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Efficacy and safety of gelatin tannate for the treatment of acute gastroenteritis in children: protocol of a randomized controlled trial

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ABSTRACT

Introduction

Worldwide, acute gastroenteritis in children, usually caused by viruses, leads to considerable morbidity and mortality. The treatment is aimed at preventing and treating dehydration, promoting weight gain after rehydration, and reducing the duration and severity of diarrhea. Effective and inexpensive interventions that could add to the effect of oral rehydration therapy are of interest. Recently, in many European countries, gelatin tannate is being widely marketed for treating acute gastroenteritis. Gelatin tannate is a complex of tannic acid, which possesses astringent and anti-inflammatory properties, and a protective gelatin. Currently, there is no evidence to support the use of gelatin tannate for treating acute gastroenteritis in children and only scant evidence to support the use of gelatin tannate in adults. We aim to assess the efficacy of gelatin tannate for the treatment of acute gastroenteritis in children.

Methods and analysis

This will be a blind, placebo-controlled, randomized trial. Children younger than 5 years of age with acute gastroenteritis defined as a change in stool consistency to 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 (typically ≥3 in 24 hours), lasting for no longer than 5 days, will be recruited. A total of 158 children will be randomized to receive either gelatin tannate (children younger than 3 years of age will receive 250 mg 4 times per day and those older than 3 years of age will receive 500 mg 4 times per day) or matching placebo for 5 days. The primary outcome measure is the duration of diarrhea.

Ethics and dissemination

The Bioethics Committee approved the study protocol. The findings of this trial will be submitted to a peer-reviewed pediatric journal. Abstracts will be submitted to relevant national and international conferences.

Registration

www.clinicaltrials.gov (NCT02280759)

STRENGTHS AND LIMITATIONS OF THIS STUDY

- The study design (randomized controlled trial, RCT) is the most robust methodology to assess the effectiveness of therapeutic interventions.
- A precise clinical question has been posed to fill a gap in knowledge as to whether gelatin tannate is safe and effective in the treatment of acute gastroenteritis in children.
- The findings of this RCT, whether positive or negative, will contribute to the formulation of recommendations on the use of gelatin tannate for the treatment of acute gastroenteritis.
- Due to practicalities, stool volume, which is one of the objective ways of assessing the efficacy of antidiarrheal drugs, will not be assessed.

INTRODUCTION

Worldwide, acute gastroenteritis in children, usually caused by rotaviruses, leads to considerable morbidity and mortality.[1] It is also the most common cause of primary care consultations among children younger than 5 years of age.[2] According to current European guidelines,[3] the mainstay of treatment for acute gastroenteritis is oral rehydration with a hypoosmolar solution. Breastfeeding should not be interrupted. Regular feeding should continue with no dietary changes including milk. 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. Currently, effective interventions that may reduce the duration and severity of diarrhea include administration of specific probiotics such as *Lactobacillus rhamnosus* GG or *Saccharomyces boulardii*, diosmectite, or racecadotril.[3]

Recently, in many European countries, gelatin tannate is being marketed for treating acute gastroenteritis. Gelatin tannate consists of tannic acid suspended in a gelatin solution. Gelatin tannate has a stable structure both in the acidic environment of the stomach as well as in a basic and neutral environment such as in the small intestine and colon.[4] Little is known about the specific mechanisms by which gelatin tannate may act against gastrointestinal infection. It is known, however, that it forms a biofilm, which mechanically protects the gastrointestinal mucosa and causes precipitation of pro-inflammatory proteins such as mucoproteins in the intestinal mucosa.[5] 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*.[5 6 7] The action of anti-inflammatory tannate also involves blocking inflammatory agents in the gastrointestinal mucosa.[8]

Only limited evidence is available on the effectiveness of gelatin tannate. In 2009, Esteban Carretero et al. published a study (n=211, mean age 2.5 ± 2.4 years, no randomization, no blinding, unbalanced baseline characteristics) that evaluated the

effectiveness of gelatin tannate in the treatment of acute gastroenteritis in children. Children received oral rehydration solution (ORS) alone or ORS in combination with gelatin tannate (dose was not specified). During the 12-h observation period, a significant reduction in the number of loose stools was found in the group receiving ORS and gelatin tannate versus the group receiving ORS alone. Both groups had similar weight gains, stool consistency, comparative risks of diarrhea with blood, peritonitis, and sepsis, vomiting intensity, and degrees of dehydration in the 12 h of observation.[9] In 2012, Allegrini and Costantini performed a blinded, randomized, placebo-controlled trial in the adult population (n = 40, mean age 43 ± 13 years). In the group receiving gelatin tannate (500 mg, 6 times per day, for 2 consecutive days) compared with the placebo group, a statistically significant decrease in both the daily number of watery stools and severity of abdominal pain for the first 48 h of the intervention was found. There were no clinically relevant adverse events.[10]

A 2014 systematic review evaluated the efficacy of gelatin tannate in treating acute gastroenteritis in children and adults.[11] The two above-described studies were included. None of the included studies evaluated the effect of gelatin tannate on the primary outcome measures for the review, such as stool output, duration of diarrhea, 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 gelatin tannate for treating acute gastroenteritis in children and only sparse evidence to support the use of gelatin tannate in adults.

Taken together, currently, the evidence to support the use of gelatin tannate for treating acute gastroenteritis in children or adults is very limited. According to the current (2014) European guidelines,[3] gelatin tannate is not recommended for the management of acute gastroenteritis in children.

Trial objectives and hypotheses

The main objective of this trial is to assess the effectiveness and safety of gelatin tannate in the treatment of acute gastroenteritis in children. We aim to conduct a

well-designed and executed study, with sufficient power, an adequate follow-up period, and relevant clinical endpoints. In our trial, we choose to use placebo for a comparator as it is widely regarded as the gold standard for testing the efficacy of new treatments.[12]

METHODS AND ANALYSIS

The trial is registered at www.clinicaltrials.gov (NCT02280759) and any important changes in the protocol will be implemented there.

Study design

This study is designed as a randomized, blinded, placebo-controlled trial, with allocation 1:1, and is described in more detail in subsequent sections.

