RESEARCH PAPER

Intravenous Magnesium Sulfate Reduces Post-Endoscopic Esophageal Symptoms and Attenuates the Interleukin-6 Response Following Upper Gastrointestinal Endoscopy with Biopsy: A Randomized Controlled Trial

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ABSTRACT

Background: Upper gastrointestinal endoscopy (UGIE) with mucosal biopsy is a commonly performed diagnostic procedure that may result in post-endoscopic esophageal symptoms due to mucosal injury and the subsequent inflammatory response. Interleukin-6 (IL-6) is an early pro-inflammatory cytokine that increases following tissue injury and may contribute to postprocedural symptom severity. Magnesium sulfate possesses both analgesic and anti-inflammatory properties through N-methyl-D-aspartate (NMDA) receptor antagonism and modulation of inflammatory signaling. However, evidence regarding its effect on post-endoscopic esophageal symptoms and inflammatory responses following UGIE with biopsy remains limited.

Methods: This randomized controlled trial enrolled 60 adult patients undergoing elective UGIE with biopsy. Participants were randomly allocated in a 1:1 ratio to receive either intravenous magnesium sulfate or placebo before anesthesia induction using computer-generated block randomization with concealed allocation. The primary outcome was post-endoscopic esophageal symptom severity assessed using the Modified Esophageal Symptoms Questionnaire (M-ESQ) at 1, 4, 24, and 48 hours after the procedure. The secondary outcome was the peri-procedural change in serum IL-6 concentration. Repeated M-ESQ measurements were analyzed using generalized estimating equations (GEE), while changes in IL-6 were analyzed using appropriate non-parametric methods. Correlations between IL-6 and M-ESQ were evaluated using Spearman correlation analysis.

Results: Patients receiving intravenous magnesium sulfate demonstrated significantly lower M-ESQ scores than the control group at all postoperative time points (all $P<0.001$). Longitudinal analysis confirmed a sustained reduction in symptom severity throughout the 48-hour observation period, with a significantly greater improvement during the early postoperative phase. Although serum IL-6 increased after UGIE with biopsy in both groups, the magnitude of increase was significantly smaller in the magnesium sulfate group ($P<0.001$). Postprocedural IL-6 concentrations showed significant positive correlations with M-ESQ scores across all assessment time points.

Conclusions: Intravenous magnesium sulfate significantly reduced post-endoscopic esophageal symptom severity and attenuated the postprocedural IL-6 response following UGIE with biopsy. These findings support the potential role of magnesium sulfate as an adjunctive strategy for improving post-endoscopic recovery while modulating procedure-related inflammatory responses.

Keywords: *Upper gastrointestinal endoscopy; magnesium sulfate; interleukin-6; post-endoscopic esophageal symptoms*

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INTRODUCTION

Upper gastrointestinal endoscopy (UGIE) is one of the most frequently performed diagnostic and therapeutic procedures for evaluating diseases of the upper gastrointestinal tract. Each year, millions of endoscopic procedures are performed worldwide for the diagnosis and management of esophageal, gastric, and duodenal disorders. Although UGIE is generally considered minimally invasive and safe, mucosal biopsy remains an essential component for establishing histopathological diagnoses in patients with suspected malignancy, chronic

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gastritis, Barrett's esophagus, eosinophilic esophagitis, and other inflammatory gastrointestinal diseases. Despite its diagnostic value, mucosal biopsy inevitably causes localized tissue injury that may trigger postoperative symptoms, including sore throat, odynophagia, dysphagia, retrosternal discomfort, and esophageal pain, which may negatively affect patient satisfaction and recovery. (1–3)

The incidence of post-endoscopic upper gastrointestinal symptoms varies considerably depending on patient characteristics, procedural techniques, and the extent of mucosal manipulation. Previous studies have reported that mild to moderate upper gastrointestinal discomfort occurs in approximately 20–50% of patients following diagnostic endoscopy with biopsy, although severe symptoms are uncommon. While these symptoms are usually self-limiting, they may persist for several days and contribute to delayed oral intake, increased analgesic requirements, reduced patient satisfaction, and reluctance to undergo repeat endoscopic examinations. Consequently, strategies to minimize post-endoscopic symptoms have become increasingly important as the volume of gastrointestinal endoscopy continues to increase worldwide. (4–6) The development of post-endoscopic esophageal symptoms is a multifactorial process involving both mechanical tissue injury and the subsequent inflammatory response. During mucosal biopsy, disruption of the epithelial barrier initiates the release of damage-associated molecular patterns (DAMPs), leading to activation of resident macrophages, dendritic cells, and endothelial cells. These activated immune cells subsequently produce pro-inflammatory cytokines, including interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α), and particularly interleukin-6 (IL-6). Among these mediators, IL-6 plays a central role in amplifying the acute inflammatory response through activation of the Janus kinase/signal transducer and activator of transcription (JAK/STAT) signaling pathway, stimulation of hepatic acute-phase protein synthesis, recruitment of inflammatory cells, and sensitization of peripheral nociceptors. Consequently, elevated IL-6 concentrations have consistently been associated with greater postoperative pain and tissue inflammation across various surgical procedures. (7–10)

