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Gelatine tannate in the management of acute gastroenteritis in children: a randomised controlled trial

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ABSTRACT

Objective To assess the efficacy of gelatine tannate (a complex of tannic acid with astringent and anti-inflammatory properties, and a protective gelatine) for the treatment of acute gastroenteritis (AGE) in children.

Design Randomised, double-blind, placebo-controlled trial. Intention-to-treat analysis.

Setting Two paediatric hospitals in Warsaw.

Participants Children younger than 5 years of age with AGE, defined as a change in stool consistency to a loose or liquid form (according to the Bristol Stool Form Scale or Amsterdam Stool Form Scale) and/or an increase in the frequency of evacuations (≥3 in 24 hours), lasting for no longer than 5 days.

Interventions Seventy-two children were assigned to receive gelatine tannate (n=36) or placebo (n=36) in addition to standard rehydration therapy. The gelatine tannate was administered at an age-dependent dose (250–500 mg), and both study products were taken four times per day for 5 days.

Primary and secondary outcome measures The main outcome measure was duration of diarrhoea. Secondary outcomes included the need for intravenous rehydration, need for hospitalisation of outpatients, number of watery stools per day, vomiting, weight gain, adverse events, recurrence of diarrhoea, severity of diarrhoea according to the Vesikari Scale and use of concomitant medications.

Results Sixty-four children (89%) completed the intervention and were included in the analysis. The duration of diarrhoea after randomisation was similar in the gelatine tannate and placebo groups (75.6±27.8 vs 75.5±29.0 hours, respectively, mean difference 0.1 hours, 95% CI −14.1 to 14.3 hours). There was no significant difference between groups in the number of watery stools per day throughout the study period. There were also no differences in any other secondary outcome measures between groups.

Conclusion In children with AGE younger than 5 years of age, gelatine tannate was ineffective as an adjunct to rehydration therapy.

Trial registration number NCT02280759.

Strengths and limitations of this study

- This study was a randomised controlled trial, which is the design of choice for interventional studies.
- The protocol of the study was published in a peer-reviewed journal (*BMJ Open*).
- This study answers a specific clinical question filling a gap in knowledge about the effectiveness and safety of gelatine tannate.
- The guidelines from the Consolidated Standards of Reporting Trials statement were followed for reporting this trial.
- A limitation of the study is the lack of assessment of stool volume, which is a clinically meaningful endpoint.

INTRODUCTION

The main objectives in the management of acute gastroenteritis are the prevention or treatment of dehydration, promotion of weight gain following rehydration and reduction of the duration of diarrhoea and quantity of stool output. The key treatment is oral rehydration with a hypo-osmolar solution.[1] Considering the burden of acute gastroenteritis both to children and the healthcare system, effective and inexpensive interventions that could add to the effect of oral rehydration therapy are of interest. Recently, in many countries, gelatine tannate is being marketed for the treatment of acute gastroenteritis. Gelatine tannate consists of tannic acid suspended in a gelatine solution. It has a stable structure both in the acidic environment of the stomach as well as in basic and neutral environments such as in the small intestine and colon.[2] The specific mechanisms by which gelatine tannate may act against gastrointestinal infections remain unknown. It is known, however, that it forms a biofilm, which mechanically protects the gastrointestinal mucosa and causes precipitation of proinflammatory proteins such as mucoproteins in the intestinal mucosa.[3] In addition, it inhibits the growth of bacteria such as *Bacteroides fragilis*, *Clostridium perfringens*, *Escherichia coli*, *Enterobacter cloacae*, *Salmonella typhimurium*, *Helicobacter pylori*, *Listeria monocytogenes* and in vitro mycobacterial *Vibrio cholerae*.[3–5] The anti-inflammatory action of gelatine tannate also involves

blocking inflammatory agents in the gastrointestinal mucosa.[6]

At the time of designing this study, only limited evidence was available on the effectiveness of gelatine tannate in the management of acute gastroenteritis in children. This evidence is summarised in a 2014 systematic review,[7] which only included two studies: one randomised trial in adults and one non-randomised trial in children. Neither of the included studies evaluated the effects of gelatine tannate on outcome measures such as stool output, duration of diarrhoea, need for admission to the hospital, duration of hospital stay and (in children) weight gain after rehydration. The review concluded that there is no evidence to support the use of gelatine tannate for treating acute gastroenteritis in children (ie, no randomised controlled trials; important outcomes not addressed) and only scant evidence to support the use of gelatine tannate in adults. Further studies are needed. Thus, our aim was to assess the efficacy of gelatine tannate for the management of acute gastroenteritis in children.