Setting and participants

The recruitment will take place primarily in the emergency room of the pediatric hospital of the Medical University of Warsaw. However, other recruiting sites are under consideration provided that the personnel are adequately trained and competent in conducting clinical trials. Participants will be randomized after their first visit to the emergency room or after admission to the clinic. Caregivers will receive oral and written information on the study. Written informed consent will by obtained by physicians involved in the study.

Inclusion criteria

Children eligible for the trial must fulfill all of the following criteria:

- Acute gastroenteritis defined as a change in stool consistency to loose or liquid form (according to the Bristol Stool Form, BSF, scale or Amsterdam Stool Form, ASF, scale) and/or an increase in the frequency of evacuations (typically ≥3 in 24 hours), lasting for no longer than 5 days
- Age younger than 5 years
- A caregiver must provide written informed consent.

Exclusion criteria

- Use of antibiotics, gelatin tannate, diosmectite, probiotics, or racecadotril within a week prior to enrollment.
- Exclusive or predominant (>50%) breastfeeding.
- Chronic diarrheal gastrointestinal disease (e.g., inflammatory bowel diseases, cystic fibrosis, celiac disease, food allergy).
- Immunodeficiencies.
- Malnutrition (weight/height/length under 3rd percentile) (WHO Childgrowth Standards will be used).[13]
- If needed, discontinuation or modification of the treatment may be considered at the discretion of the physician.

Randomization criteria

After re-checking the inclusion and exclusion criteria, participants will be assigned into one of two groups (experimental or control). After determination of eligibility, caregivers will receive a diary of symptoms to record the number of stools and their consistency during the intervention. BSF and ASF scales will be provided. Additionally, caregivers will be asked to write down any adverse events during the intervention period.

Interventions

The intervention under investigation is gelatin tannate manufactured by ICN Polfa Rzeszów/Valeant. The manufacturer does not have and will not have a role in the design or conduct of the study. The placebo will contain maltodextrine, which is an almost flavorless, easily digestible polysaccharide commonly used as a food additive. The dose of the active product or placebo will be age dependent (i.e., in children younger than 3 years of age the dose is 250 mg and in children older than 3 year of age – 500 mg). Both the gelatin tannate and placebo will be taken orally, 4 times per day, for 5 days. Caregivers will be instructed to administer the daily dose at the same time of a day, after mixing the contents of the sachet with a small amount of water. The study products used in this trial will be prepared by the hospital pharmacy at

the Medical University of Warsaw as identically appearing sachets.

For initial rehydration, all children will be treated according to 2014 European recommendations (fast oral rehydration over 3–4 hours by mouth or via nasogastric tube with the recommended hypotonic solution). After all signs of dehydration have disappeared, oral rehydration solution will be given for ongoing losses until the diarrhea stops. Rapid reintroduction of the previous diet after successful rehydration will be recommended. At all times, breastfeeding will be allowed.

At any time, caregivers will have the right to withdraw the participating child from the study; they will be not obliged to give reasons for this decision, and there will be no effect on subsequent physician and/or institutional medical care.

Concomitant medications

The concomitant administration of any other medication, including antipyretics and antiemetics, will be at the discretion of the physician to provide adequate care. However, it is recommended that no unnecessary concomitant medication be used.

Follow up

All study participants will be followed-up for the duration of the intervention (5 days) and then for an additional 48 h.

Allocation concealment and blinding

A computer-generated randomization list prepared by a person unrelated to the trial will be used to allocate subjects to the study groups in blocks of eight. Consecutive randomization numbers will be given to participants at enrollment. This procedure will be performed by one of two physicians involved. The study product will be weighed, packaged, and signed by consecutive numbers according to the randomization list by the hospital pharmacy at the Medical University of Warsaw by independent personnel not involved in the conduct of the study. The study products will be delivered to the physicians in small envelopes labeled with the consecutive

numbers and dose (with the meaning of numbers blinded and information deposited in a sealed envelope in a safe place in the administrative part of the department). The active product and placebo will be packaged in identical sachets. Contents will look and taste the same. Researchers, caregivers, outcome assessors, and a person responsible for the statistical analysis will be blinded to the intervention until the completion of the study. The information on intervention assignments will be stored in a sealed envelope in a safe in the administrative part of the department. The personal information about potential and enrolled participants will be stored in a locker within the study site, accessible for the involved researchers only.

Compliance

The caregivers will be asked to bring the remaining study product and diary to the study site at the end of the intervention period. Compliance with the study protocol will be checked by counting the number of sachets left unused. Based on previously published trials, it seems to be appropriate to consider those subjects receiving less than 75% of the recommended doses as noncompliant.

Primary outcome

The primary outcome will be the duration of diarrhea, defined as the time until the normalization of stool consistency according to the BSF or ASF scale (in BSF Scale, numbers 2, 3, 4 and 5, and in ASF Scale, letters B or C), or the time until the normalization of the number of stools (compared with the period before the onset of diarrhea), and the presence of normal stools for 48 h.

Secondary outcomes

- need for intravenous rehydration
- need for hospitalization in outpatients
- number of watery stools per day
- vomiting
- weight gain
- adverse events

- recurrence of diarrhea (48 h after intervention)
- severity of diarrhea according to Vesikari scale.[14]

Table 1. Timetable of activities planned during the study.

Days / Activity	1	2	3	4	5	6	7
Enrollment	+						
Randomization	+						
Intervention	+	+	+	+	+		
Return of diary					+		
Follow up						+	+
Adverse events	+	+	+	+	+	+	+

Power calculation

The primary outcome of the study is the duration of diarrhea. Based on available data in the literature, the average duration of gastroenteritis in children is 5-7 days.[3] We assume that a clinically significant difference in the effectiveness of gelatin tannate versus placebo will shorten the duration of symptoms by 12 hours. To detect such a difference in the duration of diarrhea between the study groups with a power of 80% and α =0.05, a sample of 126 infants is needed in each study group. Assuming about a 20% loss to follow up, we aim to recruit a total of 158 children for this study.

In the Department of Paediatrics of The Medical University of Warsaw, there are 200 admissions of children with diarrhea per year and the same number of such patients who present to the emergency room. Assuming that 20% of these children will be eligible for the study, we will achieve adequate participant enrollment to reach the target sample size after 2 years of recruiting.

