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Adjunctive highly dispersed silicon dioxide for nausea and fever in adults with acute watery diarrhea: A two-center randomized, double-blind, placebo-controlled trial

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Abstract

Adult acute infectious diarrhea commonly presents to emergency departments (EDs); oral rehydration does not relieve associated nausea or fever. Highly dispersed silicon dioxide is a non-absorbable intestinal sorbent that binds microbial toxins, but adult symptom data are limited. We aimed to determine whether adjunctive highly dispersed silicon dioxide, added to standard oral rehydration therapy, accelerates the resolution of nausea and fever in adults with acute watery diarrhea presenting to the ED. In a randomized, double-blind, placebo-controlled, two-center trial, adults aged 18-65 years with acute watery diarrhea (onset < 48 h), nausea, and recent febrile symptoms were randomized 1:1 to 3 g of highly dispersed silicon dioxide (Polisorb®) three times daily or matched microcrystalline cellulose placebo for ≤5 days with standard oral rehydration. The primary endpoint was change in nausea Numeric Rating Scale (NRS, 0-10) from baseline to 72 hours, analyzed by analysis of covariance (ANCOVA) on the intention-to-treat population. Secondary endpoints included fever score, time to first afebrile measurement, ≥ 2-point NRS reduction, cumulative duration of temperature ≥ 38.0°C, and safety. Of 136 patients randomized (68 per arm), 129 (94.9%) completed the 72-hour assessment. The adjusted between-group difference in nausea NRS at 72 hours favored silicon dioxide (-1.9 points, 95% confidence interval (CI) -2.5 to -1.3; $p < 0.001$). At 72 hours, ≥ 2-point nausea recovery occurred in 88.2% versus 64.7% ($p = 0.001$). Median time to afebrile state was 22.0 versus 36.0 hours (hazard ratio (HR) 1.79, 95% CI 1.27 – 2.52; $p < 0.001$), and cumulative duration of temperature ≥ 38.0°C was reduced by approximately 8 hours. Adverse events were mostly mild, with no serious events attributed to the study product. Adjunctive highly dispersed silicon dioxide improved nausea and accelerated defervescence versus placebo in adults with acute watery diarrhea, with comparable safety. Larger registered trials are warranted.

Keywords: Diarrhea; silicon dioxide; enterosorption; nausea; fever; emergency service, hospital

Introduction

Acute infectious diarrhea remains one of the most common reasons for unscheduled medical contact and a major driver of global morbidity. The Global Burden of Disease Study attributed an estimated 1.6 million deaths and approximately 2.4 billion incident episodes to diarrheal diseases worldwide in 2016 [1,2]. Although mortality predominates in low-resource settings, adult acute gastroenteritis is also a frequent reason for emergency department (ED) attendance, lost workdays, and avoidable admissions in high- and middle-income countries, including Türkiye, where it shows two seasonal peaks: a viral (largely norovirus) peak in late winter-early spring and a bacterial, foodborne/waterborne peak in late summer-autumn [3-5].

Most cases are viral (norovirus, rotavirus), followed by bacterial and, less often, parasitic agents [4,6]. Microbial toxins and local inflammation activate enterocyte secretory pathways and vagal and area postrema afferents, producing the nausea, anorexia,

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and fever that often dominate the early clinical picture and limit oral rehydration in the ED, beyond fluid and electrolyte loss alone [6,7].

Despite extensive guidance, the pharmacological armamentarium for adult acute watery diarrhea remains limited. Oral rehydration therapy is the cornerstone of treatment but does not target the toxic load and has only modest effects on nausea and fever [4,8,9]. Antimicrobial therapy is reserved for selected infections and discouraged in uncomplicated watery diarrhea because of resistance, hemolytic-uremic syndrome, and microbiota disruption [4,6,10,11]. Loperamide reduces stool frequency but is contraindicated in invasive disease and offers no benefit for nausea or fever [4]. Probiotics and zinc show modest, mostly pediatric effects [12-14]; racecadotril reduces stool output and duration but has limited nausea/fever data [15,16]; and clay-derived adsorbents such as diosmectite shorten illness duration, again mainly in children [17-20]. Whether sorbent therapy meaningfully relieves nausea and fever — the symptoms most often prompting ED reassessment — has rarely been tested in adequately powered adult trials.

Enterosorbents are orally administered, non-absorbable agents that physically bind microbial cells, toxins, and inflammatory mediators within the intestinal lumen, reducing the toxic load on a damaged mucosa [21]. Highly dispersed silicon dioxide has a very high specific surface area (up to 300 m^2/g) and high non-selective adsorption capacity for bacterial and viral antigens and lipopolysaccharide; because it is not absorbed, its mechanism is purely intraluminal, with bound material eliminated in feces and no systemic exposure [21-23]. Beyond toxin sequestration, it may stabilize the mucus layer and support gut-barrier recovery — biologically plausible substrates for relieving toxin- and cytokine-driven nausea and fever, though these effects have not been confirmed in clinical-outcome trials [7,21,22].

The clinical efficacy of silicon dioxide-based enterosorbents has been best characterized for the duration of diarrhea itself. Tieroshyn et al. showed that high-dispersion silicon dioxide reduced median time to recovery by ~0.9 days and lowered antibiotic initiation [22], and a recent multicenter ED trial reported a ~51-hour reduction in recovery time with faster improvement of stool consistency and gastrointestinal symptoms [5]; a chemically distinct silicon-based sorbent gave similar results in primary care [24]. However, these trials were designed around stool-related endpoints, and structured assessment of nausea with validated scales and quantitative tracking of fever has rarely been reported [18,19,22]. Because nausea strongly predicts failed oral rehydration and secondary ED attendance, and persistent fever often triggers unnecessary antibiotics [4,25], a trial dedicated to these symptoms in adult ED patients is needed.

Against this background, we designed a randomized, double-blind, placebo-controlled trial to test whether adjunctive highly dispersed silicon dioxide, administered together with standard oral rehydration therapy, accelerates the resolution of nausea and fever in adults presenting to the ED with acute watery diarrhea. We hypothesized that, compared with placebo, highly dispersed silicon dioxide would produce a clinically meaningful greater reduction in nausea severity at 72 hours, shorten the time to afebrile state, and increase the proportion of patients achieving symptom recovery within the first three days of treatment, with a safety profile comparable to that of placebo.

