diarrhea in children compared to children who receive ORS without prebiotics?

**Key Practice Point**

Although there is limited evidence, currently ORS with prebiotics does not show any decrease in duration and output of diarrhea. However, ORS with zinc and prebiotics decreased output and decreased duration of diarrhea.

**Evidence Grade: C**

a. Randomized controlled single-blinded trial with 2 groups of children, 65 children aged 3-36 months in each group. The first group received a standard ORS 225 mOsm/L. The second group received “Super ORS” with reduced osmolarity 200 mOsm/L, 1 mmol/L zinc, 0.35g/L fructooligosaccarides and 0.35 g/L xilooligosaccarides. Requirements for
inclusion were diarrhea defined as 3 or more loose or liquid stools in 24 hours and mild to moderate dehydration. Significant differences seen between group 1 and 2 were 72.9% of children in group 2 diarrhea was resolved within 72 hours, compared to 50% of children in group 1 (p=0.01). Stool output was less in group 2 (4.5/day), group 1 was 5.9/day (p=0.002). Limitations of this study is that Super ORS had zinc, hypotonic and prebiotics so it is hard to differentiate the specific effect of prebiotics apart from zinc and lower osmolarity. One theory is that there is a synergistic effect between zinc and prebiotics, further research is needed to determine the extent of this effect (8).

b. Randomized controlled trial in 7 countries – Egypt, Greece, Israel, Italy, Holland, Poland, Portugal and Slovenia. Participants were males aged 1-36 months, symptoms of diarrhea were three or more liquid stools for more than 1 but less than 5 days and mild or moderate dehydration. Seventy participants randomly assigned to group 1 received ORS with non-digestible carbohydrates, 74 assigned to group 2 received ORS and placebo. Non-digestible carbohydrate: 25% soy polysaccharide, 9% alfa-cellulose, 19% gum Arabic, 18.5% fructo-oligosaccharides, 21.5% inulin, 7% resistant starch. The prebiotic content of the non-digestible carbohydrate mixture was fructo-oligosaccharides and inulin. 1 g of this mixture in every 100 ml ORS. No harmful effects were detected in the ORS with non-digestible carbohydrates in comparison to normal ORS with placebo. There was no significant difference between the groups for amount of stool produced and there was no difference in duration of diarrhea between the groups (5).

**Practice Question 2**

Does ORS with zinc cause a greater decrease in diarrhea duration and output in children compared to ORS without zinc?
Key Practice Points

1. Recommended by World Health Organization (WHO) to take 20 mg zinc for 10-14 days for children over 6 months, 10 mg for 10-14 days for infants under 6 months after acute diarrhea to decrease diarrhea in following 2-3 months. Zinc supplementation decreases severity and duration of diarrhea. There is limited evidence that zinc supplementation decreases stool volume.

Evidence Grade: B

a. WHO recommendations based on 12 studies, 5 of which had evidence that zinc decreased stool volume, eleven studies had evidence that zinc supplementation decreased length of diarrhea. Taking zinc supplementation 20 mg dose during diarrhea also decreased the length of diarrhea. This recommendation is for developing countries only due to higher zinc deficiency prevalence in comparison to developed countries where zinc deficiency is rare due to fortification (14).

b. Systematic review of 5 meta-analyses and 26 human randomized controlled trials for acute diarrhea, 6 randomized controlled trials for persistent diarrhea. Previous meta-analyses had all shown improvements in diarrhea with zinc supplementation improving diarrhea, the purpose of this review was to look further into the cause of varying strength of effects of zinc on diarrhea due to the heterogeneity between studies. Statistical analysis of all of the reviews found that zinc supplementation caused a decrease in length of acute diarrhea by 20% and persistent diarrhea by 15-30%. Trials using larger doses of zinc showed a greater decrease in mean diarrheal duration. No statistically significant effect on stool frequency or stool output (15).
2. An adverse effect for zinc supplementation was that children receiving zinc supplementation had an increased risk of vomiting.

**Evidence Grade:** B

a. Cochrane Review of 24 Randomized controlled trials studying 9128 children aged 1 month to 5 years old receiving 20 mg zinc supplementation with acute or persistent diarrhea. Studies were gathered from MEDLINE, EMBASE, LILACS, CINAHL, mRCT, and reference lists. The review included data from 13 studies that reported vomiting as a side effect to zinc supplementation. Vomiting was more common in children receiving zinc compared to those who didn’t; this was statistically significantly at 95% confidence. Groups receiving zinc reported 557 cases of vomiting, compared to 344 cases of vomiting in placebo group. Zinc supplementation showed an increase in vomiting in children of all ages due to its metallic taste (16).

b. Randomized, double blind controlled trial with 1600 children aged 3 to 59 months old in a hospital in Dhaka, India. They were randomized into one of three groups: placebo, 20 mg zinc or no treatment. This trial was completed to test the risk of vomiting when children were given a newly developed encapsulated zinc tablet that masks the metallic taste of zinc. This trial was with elemental zinc supplements, not combined with ORS. Previous research gave evidence that vomiting could be related to the unpleasant taste of zinc, therefore this trial will test the vomiting response of this newly encapsulated tablet compared to a placebo tablet and no tablet. The proportion of vomiting after the zinc treatment was 40%, after placebo was 26% and no treatment was 34%. In 90% of children who received zinc there was one episode of vomiting roughly 10 minutes after treatment. There was significant vomiting in the placebo group, this could be because
some children vomit in response to any medication. There was also vomiting in the group that received no treatment, this could be because of their diseases. Further research is needed to further determine the specific causes of vomiting between treatment of zinc, placebo effect or the disease symptoms. History of vomiting increase risk of vomiting a limitation of this study is that 50% of the participants had vomited in the three hours leading up to the study. Another limitation of the study was that children were only observed for 1 hour so that longer term risk of vomiting was not assessed (17).