Unlike major surgery, the inflammatory response following endoscopic biopsy is relatively subtle but remains biologically relevant. Previous investigations have demonstrated that minimally invasive procedures are capable of inducing measurable increases in circulating IL-6 concentrations, reflecting the degree of tissue injury despite the absence of extensive surgical trauma. Labib et al. reported that postoperative IL-6 concentrations increased following gynecological surgery and correlated with surgical tissue injury, while Pan et al. observed significantly lower postoperative IL-6 levels following minimally invasive lumbar discectomy compared with conventional open surgery. These findings suggest that even limited tissue injury is sufficient to induce cytokine release and that attenuation of this inflammatory response may contribute to improved postoperative recovery. (8,9)

Magnesium sulfate has attracted increasing attention as an adjunctive agent in perioperative analgesia because of its dual analgesic and anti-inflammatory properties. Magnesium acts as a physiological calcium antagonist and a non-competitive antagonist of the N-methyl-D-aspartate (NMDA) receptor, thereby reducing central sensitization and limiting nociceptive transmission. Experimental studies further suggest that magnesium suppresses inflammatory signaling by inhibiting intracellular calcium influx, reducing nuclear factor-kappa B (NF-κB) activation, and decreasing the production of pro-inflammatory cytokines, including IL-6. Through these mechanisms, magnesium sulfate may attenuate both peripheral inflammation and central pain sensitization following tissue injury. (11–15)

Substantial clinical evidence supports the analgesic efficacy of perioperative magnesium sulfate. Several randomized controlled trials and meta-analyses have demonstrated that intravenous magnesium reduces postoperative pain scores, opioid consumption, and analgesic requirements after abdominal, orthopedic, gynecological, and laparoscopic surgery. More recently, umbrella reviews have confirmed consistent benefits of perioperative magnesium as part of multimodal analgesia with a favorable safety profile. Nevertheless, almost all available evidence has been derived from major surgical procedures involving extensive tissue injury, whereas evidence in minimally invasive endoscopic procedures remains scarce. (11–16)

To date, no randomized controlled trial has specifically evaluated whether intravenous magnesium sulfate can simultaneously reduce post-endoscopic esophageal symptom severity and attenuate the accompanying inflammatory response following UGIE with mucosal biopsy. Furthermore, the relationship between postprocedural symptom severity and IL-6 concentrations after endoscopic biopsy has not been adequately explored. Establishing this relationship may improve understanding of the biological mechanisms underlying post-endoscopic symptoms and provide evidence supporting anti-inflammatory strategies in endoscopic practice.

Therefore, the present randomized controlled trial aimed to evaluate the effect of intravenous magnesium sulfate on post-endoscopic esophageal symptom severity, assessed using the Modified Esophageal Symptoms Questionnaire (M-ESQ), and on the postprocedural IL-6 response in adult patients undergoing elective upper gastrointestinal endoscopy with biopsy. We hypothesized that intravenous magnesium sulfate would reduce post-endoscopic esophageal symptom severity while attenuating the increase in serum IL-6 concentrations compared with placebo.

METHODS

Study Design

This study was a prospective, parallel-group, randomized, placebo-controlled clinical trial conducted to evaluate the

effect of intravenous magnesium sulfate on post-endoscopic esophageal symptom severity and the inflammatory response following upper gastrointestinal endoscopy (UGIE) with mucosal biopsy. The study was conducted at Dr. Wahidin Sudirohusodo Hospital, Makassar, Indonesia, between January and July 2026. The trial was designed in accordance with the principles of the Declaration of Helsinki and followed the Consolidated Standards of Reporting Trials (CONSORT) 2010 guidelines for randomized controlled trials.

