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Original Article

Esomeprazole plus trimebutine maleate improves symptoms, esophageal function, and acid control without increasing risks in elderly GERD: a real-world retrospective study

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Abstract: Objectives: Elderly patients with gastroesophageal reflux disease (GERD) often exhibit inadequate response to proton pump inhibitor monotherapy due to accompanying motility disorders. This study evaluated the real-world safety and efficacy of esomeprazole (EMZ) combined with trimebutine maleate (TM) in this population. Methods: This retrospective analysis included elderly GERD patients treated at The People's Hospital of Yongcheng from July 2022 to June 2025, categorized into EMZ monotherapy and EMZ + TM combination groups. Symptom efficacy and GerdQ scores were assessed at baseline, 4 and 8 weeks. Esophageal motility, 24-hour pH monitoring, inflammatory markers, liver and kidney function, and adverse reactions were evaluated before and after 8 weeks. Results: A total of 184 patients were included (86 monotherapy, 98 combination). The combination group showed a higher total effective rate and lower GerdQ scores at 4 weeks and 8 weeks (all $P<0.05$). After 8 weeks, lower esophageal sphincter resting pressure, lower esophageal sphincter relaxation rate, and distal contractile integral were significantly higher, while ineffective contractions and total acid exposure time were significantly lower in the combination group (all $P<0.05$). Inflammatory markers were also significantly lower (all $P<0.05$). No significant differences in liver, kidney function, or adverse reactions were observed. Conclusions: Adding TM to EMZ improves symptom control, esophageal motility, acid exposure, and inflammatory markers in elderly GERD patients without compromising safety.

Keywords: Gastroesophageal reflux disease, esomeprazole, trimebutine, aged, drug therapy, treatment outcome

Introduction

Gastroesophageal reflux disease (GERD) is a chronic gastrointestinal disorder characterized by the retrograde flow of gastric contents into the esophagus, leading to symptoms such as heartburn and acid regurgitation, as well as potential complications like esophagitis and Barrett's esophagus, which severely impair quality of life [1, 2]. The pathogenesis of GERD is multifactorial, involving lower esophageal sphincter (LES) dysfunction, transient LES relaxations, and impaired esophageal clearance, all of which collectively increase esophageal acid exposure and trigger inflammatory responses [3, 4]. Esomeprazole (EMZ) and other proton pump inhibitors (PPIs) remain the cornerstone of GERD treatment by effectively inhibiting gastric acid secretion [5]. Despite their efficacy, a significant proportion of patients, particularly the elderly, exhibit incomplete symptom relief or persistent reflux episodes [6]. This suboptimal response is often attributed to accompanying esophageal motility disorders, which cannot be addressed solely by acid suppression [7]. Therefore, combining PPIs with prokinetic agents has emerged as a potential strategy for optimizing outcomes.

New evidence highlights the critical role of esophageal motility dysfunction and exacerbated inflammatory responses in the pathogen-

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esis and persistence of GERD. Impaired lower esophageal sphincter pressure and ineffective esophageal peristalsis promote pathological acid exposure, while sustained local inflammation driven by cytokines exacerbates mucosal damage [8, 9]. Trimebutine maleate (TM) is a gastrointestinal motility modulator that regulates smooth muscle activity via the enkephalinergic pathway and it has shown anti-inflammatory properties in preclinical models [10, 11]. The specific impacts of combined EMZ and TM on esophageal function, acid exposure, and inflammatory markers in elderly GERD populations have not been fully explored, particularly in real-world clinical settings.

This study evaluates the safety and efficacy of EMZ combined with TM in elderly GERD patients via retrospective monitoring data analysis. It compares symptom improvement, esophageal function, acid exposure, inflammatory markers, and adverse events between combination therapy and EMZ monotherapy to provide clinical evidence for optimizing GERD management in the elderly. Focusing on a real-world setting, this study captures the heterogeneity of elderly patients often missed in randomized trials, aiming to inform evidence-based decisions and support the integration of combination therapy into routine gastroenterological practice.

