ISSN 1948-5190 (online)

World Journal of *Gastrointestinal Endoscopy*

World J Gastrointest Endosc 2024 May 16; 16(5): 227-272

Published by Baishideng Publishing Group Inc

World Journal of Gastrointestinal Endoscopy

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The *WJGE* is now abstracted and indexed in Emerging Sources Citation Index (Web of Science), PubMed, PubMed Central, Reference Citation Analysis, China Science and Technology Journal Database, and Superstar Journals Database. The 2023 Edition of Journal Citation Reports® cites the 2022 impact factor (IF) for *WJGE* as 2.0; IF without journal self cites: 1.9; 5-year IF: 3.3; Journal Citation Indicator: 0.28.

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NAME OF JOURNAL
World Journal of Gastrointestinal Endoscopy

ISSN
ISSN 1948-5190 (online)

LAUNCH DATE
October 15, 2009

FREQUENCY
Monthly

EDITORS-IN-CHIEF
Anastasios Koulaouzidis, Bing Hu, Sang Chul Lee, JooYoung Cho

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/1948-5190/editorialboard.htm

PUBLICATION DATE
May 16, 2024

PUBLISHING PARTNER
Digestive Endoscopy Center of West China Hospital, SCU

INSTRUCTIONS TO AUTHORS
https://www.wjgnet.com/bpg/gerinfo/204

GUIDELINES FOR ETHICS DOCUMENTS
https://www.wjgnet.com/bpg/GerInfo/287

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH
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PUBLICATION ETHICS
https://www.wjgnet.com/bpg/GerInfo/288

PUBLICATION MISCONDUCT
https://www.wjgnet.com/bpg/gerinfo/208

ARTICLE PROCESSING CHARGE
https://www.wjgnet.com/bpg/gerinfo/242

STEPS FOR SUBMITTING MANUSCRIPTS
https://www.wjgnet.com/bpg/GerInfo/239

ONLINE SUBMISSION
https://www.f6publishing.com

PUBLISHING PARTNER's OFFICIAL WEBSITE
http://www.cd120.com/index.html

World Journal of Gastrointestinal Endoscopy

Submit a Manuscript: https://www.f6publishing.com

World J Gastrointest Endosc 2024 May 16; 16(5): 259-272

DOI: 10.4253/wjge.v16.i5.259

ISSN 1948-5190 (online)

ORIGINAL ARTICLE

Prospective Study

Effect of vinegar supplementation on patients with esophageal lesions lightly stained with Lugol's iodine solution: Prospective single-centre trial

Yuan Gao, Lian-Song Ye, Xu Li, Bin Yu, Ke Liao, Jia Xie, Jiang Du, Qiong-Ying Zhang, Bing Hu

Specialty type: Gastroenterology and hepatology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade C, Grade C

Novelty: Grade B, Grade B

Creativity or Innovation: Grade B, Grade B

Scientific Significance: Grade B, Grade B

P-Reviewer: Tangsuwanaruk T, Thailand

Received: February 5, 2024

Revised: March 12, 2024

Accepted: April 22, 2024

Published online: May 16, 2024

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Abstract

BACKGROUND

Esophageal chromoendoscopy with iodine solution is important for detecting early esophageal cancer. The effect of routine treatment for lesions lightly stained with Lugol's iodine solution is limited, and the addition of natural substances to a regular diet is becoming increasingly common. Vinegar has antitumor effects as reported in previous studies.

AIM

To evaluate whether vinegar supplementation could improve the prognosis of patients with lightly stained esophageal lesions.

METHODS

This prospective single-centre trial included consecutive patients with lightly stained lesions between June 2020 and April 2022. Patients in the experimental group received increased amounts of vinegar for 6 months. The primary outcome of the study was the clinical therapeutic effect. Complications related to vinegar ingestion and adverse events were also recorded in detail.

RESULTS

A total of 166 patients were included in the final analysis. There was no significant difference in the baseline data between the two groups. Intention-to-treat (ITT) analysis demonstrated that the rates at which endoscopic characteristics improved were 33.72% in the experimental group and 20.00% in the conventional group (P = 0.007); and the rates at which biopsy pathology improved were 19.77% and 8.75%, respectively (P = 0.011). Additional vinegar consumption had a statistically protective effect on the rate at which endoscopic characteristics improved [hazard ratio (HR) $_{ITT}$ = 2.183, 95%CI: 1.183-4.028; $HR_{per\text{-}protocol\ (PP)}$ = 2.307, 95%CI: 1.202-4.426] and biopsy pathology improved (HR_{ITT} = 2.931, 95%CI: 1.212-7.089; HR_{PP} = 3.320, 95%CI: 1.295-8.507). No statistically significant effect of increased vinegar consumption on preventing high-grade intraepithelial neoplasia or early cancer was observed (HR_{ITT} = 0.382, 95%CI: 0.079-1.846; HR_{PP} = 0.382, 95%CI: 0.079-1.846). The subgroup analyses indicated that the overall therapeutic improvement of endoscopic characteristics and biopsy pathology seemed more obvious in older (age > 60) male patients with small lesions (lesion size ≤ 0.5 cm). Three patients in the experimental group reported acid regurgitation and heartburn. No adverse event during gastroscopy were recorded during follow-up.

CONCLUSION

A moderately increased ingestion of vinegar could not directly reduce the risk of esophageal cancer in the mucosa dysplasia population, but it improved the endoscopic characteristics and ameliorated the biopsy pathology to a certain extent. Further research is needed to verify the effect of nutritional intervention on precancerous esophageal lesions.

Key Words: Chromoendoscopy; Esophageal squamous epithelium; Vinegar; Atypical hyperplasia; Prognosis

Core Tip: Esophageal lesions stained lightly with iodine solution may progress pathologically even though they have a relatively better prognosis. Vinegar was thought to have an antitumor effect according to previous studies. However, its effect on lesion progression is still unclear. In the present study, we reported that moderate vinegar consumption improved the prognosis of several esophageal lesions lightly stained with Lugol's iodine solution at a tertiary referral endoscopy centre in China.