Material and Methods

Study Design and Oversight

This was an investigator-initiated, randomized, double-blind, placebo-controlled, parallel-group, two-center clinical trial conducted in the adult EDs of two participating centers in Türkiye. Recruitment took place between 5 March 2026 and 22 April 2026. The protocol was approved by the Clinical Research Ethics Committee of Ankara Etlik City Hospital (date: 4 March 2026; approval number: AEŞH-EK-2026-049) and conducted in accordance with the Declaration of Helsinki [26] and the principles of Good Clinical Practice. The study was reported in line with the Consolidated Standards of Reporting Trials (CONSORT) recommendations for parallel-group trials [27]; the participant flow diagram is shown in Figure 1, and the CONSORT checklist is provided as supplementary material. The trial was not prospectively registered in an international clinical trials registry; this is acknowledged as a limitation. The full protocol and statistical analysis plan are available from the corresponding author upon reasonable request.

Participants

Adults aged 18-65 years presenting to the ED with acute watery diarrhea (defined as ≥ 3 unformed stools within the preceding 24 hours, with onset within 48 hours of presentation), accompanied by nausea and a history of febrile symptoms (subjective fever, chills, or measured temperature elevation) within the preceding 24 hours, were eligible. Written informed consent was required for inclusion. Exclusion criteria were bloody or mucoid diarrhea; clinical signs of severe dehydration (per World Health Organization criteria) requiring intravenous resuscitation as the primary intervention; antibiotic exposure within the previous four weeks; known chronic gastrointestinal disease (including inflammatory bowel disease, celiac disease, chronic pancreatitis, and previous bowel resection); pregnancy or breastfeeding; active malignancy or current immunosuppressive therapy; severe hypotension (systolic blood pressure < 90 mmHg) or other clinical instability; and inability or unwillingness to comply with telephone follow-up.

Randomization and Blinding

Eligible patients were randomized 1:1 to highly dispersed silicon dioxide or placebo using a computer-generated allocation sequence with permuted blocks of variable size (4 and 6) and stratification by recruitment center. The allocation sequence was prepared by an independent statistician not involved in clinical assessments. Sequentially numbered, opaque, sealed containers identical in size, weight, color, taste, and texture were prepared by the hospital pharmacy of the coordinating center

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and labeled solely with a study code and randomization number. Investigators, outcome assessors, treating physicians, and participants remained blinded to allocation throughout the study and during database lock; the randomization key was disclosed only after final data verification.

Interventions

Patients allocated to the active arm received highly dispersed silicon dioxide (Polisorb®, Polisorb JSC, Russia; locally licensed in Türkiye by Galepharma İlaç A.Ş.) at the licensed adult dosage of 3 g reconstituted in 100-150 mL of water, administered three times daily. The control arm received an identically appearing microcrystalline cellulose placebo prepared and packaged to be indistinguishable from the active product in appearance, taste, and reconstitution behavior. Both products were taken orally for up to five days or until full recovery, whichever came first, with at least a two-hour interval from any concomitant oral medication, in line with the licensed prescribing information. All participants in both arms received standard low-osmolarity oral rehydration solution and routine supportive care according to local ED protocols, which remained at the discretion of the treating emergency physician [4,9]. Concomitant antiemetics, antipyretics, intravenous fluids, and antibiotics were permitted when clinically indicated and were systematically recorded as concomitant medications, including the agent class, dose, route, and timing.

Outcomes

Assessments were performed at baseline (Day 0, ED admission) and through structured telephone interviews at 12, 24, 48, and 72 hours, with a final assessment on Day 5. Nausea severity was measured on a Numeric Rating Scale (NRS) ranging from 0 (no nausea) to 10 (worst imaginable nausea); scores were classified as none (0), mild (1-3), moderate (4-6), or severe (7-10) [28]. Body temperature was measured tympanically at baseline by trained ED nursing staff using calibrated devices, and categorized using a five-point fever scale: afebrile (< 37.3°C, score 0), subfebrile (37.3 – 37.9°C, score 1), mild fever (38.0 – 38.4°C, score 2), moderate fever (38.5 – 38.9°C, score 3), and high fever (≥ 39.0°C, score 4). Fever was defined a priori as ≥ 38.0°C. Baseline temperature was recorded for all participants at presentation; eligibility was based on the history of febrile symptoms rather than on a specific measured temperature threshold, reflecting the clinical reality that patients with acute gastroenteritis frequently present after self-administration of antipyretics or after spontaneous fluctuation of body temperature. To support reliable post-discharge measurement, participants were issued a standardized tympanic thermometer (uniform model within each center) at enrollment together with written and verbal instructions on consistent technique (same ear, ≥ 30-minute interval after eating, drinking, or physical activity, and recording before any antipyretic intake whenever possible). At each scheduled telephone contact, participants reported the most recent measured temperature, the time of measurement, and the timing and dose of any antipyretic intake. The first afebrile measurement (< 37.3°C) was defined operationally as the earliest reported temperature below this threshold during scheduled or interim self-measurements; the interval-based nature of these data is acknowledged in the limitations.

The pre-specified primary endpoint was the change in nausea NRS score from baseline to 72 hours, with a reduction of ≥ 2 points considered the minimal clinically important difference. This threshold is consistent with the minimum clinically significant difference in nausea severity established specifically for ED populations, in which changes of approximately 15-22 mm on a 0-100 mm visual analog scale — corresponding to roughly 1.5-2.2 points on a 0-10 scale — have been reported as clinically meaningful [29,30]. Secondary endpoints comprised the change in fever score over time; the time from treatment initiation to the first recorded afebrile measurement (< 37.3°C); the proportions of patients with ≥ 2-point NRS reduction at 12, 24, 48, and 72 hours; the cumulative duration of temperature ≥ 38.0°C; patient-reported treatment satisfaction (5-point Likert scale) on Day 5; and safety, comprising all-cause and treatment-related adverse events, serious adverse events, and treatment discontinuations. Adverse events were graded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0, and recorded by investigators blinded to allocation. Each adverse event was further attributed by a blinded clinician to one of three causality categories (related, possibly related, unrelated).

Sample Size

The sample size was calculated a priori for the pre-specified primary endpoint—the between-group difference in change in nausea NRS from baseline to 72 hours—within an analysis of covariance (ANCOVA) framework. Assuming a clinically relevant difference of 1.5 points on the 0-10 NRS, a common between-group standard deviation of 1.8, a baseline-to-72-hour residual correlation of 0.4, two-sided $\alpha = 0.05$, and statistical power of 0.95, a minimum of 62 evaluable participants per arm (124 total) was required to detect the pre-specified treatment effect using ANCOVA adjusted for baseline NRS. The same total sample size additionally provides ≥ 0.95 power to detect a moderate treatment-by-time effect (Cohen $f = 0.25$) on the longitudinal nausea NRS trajectory across six measurement occasions (baseline; 12, 24, 48, 72 hours; Day 5) under a repeated-measures framework with within-subject correlation of 0.5, ensuring adequate power for the planned supportive longitudinal mixed-effects model for repeated measures (MMRM) analysis. To accommodate an anticipated 10% attrition rate, the total target enrollment was set at 136 participants (68 per arm). All calculations were performed using G*Power v3.1.9.

