Scholars Journal of Applied Medical Sciences
Abbreviated Key Title: Sch J App Med Sci
ISSN 2347-954X (Print) | ISSN 2320-6691 (Online)
Journal homepage: https://saspublishers.com

OPEN ACCESS

Medicine

Gelatin Tannate: A Promising Agent for the Treatment of Diarrhea in Children with Cancer

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DOI: https://doi.org/10.36347/sjams.2025.v13i06.006 | **Received:** 03.05.2025 | **Accepted:** 10.06.2025 | **Published:** 13.06.2025

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Abstract | **Original Research Article**

Background*:** Acute diarrhea is a frequent and exacerbated side effect in pediatric cancer patients on immunosuppressive therapies, with limited treatment options, especially for the immunocompromised. Gelatin tannate (GT) shows promise in improving stool consistency and shortening diarrhea, but its efficacy and safety in these patients are unclear. ***Objectives: This study assessed GT's effectiveness in treating acute diarrhea in children with cancer, compared to cancer patients not using GT and healthy children using GT. ***Methods***: A retrospective case-control study at a tertiary hospital included children aged 1-18 years with acute diarrhea. Three groups were analyzed: cancer patients not using GT (Group 1), cancer patients using GT (Group 2), and healthy children using GT (Group 3). Stool frequency, Bristol Stool Scale (BSS) scores, and diarrhea duration were assessed. ***Results***: GT significantly improved stool consistency ($p = 0.024$) and reduced diarrhea duration ($p = 0.007$). From day 3 ($p = 0.001$) to day 5 ($p < 0.001$), immunocompromised children (Group 2) and healthy controls (Group 3) had significantly lower BSS scores and faster diarrhea resolution than Group 1. No notable adverse effects occurred. ANOVA showed significant group differences in leukocyte counts ($p < 0.001$), diagnosis ($p < 0.001$), and clinical indicators of diarrhea. ***Conclusions***: GT significantly improves stool consistency and reduces diarrhea duration in pediatric cancer patients, suggesting it is safe and effective treatment. Its non-absorbable nature makes it a potential probiotic alternative for immunocompromised children. Further prospective studies are needed.

Keywords: Gelatin Tannate, Gut Microbes, Bristol Stool Scale, Immunosuppressed, Gut Barrier, Diarrhea.

INTRODUCTION

Diarrhea is one of the major causes of death among children, younger than five years of age. Approximately 1.7 billion children contract diarrhea every year, 525,000 of whom eventually die [1]. Untreated survivors experience dehydration and electrolyte imbalance in the acute phase and malnutrition in the chronic phase. Younger children, and those weaned early, with low parental education levels, and exposed to unsafe water, poor sanitation, and insufficient hygiene are generally particularly prone to diarrheal diseases [2]. Malnourishment or impaired immunity due to primary immunodeficiencies, cancer, cancer treatment, HIV, etc. also increase the risk of life-threatening diarrhea. The condition and its consequences are mostly preventable and preventing or treating dehydration if present represents the mainstay of treatment.

Several guidelines recommend Oral Rehydration Therapy (ORT) as a cost-effective option for most mild-moderate cases, irrespective of the patient's immune status. Prompt initiation of an age-appropriate diet, including breast-feeding for infants, zinc supplementation, and probiotics, is advised and widely used for the treatment and prevention of acute gastroenteritis [3]. Probiotics have even been shown to be beneficial in patients with antibiotic-associated, as well as diarrhea induced by radiation [4, 5]. A meta-analysis comparing the clinical benefits of probiotic supplementation with placebo in adult patients reported that probiotics resulted in decrement in the incidence of diarrhea induced by radiation, although no significant

difference was determined in terms of usage of anti-diarrheal drugs or the Bristol Stool Scale (BSS) [5].

