Gelatin tannate for treating acute gastroenteritis: a systematic review

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Abstract
Gelatin tannate (GT) is a complex of tannic acid, which possesses astringent, antibacterial, and anti-inflammatory properties, and a protective gelatin. It is increasingly being marketed as an antidiarrheal drug. Our aim was to review data on the effectiveness of GT in treating acute gastroenteritis (AGE) in children and adults. The MEDLINE, EMBASE, and the Cochrane Library databases were searched in July 2013, with no language restrictions, for controlled clinical trials. Additional references were obtained from reviewed articles. Two trials met the inclusion criteria. In adults, one randomized controlled trial involving 40 subjects (mean age: 43±13 years) found that, compared with placebo, GT may be more effective at reducing some symptoms of AGE in the first 48 h after initiation of treatment. In children, one poor quality study (no randomization and no blinding) involving 211 children (mean age: 2.5±2.4 years) reported some beneficial effect of GT at 12 h after initiation of treatment. None of the studies evaluated the effect of GT on the primary outcome measures for this review such as stool output, duration of diarrhea, admission to hospital, duration of hospital stay, and (in children) weight gain after rehydration. Currently, there is no evidence to support the use of GT for treating AGE in children and only sparse evidence to support the use of GT in adults. Further well-designed trials, with sufficient power, adequate follow-up periods, and clinically relevant outcome measures, are needed. These include stool volume, duration of diarrhea, admission to hospital, duration of hospital stay, weight gain after rehydration, and adverse effects.

Keywords RCT, systematic review, antidiarrheal drugs, tannins, acute diarrhea

Introduction
Acute gastroenteritis remains a common reason for presentation of patients to healthcare professionals, especially in the pediatric population. In Europe, it is usually a mild disease; however, dehydration can be responsible for hospital admission. Oral rehydration should be used as first-line therapy to prevent or treat dehydration [1]. However, oral rehydration therapy neither reduces the frequency of bowel movements and fluid loss nor shortens the duration of illness, which limits its acceptance [2]. Effective and inexpensive interventions that could add to the effect of oral rehydration therapy are of interest to caregivers and healthcare professionals.

Recently, in many European countries, gelatin tannate (GT) is being widely marketed for treating acute gastroenteritis.

GT is a complex of tannic acid and a protective gelatin. The exact mechanisms by which GT might exert its actions on diarrheal diseases are unclear. However, a number of actions have been postulated, mainly related to tannins (water-soluble polyphenols, i.e., polymers of gallic acid and glucose). First, tannins are known for their astringent properties, allowing the precipitation of proinflammatory proteins such as mucoproteins of intestinal mucus; their precipitation reduces local inflammation [3]. Second, there are antibacterial properties of tannins through inhibiting the growth of pathogens such as Bacteroides fragilis, Clostridium perfringens, Escherichia coli, Enterobacter cloacae, Salmonella typhimurium, Helicobacter pylori (H. pylori), and Listeria monocytogenes [4-5,6]. In vitro, tannins have shown the ability to inhibit certain bacterial toxins such as toxins of Vibrio cholerae [7]. Tannic acid also has a potential antiparasitic effect. In animal models, it has been shown that the consumption of tannins may lead to higher resistance to various nematodes [8,9]. Third, tannic acid has anti-inflammatory properties exerted by inhibiting the cytokines and adhesion molecules involved in inflammatory disorders [10].

Tannic acid, when consumed alone, may cause undesirable symptoms such as nausea, vomiting, and inhibition of metals absorption. One of the attempts to eliminate or alleviate
these side effects was the development of GT. Gelatin affords mechanical protection of the gut through the formation of a protein-based film that lines the gut walls. It protects against the effects of acids and alkaloids from bacterial fermentation or putrefaction during gastrointestinal transit [11].

Little is known about the clinical efficacy of GT. The present review, initiated as part of the update of the guidelines for the management of acute gastroenteritis in children [1], was undertaken to systematically review the effectiveness of GT in the treatment of acute gastroenteritis in children and adults.

Methods

We searched The Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, and EMBASE databases in June 2013 for clinical trials comparing GT with placebo or no intervention in the management of children or adults with acute gastroenteritis (as defined by the investigators) using the following text word terms and MESH headings: diarrhea/diarrhoea, diarrh*, gastroenteritis, gastritis*, gelatin*, and tannate*. We did not impose any language restrictions. In order to identify any other relevant studies, we also searched the reference lists from identified studies and key review articles. Furthermore, the ClinicalTrials.gov website https://clinicaltrials.gov/ and EU Clinical Trials Register website https://www.clinicaltrialsregister.eu were searched for randomized controlled trials (RCTs) that were registered, but not yet published.