3. Most children who are well-nourished and not zinc deficient in developed countries do not seem to have improved diarrhea symptoms after receiving zinc supplementation.

**Evidence Grade: B**

a. Randomized, double-blind controlled trial with 141 well-nourished children with acute gastroenteritis aged 3 to 48 months in Poland. Children had diarrhea for more than 1 day but less than 5 days and had mild to moderate dehydration. Children were given ORS according to WHO standards and given immediate refeeding. They were randomized into group receiving zinc (10 mg for infants under 6 months, 20 mg 6 to 48 months) every day for 10 days. There was no significant difference between the groups for diarrhea duration (p<0.05), stool output or vomiting. Polish children are not at high risk of zinc deficiency and it was assumed that these children would be representative of a population that is well-nourished and not zinc deficient. One limitation of this study is that they did not test the zinc status of the participants to confirm that they were not zinc deficient (18).

b. Randomized controlled trial with 280 children with acute diarrhea, 150 were in group that received zinc daily for 14 days with ORS treatment, 130 children were in control
group receiving only ORS. Fifteen mg zinc given to children aged 6-12 months, 30 mg 12-60 months. Children were 6 to 60 months old well nourished from Turkey. Zinc deficiency was seen in 2.6 % of children in zinc group, 3.3% of control group were zinc deficient. Malnourished status was an exclusion factor. There was no significant difference in diarrhea duration or stool output between the groups at 95% confidence (19).

Practice Question 3

Do children who receive combined zinc and vitamin A supplementation have decreased duration of diarrhea and amount of stool output compared to children who receive only zinc supplementation?

Key Practice Point

1. There is no significant synergistic effect of zinc and vitamin A supplementation in decreasing diarrhea output or duration. There was one study that showed evidence that zinc and vitamin A might interact to decrease diarrhea prevalence over 6 months. Further research is needed in this area to determine how zinc and vitamin A affect the long term prevalence of diarrhea.

Evidence Grade: B

a. Randomized controlled trial double-blinded intervention in children in Bangladesh who had persistent diarrhea (>14 days). Children between 6 months and 3 years old. Children received WHO standard rehydration therapy for dehydration either intravenously or orally. One hundred children were randomized into 4 groups receiving the following intervention: 20 mg zinc daily for 1 week with multivitamin syrup (see ingredients below), vitamin A dose with multivitamin syrup for 1 week (100 000 IU <1 yo, 200 000 IU >1yo), zinc plus vitamin A plus multivitamin, placebo only received multivitamin.
This intervention found that zinc significantly decreased stool output, increased weight gain and increased recovery time. Vitamin A group nor vitamin A combined with zinc treatment group had no significant decreases in stool output or weight gain compared to zinc group. The limitation of this study is all of the groups of children received the multivitamin syrup as part of the intervention. It is hard to distinguish the specific effects of zinc and vitamin A on diarrhea because of the confounding variables of the other vitamins in the syrup and the unknown effect that they might have had on diarrheal status (20). Multivitamin syrup: 640 IU vitamin D, 50 mg vitamin C, 1.6 mg vitamin B1, 1.37 mg vitamin B2, 1.0 mg vitamin B6, 10.0 mg nicotinamide, other non-vitamin ingredients

b. Randomized controlled double blind study with children aged 6 months to 2 years with acute diarrhea (<3 days, 3 or more watery stools in 24 hours, moderate dehydration) in Dhaka, Bangladesh. Randomized into four groups: receiving zinc, receiving vitamin A, receiving zinc and vitamin A, placebo. In the zinc group there were 172 children, the first 417 children received 14.2 mg zinc for 15 days, the last 273 patients in this group received 40 mg zinc for 15 days. The vitamin A group consisted of 170 patients who received 4500 ug RE for 15 days, there were 171 children in zinc & vitamin A group, 171 children in placebo group. The zinc group received two different doses of zinc to study the difference in dose-response to see if diarrhea outcome would change depending on amount of zinc administered. This had no effect on the validity of other results. Children were followed for 16 days after initial hospital visit. Stool output did not vary between groups. Duration of diarrhea was decreased by 13% in the group that received zinc supplementation compared to placebo. There was no statistical significant evidence that vitamin A with zinc improved the effect of zinc on stool output. The mean duration of
diarrhea in the vitamin A supplemented group was similar to that in the unsupplemented group. One limitation of this study is that it did not study children longer after the intervention to see the long-term effects of vitamin A supplementation on long-term prevalence and incidence of diarrhea (21).

