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GELATINE TANNATE IN THE MANAGEMENT OF ACUTE GASTROENTERITIS IN CHILDREN: A RANDOMIZED CONTROLLED TRIAL

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ABSTRACT

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

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

Setting Two pediatric hospitals in Warsaw

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

Interventions 72 children were assigned to receive gelatine tannate (n=36) or placebo (n=36) in addition to standard rehydration therapy. The gelatine tannate was administered at an age-dependent dose (250 to 500 mg), and both study products were taken 4 times/day for 5 days

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

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

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

Trial registration ClinicalTrials.gov NCT02280759.

Strengths and limitations of this study

- **This study was a randomized controlled trial, which is the design of choice for interventional studies**
- **The protocol of the study was published in a peer reviewed journal (BMJ open)**
- **This study answers a precised clinical question filling a gap in knowledge about effectiveness and safety of gelatin tannate**
- **The guidelines from the CONSORT statement were followed for reporting this trial.**

INTRODUCTION

The main objectives in the management of acute gastroenteritis are the prevention or treatment of dehydration, promotion of weight gain following rehydration, and reduction of the duration of diarrhea and quantity of stool output. The key treatment is oral rehydration with a hypoosmolar solution.[1] Considering the burden of acute gastroenteritis both to children and the healthcare system, effective and inexpensive interventions that could add to the effect of oral rehydration therapy are of interest. Recently, in many countries, gelatine tannate is being marketed for the treatment of acute gastroenteritis. Gelatine tannate consists of tannic acid suspended in a gelatine solution. It has a stable structure both in the acidic environment of the stomach as well as in basic and neutral environments such as in the small intestine and colon.[2] The specific mechanisms by which gelatine tannate may act against gastrointestinal infections remain unknown. It is known, however, that it forms a biofilm, which mechanically protects the gastrointestinal mucosa and causes precipitation of proinflammatory proteins such as mucoproteins in the intestinal mucosa.[3] In addition, it inhibits the growth of bacteria such as *Bacteroides fragilis, Clostridium perfringens, Escherichia coli, Enterobacter cloacae, Salmonella typhimurium, Helicobacter pylori, Listeria monocytogenes,* and in vitro mycobacterial *Vibrio cholerae*.[3, 4, 5] The anti-inflammatory action of gelatine tannate also involves blocking inflammatory agents in the gastrointestinal mucosa.[6]

At the time of designing this study, only limited evidence was available on the effectiveness of gelatine tannate in the management of acute gastroenteritis in children. This evidence is summarized in a 2014 systematic review, which only included 2 studies. Neither of the included studies evaluated the effects of gelatine tannate on outcome measures 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 gelatine tannate for treating acute gastroenteritis in children and only scant evidence to support the use of gelatine tannate in adults.[7] Further studies are needed. Thus, our aim was to assess the efficacy of gelatine tannate for the management of acute gastroenteritis in children.

METHODS

Trial design

This was a randomized, double-blind, placebo-controlled trial, conducted in 2 pediatric hospitals in Warsaw, Poland (The Medical University of Warsaw and the Niekłanska Hospital). The Ethics Committee of the Medical University of Warsaw approved the study. Parents or legal guardians were fully informed about the aims of the study, and informed written consent was obtained from them. The trial was registered at ClinicalTrials.gov (NCT02280759) before enrollment of the first patient. The full protocol of this trial was published in BMJ Open.[8] The guidelines from the CONSORT statement were followed for reporting this trial.[9]

Participants

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

Intervention

Participants were randomly assigned to receive gelatine tannate or a comparable placebo in addition to standard rehydration therapy. Gelatine tannate was manufactured by ICN Polfa Rzeszów/Valeant. The manufacturer did not have role in the design or conduct of the study. The placebo contained maltodextrin. The dose of the active product or placebo was age dependent (i.e., in children younger than 3 years of age, the dose was 250 mg, and, in children older than 3 years of age, the dose was 500 mg). Both the gelatine tannate and placebo were taken orally, 4 times/day, for 5 days. All study participants were followed up for the duration of the intervention (5 days), and then for an additional 48 h. Compliance was assessed by counting the number of sachets of study products left unused.