Survival among patients who are immunocompromised due to cancer has increased significantly over recent decades in line with the development of cancer treatments. However, in addition to the benefits of chemotherapeutic agents, they also induce gastrointestinal toxicity in approximately 80% of patients [6]. Chemotherapeutics result in the destruction of enterocytes and changes in the composition of gastrointestinal flora and metabolism of intestinal enzymes. The resulting dysbiosis presents as diarrhea, abdominal bleeding, pain, and alterations in the defense barrier in the intestines, immune function, and absorption of vital nutrients [7]. The type of cancer involved, chemotherapeutic drugs, radiotherapy, neutropenia and immune status, and wide spectrum antibiotics all affect the incidence and severity of diarrhea in these children. Fluorouracil, irinotecan, and tyrosine-kinase inhibitors are some of the drugs most frequently associated with diarrhea [7].

Early recognition and prompt management are essential in order to prevent morbidities, prolonged hospitalization, economic burdens, and life-threatening conditions. The use of probiotics in children with hemato-oncological cancer is contraindicated due to the risk of microorganism translocation into the circulatory system, followed by the development of bacteremia/fungemia, sepsis, and finally multi-organ failure. Invasive infections by *Saccharomyces boulardii*, one of the most widely used probiotic agents worldwide, have been reported in such patients [8-10]. A study of 43 patients with *Lactobacillus* bacteremia reported hemato-oncological malignancies during follow-up in six cases [11].

Gelatin tannate (GT) has recently emerged as an option in the treatment of diarrhea. This consists of a combination of tannic acid, with known antibacterial, anti-inflammatory, and antiparasitic properties, and a gelatin structure that protects the tannic acid against bacterial fermentation or degradation during its gastrointestinal passage [12]. It does not pass into the systemic circulation, acts locally, and constitutes a fairly reliable agent with no undesirable side-effects [12]. Previous clinical studies have revealed that GT reduces the frequency of defecations and increases the consistency of stool in children with diarrhea [13-15]. However, although GT has not yet been studied in a clinical trial in immunocompromised patients, its use has been anecdotally described as quite successful in our clinic, with no obvious significant side-effects. It may thus represent an effective and reliable treatment option in this patient group. In this study we aimed to investigate the efficacy and safety of GT in children with cancer.

MATERIALS AND METHODS

This case-control study which was performed retrospectively in our tertiary hospital among children with diarrhea aged 1-18 years between 01 September 2019, and 01 September 2021. The children had three or more loose or watery stools per day for the previous 24-72 hours. Children with cancer followed up in the pediatric hematology-oncology department and otherwise healthy children (with no malignity of any kind) with similar sociodemographic characteristics followed up in the pediatric infectious diseases department were included in the research.

- Children with cancer not using GT in the department of pediatric hematology-oncology (n=32) constituted Group 1.
- Children with cancer using GT in the department of pediatric hematology-oncology (n=33) constituted Group 2.
- Children without cancer attending the pediatric infectious diseases department, all of whom were using GT (n=30), represented Group 3.

The children in Group 1 received only their routine medications, while those in groups 2 and 3 received GT sachets/capsules (Tasectan®) four times a day for five days. All patients received intravenous hydration, zinc supplementation (1-3 mg/kg/day), and a diarrhea diet appropriate to their age, body weight, and blood biochemistry.

We excluded the children with shock or requiring inotropic drug support, with persistent/chronic diarrhea, who were started on GT later than the 72nd hour of diarrhea, who has experienced a previous diarrhea episode during the previous two weeks, concurrently using any probiotics or medications influencing the gastrointestinal absorption or motility (for healthy children), or with any other chronic diseases (such as chronic renal, liver, or lung diseases, primary immunodeficiency, and severe malnutrition) from the study.

