Probiotics for Treating Acute Infectious Diarrhoea (Review)
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Episodes of acute infectious diarrhoea remain a major disease burden throughout the world, especially in developing countries. They are due to infection by many different organisms. Most episodes are self-limiting and usually investigations are not done to identify the infectious agent. The main risk to health is dehydration and management aims to improve and maintain hydration status. However, rehydration fluids do not reduce the stool volume or shorten the episode of diarrhoea. Probiotics are "friendly" bacteria that improve health and are not harmful in themselves. A number of randomized controlled trials have been done to see whether probiotics are beneficial in acute infectious diarrhoea. We have searched for as many of these trials as possible and collected together the data in a systematic way to try to discover whether or not probiotics are beneficial in acute diarrhoea. We identified 63 trials, which included a total of 8014 people - mainly infants and children. Probiotics were not associated with any adverse effects. Nearly all studies reported a shortened duration of diarrhoea and reduced stool frequency in people who received probiotics compared to the controls. Overall, probiotics reduced the duration of diarrhoea by around 25 hours, the risk of diarrhoea lasting four or more days by 59% and resulted in about one fewer diarrhoeal stool on day 2 after the intervention. However, there was very marked variability in the study findings and so these estimates are approximate. We concluded that these results were very encouraging but more research is needed to identify exactly which probiotics should be used for which groups of people, and also to assess the cost effectiveness of this treatment.

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The last ten years had seen a rise in publications on probiotics. Presently, the uses of probiotics locally seem to look like a panacea or "cure-all" drug. Purported benefits aside from acute diarrhea include: respiratory infections, urinary tract infection, febrile neutropenia, dengue fever and tuberculosis. Most of the studies are not published in peer-reviewed journals and suffer from methodological flaws with either inappropriate research designs, small sample sizes or the failure to utilize "pure" probiotic preparation. Unless larger, better quality researches whose results can be replicated are undertaken then the conclusions on the benefits of such probiotics are put into question. This Cochrane meta-analysis aimed to assess the effects of probiotics by reviewing 63 randomized trials in only one indication: proven or presumed acute infectious diarrhea.

The most quoted definition is that "probiotics are living organisms which when taken in adequate amounts confer beneficial effects on the host[1,2]". It can be both a pharmaceutical product or a nutritional supplement depending on whether evidences from clinical trials for both efficacy and safety are submitted to regulatory agencies for certification. But unlike the classical drug that we know, probiotics have no specific dose on a per weight basis, dose ranges for both children and adults are almost the same, the pharmacokinetics have not been well elucidated and the mechanisms of action are largely deduced from theoretical suppositions or in-vitro studies rather than rigorous scientific evidence. Nevertheless, the use of probiotics has gained considerable acceptance from the medical community based on limited evidences of its usefulness in health and disease for both pediatric and adult populations.

In contrast, the authors adopted the definition which also included components of microbial cells in addition to the whole organisms themselves. However, only trials which utilized whole microorganisms were included. The search criteria did not include cell components with probiotic-like effects. To include cell components and by-products as probiotics has created scientific controversy. Some mechanisms of action related to beneficial effects of probiotics require an intact organism and these include release of microbial enzymes in the intestine, secretion of proteins or other macromolecules associated to microbial envelopes that interact with pattern-recognizing receptors in host cells,[3] and production of metabolites or peptides with antimicrobial activity (e.g. bacteriocins).

The focus of the article is on the use of probiotics in acute diarrhea, regardless of age of patients. The best indication of probiotic use as evidenced from clinical trials and previous meta-analyses particularly involving children, is in acute, non-bloody diarrhea, of presumed viral origin, given early in the course of the disease in developed countries.[4] The effect of probiotics is species- or even strain-specific. The genomic sequence of some probiotic strains have already been identified and based on this, their sites of

action along the gut and specific mechanisms of action differ. Although the article tried to see the effect of a limited number of different genera of bacteria (Lactobacilli, Enterococcus) and Saccharomyces, the effects of the strain of specific bacteria/yeast may still differ. The significant heterogeneity of the results can in part be explained by the different strains of probiotics used.

The major issues concerning probiotic use have been addressed by the review: dose, severity of illness, economic strata and effect of single versus multiple species. It was shown that these variables did not have an effect on the primary outcome except the use of live or killed organisms. Of note are the three trials which dealt with killed organisms. Two out of these three trials favored probiotic use in reducing duration of diarrhea. The third study had inconclusive result. The overall effect of the three trials favored probiotic use but is inconclusive. This emphasizes one of the characteristics of a good probiotic: it should be a live organism,[2] which should be able to adhere, colonize transiently and survive in the gut where it should exert its beneficial effect.

What are the implications of this meta-analysis? Can one day reduction in duration of diarrhea, 60% reduction in the risk of having continued diarrhea after two days of treatment and having one less stool episode after one day translate to clinical significance? For some skeptics, these outcomes may be intangible. For most patients and care-givers this could translate to reduction in cost of treatment, days of absence from work, incidental expenses and emotional suffering. I think this can be best answered by performing an economic evaluation which takes into consideration both direct and indirect costs of the impact of probiotic use in acute diarrhea.

Now that the benefits of probiotics in acute, infectious diarrhea especially in children have been documented, this should not send a message to divert the spotlight from the recommended treatment options in developing countries expounded by WHO[5]: oral rehydration therapy, continued feeding and zinc supplementation. The use of drugs like antibiotics is only reserved for bloody diarrhea, cholera, giardiasis, amoebiasis and in treatment of systemic infections accompanying the diarrhea. The use of anti-motility and anti-diarrheal drugs is not advocated because of safety concerns and unproven efficacy. Preparations such as probiotics, should only be considered as ADJUNCT TREATMENT RATHER THAN FIRST-LINE TREATMENT. For after all, the cornerstone of diarrheal management in children is essentially maintaining hydration and nutrition status.

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