Study procedure

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

Outcome measures

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

Allocation concealment and blinding

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

Sample size calculation

The primary outcome of the study was the duration of diarrhea. Based on available data in the literature, the average duration of acute gastroenteritis in children is 5–7 days.[1] We assumed that a clinically significant difference in the effectiveness of gelatine tannate versus placebo would shorten the duration of symptoms by 24 hours (±12 h). To detect such a difference in the duration of diarrhea between the study groups with a power of 90% and α=0.01, we determined that a sample of 60 children

was needed. Assuming approximately 20% loss to follow-up, we aimed to recruit a total of 72 children for this study. The sample size calculation was performed with the Sealed Envelope Ltd. software.[12]

Statistical analysis

The statistical analyses were conducted using StatsDirect version 3.0.181 (01.11.2016, Stats Direct Ltd.) computer software. The Shapiro-Wilk W test was used to investigate a sample for evidence of non-normality. Student's t test was used to compare means of continuous variables approximating a normal distribution. For non-normally distributed variables, the Mann-Whitney U test was used. The x^2 test or Fisher's exact test was used, as appropriate, to compare percentages. The same computer software was used to calculate the risk ratio (RR) and mean or median difference (MD), as appropriate, both with a 95% confidence interval (CI). The difference between study groups was considered significant when the 95% CI for RR did not include 1.0 and the 95% CI for MD did not include 0 (equivalent to $P < 0.05$). All statistical tests were 2-tailed and performed at the 5% level of significance. All analyses were conducted on an intention-to-treat basis, including all patients in the groups to which they were randomized for whom outcomes were available.

RESULTS

Overall, 230 children with acute gastroenteritis who presented for treatment between February 2015 and June 2017 were assessed for eligibility; 72 were enrolled in the study and randomly assigned to one the 2 study groups: 36 to the gelatine tannate group and 36 to the placebo group. Eight children were lost to follow-up. Sixty-four

children (89%) completed the intervention and were included in the analysis (**Figure 1**). Baseline demographic and clinical characteristics are shown in **Table 1.** The two groups were comparable in regard to these characteristics at study entry.

Table 1. Baseline demographic and clinical characteristics

Characteristics	Gelatine tannate group	Placebo group
n	36	36
Age, mo, mean (sd)	27.7 (29.3)	26.8 (28.5)
Age, mo, median [IQR]	16.0 [10.8 to 33.0]	18.0 [10.8 to 27.5]
Sex, male/female, n	17/19	22/14
Dehydration level before enrollment, n (%)		
• mild	21 (58.3%)	22 (61.1%)
• moderate	15 (41.7%)	14 (38.9%)
• severe	0	0
Fever (≥ 38 °C), n (%)	20 (62.5%)	21 (63,5%)
Blood in stool, n (%)	0	1 (2.9%)
Etiology of acute gastroenteritis		
Rotavirus, n (%)	12 (33.3%)	11 (30.6%)
Adenovirus, n (%)	2 (5.5%)	0
Norovirus, n (%)	1 (2.8%)	1 (2.8%)
Salmonella enteritidis, n (%)	1 (2.8%)	1 (2.8%)
Campylobacter spp., n (%)	0	1 (2.8%)
Unknown etiology, n (%)	20 (55.6%)	23 (63.8%)

IQR, interquartile range; sd, standard deviation

Primary and secondary outcomes

The primary and secondary outcome measures are presented in **Table 2**. The duration of diarrhea after randomization was similar in both groups (MD 0.1 h, 95% CI -14.1 to 14.3). The risk of unscheduled intravenous rehydration was similar in the gelatine tannate and placebo groups (RR 0.99; 95% CI 0.78 to 1.25). The number of watery stools per day was similar in both groups throughout the study period (for details – see **Table 2).** In both groups, the risk of vomiting (RR 1.27, 95% CI 0.93 to 1.73), weight gain (MD -59.1 g, 95% CI -133.1 to 15), risk of recurrence of diarrhea 48

h after the intervention (RR 0.12, 95% CI 0.01 to 2.0), and severity of diarrhea according to the Vesikari scale (MD 1.1, 95% CI -0.7 to 2.9) were similar. Adverse effects were similar in both groups (RR 0.6, 95% CI 0.17 to 2.45).