METHODS

Trial design

This was a randomised, double-blind, placebo-controlled trial, conducted in two paediatric hospitals in Warsaw, Poland (The Medical University of Warsaw and the Niekłańska Hospital). Parents or legal guardians were fully informed about the aims of the study, and informed written consent was obtained from them. The trial was registered at ClinicalTrials.gov (NCT02280759) before enrolment of the first patient. The full protocol of this trial was published in *BMJ Open*.[8] The guidelines from the Consolidated Standards of Reporting Trials statement were followed for reporting this trial.[9]

Participants

Eligible participants were children younger than 5 years with acute gastroenteritis, defined as a change in stool consistency to a loose or liquid form (according to the Bristol Stool Form (BSF) Scale, or, in the case of infants, the Amsterdam Stool Form (ASF) Scale) and/or an increase in the frequency of evacuations (typically ≥3 in 24 hours), lasting for no longer that 5 days. Exclusion criteria included the use of antibiotics, gelatine tannate, diosmectite, probiotics, racecadotril or zinc (including zinc-containing oral rehydration solution (ORS)) within a week prior to enrolment; exclusive breast feeding; chronic diarrhoeal gastrointestinal disease (eg, inflammatory bowel diseases, cystic fibrosis, coeliac disease, food allergy); immunodeficiencies and malnutrition (weight/height/length under third percentile, WHO Child Growth Standards were used).[10]

Intervention

Participants were randomly assigned to receive gelatine tannate or a comparable placebo in addition to standard rehydration therapy. Gelatine tannate was manufactured by ICN Polfa Rzeszów/Valeant. The manufacturer did not have any role in the design or conduct of the study. The placebo contained maltodextrin. In line with the manufacturer's recommendation, the dose of the active product or placebo was age dependent (ie, in children younger than 3 years of age, the dose was 250 mg, and, in children older than 3 years of age, the dose was 500 mg). Both the gelatine tannate and placebo were taken orally, four times per day, for 5 days. The intervention was started immediately after recruitment of the participant into the study. All study participants were followed up for the duration of the intervention (5 days), and then for an additional 48 hours. Compliance was assessed by counting the number of sachets of study products left unused. As stated in the protocol of the study, based on previously published trials, we assumed that participants receiving <75% of the recommended doses were treated as non-compliant.

Study procedure

For initial rehydration, all children were treated according to 2014 European recommendations (fast oral rehydration over 3–4 hours by mouth with a hypotonic solution).[1] Intravenous fluid therapy was administered during the rehydration phase if there was failure to achieve adequate rehydration within the first 3–4 hours or if there were intensified signs of dehydration despite the intake of the estimated fluid requirements. During the maintenance phase, intravenous fluid therapy was started if dehydration recurred despite the intake of estimated fluid requirements, including ORS, for ongoing losses. After all of the signs of dehydration had disappeared, ORS was given for ongoing losses until the diarrhoea stopped. Rapid reintroduction of the previous diet after successful rehydration was recommended. At all times, breast feeding was allowed. Children were discharged from the hospital once a stable clinical condition had been achieved.

Outcome measures

The primary outcome measure was the duration of diarrhoea, defined as the time until the normalisation of stool consistency according to the BSF or ASF Scale (on BSF Scale, numbers 2, 3, 4 and 5; on ASF scale, letters B or C) or the time until the normalisation of the number of stools (compared with the period before the onset of diarrhoea) as well as the presence of normal stools for 48 hours. The secondary outcome measures included the need for intravenous rehydration, need for hospitalisation of outpatients, number of watery stools per day, vomiting, weight gain, adverse events, recurrence of diarrhoea (48 hours after the intervention), severity of diarrhoea according to the Vesikari Scale[11] and use of concomitant medications.