Statistical Analysis

Analyses were performed using SPSS v22.0 (IBM Corp., Armonk, NY, USA) and R v4.3 (R Foundation for Statistical Computing, Vienna, Austria). The Shapiro-Wilk test was used

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to assess normality. Continuous variables were summarized as mean ± standard deviation or median (interquartile range, IQR), as appropriate, and categorical variables as frequencies (percentages). Between-group comparisons used Student's t-test or the Mann-Whitney U test for continuous variables and the χ^2 test or Fisher's exact test for categorical variables.

The primary efficacy analysis was conducted on the intention-to-treat (ITT) population, defined as all 136 randomized patients. The pre-specified primary analysis of the primary endpoint—change in nausea NRS from baseline to 72 hours—was an ANCOVA model with the 72-hour NRS as the dependent variable and treatment arm, baseline NRS, and recruitment center as covariates; the adjusted between-group mean difference (MD) and 95% confidence interval (CI) were derived from the treatment-arm coefficient. To preserve the ITT principle in the presence of missing 72-hour values, multiple imputation (m = 20) by chained equations was performed under a missing-at-random assumption as the primary handling of missing data, with baseline NRS, intermediate NRS values (12, 24, and 48 hours), age, sex, recruitment center, and baseline temperature as auxiliary variables; estimates were pooled across imputations using Rubin's rules. A complete-case ANCOVA restricted to participants with observed 72-hour data (n = 129) was performed as a sensitivity analysis. As a pre-specified supportive longitudinal analysis, an MMRM was fitted with treatment, time, treatment-by-time interaction, baseline NRS, and recruitment center as fixed effects, an unstructured covariance matrix (with compound symmetry as a pre-specified fallback in case of non-convergence), and patient as a random effect; this model uses all available longitudinal observations to characterize the trajectory of effect across the six time points. Results across the three approaches were compared and interpreted concordantly.

To address the potential confounding effect of permitted concomitant medication, a pre-specified sensitivity analysis re-estimated the primary ANCOVA with additional adjustment for any antiemetic and antipyretic use during the 72-hour follow-up window. Longitudinal patterns of fever score were examined using mixed-effects linear models with subject-level random intercepts, fixed effects for treatment arm, time, and the treatment-by-time interaction, and adjustment for baseline value, age, sex, and center; the ordinal nature of the fever score was additionally explored using a mixed-effects ordinal regression as a secondary sensitivity analysis. Time-to-event endpoints (time to afebrile state, time to nausea recovery) were analyzed using Kaplan-Meier estimates compared with the log-rank test, and Cox proportional hazards regression with hazard ratios (HR) and 95% CIs; the proportional hazards assumption was tested using Schoenfeld residuals. Because data on temperature were captured at scheduled time points, the time-to-event analyses are interval-based and were therefore complemented by a parametric interval-censored survival model as a sensitivity check. The number needed to treat (NNT) and its 95% CI were calculated from the absolute risk difference using Wilson score-based intervals. Two-sided p-values < 0.05 were considered statistically significant. No interim analyses were performed and no formal adjustment for multiple comparisons was applied to secondary endpoints, which are accordingly reported as supportive evidence.

Results

Participant Flow and Baseline Characteristics

Between 5 March 2026 and 22 April 2026, a total of 178 patients were assessed for eligibility, of whom 42 were excluded (24 did not meet inclusion criteria, 11 met exclusion criteria, and 7 declined participation). The remaining 136 participants were randomized to highly dispersed silicon dioxide (n = 68) or placebo (n = 68). Four participants in the silicon dioxide group and three in the placebo group were lost to telephone follow-up between the 24-hour and 72-hour assessments, yielding 129 participants (94.9%) with observed 72-hour primary endpoint data. All 136 randomized participants were included in the ITT primary ANCOVA, with missing 72-hour values addressed by multiple imputation (m = 20) under a missing-at-random assumption; the supportive MMRM additionally incorporated all available intermediate observations to characterize the longitudinal trajectory. No participants withdrew because of adverse events. The participant flow is summarized in Figure 1.

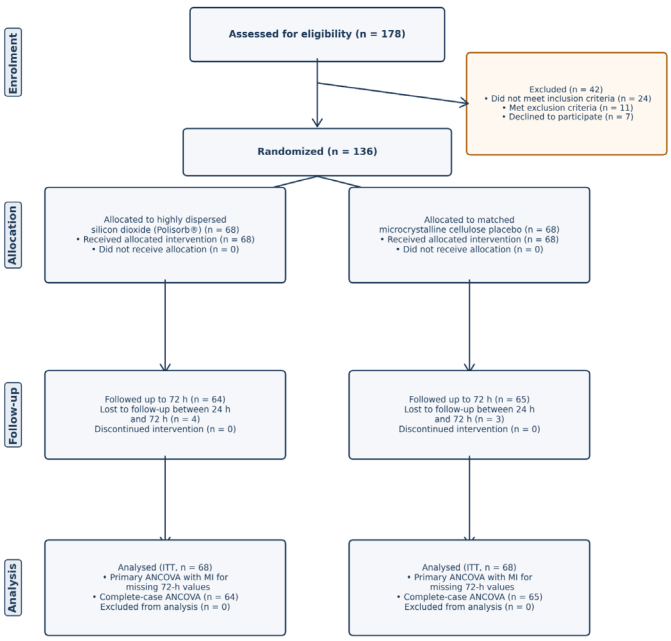


Figure 1. CONSORT 2010 flow diagram showing screening, exclusions, randomization, allocation, follow-up, and intention-to-treat analysis. Of 178 adults assessed for eligibility, 42 were excluded (24 did not meet inclusion criteria, 11 met exclusion criteria, and 7 declined to participate); 136 were randomized 1:1 to highly dispersed silicon dioxide (n = 68) or matched microcrystalline cellulose placebo (n = 68). Seven participants (4 silicon dioxide, 3 placebo) were lost to telephone follow-up between the 24-hour and 72-hour assessments. All 136 participants were included in the intention-to-treat (ITT) primary ANCOVA with multiple imputation (m = 20) for missing 72-hour values; the complete-case ANCOVA included 64 (silicon dioxide) and 65 (placebo) participants with observed 72-hour data. ITT, intention-to-treat; MI, multiple imputation; ANCOVA, analysis of covariance.