Statistical analysis

All analysis will be conducted on an intention-to-treat basis, including all patients in the groups to which they are randomized for whom outcomes will be available (including dropouts and withdrawals). Descriptive statistics will be used to summarize baseline characteristics. The Student t test will be used to compare mean values of continuous variables approximating a normal distribution. For non-normally distributed variables, the Mann–Whitney U test will be used. The $\chi 2$ test or Fisher exact test will be used, as appropriate, to compare percentages. For continuous outcomes, differences in means or differences in medians (depending on the distribution of the data), and for dichotomous outcomes, the relative risk (RR) and number needed to treat, all with a 95% confidence interval, will be calculated. The difference between study groups will be considered significant when the p value is <0.05, when the 95% CI for RR does not include 1.0, or when the 95% CI for MD does not include 0. All statistical tests will be two tailed and performed at the 5%level of significance.

ETHICS AND DISSEMINATION

The Bioethical Committee of The Medical University of Warsaw issued approval for the study before recruitment commenced. Verbal and written information regarding informed consent will be presented to the caregivers. Any modifications to the protocol that may affect the conduct of the study will be presented to the Committee. The full protocol will be available freely due to open access publication. The findings of this RCT will be submitted to a peer-reviewed journal. Abstracts will be submitted to relevant national and international conferences.

FUNDING STATEMENT

This trial will be funded by The Medical University of Warsaw. At the time of submission of this protocol for publication, no specific grant from any funding agency in the public, commercial, or not-for-profit sectors has been awarded to this project.

AUTHORS' CONTRIBUTIONS

HS conceptualized the study. All authors contributed to the design of the study and read and approved the manuscript. DM and MK developed the first draft of the manuscript. All authors contributed to the development of the study protocol and approved the final draft of the manuscript.

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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym √
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry √
	2b	All items from the World Health Organization Trial Registration Data Set []
Protocol version	3	Date and version identifier √
Funding	4	Sources and types of financial, material, and other support √
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors √
	5b	Name and contact information for the ~~trial sponsor~~
	5c	~~Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities~~
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) XXX
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention √
	6b	Explanation for choice of comparators √
Objectives	7	Specific objectives or hypotheses √
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) √

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained √
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) √
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered √
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) √
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) √
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial √
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended √
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) √
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations √
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size √

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions √

Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned √
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions √
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how √
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial √
Methods: Data collection, management, and analysis		
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol √
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol √
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) √
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)
Methods: Monitoring		
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed ??

	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial √
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct √
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor √
Ethics and dissemination		
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval √
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) √
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) √
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable X
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial √
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site √
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators √
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation √
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions √
	31b	Authorship eligibility guidelines and any intended use of professional writers ?
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code √

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates √
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable √

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	1
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	4-5
	2b	Specific objectives or hypotheses	5-6
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	6
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	6
Participants	4a	Eligibility criteria for participants	6
	4b	Settings and locations where the data were collected	6
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	7
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	9
	6b	Any changes to trial outcomes after the trial commenced, with reasons	-
Sample size	7a	How sample size was determined	10
	7b	When applicable, explanation of any interim analyses and stopping guidelines	-
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	8
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	8
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	8
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	6,8
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	8

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	7
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	10
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	-
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	-
	13b	For each group, losses and exclusions after randomisation, together with reasons	-
Recruitment	14a	Dates defining the periods of recruitment and follow-up	-
	14b	Why the trial ended or was stopped	-
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	-
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	-
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	-
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	-
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	-
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	-
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	-
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	-
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	-
Other information			-
Registration	23	Registration number and name of trial registry	2
Protocol	24	Where the full trial protocol can be accessed, if available	-
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	1

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

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Efficacy and safety of gelatin tannate for the treatment of acute gastroenteritis in children: protocol of a randomized controlled trial

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Efficacy and safety of gelatin tannate for the treatment of acute gastroenteritis in children: protocol of a randomized controlled trial

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ABSTRACT

Introduction

Worldwide, acute gastroenteritis in children, usually caused by viruses, leads to considerable morbidity and mortality. The treatment is aimed at preventing and treating dehydration, promoting weight gain after rehydration, and reducing the duration and severity of diarrhea. Effective and inexpensive interventions that could add to the effect of oral rehydration therapy are of interest. Recently, in many European countries, gelatin tannate is being widely marketed for treating acute gastroenteritis. Gelatin tannate is a complex of tannic acid, which possesses astringent and anti-inflammatory properties, and a protective gelatin. Currently, there is no evidence to support the use of gelatin tannate for treating acute gastroenteritis in children and only scant evidence to support the use of gelatin tannate in adults. We aim to assess the efficacy of gelatin tannate for the treatment of acute gastroenteritis in children.

Methods and analysis

This will be a blind, placebo-controlled, randomized trial. Children younger than 5 years of age with acute gastroenteritis defined as a change in stool consistency to 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 (typically ≥3 in 24 hours), lasting for no longer than 5 days, will be recruited. A total of 158 children will be randomized to receive either gelatin tannate (children younger than 3 years of age will receive 250 mg 4 times per day and those older than 3 years of age will receive 500 mg 4 times per day) or matching placebo for 5 days. The primary outcome measure is the duration of diarrhea.

Ethics and dissemination

The Bioethics Committee approved the study protocol. The findings of this trial will be submitted to a peer-reviewed pediatric journal. Abstracts will be submitted to relevant national and international conferences.

Registration

www.clinicaltrials.gov (NCT02280759)

STRENGTHS AND LIMITATIONS OF THIS STUDY

- The study design (randomized controlled trial, RCT) is the most robust methodology to assess the effectiveness of therapeutic interventions.
- A precise clinical question has been posed to fill a gap in knowledge as to whether gelatin tannate is safe and effective in the treatment of acute gastroenteritis in children.
- The findings of this RCT, whether positive or negative, will contribute to the formulation of recommendations on the use of gelatin tannate for the treatment of acute gastroenteritis.
- Due to practicalities, stool volume, which is one of the objective ways of assessing the efficacy of antidiarrheal drugs, will not be assessed.

