Evaluation of Gelatin Tannate Against Symptoms of Acute Diarrhea in Pediatric Patients

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Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Background: Acute diarrhea is the second most common cause of morbidity and mortality worldwide, especially in children aged ≤3 years. Some drugs (e.g., the mucoprotector gelatin tannate) plus a reduced osmolality oral rehydration solution (ORS) may effectively reduce symptom duration and severity. The current trial was therefore designed to assess the efficacy and safety of gelatin tannate in pediatric patients with acute diarrhea.

Material/Methods: This was a randomized, controlled, double-blind, parallel-group, single-center study comparing gelatin tannate plus ORS (103 patients) with ORS plus placebo (100 patients) in children aged 3 months to 12 years with infectious or noninfectious acute diarrhea. Details about stool consistency and total time to resolution of diarrhea comprised the primary study endpoints. Secondary study endpoints included symptoms of diarrhea at 12, 24, 36, 48, and 72 hours after the first dose of study medication.

Results: From 12 hours onwards, the incidence of watery stools was significantly lower in the gelatin tannate group than in the ORS group (at 12 hours: 59.2% *vs.* 77.0%; p=0.01). The same was true for stool frequency (at 12 hours: mean 2 *vs.* 3 stool productions in the previous 12 hours; p<0.01). At all timepoints during the study, the proportion of patients with Stool Decrease Index improvement was significantly greater (p<0.01) in the gelatin tannate group than in the placebo group (at 12 hours: 66.6% *vs.* 33.3%; p<0.01).

Conclusions: Gelatin tannate plus ORS is an effective and safe option for the treatment of acute diarrhea in children. Significant symptom relief is evident 12 hours after starting treatment.

MeSH Keywords: **Diarrhea • Pediatrics • Rehydration Solutions**

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Background

Acute diarrhea, with or without vomiting, is a frequent problem in childhood. It is the second most common cause of morbidity and mortality globally, especially in children aged ≤3 years [1,2], and mortality is most frequent in low-income regions [3].

Rehydration is a key intervention for acute diarrhea and should be introduced as soon as possible [1]; a reduced osmolality oral rehydration solution (ORS) should be started promptly (i.e., within 3–4 hours of symptom onset) and used frequently. After initial rehydration, routine feeding should not be disrupted. Drug treatment is usually not required, although some probiotics may decrease symptom duration and severity. Antibacterial therapy is usually not needed, as it can lead to carrier status for *Salmonella* spp. However, some drugs used in combination with ORS may effectively reduce symptom duration and severity, although further investigations are warranted [1,4,5].

'Mucoprotectors' have now been developed for use in gastroenteric disorders. These agents form a protective biofilm in the intestinal mucosa and enhance mucosal resistance to pathological insults [6,7]. Indeed, pathogenic microorganisms adhere to the intestinal mucosa, weaken cellular tight-junction function, and reduce transepithelial electrical resistance (TEER). They can then penetrate the mucosa, and become internalized and proliferate within intestinal cells. This sequence of events can precipitate and worsen diarrhea [8]. Conversely, mucoprotective agents such as gelatin tannate and xyloglucan help to re-establish normal intestinal function. Additional randomized studies are now needed to clearly define the clinical profiles of these mucoprotectors in patients with acute diarrhea [6,7,9].

Besides its mucoprotective activity, additional evidence suggests that gelatin tannate reduces inflammation, prevents growth of some bacterial species, and preserves the intestinal mucous layer [6,10–13]. Thus, in line with the need for additional assessment of mucoprotectors [1,4,5], the present single-center, randomized, controlled, double-blind trial was designed to assess the efficacy and safety of gelatin tannate in pediatric patients with acute diarrhea.

Material and Methods

Study design

This randomized, controlled, double-blind, parallel-group, single-center clinical trial was conducted to determine the efficacy and safety of gelatin tannate plus ORS compared with ORS plus placebo in pediatric patients (aged 3 months to 12 years) with infectious or noninfectious acute diarrhea. If considered necessary, antibacterial therapy was permitted during the study.