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Baseline demographic and clinical characteristics were well balanced between groups (Table 1). The mean age was 38.4 ± 12.6 years, 53.7% of participants were women, and the median time from symptom onset to enrollment was 24.0 hours (IQR 18.0 – 34.0). At presentation, mean tympanic temperature was 38.4 ± 0.5°C, mean nausea NRS was 6.7 ± 1.4, and the median number of unformed stools in the preceding 24 hours was 6 (IQR 5 – 8). Vomiting was reported by 64.0% of participants. Pre-ED antipyretic use (within the 12 hours preceding presentation) was reported by 27.9% of participants in the silicon dioxide arm and 30.9% in the placebo arm; pre-ED antiemetic use by 5.9% and 7.4%, respectively. There were no clinically meaningful differences between treatment arms in vital signs, biochemistry, or self-reported symptom severity.

Table 1. Baseline demographic and clinical characteristics of the study population

Characteristic	Silicon dioxide (n = 68)	Placebo (n = 68)	p-value
Age, years (mean ± SD)	37.9 ± 12.4	38.9 ± 12.8	0.65
Female sex, n (%)	37 (54.4)	36 (52.9)	0.86
Body mass index, kg/m² (mean ± SD)	26.1 ± 3.7	25.8 ± 3.9	0.66
Time since symptom onset, h (median, IQR)	23.0 (17.0 – 32.0)	25.0 (19.0 – 35.0)	0.41
Tympanic temperature, °C (mean ± SD)	38.4 ± 0.5	38.3 ± 0.5	0.41
Fever scale ≥ 2, n (%)	55 (80.9)	53 (77.9)	0.67
Nausea NRS (mean ± SD)	6.8 ± 1.3	6.7 ± 1.4	0.71
Severe nausea (NRS 7-10), n (%)	30 (44.1)	29 (42.6)	0.86
Vomiting present, n (%)	44 (64.7)	43 (63.2)	0.86
Vomiting episodes in past 24 h (median, IQR)	3 (2 – 4)	3 (2 – 4)	0.79
Unformed stools in past 24 h (median, IQR)	6 (5 – 8)	6 (5 – 8)	0.84
Heart rate, bpm (mean ± SD)	94.6 ± 11.2	93.8 ± 10.7	0.67
Systolic blood pressure, mmHg (mean ± SD)	118.4 ± 12.5	119.7 ± 11.9	0.54
Pre-ED antipyretic use, n (%)	19 (27.9)	21 (30.9)	0.71
Pre-ED antiemetic use, n (%)	4 (5.9)	5 (7.4)	1.00
IV fluid at ED triage, n (%)	12 (17.6)	14 (20.6)	0.67
Recruitment at Center 1, n (%)	42 (61.8)	43 (63.2)	0.86
Recruitment at Center 2, n (%)	26 (38.2)	25 (36.8)	0.86

p-values from Student's t-test, Mann-Whitney U test, χ^2 test, or Fisher's exact test as appropriate. Abbreviations: bpm, beats per minute; ED, emergency department; IQR, interquartile range; NRS, numeric rating scale; SD, standard deviation.

Primary Endpoint: Change in Nausea Severity at 72 Hours

At 72 hours, the mean nausea NRS had declined from 6.8 ± 1.3 to 1.5 ± 1.5 in the silicon dioxide group and from 6.7 ± 1.4 to 3.3 ± 1.7 in the placebo group, corresponding to mean within-group reductions of -5.3 ± 1.6 and -3.4 ± 1.8 points, respectively. In the pre-specified primary ITT ANCOVA (multiply-imputed dataset, n = 136), adjusted for baseline NRS and recruitment center, the between-group adjusted MD favored silicon dioxide by -1.9 points (95% CI -2.5 to -1.3; $p < 0.001$). The complete-case ANCOVA (n = 129; adjusted MD -1.9, 95% CI -2.5 to -1.3) produced an essentially identical estimate. The pre-specified sensitivity ANCOVA additionally adjusted for any antiemetic or antipyretic use during the 72-hour follow-up window also yielded a closely similar effect (adjusted MD -1.8, 95% CI -2.4 to -1.2; $p < 0.001$), indicating that the observed benefit was not attributable to imbalance in concomitant symptomatic medication. The supportive MMRM longitudinal analysis confirmed a significant treatment-by-time interaction ($F = 14.6$; $p < 0.001$), demonstrating a faster trajectory of nausea resolution in the active arm across all post-baseline time points (Figure 2A; Table 2).

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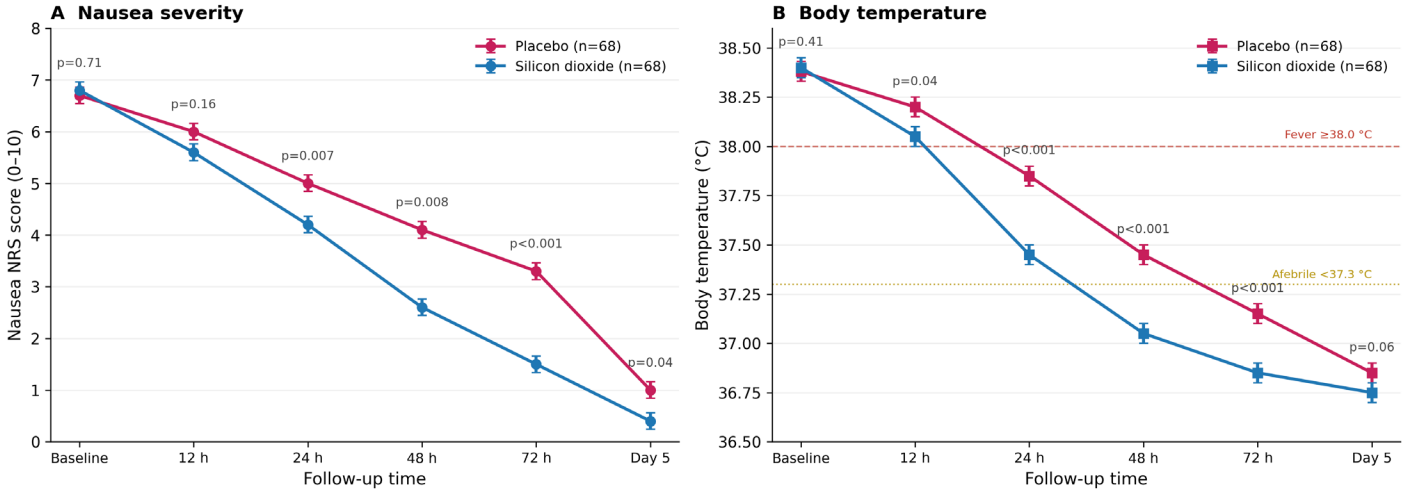


Figure 2. Longitudinal trajectories of (A) nausea severity and (B) body temperature over the follow-up period, by treatment arm. Data points represent group means; error bars represent the standard error of the mean. Per-visit between-group p-values are shown. In panel B, the dashed line indicates the fever threshold (≥ 38.0°C) and the dotted line the afebrile threshold (< 37.3°C). The pre-specified ITT ANCOVA adjusted between-group difference in nausea NRS at 72 hours was -1.9 points (95% CI -2.5 to -1.3; p < 0.001), with a significant treatment-by-time interaction in the MMRM (p < 0.001). Median time to first afebrile measurement was 22.0 versus 36.0 hours; the cumulative duration of temperature ≥ 38.0°C differed by -8.1 hours (95% CI -13.0 to -3.2; p = 0.001).