INTRODUCTION

Worldwide, acute gastroenteritis in children, usually caused by rotaviruses, leads to considerable morbidity and mortality.[1] It is also the most common cause of primary care consultations among children younger than 5 years of age.[2] According to current European guidelines,[3] the mainstay of treatment for acute gastroenteritis is oral rehydration with a hypoosmolar solution. Breastfeeding should not be interrupted. Regular feeding should continue with no dietary changes including milk. 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. Currently, effective interventions that may reduce the duration and severity of diarrhea include administration of specific probiotics such as *Lactobacillus rhamnosus* GG or *Saccharomyces boulardii*, diosmectite, or racecadotril.[3]

Recently, in many European countries, gelatin tannate is being marketed for treating acute gastroenteritis. Gelatin tannate consists of tannic acid suspended in a gelatin solution. Gelatin tannate has a stable structure both in the acidic environment of the stomach as well as in a basic and neutral environment such as in the small intestine and colon.[4] Little is known about the specific mechanisms by which gelatin tannate may act against gastrointestinal infection. It is known, however, that it forms a biofilm, which mechanically protects the gastrointestinal mucosa and causes precipitation of pro-inflammatory proteins such as mucoproteins in the intestinal mucosa.[5] 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*.[5 6 7] The action of anti-inflammatory tannate also involves blocking inflammatory agents in the gastrointestinal mucosa.[8]

Only limited evidence is available on the effectiveness of gelatin tannate. In 2009, Esteban Carretero et al. published a study (n=211, mean age 2.5 ± 2.4 years, no randomization, no blinding, unbalanced baseline characteristics) that evaluated the

effectiveness of gelatin tannate in the treatment of acute gastroenteritis in children. Children received oral rehydration solution (ORS) alone or ORS in combination with gelatin tannate (dose was not specified). During the 12-h observation period, a significant reduction in the number of loose stools was found in the group receiving ORS and gelatin tannate versus the group receiving ORS alone. Both groups had similar weight gains, stool consistency, comparative risks of diarrhea with blood, peritonitis, and sepsis, vomiting intensity, and degrees of dehydration in the 12 h of observation.[9] In 2012, Allegrini and Costantini performed a blinded, randomized, placebo-controlled trial in the adult population (n = 40, mean age 43 ± 13 years). In the group receiving gelatin tannate (500 mg, 6 times per day, for 2 consecutive days) compared with the placebo group, a statistically significant decrease in both the daily number of watery stools and severity of abdominal pain for the first 48 h of the intervention was found. There were no clinically relevant adverse events.[10]

A 2014 systematic review evaluated the efficacy of gelatin tannate in treating acute gastroenteritis in children and adults.[11] The two above-described studies were included. None of the included studies evaluated the effect of gelatin tannate on the primary outcome measures for the review, such as stool output, duration of diarrhea, 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 gelatin tannate for treating acute gastroenteritis in children and only sparse evidence to support the use of gelatin tannate in adults.

Taken together, currently, the evidence to support the use of gelatin tannate for treating acute gastroenteritis in children or adults is very limited. According to the current (2014) European guidelines,[3] gelatin tannate is not recommended for the management of acute gastroenteritis in children.

Trial objectives and hypotheses

The main objective of this trial is to assess the effectiveness and safety of gelatin tannate in the treatment of acute gastroenteritis in children. We aim to conduct a

well-designed and executed study, with sufficient power, an adequate follow-up period, and relevant clinical endpoints. In our trial, we choose to use placebo for a comparator as it is widely regarded as the gold standard for testing the efficacy of new treatments.[12]

METHODS AND ANALYSIS

The trial is registered at www.clinicaltrials.gov (NCT02280759) and any important changes in the protocol will be implemented there.

Study design

This study is designed as a randomized, blinded, placebo-controlled trial, with allocation 1:1, and is described in more detail in subsequent sections.

Setting and participants

The recruitment will take place primarily in the emergency room of the pediatric hospital of the Medical University of Warsaw. However, other recruiting sites are under consideration provided that the personnel are adequately trained and competent in conducting clinical trials. Participants will be randomized after their first visit to the emergency room or after admission to the clinic. Caregivers will receive oral and written information on the study. Written informed consent will by obtained by physicians involved in the study.

Inclusion criteria

Children eligible for the trial must fulfill all of the following criteria:

- Acute gastroenteritis defined as a change in stool consistency to loose or liquid form (according to the Bristol Stool Form, BSF, scale or, in case of infants, Amsterdam Stool Form, ASF, scale) and/or an increase in the frequency of evacuations (typically ≥3 in 24 hours), lasting for no longer than 5 days
- Age younger than 5 years
- A caregiver must provide written informed consent.

Exclusion criteria

- Use of antibiotics, gelatin tannate, diosmectite, probiotics, racecadotril, or zinc (including zinc containing oral rehydration solution) within a week prior to enrollment.
- Exclusive breastfeeding.
- Chronic diarrheal gastrointestinal disease (e.g., inflammatory bowel diseases, cystic fibrosis, celiac disease, food allergy).
- Immunodeficiencies.
- Malnutrition (weight/height/length under 3rd percentile) (WHO Childgrowth Standards will be used).[13]
- If needed, discontinuation or modification of the treatment may be considered at the discretion of the physician.

Randomization criteria

After re-checking the inclusion and exclusion criteria, participants will be assigned into one of two groups (experimental or control). After determination of eligibility, caregivers will receive a diary of symptoms to record the number of stools and their consistency during the intervention (including recording of the timing of stools) BSF and ASF scales will be provided. Additionally, caregivers will be asked to write down any adverse events during the intervention period.

Interventions

The intervention under investigation is gelatin tannate manufactured by ICN Polfa Rzeszów/Valeant. The manufacturer does not have and will not have a role in the design or conduct of the study. The placebo will contain maltodextrine, which is an almost flavorless, easily digestible polysaccharide commonly used as a food additive. The dose of the active product or placebo will be age dependent (i.e., in children younger than 3 years of age the dose is 250 mg and in children older than 3 year of age – 500 mg). Both the gelatin tannate and placebo will be taken orally, 4 times per day, for 5 days. Caregivers will be instructed to administer the daily dose at the same time of a day, after mixing the contents of the sachet with a small amount of water.

The study products used in this trial will be prepared by the hospital pharmacy at the Medical University of Warsaw as identically appearing sachets. See **Table 1** for timetable of activities planned during the study.