The patients' data were retrieved retrospectively from the written medical records and hospital digital information system. Age, gender, accompanying symptoms (nausea, abdominal pain, vomiting, fever, rhinorrhea, cough, and skin eruptions), body weight, physical examination findings, CDC and modified Vesikari scores on admission, daily stool frequencies and BSS scores on days 1, 2, 3, 4, and 5, and stool properties were recorded. Total duration of diarrhea in all patients was calculated until their BSS scores decreased to lower than 5 [16]. Additionally, the underlying disorder, immunosuppressive drugs (types and durations until the specific diarrhea episode), antibiotic usage, the incidence of bacteremia development during the study period, and levels of immunoglobulins (immunoglobulin A, M, and G) were recorded for group 1 and 2 patients.

Stool analysis results, including microscopic examinations (for the presence of leukocytes, erythrocytes, and parasitic infestations), rotavirus-adenovirus antigens, culture (for *Salmonella*, *Shigella*, and *Campylobacter* spp.), and PCR tests for *Clostridium difficile* toxin A and B in selected patients were also recorded.

The patients in each group were compared with one another in terms of numbers of stools and BSS scores on days 1, 2, 3, 4, and 5 and with regards to the total diarrhea duration (in days). The numbers of patients with diarrhea persisting on the fifth day of the study in each group were also compared.

Local ethical committee approved the study protocol (protocol and decision number 2022/21 – 08 dated 27/01/2022).

Statistical analyses were performed on Statistical Package for Social Science (SPSS) (IBM Corp. released 2012. IBM SPSS Statistics for Windows, version 21.0. Armonk, NY, USA). Mean±standard deviation, percentage, and frequency were used to show descriptive statistics. The compatibility of continuous variables with normal distribution was evaluated by means of descriptive statistics, steepness and skew coefficients, histograms, and the Shapiro-Wilk test. We used chi-square test to analyze the categorical data, ANOVA if the data were compatible with normal distribution for variance analysis (Tukey's test if the variances were homogeneous for post-hoc evaluation and the Tamhane test if not), and the Kruskal Wallis H test if the data were not normally distributed (Dunn's test for post-hoc evaluation). The type I error level was determined as 0.05.

RESULTS

The children's mean ages were 9.1±4.7, 5.8±4.1, and 6.7±4.6 years in groups 1, 2, and 3, respectively (p=0.01). The parameters such as gender, body weight, initial stool properties (number, consistency, and presence of macroscopic blood or mucus), accompanying symptoms, and degree of dehydration (clinical dehydration score and modified Vesikari score) on admission were not statistically significantly different between the groups (p>0.05). Uthe underlying disorder, types of chemotherapeutic, antibiotic usage, or immunoglobulins levels were not significantly different between groups 1 and 2 (p>0.05). The results of the stool analyses in the study patients on admission are shown in Table 1. Intergroup comparisons revealed no statistically significant differences. No bacteria growth was observed in blood cultures from any of the study group patients.

Comparison of groups 1, 2, and 3 revealed the following:

- The number of stools on each day were similar between the groups. However, the proportions of patients whose diarrhea had resolved differed significantly at the end of the fifth day (15[46.9%], 22[66.7%], and 25[83.3%], in groups 1, 2, and 3, respectively, p<0.0001) (Table 2).
- No difference was observed in mean BSS scores between the groups on days 1 and 2 (Figure 1, Table 2).
- On day 3, Group 3 patients registered a lower mean BSS score than those in Group 1 (4.5±1.1 vs. 5.5±0.9), and mean BSS scores were also lower in Group 2 than in Group 1 (4.8±1.0 vs. 5.5±0.9) (p=0.001).
- On day 4, Group 3 patients registered a lower mean BSS score than those in Group 2 patients (3.2±1.5 vs. 4.1±1.0), and Group 2 patients lower mean BSS score than those in Group 1 (4.1±1.0 vs. 5.0±1.4) (p<0.0001).
- On day 5, Group 3 patients registered a lower mean BSS score than those in Group 1 (2.6±1.2 vs. 4.5±1.8) (p<0.0001).
- The mean of total duration of diarrhea also differed between the groups (5.0±1.9, 4.5±1.8, and 3.6±1.3 days, respectively, p=0.007).