Materials and methods

Research subjects

A retrospective analysis was conducted on the complete clinical data of 184 elderly patients diagnosed with GERD, who were treated according to standard protocols at the Department of Gastroenterology in The People's Hospital of Yongcheng from July 2022 to June 2025. According to the treatment regimens actually used in clinical practice, the 184 GERD patients were categorized into an EMZ monotherapy group (n=86) and an EMZ combined with TM group (n=98).

This study was conducted in strict accordance with the ethical principles of the Declaration of Helsinki. The study protocol was reviewed and approved by the Medical Ethics Committee of The People's Hospital of Yongcheng. As a retrospective analysis of anonymized clinical data, the requirement for individual informed consent was waived by the ethics committee. All patient data were de-identified prior to analysis to protect privacy.

Inclusion and exclusion criteria

Inclusion Criteria: ① Met the diagnostic criteria for GERD [12] and were diagnosed with reflux esophagitis for the first time; ② Aged ≥60 years, without gender restriction; ③ Classified as Los Angeles grade B; ④ Received standard treatment with EMZ or EMZ combined with TM and completed a treatment course of ≥8 weeks; ⑤ Had complete clinical records, laboratory tests, endoscopic examinations, and follow-up data that met the statistical and analytical requirements of all observation indicators in this study. Exclusion Criteria: ① Presence of other gastrointestinal diseases; ② History of gastrointestinal surgery; ③ Used other medications during the treatment period that could interfere with the study indicators; ④ Comorbid with malignant tumors, or had severe heart, liver, kidney, lung, or other vital organ dysfunction, as well as coagulation disorders, autoimmune diseases, or other serious systemic conditions; ⑤ History of allergy to EMZ or TM; ⑥ Comorbid with mental system diseases or cognitive dysfunction, unable to cooperate with treatment and follow-up; ⑦ Had a history of long-term alcohol abuse or drug misuse.

Treatment regimens

Both groups received standard basic treatments, including lifestyle and dietary interventions. The treatment regimen for the EMZ monotherapy group involved the use of EMZ enteric-coated capsules (Approval No. H20213071, CTD Group Co., Ltd., Jiangsu Province), 20 mg each time, twice daily, taken orally 30 minutes before breakfast and dinner. The treatment regimen for the EMZ combined with TM group combined EMZ enteric-coated capsules with TM tablets (Approval No. H20010696, Shanxi Shuangyan Pharmaceutical Co., Ltd., Shanxi Province). The dosage and administration of EMZ enteric-coated capsules were consistent with those of the EMZ monotherapy group, while the TM tablets were administered at 0.2 g each time, three times daily, taken orally 30 minutes before each meal. Both groups of patients received continuous treatment for at least 8 weeks.