Ethical Approval

The study protocol was reviewed and approved by the Health Research Ethics Committee of Dr. Wahidin Sudirohusodo Hospital and the Faculty of Medicine, Hasanuddin University, Makassar, Indonesia (Approval No. 544/UN4.6.4.5.31/ PP36/2026).

Participants

Adult patients undergoing elective upper gastrointestinal endoscopy (UGIE) with mucosal biopsy under general anesthesia at Dr. Wahidin Sudirohusodo Hospital, Makassar, Indonesia, were consecutively screened for study eligibility. Eligible participants were adults aged **18 years or older**, classified as **American Society of Anesthesiologists (ASA) physical status I–III**, scheduled for elective UGIE with biopsy, and capable of providing written informed consent.

Patients were excluded if they had a history of hypersensitivity to magnesium sulfate, severe renal dysfunction, second- or third-degree atrioventricular block, neuromuscular disease, chronic opioid therapy, pregnancy or lactation, or any condition that could interfere with completion of the postoperative assessments. Consecutive eligible patients who met all inclusion criteria and none of the exclusion criteria were enrolled until the required sample size was achieved.

Randomization and Allocation Concealment

Eligible participants were randomly assigned in a 1:1 ratio to either the magnesium sulfate group or the placebo group using computer-generated block randomization with variable block sizes of 4 and 6.

The randomization sequence was generated before participant recruitment using IBM SPSS Statistics together with a validated computerized randomization application by an investigator who was not involved in patient recruitment or postoperative outcome assessment.

Allocation concealment was maintained using sequentially numbered opaque sealed envelopes (SNOSE). Each envelope contained the treatment assignment and was opened immediately before preparation of the study medication by a designated investigator.

Blinding

Participants, endoscopists, postoperative outcome assessors, and statisticians remained blinded to treatment allocation throughout the study. Because treatment allocation was indicated on blood specimen labels for laboratory processing, laboratory personnel responsible for IL-6 analysis were not blinded. The attending anesthesiologist administering anesthesia was aware of group allocation to ensure appropriate intraoperative management and patient safety but was not involved in postoperative symptom assessment or statistical analysis.

Interventions

Patients allocated to the intervention group received intravenous magnesium sulfate at a dose of 50 mg/kg body weight diluted to a total volume of 20 mL with normal saline. The solution was administered intravenously over approximately 15 minutes before induction of anesthesia. Patients in the control group received 20 mL of normal saline administered using an identical syringe and infusion duration. All patients subsequently underwent standardized general anesthesia according to institutional protocols.

Perioperative Management

All patients received standardized intraoperative monitoring according to the American Society of Anesthesiologists (ASA) monitoring standards, including continuous electrocardiography, non-invasive blood pressure monitoring, pulse oximetry, and capnography. General anesthesia was induced using intravenous fentanyl, propofol, and rocuronium at standardized weight-adjusted doses. After successful endotracheal intubation, anesthesia was maintained with sevoflurane in an oxygen–air mixture throughout the procedure. All UGIE procedures and mucosal biopsies were performed by experienced gastroenterologists using standardized endoscopic techniques. Apart from the study intervention, perioperative management was standardized for all participants to minimize potential confounding factors and ensure comparability between the two study groups.

Outcome Measures

The primary outcome was post-endoscopic esophageal symptom severity, assessed using the Modified Esophageal Symptoms Questionnaire (M-ESQ). The M-ESQ is a validated patient-reported outcome instrument that evaluates the severity of esophageal symptoms following upper gastrointestinal endoscopy. Assessments were performed at 1, 4, 24, and 48 hours after completion of the procedure. Higher scores indicated greater post-endoscopic esophageal symptom severity.

The secondary outcome was the peri-procedural inflammatory response, evaluated by changes in serum interleukin-6 (IL-6) concentrations. Venous blood samples were obtained immediately before administration of the study intervention and immediately after completion of the endoscopic procedure. Serum IL-6 concentrations were measured using a commercially available enzyme-linked immunosorbent assay (ELISA) kit according to the manufacturer's instructions. Details of the ELISA assay, including the manufacturer, country of origin, detection range, analytical sensitivity, and intra- and inter-assay coefficients of variation, are provided in the Supplementary Methods.