Citation: Gao Y, Ye LS, Li X, Yu B, Liao K, Xie J, Du J, Zhang QY, Hu B. Effect of vinegar supplementation on patients with esophageal lesions lightly stained with Lugol's iodine solution: Prospective single-centre trial. *World J Gastrointest Endosc* 2024; 16(5): 259-272

URL: https://www.wjgnet.com/1948-5190/full/v16/i5/259.htm

DOI: https://dx.doi.org/10.4253/wjge.v16.i5.259

INTRODUCTION

Esophageal cancer is the eighth most common malignancy worldwide with more than 600000 new cases diagnosed annually[1]. The poor prognosis and increasing incidence of esophageal cancer highlight the need for improved detection and prediction methods[2-4]. Esophageal chromoendoscopy with iodine solution is an important diagnostic method for detecting superficial esophageal cancer[5]. The esophageal mucosa is considered abnormal when there are "unstained" or "lightly stained" lesions[6]. Generally, unstained areas indicate high-grade intraepithelial neoplasia (HGIN) or early cancer, while lightly stained areas generally indicate inflammation, squamous epithelial hyperplasia, low-grade intraepithelial neoplasia (LGIN), *etc.*[7]. Endoscopic resection is recommended for treating HGIN and early cancer, while continuous surveillance is recommended mainly for treating LGIN and squamous hyperplasia because these conditions are thought to have relatively better prognoses[3,8]. Most authorities recommend increased endoscopic surveillance with biopsies and a healthy diet for these lightly stained lesions, but the progression of these lesions cannot be ignored[9,10].

Previous laboratory experiments and trials have demonstrated that vinegar can block the synthesis of N nitroso compounds and proline nitrosamines, which can induce cancer in the human body, making this agent capable of preventing cancer[11-14]. Retrospective clinical studies have also reported that vinegar consumption is associated with a decreased risk for esophageal cancer[15,16]. However, no prospective clinical study has verified these findings.

This prospective clinical trial was designed to evaluate whether increased vinegar consumption could improve the prognosis of patients with lightly stained esophageal lesions.

MATERIALS AND METHODS

Study design

This prospective clinical trial was conducted at the Endoscopy Center of West China Hospital, Sichuan University, China. The study protocol was approved by the Biomedical Research Ethics Committee, West China Hospital of Sichuan University (No. HX-IRB-AF-03-V3.0) and was registered in the Chinese Clinical Trial Registry (No. ChiCTR1900024686).

Patient enrolment

Patients were enrolled in this study after receiving endoscopic evaluations from June 1, 2020, to April 30, 2022 , at a tertiary referral endoscopy centre in China. In accordance with the inclusion criteria, patients were selected as follows: (1) Patients aged 18–80 years; (2) underwent gastroscopy and biopsy histopathology; and (3) had esophageal lesions lightly stained with Lugol's iodine solution. The exclusion criteria prohibited inclusion of the following patients: (1) Patients were pregnant or lactating; (2) patients who had an allergy to iodine and its derivatives; (3) patients who had a tumour requiring surgery, chemotherapy or radiotherapy; (4) patients who had reflux esophagitis; and (5) patients who refused to participate in the study or were unable to provide informed consent. All patients received a preoperative consultation with a detailed explanation of the pros and cons of different approaches, including endoscopic resection, increased vinegar intake and surveillance. Written informed consent was obtained from all patients or their legal representatives.

Allocation and intervention

A total of 166 patients who underwent gastroscopy and had histopathological proof of lightly stained esophageal lesions were recruited for the study and assigned to two groups according to patient choice: The experimental group and the conventional group. Allocation of eligible patients was completed by two nurses who were not directly involved in the data analysis or patient enrolment. Investigators who were involved in the data analysis and endoscopists were blinded to the group assignments until all the data collection and data queries had been completed and the database was locked.

Patients assigned to the experimental group received 20 mg of 9% Baoning vinegar (Sichuan Baoning Vinegar Co., Ltd., Langzhong, China) three times a day (tid) diluted with 50 mL of warm water for 6 months. The amount of vinegar used was determined according to previous retrospective reports, which showed that the incidence rate of esophageal cancer in people who consumed ≥ 40 g/w vinegar was significantly lower than that in people who consumed 0-39 g/w vinegar [16]. The use of other drugs was stopped when the patient consumed more vinegar. Patients assigned to the conventional group received the same health education to quit smoking, stop drinking, and avoid hot and spicy food.

Outcomes and study evaluations

The primary outcome of the study was the clinical therapeutic effect, which was classified into the following four categories. Endoscopic characteristics improved is defined as a reduction of more than 50% in the maximum diameter of the lesion, or a reduction of more than 50% in the number of lesions. Endoscopic characteristics deteriorated is defined as an increase of more than 50% in the maximum diameter of the lesion or an increase of more than 50% in the number of lesions. Biopsy pathology improved is defined as less malignant pathological results than before. Biopsy pathology deteriorated is defined as more malignant pathological results than before. The incidence of lesions progressing to HGIN or early cancer in patients was also concerned. The rates were determined by both intention-to-treat (ITT)- and per-protocol (PP)-based analyses. All enrolled patients were included in the ITT analysis, but the PP analysis excluded those patients who dropped out due to side effects, loss to follow-up, or poor compliance.

During the experiment, members of the quality supervision team contacted the patients through interviews and phone calls every month to remind them to consume vinegar. The investigator recorded all complications related to vinegar therapy, such as acid regurgitation, heartburn, nausea, vomiting, taste abnormalities, abdominal pain, abdominal distension, and diarrhoea[12]. The compliance of patients with medication and incidence of complications was assessed by conducting a questionnaire at the following points: Before treatment, during treatment (1 wk, 2 wk, 3 wk, 1 month, 3 months), and after treatment (6 months). The gastroscopy and biopsy histopathology re-examinations were arranged after treatment completion and follow-up. Adverse events during gastroscopy were also recorded and were defined as bleeding, perforation or severe cardiopulmonary accidents[17]. After treatment completion, the patients were followed up monthly, hospital medical records were reviewed, and endoscopic and pathological examination results were collected. All patients were followed until December 13, 2023. The time to show treatment effect was also recorded, and deterioration of the lesion was treated with caution. A team of senior doctors conducted a review to ultimately determine the changes in the lesions and ensure the accuracy of the judgement. Two people completed the data analysis in parallel to ensure the accuracy of the data.