Observation indicators

Medical records of patients before treatment and after 8 weeks of treatment were reviewed, and the following observation indicators were statistically analyzed: ① Efficacy of Symptom Improvement: The efficacy was assessed based on the "2020 Expert Consensus on Gastroesophageal Reflux Disease in China" [13]. Criteria for symptom improvement were as follows: Markedly effective: Complete disappearance of heartburn and acid regurgitation symptoms; Effective: Significant improvement in symptoms; Ineffective: No improvement or worsening of symptoms. The total effective rate was calculated as (number of markedly effective cases + effective cases)/ Total number of cases × 100%; ② Gastroesophageal Reflux Disease Questionnaire (GerdQ) Scores: GerdQ scores before treatment and after 4 and 8 weeks of treatment were collected. The GerdQ score includes six items: frequency of heartburn, frequency of regurgitation, frequency of sleep disturbance due to heartburn and regurgitation, frequency of using antacids to relieve heartburn and regurgitation, frequency of upper abdominal pain, and frequency of nausea. Each item is scored from 0 to 3, with a total possible score of 18. Higher scores indicate more severe symptoms. The Cronbach's α coefficient for the GerdQ is 0.86 [14]; ③ Esophageal Motility Indicators: Data from multichannel gastrointestinal function tests (Solar GI, MMS, the Netherlands) before treatment and after 8 weeks of treatment were collected. The following parameters were recorded: lower esophageal sphincter resting pressure (LESP), lower esophageal sphincter relaxation rate (LESR), distal contractile integral (DCI), and the percentage of ineffective esophageal body contractions; ④ Esophageal pH Monitoring Indicators: Data from Solar GI monitoring before treatment and after 8 weeks of treatment were collected. The following parameters were recorded for a 24-hour period: total acid exposure time (AET) percentage (percentage of cumulative time with pH<4 out of 24 hours), upright AET percentage, supine AET percentage, number of acid reflux episodes (pH<4), number of long reflux episodes (reflux events lasting more than 5 minutes), and the longest single reflux duration; ⑤ Inflammatory Marker Levels: Data on C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α) before treatment and after 8 weeks of treatment were collected. These markers were measured using ELISA kits (CB10116, CB10373, CB11762, CoreAb Biotech Co., Ltd., Shanghai, China); ⑥ Liver and Kidney Function Indicators: Data on alanine aminotransferase (ALT), aspartate transaminase (AST), creatinine (Cr), and blood urea nitrogen (BUN) before treatment and after 8 weeks of treatment were collected. These indicators were measured using an automated biochemical analyzer (AU5800, Beckman Coulter, Brea, CA, USA); ⑦ Adverse Reactions: Adverse reactions during the treatment period were recorded, including headache, diarrhea, rash, palpitations, and liver function abnormalities.

Statistical analysis

All data in this study were analyzed using SPSS 29.0 statistical software (IBM Corp., Armonk, NY, USA). All hypothesis tests were two-tailed, with a significance level of $P<0.05$ indicating statistical significance. Initially, all continuous variables were tested for normality using the Shapiro-Wilk test. It was confirmed that all continuous variables in this study followed a normal distribution and were described using means ± standard deviations (M ± SD). Group comparisons for continuous variables were conducted using independent samples t-tests. Categorical variables were described using frequencies (proportions) [n (%)] and group comparisons were performed using χ^2 tests.

Findings

General information

In the comparison of general information between the EMZ monotherapy group and the EMZ combined with TM group, no significant differences were observed across all parameters evaluated, including age, gender distribution, BMI, smoking history, drinking history, hypertension, diabetes, educational level, and medical insurance type (all $P>0.05$). These results indicate that the baseline characteristics were well balanced between the two groups (**Table 1**).

Symptom evaluation

In the comparison of symptom improvement efficacy between the two treatment regimens,

Table 1. Comparison of general information between the two groups

Parameter	EMZ monotherapy group (n=86)	EMZ combined with TM group (n=98)	t/χ^2	P
Age (years)	72.53 ± 5.21	73.06 ± 5.34	0.675	0.500
Gender [n (%)]			0.033	0.856
Male	38 (44.19%)	42 (42.86%)		
Female	48 (55.81%)	56 (57.14%)		
BMI (kg/m^2)	19.86 ± 1.32	20.13 ± 1.51	1.283	0.201
Smoking history [n (%)]			0.230	0.632
Yes	39 (45.35%)	41 (41.84%)		
No	47 (54.65%)	57 (58.16%)		
Drinking history [n (%)]			0.304	0.582
Yes	35 (40.70%)	36 (36.73%)		
No	51 (59.30%)	62 (63.27%)		
Hypertension [n (%)]			0.529	0.467
Yes	37 (43.02%)	37 (37.76%)		
No	49 (56.98%)	61 (62.24%)		
Diabetes [n (%)]			0.114	0.736
Yes	31 (36.05%)	33 (33.67%)		
No	55 (63.95%)	65 (66.33%)		
Educational level [n (%)]			0.317	0.853
Junior high school and below	33 (38.37%)	34 (34.69%)		
High school	35 (40.70%)	41 (41.84%)		
College degree or above	18 (20.93%)	23 (23.47%)		
Medical insurance type [n (%)]			0.230	0.892
Employee	52 (60.47%)	56 (57.14%)		
Resident	10 (11.63%)	13 (13.27%)		
Own expense	24 (27.91%)	29 (29.59%)		

Notes: EMZ, Esomeprazole; TM, Trimebutine Maleate; BMI, Body Mass Index.