Table 2. Primary and secondary outcomes

Outcomes	Gelatine tannate group (n=31)	Placebo group (n=33)	P value	MD/RR	95% CI
Duration of diarrhea, h, mean (sd)	75.6 (27.8)	75.5 (29.0)	0.99	0.1	-14.1 to 14.3
Need for intravenous rehydration, n (%)	25 (80.6%)	27 (81.8%)	0.9	0.9	0.78 to 1.25
Number of watery stools per day*					
Day 1 (median [IQR]	5.0 [4.0, 6.0]	4.0 [3.0, 6.0]	0.160	1.00	0.00 - 2.00
Day 1 (mean (sd)	5.5 (3.0)	4.6 (2.3)	0.165	0.90	-0.40 - 2.30
Day 2 (median [IQR]	4.0 [3.0, 5.0]	3.0 [1.0, 6.0]	0.147	1.00	-1.00 - 2.00
Day 2 (mean (sd))	4.7 (2.8)	3.8 (3.0)	0.236	0.90	-0.60 - 2.30
Day 3 (median [IQR)	2.0 [0.0, 4.0]	1.0 [0.0, 3.0]	0.566	1.00	-2.00 - 3.00
Day 3 (mean (sd)	2.6 (3.2)	2.1 (2.9)	0.499	0.50	-1.00 - 2.10
Day 4 (median [IQR]	0.0 [0.0, 2.0]	0.0 [0.0, 2.0]	0.929	0.00	-1.00 - 2.00
Day 4 (mean (sd)	1.2 (1.7)	1.0 (1.3)	0.620	0.20	-0.60 - 1.00
Day 5 (median [IQR]	0.0 [0.0, 0.0]	0.0 [0.0, 0.0]	0.476	0.00	0.00 - 0.00
Day 5 (mean (sd)	0.5 (1.3)	0.4 (1.5)	0.866	0.10	-0.60 - 0.80
Day 6 (median [IQR]	0.0 [0.0, 0.0]	0.0 [0.0, 0.0]	>0.999	0.00	0.00 - 0.00
Day 6 (mean (sd)	0.06 (0.4)	0.1 (0.7)	0.681	-0.10	-0.30 - 0.20
Day 7 (median [IQR]	0.0 [0.0, 0.0]	0.0 [0.0, 0.0]	NA	0.00	0.00 - 0.00
Day 7 (mean (sd)	0.0 (0.0)	0.0 (0.0)	NA	0.00	0.00 - 0.00
Vomiting, n (%)	25 (80.6%)	21 (63.6%)	0.22	1.27	0.93 to 1.73
Weight gain, g ± SD	70 ±142	129 ±155	0.12	-59.1	-133.1 to 15
Recurrence of diarrhea (48 h after intervention), n (%)	0	4 (12%)	0.12	0.12	0.01 to 2.11
Severity of diarrhea according to Vesikari scale					
median [IQR]	10.0 [8.0, 12.0]	10.0 [4.0, 11.0]	0.339	0.00	-2.00 -

					3.00
mean (sd)	9.7 (3.4)	8.6 (3.9)	0.241	1.10	-0.70 - 2.90
Need for hospitalization in outpatients, n	0	0	-	-	-
Adverse events, n (%)	3 (9.6%)	5 (15.1%)	0.7	0.64	0.17 to 2.45
• Spitting after the administration	0	2 (6.1%)	0.49	0.21	0.01 to 4.26
• Abdominal pain	1 (3.2%)	0	0.48	3.19	0.13 to 75.43

IQR, interquartile range; MD, mean or median difference, as appropriate; RR, relative risk; sd, standard deviation

*According to the Bristol Stool Form scale (BSF) or Amsterdam Stool Form (ASF) scale (on BSF scale, numbers 2, 3, 4 and 5; on ASF scale, letters B or C).