c. Randomized controlled trial in Australian hospital for Indigenous children under the age of 11, acute diarrhea defined as <3 watery stools/day, none had more than mild dehydration. Serum vitamin A levels were low in almost all children, zinc levels were normal. The study consisted of 436, randomized into four groups: receiving zinc, receiving vitamin A, receiving zinc & vitamin A, receiving placebo. Children under 12 months – 50 000 IU vitamin A on day 1 and 5, 20 mg zinc daily for 5 days, children aged 1 to 10 – 100 000 IU vitamin A day 1 and 5, 40 mg zinc daily for 5 days. Differences in diarrhea duration and weight gain between any of these groups were not statistically significant (22).

d. Randomized controlled double blinded trial with children aged 12-35 months in Bangladesh into four groups – 170 children received 20 mg zinc daily for 14 days, 159 children received 200 000 IU vitamin A on day 14, 175 received zinc and vitamin A treatment, 161 received placebo. Follow up was done with children weekly for 6 months. Assessed using risk ratios, placebo is 1.0 because no change in risk. <1.0 indicates decreased risk, >1.0 indicates increased risk. There was a small but significant decrease in prevalence of diarrhea in zinc with 0.82 risk ratio and vitamin A with 0.89 risk ratio. There was no interaction between zinc and vitamin A because in the combined group the risk ratio was 1.08. For the outcome of persistent diarrhea zinc caused a decrease in prevalence with 0.81 risk ratio, vitamin A did not decrease risk with ratio of 1.08, there
was an interaction with vitamin A and zinc because together they decreased persistent diarrhea, risk ratio was 0.79 compared to placebo of 1.0. The strength of this study was that it followed up with children over a longer time span of 6 months. This study shows evidence that vitamin A and zinc supplementation could decrease persistent diarrhea over the long-term, in this case 6 months (23).

**Conclusion**

Diarrhea is a prevalent disease in the developing world that affects the lives of many children. Oral rehydration solution is a proven treatment and retracts the symptom of dehydration, however research is still ongoing for how to decrease the duration and output of diarrhea. Research is conclusive that zinc decreases the duration of diarrhea, however it is still debated whether zinc decreases stool output. Zinc supplementation is recommended for children in developing countries who are at risk of zinc deficiency, however it has not been found to benefit children in developed countries who are well nourished and most likely not zinc deficient. One adverse effect of zinc supplementation found was that it increases the risk of vomiting right after receiving supplement. Further research is needed to determine the cause of this vomiting, whether it is the metallic taste, the disease or just the action of taking medication. Prebiotics without zinc did not improve the diarrhea duration or stool output, however there was an improvement when prebiotics was supplemented with zinc. Further research is required to determine if there is a synergistic effect with prebiotics or zinc, or whether the improvement was seen only due to the presence of zinc. Vitamin A in combination with zinc did not improve diarrhea symptoms any more than zinc on its own. Vitamin A with zinc may decrease diarrhea risk over six months, further research is needed to confirm this. Research in this review was of high value because they were all randomized controlled trials, most were double-blinded with a
placebo group. All had large enough sample sizes to have statistically significant results. In further studies it would be beneficial to do longitudinal studies and follow-up with participants at 6 months or even longer to determine the effects of supplementation of zinc, prebiotics or vitamin A and how it affects risk of diarrhea later on. Recommendations for health care providers are to provide zinc supplementation with ORS for children at risk of zinc deficiency, often in developing countries, to decrease the duration of diarrhea. Currently supplementation of prebiotics or vitamin A combined with zinc supplementation shows no improvement in diarrhea duration or stool output.
### Appendix 1: Clinical Assessment of Degrees of Dehydration (3)

<table>
<thead>
<tr>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5% loss of body weight</td>
<td>5-10% loss body weight</td>
<td>&gt;10% loss body weight</td>
</tr>
<tr>
<td>Slightly decreased urine output</td>
<td>Decreased urine output</td>
<td>Markedly decreased or absent urine output</td>
</tr>
<tr>
<td>Slightly increased thirst</td>
<td>Moderately increased thirst</td>
<td>Greatly increased thirst</td>
</tr>
<tr>
<td>Slightly dry mucous membrane</td>
<td>Dry mucous membrane</td>
<td>Very dry mucous membrane</td>
</tr>
<tr>
<td>Slightly elevated heart rate</td>
<td>Elevated heart rate</td>
<td>Greatly elevated heart rate</td>
</tr>
<tr>
<td>Slightly increased heart rate</td>
<td>Decreased skin turgor</td>
<td>Decreased skin turgor</td>
</tr>
<tr>
<td>Sunken eyes</td>
<td>Very sunken eyes</td>
<td></td>
</tr>
<tr>
<td>Sunken anterior fontanelle</td>
<td>Very sunken anterior fontanelle</td>
<td></td>
</tr>
<tr>
<td>Lethargy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cold extremities</td>
<td>Hypotension</td>
<td></td>
</tr>
<tr>
<td>Coma</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