Sample size and statistical analysis

Based on previous studies showing that increased vinegar consumption reduces the incidence of esophageal cancer[6,15], we expected a difference in the incidence rate of esophageal cancer between health education therapy combined with increased vinegar ingestion and health education therapy alone (10% *vs* 25%). The model has a power of 80% and a two-sided significance level of 0.05 with an assumed 10% dropout rate. Survival analysis based on the Log-rank test was performed with a final sample size of 154 patients (77 per group). The full analysis set should be as close as possible to the ITT set. The standards and population of the PP dataset was to be finalized after data-blinding verification. The direct deletion method was used to treat missing data.

In this study, the demographic and clinical characteristics of the patients are summarized as the mean ± SD or median (interquartile range) based on their distribution type. The incidence rates of therapeutic outcomes are expressed in terms of the number of patients and percentage. Qualitative variables were compared using the Chi-squared test, while Student's *t*-test was used for quantitative variables. The specific test methods used are listed below the table. A Cox proportional hazard model was used to estimate the hazard ratio (HR) and 95%CI. Comparisons of clinical therapeutic effects between two groups were performed using the Log-rank test, Kaplan-Meier curves were generated, and a two-tailed P value < 0.05 was considered to indicate statistical significance. Subgroup analyses were performed by age, gender, lesion size, lesion location and biopsy characteristics[18-20]. All the statistical analyses were performed by blinded professional statisticians with IBM SPSS for Mac (version 26.0 statistical software package; Armonk, NY: IBM Corp.).

RESULTS

Patient disposition and baseline characteristics

A total of 194 patients who fulfilled the inclusion criteria were enrolled in this trial, with 86 patients in the experimental group and 80 patients in the conventional group were included in the ITT analysis. Ten patients (6.0%) were excluded from the PP analysis. Three patients in the experimental group discontinued treatment because of severe acid regurgitation and heartburn, while 1 patient in the conventional group discontinued treatment because of excessive alcohol consumption. Poor treatment compliance was reported for 2 (2.3%) patients and 1 (1.3%) patient in the experimental group and conventional group, respectively. In addition, there was 1 patient in the experimental group who dropped out of treatment because of pregnancy (Figure 1). Two patients in the conventional group were lost to follow-up. At baseline, there were no statistically significant differences in the baseline characteristics of the patients included in the two study groups in either the ITT analysis or the PP analysis (Tables 1 and 2).

Clinical therapeutic outcomes

ITT analysis demonstrated that the incidence rates of endoscopic characteristics improved were 33.72% in the experimental group and 20.00% in the conventional group (P = 0.007). PP analysis indicated that 32.50% of the patients in the experimental group and 18.42% of the patients in the conventional group achieved endoscopic improved (P = 0.007). ITT analysis demonstrated that the incidence rates of biopsy pathology improved were 19.77% in the experimental group and 8.75% in the conventional group (P = 0.011). PP analysis indicated that the percentage of patients whose biopsy pathology improved was 20.00% in the experimental group and 7.89% in the conventional group (P = 0.007). Both ITT and PP analyses revealed no significant differences in the incidence rates of endoscopic characteristics deteriorate or biopsy pathology deteriorate between the experimental group and conventional group. Figures 2 and 3 depict the Kaplan-Meier survival curves for each group in the ITT analysis or PP analysis, respectively, considering the time interval before progression or improvement of each patient.

An increase in vinegar consumption had a statistically protective effect on the rate of improvement of endoscopic characteristics (HR_{ITT} = 2.183, 95%CI: 1.183-4.028; HR_{PP} = 2.307, 95%CI: 1.202-4.426), and biopsy pathology improved (HR_{ITT} = 2.931, 95%CI: 1.212-7.089; HR_{PP} = 3.320, 95%CI: 1.295-8.507). However, no statistically significant protective effect of increasing vinegar consumption on preventing the risk of developing HGIN or early cancer was observed (HR_{ITT} = 0.382, 95%CI: 0.079-1.846; HR_{PP} = 0.382, 95%CI: 0.079-1.846). After adjusting for age, gender, lesion size, lesion location and biopsy characteristics, an impact of vinegar consumption on decreasing cancer risk was not observed (Tables 3 and 4).

The subgroup analyses (Tables 5 and 6) indicated that the overall therapeutic improvement in endoscopic characteristics and biopsy pathology seemed more obvious in older (age > 60) male patients with small lesions (lesion size ≤ 0.5 cm).

Adverse events

Only 3 patients in the experimental group experienced adverse events related to vinegar therapy; 2 patients experienced severe acid regurgitation and heartburn, and 1 patient claimed taste abnormalities. These patients experienced symptom relief after the cessation of vinegar ingestion, and the symptoms may have been related to mucosal stimulation in the mouth, pharynx, and esophagus caused by vinegar. No severe adverse events during gastroscopy were recorded during reexamination.

DISCUSSION

This prospective clinical trial was designed to explore the influence of increased vinegar consumption on the prognosis of patients with lightly stained esophageal lesions. Our study revealed that increased vinegar consumption did not reduce the risk of esophageal cancer in the esophageal mucosa dysplasia population, but it improved the endoscopic characteristics of a considerable number of patients with early lesions of the esophageal mucosa according to the ITT analysis (33.72% *vs* 20.00%, P = 0.007), and biopsy pathology improved (19.77% *vs* 8.75%, P = 0.011).