DISCUSSION

Principal findings

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

Strengths and limitations

This study was a randomized controlled trial, which is the design of choice for interventional studies. The protocol of the study was published in a peer reviewed journal. We used adequate methods for the generation of the allocation sequence and allocation concealment. We maintained blinding throughout the selection, treatment, data management, and data analyses phases of the study. Follow-up was adequate; data were obtained from 89% of the participants. For assessment of the consistency of stools, we used the validated Bristol Stool Form Scale or the Amsterdam Stool Form scale, depending on the age of the participants. The sample size was predefined. These features minimize the risk of bias. The potential limitation of this trial is that

we did not assess stool volume as the primary outcome measure, which is a clinically meaningful endpoint. This decision was based on feasibility reasons and our previous negative experiences (unwillingness of parents and/or hospital nurses to collect stools).

Comparison with previous findings

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

assessed the number of any type of bowel movements, while we assessed the number of watery stools. Thus, these findings are not directly comparable. However, for comparison, *post hoc,* we evaluated the number of any type of stools. Throughout the study period, there were no differences in the number of stools per day between the study groups (data are not shown, however, are available upon request).

A 2017 randomized, controlled, double-blind trial conducted by Çağan et al. compared administration of gelatin tannate plus oral rehydration solution with oral rehydration solution alone in 203 children aged 3 months to 12 years with acute gastroenteritis. From 12 h onwards, per-protocol analysis showed that the incidence of watery stools was significantly lower in the gelatin tannate plus oral rehydration solution group than in the oral rehydration solution alone group (at 12 hours, 59.2% vs. 77.0%, respectively; P=0.01).[14] Again, there are several possible reasons for the differences in findings between the studies. Compared with our study, Çağan et al. included older children (mean age: 27 ± 30 vs. 40 ± 36 months, respectively). In the study by Çağan et al., there was a significant difference in the percentage of children with dehydration at baseline between the experimental and control groups (60% vs. 40%, respectively), thus, the randomization did not work properly. In our study, the sample size was smaller. However, the sample size was based on a sample size calculation designed to detect 24 h (± 12 h) shortening of the duration of diarrhea between the study groups with a power of 90% and α=0.01; thus, a sufficient number of participants was randomized in our study, allowing us to be reasonably certain that no difference between the interventions exists. In the study by Çağan et al.,

while the sample size calculation was provided, it is unclear what assumptions were made by the authors. While one of the primary study endpoints in the study by Çağan et al. was the total time to resolution of diarrhea, no data relevant to this endpoint were provided; thus, a comparison between the studies is not possible. Both studies reported data on watery stools. However, the data were presented differently (i.e., percentage of patients with watery stools in the study by Çağan et al. compared with number of watery stools per day in our study). Finally, the method of analysis in the study by Çağan et al. (per-protocol analysis) differed from that used in our study (intention-to-treat analysis).

Taken together, direct comparison of our findings with the results reported by others is difficult. It is possible that the differences in the study design and execution contributed to the differences in findings. Further well-designed and carefully conducted randomized controlled trials, with relevant inclusion/exclusion criteria, adequate sample sizes, and validated clinical outcome measures (with definitions), may help to resolve the uncertainty with regard to the efficacy of gelatine tannate in the management of acute gastroenteritis in children.

CONCLUSIONS

In summary, gelatine tannate, as dosed in this study, administered as an adjunct to rehydration for the management of acute gastroenteritis in children younger than 5 years was not effective. According to current European guidelines, the mainstay of treatment for acute gastroenteritis should be oral rehydration with a hypoosmolar solution. Breastfeeding should not be interrupted. Regular feeding should continue

with no dietary changes, including milk. Currently, effective interventions that may reduce the duration and severity of diarrhea include the administration of specific probiotics such as *Lactobacillus rhamnosus* GG or *Saccharomyces boulardii*, diosmectite, or racecadotril.[1]

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Authors' contribution HS initially conceptualized this study. All authors (MK, DB, ZK, HS) contributed to the study protocol. MK and DB conducted the study. MK analyzed the data under the supervision of HS. HS and MK wrote the manuscript. All authors (MK, DB, ZK, HS) contributed to (and agreed upon) the final version.

