

A comparative analysis of response to ORS (oral rehydration solution) vs. ORS + gelatin tannate in two cohorts of pediatric patients with acute diarrhea

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ABSTRACT

Aim: the study aims to observe the response to treatment with ORS only or ORS + gelatin tannate in two cohorts of pediatric patients with acute diarrhea, with the primary efficacy endpoint being the number of stools at 12 hours from baseline.

Methods: children aged 3 months to 12 years were included in the study. Only children with acute diarrhea, more than 3 liquid stools, and duration inferior to 72 h were included. Number of stools was recorded as absolute number, categorized as ≤ 3 and ≥ 4 stools over 12 hours, and as a stool decrease index (SDI). Other clinical variables were recorded, including weight, fever, vomiting, stool characteristics, and signs of peritonitis/sepsis.

Results: baseline characteristics for the two populations included a mean age of 2.3 years in the ORS group and 2.6 years in the ORS + gelatin tannate group. Children younger than 2 years represented 59.8 and 54.3% in the ORS and ORS + gelatin tannate groups, respectively. Clinical variables such as vomiting, dehydration, weight, and stool decrease index were used to compare the two groups. We found a statistical significant difference between the two groups ($p < 0.0001$) -- SDI for the ORS group was -0.1894; for the ORS + gelatin tannate group was -0.6023.

Conclusions: we observed a significant decrease in the number of stools and an improvement in the consistency of stools in the ORS + gelatin tannate group. Other clinical variables such as vomiting, dehydration, weight, bloody stools, and peritonitis/sepsis signs showed no statistical differences between the two groups, but did show a general trend toward improvement. The Stool Decrease Index (SDI) showed a 18% decrease in the number of stools for the ORS group and 60% for the ORS + gelatin tannate group. The use of ORS + gelatin tannate was associated with a greater decrease in SDI. Gelatin tannate decreased the number of stools at twelve hours in children.

Key words: Acute diarrhea. Gelatin tannate. Tannic acids. Intestinal infection.

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INTRODUCTION

In the 1980s the annual global mortality rate as a result of acute diarrhea was estimated at 4.6 million people. Since the introduction of oral rehydration therapies it has fallen to 2.5 million people, although this figure continues to be an estimate. In any event, mortality figures are still very high.

It is estimated that acute diarrhea is the third cause of death (15%) in children under the age of 5 living in developing countries, after perinatal death (23%) and acute respiratory infection (18%) (1).

Intestinal infection is by far the most common cause of acute diarrhea. There are two well-defined risk factors which stand out from the rest, living in the world's most depressed regions (Indian sub-continent, Africa, and Latin America) and pediatric age, particularly newborn babies and toddlers. Other risk factors such as immune suppression, travel, and intake of acid secretion inhibitors and antibiotics play a less significant role (2).

In acute infectious diarrhea the stimulation of intestinal secretion is induced in most cases by enterotoxins binding to receptors in the apical pole of the enterocyte and in other cells such as enterochromaffin cells. A "second messenger" intracellular cascade is activated (espe-

The study was conducted according to the principles of the Declaration of Helsinki.

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cially in the case of the *V. cholerae* toxin) of substance P, VIP and 5 HT receptors, causing changes in the intracellular concentration of cAMP, which opens Cl channels, leading to a net flow of chlorine into the intestine. Sodium attempts to maintain electroneutrality, and there is a secondary passive movement of water to maintain isotonicity. Multiple substances have been sought to antagonize the pro-secretory effects of these substances (3).

According to the WHO, the recommended treatment for acute diarrhea consists of oral rehydration. Only in certain, very specific situations can some antibiotics, motility inhibitors such as loperamide, or substances which decrease water and electrolyte secretion such as racecadotril be useful. It is well known that the administration of motility-reducing drugs can favor bacterial overgrowth.

Some controlled studies have shown the efficacy of tannins in the treatment of acute diarrhea, with a greater effect than placebo (4), shortening the duration of the disorder with no undesirable effects. This is supported by a high prescription volume of over 350,000 units of Gelatin Tannate.