The primary outcome measures were stool output, duration of diarrhea (time until permanent cessation), admission to hospital, duration of hospital stay, weight gain after rehydration, episodes of vomiting, fever, and adverse effects. These outcomes are typically considered when evaluating interventions for treating acute gastroenteritis [12]. In addition to these outcomes, a priori we decided to extract other data reported by the investigators if clinically relevant to the current review.

The reviewers, using a standardized approach, independently undertook the literature search, data extraction, and quality assessment. The data sought included baseline characteristics of the participants, details related to the use of experimental and control interventions (including dose and duration), outcomes, setting and funding.

The risk of bias in the studies meeting the inclusion criteria was assessed independently by the reviewers with the implementation of The Cochrane Collaboration’s tool for assessing risk of bias. The following criteria were used: adequacy of sequence generation, allocation concealment and blinding of participants, personnel and outcome assessors; and extent of loss to follow up, i.e., the proportion of patients in whom the investigators were not able to determine outcomes (incomplete outcome data). A low risk of bias was indicated by an answer of ‘yes’, and a high risk, by an answer of ‘no’ [13].

If original publications allowed, the dichotomous outcomes are reported as the risk ratio (RR) between the experimental and control groups with 95% confidence intervals (95% CI). The continuous outcomes are reported as the mean difference (MD) with 95% CI. If no data were provided, we report the results in a narrative format. The Cochrane Review Manager (RevMan) [Computer program, Version 5.1. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011] was used for statistical analysis.

Results

The literature search yielded 4 eligible articles. Two articles were excluded. Of these, one was a case report [14], and one was a study conducted in patients treated for H. pylori infection [15]. Table 1 summarizes the key characteristics of the only 2 included trials (Allegrini et al [16]; Esteban Carretero et al [17]). Both studies were carried out in Europe (in Italy and Spain, respectively). Only one of them was a double-blind RCT [16]. This study was carried out in adults (n=40; mean age: 43±13 years) and compared GT administered at a dose of 500 mg, six times daily for 2 consecutive days, with placebo.

The duration of follow-up was 48 h. The second study was a controlled clinical trial [17]. In this study, children (n=211) aged 3 months to 12 years (mean age: 2.5±2.42 years) with acute gastroenteritis treated with oral rehydration solution (ORS) and GT were compared with children treated with ORS only. At baseline, there was a difference in the absolute number of stools between groups, which was statistically lower in the GT plus ORS group compared with the control group (ORS only). The dose of GT was not reported. The duration of follow up was 12 h (of note, the authors stated that the efficacy of GT was evaluated at 24 h and 48 h after initiation of the treatment, but no data were presented). Only the RCT conducted in adults was of adequate methodological quality; the quality of the non-RCT conducted in children was poor (Table 1).

Children

Primary outcomes

None of the predefined primary outcome measures (i.e., stool volume, duration of diarrhea, admission to hospital, duration of hospital stay, weight gain after rehydration, and adverse effects) were reported in the only pediatric study published so far.

Other outcomes

Number of stools. In the patients treated with ORS plus GT compared with the controls (ORS only), a statistically significant difference in the mean number of stools 12 h after the initiation of the treatment was found (2.06±1.04 vs. 5.86±2.45, respectively, MD -3.8, 95% CI -4.3 to -3.3, calculated from data in the article; P<0.0001). However, as stated earlier, there was a significant difference in the absolute number of stools between groups at baseline (P<0.05).

Stool decrease index. The stool decrease index (SDI) was
developed by the authors of the study according to the following formula: final (12 h) - baseline stools/baseline stools). Compared with the control group, a statistically significant reduction in the SDI was found in the group of children treated with GT plus ORS (18.9%±20.2% vs. 60.2%±18.8%, respectively, MD 41.3%, 95% CI 36 to 46.6, calculated from data in the article; P<0.0001).

**Liquid stools.** In the GT plus ORS group, compared with the control group (ORS only), there was a lower percentage of subjects with liquid stools at 12 h (28.3% vs. 71.9%, respectively, RR 0.39, 95% CI 0.28 to 0.54, calculated from data in the article; P value not reported).

**Fever.** In the GT plus ORS group, compared with the control group (ORS only), there was a lower temperature at 12 h (36.6°C vs. 36.9°C, respectively). The difference was reported as statistically significant (P<0.0001).

**Others.** In the GT plus ORS group compared with the control group (ORS only), there was no difference reported in episodes of vomiting at 12 h (35% vs. 41.6%, respectively), dehydration (4.5% vs. 0.9%, respectively), bloody diarrhea (3.3% vs. 2.7%, respectively), weight (no data), and peritonitis/sepsis (no data). However, P values were not stated for any of these outcomes.

