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Effects of Drinking Electrolyzed Alkaline-Reduced Water on Functional Dyspepsia: A Randomized, Double-Blind, Controlled Prospective Trial

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Abstract: A well-known functional gastrointestinal disorder called functional dyspepsia (FD) is defined by dyspeptic symptoms without any structural abnormalities. In alternative intervention, electrolyzed alkaline-reduced water (EARW) consumption is regarded as a treatment modality for gastrointestinal symptoms despite its mechanism not yet fully understood. The present clinical study aimed to investigate the effects of EARW on gastrointestinal symptoms of patients with FD. Forty-eight participants with FD were screened, and 42 were enrolled. Participants were randomly allocated to the EARW (n = 21) and purified water (PW) (n = 21) groups. The EARW group ingested EARW (10 mL/kg body weight/day) for 6 weeks. The gastrointestinal symptom rating scale (GSRS), functional dyspepsia-related quality of life (FD-QoL), the Korean version of the Nepean Dyspepsia Index (NDI-K) were used as primary outcome measures at baseline and at 6 weeks, and inflammatory markers were measured as the secondary outcome. Two participants dropped out, and 40 participants (EARW = 20 and PW = 20) completed the trial. Total GSRS score was significantly lower in the EARW group (34.27%, $p < 0.01$) than in the PW (18.16%) group. In the five subcategories of GSRS, the decreased score between baseline and post-intervention for the EARW and PW groups were 43.59% and 21.33% in abdominal pain score, respectively; 38.98% and 18.92% in reflux syndrome, respectively; 25.42% and 20.90% in diarrhea, respectively; 35.87% and 21.48% in indigestion, respectively; and 32.81% and 10.71% in constipation, respectively, and all the parameters were significantly different in the EARW group compared with those in the PW group. The NDI-K score was also lower in the EARW group ($p < 0.01$) than in the PW group. FD-QoL score decreased significantly more in the EARW group after intervention than in the PW group ($p < 0.05$). Additionally, inflammatory cytokines (TNF-α and IFN-γ) levels significantly suppressed in the EARW group after 6 weeks of drinking compared with the levels at the baseline. Our clinical study suggests that long-term drinking of EARW (pH 9.5) may improve FD-related symptoms and the quality of life of FD patients through home-based administration.

Keywords: functional dyspepsia; electrolyzed alkaline-reduced water; gastrointestinal symptom rating scale; functional dyspepsia-related quality of life; Korean version of the Nepean dyspepsia index

Citation: Bajgai, J.; Lee, M.; Jang, Y.-G.; Lee, K.; Sharma, S.; Jeong, Y.J.; Park, H.J.; Goh, S.H.; Kim, C.-S.; Kim, H.I.; et al. Effects of Drinking Electrolyzed Alkaline-Reduced Water on Functional Dyspepsia: A Randomized, Double-Blind, Controlled Prospective Trial. *Processes* **2023**, *11*, 968. https://doi.org/10.3390/pr11030968

Academic Editors: Ángeles Alonso-Moraga and Chi-Fai Chau

Received: 3 January 2023
Revised: 17 March 2023
Accepted: 20 March 2023
Published: 22 March 2023

1. Introduction

Functional dyspepsia (FD) is a common digestive disorder characterized by recurrent dyspeptic symptoms, such as epigastric pain, bloating, vomiting, reflux, nausea, early

satiety, and postprandial fullness without any structural anomalies, and metabolic diseases [1]. The symptoms of FD are divided into postprandial distress and epigastric pain syndrome (epigastric pain and epigastric burning/soreness), according to the Rome IV criteria, and the feeling of sickness (but not vomiting) may worsen after meals [1,2]. The prevalence of FD has been reported to be in the range of 8–23% in Asia and 10.3–20.4% in South Korea [2–4]. Additionally, an endoscopic evaluation of >70% of dyspepsia patients reveals no detectable organic pathology to explain their symptoms. Epigastric pain syndrome, postprandial distress syndrome, and overlapping variations such as irritable bowel syndrome and heartburn are three subtypes of FD [5]. FD patients generally experience impaired quality of life (QoL) due to inability to participate in some activities of daily living, along with direct or indirect financial burden [6,7]. Additionally, the associated psychological disturbances, such as anxiety and depression, can reduce health-related QoL [7]. Nevertheless, the exact mechanism and cause of the various symptoms of FD have not been fully elucidated.

Prokinetics, antidepressants, and proton pump inhibitors have been proposed as therapeutic options for FD. However, these conventional therapies remain controversial due to their adverse effects, which are experienced especially during long-term treatment, and patients have a low satisfaction rate due to their adverse effects [8,9]. For this reason, many patients seek alternative and complementary treatment options, such as lifestyle modifications and ingestion of probiotics and functional waters, such as mineral-rich water and alkaline-reduced water [10–13]. Electrolyzed alkaline-reduced water (EARW), a functional water, is popularly consumed in many countries such as Japan, China, and Korea, owing to its various health benefits. It is generated by the electrolysis of water and has properties such as high alkalinity (pH 8.5–10.0), small water cluster size, high hydrogen content, and low oxidation-reduction potential (ORP). Previous studies have reported various biological effects of ARW, such as its anti-oxidative, anti-inflammatory, and anti-apoptotic properties [14–17]. Previous studies have also reported that ARW consumption has a positive effect on gastrointestinal disease models such as acute inflammatory bowel disease, reflux disease, and hemorrhagic gastric injury [11,18,19]. A clinical study also showed that daily ingestion of EARW has beneficial effects on human health, including improvement in gastrointestinal symptoms [20].

Recently, EARW gained attention as one of the alternative treatments for oxidative stress and inflammation-related diseases, including gastrointestinal disorders; however, until now, only a few clinical studies have been conducted to investigate the efficacy of EARW consumption in dyspepsia treatment [11,12]. As a result, we performed a randomized controlled clinical trial to assess how EARW consumption affected FD symptoms.

2. Materials and Methods

2.1. Ethical Approval

This study was approved by Institutional Review Board, Wonju Severance Christian Hospital, Yonsei University, Republic of Korea (IRB Number: CR221022), and was conducted from 10 August 2022 to 28 October 2022 in compliance with the Declaration of Helsinki [21] and the Good Clinical Practice guidelines (https://www.ema.europa.eu/en/ich-e6-r2-good-clinical-practice-scientific-guideline (accessed on 2 January 2023)). It was registered at ClinicalTrials.gov with identifier NCT05693259.