Gelatin tannate powder (gelatin tannate) is a mixture of tannic acid and gelatine. Tannic acid is a gallic acid and glucose polymer with the capacity to form macromolecular complexes with the proteins to which it binds by means of hydrogen links (astringent property), polysaccharides, alkaloids, and saponins. It is also attributed antibacterial and antioxidant properties.

It has been shown that tannins are capable of inhibiting the *Vibrio cholerae* toxin, thus reducing intracellular cAMP formation by inhibiting ADP ribosylation, hence reducing the intestinal secretion of chlorine and water. The cholera toxin (CT) is an oligomeric protein formed by a single A unit and five B sub-units. Its biological action starts when the B unit binds to the GM receptor at the apical membrane of the enterocyte causing a number of changes in the CT molecule which lead to A sub-unit insertion in the cell, which activates adenylyl cyclase and thus induces prostaglandin activation, with Na and water accumulating in the intestine. Tannins are capable of inhibiting ADP ribosyltransferase activity (5), probably by forming macromolecular aggregates with CT, preventing it from binding to GM receptors at the apical portion of the enterocyte and thus inhibiting cAMP synthesis (6).

Tannic acids have several undesirable gastrointestinal effects; they induce digestive symptoms such as nausea and vomiting, and inhibit the absorption of Fe and other metals. The use of tannic derivatives such as albumin tannate and gelatin tannate, which is hydrolyzed to gelatin and tannic acids in the intestine, thus prevent gastric lesions affecting the gastric mucosa from developing due to tannic acid. There are very few studies on the effect of tannins on intestinal motility, but they appear to confirm the absence of an inhibiting effect (7).

The objective of this study is to show the clinical effectiveness and safety of gelatin tannate in the pediatric

population of Spain under regular prescription conditions, and to evaluate its speed of action which, according to some studies, is less than 12 hours.

MATERIAL AND METHODS

We realized an observational study of two cohorts of patients (ORS and ORS + gelatin tannate) with acute diarrhea in medical centers at Almería, Spain. The inclusion criteria were: children aged 3 months to 12 years, patients with a diagnosis of acute diarrhea, three or more liquid stools a day for less than 72 hours. Exclusion criteria included: chronic or toxic diarrhea, use of anti-diarrheics (other than gelatin tannate), and impossibility to follow the patient for more than 12 hours. Antibiotic use was allowed in both groups according to the preferences of the treating physician. The primary study endpoint was the number of stools at two time points: baseline and 12 h later. In addition to number of stools we collected stool characteristics, presence of blood in the stool, vomiting, dehydration, signs of peritonitis and/or sepsis, and weight. Standard socio-demographic variables such as age and sex were collected.

Statistical analysis

An initial quality control check of the database was performed to ensure that data used for the statistical analysis were adequate. The effectiveness of treatment was analyzed as a decrease in the symptoms of diarrhea at 12 hours after treatment onset. In order to achieve this we analyzed the differences between baseline and final values for the collected variables in each group of patients using the McNemar 2-by-2 test for categorical variables and Wilcoxon's test for quantitative variables (when normality conditions were not present). Comparisons between the two groups at baseline and after 12 h used the Chi-square or Fisher's exact test for categorical variables and the t-test or Mann-Whitney U test (when normality conditions were not present) for quantitative variables.

RESULTS

A total of 239 children were included in the study. Twenty-eight patients did not fulfill inclusion criteria and were not included for the analysis. A total of 211 patients were included in the final analysis distributed as follows -- 114 patients in the ORS group and 97 patients in the ORS + gelatin tannate group.

Socio-demographic characteristics

Mean age of the study population was 2.5 years (SD \pm 2.42) with a median of 1.7 years; 54.1% of patients were

male and 42.7% female. Mean age for the ORS group was 2.3 years (SD \pm 2.46), and for the ORS + gelatin tannate group was of 2.6 years (SD \pm 2.39). Children younger than 2 years were 59.8% and 54.3% for the ORS and ORS + gelatin tannate group, respectively. The distribution for sex in the ORS group was even at 50% each, and for the ORS + gelatin tannate was 59% males and 41% females.