Allocation concealment and blinding

A computer-generated randomisation list prepared by a person unrelated to the trial was used to allocate

participants to the study groups in blocks of eight. Consecutive randomisation numbers were given to participants at enrolment. The study product was weighed, packaged and signed by consecutive numbers according to the randomisation list at the hospital pharmacy at the Medical University of Warsaw by independent personnel not involved in the conduct of the study. The study products were delivered to the physicians in small envelopes labelled with the consecutive numbers and doses. The physicians were blinded to the meaning of the numbers, and the sealed envelopes were deposited in a safe place in the administrative part of the department. The active product and placebo were packaged in identical sachets. The contents of the sachets looked and tasted the same. Researchers, caregivers, outcome assessors and the person responsible for the statistical analysis were blinded to the intervention until the completion of the study and the analysis of the data.

Sample size calculation

The primary outcome of the study was the duration of diarrhoea. Based on available data in the literature, the average duration of acute gastroenteritis in children is 5–7 days.[1] We assumed that a clinically significant difference in the effectiveness of gelatine tannate versus placebo would shorten the duration of symptoms by 24 hours (±12 hours). To detect such a difference in the duration of diarrhoea between the study groups with a power of 90% and α=0.01, we determined that a sample of 60 children was needed. Assuming approximately 20% loss to follow-up, we aimed to recruit a total of 72 children for this study. The sample size calculation was performed with the Sealed Envelope software.[12]

Statistical analysis

The statistical analyses were conducted using StatsDirect V.3.0.181 (1 November 2016, StatsDirect) computer software. The Shapiro-Wilk W test was used to investigate a sample for evidence of non-normality. Student's t-test was used to compare means of continuous variables approximating a normal distribution. For non-normally distributed variables, the Mann-Whitney U test was used. The χ^2 test or Fisher's exact test was used, as appropriate, to compare percentages. The same computer software was used to calculate the risk ratio (RR) and mean or median difference (MD), as appropriate, both with a 95% CI. The difference between study groups was considered significant when the 95% CI for RR did not include 1.0 and the 95% CI for MD did not include 0 (equivalent to $p<0.05$). All statistical tests were two tailed and performed at the 5% level of significance. All analyses were conducted on an intention-to-treat basis, including all patients in the groups to which they were randomised for whom outcomes were available.

Patient involvement

Patients were not involved in setting the study protocol and implementation, and the dissemination of the results.

RESULTS

Overall, 230 children with acute gastroenteritis who presented for treatment between February 2015 and June 2017 were assessed for eligibility; 72 were enrolled in the study and randomly assigned to one of the two study groups: 36 to the gelatine tannate group and 36 to