2.2. Study Design

This study had a randomized, double-blind, parallel, and controlled design, and the flowchart is provided in Figure 1. The sample size (n = 48) was calculated using the G*Power program [22] (G*Power 3.1.9.7, Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Germany) based on the following standard assumptions: α = 0.05, power = 0.80, dropout rate = 20%, and partial η^2 = 0.07. We recruited participants and obtained informed consent, which was signed voluntarily after the participants were provided sufficient explanation about the clinical study, including the objective, protocols, and safety. The

participants were enrolled through eligibility screening tests based on inclusion and exclusion criteria (Table 1), physical examination, vital sign measurements, and responses to a medical history questionnaire.

Table 1. Inclusion and exclusion criteria for participants.

Inclusion Criteria	• Onset of symptoms beginning at least six months prior to identification and based on one or more of the symptoms listed below Rome IV standards (unpleasant postprandial fullness, early satiety, epigastric pain). • No evidence of structural disease by gastroscopy within the last 3 months. • Aged 19–70 years. • Patients meeting the Rome IV criteria for functional dyspepsia. • Patients who meet 4 or more symptoms based on the GI symptoms rating scale. • Patients who signed a written consent form and voluntarily consented to take part in the research.
Exclusion Criteria	• Patients with a history of serious malignancy, including gastrointestinal malignancy, cerebrovascular disease, or heart disease in at least 6 months period. • Patients with uncontrolled diabetes and hypertension despite appropriate management. • Patients with a history of peptic ulcer or reflux esophagitis within the past 6 months. • Patients who have previously undergone gastrointestinal operations. • Women who are expecting or nursing. • Patients taking drugs that may affect the gastrointestinal tract (a minimum 2-week washout period was necessary before participating in the trial) (medications included H_2 receptor blockers, anticholinergics, prostaglandins, proton pump inhibitors, gastromucosal protection agents, corticosteroids, non-steroidal, and anti-inflammatory drugs). • Patients taking drugs for therapeutic purposes such as functional food that promotes gastric health. • Patients who have drinking history more than 14 units/week for men and 7 units/week for women in the past month.

The participants were divided into two groups at random: experimental and control. The randomization was carried out by a statistician using 1:1 computerized block randomization with a preset random code. A study coordinator carried out the randomization, and both the researcher and the patients were double-blinded. The study's conclusion marks the first time the research coordinator informed patients or researchers about randomization. Additionally, the therapy was hidden from the patients as well as the researchers.

For baseline data collection, patients filled out the following survey questionnaires: the GI symptoms rating scale (GSRS), functional dyspepsia-related quality of life (FD-QoL), and Korean version of the Nepean dyspepsia index (NDI-K), for the primary outcome. For the secondary outcome, blood samples were collected before starting the intervention (baseline/visit 1). The researcher instructed the participants on how to operate the device and how to drink the water over the following 6-week study period. The experimental devices were installed in each participant's house prior to the start of the experiment. Participants were allowed to consume their regular diet. Additionally, participants were instructed to stop intervention immediately and contact the researcher if they experienced any adverse effects. After 6 weeks of intervention, participants made their last visit (visit 2) and completed the survey questionnaire and blood collection as they did in visit 1.

2.3. Study Participants

The participants, aged 19–70 years with diagnoses of FD as defined by the Rome IV criteria were recruited at the Department of Gastroenterology at Yonsei University, Wonju Severance Christian Hospital according the inclusion and exclusion criteria during the period March 2022 to August 2022. The criteria are listed in Table 1.

2.4. Research Equipment

The experimental device was an alkaline-reduced water generator (CGM MWPI-2101, CERAGEM Co., Ltd., Cheonan, Republic of Korea), which produces EARW (pH 9.5) by electrolyzing water. It is officially registered as a class-II medical device at the Ministry of Food and Drug safety, South Korea. The EARW was produced by actuating the button on the device for intervention in the experimental group. Placebo water (PW) was produced by using the sham device (Sham CGM MWPI-2101, CERAGEM Co., Ltd., Cheonan, Republic of Korea) for the intervention of the control group. The sham device was indistinguishable from the experimental device in terms of both the appearance and operating method. The device was installed in the patients' houses individually, according to the randomized code, and patients drank water according to the instructed drinking method.

