Annals of Gastroenterology (2014) **27,** 121-124

Gelatin tannate for treating acute gastroenteritis: a systematic review

Marek Ruszczyński, Magdalena Urbańska, Hania Szajewska

The Medical University of Warsaw, Poland

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

Ann Gastroenterol 2014; 27 (2): 121-124

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

Department of Pediatrics, The Medical University of Warsaw, Poland

Conflict of Interest: None

Correspondence to: Hania Szajewska, MD, The Medical University of Warsaw, Department of Pediatrics, 01184 Warsaw, Dzialdowska 1, Poland, Tel./Fax: +48 22 452 33 09, e-mail: hania@ipgate.pl

Received 12 October 2013; accepted 28 November 2013

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 http://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

Table 1 Characteristics of included trials

Country [Ref.]	Randomization	Allocation concealment	Blinding	ITT analysis	Participants	Intervention	Comparison	Funding
Spain [17]	No	No	No	No	N=211 Children, aged 3 mo to 12 y, with acute diarrhea (>3 liquid stools a day, <72 h)	N=97 ORS + GT (dose not stated)	N=114 ORS	Not stated
Italy [16]	Yes (computer-generated scheme)	Not stated	Yes	Yes	N=40 Adults with acute diarrhea caused by intestinal infection (>3 watery stools in the 24 h prior to inclusion into the study, no >3 and basal abdominal pain of the least 20 mm evaluated through a 100-mm visual analogue scale)	N=20 500 mg of GT administered six times daily for 2 consecutive days	N=20 Placebo	Novintethical Pharma Sagl, Lugano, Switzerland

GT, gelatin tannate; ORS, oral rehydration solution; ITT, intention to treat

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.* 36.98°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

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 proprieties 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

1. Guarino A, Albano F, Ashkenazi S, et al. Expert Working Group. The ESPGHAN/ESPID evidenced-based guidelines for the management of acute gastroenteritis in children in Europe. *J Pediatr Gastroenterol Nutr* 2008;**46**(Suppl 2):S81-S122.
2. Guarino A, Albano F, Guandalini S, for the ESPGHAN Working Group on Acute Diarrhea. Oral rehydration solution: toward a real solution. *J Pediatr Gastroenterol Nutr* 2001;**33**:S2-S12.
3. Ashok PK, Upadhyaya K. Tannins are astringent. *J Pharmacognosy Phytochem* 2012;**1**:45-50.
4. Chung KT, Stevens SE Jr, Lin WF, Wei CI. Growth inhibition of selected foodborne bacteria by tannic acid, propyl gallate and related compounds. *Lett Appl Microbiol* 1993;**17**:29-32.
5. Scalbert A. Antimicrobial properties of tannins. *Phytochemistry* 1991;**30**:3875-3883.
6. De Servi B, Moreira da Silva R, Meloni M. New insight into the mechanism of action of gelatine tannate for acute diarrhoea. Pat 2: antibacterial activity. http://www.tasectan.ie/wp-content/uploads/2012/10/4.2_Abstract_GFHGHP-2012_2ndPart1.pdf.
7. Oi H, Matsuura D, Miyake M, et al. Identification in traditional herbal medications and confirmation by synthesis of factors that inhibit cholera toxin-induced fluid accumulation. *Proc Natl Acad Sci* 2002;**99**: 3042-3046.
8. Bennet-Jenkins E, Bryant C. Novel sources of anthelmintics. *Int J Parasitol* 1996;**26**:937-947.
9. Lorimer SD, Perry NB, Foster LM, Burgess EL. A nematode larval motility inhibition assay for screening plant extracts and natural products. *J Agric Food Chem* 1996;**44**:2842-2845.
10. Frasca G, Cardile V, Puglia C, Bonina C, Bonina F. Gelatin tannate reduces the proinflammatory effects of lipopolysaccharide in human intestinal epithelial cells. *Clin Exp Gastroenterol* 2012;**5**:61-67.
11. Freli V, Moreira da Silva R, Pescio P. New insights into the mechanism of action of gelatine tannate for acute diarrhoea. Part 1: film-forming effect. http://www.tasectan.ie/wp-content/uploads/2012/10/1.1_Abstract_GFHGHP-2012_1stPart.pdf
12. Dalby-Payne JR, Elliott EJ. Gastroenteritis in children. Clinical evidence 2011. BMJ Publishing Group Ltd. 2011.
13. Higgins JPT, Altman DG (eds). Assessing risk of bias in included studies. In: Higgins JPT, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions. Version 5.0.1. [updated September 2008]. Cochrane Collaboration, 2008. www.cochrane-handbook.org
14. Guzganu IL. Severe diarrhea in a 4-month-old baby girl with acute gastroenteritis: a case report and review of the literature. *Case Rep Gastrointest Med* 2012;**2012**:920375.
15. Gigante G, Caracciolo G, Campanale M, et al. Gelatine tannate reduces antibiotics associated side-effects of anti-helicobacter pylori first-line therapy. *Dig Liver Dis* 2013;**45**(Suppl 2):152.
16. Allegrini A, Costantini M. Gelatine tannate for the treatment of acute diarrhoea in adults. *J Gastroint Dig Syst* 2012;**2**:3.
17. Esteban Carretero J, Durbán Reguera F, López-Argüeta Alvarez S, López Montes J. A comparative analysis of response to vs. ORS + gelatin tannate pediatric patients with acute diarrhea. *Rev Esp Enferm Dig* 2009;**101**:41-48.
18. Loeb H, Vandenplas Y, Würsch P, Guesry P. Tannin-rich carob pod for the treatment of acute-onset diarrhea. *J Pediatr Gastroenterol Nutr* 1989;**8**:480-485.