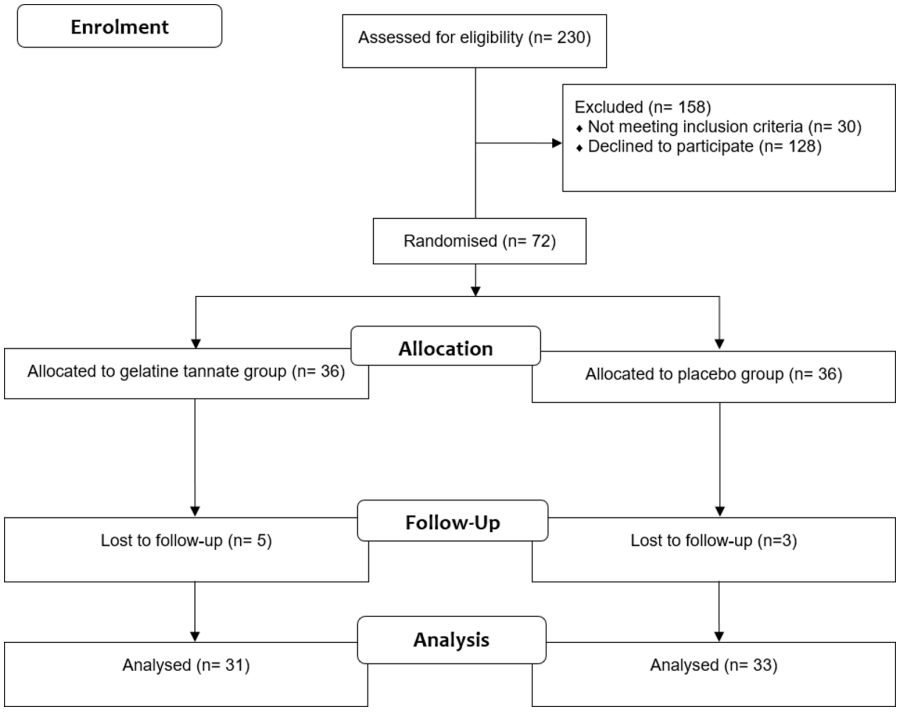

Figure 1 Flow diagram.

Table 1 Baseline demographic and clinical characteristics

Characteristics	Gelatine tannate group	Placebo group
n	36	36
Age, months, mean (SD)	27.7 (29.3)	26.8 (28.5)
Age, months, median (IQR)	16.0 (10.8–33.0)	18.0 (10.8–27.5)
Sex, male/female, n	17/19	22/14
Dehydration level before enrolment, n (%)		
Mild	21 (58.3)	22 (61.1)
Moderate	15 (41.7)	14 (38.9)
Severe	0	0
Fever (≥38°C), n (%)	20 (62.5)	21 (63.5)
Blood in stool, n (%)	0	1 (2.9)
Aetiology of acute gastroenteritis		
Rotavirus, n (%)	12 (33.3)	11 (30.6)
Adenovirus, n (%)	2 (5.5)	0
Norovirus, n (%)	1 (2.8)	1 (2.8)
Salmonella Enteritidis, n (%)	1 (2.8)	1 (2.8)
Campylobacter spp, n (%)	0	1 (2.8)
Unknown aetiology, n (%)	20 (55.6)	23 (63.8)

the placebo group. Eight children were lost to follow-up. Sixty-four children (89%) completed the intervention and were included in the analysis (figure 1). Baseline demographic and clinical characteristics are shown in table 1. The two groups were comparable in regard to these characteristics at study entry.

Primary and secondary outcomes

The primary and secondary outcome measures are presented in table 2. The duration of diarrhoea after randomisation was similar in both groups (MD 0.1 hours, 95% CI −14.1 to 14.3). The risk of unscheduled intravenous rehydration was similar in the gelatine tannate and placebo groups (RR 0.99, 95% CI 0.78 to 1.25). The number of watery stools per day was similar in both groups throughout the study period (for details, see table 2). In both groups, the risk of vomiting (RR 1.27, 95% CI 0.93 to 1.73), weight gain (MD −59.1 g, 95% CI −133.1 to 15), risk of recurrence of diarrhoea 48 hours after the intervention (RR 0.12, 95% CI 0.01 to 2.0) and severity of diarrhoea according to the Vesikari Scale (MD 1.1, 95% CI −0.7 to 2.9) were similar. Adverse effects were similar in both groups (RR 0.6, 95% CI 0.17 to 2.45). None of the participants used concomitant medication. All participants were compliant, that is, received >75% of the recommended doses.

DISCUSSION

Principal findings

This randomised, double-blind, placebo-controlled study showed that in children younger than 5 years with acute gastroenteritis, administration of gelatine tannate compared with placebo was ineffective as an adjunct to oral rehydration therapy.