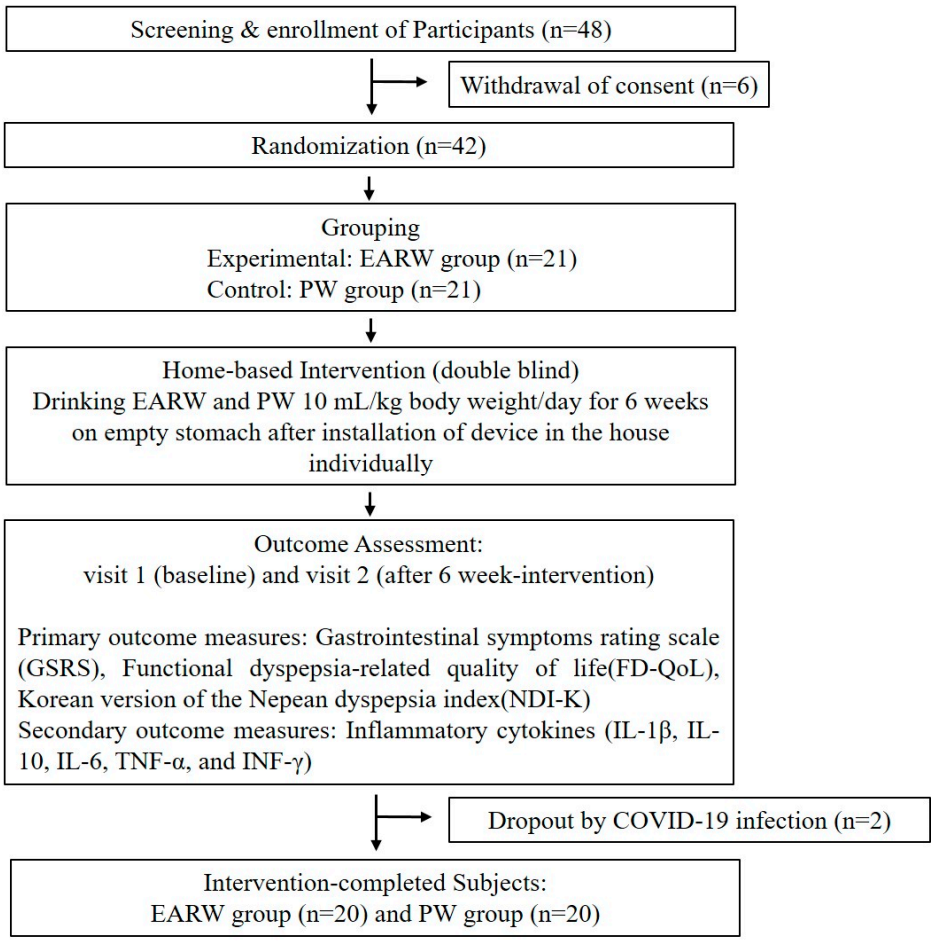

Figure 1. Flow chart of the clinical trial. Abbreviations: EARW: electrolyzed alkaline-reduced water; FD-QoL: functional dyspepsia-related quality of life; GSRS: gastrointestinal symptom rating scale; IFN-γ: interferon-gamma; IL: interleukin; NDI-K: Nepean dyspepsia index; PW: purified water; TNF-α: tumor necrosis factor alpha.

2.5. Interventions

The participants were instructed to drink 10 mL/kg body weight/day (total volume = body weight (kg) × 10 mL) of water by dividing it into three doses throughout the day, using the provided measuring cup. The intervention period was six weeks. The researcher recommended drinking water on an empty stomach as soon as possible after generation of water, without storing the water. The devices were installed at each participant's house before starting intervention for the home-based intervention. The researcher sent a text message using a mobile phone application each day to check the amount of water, and the patients' responses were used for monitoring patient's compliance.

2.6. Outcome Measurements

2.6.1. Primary Outcome Measures

GSRS Score

The GSRS is a survey tool created to evaluate the symptoms of prevalent GI disorders. It has 15 questions on a range from 1 to 7 that rate how bothersome the symptoms have been over the previous few days. More bothersome symptoms are indicated by a greater GSRS score. The 15 questions were divided into five subcategories: diarrhea syndrome (diarrhea, loose stools, and an urgent need to defecate), indigestion syndrome (gastric borborygmus, gastric bloating, eructation, and increased flatus), abdominal pain (stomachache, gastric hunger pain, and nausea), and constipation syndrome (constipation, hard stools, and feeling of incomplete evacuation) [23,24]. GSRS was evaluated at baseline and after 6 weeks of intervention. We used volunteers 19–70 years of age for our study, but after screening all the participants, the age ranges were (48.25 $\pm$ 10.74 years of age in PW group, and 50.50 $\pm$ 11.92 years of age in EARW group), and we randomized into two different groups.

FD-QoL

The FD-QoL questionnaire was used to measure the quality of life of FD patients. It includes 21 items total and is categorized into 4 [25]: eating/diet (five items), daily activity (four items), emotion (six items), and social functioning (six items) on a 5-point Likert scale. A higher score indicates worse QoL, and the score was measured at baseline and after six weeks of intervention. FD-QoL was evaluated at baseline and after 6 weeks of intervention.

NDI-K

A validated instrument called the NDI-K is used to assess clinically significant FD changes, symptoms of gastrointestinal issues, and its impacts on health-related QoL. A few of the 15 symptoms-based questions in this survey questionnaire include upper abdominal pain, discomfort, burning, heartburn, cramps, chest discomfort, inability to finish a regular meal, bitter-tasting liquid in the mouth, feeling full after eating, pressure in the upper abdomen, bloating, nausea, belching, vomiting, and bad breath. Moreover, the frequency was calculated using a 5-point Likert scale (0 = none, 1 = 1–4 days, 2 = 5–8 days, 3 = 9–12 days, and 4 = daily or almost daily). Severity was measured using a 6-point Likert scale (0 = not at all or not applicable, 1 = very mild, 2 = mild, 3 = moderate, 4 = considerable, and 5 = extreme). The degree of distress was measured using a 5-point Likert scale (0 = not at all, 1 = mild, 2 = moderate, 3 = considerable, and 4 = extreme) [26,27]. In the present trial, we measured NDI-K scores at baseline and after 6 weeks of intervention. NDI-K was evaluated at baseline and after 6 weeks of intervention.

2.6.2. Secondary Outcome Measures

The following biochemical tests were performed to investigate the safety and effectiveness of the intervention at screening and after six weeks of intervention.

Measurement of Inflammatory Cytokines Activities

We measured the concentration of inflammatory cytokines in the blood using the Milliplex® Magnetic Bead Panel 96-well plate assay (Cat: HCYTOMAG-60K, Millipore Corporation, Billerica, MA, USA) as a Luminex-based multiplex technology. Interleukin (IL)-1β, IL-10, IL-6, tumor necrosis factor (TNF)-α, and interferon gamma (IFN-γ) levels were measured using a multiplex immunoassay following the manufacturer's protocol. Each of the standard concentration solutions was serially reduced with the help of standard diluents, to put it briefly. Both the standard and serum samples received the bead combination. The dish was washed, then incubated at 4 °C for 18 h. The addition of the detection antibody was followed by an hour of room temperature incubation in the plate. The dish was then mixed with streptavidin and phycoerythrin and left to sit at room temperature for 30 min. The plate was then washed, an assay buffer was added, and the Luminex 200 Bio-Plex system was used to evaluate the results.

Blood Sample Analysis for Complete Blood Count (CBC)

The CBC examination was conducted at the ONE laboratories (EONE laboratory, Wonju, Gangwon-do, Republic of Korea) to observe safety of drinking EARW at baseline and after 6-week intervention. CBC parameters were hemoglobin (Hb), hematocrit (Hct), red blood cell (RBC) count, white blood cell (WBC) count, and platelet count. The CBC was measured using a Beckman Coulter ACT 5 DIFF CP analyzer (Brea, CA, USA).

