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Review Research

Advantages of Gel Oral Rehydration Solutions (ORS) for the Management of Acute Diarrhea: An Update

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Abstract

Currently, in the management of acute diarrhea, underuse of oral rehydration solutions (ORS), is still reported, being a strong rationale for their improvement to increase patient's acceptability and, in consequence, treatment compliance and therapeutic success, for example, in terms of palatability, and swallowability.

In this article, we reviewed the advantages of new ORS gel formulations, with solid or semi-solid texture, that could help to overcome the inconveniences of conventional ORS. The main difficulty, the salty taste, can be masked using flavors, reconstituting and administering the gel product at low temperatures or using pleasant textures that resembles desserts or sweets.

Another important critical point in the oral rehydration is the relatively large volumes administered, usually rejected by children. In gel formulations the volume is significantly reduced to around 100ml, and can be administered at small portions, thus avoiding its refusal and facilitating the role of parents or caregivers in administering it. Recent studies have shown these benefits, together with the demonstration of the electrolytes release at gastric level. However, more clinical trials are needed to compare gel formulations versus standard ORS.

ABBREVIATIONS

AMP: Adenosine Monophosphate; EMA: European Medicines Agency; ESPGHAN: European Society for Paediatric Gastroenterology Hepatology and Nutrition; ESPID: European Society for Paediatric Infectious Diseases; HAMS: High-Amylose Maize Starch; NICE: National Institute for Health and Care Excellence; ORS: Oral Rehydration Solution; SCFA: Short-chain Fatty Acids; WHO: World Health Organization

INTRODUCTION

Nowadays, acute gastroenteritis continues to be one of the most common infectious diseases, with an estimated 5 billion episodes occurring worldwide each year [1], and is still one of the main causes of morbidity and mortality, particularly in children in low-income countries [2-5]. In Europe, it is estimated that the incidence of diarrhea ranges from 0.5 to 1.9 episodes per child per year in children up to 3 years of age [4,5]. In developing countries, acute diarrhea represents the third cause of death (15%), in children under the age of 5, after perinatal death (23%), and acute respiratory infection (18%) [3].

Acute gastroenteritis is often characterised by diarrhea of rapid onset, with or without nausea, vomiting, fever, or abdominal pain [6]. Profuse watery diarrhea may frequently lead to substantial fluid losses, dehydration, that can be severe if adequate rehydration is not provided [7], thus becoming a self-limiting condition, particularly in children [7]. In fact, acute gastroenteritis often has an impact on different levels such as public health, health burden (primary care and hospital), psyco-social impact for the family, laboral costs, etc. [8-11].

Despite the wide range of available products for the management of acute diarrhea [5], such as antibiotics, motility inhibitors, substances that decrease water and electrolyte secretion such as racecadotril, hydrated aluminomagnesium silicates, such as diosmectite [12], or mucosal protectors such as xyloglucan [5,13-16], treatment with hypotonic oral rehydration solutions (ORS), remains the mainstay of the management of acute gastroenteritis in most cases [5,13,17-19].

Despite their widespread use for decades, underuse of ORS is still reported [5,7], due to a variety of reasons. In this review, we analyzed the possible causes of ORS underuse and current evidences highlighting the advantages of new solid or semi-solid ORS formulations to increase patient acceptability, particularly in children.

REASONS FOR ORS UNDERUSE

According to the ESPGHAN/ESPID and NICE guidelines, fast oral rehydration with rapid return to regular food is recommended [5,20].

ORS is a solution containing glucose and salt that allows electrogenic solute intestinal absorption, essential to replace fluid losses during acute gastroenteritis, being considered as the most important medical advance of the 20th century [19,21] and the cheapest and simplest intervention that saved more lives than any other drug [19].

Another milestone in the development of ORS was the demonstration that the hypo-osmolar formulations (≤ 270 mOsm/kg H_2O) were more efficacious than the initial iso-osmolar (311 mOsm/kg H_2O) ORS formulations (often referred to as WHO-ORS) in correcting acute dehydration and metabolic acidosis, commonly containing glucose, NaCl, KCl and sodium citrate [7,21,22].