No obvious complication or mortality related to GT treatment was observed during the study period.

Table 1: Stool Analysis Results on Admission in the Study Population

	Group 1 (n=32, %)	Group 2 (n=33, %)	Group 3 (n=30, %)	p
Presence of leukocytes	7(26.9)	11(42.3)	8(30.8)	0.52
Presence of erythrocytes	2(25.0)	2(25.0)	4(50.0)	0.51
Presence of adenovirus	2(20.0)	3(30.0)	5(50.0)	0.48
Presence of rotavirus	2(20.0)	2(20.0)	6(60.0)	0.19
Growth in culture[a]	2(40.0)	3(60.0)	0(0)	1.00
Presence of parasites[b]	0(0)	1(33.3)	2(66.6)	0.30
Presence of *Clostridium difficile*	1(50)	1(50)	0(0)	1.00

GT, gelatin tannate
Group-1, Children with cancer who did not use GT
Group-2, Children with cancer who used GT
Group-3, Children without cancer who used GT
[a] *Salmonella* spp. in two patients, *Shigella* spp. in three
[b] *Entamoeba histolytica* in three patients

Table 2: Bristol Stool Scale Scores of Children with Diarrhea by Groups during the Study Period

	Group 1 (n=32, %)	Group 2 (n=33, %)	Group 3 (n=30, %)	p
Bristol Stool Scale (mean±SD)				
1st day	5.9±0.8	6.0±0.8	6.2±0.7	0.30
2nd day	5.7±0.8	5.4±0.8	5.4±0.7	0.28
3rd day	5.5±0.9	4.8±1.0	4.5±1.1	**0.001**[a]
4th day	5.0±1.4	4.1±1.0	3.2±1.5	**<0.0001**[a]
5th day	4.5±1.8	3.7±1.2	2.6±1.2	**<0.0001**[b]
Diarrhea on the 5th day				
Stopped	15(46.9)	22(66.7)	25(83.3)	
Decreased	5(15.6)	8(24.2)	5(16.7)	
Persisted	12(37.5)	3(9.1)	0	**<0.0001**[c]
Duration of diarrhea (days, mean±SD)	5.0±1.9	4.5±1.8	3.6±1.3	**0.007**[d]

GT, gelatin tannate; SD, standard deviation
Group 1, Children with cancer who did not use GT
Group 2, Children with cancer who used GT
Group 3, Children without cancer who used GT
[a] Group 3 vs Group 1 and Group 2 vs Group 1
[b] Group 3 vs Group 2 and Group 2 vs Group 1
[c] Group 3 vs Group 1
[d] Persistence of diarrhea in Group 1 patients and cessation of diarrhea in Group 3 patients