2.7. Statistical Analysis

Statistical analysis was performed on participants who successfully completed the clinical trial using GraphPad Prism software (version 8.0; GraphPad Prism software (version 8.0; GraphPad Software, La Jolla, CA, USA). Descriptive statistics were performed to calculate the mean and standard deviation for all related data. Comparisons of the baseline characteristics of participants in the two groups were performed using an independent sample t-test. Changes in GSRS, FD-QoL, and NDI-K scores were evaluated using two-way analysis of variance (ANOVA) with Sidak's multiple comparisons test. Additionally, for the change in the five subcategories of GSRS, a paired sample t-test was performed for the change at baseline and after treatment. Cytokines results were analyzed using one-way ANOVA with Tukey's multiple comparisons test. The statistical significance was set at $p < 0.05$.

3. Results

3.1. Baseline Characteristics of Participants

Fourty-two participants in total were enrolled in this research, but two withdrew due to COVID-19 infection and quarantine during the study. Finally, 40 participants (20 in the EARW group and 20 in the PW group) completed the clinical trial. The mean age of the participants was 49.38 ± 11.26 years (Table 2). As shown in Table 2, baseline data also included measurements of sex, weight, height, systolic blood pressure, and diastolic blood pressure; no substantial differences were found between the PW and EARW groups.

3.2. Effects of Drinking EARW Evaluated by GSRS Score in FD Patients

GSRS scores related to gastrointestinal symptoms were measured on the day of visits 1 and 2. Since the GSRS consists of numerous variables, we categorized the 15 questions into five subcategories: abdominal pain, reflux syndrome, diarrhea, indigestion, and constipation as the primary outcome variables. Our results revealed that total GSRS scores were significantly lower in the EARW (Pre; 3.57 ± 0.53, Post; 2.34 ± 0.34, P.D.%; 34.27%) group compared with those in the PW (Pre; 3.70 ± 0.54, Post; 3.02 ± 0.40, P.D.%; 18.16%) group ($F = 4.90$, $p < 0.01$) (Figure 2).

Total GSRS score were significantly decreased at visit 2 compared with visit 1 in the both PW and EARW groups; however, the degree of mean difference in the EARW group ($p < 0.01$) was more significant to compared PW group. Likewise, the percentage of decrease in the five parameters was significantly higher in the EARW group than in the PW group (Table 3). The percentage decreases in the EARW and PW groups were 43.59% and 21.33% in abdominal pain, respectively; 38.98% and 18.92% in reflux syndrome score, respectively; 25.42% and 20.90% in diarrhea score, respectively; 35.87% and 21.48% in indigestion score, respectively; and 32.81% and 10.71% in constipation score, respectively.

3.3. Effects of Drinking EARW Assessed by FD-QoL in FD Patients

Changes in the FD-QoL were categorized into four categories, namely eating status, vitality, emotion, and social functioning, to assess the efficacy of drinking EARW compared with that of drinking PW. For all four FD-QoL subcategories such as eating, vitality, emotion, and social behavior, the EARW eating (Pre; 1.49 ± 0.07, Post; 0.62 ± 0.10, P.D.%; 58.39%), vitality (Pre; 2.06 ± 0.35, Post; 0.88 ± 0.16, P.D.%; 57.58%), emotion (Pre; 1.51 ± 0.36, Post; 0.53 ± 0.13, P.D.%; 65.19%), and social functioning (Pre; 1.58 ± 0.22, Post; 0.64 ± 0.06, P.D.%; 59.47%) group compared with those in PW eating (Pre; 1.27 ± 0.03, Post; 0.94 ± 0.07,

P.D.%; 25.98%), vitality (Pre; 2.16 ± 0.41, Post; 1.93 ± 0.26, P.D.%; 10.98%), emotion (Pre; 1.85 ± 0.34, Post; 1.28 ± 0.17, P.D.%; 30.63%), and social functioning (Pre; 1.58 ± 0.41, Post; 1.13 ± 0.23, P.D.%; 28.93%) group had a significantly lower score compared with that of the PW group on visit 2 eating ($F = 77.8$, $p < 0.001$), vitality ($F = 8.12$, $p < 0.01$), emotion ($F = 3.57$, $p < 0.001$), social functioning ($F = 5.16$, $p < 0.05$) while there were no significant differences between groups at visit 1 (Figure 3).

Table 2. Baseline characteristics of participants.

Variable	PW Group	EARW Group	*p*-Value
Sex			
Total	20	20	-
Male	8	8	-
Female	12	12	-
Age (years)			
Total	48.25 ± 10.74	50.50 ± 11.92	0.987
Male	49.00 ± 8.49	42.38 ± 10.41	0.831
Female	47.75 ± 12.36	55.92 ± 9.82	0.457
Height (cm)			
Total	159.89 ± 9.30	159.63 ± 10.00	>0.999
Male	169.33 ± 6.16	164.99 ± 9.83	0.915
Female	153.60 ± 4.17	156.05 ± 8.74	0.982
Weight (kg)			
Total	63.93 ± 14.04	65.25 ± 11.20	>0.999
Male	74.14 ± 14.52	69.15 ± 7.99	0.961
Female	57.12 ± 8.95	62.54 ±12.55	0.868
Blood pressure (mmHg)			
Systolic	126.00 ± 9.67	134.05 ± 10.57	0.217
Male	129.12 ± 10.53	130.88 ± 8.22	>0.999
Female	123.50 ± 8.65	136.17 ± 11.74	0.062
Diastolic	86.78 ± 11.10	85.85 ± 9.21	0.843
Male	92.50 ± 10.11	87.25 ± 11.46	0.996
Female	82.02 ± 10.04	84.92 ± 7.78	0.385

Values are presented as mean ± SD. Significant differences were analyzed using independent samples *t*-test.