Table 2. Comparison of efficacy of symptom improvement between the two groups [n (%)]

Parameter	EMZ monotherapy group (n=86)	EMZ combined with TM group (n=98)	χ^2	P
The total efficacy rate	72 (83.72%)	93 (94.90%)	6.180	0.013
Markedly effective	43 (50.00%)	58 (59.18%)		
Effective	29 (33.72%)	35 (35.71%)		
Ineffective	14 (16.28%)	5 (5.10%)		

Notes: EMZ, Esomeprazole; TM, Trimebutine Maleate.

the total effectiveness rate of the EMZ combined with TM group was significantly higher than that of the EMZ monotherapy group (P= 0.013). In the EMZ combined with TM group, the proportion of patients with a markedly effective response was higher, while the proportion of patients showing an ineffective response was lower (**Table 2**).

There was no significant difference in GerdQ scores between the two groups before treatment (P=0.679), indicating similar baseline conditions. After 4 weeks and 8 weeks of treatment, the GerdQ scores in the EMZ combined with TM group were significantly lower than those in the EMZ monotherapy group (all P<0.001). This suggests that during the treatment period, the combination of EMZ and TM can more effectively reduce patients' GerdQ scores, and that combination therapy has a more significant effect on improving the symptoms of GERD (**Figure 1**).

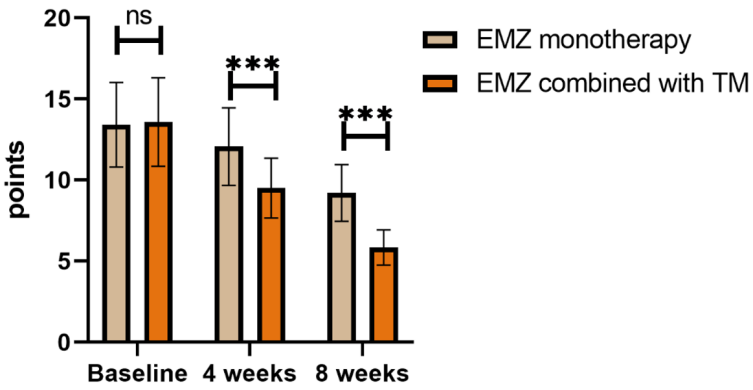

Figure 1. Comparison of GerdQ scores between the two groups. ns, no significance; ***, P<0.001. Notes: GerdQ, Gastroesophageal Reflux Disease Questionnaire; EMZ, Esomeprazole; TM, Trimebutine Maleate.

Esophageal function evaluation

There were no significant differences in the baseline values of LESP, LESR, DCI, and the percentage of ineffective esophageal body contractions between the two groups (all P> 0.05). After 8 weeks of treatment, the LESP, LESR, and DCI in the EMZ combined with TM group were significantly higher than those in the EMZ monotherapy group (LESP: P=0.002; LESR: P=0.003; DCI: P=0.002), while the percentage of ineffective esophageal body contractions was significantly lower (P=0.007). These results indicate that, in terms of improving esophageal motility indices, the combination of EMZ and TM resulted in greater improvements than EMZ monotherapy (**Figure 2**).

Acid exposure evaluation

There were no significant differences in the baseline values of total AET percentage, upright AET percentage, supine AET percentage, number of acid reflux episodes, number of long reflux episodes, and longest single reflux duration between the two groups (all P>0.05). After 8 weeks of treatment, the EMZ combined with TM group showed significantly lower values than the EMZ monotherapy group in total AET percentage (P=0.003), upright AET percentage (P=0.011), supine AET percentage (P=0.003), number of acid reflux episodes (P=0.009), number of long reflux episodes (P=0.006), and longest single reflux duration (P=0.002). These results suggest that combination therapy is more effective in reducing patients' gastroesophageal reflux symptoms (**Table 3**).