Table 1. Timetable of activities planned during the study.

Days / Activity	1	2	3	4	5	6	7
Enrollment	+						
Randomization	+						
Intervention	+	+	+	+	+		
Return of diary					+		
Follow up						+	+
Adverse events	+	+	+	+	+	+	+

For initial rehydration, all children will be treated according to 2014 European recommendations (fast oral rehydration over 3–4 hours by mouth or via nasogastric tube with the recommended hypotonic solution). After all signs of dehydration have disappeared, oral rehydration solution will be given for ongoing losses until the diarrhea stops. Rapid reintroduction of the previous diet after successful rehydration will be recommended. At all times, breastfeeding will be allowed.

At any time, caregivers will have the right to withdraw the participating child from the study; they will be not obliged to give reasons for this decision, and there will be no effect on subsequent physician and/or institutional medical care.

Concomitant medications

The concomitant administration of any other medication, including antipyretics and antiemetics, will be at the discretion of the physician to provide adequate care. However, it is recommended that no unnecessary concomitant medication be used.

In particular, the use of antibiotics, diosmectite, probiotics, or racecadotril (all included in the exclusion criteria), should be avoided.

Follow up

All study participants will be followed-up for the duration of the intervention (5 days) and then for an additional 48 h.

Allocation concealment and blinding

A computer-generated randomization list prepared by a person unrelated to the trial will be used to allocate subjects to the study groups in blocks of eight. Consecutive randomization numbers will be given to participants at enrollment. This procedure will be performed by one of two physicians involved. The study product will be weighed, packaged, and signed by consecutive numbers according to the randomization list by the hospital pharmacy at the Medical University of Warsaw by independent personnel not involved in the conduct of the study. The study products will be delivered to the physicians in small envelopes labeled with the consecutive numbers and dose (with the meaning of numbers blinded and information deposited in a sealed envelope in a safe place in the administrative part of the department). The active product and placebo will be packaged in identical sachets. Contents will look and taste the same. Researchers, caregivers, outcome assessors, and a person responsible for the statistical analysis will be blinded to the intervention until the completion of the study. The information on intervention assignments will be stored in a sealed envelope in a safe in the administrative part of the department. The personal information about potential and enrolled participants will be stored in a locker within the study site, accessible for the involved researchers only.

Compliance

The caregivers will be asked to bring the remaining study product and diary to the study site at the end of the intervention period. Compliance with the study protocol will be checked by counting the number of sachets left unused. Based on previously

published trials, it seems to be appropriate to consider those subjects receiving less than 75% of the recommended doses as noncompliant.

Primary outcome

The primary outcome will be the duration of diarrhea, defined as the time until the normalization of stool consistency according to the BSF or ASF scale (in BSF Scale, numbers 2, 3, 4 and 5, and in ASF Scale, letters B or C), or the time until the normalization of the number of stools (compared with the period before the onset of diarrhea), and the presence of normal stools for 48 h.

Secondary outcomes

- need for intravenous rehydration
- need for hospitalization in outpatients
- number of watery stools per day
- vomiting
- weight gain
- adverse events
- recurrence of diarrhea (48 h after intervention)
- severity of diarrhea according to Vesikari scale.[14]

Power calculation

The primary outcome of the study is the duration of diarrhea. Based on available data in the literature, the average duration of gastroenteritis in children is 5-7 days.[3] We assume that a clinically significant difference in the effectiveness of gelatin tannate versus placebo will shorten the duration of symptoms by 24. To detect such a difference in the duration of diarrhea between the study groups with a power of 90% and α =0.01, a sample of 60 children is needed. Assuming about a 20% loss to follow up, we aim to recruit a total of 72 children for this study. In the Department of Paediatrics of The Medical University of Warsaw, there are 200 admissions of children with diarrhea per year and the same number of such patients who present to the emergency room. Assuming that 20% of these children will be eligible for the

study, we will achieve adequate participant enrollment to reach the target sample size after 2 years of recruiting.

Statistical analysis

All analysis will be conducted on an intention-to-treat basis, including all patients in the groups to which they are randomized for whom outcomes will be available (including dropouts and withdrawals). Descriptive statistics will be used to summarize baseline characteristics. The Student t test will be used to compare mean values of continuous variables approximating a normal distribution. For non-normally distributed variables, the Mann–Whitney U test will be used. The $\chi 2$ test or Fisher exact test will be used, as appropriate, to compare percentages. For continuous outcomes, differences in means or differences in medians (depending on the distribution of the data), and for dichotomous outcomes, the relative risk (RR) and number needed to treat, all with a 95% confidence interval, will be calculated. The difference between study groups will be considered significant when the p value is <0.05, when the 95% CI for RR does not include 1.0, or when the 95% CI for MD does not include 0. All statistical tests will be two tailed and performed at the 5%level of significance.

ETHICS AND DISSEMINATION

The Bioethical Committee of The Medical University of Warsaw issued approval for the study before recruitment commenced. Verbal and written information regarding informed consent will be presented to the caregivers. Any modifications to the protocol that may affect the conduct of the study will be presented to the Committee. The full protocol will be available freely due to open access publication. The findings of this RCT will be submitted to a peer-reviewed journal. Abstracts will be submitted to relevant national and international conferences.

FUNDING STATEMENT

This trial will be funded by The Medical University of Warsaw. At the time of submission of this protocol for publication, no specific grant from any funding

agency in the public, commercial, or not-for-profit sectors has been awarded to this project.

Competing interest statement: None declared.

Contributorship statement: HS conceptualized the study. All authors contributed to the design of the study. DM and MK developed the first draft of the manuscript and contributed equally. All authors approved the final draft of the manuscript.

Funding statement: This study will be fully funded by The Medical University of Warsaw.