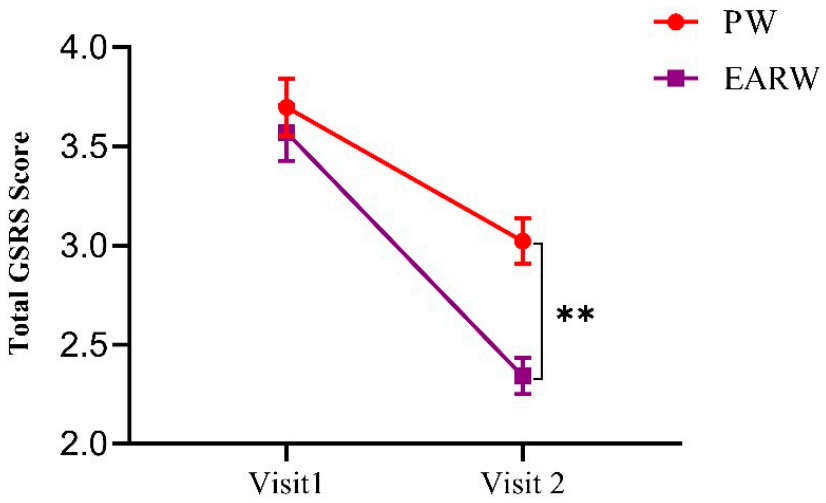

Figure 2. Effects of drinking EARW assessed by using GSRS in FD patients. Survey data were collected at baseline (visit 1) and after 6 weeks of intervention (visit 2). Data are presented as mean, SD and *p*-value between two groups. Significant differences were analyzed using two-way ANOVA with Sidak's multiple comparisons test. ** $p < 0.01$. Abbreviations: GSRS: gastrointestinal symptoms rating scale; PW: purified water group; EARW: electrolyzed alkaline-reduced water group.

Table 3. Drinking effects of EARW assessed by GSRS in FD patients.

	PW Group (n = 20) Visit 1 vs. Visit 2				**EARW Group (n = 20) Visit 1 vs. Visit 2**			
Parameters	PW (V1)	PW (V2)	P.D. (%)	p-value	EARW (V1)	EARW (V2)	P.D. (%)	p-value
Total GSRS score	3.69 ± 0.54	3.02 ± 0.42	18.16	** $p < 0.01$	3.56 ± 0.53	2.34 ± 0.34	34.27	*** $p < 0.001$
Abdominal pain score	3.75 ± 1.41	2.95 ± 1.31	21.33	*** $p < 0.001$	3.90 ± 1.86	2.20 ± 1.28	43.59	*** $p < 0.001$
Reflux syndrome score	3.70 ± 1.75	3.00 ± 1.41	18.92	*** $p < 0.001$	2.95 ± 1.43	1.80 ± 0.89	38.98	*** $p < 0.001$
Diarrhea score	3.35 ± 1.76	2.65 ± 1.53	20.90	** $p < 0.01$	2.95 ± 1.54	2.20 ± 1.19	25.42	*** $p < 0.001$
Indigestion score	4.33 ± 1.3	3.40 ± 1.72	21.48	*** $p < 0.001$	4.60 ± 1.5	2.95 ± 1.43	35.87	*** $p < 0.001$
Constipation score	2.80 ± 2.01	2.50 ± 1.95	10.71	n.s.	3.20 ± 1.96	2.15 ± 1.18	32.81	*** $p < 0.001$

Abbreviations: Values are presented as mean ± SD; P.D.: percentage of decrease; n.s.: not significant; V1: visit 1 (at baseline); V2: visit 2 (after 6-week intervention); significant differences were analyzed using paired sample t-test, which was performed for the change at baseline and after treatment between groups. ** $p < 0.01$, *** $p < 0.001$.

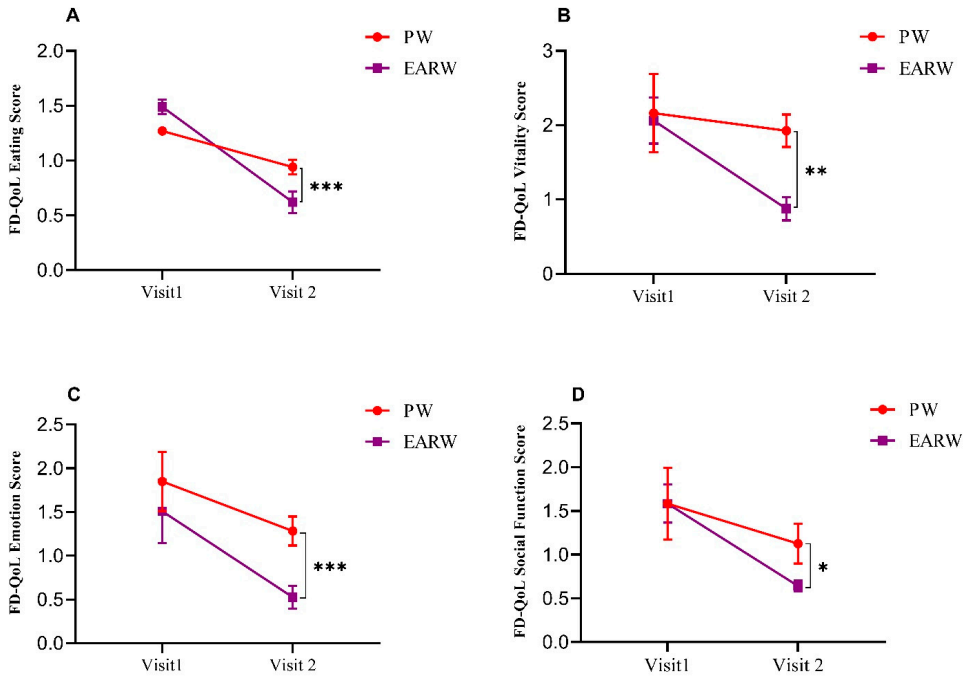

Figure 3. Drinking effects of EARW were assessed by using FD-QoL questionnaire in FD patients. Eating (**A**), vitality (**B**), emotion (**C**) and social function (**D**). Survey data were collected at baseline (visit 1) and after 6 weeks of intervention (visit 2). Data are presented as mean, SD, and p-value between two groups. Significant differences were analyzed using two-way ANOVA with Sidak's multiple comparisons test. *** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$. Abbreviations: GSRS: gastrointestinal symptoms rating scale; PW: purified water group; EARW: electrolyzed alkaline-reduced water group.