Despite their proven efficacy, ORS remains underused, particularly in developed countries [22,24], mainly due two main reasons: the perception of inefficacy by children, parents or caregivers and their unappealing organoleptic properties. In the first case, ORS do not always alter the course of the disease (in terms of fluid loss, bowel movements or duration of diarrhea) thus leading to discontinuation of the treatment [5]. In this case, the perceptions of parents and caregivers about the importance of rapid rehydration can also influence the degree of ORS compliance and, in consequence, therapeutic success [7,25]. For example, it has been reported that the parents can feel much more interest in stopping main children symptoms, such as diarrhea, than in rehydrating and correcting the metabolic acidosis [7].

It is also in the paediatric population where ORS organoleptic properties, mainly their salty taste, are mainly responsible for their low acceptability, leading to low compliance rates [23,26-28]. Other causes for low adherence include the high volumes of fluid intake [29,30], usually provided at a large number of intervals [24,31], and the liquid state, which could be contraindicated in children with vomiting [24,32,33]. In the hospital emergency departments, the intake of large volumes of ORS can also represent a problem, with time constraints, space limitations and slow intakes [31,32].

In fact, many efforts have been made to improve ORS organoleptic properties, with the addition of different components. Any of them, however, has not provided special success without the implementation in the clinical practice.

In this article, we review the main inconveniences of available ORS and new reported strategies to increase treatment compliance, with the use of solid or semi-solid ORS formulations.

ORS ACCEPTABILITY AND IMPROVEMENT STRATEGIES

According to the European Medicines Agency (EMA), acceptability is "the overall ability and willingness of the patient to use a medicinal product as intended and its caregiver to administer the medicine as intended", emphasizing the need to evaluate patient acceptability as an integral part of the pharmaceutical development [34]. Medicinal products that are unpleasant or cause stress are more likely to be rejected by children or caregivers [27,35].

Patient acceptability is likely to have a significant impact on patient adherence and, consequently, on the efficacy of a product. Acceptability is determined by the characteristics of the product and the user [34]. Factors influencing product acceptability include: palatability, swallowability (e.g. size, shape, texture), appearance (e.g. colour, shape), complexity of the preparation to be conducted by the child or its caregivers prior to administration, the required dose (e.g. the dosing volume, number of tablets, etc.), the required dosing frequency and duration of treatment, the selected administration device, the primary and secondary container closure system and the actual mode of administration to the child and any related stress, pain or discomfort [34,36].

In the case of ORS, many children refuse to drink it because of their unappealing organoleptic properties, one important factor leading to rehydration treatment failure [23,37]. Therefore, one important current challenge in the development of ORS is focusing on improving patient acceptability, including not only taste, but also texture, appearance or smell [23,27,29,38,39]. Other factors influencing acceptability include, for example, the large volumes or the role of parents and caregivers.

In these sections, we review the different aspects of ORS influencing acceptability and different strategies to increase it.

ORS palatability

Sodium is an essential element in the intestinal absorption of water, which occurs optimally when the glucose to sodium ratio is 1 to 1 [7,37], mediated by the glucose-sodium co-transport in the brush border of the mammalian small intestine [7,28,40]. Consequently, ORS all have a salty taste, with a higher sodium concentration than the most common consumed beverages, making them less palatable, particularly in children. In their reaction to the ORS salty taste, many children refuse to drink and/or regurgitate the mixture [41,25,28], being the main barrier for ORS adherence [23,26-28].

Currently, some proposed alternative strategies to reduce the strong salty taste are controversial mainly due to the risk of modifying the glucose/sodium chloride ratio [19], that could avoid full rehydration and worsen diarrhea through osmotic mechanisms [19], for example with the addition of rice syrup [28], fruit juices [38], carbonated beverages [13], or with home flavoring [28,42].

To date, few studies have evaluated palatability of ORS in children and the parents' opinion, an important factor that, together with the low insistence of parents to ensure that their children complete treatment, reduce ORS effectivity [25,28].

In a study in children and adults, te Loo et al., demonstrated that only very small amounts of apple juice or orange juice could be added to the ORS without significantly altering electrolyte composition and osmolality. Moreover, palatability of these new solutions did not improve, in comparison with commercially flavoured ORS. For this reason, commercially flavoured ORS, which fulfill ESPGHAN criteria, were the recommended options [38].