The study protocol was approved by the local ethics committee and the Turkish Medicines and Medical Devices Agency (online follow-up number 1997575), and procedures were carried out in accordance with ethical standards of the Declaration of Helsinki (revised 2000). Written informed consent was obtained from each child's parents or legal guardian.

Exclusion criteria

Potential study participants were excluded for the following reasons: chronic or toxic diarrhea; celiac disease; diarrhea due to milk or protein intolerance; immune disorders; infantile colic; other gastrointestinal disorders (e.g., Crohn's disease); or the use of oral antidiarrheal or other treatments during the study period. Patients who could not be followed-up for at least 48 hours in hospital were also excluded. Patients who received antibacterial therapy were not excluded from the trial.

Treatment and randomization

Patients were randomly assigned to receive gelatin tannate plus ORS, or ORS plus placebo at a ratio of 1: 1. Gelatin tannate was administered in the form of 250 mg oral sachets (Tasectan®; Onko & Koçsel İlaçlari, Istanbul, Turkey) at a dosage of 1 sachet every 6 hours. The sachet contents could be mixed with a milk feed, water, fruit juice, or yoghurt. ORS (Ge-Oral®; Kansuk Laboratuari, Istanbul, Turkey) 50 mL/kg *ad libitum* was administered as a powder for oral solution, containing sodium chloride, trisodium citrate, potassium chloride, and glucose.

This single-center study involved a total of 5 pediatric clinical services. Patients were divided into 4 age groups: 3–<12 months; 1–<3 years; 3–<7 years; and 7 years and older. Regardless of the clinical service, newly hospitalized patients were randomized to placebo or gelatin tannate. Every 2–3 weeks, patient numbers were calculated and recruitment adjustments made, if necessary, to try to equalize group numbers. As such, the study was conducted on a 'triple-blind' basis: physicians and nurses did not know whether the study drug administered was placebo or gelatin tannate; patients were not informed about whether they were being given placebo or gelatin tannate; and physicians and nurses did not know from which clinical service each patient had been referred.

Study procedure

During the first study visit, patients were randomized into 2 groups (gelatin tannate plus ORS, or ORS plus placebo) to receive at least 48-hour treatment in hospital; some patients continued treatment after discharge from hospital. During treatment, all patients were reviewed every 24 hours in hospital, or by telephone or call back to the hospital after hospital discharge.

At the time of hospitalization, baseline demographic (body-weight) and clinical characteristics (comorbidities, symptoms of acute diarrhea during the previous 3 days, and vital signs) were recorded. Symptoms of acute diarrhea were evaluated during patient interview and included: abdominal pain; anorexia; dehydration (abnormal skin turgor, and bodyweight reduction); fever; flatulence; nausea; signs of peritonitis and/or sepsis; and stools (duration of diarrhea, presence of blood/mucus/pus in feces, stool frequency, and stool type).

Investigators recorded details about stool consistency and total time to resolution of diarrhea (primary study endpoint). Stool production (number in the previous 24 hours), with mucus and/or blood, was recorded, as was stool consistency, according to the Bristol Stool Scale (BSS): e.g., type 6 refers to diarrhea with soft stools; type 7 refers to watery stools, no solid pieces, and entirely liquid [14,15]. At study start, all patients had stool consistency type 7. Evaluation was subsequently made of the Stool Decrease Index (SDI): the proportion of patients whose stool consistency improved from diarrhea (BSS 6 or 7) to non-diarrhea (BSS ≤5).

Secondary study endpoints comprised symptoms of acute diarrhea at 12, 24, 36, 48, and 72 hours after the first dose of study medication, and adverse events throughout the trial. In addition, the following biochemical tests could be performed (at study start) if required according to patient condition: blood culture (e.g., for patients with fever for >2 days); complete blood count; serum C-reactive protein; and serum electrolyte measurement (calcium, chlorine, potassium, and sodium).