Table 2. Primary efficacy endpoint (intention-to-treat population)

Endpoint	Silicon dioxide	Placebo	Effect (95% CI)	p
Primary: Δ Nausea NRS at 72 h, ITT ANCOVA (adj. MD)	-5.3 ± 1.6	-3.4 ± 1.8	MD -1.9 (-2.5 to -1.3)	< 0.001
Nausea NRS at 72 h (mean ± SD) [observed n = 64/65]	1.5 ± 1.5	3.3 ± 1.7	MD -1.8 (-2.4 to -1.3)	< 0.001

Abbreviations: adj., adjusted; ANCOVA, analysis of covariance; CI, confidence interval; ITT, intention-to-treat; MD, mean difference; NRS, numeric rating scale; SD, standard deviation; Δ, change from baseline.

Secondary Endpoints

Recovery rates, defined as a ≥ 2-point reduction in nausea NRS from baseline, were higher in the silicon dioxide group at every assessment point (Table 3). At 12 hours, the difference was numerical and not statistically significant (20.6% vs 11.8%; p = 0.16). However, by 24 hours, recovery had occurred in 45.6% of participants in the silicon dioxide arm versus 23.5% in the placebo arm (relative risk [RR] 1.94, 95% CI 1.18 – 3.18; p = 0.007), with the gap widening at 48 hours (72.1% vs 50.0%; RR 1.44, 95% CI 1.10 – 1.89; p = 0.008) and at 72 hours (88.2% vs 64.7%; RR 1.36, 95% CI 1.13 – 1.64; p = 0.001). The NNT to achieve nausea recovery at 72 hours was 5 (95% CI 3 – 10; calculated from the absolute risk difference and Wilson score-based CIs). The Kaplan-Meier curves for time to ≥ 2-point nausea recovery are shown in Figure 3 (right panel).

Fever responded similarly. The mean fever scale score declined from 2.4 ± 0.7 at baseline to 0.4 ± 0.6 at 72 hours in the silicon dioxide group, compared with 2.3 ± 0.7 to 0.9 ± 0.8 in the placebo group (between-group adjusted MD -0.5, 95% CI -0.7 to -0.2; p < 0.001). The mixed-effects ordinal regression sensitivity analysis yielded a directionally consistent treatment effect for the ordinal fever score. The median time to first afebrile measurement (< 37.3°C) was 22.0 hours (IQR 14.0 – 34.0) with silicon dioxide and 36.0 hours (IQR 22.0 – 52.0) with placebo, with significantly faster defervescence in the active arm (log-rank p < 0.001; HR 1.79, 95% CI 1.27 – 2.52; Figure 3, left panel); the parametric interval-censored sensitivity analysis produced a comparable HR (1.76, 95% CI 1.22 – 2.55). The longitudinal trajectory of mean tympanic temperature is shown in Figure 2B. The cumulative duration of temperature ≥ 38.0°C was reduced from a mean of 32.1 ± 14.7 hours in the placebo arm to 24.0 ± 12.8 hours in the silicon dioxide arm (MD -8.1 hours, 95% CI -13.0 to -3.2; p = 0.001). Patient-reported treatment satisfaction on Day 5 was higher in the silicon dioxide group, with 79.4% rating treatment as “good” or “very good” compared with 55.9% in the placebo group (p = 0.004).

Concomitant medication use during the 72-hour follow-up was numerically lower in the silicon dioxide arm. Use of as-needed antiemetics was reported by 16.2% versus 27.9% (p = 0.10), and antipyretic use by 51.5% versus 60.3% (p = 0.30). Antibiotic initiation by the treating physician occurred in 5.9% versus 11.8% of patients (p = 0.23). New requirement for

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intravenous fluids during the follow-up period was recorded in 5.9% versus 11.8% (p = 0.23). None of these differences reached statistical significance, and the study was not powered to detect them. Concomitant treatment use is summarized in Table 4, and detailed primary and secondary efficacy data in Table 2 and Table 3.

Table 3. Secondary efficacy endpoints (intention-to-treat population)

Endpoint	Silicon dioxide	Placebo	Effect (95% CI)	p
Nausea recovery at 12 h, n/N (%)	14/68 (20.6)	8/68 (11.8)	RR 1.75 (0.79 – 3.91)	0.16
Nausea recovery at 24 h, n/N (%)	31/68 (45.6)	16/68 (23.5)	RR 1.94 (1.18 – 3.18)	0.007
Nausea recovery at 48 h, n/N (%) [observed n = 66/67]	49/68 (72.1)	34/68 (50.0)	RR 1.44 (1.10 – 1.89)	0.008
Nausea recovery at 72 h, n/N (%) [observed n = 64/65]	60/68 (88.2)	44/68 (64.7)	RR 1.36 (1.13 – 1.64)	0.001
Δ Fever scale at 72 h (mean ± SD)	-2.0 ± 0.8	-1.4 ± 0.9	MD -0.5 (-0.7 to -0.2)	< 0.001
Time to afebrile state, h (median, IQR); events n/N	22.0 (14.0 – 34.0); 64/68	36.0 (22.0 – 52.0); 60/68	HR 1.79 (1.27 – 2.52)	< 0.001
Cumulative duration of temperature ≥ 38.0°C, h (mean ± SD)	24.0 ± 12.8	32.1 ± 14.7	MD -8.1 (-13.0 to -3.2)	0.001
Treatment rated good/very good, n (%)	54 (79.4)	38 (55.9)	RR 1.42 (1.13 – 1.79)	0.004

The primary endpoint (Δ Nausea NRS at 72 h) is reported on the ITT population (n = 68/68) using ANCOVA adjusted for baseline NRS and recruitment center, with missing 72-hour values addressed by multiple imputation (m = 20) under a missing-at-random assumption; the observed-data complete-case 72-hour denominators (n = 64 silicon dioxide, n = 65 placebo) for direct point estimates are indicated. The MMRM longitudinal analysis is reported as supportive. Nausea recovery proportions through 24 h were computed using the randomized denominator (n = 68 per arm); for later time points, missing observations were addressed conservatively when patients had not reported recovery prior to last contact (sensitivity analyses excluding such patients did not materially change the estimates). Time-to-event analyses are based on the observed time of first afebrile measurement and were complemented by an interval-censored sensitivity analysis (HR 1.76, 95% CI 1.22 – 2.55). Nausea recovery was defined as ≥ 2-point reduction in NRS from baseline; afebrile was defined as tympanic temperature < 37.3°C. Abbreviations: CI, confidence interval; HR, hazard ratio (Cox proportional hazards model); IQR, interquartile range; ITT, intention-to-treat; MD, adjusted mean difference (ANCOVA adjusted for baseline value and center); MMRM, mixed-effects model for repeated measures; NRS, numeric rating scale; RR, relative risk; SD, standard deviation; Δ, change from baseline.