3.4. Drinking Effects of EARW Assessed by NDI-K in FD Patients

NDI-K score was measured at baseline (visit 1) and post-intervention (visit 2) for the EARW and PW groups. Our result showed that the total NDI-K score in the EARW group (Pre; 2.20 ± 0.49, Post; 1.05 ± 0.29, P.D%; 52.27%) was significantly lower ($F = 9.11$, $p < 0.01$) than that in the PW (Pre; 2.11 ± 0.54, Post; 1.35 ± 0.33, P.D%; 36.25%) group at visit 2 (Figure 4).

3.5. Effects of Drinking EARW on Levels of Inflammatory Cytokines in FD Patients

Pro-inflammatory cytokines such as TNF-α, IFN-γ, IL-1β, IL-6, and IL-10 are released by inflammatory cells in FD and are crucial immune response indicators as well as regulators of the inflammatory cascade [28]. Our results showed that TNF-α levels ($p < 0.05$)

were significantly lower in the EARW group compared with those in the PW group at visit 2 (Figure 5A). In addition, the IFN-γ levels in the EARW group significantly decreased at visit 2 ($p < 0.05$) compared with those measured at baseline (Figure 5C), whereas, in Figure 5C, the level of IFN-γ ($p = 0.73$), IL-1β ($p = 0.993$) and IL-10 ($p = 0.102$) showed a decreased tendency but not significant.

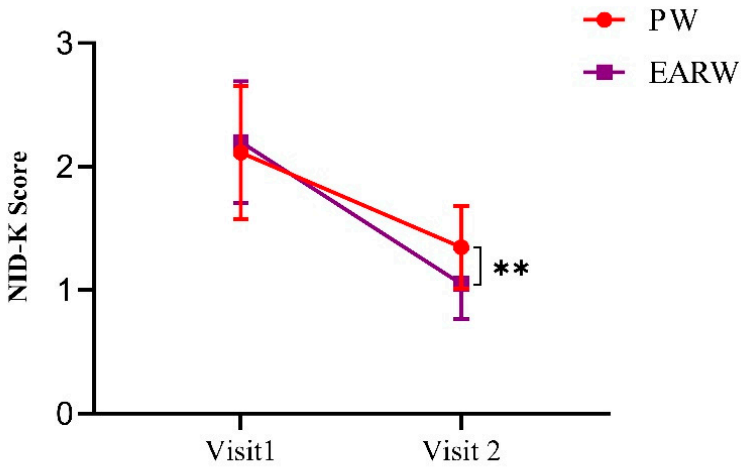

Figure 4. Effects of drinking EARW on gastrointestinal symptom assessed by Korean version of the Nepean Dyspepsia Index (NDI-K) score in FD patients. Data were collected at baseline (visit 1) and after 6 weeks of intervention (visit 2). Data are presented as mean, SD and *p*-value between two groups. Significant differences were analyzed using two-way ANOVA by Sidak's multiple comparisons test. ** $p < 0.01$. Abbreviations: GSRS: gastrointestinal symptoms rating scale; PW: purified water group; EARW: electrolyzed alkaline-reduced water group.

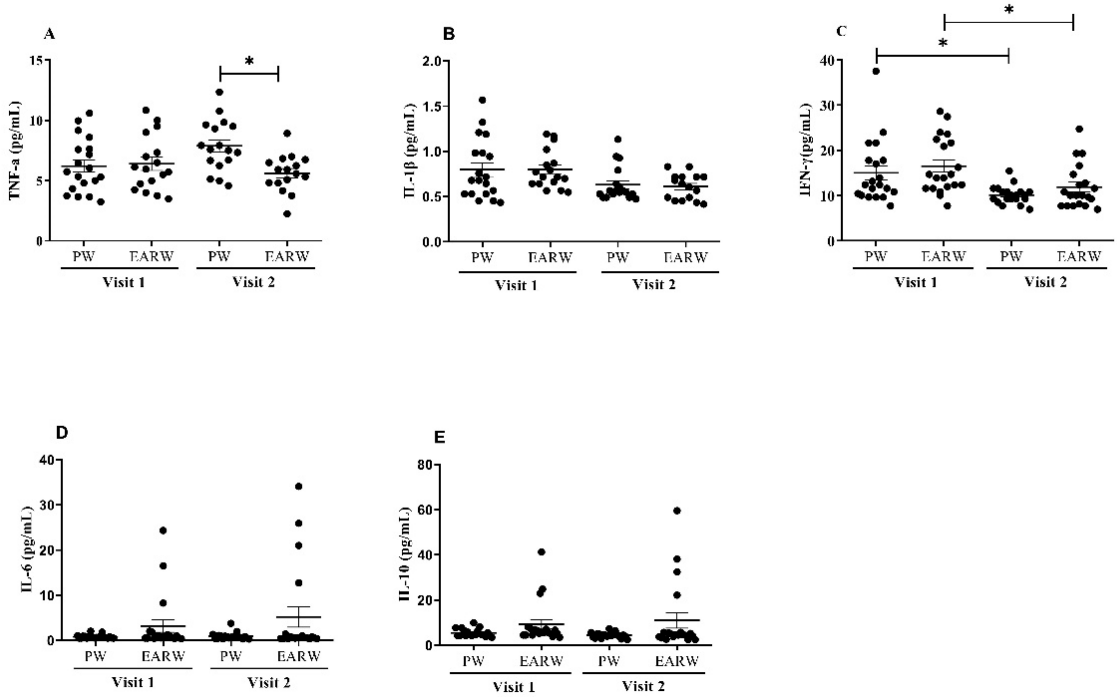

Figure 5. Effects of drinking EARW on the levels of serum inflammatory cytokines in FD patients. Blood was collected from the participants at baseline (visit 1) and after 6 weeks of intervention (visit 2). The charts show serum TNF-α (**A**), serum IL-1β (**B**), serum IFN-γ (**C**), serum IL-6 (**D**), and IL-10 (**E**) levels. Data are presented as mean, MD, and *p*-value between two groups. Significant differences were analyzed using one-way ANOVA by Tukey's multiple comparisons test. * $p < 0.05$. PW: purified water group; EARW: electrolyzed alkaline-reduced water group.