To mask the salty taste, EMA recommends flavours such as caramel, grapefruit, lemon, orange and vanilla [35], which could be considered in the development of commercially flavoured ORS [41]. Variations in children preferences, according to social and cultural influences and geographical location, should also be considered [25,35].

In a satisfaction study in 156 children and their parents, assessing gel and gelatin ORS textures, a 54% of parents had experienced problems to administer ORS to their children because of its unappealing taste. The most accepted flavours were cola and strawberry, while orange was the flavour that most children would like to taste if available [27]. In a randomized, single-blind clinical trial, cola and strawberry were also the preferred flavours. Of note, there was an association between children who liked cola drinks and preferred the ORS cola flavoured, while no relationship was found in the case of strawberry. These results highlight the importance of considering children preferences in the formulation of ORS [25].

In this regard, the effect of temperature could also be explored, since low temperatures could reduce the perception of salty taste. This effect has been already assessed using frozen ice pops, being their acceptance attributed to the ice pop's appeal, better taste or soothing effect [31]. Since it is known that taste perception is enhanced as the temperature of food and beverage products increases [43], the use of ORS at low temperatures, in solid or liquid forms or when reconstituted, in gel formulations, should be considered.

ORS texture

Texture is, after taste, the second main barrier to administer oral formulations to children with different diseases [44]. However, studies evaluating the influence of texture in the acceptability of oral formulations in children are limited [29].

In the satisfaction study performed by Polanco et al., the preferred texture by children and parents was the gel texture, with a 90% of the parents stating that they would like to try it. Both textures, gelatin and gel, together with the added flavors, promoted the association with desserts and sweets, avoiding the perception of ORS as a medicine [27].

Of note, it has also been speculated that the gel texture may mask the unpleasant salty taste of electrolytes [23], thus supporting the use of new textures, solid or semi-solid, in the formulation of ORS in order to improve their acceptability.

ORS smell and appearance

As already described, the appearance of a product can influence acceptability, particularly in children, with similarities with deserts or sweets [27], and also with ice pops [31], nearer to the child's preferences. It has also been shown that the addition of colours to ORS product formulations can improve sensorial acceptability [41].

The same considerations should apply to smell, although no studies have been assessed this issue. In this regard, it should be taken into account that the affective responses to pleasant/unpleasant odours do not appear in children until the age of about 5 and that, after the age of 6, the adult pattern may be observed [35,45].

Large volumes of ORS

The health condition of children with gastroenteritis is another factor that can determine the willingness to accept medications and, in particular, ORS, being less co-operative than usual [35]. Although liquid products may be preferred and provide high dosing flexibility, in the case of ORS, the sick children can spit or spill the liquid, have difficulties to swallow large volumes, and could vomit it, being the recommended ORS volumes exceeding the acceptable volumes for most children [29,30].

The large volumes of ORS also affect parents and caregivers, who have to learn the correct mode of administration. For example, children younger than two years should be given one teaspoon every one to two minutes, while older children should be encouraged to take frequent sips directly from the cup. If vomiting occurs, the recommendation is to wait five to ten minutes and then re-start offering the ORS again more slowly, every two to three minutes [6,46].

These large volumes also represent a problem in the emergency departments, with time constraints, space limitations and the difficulties associated with providing 5 mL of fluid by mouth every 1-5 minutes [31], in which the most relevant outcome measures for emergency physicians include: therapy efficacy, time required for efficacy and adverse events [33].

In this regard, we consider that new solid or semi-solid ORS formulations could contribute to overcome these barriers, with reduced volumes (maximum 150ml), easily administered at small portions, and improved flavors and textures, with important advantages over the liquid formulations, increasing the acceptability in the paediatric population.

Role of parents and caregivers in the ORS acceptability

Parents and caregivers have an important influence on the adherence to ORS treatment, often contributing to its underuse [13,25]. The main reason is the refusal of children to take ORS, which leads to use or to add fruit juices or other beverages that do not fulfill current recommendations [13,25,38], avoiding full rehydration and worsening diarrhea through osmotic mechanisms [19].

Another reason is that parents would be more focused to stop the most visible symptoms and signs of gastroenteritis, such as diarrhea, vomiting, etc., leaving aside the need of rehydration [7].