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Competing interests None declared.

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

Data sharing statement All data pertaining to this work are stored in the Pediatric Hospital of 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)	2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	3-4
	2b	Specific objectives or hypotheses	4
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	4
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	-
Participants	4a	Eligibility criteria for participants	5
	4b	Settings and locations where the data were collected	4
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	5-6
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	6
	6b	Any changes to trial outcomes after the trial commenced, with reasons	-
Sample size	7a	How sample size was determined	7-8
	7b	When applicable, explanation of any interim analyses and stopping guidelines	-
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	7
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	7
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	7
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	7
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	7

		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	8
	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	17
	13b	For each group, losses and exclusions after randomisation, together with reasons	17
Recruitment	14a	Dates defining the periods of recruitment and follow-up	6/8
	14b	Why the trial ended or was stopped	-
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	15
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	17
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)	16/ 8-9
	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	9-10
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	13
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	13
Other information			
Registration	23	Registration number and name of trial registry	2
Protocol	24	Where the full trial protocol can be accessed, if available	4
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	14

*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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GELATINE TANNATE IN THE MANAGEMENT OF ACUTE GASTROENTERITIS IN CHILDREN: A RANDOMIZED CONTROLLED TRIAL

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GELATINE TANNATE IN THE MANAGEMENT OF ACUTE GASTROENTERITIS IN CHILDREN: A RANDOMIZED CONTROLLED TRIAL

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ABSTRACT

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

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

Setting Two pediatric hospitals in Warsaw.

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

Interventions Seventy-two children were assigned to receive gelatine tannate (n=36) or placebo (n=36) in addition to standard rehydration therapy. The gelatine tannate was administered at an age-dependent dose (250 to 500 mg), and both study products were taken 4 times/day for 5 days.

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

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

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

Trial registration ClinicalTrials.gov NCT02280759.

Strengths and limitations of this study:

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

INTRODUCTION

The main objectives in the management of acute gastroenteritis are the prevention or treatment of dehydration, promotion of weight gain following rehydration, and reduction of the duration of diarrhea and quantity of stool output. The key treatment is oral rehydration with a hypoosmolar solution.[1] Considering the burden of acute gastroenteritis both to children and the healthcare system, effective and inexpensive interventions that could add to the effect of oral rehydration therapy are of interest. Recently, in many countries, gelatine tannate is being marketed for the treatment of acute gastroenteritis. Gelatine tannate consists of tannic acid suspended in a gelatine solution. It has a stable structure both in the acidic environment of the stomach as well as in basic and neutral environments such as in the small intestine and colon.[2]

The specific mechanisms by which gelatine tannate may act against gastrointestinal infections remain unknown. It is known, however, that it forms a biofilm, which mechanically protects the gastrointestinal mucosa and causes precipitation of proinflammatory proteins such as mucoproteins in the intestinal mucosa.[3] In addition, it inhibits the growth of bacteria such as *Bacteroides fragilis, Clostridium perfringens, Escherichia coli, Enterobacter cloacae, Salmonella typhimurium, Helicobacter pylori, Listeria monocytogenes,* and in vitro mycobacterial *Vibrio cholerae*.[3, 4, 5] The anti-inflammatory action of gelatine tannate also involves blocking inflammatory agents in the gastrointestinal mucosa.[6]

At the time of designing this study, only limited evidence was available on the effectiveness of gelatine tannate in the management of acute gastroenteritis in children. This evidence is summarized in a 2014 systematic review,[7] which only included 2 studies: one randomized trial in adults and one non-randomized trial in children. Neither of the included studies evaluated the effects of gelatine tannate on outcome measures 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 gelatine tannate for treating acute gastroenteritis in children (i.e., no randomized controlled trials; important outcomes not addressed) and only scant evidence to support the use of gelatine tannate in adults. Further studies are needed. Thus, our aim was to assess in the efficacy of gelatine tannate for the management of acute gastroenteritis in children.