Table 2 Primary and secondary outcomes

Outcomes	Gelatine tannate group (n=31)	Placebo group (n=33)	P values	MD/RR	95% CI
Duration of diarrhoea, hours, mean (SD)	75.6 (27.8)	75.5 (29.0)	0.99	0.1	−14.1 to 14.3
Need for intravenous rehydration, n (%)	25 (80.6)	27 (81.8)	0.9	0.9	0.78 to 1.25
Number of watery stools per day* (mean (SD))					
Day 1	5.5 (3.0)	4.6 (2.3)	0.165	0.90	−0.40 to 2.30
Day 2	4.7 (2.8)	3.8 (3.0)	0.27	0.90	−0.60 to 2.30
Day 3	2.6 (3.2)	2.1 (2.9)	0.50	0.50	−1.00 to 2.10
Day 4	1.2 (1.7)	1.0 (1.3)	0.62	0.20	−0.60 to 1.00
Day 5	0.5 (1.3)	0.4 (1.5)	0.87	0.10	−0.60 to 0.80
Day 6	0.06 (0.4)	0.1 (0.7)	0.68	−0.10	−0.30 to 0.20
Day 7	0.0 (0.0)	0.0 (0.0)	NA	0.00	0.00 to 0.00
Vomiting, n (%)	25 (80.6%)	21 (63.6%)	0.22	1.27	0.93 to 1.73
Weight gain, g±SD	70±142	129±155	0.12	−59.1	−133.1 to 15
Recurrence of diarrhoea (48 hours after intervention), n (%)	0	4 (12)	0.12	0.12	0.01 to 2.11
Severity of diarrhoea according to Vesikari Scale (mean (SD))	9.7 (3.4)	8.6 (3.9)	0.24	1.10	−0.70 to 2.90
Need for hospitalisation in outpatients, n	0	0	–	–	–
Adverse events, n (%)	3 (9.6%)	5 (15.1%)	0.7	0.64	0.17 to 2.45
Spitting after the administration	0	2 (6.1%)	0.49	0.21	0.01 to 4.26
Abdominal pain	1 (3.2%)	0	0.48	3.19	0.13 to 75.43

*According to the Bristol Stool Form Scale (BSF) or Amsterdam Stool Form (ASF) Scale (on BSF scale, numbers 2, 3, 4 and 5; on ASF scale, letters B or C).
MD, mean or median difference, as appropriate; NA, not applicable; RR, relative risk.

Strengths and limitations

This study was a randomised controlled trial, which is the design of choice for interventional studies. The protocol of the study was published in a peer-reviewed journal. We used adequate methods for the generation of the allocation sequence and allocation concealment. We maintained blinding throughout the selection, treatment, data management and data analyses phases of the study. Follow-up was adequate; data were obtained from 89% of the participants. For assessment of the consistency of stools, we used the validated BSF Scale or the ASF Scale, depending on the age of the participants. The sample size was predefined. These features minimise the risk of bias. A potential limitation of this trial is that we did not assess stool volume as the primary outcome measure, which is a clinically meaningful endpoint. This decision was based on feasibility reasons and our previous negative experiences (unwillingness of parents and/or hospital nurses to collect stools).

Comparison with previous findings

Our findings are in contrast with the findings of two, recent, randomised controlled trials that assessed the effectiveness of administering gelatine tannate for the treatment of acute gastroenteritis in children. The 2017 study by Mennini *et al*[13] was a single-blind, randomised, open-label trial involving 60 children aged 3–72 months with acute gastroenteritis. Compared with only oral rehydration, the addition of gelatine tannate (at a dose, depending on the age, of 250–500 mg, every 6 hours) significantly decreased bowel movements at 72 hours (2.0±1.7 vs 1.0±1.4, respectively; p=0.01) and reduced the duration of diarrhoea (108±24.0 vs 76.8±19.2 hours, respectively; p<0.0001). There are several possible reasons for the differences in findings. First, in contrast to the study by Mennini *et al*, our study had a double-blind design, which reduces the risk of performance and detection biases. The study by Mennini *et al* did not provide the sample size calculation, which is needed to avoid false-positive and false-negative conclusions. In our study, we included children with diarrhoea lasting for no longer than 5 days compared with no longer than 3 days in the study by Mennini *et al*. The lack of an effect in our study may suggest that in order for gelatine tannate to be effective, it has to be administered early in the course of the disease. In both studies, the duration of diarrhoea was assessed. However, in contrast to our study, it was unclear how this outcome was defined in the Mennini *et al* study. Mennini *et al* also assessed the number of any type of bowel movements, while we assessed the number of watery stools. Thus, these findings are not directly comparable. However, for comparison, post hoc, we evaluated the number of any type of stools. Throughout the study period, there were no differences in the number of stools per day between the study groups (data are not shown, however, are available on request).