Laboratory indicator evaluation

Before treatment, there were no significant differences in CRP, IL-6, and TNF-α levels between the two groups (all P>0.05). After 8 weeks of treatment, the levels of CRP (P= 0.004), IL-6 (P=0.003), and TNF-α (P=0.001) in the EMZ combined with TM group were significantly lower than those in the EMZ monotherapy group. These results suggest that combination therapy is more effective in reducing inflammatory responses (**Table 4**).

Before treatment and after 8 weeks of treatment, there were no significant differences in ALT, AST, Cr, and BUN levels between the two groups (all P>0.05). These results indicate that the combination of EMZ and TM did not show additional effects or burdens on liver and kidney function (**Table 5**).

Adverse reaction evaluation

There was no significant difference in the incidence of any adverse reactions between the EMZ monotherapy group and the EMZ combined with TM group (P=0.930). Additionally, neither group reported cases of liver function abnormalities. These results indicate that the combination of EMZ and TM did not increase additional risks, suggesting that this combination therapy has similar safety profiles to monotherapy (**Table 6**).

Discussion

This real-world retrospective study shows that adding TM maleate to EMZ treatment in elderly GERD patients provides superior relief of symptoms and physiological improvements without compromising safety. Compared to EMZ monotherapy, the combination strategy resulted in more pronounced improvements in reflux symptoms, esophageal motility, acid exposure parameters, and systemic inflammatory markers, while the incidence of liver, kidney, and adverse events remained comparable. These