METHODS

Trial design

This was a randomized, double-blind, placebo-controlled trial, conducted in 2 pediatric hospitals in Warsaw, Poland (The Medical University of Warsaw and the Niekłanska Hospital). The Ethics Committee of the Medical University of Warsaw approved the study. Parents or legal guardians were fully informed about the aims of the study, and informed written consent was obtained from them. The trial was registered at ClinicalTrials.gov (NCT02280759) before enrollment of the first patient. The full protocol of this trial was published in BMJ Open.[8] The guidelines from the CONSORT statement were followed for reporting this trial.[9]

Participants

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

Intervention

Participants were randomly assigned to receive gelatine tannate or a comparable placebo in addition to standard rehydration therapy. Gelatine tannate was manufactured by ICN Polfa Rzeszów/Valeant. The manufacturer did not have role in the design or conduct of the study. The placebo contained maltodextrin. In line with the manufacturer's recommendation, the dose of the active product or placebo was age dependent (i.e., in children younger than 3 years of age, the dose was 250 mg, and, in children older than 3 years of age, the dose was 500 mg). Both the gelatine tannate and placebo were taken orally, 4 times/day, for 5 days. The intervention was started immediately after recruitment of the participant into the study. All study participants were followed up for the duration of the intervention (5 days), and then for an additional 48 h. Compliance was assessed by counting the number of sachets of study products left unused. As stated in the protocol of the study, based on previously published trials, we assumed that participants receiving <75% of the recommended doses were treated as noncompliant.

Study procedure

For initial rehydration, all children were treated according to 2014 European recommendations (fast oral rehydration over 3–4 h by mouth with a hypotonic solution).[1] Intravenous fluid therapy was administered during the rehydration phase if there was failure to achieve adequate rehydration within the first 3–4 hours or if there were intensified signs of dehydration despite the intake of the estimated fluid requirements. During the maintenance phase, intravenous fluid therapy was started if dehydration recurred despite the intake of estimated fluid requirements, including oral rehydration solution, for ongoing losses. After all of the signs of dehydration

had disappeared, oral rehydration solution was given for ongoing losses until the diarrhea stopped. Rapid reintroduction of the previous diet after successful rehydration was recommended. At all times, breastfeeding was allowed. Children were discharged from the hospital once a stable clinical condition had been achieved.

Outcome measures

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

Allocation concealment and blinding

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

numbers and doses. The physicians were blinded to the meaning of the numbers, and the sealed envelopes were deposited in a safe place in the administrative part of the department. The active product and placebo were packaged in identical sachets. The contents of the sachets looked and tasted the same. Researchers, caregivers, outcome assessors, and the person responsible for the statistical analysis were blinded to the intervention until the completion of the study and the analysis of the data.

Sample size calculation

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

Statistical analysis

The statistical analyses were conducted using StatsDirect version 3.0.181 (01.11.2016, Stats Direct Ltd.) computer software. The Shapiro-Wilk W test was used to investigate a sample for evidence of non-normality. Student's t test was used to compare means of continuous variables approximating a normal distribution. For

non-normally distributed variables, the Mann-Whitney U test was used. The x^2 test or Fisher's exact test was used, as appropriate, to compare percentages. The same computer software was used to calculate the risk ratio (RR) and mean or median difference (MD), as appropriate, both with a 95% confidence interval (CI). The difference between study groups was considered significant when the 95% CI for RR did not include 1.0 and the 95% CI for MD did not include 0 (equivalent to $P < 0.05$). All statistical tests were 2-tailed and performed at the 5% level of significance. All analyses were conducted on an intention-to-treat basis, including all patients in the groups to which they were randomized for whom outcomes were available.