Sample Size Calculation

The minimum required sample size was calculated as 25 participants per group after accounting for anticipated attrition or unusable laboratory specimens. Because the study involved biomarker analysis, additional eligible participants were recruited to ensure an adequate number of analyzable IL-6 samples. A total of 64 participants were randomized, with 32 assigned to each group. Four IL-6 specimens, two from each group, were not analyzable; consequently, 60 participants were included in the IL-6 analysis, whereas all 64 randomized participants were included in the primary M-ESQ analysis.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics version 31.0 (IBM Corp., Armonk, NY, USA). Continuous variables were assessed for normality using the Shapiro–Wilk test. Normally distributed variables are presented as mean ± standard deviation (SD), whereas non-normally distributed variables are presented as median (interquartile range [IQR]). Categorical variables are expressed as number (percentage). Baseline characteristics were compared using the Welch independent *t*-test, Mann–Whitney U test, Chi-square test, or Fisher's exact test, as appropriate. Repeated M-ESQ measurements were analyzed using Generalized Estimating Equations (GEE) with a Gaussian distribution, identity link function, exchangeable working correlation matrix, and robust standard errors. Changes in serum IL-6 concentrations within each group were analyzed using the Wilcoxon signed-rank test, whereas between-group comparisons of IL-6 changes were performed using the Mann–Whitney U test. The association between postprocedural IL-6 concentrations and M-ESQ scores was evaluated using Spearman correlation analysis. Two-sided P values <0.05 were considered statistically significant.

RESULTS

Participant Flow

A total of 64 patients undergoing elective upper gastrointestinal endoscopy (UGIE) with mucosal biopsy were enrolled and randomly assigned in a 1:1 ratio to receive either intravenous magnesium sulfate (n = 32) or placebo (n = 32). All randomized participants completed the postoperative follow-up and were included in the analysis of the primary outcome, post-endoscopic esophageal symptom severity. Four blood specimens, two from each treatment group, could not be analyzed because serum IL-6 measurements failed during laboratory processing. Consequently, the secondary outcome analysis of serum IL-6 concentrations included 60 participants, comprising 30 participants in each group (Figure 1).

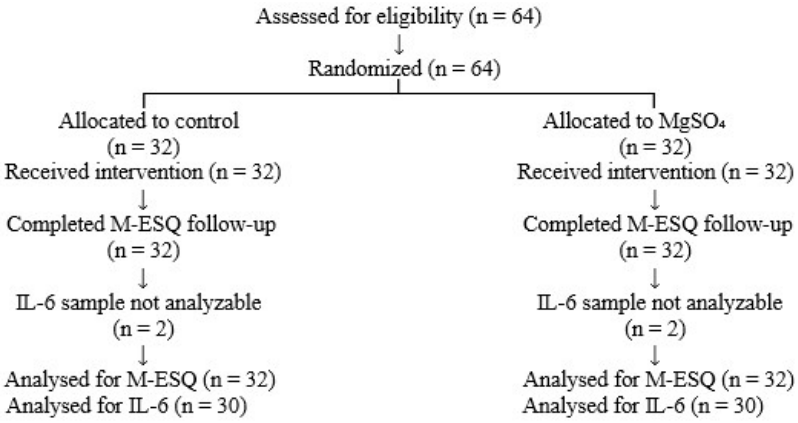

Figure 1 illustrates the participant flow according to the CONSORT 2010 statement.

Baseline Characteristics

Table 1. Baseline Characteristics of the Study Participants

Characteristic	Placebo (n = 30)	Magnesium sulfate (n = 30)	Overall (n = 60)	P value
Sex, n (%)				1.000[c]
Male	15 (50.0)	15 (50.0)	30 (50.0)	
Female	15 (50.0)	15 (50.0)	30 (50.0)	
Age (years), mean ± SD	42.60 ± 9.69	44.80 ± 12.86	43.70 ± 11.34	0.457[a]
Body weight (kg), mean ± SD	72.00 ± 10.03	66.66 ± 12.83	69.33 ± 11.77	0.037[b]
Height (cm), mean ± SD	164.25 ± 6.42	166.22 ± 7.49	165.24 ± 6.99	0.280[a]
ASA physical status, n (%)				0.733[c]
ASA I	8 (26.7)	10 (33.3)	18 (30.0)	
ASA II	19 (63.3)	16 (53.3)	35 (58.3)	
ASA III	3 (10.0)	4 (13.3)	7 (11.7)	

[a] Welch independent *t*-test [b] Mann–Whitney U test

[c] Chi-square test

Baseline demographic and clinical characteristics of the study participants are summarized in Table 1. No statistically significant differences were observed between the placebo and magnesium sulfate groups with respect to age ($P = 0.457$), sex distribution ($P = 1.000$), height ($P = 0.280$), or American Society of Anesthesiologists (ASA) physical status ($P = 0.733$). However, patients allocated to the magnesium sulfate group had a significantly lower body weight than those in the placebo group (66.66 ± 12.83 vs. 72.00 ± 10.03 kg, $P = 0.037$). Because body weight differed significantly at baseline and could potentially influence perioperative drug dosing and postoperative outcomes, it was included as a covariate in the multivariable analyses. Overall, the baseline characteristics indicate that the two study groups were clinically comparable prior to administration of the study intervention.