3.6. Total CBC Results

To assess the safety of drinking EARW, CBC measures such as Hb, Hct, RBC, WBC, and platelet were investigated after completion of the intervention. The CBC results showed that none of the parameters significantly differed between visits 1 and 2 or between the PW and EARW groups. All values were within the normal ranges (Table 4).

Table 4. Effect of drinking EARW on CBC.

Parameter	PW Group		EARW Group		Normal Range
	(Visit 1)	(Visit 2)	(Visit 1)	(Visit 2)	
Hemoglobin (g/dL)	14.09 ± 0.34	13.75 ± 0.35	14.29 ± 0.31	13.81 ± 0.28	12–17.5
Hematocrit (%)	43.52 ± 0.88	42.79 ± 0.922	44.11 ± 0.88	43.39 ± 0.78	36–54
RBC ($10^6/\mu L$)	4.63 ± 0.09	4.56 ± 0.09	4.62 ± 0.10	4.51 ± 0.09	4–6.5
WBC ($10^3/\mu L$)	6.55 ± 0.33	5.55 ± 0.48	6.17 ± 0.26	4.69 ± 0.35	4–10
Platelet ($10^6/\mu L$)	269 ± 21.89	238.7 ± 19.25	255.1 ± 10.55	223.5 ± 10.57	150–450

CBC was measured at visit 1 (baseline) and visit 2 (after intervention) and calculated pre-to post-intervention. Abbreviations: ARW: alkaline-reduced water; Hct: hematocrit; RBCs: red blood cells; WBCs: white blood cells. Data are shown as mean ± SEM.

4. Discussion

EARW is generated from EARW apparatus which was approved as a home-use medical device by the Ministry of Health, Labor, and Welfare in Japan in 1965, and by Ministry of Food and Drug Safety in Korea in 1981. The effectiveness of EARW as a novel material for the treatment of GI disorders such as abnormal intestinal fermentation, chronic diarrhea, gastric hyperacidity, and dyspepsia has been formally recognized by the government. This clinical trial was designed to investigate the effects of drinking EARW on the GI-related symptoms, especially FD-related symptoms as an alternative supplement for the symptomatic treatment of FD patients using three types of questionnaire instruments. Our result showed that drinking EARW has the potential to relieve the symptoms associated with GI-related disorders. Moreover, no signs of adverse effects were detected and based on the CBC and inflammatory marker findings.

Due to its high prevalence rate, persistent and recurrent symptoms, and financial burden, evidence has shown that FD is a clinical and social issue of significant magnitude [29,30]. In addition, FD commonly results in personal distress and bodily symptoms and influences the quality of life of patients [30]. Due to this reason, management of FD is challenging for gastroenterologists as well as patients. However, therapeutic options for FD are limited because of the difficulty of an accurate diagnosis and the potential side effects [9,10,31]. FD patients do not show structural or biochemical abnormalities in routine diagnostic investigations including even endoscopy, nevertheless the various symptoms of FD and their recurrence decrease the QoL of FD patients. Therefore, the assessment of FD symptoms can provide meaningful information for understanding the patients' health status and perception of the treatment regime.

As primary outcome measures of this clinical trials, GSRS, NDI-K, and FD-QoL questionnaires used in the present clinical trial are well-validated and responsive disease-specific measures available for assessing gastrointestinal symptoms, clinically meaningful FD changes, their impact on patients' daily functioning and the effects on health-related QoL [23–27]. In the present trial, we assessed changes in participants with FD after EARW intervention for six weeks using the GSRS, FD-QoL, and NDI-K questionnaires. The 15 items of GSRS were divided into five subcategories (abdominal pain, reflux syndrome, diarrhea, indigestion, and constipation) and the 21 items of FD-QoL into four subcategories (eating/diet, daily activity, emotion, and social functioning). As a result, the EARW-intervention group showed a significant improvement in GI symptoms after 6 weeks compared with the baseline. Moreover, the EARW group showed significant improvement

in GI symptoms compared with the PW group based on the decrease in the percentage of the total GSRS cores and its five subcategory scores. In our FD-QoL results, we found that the FD-related QoL of the EARW group was markedly better than that of PW group, as evidenced by the significantly decreased scores for all four FD-QoL subcategories after six weeks of EARW intervention. In addition, the NDI-K questionnaire results showed more positive changes in FD symptoms and better health-related QoL after EARW intervention compared with PW intervention. These primary outcomes of the questionnaires indicate that long-term EARW consumption can improve GI-related symptoms including abdominal pain, reflux, diarrhea, indigestion, constipation, and FD-related QoL of patients. From our results we can demonstrate that normal drinking water is good for health; however, drinking EARW is better for health compared with normal drinking water, and EARW might improve functional dyspepsia-related symptom such as, abdominal pain, reflux syndrome, diarrhea, indigestion, constipation, etc.

Recently, there has been a fast increase in interest in alternative therapeutic methods that have no side effects even after prolonged use [11,32]. Several studies with this goal have reported the efficacy of EARW consumption in treating functional gastrointestinal disorders [12,15]; however, only a limited number of clinical trials have been conducted. The characteristics of EARW such as high pH, negative ORP, and rich in hydrogen have been reported as an underlying mechanism to explain the health-related effects of EARW [15]. Regarding alkaline pH, EARW (pH 8.8) can irreversibly inactivate human pepsin (in vitro) and have higher hydrochloric acid-buffering capacity compared with neutral water (pH 6.7 to 7.4). At a pH of 7.4, human pepsin is stable and can be revived by hydrogen ions. Because pepsin is a critical factor in harming the macro- and microenvironment of the cellular structure in the gastrointestinal tract, this may be beneficial as a treatment for reflux disease [12]. In the other clinical study on the subject of 50 gastritis patients who routinely consumed acidic water (lower than pH 5.0), ingestion of alkaline water (pH 8.5–10.0) for 5 months reduced the severity of gastritis symptoms, which implies that alkaline pH may have function to neutralize hydrochloric acid in the stomach [33]. Consequentially, this mechanism is likely to contribute to the improvement of reflux symptoms and abdominal pain in our GSRS results. EARW is one type of functional water that has several benefits in humans and this water includes special characteristics that make this water distinct from any other regular water or tap water. Depending on the generating mechanism, it has a pH between 8 and 10, a lower ORP, less oxygen, and is abundant in H_2 [14]. However, these function properties of this specific water characteristic such as OPR, pH, and H_2 are relatively unstable, hence drinking it on an empty stomach is suggested to improve the advantageous effects functional dyspepsia.