Statistical analyses

Based on findings of a previous trial [16], it was determined that a total of 240 children (approximately 120 per group) would be sufficient to identify clinically significant differences between the 2 treatment arms, and a period of 6 months would be sufficient to enroll this number of patients.

Data were classified as numerical or categorical, and were checked by the Shapiro-Wilk test to ascertain whether they conformed to a normal distribution (numerical data). An independent-sample t test was used for data conforming to a normal distribution, whereas the Mann-Whitney U test was used for data not conforming to a normal distribution (independent numerical data). A dependent-sample t test was used for data conforming to a normal distribution, whereas the Wilcoxon test was used for data not conforming to a normal distribution (dependent numerical data). Fisher's chi-squared test was used for comparison of categorical data in independent groups, whereas the McNemar test was used for comparison of categorical data in dependent groups. For all results, $p<0.05$ was considered significant.

Results

Patient characteristics

Children were aged between 3 months and 12 years, and had acute diarrhea of infectious origin (bacterial, parasitic, or viral) or noninfectious origin (antibiotic-related) for ≤72 hours. Patients had dehydration, and all were hospitalized for ≥48 hours. Acute diarrhea was defined as ≥3 stools per day, graded as BSS 7 [14,15]. The diagnosis of acute diarrhea was made based on investigators' judgement of the clinical picture of objective (e.g., stools, vomiting, or fever) and subjective e.g., (abdominal pain, or nausea) symptoms.

A total of 251 eligible patients were enrolled in the trial. However, 48 patients were excluded for the following reasons: early discharge from hospital (n=6); loss of contact with patient after discharge from hospital (7); duty physician not familiar with the study (20); patients received additional antidiarrheal medication (8); patients refused to take oral medication (4); and increased severity of vomiting or diarrhea (3). Thus, 203 patients completed the study (gelatin tannate plus ORS, n=103; ORS alone, n=100) and received at least 1 dose of study medication (per-protocol population). Results were recorded and data analyzed for the per-protocol population. Table 1 shows demographic and clinical characteristics for these patients. Mean patient age was 40 months, 117 patients were male (57.6%), and mean (± standard deviation) stool frequency in the previous 24 hours was 7.7±5.0. Approximately 60% of patients had accompanying nausea at baseline and 50% had abdominal pain. More than one-third of patients (36.2%) received antibacterial therapy during the trial.

Effects on symptoms of acute diarrhea

At all study assessment timepoints from 24 hours onwards, the incidence of nausea was significantly lower in the gelatin tannate plus ORS group than in the ORS group alone (at 24 hours: 11.7% vs. 26.0% of patients; p=0.01; Figure 1A). The same was true for abdominal pain (at 24 hours: 10.7% vs. 24.0% of patients; p=0.02; Figure 1B). From 12 hours onwards, the incidence of watery stools was significantly lower in the gelatin tannate plus ORS than ORS-alone group (at 12 hours: 59.2% vs. 77.0%; p=0.01; Figure 1C). Significantly more patients in the combination than ORS-alone group had dehydration at baseline (35.0% vs. 16.0%; p<0.01). Subsequently, no significant difference in the occurrence of dehydration was noted between the 2 groups, since all patients in both groups were treated with ORS. Nonetheless, from 36 hours onwards, a nonsignificant trend (p=0.05) was evident towards a lower incidence of dehydration in the combination group than in the ORS-alone group (Figure 1D). After 36- and 72-hours' hospitalization, fever was recorded in significantly fewer patients

Table 1. Demographic and clinical characteristics of the per-protocol study population (n=203).