Patient involvement

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

RESULTS

Overall, 230 children with acute gastroenteritis who presented for treatment between February 2015 and June 2017 were assessed for eligibility; 72 were enrolled in the study and randomly assigned to one of the 2 study groups: 36 to the gelatine tannate group and 36 to the placebo group. Eight children were lost to follow-up. Sixty-four children (89%) completed the intervention and were included in the analysis (**Figure 1**). Baseline demographic and clinical characteristics are shown in **Table 1.** The two groups were comparable in regard to these characteristics at study entry.

Table 1. Baseline demographic and clinical characteristics

Characteristics	Gelatine tannate group	Placebo group
n	36	36
Age, mo, mean (sd)	27.7 (29.3)	26.8 (28.5)
Age, mo, median [IQR]	16.0 [10.8 to 33.0]	18.0 [10.8 to 27.5]
Sex, male/female, n	17/19	22/14
Dehydration level before enrollment, n (%)		
• mild	21 (58.3%)	22 (61.1%)
• moderate	15 (41.7%)	14 (38.9%)
• severe	0	0
Fever (≥ 38 °C), n (%)	20 (62.5%)	21 (63,5%)
Blood in stool, n (%)	0	1 (2.9%)
Etiology of acute gastroenteritis		
Rotavirus, n (%)	12 (33.3%)	11 (30.6%)
Adenovirus, n (%)	2 (5.5%)	0
Norovirus, n (%)	1 (2.8%)	1 (2.8%)
Salmonella enteritidis, n (%)	1 (2.8%)	1 (2.8%)
Campylobacter spp., n (%)	0	1 (2.8%)
Unknown etiology, n (%)	20 (55.6%)	23 (63.8%)

IQR, interquartile range; sd, standard deviation

Primary and secondary outcomes

The primary and secondary outcome measures are presented in **Table 2**. The duration of diarrhea after randomization was similar in both groups (MD 0.1 h, 95% CI -14.1 to 14.3). The risk of unscheduled intravenous rehydration was similar in the gelatine tannate and placebo groups (RR 0.99; 95% CI 0.78 to 1.25). The number of watery stools per day was similar in both groups throughout the study period (for details – see **Table 2).** In both groups, the risk of vomiting (RR 1.27, 95% CI 0.93 to 1.73), weight gain (MD -59.1 g, 95% CI -133.1 to 15), risk of recurrence of diarrhea 48 h after the intervention (RR 0.12, 95% CI 0.01 to 2.0), and severity of diarrhea according to the Vesikari scale (MD 1.1, 95% CI -0.7 to 2.9) were similar. Adverse effects were similar in both groups (RR 0.6, 95% CI 0.17 to 2.45). None of the

participants used concomitant medication. All participants were compliant, i.e. received >75% of the recommended doses were treated as noncompliant.

Table 2. Primary and secondary outcomes

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

IQR, interquartile range; MD, mean or median difference, as appropriate; RR, relative risk; SD, standard deviation

*According to the Bristol Stool Form scale (BSF) or Amsterdam Stool Form (ASF) scale (on BSF scale, numbers 2, 3, 4 and 5; on ASF scale, letters B or C).

DISCUSSION

Principal findings

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

Strengths and limitations

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

Comparison with previous findings

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

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

differently (i.e., percentage of patients with watery stools in the study by Çağan et al. compared with number of watery stools per day in our study). Finally, the method of analysis in the study by Çağan et al. (per-protocol analysis) differed from that used in our study (intention-to-treat analysis).

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

CONCLUSIONS

In summary, gelatine tannate, as dosed in this study, administered as an adjunct to rehydration for the management of acute gastroenteritis in children younger than 5 years was not effective. According to current guidelines,[1 15] the mainstay of treatment for acute gastroenteritis should be oral rehydration with a hypoosmolar solution. Breastfeeding should not be interrupted. Regular feeding should continue with no

dietary changes, including milk. In the hospital setting, in non–breastfed infants and young children, lactose-free feeds can be considered in the management of gastroenteritis**.** Oral zinc supplementation reduces the duration of diarrhea in children 6 months to 5 years of age who reside in countries with a high prevalence of zinc deficiency or who have signs of malnutrition. However, in regions where zinc deficiency is rare, no benefit from the use of zinc is expected. Other effective interventions that may reduce the duration and severity of diarrhea include the administration of specific probiotics such as *Lactobacillus rhamnosus* GG or *Saccharomyces boulardii*, diosmectite, or racecadotril.