It has been reported that the progression of esophageal mucosa generally progresses through the stages of normal epithelium, mild atypical hyperplasia, moderate atypical hyperplasia, severe atypical hyperplasia, carcinoma in situ,

Table 1 Characteristics of patients and lesions (intention-to-treat population), *n* (%)

Characteristics	Experimental group	Conventional group	*P* value
No. of participants	86	80	
Age, mean ± SD, yr	59.84 ± 8.40	59.75 ± 9.21	0.949[1]
BMI, mean ± SD, kg/m^2	23.89 ± 3.35	23.49 ± 2.29	0.372[1]
Sex			0.798[2]
Male	51 (59.30)	49 (61.25)	
Female	35 (40.70)	31 (38.75)	
Basic diseases			
Diabetes	9 (10.47)	8 (10.00)	0.921[2]
Hypertension	14 (16.28)	6 (7.50)	0.083[2]
Coronary heart disease	4 (4.65)	4 (5.00)	0.916[2]
Family history of esophageal cancer or stomach cancer			0.800[2]
No	67 (77.91)	61 (76.25)	
Yes	19 (22.09)	19 (23.75)	
Smoking			0.899[2]
No-smoker	46 (53.49)	42 (52.50)	
Smoker	40 (46.51)	38 (47.50)	
Smoking index			0.618[2]
≤ 200	15 (17.44)	11 (13.75)	
200-400	14 (16.28)	13 (16.25)	
≥ 400	11 (12.79)	14 (17.50)	
Alcohol drinking			0.712[2]
No-drinker	39 (45.35)	34 (42.50)	
Drinker	47 (54.65)	46 (57.50)	
Alcohol ingestion, g/d			0.833[2]
≤ 20	23 (26.74)	20 (25.00)	
20-60	13 (15.12)	13 (16.25)	
≥ 60	11 (12.79)	13 (16.25)	
Prefer hot dishes/hot tea			0.459[2]
No	50 (59.14)	51 (63.75)	
Yes	36 (41.86)	29 (36.25)	
Prefer spicy food			0.227[2]
No	76 (88.37)	75 (93.75)	
Yes	10 (11.63)	5 (6.25)	
Prefer pickled dishes			0.095[2]
No	77 (89.53)	77 (96.25)	
Yes	9 (10.47)	3 (3.75)	
Multiple Lugol's voiding lesions			0.208[2]
No	52 (65.00)	57 (75.00)	
Yes	28 (35.00)	19 (25.00)	
Lesion location			0.197[2]

Upper thoracic esophagus	12 (13.95)	8 (10.00)	
Middle thoracic esophagus	44 (51.16)	52 (65.00)	
Lower thoracic esophagus	30 (34.88)	20 (25.00)	
Maximum diameter			0.134[2]
Lesion size ≤ 0.5 cm	65 (75.58)	54 (67.50)	
Lesion size > 0.5 cm	21 (24.42)	26 (32.50)	
Morphology			0.324[2]
Quasi circular	31 (36.05)	30 (37.50)	
Bar-type	3 (3.49)	7 (8.75)	
Irregular shape	52 (60.47)	43 (53.75)	
Biopsy pathology			0.506[2]
Squamous epithelial hyperplasia	77 (89.53)	74 (92.50)	
Low grade intraepithelial neoplasia	9 (10.47)	6 (7.50)	
Follow-up time	28.92 ± 6.04	30.48 ± 5.88	0.0958[1]

[1]Student's *t*-test.
[2]Chi-squared test.
Multiple Lugol's voiding lesions: ≥ 10 Lugol's voiding lesions per endoscopic field of vision. Smoking index = length of smoking (year) × daily cigarette consumption. Alcohol ingestion = daily alcohol consumption (mL) × alcohol concentration × 0.8.

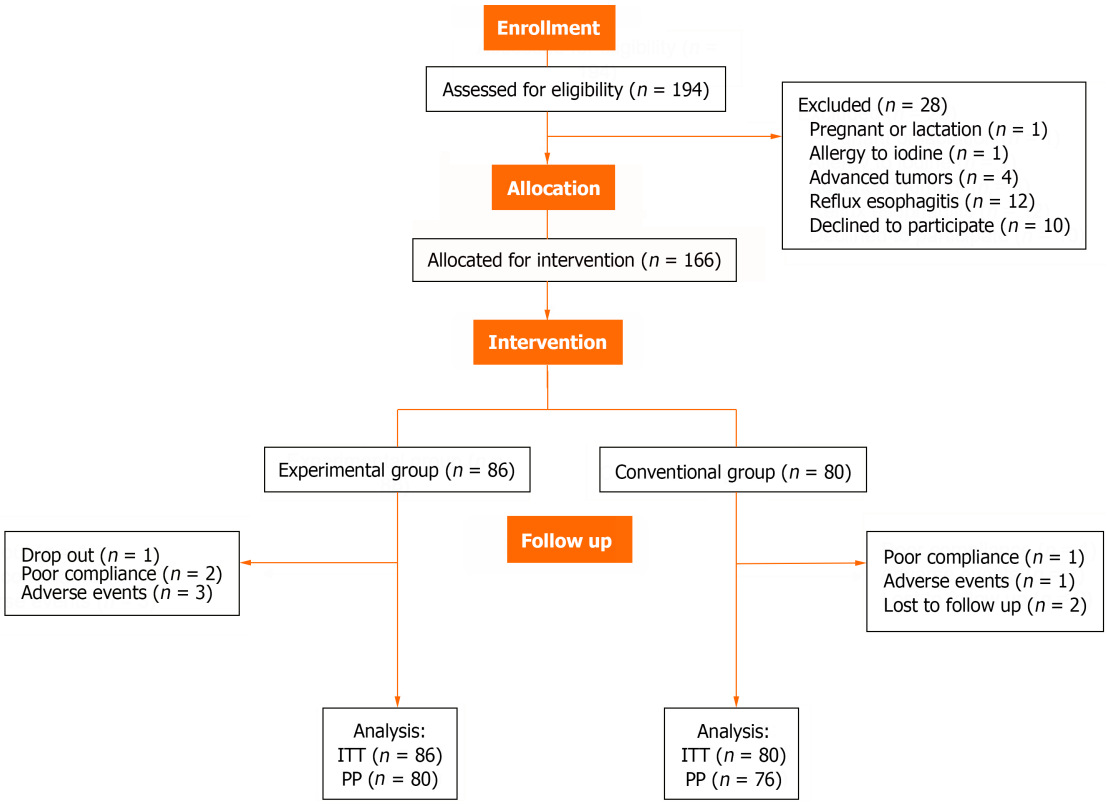

Figure 1 Flow chart of the patients in the cohort study. ITT: Intention-to-treat; PP: Per-protocol.

invasive carcinoma, *etc*[21]. Although esophageal dysplasia does not require immediate endoscopic resection, surveillance should be maintained because of the potential risk of early esophageal cancer or precancerous lesions[22-24]. Early treatment of esophageal mucosal lesions is helpful for preventing progression to esophageal cancer. Currently, treatment for esophageal cancer relies mainly on early screening and diagnosis. For these early lesions, endoscopic resection or special drug intervention is not yet necessary, but preventing progression at an early stage through dietary intervention is very meaningful.