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CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	1
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	4-5
	2b	Specific objectives or hypotheses	5-6
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	6
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	6
Participants	4a	Eligibility criteria for participants	6
	4b	Settings and locations where the data were collected	6
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	7
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	9
	6b	Any changes to trial outcomes after the trial commenced, with reasons	-
Sample size	7a	How sample size was determined	10
	7b	When applicable, explanation of any interim analyses and stopping guidelines	-
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	8
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	8
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	8
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	6,8
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	8

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	7
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	10
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	-
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	-
	13b	For each group, losses and exclusions after randomisation, together with reasons	-
Recruitment	14a	Dates defining the periods of recruitment and follow-up	-
	14b	Why the trial ended or was stopped	-
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	-
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	-
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	-
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	-
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	-
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	-
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	-
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	-
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	-
Other information			-
Registration	23	Registration number and name of trial registry	2
Protocol	24	Where the full trial protocol can be accessed, if available	-
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	1

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym √
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry √
	2b	All items from the World Health Organization Trial Registration Data Set []
Protocol version	3	Date and version identifier √
Funding	4	Sources and types of financial, material, and other support √
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors √
	5b	Name and contact information for the ~~trial sponsor~~
	5c	~~Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities~~
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) XXX
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention √
	6b	Explanation for choice of comparators √
Objectives	7	Specific objectives or hypotheses √
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) √

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained √
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) √
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered √
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) √
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) √
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial √
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended √
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) √
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations √
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size √

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions √

Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned √
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions √
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how √
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial √
Methods: Data collection, management, and analysis		
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol √
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol √
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) √
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)
Methods: Monitoring		
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed ??

	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial √
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct √
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor √

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval √
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) √
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) √
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable X
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial √
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site √
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators √
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation √
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions √
	31b	Authorship eligibility guidelines and any intended use of professional writers ?
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code √

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates √
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable √

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Efficacy and safety of gelatin tannate for the treatment of acute gastroenteritis in children: protocol of a randomized controlled trial

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Efficacy and safety of gelatin tannate for the treatment of acute gastroenteritis in children: protocol of a randomized controlled trial

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Number of figures: 0

Number of tables: 1

Number of references: 14.

ABSTRACT

Introduction

Worldwide, acute gastroenteritis in children, usually caused by viruses, leads to considerable morbidity and mortality. The treatment is aimed at preventing and treating dehydration, promoting weight gain after rehydration, and reducing the duration and severity of diarrhea. Effective and inexpensive interventions that could add to the effect of oral rehydration therapy are of interest. Recently, in many European countries, gelatin tannate is being widely marketed for treating acute gastroenteritis. Gelatin tannate is a complex of tannic acid, which possesses astringent and anti-inflammatory properties, and a protective gelatin. Currently, there is no evidence to support the use of gelatin tannate for treating acute gastroenteritis in children and only scant evidence to support the use of gelatin tannate in adults. We aim to assess the efficacy of gelatin tannate for the treatment of acute gastroenteritis in children.

Methods and analysis

This will be a blind, placebo-controlled, randomized trial. Children younger than 5 years of age with acute gastroenteritis defined as a change in stool consistency to 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 (typically ≥3 in 24 hours), lasting for no longer than 5 days, will be recruited. A total of 158 children will be randomized to receive either gelatin tannate (children younger than 3 years of age will receive 250 mg 4 times per day and those older than 3 years of age will receive 500 mg 4 times per day) or matching placebo for 5 days. The primary outcome measure is the duration of diarrhea.

Ethics and dissemination

The Bioethics Committee approved the study protocol. The findings of this trial will be submitted to a peer-reviewed pediatric journal. Abstracts will be submitted to relevant national and international conferences.

Registration

www.clinicaltrials.gov (NCT02280759)

STRENGTHS AND LIMITATIONS OF THIS STUDY

- The study design (randomized controlled trial, RCT) is the most robust methodology to assess the effectiveness of therapeutic interventions.
- A precise clinical question has been posed to fill a gap in knowledge as to whether gelatin tannate is safe and effective in the treatment of acute gastroenteritis in children.
- The findings of this RCT, whether positive or negative, will contribute to the formulation of recommendations on the use of gelatin tannate for the treatment of acute gastroenteritis.
- Due to practicalities, stool volume, which is one of the objective ways of assessing the efficacy of antidiarrheal drugs, will not be assessed.

INTRODUCTION

Worldwide, acute gastroenteritis in children, usually caused by rotaviruses, leads to considerable morbidity and mortality.[1] It is also the most common cause of primary care consultations among children younger than 5 years of age.[2] According to current European guidelines,[3] the mainstay of treatment for acute gastroenteritis is oral rehydration with a hypoosmolar solution. Breastfeeding should not be interrupted. Regular feeding should continue with no dietary changes including milk. 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. Currently, effective interventions that may reduce the duration and severity of diarrhea include administration of specific probiotics such as *Lactobacillus rhamnosus* GG or *Saccharomyces boulardii*, diosmectite, or racecadotril.[3]

Recently, in many European countries, gelatin tannate is being marketed for treating acute gastroenteritis. Gelatin tannate consists of tannic acid suspended in a gelatin solution. Gelatin tannate has a stable structure both in the acidic environment of the stomach as well as in a basic and neutral environment such as in the small intestine and colon.[4] Little is known about the specific mechanisms by which gelatin tannate may act against gastrointestinal infection. It is known, however, that it forms a biofilm, which mechanically protects the gastrointestinal mucosa and causes precipitation of pro-inflammatory proteins such as mucoproteins in the intestinal mucosa.[5] 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*.[5 6 7] The action of anti-inflammatory tannate also involves blocking inflammatory agents in the gastrointestinal mucosa.[8]

Only limited evidence is available on the effectiveness of gelatin tannate. In 2009, Esteban Carretero et al. published a study (n=211, mean age 2.5 ± 2.4 years, no randomization, no blinding, unbalanced baseline characteristics) that evaluated the

effectiveness of gelatin tannate in the treatment of acute gastroenteritis in children. Children received oral rehydration solution (ORS) alone or ORS in combination with gelatin tannate (dose was not specified). During the 12-h observation period, a significant reduction in the number of loose stools was found in the group receiving ORS and gelatin tannate versus the group receiving ORS alone. Both groups had similar weight gains, stool consistency, comparative risks of diarrhea with blood, peritonitis, and sepsis, vomiting intensity, and degrees of dehydration in the 12 h of observation.[9] In 2012, Allegrini and Costantini performed a blinded, randomized, placebo-controlled trial in the adult population (n = 40, mean age 43 ± 13 years). In the group receiving gelatin tannate (500 mg, 6 times per day, for 2 consecutive days) compared with the placebo group, a statistically significant decrease in both the daily number of watery stools and severity of abdominal pain for the first 48 h of the intervention was found. There were no clinically relevant adverse events.[10]

A 2014 systematic review evaluated the efficacy of gelatin tannate in treating acute gastroenteritis in children and adults.[11] The two above-described studies were included. None of the included studies evaluated the effect of gelatin tannate on the primary outcome measures for the review, such as stool output, duration of diarrhea, 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 gelatin tannate for treating acute gastroenteritis in children and only sparse evidence to support the use of gelatin tannate in adults.