Age; months Mean ± SD (range)	40±36 (3–144)
Gender (male: female;%)	57.6: 42.4
Stool frequency; number of watery stools in previous 24 hours Mean ±SD (range)	7.7±5.0 (3–30)
Vomiting frequency; number of episodes in previous 24 hours Mean ±SD (range)	3.2±3.6 (0–20)
Nausea (% patients)	59.1
Abdominal pain (% patients)	49.3
Dehydration (% patients)	25.6
Fever (% patients)	35.0
Antibacterial therapy (% patients)	
Ceftriaxone	9.9
Cefuroxime	4.9
Ampicillin-sulbactam + amikacin, azithromycin, clarithromycin or metronidazole	4.0
Metronidazole	3.4
Ceftriaxone-metronidazole	3.0
Amoxicillin-clavulanic acid	2.5
Ampicillin-sulbactam	2.5
Cefdinir + amoxicillin-clavulanic acid or metronidazole	1.0
Cefixime	1.0
Cefuroxime-metronidazole	1.0
Cefdinir	0.5
Cefixime, ceftriaxone	0.5
Ceftazidime	0.5
Piperacillin, vancomycin, fluconazole	0.5
Other	1.0

treated with gelatin tannate plus ORS rather than in the ORS-alone group (at 36 hours: 13.6% *vs.* 65.0%; p<0.01; Figure 1E).

Effects on stool frequency

As shown in Figure 2, from 12 hours onwards, stool frequency was significantly lower in the gelatin tannate plus ORS group than in the ORS-alone group (at 12 hours: mean 2 *vs.* 3 stool productions in the previous 12 hours; p<0.01).

Effects on secondary study endpoints

At all timepoints during the study, the proportion of patients with SDI improvement, indicating resolution of diarrhea, was significantly greater (p<0.01) in the gelatin tannate plus ORS group than in the ORS-alone group (at 12 hours: 66.6% *vs.* 33.3%; p<0.01; Figure 3). No adverse events occurred during the trial.

Discussion

The principal intervention for pediatric patients with acute diarrhea is rehydration, which should be used as soon as possible after symptoms occur [1]. In this way, complications and risks can be avoided, such as serious dehydration, electrolyte disturbances, and altered nutrient absorption and digestion with worsening nutritional status. Such complications can lead to increased requirements for enteral or parenteral rehydration and nutrition, and hospitalization [1,2,17]. Thus, treatments such as gelatin tannate, with the potential to enhance efficacy of oral rehydration therapy and obviate the need for enteral or parenteral intervention, clearly warrant detailed investigation.

In the present study, gelatin tannate plus ORS was significantly more effective than ORS alone in reducing symptoms (e.g., nausea, abdominal pain, fever, and watery stools) and stool frequency in children hospitalized with acute diarrhea. The symptom reduction was particularly evident for nausea and abdominal pain at 24–72 hours of hospitalization, and for watery stools after 12–72 hours of treatment.

Another interesting aspect of the present trial is that average direct costs per patient (e.g., total costs of drugs, diagnostic tests, and consultations) were approximately 40% lower in the gelatin tannate plus ORS group than in the ORS-placebo group (229.26 *vs.* 386.56 Turkish lira). This creates significant scope for future, more-detailed cost-utility analyses of gelatin tannate in children with acute diarrhea.

A potential limitation of the trial is that the exact proportions of patients who completed the 72-hour study period in hospital or at home were unclear. Clearly, patients in the hospital environment are more likely to have adhered to the gelatin tannate plus ORS schedule than patients in the home setting. In addition, we did not manage to include the anticipated number of children during the study period. However, this was not materially important since the numbers were sufficient to demonstrate both clinically and statistically significant differences between the 2 treatments.