Clinical characteristics

The absolute number of stools at baseline for the ORS group was 114 and for the ORS + gelatin tannate group was 93. A mean of 7.26 (SD \pm 2.95) stools for the ORS and a mean of 6.19 (SD \pm 1.76) stools for the ORS + gelatin tannate group were estimated at baseline. The mean number of stools at 12 hours was 5.86 (SD \pm 2.45) for the ORS group and 2.06 (SD \pm 1.04) for the ORS + gelatin tannate group. The differences in the number of stools were statistically significant between groups ($p < 0.0001$). A stool decrease index was created (SDI = Final (12 h) - Baseline stools / Baseline Stools) in order to compare both groups. We found a statistical significant difference between the two groups ($p < 0.0001$), the SDI for the ORS group was 18.9% (SD \pm 20.2) and for the ORS + gelatin tannate group was 60.2% (SD \pm 18.8). We also grouped the number of stools as ≥ 4 and < 4 , and found also statistically significant differences between the two groups at baseline and treatment end ($p 0.037$).

We also found improved stool consistency from baseline to endpoint (12 h) in the two groups, from liquid stools in 90.3% and 97.8% for the ORS and ORS + gelatin tannate groups, respectively, to 71.9 and 28.3% at treatment end for the ORS and ORS + gelatin tannate groups, respectively.

The presence of vomiting at baseline was 78.1% for the ORS and 72.6% for the ORS + gelatin tannate group; at 12 h vomiting was present in 41.6% of the ORS and 35% of the ORS + gelatin tannate groups. No statistical significant differences were observed between the two groups. As per dehydration we observed 9.7% dehydration in the ORS group and 12% in the ORS + gelatin tannate group at baseline; at endpoint 0.9% dehydration was observed in the ORS group and 4.5% in the ORS + gelatin tannate groups; again no statistically significant differences were observed.

Bloody diarrhea was found in only 2.7 and 8.4% of patients at baseline for the ORS and ORS + gelatin tannate groups, respectively. The ORS group maintained the same values while the ORS + gelatin tannate group showed a decrease to 3.3%; no statistically significant differences were found between treatment groups. As for weight and peritonitis/sepsis signs we did not find any statistically significant difference between groups. Fever showed a statistically significant difference ($p < 0.001$) between the two groups at endpoint; however, we observed a decrease in temperature values for the two study groups from 37.81 °C

to 36.98 °C in the ORS group and 37.7 °C to 36.6 °C in the ORS + gelatin tannate group (Figs. 1 and 2).

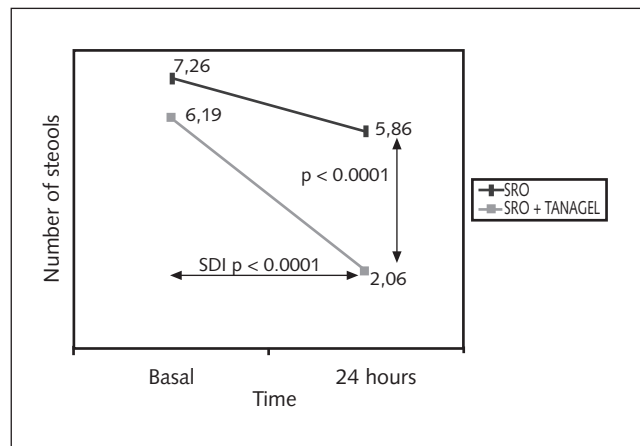


Fig. 1. Number of stools between the groups at baseline and final (12 h).
Número de deposiciones en los dos grupos al inicio y al final (12 h).

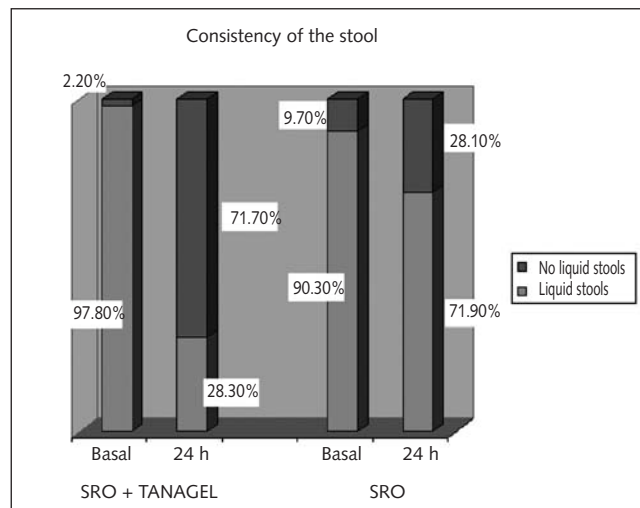


Fig. 2. Consistency of the stool.
Consistencia de la deposición.