Procedural Characteristics

Table 2. Procedural Characteristics and Perioperative Management

Variable	Placebo (n = 30)	Magnesium sulfate (n = 30)	P value
Procedure duration (min), mean ± SD	18.17 ± 5.11	19.36 ± 3.48	0.294[a]
Number of biopsy specimens, mean ± SD	4.43 ± 0.94	4.57 ± 1.01	0.594[b]
Fentanyl dose (μg), mean ± SD	179.99 ± 25.07	166.65 ± 32.08	0.037[b]
Propofol dose (mg), mean ± SD	143.99 ± 20.06	133.32 ± 25.66	0.037[b]
Biopsy location, n (%)			0.186[c]
• Antrum	3 (10.0)	5 (16.7)	
• Antrum + corpus	4 (13.3)	3 (10.0)	
• Bulbus	3 (10.0)	5 (16.7)	
• Corpus	6 (20.0)	5 (16.7)	
• Corpus + fundus	4 (13.3)	5 (16.7)	
• Fundus	8 (26.7)	1 (3.3)	
• Total mapping	2 (6.7)	6 (20.0)	

[a] Welch independent *t*-test [b] Mann–Whitney U test

[c] Chi-square test

Procedural characteristics are presented in Table 2. The mean duration of UGIE was similar between the placebo and magnesium sulfate groups (18.17 ± 5.11 vs. 19.36 ± 3.48 minutes, $P = 0.294$). Likewise, the mean number of biopsy specimens obtained during the procedure did not differ significantly between groups (4.43 ± 0.94 vs. 4.57 ± 1.01, $P = 0.594$).

Although the absolute doses of fentanyl and propofol were significantly lower in the magnesium sulfate group ($P = 0.037$ for both), these differences reflected the lower baseline body weight in this group because anesthetic agents were administered according to body weight using a standardized dosing protocol. Therefore, the observed differences in absolute drug doses were considered clinically expected and did not indicate differences in anesthetic management. Furthermore, the distribution of biopsy locations was comparable between groups ($P = 0.186$), suggesting that procedural characteristics were well balanced and were unlikely to have influenced the study outcomes.

Post-Endoscopic Esophageal Symptoms

Table 3. Comparison of Post-Endoscopic Esophageal Symptom Severity Between Treatment Groups

Time after UGIE	Placebo (n = 30) Mean ± SD	Magnesium sulfate (n = 30) Mean ± SD	Mean Difference (95% CI)	*P* value	Cohen's *d*
1 hour	32.37 ± 3.39	25.47 ± 2.61	−6.90 (−8.47 to −5.33)	<0.001	−2.28
4 hours	29.87 ± 2.91	20.97 ± 2.62	−8.90 (−10.33 to −7.47)	<0.001	−3.22
24 hours	23.17 ± 3.43	14.87 ± 1.78	−8.30 (−9.72 to −6.88)	<0.001	−3.04
48 hours	18.83 ± 2.18	11.57 ± 1.57	−7.27 (−8.25 to −6.28)	<0.001	−3.82

Data are presented as mean ± standard deviation (SD). Between-group comparisons were performed using Welch's independent *t*-test. Cohen's *d* was calculated to estimate effect size. Negative values indicate lower M-ESQ scores in the magnesium sulfate group.

Post-endoscopic esophageal symptom severity, assessed using the Modified Esophageal Symptoms Questionnaire (M-ESQ), was consistently lower in patients receiving intravenous magnesium sulfate than in those receiving placebo throughout the postoperative observation period (Table 3). Statistically significant differences between treatment groups were observed at every assessment time point (all $P < 0.001$).