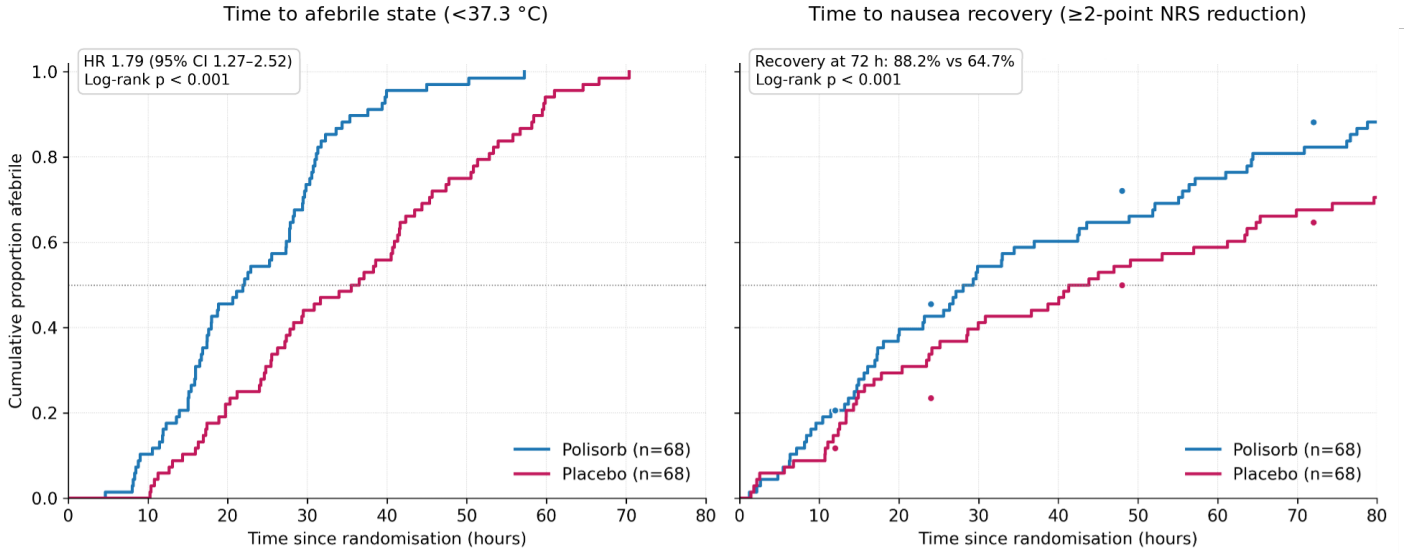


Figure 3. Kaplan-Meier cumulative incidence curves for the two key time-to-event outcomes. Left panel: time to first afebrile measurement (< 37.3°C); hazard ratio for silicon dioxide versus placebo 1.79 (95% CI 1.27 – 2.52); log-rank p < 0.001. Right panel: time to ≥ 2-point reduction in nausea NRS from baseline; cumulative recovery at 72 hours 88.2% (silicon dioxide) versus 64.7% (placebo); log-rank p < 0.001. Reported recovery proportions at 12, 24, 48 and 72 hours are indicated as anchor points on the right panel.

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Table 4. Concomitant treatments and supportive care (intention-to-treat population)

Concomitant treatment	Silicon dioxide (n = 68)	Placebo (n = 68)	Effect (95% CI)	p-value
Antipyretic use before ED (prior 12 h), n (%)	19 (27.9)	21 (30.9)	—	0.71
Antiemetic use before ED, n (%)	4 (5.9)	5 (7.4)	—	1.00
IV fluid at ED triage, n (%)	12 (17.6)	14 (20.6)	—	0.67
Antiemetic use, 0-72 h, n (%)	11 (16.2)	19 (27.9)	RR 0.58 (0.30 – 1.13)	0.10
Antipyretic use, 0-72 h, n (%)	35 (51.5)	41 (60.3)	RR 0.85 (0.63 – 1.15)	0.30
Antibiotic initiation, 0-72 h, n (%)	4 (5.9)	8 (11.8)	RR 0.50 (0.16 – 1.59)	0.23
New IV fluid requirement, 0-72 h, n (%)	4 (5.9)	8 (11.8)	RR 0.50 (0.16 – 1.59)	0.23

Abbreviations: CI, confidence interval; ED, emergency department; IV, intravenous; RR, relative risk

Safety

Adverse events were generally mild, transient, and gastrointestinal in nature. At least one treatment-emergent adverse event was reported by 16 participants (23.5%) in the silicon dioxide arm and 12 participants (17.6%) in the placebo arm (p = 0.40). Constipation was the most commonly reported event in the silicon dioxide group, occurring in 6 patients (8.8%) compared with 2 patients (2.9%) in the placebo group (p = 0.16). Other reported events included transient abdominal discomfort, mild bloating, and dry mouth, occurring at similar low frequencies in both arms (Table 5). All adverse events were CTCAE grade 1 (n = 24) or grade 2 (n = 4); none were grade 3 or higher. By blinded clinician adjudication, constipation cases in the silicon dioxide arm were assessed as possibly related (n = 4) or related (n = 2) to study product, with median onset on day 2 (range 1-4); all resolved spontaneously or after a single laxative dose, and none required treatment discontinuation. No serious adverse events occurred during the study, and no participant discontinued the study product because of toxicity. There were no clinically significant changes in vital signs, and no allergic or hypersensitivity reactions were observed.