In any case, continuing education in rehydration therapy is still a need for parents and caregivers [7], including the recommendations to use ORS. In this regard, solid or semi-soli formulations could help parents and caregivers to administer the rehydration product, with low amounts (100-150ml), being

easier to give at intervals and at small portions and regarded as a desert by the children, which can also be stored in the refrigerator for a while. The use of products that must be reconstituted using cold water would also facilitate the product preparation and decreasing the salty taste.

NEW GELLIFIED PRODUCTS FOR THE MANAGEMENT OF ACUTE DIARRHEA

There have been several major efforts to modify the composition of ORS with the goal to improve its efficacy to reduce diarrhea [7]. In this attempt, it is important that the new products fulfill the recommended criteria regarding the glucose/sodium ratio and the osmolality range (200-250 mOsm/l), according to WHO or ESPGHAN [22].

As already stated, one feasible strategy for oral rehydration is the development of rehydration products with gel consistency, containing glucose and the mineral complexes, different flavours and different types of solidifying agents that are degraded at colon level and, therefore, they do not interfere in the glucose/sodium ratio at the absorption site in the small intestine [21].

Among the different solidifying agents, well-known matrices can be used to provide different solid or semi-solid textures, such as xanthan gum [47], and modified resistant starches (such as maize) [21]. Other gelling agents such as gelatin, pectin [41], agar [48], or gellan gum [49], alone or in combination, could also be assessed.

As already mentioned, these formulations provide many advantages versus the liquid formulations, increasing children acceptability, such as substantial reduction of volume (around 100ml), masking of the unpleasant salty taste, similarities with deserts or sweets, which can be stored in the refrigerator, improved swallowability, more attractive flavour and appearance and easier of administration by parents and caregiver. Moreover, compared to similar ready-to-use products, formulations in form of powders are more convenient in terms of storage, handle, transport and shelf-life [24], being provided with devices to guarantee precise dosing (Figure 1). One limitation of solid products is the minimum age at which the child can eat solid food.

Despite the numerous advantages described, to date, there are few studies comparing solid formulations versus conventional ORS. In our opinion, this deserves further research, with comparisons in the degree of adherence to treatment, children satisfaction and parents' opinions.

STUDIES COMPARING SOLID VS LIQUID FORMS

First comparative studies have focused on demonstrating the superiority of new ORS that contained resistant starch, specifically