**Adults**

**Primary outcomes**

None of the predefined outcome measures for this review were reported except for adverse effects. For the latter, no difference between the study groups was reported.

**Other outcomes**

**Number of stools.** In the GT group compared with the placebo group, a similar daily number of watery stools on day 1, as well as a reduced number on day 2, was found (P<0.01). In the original publication, data were presented as figures only so data are not reported here.

**Stool decrease index.** In the GT group compared with the placebo group, there was a statistically reduced SDI (defined similarly as in the study in children). However, the data were not presented. Moreover, the pain decrease index (PDI), which refers to the severity of abdominal pain evaluated on a 100-mm visual analogue scale, was also reduced.

**Responder rates.** The RCT conducted in adults defined a responder as a patient who exhibits an SDI and PDI on day 2 of at least of 30%. In patients receiving GT compared with those receiving placebo, there was a statistically significant difference in responder rates on day 2 (17/20 vs. 5/20, respectively, RR 3.4, 95% CI 1.56 to 7.43, calculated from data in the article; P<0.001) [16].

**Discussion**

The objective of this review was to provide resolution to the uncertainty regarding the use of GT in treating acute gastroenteritis. Only two trials were identified (one in children and one in adults). None of the included studies evaluated the effects of GT on the primary outcome measures for this review, i.e., stool output, duration of diarrhea, admission to hospital, duration of hospital stay, and weight gain after rehydration. With regard to other reported outcomes, in adults, compared with placebo, GT may be more effective at reducing some symptoms of acute diarrhea in the first 48 h after initiation of treatment. In children, the evidence is even more limited and the quality of the evidence is very low. This is because of the lack of randomization and blinding, as well as differences in some baseline characteristics, in the only study that evaluated the effect of GT in children. Although some beneficial effect was reported at 12 h after initiation of

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**Table 1 Characteristics of included trials**

<table>
<thead>
<tr>
<th>Country</th>
<th>Randomization</th>
<th>Allocation concealment</th>
<th>Blinding</th>
<th>ITT analysis</th>
<th>Participants</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Funding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spain [17]</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>N=211</td>
<td>ORS + GT (dose not stated)</td>
<td>ORS</td>
<td>Not stated</td>
</tr>
<tr>
<td>Italy [16]</td>
<td>Yes (computer-generated scheme)</td>
<td>Not stated</td>
<td>Yes</td>
<td>Yes</td>
<td>N=40</td>
<td>500 mg of GT administered six times daily for 2 consecutive days</td>
<td>Placebo</td>
<td>Novintethical Pharma Sagl, Lugano, Switzerland</td>
</tr>
</tbody>
</table>

GT, gelatin tannate; ORS, oral rehydration solution; ITT, intention to treat
treatment, the evidence is insufficient to draw conclusions on the effects of GT in children. Only one study conducted in adults addressed adverse effects, and none were reported.

There are limitations to this review. The number of trials was very small. The methodological quality of the trial conducted in children was very low due to weak methodology. The findings are, therefore, likely to be biased. None of the trials reported clinically relevant outcomes such as stool volume or the total duration of diarrhea after the initiation of the intervention. In both studies, the follow-up period was very short. The degree of dehydration was not stated. Furthermore, the etiology of the diarrhea was not evaluated.

Previously, the effect of tannins for the treatment of acute gastroenteritis was evaluated in one trial only. This was a randomized, double-blind trial involving 41 infants aged 3–21 months. It showed that compared with placebo, administration of tannin-rich carob pod powder significantly reduced the duration of diarrhea by 1.75 days (3.75±0.3 days vs. 2.0±0.27 days, respectively, P<0.001) and was well tolerated [18]. These results, together with preliminary findings of the trials with GT, suggest that the antidiarrheal properties of tannins are worth exploring.

Currently, there is no evidence to support the use of GT for treating acute gastroenteritis in children, and there is only very weak evidence to support the use of it in adults. Our review documents that there is a gap in the knowledge about the clinical efficacy of GT which is not registered as a drug and was not subject to the approval of the European Medicines Agency or Food and Drug Administration. Further well-designed and executed studies, with sufficient power and adequate follow-up periods, are needed. These trials should include clinically relevant outcome measures such as stool volume, duration of diarrhea, duration of hospital stay, weight gain, and the persistence of diarrhea. The CONSORT statement for reporting should be adopted. If GT proves to be effective, country-specific studies to examine the cost-effectiveness of using GT for the treatment of acute gastroenteritis will be needed.

References