Table 2 Characteristics of patients and lesions (per-protocol population), *n* (%)

Characteristics	Experimental group	Conventional group	*P* value
No. of participants	80	76	
Age, mean ± SD, yr	59.69 ± 8.47	59.32 ± 9.22	0.793[1]
BMI, mean ± SD, kg/m^2	23.93 ± 3.43	23.49 ± 2.28	0.070[1]
Sex			0.535[2]
Male	49 (61.25)	47 (61.84)	
Female	31 (38.75)	29 (38.16)	
Basic diseases			
Diabetes	9 (11.25)	8 (10.53)	0.545[2]
Hypertension	13 (16.25)	6 (7.89)	0.143[2]
Coronary heart disease	3 (3.75)	4 (5.26)	0.949[2]
Family history of esophageal cancer or stomach cancer			0.984[2]
No	62 (77.50)	59 (77.63)	
Yes	18 (22.50)	17 (22.37)	
Smoking			0.863[2]
No-smoker	41 (51.25)	40 (52.63)	
Smoker	39 (48.75)	36 (47.37)	
Smoking index			0.687[2]
≤ 200	14 (17.50)	10 (13.16)	
200-400	14 (17.50)	13 (17.11)	
≥ 400	11 (13.75)	13 (17.11)	
Alcohol drinking			0.836[2]
No-drinker	35 (45.75)	32 (42.11)	
Drinker	45 (56.25)	44 (57.89)	
Alcohol ingestion, g/d			0.936[2]
≤ 20	21 (26.25)	19 (25.00)	
20-60	13 (16.25)	13 (17.11)	
≥ 60	11 (13.75)	12 (15.79)	
Prefer hot dishes/hot tea			0.287[2]
No	46 (57.50)	50 (65.79)	
Yes	34 (42.50)	26 (34.21)	
Prefer spicy food			0.210[2]
No	70 (8.75)	71 (93.42)	
Yes	10 (12.50)	5 (6.58)	
Prefer pickled dishes			0.087[2]
No	71 (88.75)	73 (96.05)	
Yes	9 (11.25)	3 (3.95)	
Multiple Lugol's voiding lesions			0.3018[2]
No	54 (67.50)	57 (75.00)	
Yes	26 (32.50)	19 (25.00)	
Lesion location			0.194[2]
Upper thoracic esophagus	12 (15.00)	8 (10.53)	

Middle thoracic esophagus	39 (48.75)	48 (63.16)	
Lower thoracic esophagus	29 (36.25)	20 (26.32)	
Maximum diameter			0.379[2]
Lesion size ≤ 0.5 cm	60 (75.00)	52 (68.42)	
Lesion size > 0.5 cm	20 (25.00)	24 (31.58)	
Morphology			0.518[2]
Quasi circular	29 (36.25)	28 (36.84)	
Bar-type	3 (3.75)	6 (7.89)	
Irregular shape	48 (60.00)	42 (55.26)	
Biopsy pathology			0.477[2]
Squamous epithelial hyperplasia	71 (88.75)	70 (92.11)	
Low grade intraepithelial neoplasia	9 (11.25)	6 (7.89)	
Follow-up time	29.53 ± 5.73	31.00 ± 5.52	0.514[1]

[1]Student's *t*-test.
[2]Chi-squared test.
BMI: Body mass index.

Table 3 Hazard ratio and 95%CI of clinical therapeutic outcomes (intention-to-treat population)

Therapeutic effect	HR (95%CI)	Multivariable adjusted HR (95%CI)[1]
Endoscopic characteristics improved		
Conventional group	1.00	1.00
Experimental group	2.183 (1.183, 4.028)[a]	2.515 (1.318, 4.800)[b]
Endoscopic characteristics deteriorate		
Conventional group	1.00	1.00
Experimental group	0.791 (0.305, 2.048)	0.976 (0.920, 1.035)
Biopsy pathology improved		
Conventional group	1.00	1.00
Experimental group	2.931 (1.212, 7.089)[a]	2.710 (1.066, 6.891)[a]
Biopsy pathology deteriorate		
Conventional group	1.00	1.00
Experimental group	0.690 (0.230, 2.069)	0.983 (0.911, 1.060)
HGIN or early cancer		
Conventional group	1.00	1.00
Experimental group	0.382 (0.079, 1.846)	0.833 (0.125, 5.560)

[a]P 0.05.
[b]P 0.01.
[1]Adjusted by age, sex, lesion size, lesion location and biopsy characteristics.
HR: Hazard ratio; HGIN: High-grade intraepithelial neoplasia.