Table 5. Treatment-emergent adverse events through Day 5

Adverse event	Silicon dioxide (n = 68), n (%)	Placebo (n = 68), n (%)	p-value	Causality (active arm)
Any adverse event	16 (23.5)	12 (17.6)	0.40	—
Constipation (Grade 1-2)	6 (8.8)	2 (2.9)	0.16	Related/possibly related
Mild abdominal discomfort (Grade 1)	4 (5.9)	5 (7.4)	1.00	Possibly related
Bloating (Grade 1)	3 (4.4)	2 (2.9)	1.00	Possibly related
Dry mouth (Grade 1)	2 (2.9)	2 (2.9)	1.00	Unrelated
Headache (Grade 1)	1 (1.5)	1 (1.5)	1.00	Unrelated
Skin rash	0 (0.0)	0 (0.0)	—	—
Serious adverse events	0 (0.0)	0 (0.0)	—	—
Discontinuation due to AE	0 (0.0)	0 (0.0)	—	—

Grade refers to CTCAE v5.0 severity. Causality assessment was performed by blinded clinician adjudication and is reported for events occurring in the silicon dioxide arm. p-values from χ^2 test or Fisher's exact test as appropriate. Some patients reported more than one adverse event. Abbreviations: AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events.

Discussion

In this randomized, double-blind, placebo-controlled trial conducted in two EDs, adjunctive treatment with highly dispersed silicon dioxide was associated with a clinically meaningful and statistically significant acceleration of nausea resolution and defervescence compared with placebo in adults with acute watery diarrhea. The benefit was evident across the primary endpoint of change in nausea NRS at 72 hours, time-defined recovery rates from 24 hours onwards, and time to afebrile state, with consistent direction and magnitude of effect across pre-specified sensitivity

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analyses, including those adjusted for concomitant antiemetic and antipyretic use. The safety profile of the active product was favorable, with only a numerical excess of mild, self-limited constipation and no serious adverse events—a tolerability profile concordant with the recent multicenter trial of high-dispersion silicon dioxide in adult ED patients, in which mild-to-moderate constipation was likewise the most frequent treatment-related adverse event and no serious adverse events occurred [5].

The interpretation of the primary endpoint is straightforward. The adjusted mean reduction in nausea NRS at 72 hours of approximately two points exceeded the pre-specified threshold of clinical relevance and corresponds, on a 0-10 scale, to the difference between moderate and mild-or-absent nausea—an experiential change that is highly relevant to patients in the early phase of acute gastroenteritis [28]. The internal consistency between the primary ITT ANCOVA estimate, the complete-case ANCOVA, the concomitant-medication-adjusted sensitivity analysis, and the supportive MMRM longitudinal trajectory provides reassurance that the effect is not an artifact of missing data, model assumptions, or differential symptomatic comedication. Of note, the divergence between groups began as early as 12 hours and reached statistical significance by 24 hours, mirroring the time course of intraluminal toxin clearance reported in mechanistic studies of silicon dioxide-based sorbents [22,23].

The pattern of secondary endpoints reinforces the primary finding. Recovery rates at 24, 48, and 72 hours all favored silicon dioxide, with absolute risk differences of 22.1%, 22.1%, and 23.5%, respectively, and an NNT of five at 72 hours. The reduction in time to defervescence and in cumulative duration of fever, although exploratory and not adjusted for multiplicity, is biologically coherent with a mechanism in which silicon dioxide reduces toxin and pathogen-associated molecular pattern exposure across an injured mucosa. A parallel pattern of faster across-the-board improvement in stool consistency, abdominal pain, and gastrointestinal symptom scores has been reported in the recent multicenter ED trial of high-dispersion silicon dioxide [5], reinforcing the consistency of the symptomatic effect of this enterosorbent across distinct outcome panels. The higher patient-reported satisfaction in the active arm and the trend towards lower antiemetic and antibiotic use, although not formally powered, are clinically relevant signals in an era of growing concern over inappropriate antibiotic prescribing in acute gastroenteritis [4,10,11].

From a mechanistic standpoint, the observed effects are biologically plausible. With a specific surface area of up to 300 m^2/g, highly dispersed silicon dioxide can bind bacterial cells, lipopolysaccharide, and protein toxins by non-specific adsorption, potentially lowering the luminal concentration of agents that activate enterocyte secretory pathways, enterochromaffin-cell nausea signaling, and pyrogenic cytokine responses [7,21,23,31]. Importantly, these interpretations are inferential: the trial did not measure microbial toxins, mucosal cytokines, intestinal permeability, or microbiota composition, so the findings are consistent with — but do not directly demonstrate — a sorption-mediated mechanism, and dedicated translational studies are needed for confirmation. Because silicon dioxide is not absorbed and undergoes no systemic metabolism, any benefit would arise without systemic exposure or drug-drug interactions beyond the recommended two-hour dosing interval, which is relevant in polypharmacy contexts in adult emergency care [22].

Our findings are concordant with, and extend, the available randomized evidence on enterosorbents in acute diarrhea. Tieroshyn and colleagues, in a four-center placebo-controlled trial of high-dispersion silicon dioxide in tablet form, reported a mean reduction of approximately 0.9 days in time to recovery from acute diarrhea and a halving of antibiotic initiation in the active arm [22]. More recently, a multicenter randomized double-blind trial of high-dispersion silicon dioxide powder in adult ED patients demonstrated a 51-hour reduction in median recovery time, with concurrent improvements in stool consistency, abdominal pain, and gastrointestinal symptom scores [5]. A subsequent randomized controlled trial conducted in adult primary-care patients with acute diarrhea, evaluating a chemically distinct silicon-based enterosorbent, similarly demonstrated faster symptom resolution compared with usual care, providing supportive evidence consistent with a possible class-level benefit of orally administered, non-absorbable sorbents in this population [24]. Consistent with these trials, we observed a numerically lower antibiotic initiation rate, although our study was not powered for this exploratory endpoint. Our work differs from this previous ED-based trial of high-dispersion silicon dioxide [5] in three important respects: the primary endpoint is patient-reported nausea on a validated NRS rather than time to recovery of stool form; fever is treated as a quantitative time-to-event outcome rather than a categorical symptom; and concomitant antiemetic and antipyretic use was systematically captured and incorporated as a covariate in a sensitivity analysis. Meta-analyses of diosmectite, a chemically distinct clay-based sorbent, in pediatric acute diarrhea similarly demonstrate reductions in stool output and illness duration without an increase in serious adverse events [17,18], with the principal adult randomized data also supporting symptom-shortening effects [20]. The somewhat larger effect we observed for nausea likely reflects the higher baseline symptom burden of an ED-presenting population and the use of a structured NRS sensitive to incremental change.

Several differences from prior trials warrant comment. Earlier studies of silicon dioxide and other sorbents predominantly enrolled outpatients or hospitalized inpatients, with stool-related primary endpoints and longer follow-up durations [17,18,22]. Our ED-based design captured patients earlier in the disease course, when nausea and fever are most severe, and aligned the endpoints with the symptoms that most influence ED disposition. Because recruitment was limited to late winter and early spring, the underlying pathogen distribution may differ from that of the late summer-autumn peak of foodborne and waterborne diarrheal

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disease [3,6]; this seasonal pattern is more typical of viral predominance, but the absence of systematic stool diagnostics—consistent with international guidance for uncomplicated adult diarrhea [4]—precludes pathogen-specific interpretation. Pediatric guideline frameworks have moved toward selective use of adjunctive agents (such as specific probiotic strains, diosmectite, or racecadotril) alongside oral rehydration [14,32], a direction conceptually consistent with the role of an inert, non-absorbable sorbent as a low-risk symptomatic adjunct in adults.