Altogether, our results are consistent with findings from other clinical trials of mucoprotective agents. For example, in an
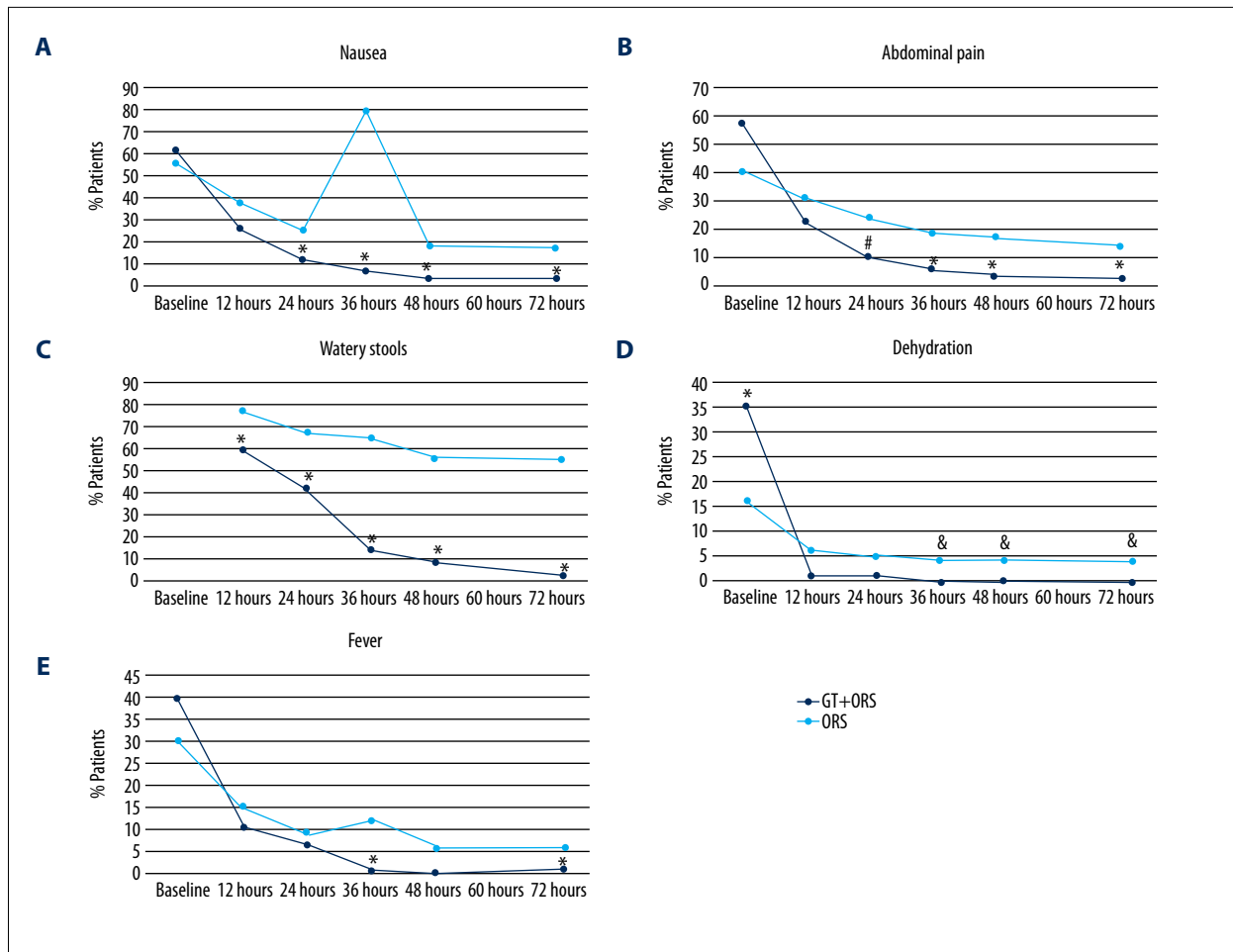
Figure 1. Effects of gelatin tannate (GT) plus oral rehydration solution (ORS) versus ORS on symptoms of acute diarrhea during hospitalization: (**A**) nausea; (**B**) abdominal pain; (**C**) watery stools; (**D**) dehydration; and (**E**) fever. Statistical significance: & p=0.05; # p=0.02; * p≤0.01.
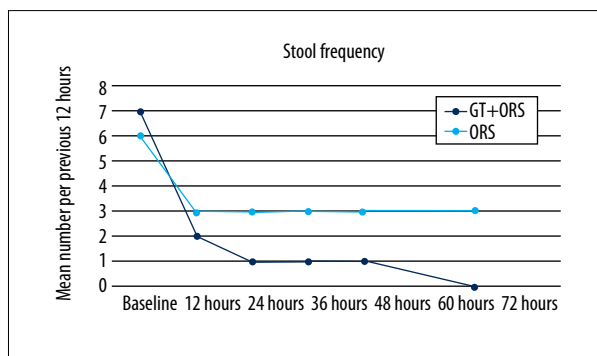