Taken together, currently, the evidence to support the use of gelatin tannate for treating acute gastroenteritis in children or adults is very limited. According to the current (2014) European guidelines,[3] gelatin tannate is not recommended for the management of acute gastroenteritis in children.

Trial objectives and hypotheses

The main objective of this trial is to assess the effectiveness and safety of gelatin tannate in the treatment of acute gastroenteritis in children. We aim to conduct a

well-designed and executed study, with sufficient power, an adequate follow-up period, and relevant clinical endpoints. In our trial, we choose to use placebo for a comparator as it is widely regarded as the gold standard for testing the efficacy of new treatments.[12]

METHODS AND ANALYSIS

The trial is registered at www.clinicaltrials.gov (NCT02280759) and any important changes in the protocol will be implemented there.

Study design

This study is designed as a randomized, blinded, placebo-controlled trial, with allocation 1:1, and is described in more detail in subsequent sections.

Setting and participants

The recruitment will take place primarily in the emergency room of the pediatric hospital of the Medical University of Warsaw. However, other recruiting sites are under consideration provided that the personnel are adequately trained and competent in conducting clinical trials. Participants will be randomized after their first visit to the emergency room or after admission to the clinic. Caregivers will receive oral and written information on the study. Written informed consent will by obtained by physicians involved in the study.

Inclusion criteria

Children eligible for the trial must fulfill all of the following criteria:

- Acute gastroenteritis defined as a change in stool consistency to loose or liquid form (according to the Bristol Stool Form, BSF, scale or, in case of infants, Amsterdam Stool Form, ASF, scale) and/or an increase in the frequency of evacuations (typically ≥3 in 24 hours), lasting for no longer than 5 days
- Age younger than 5 years
- A caregiver must provide written informed consent.

Exclusion criteria

- Use of antibiotics, gelatin tannate, diosmectite, probiotics, racecadotril, or zinc (including zinc containing oral rehydration solution) within a week prior to enrollment.
- Exclusive breastfeeding.
- Chronic diarrheal gastrointestinal disease (e.g., inflammatory bowel diseases, cystic fibrosis, celiac disease, food allergy).
- Immunodeficiencies.
- Malnutrition (weight/height/length under 3rd percentile) (WHO Childgrowth Standards will be used).[13]
- If needed, discontinuation or modification of the treatment may be considered at the discretion of the physician.

Randomization criteria

After re-checking the inclusion and exclusion criteria, participants will be assigned into one of two groups (experimental or control). After determination of eligibility, caregivers will receive a diary of symptoms to record the number of stools and their consistency during the intervention (including recording of the timing of stools) BSF and ASF scales will be provided. Additionally, caregivers will be asked to write down any adverse events during the intervention period.

Interventions

The intervention under investigation is gelatin tannate manufactured by ICN Polfa Rzeszów/Valeant. The manufacturer does not have and will not have a role in the design or conduct of the study. The placebo will contain maltodextrine, which is an almost flavorless, easily digestible polysaccharide commonly used as a food additive. The dose of the active product or placebo will be age dependent (i.e., in children younger than 3 years of age the dose is 250 mg and in children older than 3 year of age – 500 mg). Both the gelatin tannate and placebo will be taken orally, 4 times per day, for 5 days. Caregivers will be instructed to administer the daily dose at the same time of a day, after mixing the contents of the sachet with a small amount of water.

The study products used in this trial will be prepared by the hospital pharmacy at the Medical University of Warsaw as identically appearing sachets. See **Table 1** for timetable of activities planned during the study.

Table 1. Timetable of activities planned during the study.

Days / Activity	1	2	3	4	5	6	7
Enrollment	+						
Randomization	+						
Intervention	+	+	+	+	+		
Return of diary					+		
Follow up						+	+
Adverse events	+	+	+	+	+	+	+

For initial rehydration, all children will be treated according to 2014 European recommendations (fast oral rehydration over 3–4 hours by mouth or via nasogastric tube with the recommended hypotonic solution). After all signs of dehydration have disappeared, oral rehydration solution will be given for ongoing losses until the diarrhea stops. Rapid reintroduction of the previous diet after successful rehydration will be recommended. At all times, breastfeeding will be allowed.

At any time, caregivers will have the right to withdraw the participating child from the study; they will be not obliged to give reasons for this decision, and there will be no effect on subsequent physician and/or institutional medical care.

Concomitant medications

The concomitant administration of any other medication, including antipyretics and antiemetics, will be at the discretion of the physician to provide adequate care. However, it is recommended that no unnecessary concomitant medication be used.

In particular, the use of antibiotics, diosmectite, probiotics, or racecadotril (all included in the exclusion criteria), should be avoided.

Follow up

All study participants will be followed-up for the duration of the intervention (5 days) and then for an additional 48 h.

Allocation concealment and blinding

A computer-generated randomization list prepared by a person unrelated to the trial will be used to allocate subjects to the study groups in blocks of eight. Consecutive randomization numbers will be given to participants at enrollment. This procedure will be performed by one of two physicians involved. The study product will be weighed, packaged, and signed by consecutive numbers according to the randomization list by the hospital pharmacy at the Medical University of Warsaw by independent personnel not involved in the conduct of the study. The study products will be delivered to the physicians in small envelopes labeled with the consecutive numbers and dose (with the meaning of numbers blinded and information deposited in a sealed envelope in a safe place in the administrative part of the department). The active product and placebo will be packaged in identical sachets. Contents will look and taste the same. Researchers, caregivers, outcome assessors, and a person responsible for the statistical analysis will be blinded to the intervention until the completion of the study. The information on intervention assignments will be stored in a sealed envelope in a safe in the administrative part of the department. The personal information about potential and enrolled participants will be stored in a locker within the study site, accessible for the involved researchers only.