Clinically, these data have several implications for emergency and primary care. First, they suggest that highly dispersed silicon dioxide may be a useful, low-risk adjunctive symptomatic therapy in adults with acute watery diarrhea, complementary to oral rehydration. Second, faster relief of nausea may facilitate oral rehydration itself and could potentially reduce the need for intravenous fluids and shorten ED length of stay—although these utilization endpoints were not directly measured in the present trial. Third, the trend toward lower antibiotic initiation, if confirmed in larger studies, would be relevant to antimicrobial stewardship initiatives in acute gastroenteritis, in which non-antibiotic adjuncts are increasingly being explored to reduce both inappropriate prescribing and the burden of antibiotic-associated complications [4,10,11,33]. Finally, given the very low cost, oral route, and favorable tolerability of silicon dioxide, it may be a particularly suitable option in resource-constrained settings where alternative symptomatic therapies are limited.

This study has several strengths. The randomized, double-blind, placebo-controlled, two-center design with a centrally generated allocation sequence and an identical-appearing comparator minimizes selection and assessment bias. The conduct in real-world EDs enhances external validity. Endpoints were defined a priori using a structured patient-reported nausea NRS, an established symptom-rating instrument, together with a pragmatic temperature-based fever scale developed for this study. The primary endpoint was analyzed with a pre-specified ANCOVA on the ITT population using multiple imputation for missing 72-hour values, and was complemented by complete-case ANCOVA, MMRM-based longitudinal analysis, ordinal sensitivity analyses, survival and interval-censored analyses, and a pre-specified sensitivity analysis adjusting for concomitant symptomatic medication. The sample size was driven by an a priori power calculation for the pre-specified 72-hour primary endpoint, with concordant power for the supportive longitudinal trajectory analysis, and the attrition rate was within the planned tolerance.

Several limitations should also be acknowledged. First, the trial was conducted in two centers in Türkiye and recruitment was confined to late winter and early spring, the season more typically associated with viral gastroenteritis; this limits generalizability to other regions, seasons, and pathogen distributions, including the late summer-autumn peak of bacterial foodborne and waterborne illness. Second, although microbiological work-up was performed at the discretion of the treating physician, systematic stool diagnostics were not part of the protocol; pathogen-specific subgroup analyses were therefore not feasible, and the study cannot establish whether the effect differs between viral and bacterial etiologies. Because different enterosorbents may vary in their affinity for specific bacterial versus viral products, the absence of pathogen confirmation means that any differential efficacy across etiologies remains unknown, and the results should be extrapolated only cautiously to settings dominated by bacterial foodborne disease. Third, the trial was not prospectively registered in an international clinical trials registry; while the protocol and statistical analysis plan were finalized before the first enrollment, prospective registration would have provided an additional safeguard against outcome-switching. Fourth, follow-up was limited to five days, which captures the typical duration of acute illness but does not address post-infectious sequelae such as post-infectious irritable bowel syndrome. Fifth, post-discharge body temperature data were patient-reported; despite provision of standardized tympanic thermometers, written instructions, and explicit recording of antipyretic timing, residual measurement variability cannot be excluded, and time-to-event temperature outcomes are interval-based, which is a recognized limitation that we partly addressed through interval-censored sensitivity analyses. Accordingly, the fever-related secondary endpoints — time to defervescence and cumulative duration of temperature $\geq 38.0°C$ — should be regarded as estimates subject to measurement and recall bias and as hypothesis-generating rather than definitive. Sixth, given the number of secondary and sensitivity analyses performed without correction for multiple comparisons, the associated p-values and CIs should be interpreted as exploratory and hypothesis-generating, and only the pre-specified primary nausea endpoint supports confirmatory inference. Seventh, although blinding was rigorously implemented, the slightly higher rate of constipation with silicon dioxide could theoretically have unblinded a small number of participants; a sensitivity analysis excluding such patients did not change the direction of the primary result, but residual reporting bias cannot be excluded. Finally, we did not measure mucosal biomarkers, microbiota composition, intestinal permeability indices, or pharmacoeconomic endpoints; these mechanistic and health-economic dimensions remain to be addressed in dedicated studies.

Future research should aim to confirm and extend these findings in larger, prospectively registered, multinational trials with stratification by likely etiology (viral vs. bacterial), to evaluate dose-response relationships, and to compare highly dispersed silicon dioxide head-to-head with other approved sorbents such as diosmectite [20]. Mechanistic studies integrating mucosal cytokine profiling, microbiota analysis, and intestinal-permeability biomarkers would help to clarify how luminal sorption translates into systemic clinical benefit. Pragmatic trials embedded in ED workflows, with patient-reported quality-of-life and health-economic endpoints including length of stay, return visits, IV fluid use, and antibiotic prescribing, would directly inform clinical pathways. Finally, exploration in selected

populations such as elderly patients, travelers, and those with comorbidities for whom symptomatic but non-systemic therapy is particularly attractive would be of clear interest.

Conclusion

In adults presenting to the ED with acute watery diarrhea, adjunctive highly dispersed silicon dioxide added to standard oral rehydration therapy was associated with faster resolution of nausea and earlier defervescence than placebo, with a comparable safety profile. Because the fever-related and other secondary outcomes were exploratory and the trial was single-country, seasonally restricted, and not prospectively registered, these findings should be regarded as preliminary. They require confirmation in larger, prospectively registered, multinational trials with standardized pathogen assessment and health-care utilization endpoints before highly dispersed silicon dioxide can be recommended for routine use. Pending such data, it may be considered a low-risk symptomatic adjunct to oral rehydration in selected adults with uncomplicated acute watery diarrhea, rather than a substitute for established management.

Ethical Approval

The protocol was approved by the Clinical Research Ethics Committee of Ankara Etlik City Hospital (date: 4 March 2026; approval number: AEŞH-EK-2026-049) and conducted in accordance with the Declaration of Helsinki and the principles of Good Clinical Practice. All participants provided written informed consent prior to any study-related procedure.

Patient Consent

Written informed consent was obtained from all individual participants included in the study prior to any study-related procedure. Participants were informed of the nature, purpose, and potential risks of the study and provided their consent voluntarily.

Conflict of Interest

The authors confirm the absence of any conflicts associated with this work.

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