DISCUSSION

Death from diarrhea and dehydration is the second cause of death in the pediatric population after pneumonia. Oral rehydration salts (ORS) with low glucose and salt concentrations allow effective management for pediatric diarrhea, drastically reducing the number of child deaths in developing countries.

The objective of this study was to study the efficacy of treatment with ORS + gelatin tannate versus ORS alone, measured as diarrheic bowel movements ceasing at 12, 24 and 48 hours after treatment onset in a pediatric popu-

lation. Data show the efficacy and safety of gelatin tannate in combination with ORS in the treatment of acute diarrhea in children aged 3 months to 12 years.

Two hundred and eleven children with acute diarrhea for less than 72 hours and more than three diarrheic bowel movements a day met the inclusion criteria and were included in the study.

Children were assigned randomly to one of the two study groups (ORS, $n = 114$, or ORS + gelatin tannate $n = 97$). The statistical analysis of baseline socio-demographic characteristics shows that the two groups were comparable. Unfortunately, there is a baseline difference in the primary study endpoint, the number of bowel movements; the group treated with ORS + gelatin tannate started with a smaller number of bowel movements before treatment ($p < 0.05$). However, to determine the efficacy of the ORS + gelatin tannate therapy a bowel movement reduction index was created (reduction in number of bowel movements = [final bowel movements - initial bowel movements] / initial bowel movements), with a statistically significant difference in mean reduction ($p < 0.0001$). Twelve hours after starting anti-diarrheic treatment the reduction in the number of bowel movements was 18% for the ORS group and 60% for the ORS + gelatin tannate group.

In both groups there was an improvement in stool consistency, from liquid in the beginning to soft/hard at 12 hours after treatment onset. Although this improvement was greater in the ORS + gelatin tannate group, the difference was not statistically significant.

There was a reduction from initial to final body temperature in both groups of patients, related to the resolution of diarrheic symptoms. No significant differences were found between groups at the start and end of treatment with regard to the other endpoints: presence of bloody diarrhea, patient weight, peritonitis, sepsis, presence of vomiting, or dehydration.

The initial treatment of acute diarrhea is based on several alternatives with differing degrees of evidence: ORS, empirical antibiotic treatment, use of intestinal motility inhibitors such as loperamide, or use of substances that reduce water and electrolyte secretion such as racecadotril (8).

Gelatin tannate is a mixture of tannic acid and gelatin with antidiarrheic effect. Gelatin tannate is also attributed antibacterial and antioxidant properties, representing an advantage as the use of conventional antibiotics in empirical therapy can contribute to the development of resistance and dysbacteriosis (9). Furthermore, unlike other antidiarrheic agents such as loperamide, it has no effects on the central nervous system, thus enabling its safe use in children under two, and has no undesirable effects such as reactive constipation (10). No gelatin tannate-related undesirable effects were recorded during treatment, and the product's tolerance was excellent.

The efficacy and safety of a similar product in the treatment of acute diarrhea in pediatric patients were

studied by Loeb et al. (11). The patients receiving the product containing tannate had a normalization of bowel movements, body temperature, and weight, and ceased to vomit much faster than those receiving placebo.

The results of this study are consistent with many other published clinical studies showing the efficacy and good safety profile of gelatin tannate.

Plein and colleagues studied the effect of tannate on diarrhea in patients with Crohn's disease (12). The results obtained demonstrated that there was a significant reduction in bowel movement frequency at the end of treatment.

Another clinical experience was reported by Ziegenhagen and colleagues, who showed the better efficacy and safety profile of tannin salts *versus* activated charcoal (13). Moreover, in the group receiving tannin salts, the frequency of abdominal pain was lower than in the activated charcoal group (50 *versus* 82%).

Bellknap and colleagues conducted a study on the efficacy of gelatin in the prevention of diarrhea in hospitalized patients starting to receive enteral feeding by tube (14). Patients receiving gelatin showed a significantly smaller number of liquid bowel movements and more movements with normal stool than the group not receiving the gelatin product.