A 2017 randomised, controlled, double-blind trial conducted by Çağan *et al* compared the administration of gelatine tannate plus ORS with ORS alone in 203 children aged 3 months to 12 years with acute gastroenteritis. From 12 hours onwards, per-protocol analysis showed that the incidence of watery stools was significantly lower in the gelatine tannate plus ORS group than in the ORS alone group (at 12 hours, 59.2% vs 77.0%, respectively; p=0.01).[14] Again, there are several possible reasons for the differences in findings between the studies. Compared with our study, Çağan *et al* included older children (mean age: 27±30 vs 40±36 months, respectively). In the study by Çağan *et al*, there was a significant difference in the percentage of children with dehydration at baseline between the experimental and control groups (60% vs 40%, respectively); thus, the randomisation did not work properly. In our study, the sample size was smaller. However, the sample size was based on a sample size calculation designed to detect 24 hours (±12 hours) shortening of the duration of diarrhoea between the study groups with a power of 90% and α=0.01; thus, a sufficient number of participants were randomised in our study, allowing us to be reasonably certain that no difference between the interventions exists. In the study by Çağan *et al*, while the sample size calculation was provided, it is unclear what assumptions were made by the authors. While one of the primary study endpoints in the study by Çağan *et al* was the total time to resolution of diarrhoea, no data relevant to this endpoint were provided; thus, a comparison between the studies is not possible. Both studies reported data on watery stools. However, the data were presented differently (ie, percentage of patients with watery stools in the study by Çağan *et al* compared with number of watery stools per day in our study). Finally, the method of analysis in the study by Çağan *et al* (per-protocol analysis) differed from that used in our study (intention-to-treat analysis).

Taken together, direct comparison of our findings with the results reported by others is difficult. It is possible that the differences in the study design and execution contributed to the differences in findings. Additionally, other factors could explain the different results seen in our study patients compared with those of previous studies, such as differences in age, socioeconomic situation, pathogen, *Rotavirus* vaccination status or type of ORS used. Hypothetically, the lack of an effect observed in our study could also originate from the excessive excretion of the study product due to the duration of diarrhoea. However, in our study, there were no children with severe diarrhoea and/or excessive duration of diarrhoea. Further well-designed and carefully conducted randomised controlled trials, with relevant inclusion/exclusion criteria, adequate sample sizes, and validated clinical outcome measures (with definitions), may help to resolve the uncertainty with regard to the efficacy of gelatine tannate in the management of acute gastroenteritis in children.

CONCLUSIONS

In summary, gelatine tannate, as dosed in this study, administered as an adjunct to rehydration for the management of acute gastroenteritis in children younger than 5 years was not effective. According to current guidelines,[1 15] the mainstay of treatment for acute gastroenteritis should be oral rehydration with a hypo-osmolar solution. Breast feeding should not be interrupted. Regular feeding should continue with no dietary changes, including milk. In the hospital setting, in non-breastfed infants and young children, lactose-free feeds can be considered in the management of gastroenteritis. Oral zinc supplementation reduces the duration of diarrhoea in children 6 months to 5 years of age who reside in countries with a high prevalence of zinc deficiency or who have signs of malnutrition. However, in regions where zinc deficiency is rare, no benefit from the use of zinc is expected. Other effective interventions that may reduce the duration and severity of diarrhoea include the administration of specific probiotics such as *Lactobacillus rhamnosus* GG or *Saccharomyces boulardii*, diosmectite or racecadotril.

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Contributors HS initially conceptualised this study. All authors contributed to the study protocol. MK and DB conducted the study. MK analysed the data under the supervision of HS. HS and MK wrote the manuscript. All authors contributed to (and agreed upon) the final version.

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Competing interests None declared.

Patient consent Not required.

Ethics approval Ethics Committee of the Medical University of Warsaw approved the study.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement All data pertaining to this work are stored in the Pediatric Hospital of Medical University of Warsaw.

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