Figure 2. Effects of gelatin tannate (GT) plus oral rehydration solution (ORS) versus ORS on stool frequency in patients hospitalized with acute diarrhea. Note that stool frequency refers only to stools of type 6 (diarrhea with soft stools) or 7 (watery stools, no solid pieces, and entirely liquid) on the Bristol Stool Scale. Statistical significance: p<0.01 at all timepoints, including baseline.
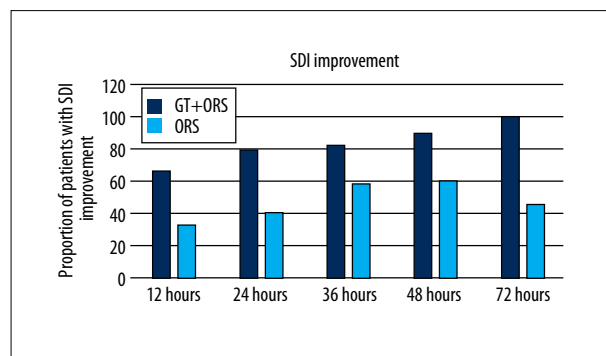

Figure 3. Effects of gelatin tannate (GT) plus oral rehydration solution (ORS), versus ORS, on Stool Decrease Index (SDI) in patients hospitalised with acute diarrhea. Statistical significance: p<0.01 for GT + ORS *vs.* ORS alone at all timepoints.

observational study involving 239 children (aged 3 months to 12 years) with acute diarrhea, gelatin tannate plus ORS versus ORS alone significantly reduced stool frequency at 12 hours post-treatment [16]. In a randomized study in adults with acute diarrhea, another mucoprotective agent, xyloglucan, was shown to significantly reduce symptoms of diarrhea and to have faster onset of action than diosmectite or *Saccharomyces boulardii* [18]. Other well-controlled studies of gelatin tannate are ongoing: for example, this mucoprotective agent is currently being compared with placebo in up to 158 children aged <5 years with acute gastroenteritis; the primary study endpoint is duration of diarrhea, and study results are soon expected to be released (study number NCT02280759) [12].

In vitro findings also endorse the mucoprotective activity of gelatin tannate, which is considered to adhere to apical epithelial cells in the intestinal mucosa and interact favorably with tight junctions, strongly increasing TEER, and thereby maintaining intestinal wall integrity [10].

Overall, it appears that sufficient data now exist to clearly endorse the use of film-forming, mucoprotective agents, such as gelatin tannate or xyloglucan, in combination with ORS to stop diarrhea, especially in the pediatric population with acute diarrhea. This is particularly pertinent given the significantly favorable action of gelatin tannate on symptoms other than

diarrhea (e.g., abdominal pain, fever, and nausea) in the current trial. Potentially, amelioration of these additional symptoms was also due to the beneficial effect of gelatin tannate on the intestinal mucosa. No adverse events were reported during the current trial, thereby further corroborating the positive safety profiles of mucoprotective agents.

Conclusions

Administration of gelatin tannate in combination with ORS is an effective and safe option for the treatment of acute diarrhea in children. Significant symptom relief is evident 12 hours after starting treatment. Clearly, results from this trial validate the use of gelatin tannate as an addition to ORS in children with acute diarrhea.

Conflict of interest

The authors have no conflicts of interest to declare.

Acknowledgements

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