The pathogenesis of GI illnesses such as IBD is caused by the overproduction of ROS as a result of mitochondrial actions that are dysfunctional, which also causes an increase in the inflammatory response [34]. However, when consumed, EARW has anti-oxidative and anti-inflammatory qualities because it is high in H_2 and has a low ORP value, which can prevent oxidative stress (OS) by selectively scavenging ROS. According to Xue et al., drinking hydrogen-rich ARW may protect healthy individuals from gastric damage brought on by oxidative stress dose-dependently because hydrogen-rich water directly interacts with the target tissue [35]. Drinking ARW can assist with GI issues and gastrointestinal discomfort [20]. According to a double-blind placebo-controlled clinical study conducted by Tashiro et al., alkaline-ionized water is proven to be effective in treating abdominal symptoms such as dysphoria, abdominal distension, chronic diarrhea, and constipation [36]. Similar to this, according to Shin et al., 8 weeks of drinking ARW substantially reduced IBS symptoms and increased the IBS-related quality-of-life score [37]. Moreover, drinking EARW was known to be helpful in relieving abdominal discomfort and gastrointestinal problems [20]. Numerous GI diseases, including diarrhea, constipation, and gastritis, may be caused by the altered makeup and unbalanced intestinal microflora in addition to OS. Vorobjeva proposed that the residential microflora in the gut is the major target for EARW on the grounds that a negative ORP value (−300 to −400 mV) of the intestinal environment

is necessary for the recovery and preservation of necessary anaerobic microflora in the intestinal track [38]. In supporting this, Tanaka et al. conducted double-blind randomized trial to investigate drinking effect of hydrogen-rich ARW (500 mL/day) on stool consistency and gut microbiota for 2 weeks [39]. As a result, EARW group was confirmed to cause an increase in *Bifidobacterium*, and stool consistency significantly was recovered to normal state of Bristol stool scale. As such, the properties of EARW such as negative ORP and rich H_2 are supposed to contribute to improve intestinal symptoms caused by imbalance of gut microbiota milieu, which partially explain our positive result of abdominal pain and constipation.

In this study, we investigated the levels of inflammatory markers such as TNF-α, IFN-γ, IL-1β, IL-6, IL-10, and CBC to assess the safety of long-term drinking of EARW. TNF-α, IL-1β, IL-6, and IL-10 levels did not show significant differences between the baseline and post-intervention measurements. The levels of TNF-γ significantly decreased in the EARW group compared with the PW group after 6 weeks, and IFN-γ levels dramatically decreased after intervention in both the PW and EARW groups. TNF-α, IFN-γ, IL-1β, IL-6, and IL-10 are essential inflammatory markers for immune response and are crucial for controlling the inflammatory cascade [30]. Our findings regarding cytokines are supported by an earlier study by Naito et al. that found chronic administration of EARW prevented gastric mucosal damage in rats by inhibiting TNF-α [39]. By stopping cellular protein breakdown and inhibiting pro-inflammatory cytokines such as IL-1β, and TNF-α, Xue et al. also showed that consuming EARW can improve gastric injury through its impacts on the immune response [36]. TNF-α also helps to increase NF-kB synthesis, which leads to repeated inflammation [40]. Aside from that, consuming electrolyzed alkaline water can lower NF-α amounts in both protein and mRNA form. TNF-αmRNA levels in the stomach were also assessed, and they did increase in the wounded stomach. TNF-α is a gastric injury early reaction that can lead to the apoptosis of gastric endothelial and epithelial cells [41]. The safety of consuming EARW is supported by the clinical trial's findings regarding inflammation cytokines. Further evidence that long-term EARW consumption is safe for human health comes from the lack of adverse events during the intervention period and the results of the CBC test.

5. Conclusions

In conclusion, the present clinical study showed significant effects of drinking EARW in improving GI- and FD-related symptoms and FD-related QoL after 6-week intervention, presumably due to anti-oxidant and anti-inflammatory mechanisms of EARW. We applied home-based self-treatment for the intervention using the experimental device installed in each participant's house under the investigators' instructions. Our results suggest that self-administration of EARW may be valuable for the FD patients to relieve the symptoms, which is helpful for an additional and complementary intervention to the pharmacological treatment and life-style recommendations. No significant adverse effects were reported. We are not aware of any published clinical studies describing the effects of EARW. Numerous scientific studies support the fact that ARW is a well-known functional drinking water with significant therapeutic advantages, including the removal of free radicals and the decrease in inflammation. EARW might be a useful therapeutic approach for FD symptom alleviation to support these endeavors. However, more clinical study, including longer intervention times, is needed for more applicable application. Additional carefully designed clinical trials to examine the exact mechanism of EARW action on FD-related diseases and its symptoms are needed to fully support the claim.

Author Contributions: Conceptualization, K.-J.L.; Methodology, J.B., M.L., K.L., H.I.K. and H.J.P.; Software, C.-S.K. and H.I.K.; Validation, C.-S.K.; Formal Analysis, M.L. and S.S.; Investigation, H.I.K. and H.J.P.; Resources, C.-S.K. and S.H.G.; Data Curation, J.B. and Y.J.J.; Writing—Original Draft Preparation, J.B.; Writing—Review and Editing, M.L., C.-S.K., K.L., J.B. and Y.-G.J.; Visualization, H.J.P.; Supervision, C.-S.K.; Project Administration, K.-J.L.; Funding Acquisition, K.-J.L. All authors have read and agreed to the published version of the manuscript.

Funding: This research was supported by a grant from Ceragem Clinical, Inc.

Institutional Review Board Statement: This study was performed after obtaining approval from the institutional review board (IRB) of the Wonju Severance Christian Hospital in the Republic of Korea on 3 March 2022 (IRB number: CR221022). Written informed consent was obtained from all participants included in this study.

Informed Consent Statement: Not applicable.

Data Availability Statement: The data presented in this study are available in the article (tables and figures).

Acknowledgments: We would like to thank all the participants for their support in performing this study.

Conflicts of Interest: The authors declare no conflict of interest.

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