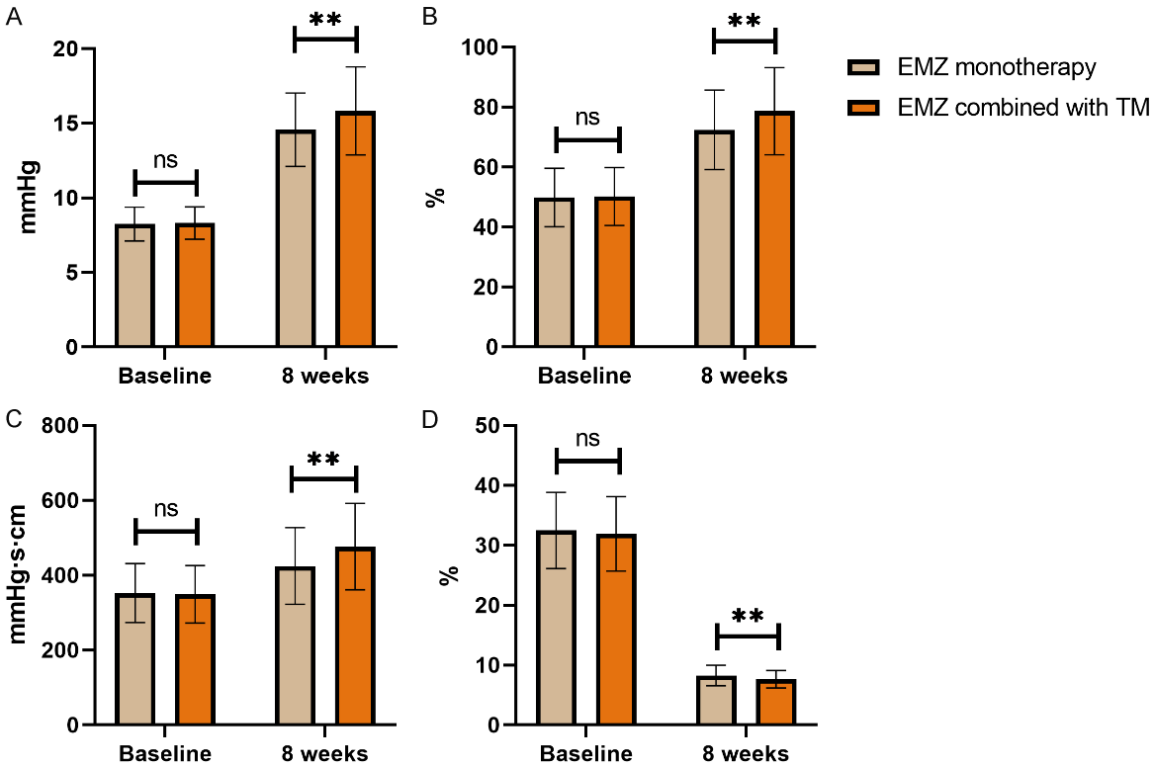

Figure 2. Comparison of the esophageal motility indicators between the two groups. A. LESP; B. LESR; C. DCI; D. Ineffective esophageal body contractions percentage. ns, no significance; **, P<0.01. Notes: EMZ, Esomeprazole; TM, Trimebutine Maleate; LESP, Lower Esophageal Sphincter Resting Pressure; LESR, Lower Esophageal Sphincter Relaxation Rate; DCI, Distal Contractile Integral.

Table 3. Comparison of esophageal pH monitoring indices between the two groups

Parameter	EMZ monotherapy group (n=86)	EMZ combined with TM group (n=98)	t	P
Total AET percentage (%)				
Before treatment	12.57 ± 2.35	12.81 ± 2.42	0.664	0.508
After 8 weeks of treatment	3.98 ± 0.87	3.65 ± 0.53	3.078	0.003
Upright AET percentage (%)				
Before treatment	10.23 ± 1.96	10.43 ± 2.01	0.667	0.505
After 8 weeks of treatment	5.12 ± 1.02	4.79 ± 0.67	2.562	0.011
Supine AET percentage (%)				
Before treatment	16.58 ± 3.21	16.89 ± 3.34	0.647	0.519
After 8 weeks of treatment	2.89 ± 0.78	2.61 ± 0.42	2.976	0.003
Number of acid reflux episodes (times)				
Before treatment	52.36 ± 10.47	53.18 ± 10.71	0.523	0.601
After 8 weeks of treatment	13.45 ± 3.65	12.23 ± 2.34	2.653	0.009
Number of long reflux episodes (times)				
Before treatment	8.74 ± 1.86	8.92 ± 1.92	0.629	0.530
After 8 weeks of treatment	2.53 ± 0.52	2.36 ± 0.28	2.768	0.006
The longest single reflux duration (min)				
Before treatment	18.28 ± 3.84	18.67 ± 3.95	0.682	0.496
After 8 weeks of treatment	5.31 ± 1.12	4.89 ± 0.61	3.099	0.002

Notes: EMZ, Esomeprazole; TM, Trimebutine Maleate; AET, Acid Exposure Time.

Table 4. Comparison of inflammatory marker levels between the two groups

Parameter	EMZ monotherapy group (n=86)	EMZ combined with TM group (n=98)	t	P
CRP (mg/L)				
Before treatment	50.37 ± 5.43	49.86 ± 5.28	0.640	0.523
After 8 weeks of treatment	12.24 ± 2.41	11.39 ± 1.33	2.896	0.004
Il-6 (pg/mL)				
Before treatment	29.22 ± 4.32	28.98 ± 4.26	0.376	0.708
After 8 weeks of treatment	13.41 ± 2.76	12.26 ± 2.34	3.058	0.003
TNF-α (pg/mL)				
Before treatment	14.53 ± 2.18	14.29 ± 2.09	0.787	0.432
After 8 weeks of treatment	10.16 ± 1.74	9.44 ± 1.16	3.250	0.001

Notes: EMZ, Esomeprazole; TM, Trimebutine Maleate; CRP, C-Reactive Protein; IL-6, Interleukin-6; TNF-α, Tumor Necrosis Factor-alpha.