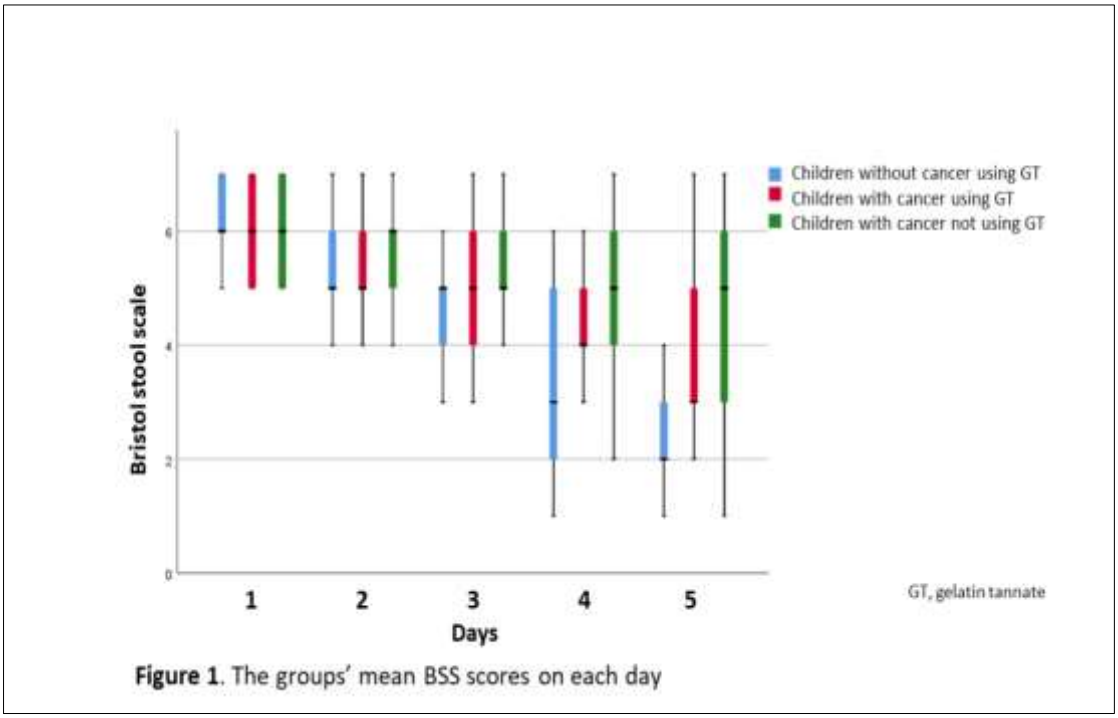

Figure 1: The groups' mean BSS scores on each day

DISCUSSION

Acute diarrhea in children with cancer often worsens rapidly and prompt and effective treatment to avoid severe outcomes is required. Like otherwise healthy children, replacement of fluid and electrolytes losses constitutes the primary treatment. Although prophylactic antimicrobials (ciprofloxacin and metronidazole), a low-fat or fat-modified diet, glutamine, celecoxib, prebiotics, nutritional supplements, and probiotics, absorbents, activated charcoal, and racecadotril have been proposed for prophylaxis or treatment of diarrhea due to either chemotherapy- or radiotherapy in cancer patients, no consensus has been achieved due to the conflicting nature of the reported evidence [7-17]. Probiotics are also generally avoided in children with immune insufficiency, prematurity, short-gut syndrome, central venous catheter use, and cardiac valvular disease. Gelatin tannin is a non-living medical agent that acts as an intestinal mucosal protector and causes no obvious

side-effects. It is one of the most promising medical treatments used as intestinal barrier modulator in cases of acute gastroenteritis. It has been proven to be effective in managing acute diarrhea since it increases mucus barrier activity and helps to restore the intestinal barrier [18]. It is a non-absorbable medical agent with very few or no side-effects and has been reported to exhibit adequate efficiency in clinical studies [13-20]. Similarly present study revealed that GT has shown its potentiality for its use in the treatment of diarrhea in children with cancer.

In this study, the mean duration of diarrhea was shorter among immunocompromised patients who used GT than in those who did not use it. A similar effect of GT has also been shown in immunocompetent patients with diarrhea. In that study, patients using GT also showed greater weight gain after 120 hours of treatment [13]. Mennini *et al*., [19]. reported that ORT plus GT had significantly shortened the mean duration of diarrhea compared to ORT only (76.8±19.2 vs. 108±24.0 h) in children without cancer. Serban & Manolache [20], noted a significantly shorter mean time for stool consistency to return normal in children using GT than in those using other antidiarrheal medications, including probiotics such as *Saccharomyces boulardii* or *Lactobacillus* GG. Those authors also reported that analysis revealed a lower risk of diarrhea after 72 hours of GT treatment compared to the other medications in healthy children.

Another important finding of this study is that five-day GT treatment resulted in fewer patients experiencing persistence of diarrhea. Similarly, fewer immunocompetent patients using GT in previous studies still had diarrhea at the end of 12, 24, 96, and 120 hours compared to patients not using GT [13, 14]. Previous studies have reported a significantly lower proportion of diarrhea persistence by the 72nd hour of treatment among immunocompetent children using GT compared to those using ORT only or other antidiarrheal medications [19, 20].