The main limitation of this study is the lack of control in the distribution of variables among the two groups. The experience, however, was positive, showing that the addition of gelatin tannate to treatment with ORS can reduce the duration of antidiarrheic treatment, and providing sufficient data to consider the combination of ORS + gelatin tannate in the treatment of acute diarrhea in the pediatric population.

The treatment of acute diarrhea with ORS + gelatin tannate meets Edelman's (15) criteria for an ideal antidiarrheic treatment as it is effective, has a rapid onset of action, and has no undesirable effects. Furthermore, adding gelatin tannate to conventional treatment with ORS represents an affordable direct cost increase, although such costs could be reduced as this treatment enables a reduction in the quantity of ORS.

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Análisis comparativo de dos cohortes de pacientes pediátricos con diarrea aguda y respuesta a la solución de rehidratación oral (SRO) frente a SRO + tanato de gelatina

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RESUMEN

Objetivo: el estudio tiene como objetivo observar la respuesta al tratamiento con SRO o SRO + tanato de gelatina en dos cohortes de pacientes pediátricos que presentan diarrea aguda, siendo el número de deposiciones a las 12 horas desde el tratamiento inicial el criterio principal de valoración de la eficacia.

Métodos: en el estudio se incluyeron niños de entre 3 meses y 12 años de edad. Únicamente se incluyeron niños con diarrea aguda, con más de 3 deposiciones líquidas y menos de 72 horas de evolución. Se registró la variable principal del número de deposiciones y de análisis como número absoluto, categorizado como ≤ 3 y ≥ 4 deposiciones en 12 horas y como un índice de disminución de deposiciones (IDD). Se registraron otras variables clínicas como peso, fiebre, vómitos, características de las deposiciones y signos de peritonitis/sepsis.

Resultados: las características principales para las dos poblaciones fueron una edad media de 2,3 años en el grupo de SRO y de 2,6 años en el grupo de SRO + tanato de gelatina. Los niños menores de 2 años representaban el 59,8% de los integrantes del grupo de SRO y el 54,3% de los del grupo de SRO + tanato de gelatina. Se registraron variables clínicas como vómitos, deshidratación, peso, fiebre, vómitos, características de las deposiciones y signos de peritonitis/sepsis. Se creó un índice de disminución de las deposiciones (IDD = final [12 h] - deposiciones iniciales/deposición inicial) para comparar los dos grupos. Encontramos una diferencia estadísticamente significativa entre los dos grupos ($p < 0,0001$), el SDI del grupo de SRO fue de -0,1894 y el del grupo de SRO + tanato de gelatina fue -0,6023.

Conclusiones: observamos una disminución significativa en el número de deposiciones y una mejora en la consistencia de las deposiciones en el grupo de SRO + tanato de gelatina. Otras variables clínicas como vómitos, deshidratación, peso, deposiciones con sangre y signos de peritonitis/sepsis no mostraron ninguna diferencia estadística entre los dos grupos de tratamiento, pero se observó una tendencia general hacia la mejoría. El índice de disminución de las deposiciones (IDD) muestra una reducción del 18% en el número de deposiciones en el grupo de SRO y del 60% en el grupo de SRO + tanato de gelatina. El uso de SRO + tanato de gelatina se asoció a un mayor descenso en el IDD. El tanato de gelatina disminuyó el número de deposiciones a las doce horas del tratamiento en niños.

Palabras clave: Diarrea aguda. Tanato de gelatina. Taninos. Infección intestinal.

INTRODUCCIÓN

En la década de los 80 la mortalidad global anual por diarrea aguda se estimaba en 4,6 millones de personas. Desde la introducción de las terapias de rehidratación oral la mortalidad ha descendido a 2,5 millones de personas al año, dato este no suficientemente contrastado. En cualquier caso, las cifras de mortalidad siguen siendo muy elevadas.

Se estima que la diarrea aguda es la tercera causa de muerte (15%) en niños menores de 5 años que habitan en países en vías de desarrollo y tan sólo superado por la

El estudio se realizó según los principios de la Declaración de Helsinki.