In recent years, the use of natural food additives for the prevention and treatment of diseases has increased. Previous nutritional intervention cohort studies have shown that appropriate doses of vitamin and mineral supplements may have a preventive effect on chronic diseases caused by malignant tumours[25,26]. However, in a study on the effect of multivitamin and mineral nutrition intervention on the mortality of upper digestive tract tumours in a population with severe esophageal squamous epithelial hyperplasia in China that had been followed up for 35 years after a 6-year intervention period, no effect of multivitamin or mineral nutrition on the mortality of upper digestive tract tumours in the population was observed[27]. Another prospective study showed that the Qilian Shupi Granule had a pathological reversal effect on

Table 4 Hazard ratio and 95%CI of clinical therapeutic outcomes (per-protocol population)

Therapeutic effect	HR (95%CI)	Multivariable adjusted HR (95%CI)[1]
Endoscopic characteristics improved		
Conventional group	1.00	1.00
Experimental group	2.307 (1.202, 4.426)[a]	2.545 (1.282, 5.052)[b]
Endoscopic characteristics deteriorate		
Conventional group	1.00	1.00
Experimental group	0.793 (0.306, 2.055)	0.979 (0.923, 1.037)
Biopsy pathology improved		
Conventional group	1.00	1.00
Experimental group	3.320 (1.295, 8.507)[a]	3.186 (1.179, 8.605)[a]
Biopsy pathology deteriorate		
Conventional group	1.00	1.00
Experimental group	0.795 (0.259, 2.440)	0.969 (0.896, 1.048)
HGIN or early cancer		
Conventional group	1.00	1.00
Experimental group	0.382 (0.079, 1.846)	0.750 (0.140, 4.015)

[a]*P* 0.05.
[b]*P* 0.01.
[1]adjusted by age, sex, lesion size, lesion location and biopsy characteristics.
HR: Hazard ratio; HGIN: High-grade intraepithelial neoplasia.

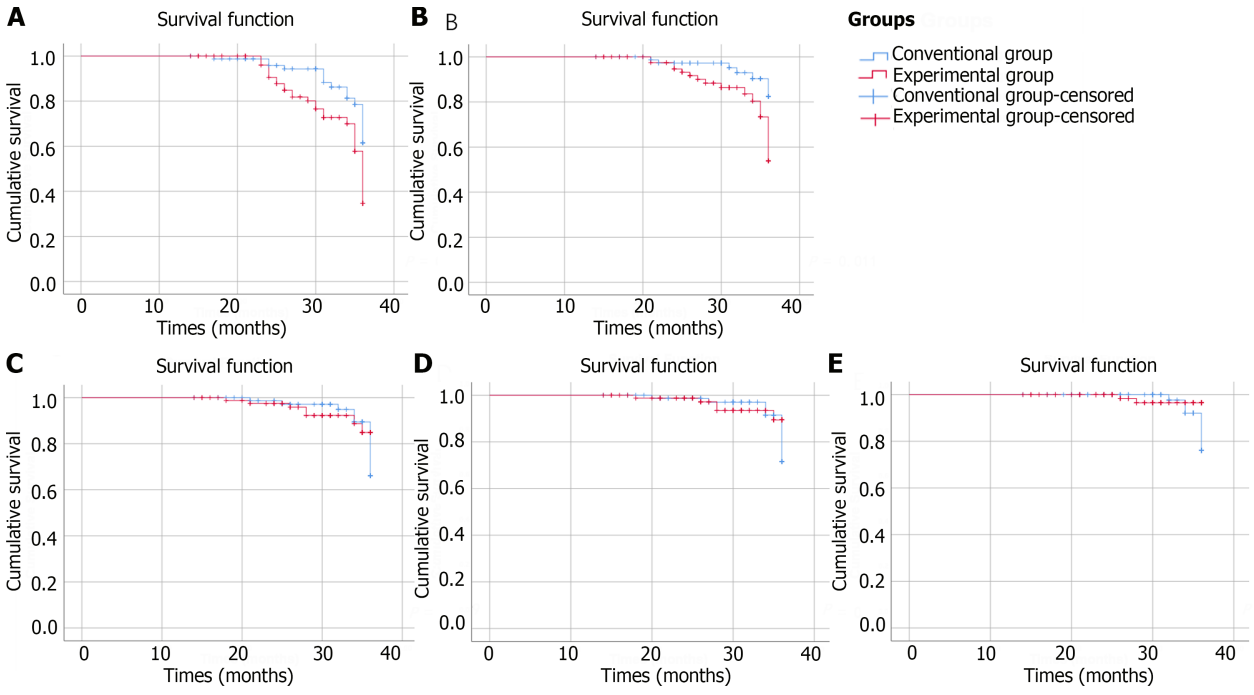

Figure 2 Kaplan-Meyer survival analysis (intention-to-treat population). A: Endoscopic characteristics improved; B: Biopsy pathology improved; C: Endoscopic characteristics deteriorated; D: Biopsy pathology deteriorated; E: Lesions progressing to high-grade intraepithelial neoplasia or early cancer.

Table 5 Subgroup analyses for endoscopic characteristics improved (intention-to-treat population)

Subgroup	Number (*n*)	Rate (%)	HR (95%CI)	*P* value
Male (*n* = 100)				0.008
Conventional group (*n* = 49)	7	14.29	1.00	
Experimental group (*n* = 51)	19	37.25	3.232 (1.353, 7.719)	
Female (*n* = 66)				0.542
Conventional group (*n* = 31)	9	29.03	1.00	
Experimental group (*n* = 35)	10	28.57	1.324 (0.537, 3.263)	
Age > 60 (*n* = 82)				0.008
Conventional group (*n* = 42)	7	16.67	1.00	
Experimental group (*n* = 40)	15	37.50	3.425 (1.380, 8.497)	
Age ≤ 60 (*n* = 84)				
Conventional group (*n* = 38)	9	23.68	1.00	0.395
Experimental group (*n* = 46)	14	30.43	1.438 (0.622, 3.323)	
Lesion size ≤ 0.5 cm (*n* = 119)				0.010
Conventional group (*n* = 54)	10	18.52	1.00	
Experimental group (*n* = 65)	24	36.92	2.708 (1.263, 5.806)	
Lesion size > 0.5 cm (*n* = 47)				0.794
Conventional group (*n* = 26)	6	23.08	1.00	
Experimental group (*n* = 21)	5	23.81	1.181 (0.339, 4.119)	
Lesion in upper thoracic esophagus (*n* = 20)				0.123
Conventional group (*n* = 8)	2	25.00	1.00	
Experimental group (*n* = 12)	5	41.67	3.686 (0.701, 19.366)	
Lesion in middle thoracic esophagus (*n* = 96)				0.245
Conventional group (*n* = 52)	12	23.08	1.00	
Experimental group (*n* = 44)	13	29.55	1.596 (0.726, 3.506)	
Lesion in lower thoracic esophagus (*n* = 50)				0.060
Conventional group (*n* = 20)	2	10.00	1.00	
Experimental group (*n* = 30)	11	36.67	4.265 (0.943, 19.298)	
Undergone esophageal ESD previously (*n* = 65)				0.078
Conventional group (*n* = 29)	5	17.24	1.00	
Experimental group (*n* = 36)	12	33.3	2.386 (0.908, 6.267)	
Not undergone esophageal ESD previously (*n* = 101)				0.076
Conventional group (*n* = 51)	11	21.57	1.00	
Experimental group (*n* = 50)	17	34.00	2.100 (0.924, 4.772)	
Lesion biopsy: Squamous epithelial hyperplasia (*n* = 151)				0.009
Conventional group (*n* = 74)	14	18.92	1.00	
Experimental group (*n* = 77)	26	33.77	2.380 (1.238, 4.575)	
Lesion biopsy: Low grade intraepithelial neoplasia (*n* = 15)				0.814
Conventional group (*n* = 6)	2	33.3	1.00	
Experimental group (*n* = 9)	3	33.3	1.241 (0.206, 7.479)	