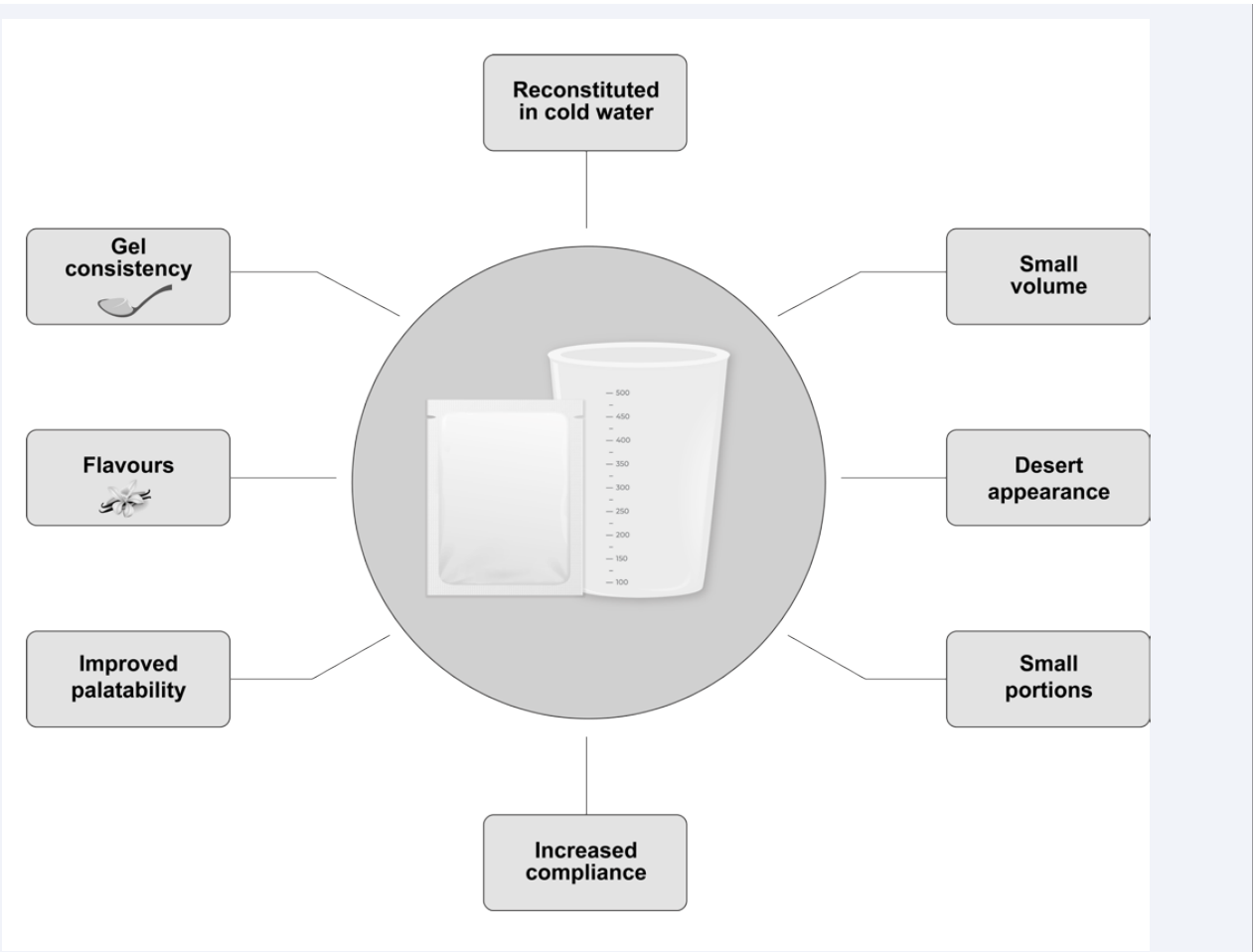

Figure 1 Advantages of ORS with gel consistency.

high-amylose maize starch (HAMS) versus ORS, based on the demonstration that the final metabolites of starch in the colon, short-chain fatty acids (SCFA), stimulate colonic sodium and fluid absorption by a cyclic AMP-independent mechanism [7,21,50], although no solid or semi-solid formulations were obtained.

In a randomized-controlled trial performed in children aged between 5 and 36 months, Passariello et al., compared the standard ORS with banana flavour with a gel hypotonic formulation containing zinc, with a vanilla flavour, observing a better compliance with the gel formulation and a higher amount consumed at 4 and 24 h. The number of children who refused taking the product was lower in the gel group. Statistically significant differences were reported in the main symptom, diarrhea. A significantly shorter duration of diarrhea ($p < 0.001$), and a significantly lower number of patients with diarrhea after 72 h of treatment ($p = 0.028$), in the gel group were reported. According to the authors, the gel formulation contributed to mask the unpleasant salty taste, thus increasing the acceptability of children for this formulation [23]. These results support the development of products for oral rehydration in gel forms and the performance of new comparative clinical trials.

Another interesting study has been published recently by Taylor et al. in which the release of salts from pectin-gelatin matrices was assessed under simulated gastric conditions. The different ORS gels developed, containing pectin and gelatin, showed favorable textural profiles, being able to rapidly release salt in gastric conditions [41]. These results suggest that different gel formulations of ORS are able to effectively release the salts before reaching the absorption site at the small intestine.

CONCLUSIONS

Currently, in the management of acute diarrhea, particularly in children, there is still a need to improve the acceptability and adherence to ORS, for example palatability, swallowability, appearance or parent's attitude towards the treatment administration.

In our opinion, the development of new ORS gel formulations could help to overcome these disadvantages. The main difficulty, the salty taste, can be masked using flavours, reconstituting and administering the gel product at low temperatures or using pleasant textures that can resemble desserts or sweets.

Another important critical point in the oral rehydration is the volume administered, which children usually do not accept. In gel formulations the volume is significantly reduced to around 100ml, and can be administered at small portions, thus avoiding its refusal and facilitating the role of parents or caregivers in administering it. Recent comparative studies are demonstrating these benefits, together with the demonstration of the electrolytes release at gastric level. However, more clinical trials are needed to compare gel formulations vs standard ORS.

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