Table 5. Comparison of hepatic and renal function parameters between the two groups

Parameter	EMZ monotherapy group (n=86)	EMZ combined with TM group (n=98)	t	P
ALT (U/L)				
Before treatment	24.36 ± 3.28	24.42 ± 3.31	0.119	0.905
After 8 weeks of treatment	24.28 ± 3.25	24.35 ± 3.29	0.146	0.884
AST (U/L)				
Before treatment	23.77 ± 3.12	23.83 ± 3.15	0.126	0.900
After 8 weeks of treatment	23.69 ± 3.08	23.78 ± 3.13	0.212	0.832
Cr (μmol/L)				
Before treatment	68.53 ± 8.46	69.12 ± 8.52	0.469	0.639
After 8 weeks of treatment	68.61 ± 8.43	69.19 ± 8.49	0.461	0.646
BUN (mmol/L)				
Before treatment	5.86 ± 0.92	5.94 ± 0.95	0.564	0.573
After 8 weeks of treatment	5.89 ± 0.91	5.97 ± 0.93	0.600	0.549

Notes: EMZ, Esomeprazole; TM, Trimebutine Maleate; ALT, Alanine Aminotransferase; AST, Aspartate Transaminase; Cr, Creatinine; BUN, Blood Urea Nitrogen.

Table 6. Comparison of the adverse reaction incidence rate between the two groups [n (%)]

Parameter	EMZ monotherapy group (n=86)	EMZ combined with TM group (n=98)	χ^2	P
Any adverse reaction incidence	5 (5.81%)	6 (6.12%)	0.008	0.930
Headache	2 (2.33%)	2 (2.04%)		
Diarrhea	2 (2.33%)	2 (2.04%)		
Rash	3 (3.49%)	2 (2.04%)		
Palpitations	0 (0.00%)	1 (1.02%)		
Liver function abnormalities	0 (0.00%)	0 (0.00%)		

Notes: EMZ, Esomeprazole; TM, Trimebutine Maleate.

findings suggest that addressing both acid secretion and esophageal motility disorders - two interrelated but distinct pathophysiological drivers - may be particularly beneficial in aging populations where traditional proton pump inhibitor monotherapy often yields suboptimal outcomes.

One of the most striking observations in the current analysis is the enhanced symptom

relief reported in the combination therapy group, reflected in higher markedly effective rates and overall efficacy. Proton pump inhibitors effectively suppress gastric acid secretion but do not restore esophageal motility or enhance the mechanical clearance of refluxate [15]. Previous trials evaluating prokinetics such as mosapride and domperidone in mixed-age GERD cohorts have reported marginal or inconsistent benefits, possibly because younger patients with preserved motility derive less benefit [16]. In contrast, elderly patients exhibit age-related declines in lower esophageal sphincter pressure and peristaltic amplitude, which exacerbate reflux burden despite acid suppression [17]. TM maleate, acting as a prokinetic through its modulatory effect on the enteric nervous system, may increase esophageal clearance and reduce the frequency of non-acid reflux episodes without causing hypermotility [18]. Our findings are consistent with smaller physiological studies showing that TM increases LES pressure but extend these results by demonstrating tangible symptom conversion in a larger real-world elderly cohort [19]. The improvement in GerdQ scores further corroborates these findings. Lower scores among patients on the combination regimen suggest that treatment benefits extend beyond subjective symptom relief to measurable improvements in health-related quality of life.

Esophageal motility indices provide nuanced insights into the mechanisms underlying combination therapy's benefits. While we observed a statistically significant increase in LESP from 14.57 mmHg to 15.82 mmHg (P=0.002), the magnitude of this ~1 mmHg improvement is unlikely to confer meaningful clinical physiological effects - even small variations in LESP within the normal range (10-30 mmHg) rarely translate to substantive changes in gastroesophageal barrier function [20]. Instead, the far more robust improvements in DCI and reductions in ineffective esophageal body contractions are the primary drivers of symptom relief. Enhanced DCI reflects stronger, more coordinated peristaltic forces, while fewer ineffective contractions directly improve esophageal clearance of refluxate - both of which address core pathophysiology in elderly GERD patients with age-related motility decline [21]. These peristaltic coordination gains, rather than minor LESP fluctuations, explain the superior symptom control observed in the combination group. Notably, TM's prokinetic effects - mediated via modulation of the enkephalinergic pathway to regulate gastrointestinal smooth muscle tone and coordination [22] - align precisely with these findings, as they target peristaltic function rather than solely altering sphincter pressure.