HR: Hazard ratio; ESD: Endoscopic submucosal dissection.

Table 6 Subgroup analyses for biopsy pathology improved (intention-to-treat population)

Subgroup	Number (*n*)	Rate (%)	HR (95%CI)	*P* value
Male (*n* = 100)				0.043
Conventional group (*n* = 49)	4	8.16	1.00	
Experimental group (*n* = 51)	11	21.57	3.285 (1.040, 10.375)	
Female (*n* = 66)				0.227
Conventional group (*n* = 31)	3	9.68	1.00	
Experimental group (*n* = 35)	6	17.14	2.356 (0.587, 9.449)	
Age > 60 (*n* = 82)				0.035
Conventional group (*n* = 42)	4	9.52	1.00	
Experimental group (*n* = 40)	9	22.50	3.609 (1.091, 11.933)	
Age ≤ 60 (*n* = 84)				0.187
Conventional group (*n* = 38)	3	7.89	1.00	
Experimental group (*n* = 46)	8	17.39	2.444 (0.648, 9.216)	
Lesion size ≤ 0.5 cm (*n* = 119)				0.042
Conventional group (*n* = 54)	3	5.56	1.00	
Experimental group (*n* = 65)	14	21.54	3.199 (1.042, 9.820)	
Lesion size > 0.5cm (*n* = 47)				0.214
Conventional group (*n* = 26)	4	15.38	1.00	
Experimental group (*n* = 21)	3	14.29	2.626 (0.573, 12.033)	
Lesion in upper thoracic esophagus (*n* = 20)				0.440
Conventional group (*n* = 8)	1	12.50	1.00	
Experimental group (*n* = 12)	2	16.67	2.610 (0.229, 29.702)	
Lesion in middle thoracic esophagus (*n* = 96)				0.108
Conventional group (*n* = 52)	5	9.62	1.00	
Experimental group (*n* = 44)	8	18.18	2.510 (0.817, 7.708)	
Lesion in lower thoracic esophagus (*n* = 50)				0.112
Conventional group (*n* = 20)	1	5.00	1.00	
Experimental group (*n* = 30)	7	23.33	5.485 (0.673, 44.705)	
Undergone esophageal ESD previously (*n* = 65)				0.088
Conventional group (*n* = 29)	2	6.90	1.00	
Experimental group (*n* = 36)	5	13.89	4.462 (0.799, 24.917)	
Not undergone esophageal ESD previously (*n* = 101)				0.135
Conventional group (*n* = 51)	5	9.80	1.00	
Experimental group (*n* = 50)	12	24.00	2.198 (0.783, 6.171)	
Lesion biopsy: Squamous epithelial hyperplasia (*n* = 151)				0.056
Conventional group (*n* = 74)	5	6.76	1.00	
Experimental group (*n* = 77)	11	14.29	2.820 (0.974, 8.161)	
Lesion biopsy: Low grade intraepithelial neoplasia (*n* = 15)				0.342
Conventional group (*n* = 6)	2	33.33	1.00	
Experimental group (*n* = 9)	6	66.67	2.184 (0.436, 10.936)	

HR: Hazard ratio; ESD: Endoscopic submucosal dissection.