Although stool weight or volume are more objective indicators of diarrhea, these are not practical for use in the clinical setting. Stool frequency and consistency are therefore more frequently used. Three or more loose or liquid stools per day and stool consistency corresponding to types 6 and 7 on the Bristol stool chart are defined as diarrhea [21]. In the present study, GT treatment resulted in a decrease in BSS scores from the third day on but had no effect in the first two days. However, on the third day, both immunocompetent and immunosuppressive patients using GT registered lower BSS scores than immunosuppressive patients not using it. On the fourth day, the lowest BSS scores were observed among immunocompetent patients using GT. By the fifth day, a marked difference was determined only between immunocompetent patients using GT and immunosuppressive patients not using it. Although no significant difference attributable to GT treatment in immunocompetent children had previously been reported at 120 hours, another study showed that a significant improvement in bowel consistency, and thus stool consistency, was achieved with GT plus ORT compared to ORT only at 48 hours [13-19]. Similarly, Serban & Manolache [20], reported a beneficial effect of GT on normalization of stool consistency starting from the 12th hour until the end of the study (72 hours) compared to other antidiarrheal medications, such as one or more of diosmectite, racecadotril, and *Saccharomyces boulardii* or *Lactobacillus* GG.

Previous studies have shown beneficial effects of GT supplementation on daily stool frequencies at various time intervals in immunocompetent children. However, in the present study, no significant difference was observed between the groups in terms of daily stool numbers [13-20]. Other beneficial effects have also emerged from studies involving immunocompetent children. Using GT has been shown to result in a decrease in nausea and abdominal pain starting after 24 hours and in fever after 36 hours [14], and in more weight gain at the end of 120 hours of treatment compared to use of ORT only [13]. However, these symptoms were beyond the scope of this study in immunocompromised children. Çagan *et al*., [14], reported that GT was advantageous in terms of direct costs per patient (drugs, diagnostic tests, and consultations). This was not examined in the present study but considering the difficulties in the treatment and management of the children with cancer, this is a valuable finding, and further investigation in randomized controlled trials may be even more illuminating.

Gelatin tannin is well-tolerated. Safety was similar in all the groups in the present research, and no obvious complication related to GT treatment was observed. Mennini *et al*., [19], reported nausea approximately 20 min after administration of GT in one patient only. Consistent with the present study, previous reports have not described any side-effects due to GT treatment in immunocompetent children [13-20].

This study is particularly valuable in demonstrating the importance of GT, which has been shown to be efficient in the treatment of diarrhea in immunosuppressed patients, with almost no side-effects. However, some limitations should also be considered when evaluating the results. One of the most important of these is that because of the retrospective design of the study, not all data, such as other symptoms including vomiting, abdominal pain, and fever, could be examined. The study population was also not sufficiently large to permit the children to be analyzed in terms of solid tumors and hematological malignancies, individually. Additionally, it was also not possible to separately evaluate the efficacy of GT on specific infectious agents and non-infectious causes. Moreover, since many of the etiological agents involved in diarrhea, such as norovirus

and enterovirus, could not be examined, the effects of GT on these infectious agents could not be assessed. Similarly, PCR tests for *C. difficile*, an important cause of diarrhea in immunocompromised patients, were not performed in most cases. However, the results of the study suggest that GT is effective against diarrhea of all causes in children with cancer.

In conclusion, GT shortened the duration of diarrhea and accelerated recovery when used in acute diarrhea attacks from various causes in pediatric patients with cancer. The fact that no side-effects were observed, and that GT was effective in this group of patients, in whom probiotics could not be used, suggests that it may represent a good therapeutic option for these patients. Further larger and prospective clinical trials evaluating the effects of GT not only on specific pathogens and but also non-infectious causes of diarrhea in children with cancer are now needed.

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