Compliance

The caregivers will be asked to bring the remaining study product and diary to the study site at the end of the intervention period. Compliance with the study protocol will be checked by counting the number of sachets left unused. Based on previously

published trials, it seems to be appropriate to consider those subjects receiving less than 75% of the recommended doses as noncompliant.

Primary outcome

The primary outcome will be the duration of diarrhea, defined as the time until the normalization of stool consistency according to the BSF or ASF scale (in BSF Scale, numbers 2, 3, 4 and 5, and in ASF Scale, letters B or C), or the time until the normalization of the number of stools (compared with the period before the onset of diarrhea), and the presence of normal stools for 48 h.

Secondary outcomes

- need for intravenous rehydration
- need for hospitalization in outpatients
- number of watery stools per day
- vomiting
- weight gain
- adverse events
- recurrence of diarrhea (48 h after intervention)
- severity of diarrhea according to Vesikari scale[14]
- use of concomitant medications.

Power calculation

The primary outcome of the study is the duration of diarrhea. Based on available data in the literature, the average duration of gastroenteritis in children is 5-7 days.[3] We assume that a clinically significant difference in the effectiveness of gelatin tannate versus placebo will shorten the duration of symptoms by 24. To detect such a difference in the duration of diarrhea between the study groups with a power of 90% and α =0.01, a sample of 60 children is needed. Assuming about a 20% loss to follow up, we aim to recruit a total of 72 children for this study. In the Department of Paediatrics of The Medical University of Warsaw, there are 200 admissions of children with diarrhea per year and the same number of such patients who present

to the emergency room. Assuming that 20% of these children will be eligible for the study, we will achieve adequate participant enrollment to reach the target sample size after 2 years of recruiting.

Statistical analysis

All analysis will be conducted on an intention-to-treat basis, including all patients in the groups to which they are randomized for whom outcomes will be available (including dropouts and withdrawals). Descriptive statistics will be used to summarize baseline characteristics. The Student t test will be used to compare mean values of continuous variables approximating a normal distribution. For non-normally distributed variables, the Mann–Whitney U test will be used. The $\chi 2$ test or Fisher exact test will be used, as appropriate, to compare percentages. For continuous outcomes, differences in means or differences in medians (depending on the distribution of the data), and for dichotomous outcomes, the relative risk (RR) and number needed to treat, all with a 95% confidence interval, will be calculated. The difference between study groups will be considered significant when the p value is <0.05, when the 95% CI for RR does not include 1.0, or when the 95% CI for MD does not include 0. All statistical tests will be two tailed and performed at the 5%level of significance.

ETHICS AND DISSEMINATION

The Bioethical Committee of The Medical University of Warsaw issued approval for the study before recruitment commenced. Verbal and written information regarding informed consent will be presented to the caregivers. Any modifications to the protocol that may affect the conduct of the study will be presented to the Committee. The full protocol will be available freely due to open access publication. The findings of this RCT will be submitted to a peer-reviewed journal. Abstracts will be submitted to relevant national and international conferences.

FUNDING STATEMENT

This trial will be funded by The Medical University of Warsaw. At the time of submission of this protocol for publication, no specific grant from any funding agency in the public, commercial, or not-for-profit sectors has been awarded to this project.

Competing interest statement: None declared.

Contributorship statement: HS conceptualized the study. All authors contributed to the design of the study. DM and MK developed the first draft of the manuscript and contributed equally. All authors approved the final draft of the manuscript.

Funding statement: This study will be fully funded by The Medical University of Warsaw.

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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym √
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry √
	2b	All items from the World Health Organization Trial Registration Data Set []
Protocol version	3	Date and version identifier √
Funding	4	Sources and types of financial, material, and other support √
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors √
	5b	Name and contact information for the ~~trial sponsor~~
	5c	~~Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities~~
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) XXX
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention √
	6b	Explanation for choice of comparators √
Objectives	7	Specific objectives or hypotheses √
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) √

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained √
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) √
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered √
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) √
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) √
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial √
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended √
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) √
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations √
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size √

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions √

Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned √
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions √
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how √
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial √
Methods: Data collection, management, and analysis		
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol √
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol √
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) √
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)
Methods: Monitoring		
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed ??

	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial √
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct √
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor √
Ethics and dissemination		
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval √
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) √
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) √
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable X
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial √
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site √
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators √
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation √
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions √
	31b	Authorship eligibility guidelines and any intended use of professional writers ?
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code √

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates √
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable √

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CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	1
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	4-5
	2b	Specific objectives or hypotheses	5-6
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	6
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	6
Participants	4a	Eligibility criteria for participants	6
	4b	Settings and locations where the data were collected	6
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	7
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	9
	6b	Any changes to trial outcomes after the trial commenced, with reasons	-
Sample size	7a	How sample size was determined	10
	7b	When applicable, explanation of any interim analyses and stopping guidelines	-
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	8
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	8
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	8
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	6,8
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	8

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	7
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	10
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	-
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	-
	13b	For each group, losses and exclusions after randomisation, together with reasons	-
Recruitment	14a	Dates defining the periods of recruitment and follow-up	-
	14b	Why the trial ended or was stopped	-
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	-
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	-
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	-
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	-
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	-
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	-
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	-
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	-
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	-
Other information			-
Registration	23	Registration number and name of trial registry	2
Protocol	24	Where the full trial protocol can be accessed, if available	-
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	1

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

Correction: Efficacy and safety of gelatine tannate for the treatment of acute gastroenteritis in children: protocol of a randomised controlled trial

Michałek D, Kołodziej M, Konarska Z, *et al*. Efficacy and safety of gelatine tannate for the treatment of acute gastroenteritis in children: protocol of a randomised controlled trial. *BMJ Open* 2016;**6**:e010530. doi: 10.1136/bmjopen-2015-010530

In the *Abstract*, the number of children to be recruited should be 72 (as shown under *Power calculation)*.

BMJ Open 2017;**0**:e010530corr1. doi:10.1136/bmjopen-2015-010530corr1