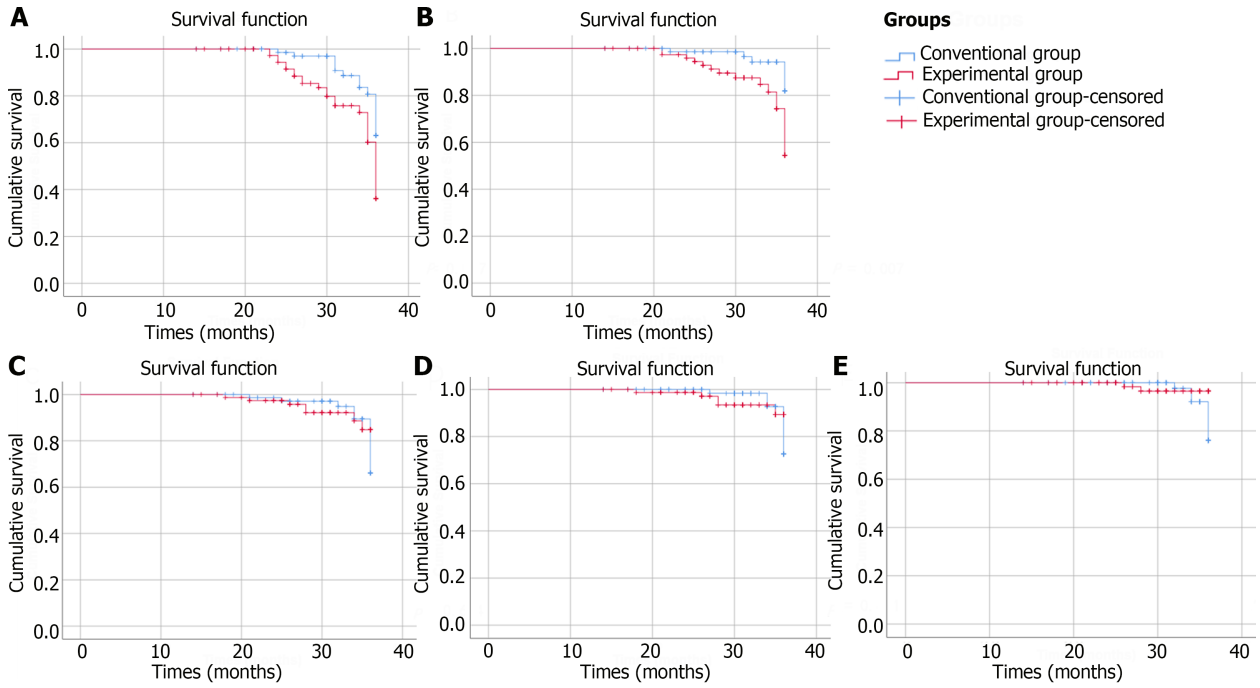

Figure 3 Kaplan-Meyer survival analysis (per-protocol population). A: Endoscopic characteristics improved; B: Biopsy pathology improved; C: Endoscopic characteristics deteriorated; D: Biopsy pathology deteriorated; E: Lesions progressing to high-grade intraepithelial neoplasia or early cancer.

mild and moderate atypical hyperplasia of the esophageal squamous epithelium, but the number of patients studied was relatively small[28]. Dietary intervention for esophageal lesions lightly stained with Lugol's iodine solution is still worth studying.

Both grain vinegar and fruit vinegar, which are fermented by traditional methods, possess a variety of physiological functions, such as antibacterial, anti-infection, antioxidative, blood glucose control, lipid metabolism regulation, weight loss, and anticancer activities[12]. Several grain vinegars, such as Shanxi aged vinegar and Japanese black vinegar, strongly inhibit the growth of several types of cancer cells *in vivo* or in vitro[29,30]. Polyphenols (such as resveratrol) in some fruits have anticancer effects; thus, the long-term ingestion of fruit vinegar may also have a positive anticancer effect in humans[31,32]. According to the results of epidemiological investigations, the incidence of esophageal cancer in Linzhou (Henan, China) is negatively correlated with grain vinegar consumption[16]. In theory, supplementation with vinegar has a positive effect on the prevention of upper gastrointestinal tumours in the general population. However, as a consumable substance, vinegar may have a notable short-term health promoting effect, but its impact on the long-term risk of disease is highly controversial. In this study, it was also observed that vinegar supplementation could improve endoscopic morphology and biopsy pathology, but there was no clear statistical significance in preventing the risk of disease progression to HGIN/early cancer after analysis. This may be because the population has already experienced esophageal squamous cell hyperplasia. Supplying vinegar to such patients cannot promote the reversion of proliferative esophageal squamous epithelial cells to a normal morphology; it delays the progression of lesions to a certain extent but cannot prevent the occurrence of cancer. Based on the above results, we speculate that the therapeutic effect of vinegar on patients may be related to the fact that vinegar can improve the proliferation and differentiation of esophageal mucosal cells, regulate the body's immunity, eliminate free radicals, and improve esophageal blood flow. In addition, the consumption of vinegar in patients with reflux esophagitis increases the risk of acid regurgitation and heartburn, so it is not recommended for these patients.

This clinical trial has several limitations. First, randomization was not performed because of patient cooperation, and selection bias may have resulted. Second, the study was limited by its single-centre nature, which also led to some data bias. Third, a larger sample size and further evaluation could more strongly support the research conclusion. The number of patients with HGIN or early cancer who developed in the experimental group within 2 years was lower than that in the conventional group, indicating that the intervention measures may have been effective and that the absolute value of occurrence may have been reduced. However, the statistical test showed no difference, which could be caused by an insufficient sample size and insufficient follow-up observation time.

CONCLUSION

This study showed that increased ingestion of vinegar could not directly reduce the risk of esophageal cancer in patients with esophageal mucosa dysplasia. A considerable number of patients benefit from vinegar ingestion, which results in improved endoscopic morphology and pathology. Due to the many limitations of this trial, including the lack of randomization, the results should be interpreted with caution, and further studies are needed.

FOOTNOTES

Author contributions: Author contributions: Ye LS and Hu B designed the research; Gao Y, Ke Liao, Xie J, Du J and Zhang QY performed the research and collected the data; Gao Y and Li X analyzed the data and drafted the manuscript; Ye LS, Zhang QY, and Hu B revised the manuscript; All authors performed acquisition of data, contributed to the article, and approved the submitted manuscript.

Supported by the 1-3-5 Project for Disciplines of Excellence-Clinical Research Incubation Project, West China Hospital, Sichuan University, No. 2020HXFH016; and the Med-X Innovation Programme of Med-X Center for Materials, Sichuan University, No. MCM202302.

Institutional review board statement: The study protocol was approved by the Biomedical Research Ethics Committee, West China Hospital of Sichuan University (No. HX-IRB-AF-03-V3.0).

Clinical trial registration statement: This registration policy applies to prospective, controlled trials. The protocol was registered at https://www.chictr.org.cn/showproj.html?proj%20=%204134, registration identifier: ChiCTR1900024686.

Informed consent statement: All study participants, or their legal guardians, provided informed written consent prior to study enrollment.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Data sharing statement: No additional data are available.

CONSORT 2010 statement: Randomization was not performed in this study, so the manuscript was prepared and revised according to the TREND (transparent reporting of evaluations with nonrandomized designs) statement. The TREND statement has a 22-item checklist Cdc-pdf specifically developed to guide standardized reporting of nonrandomized controlled trials. The TREND statement complements the widely adopted Consolidated Standards Of Reporting Trials (CONSORT) statement developed for randomized controlled trials.

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S-Editor: Li L
L-Editor: A
P-Editor: Cai YX

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