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Authors' contribution HS initially conceptualized this study. All authors (MK, DB, ZK, HS) contributed to the study protocol. MK and DB conducted the study. MK analyzed the data under the supervision of HS. HS and MK wrote the manuscript. All authors (MK, DB, ZK, HS) contributed to (and agreed upon) the final version.

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Competing interests None declared.

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

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

Figure 1. Flow diagram

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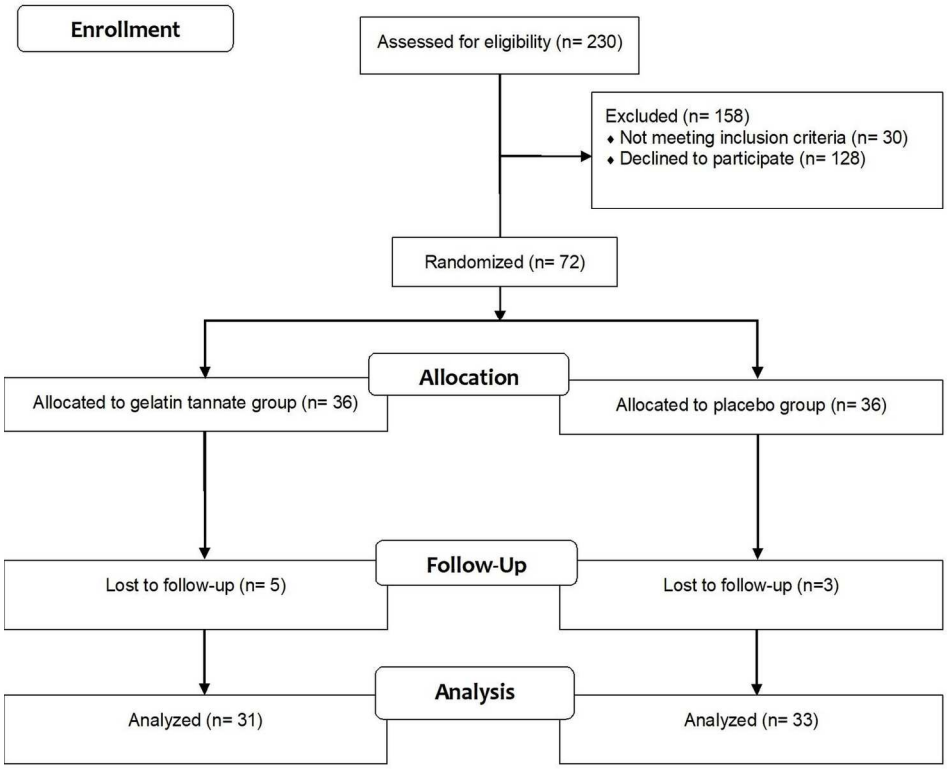
Figure 1. Flow diagram



168x213mm (300 x 300 DPI)

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)	2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	3-4
	2b	Specific objectives or hypotheses	4
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	4
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	-
Participants	4a	Eligibility criteria for participants	5
	4b	Settings and locations where the data were collected	4
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	5-6
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	6
	6b	Any changes to trial outcomes after the trial commenced, with reasons	-
Sample size	7a	How sample size was determined	7-8
	7b	When applicable, explanation of any interim analyses and stopping guidelines	-
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	7
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	7
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	7
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	7
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	7

		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	8
	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	17
	13b	For each group, losses and exclusions after randomisation, together with reasons	17
Recruitment	14a	Dates defining the periods of recruitment and follow-up	6/8
	14b	Why the trial ended or was stopped	-
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	15
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	17
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)	16/ 8-9
	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	9-10
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	13
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	13
Other information			
Registration	23	Registration number and name of trial registry	2
Protocol	24	Where the full trial protocol can be accessed, if available	4
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	14

*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.