All pH monitoring parameters were favorably reduced in the combination therapy group. Proton pump inhibitors can reduce the acidity of refluxate but do not prevent retrograde flow [23]. Therefore, patients may continue to experience persistent symptoms from non-acidic or weakly acidic reflux. By enhancing LES tone and promoting effective peristalsis, TM may reduce the volume of reflux and accelerate clearance, working synergistically with acid suppression [24]. This mechanism is particularly important in the elderly, where hypotensive LES and impaired peristalsis serve as more significant contributors to reflux than transient relaxations [25]. Studies using impedance-pH monitoring have shown that up to 40% of reflux episodes in elderly patients are weakly acidic, a proportion that could explain incomplete responses to monotherapy [26]. Our data suggest that combination therapy addresses this gap by targeting the mechanical basis of reflux.

The reduction in inflammatory markers (CRP, IL-6, TNF-α) in the combination therapy group warrants careful interpretation. While GERD is fundamentally an acid-mediated disease, sustained cytokine release can perpetuate esophageal mucosal injury and symptom chronicity [27]. EMZ reduces inflammation primarily through suppressing gastric acid secretion and facilitating mucosal healing, rather than via intrinsic immunomodulatory activity [28]. Preclinical studies in colitis models have suggested that TM may exert direct anti-inflammatory effects by activating opioid receptors on immune cells and downregulating NF-κB signaling [29]. However, extrapolating these findings to human GERD requires caution: the greater reduction in systemic inflammatory markers observed in our combination group is more plausibly explained by the synergistic improvements in acid control and esophageal mucosal repair driven by dual therapy, rather than a definitively proven direct immunomodu-

latory action of TM in this clinical context. We therefore refrain from concluding that TM has independent systemic immunomodulatory effects in GERD patients. Instead, the inflammatory marker reduction should be viewed as a secondary benefit of enhanced reflux control and tissue healing, with the preclinical anti-inflammatory pathway representing a potential, but unconfirmed, contributing mechanism that warrants investigation in future mechanistic trials.

Safety analyses showed no differences between the groups in liver enzymes, renal function tests, or adverse event incidence, confirming that the addition of TM does not increase additional liver or kidney burden over eight weeks. These results are reassuring, as polypharmacy is a concern in elderly populations due to increased risks of drug interactions and declining organ function. These findings are consistent with existing safety data for TM, which has been widely used in clinical practice with a favorable safety profile [30]. This supports the feasibility of implementing combination therapy in geriatric practice without the need for enhanced monitoring.

This study has several limitations. Its retrospective nature introduces biases like selection bias and reliance on medical record accuracy. The single-center design limits generalizability and cannot exclude unmeasured confounders. An 8-week follow-up is sufficient for short-term efficacy but insufficient for long-term remission, complication prevention, or delayed adverse effects. Lack of blinding may introduce detection bias, and the absence of quality of life and pharmacoeconomic data limits policy impact. Future studies should use prospective, multicenter, randomized controlled designs with long-term follow-up, stratify patients by GERD phenotypes, and include high-resolution manometry, impedance-pH monitoring, and mucosal biomarker assessment. Long-term safety surveillance and cost-effectiveness analyses are also needed. Studies on optimal dosing regimens and duration of TM with PPIs, and investigations into the molecular mechanisms of the observed anti-inflammatory effects, would be valuable. Finally, our definition of "elderly" as ≥60 years aligns with Chinese clinical practice but differs from the international standard of ≥65 years; caution is warranted when extrapolating results to older populations in other regions.

Summary

The addition of TM maleate to EMZ therapy enhances symptom relief, esophageal motor function, acid control, and inflammatory status in elderly GERD patients compared to EMZ alone, while maintaining a comparable safety profile.

Disclosure of conflict of interest

None.

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