At the first postoperative assessment (1 hour), the magnesium sulfate group demonstrated a mean M-ESQ score that was 6.90 points lower than the placebo group (95% CI, −8.47 to −5.33). The magnitude of this difference increased during the early postoperative period, reaching the largest absolute between-group difference at 4 hours, when symptom scores were 8.90 points lower among patients receiving magnesium sulfate. Although the difference decreased slightly thereafter, significantly lower symptom scores remained evident at both 24 hours (mean difference, −8.30 points) and 48 hours (mean difference, −7.27 points), indicating a sustained treatment effect throughout the 48-hour follow-up period.

Effect size analysis demonstrated a consistently large therapeutic effect of intravenous magnesium sulfate. Cohen's d values ranged from −2.28 to −3.82, substantially exceeding the conventional threshold for a large effect ($d \geq 0.80$). The largest standardized effect was observed at 48 hours ($d = -3.82$), suggesting that the reduction in post-endoscopic esophageal symptoms associated with magnesium sulfate was not only statistically significant but also clinically meaningful.

Overall, these findings demonstrate that perioperative intravenous magnesium sulfate markedly reduced post-endoscopic esophageal symptom severity compared with placebo, with benefits evident as early as 1 hour after UGIE and persisting throughout the 48-hour postoperative observation period.

Longitudinal Analysis of M-ESQ

Table 4. Longitudinal Analysis of Post-Endoscopic Esophageal Symptom Severity Using Generalized Estimating Equations

Variable	β	Robust SE	95% CI	*P* value
Intercept (Placebo, 1 hour)	32.367	0.608	31.175 to 33.559	<0.001
Magnesium sulfate	−6.900	0.768	−8.405 to −5.395	<0.001
Time: 4 hours	−2.500	0.743	−3.957 to −1.043	0.001
Time: 24 hours	−9.200	0.858	−10.882 to −7.518	<0.001
Time: 48 hours	−13.533	0.766	−15.034 to −12.033	<0.001
Magnesium sulfate × 4 hours	−2.000	0.948	−3.858 to −0.142	0.035
Magnesium sulfate × 24 hours	−1.400	0.980	−3.320 to 0.520	0.153
Magnesium sulfate × 48 hours	−0.367	0.935	−2.198 to 1.465	0.695

Generalized estimating equations (GEE) with Gaussian family, identity link function, exchangeable working correlation structure, and robust standard errors. The placebo group and the 1-hour assessment served as the reference categories.

To evaluate changes in post-endoscopic esophageal symptom severity over time, repeated M-ESQ measurements were analyzed using generalized estimating equations (GEE) with a Gaussian distribution, identity link function, exchangeable working correlation structure, and robust standard errors. This approach was selected to account for the within-subject correlation arising from repeated measurements performed at 1, 4, 24, and 48 hours after the procedure. The placebo group and the 1-hour postoperative assessment were used as the reference categories (Table 4).

After adjustment for repeated measurements, patients receiving intravenous magnesium sulfate had M-ESQ scores that were, on average, 6.90 points lower than those receiving placebo at the initial postoperative assessment (β = −6.900; 95% CI, −8.405 to −5.395; $P < 0.001$). This finding confirms a substantial overall treatment effect of magnesium sulfate on reducing post-endoscopic esophageal symptoms.

Within the placebo group, symptom severity progressively decreased over time compared with the 1-hour assessment. Mean M-ESQ scores declined by 2.50 points at 4 hours**,** 9.20 points at 24 hours, and 13.53 points at 48 hours, with all reductions reaching statistical significance ($P \leq 0.001$). These findings indicate that post-endoscopic esophageal symptoms gradually improved during the postoperative recovery period, irrespective of treatment allocation.

A significant treatment-by-time interaction was observed at 4 hours (β = −2.000; 95% CI, −3.858 to −0.142; $P = 0.035$), indicating that patients receiving magnesium sulfate experienced a significantly greater reduction in symptom severity during the early postoperative period than those receiving placebo. However, the interaction terms at 24 hours and 48 hours were not statistically significant ($P = 0.153$ and $P = 0.695$, respectively), suggesting that after the initial postoperative phase, both groups demonstrated a comparable rate of symptom improvement over time.

Overall, the longitudinal analysis demonstrated that intravenous magnesium sulfate was associated with consistently lower post-endoscopic esophageal symptom scores throughout the 48-hour observation period. In addition to reducing symptom severity immediately after UGIE, magnesium sulfate accelerated symptom improvement during the first four postoperative hours,

after which recovery trajectories were similar between treatment groups while maintaining a persistent overall reduction in symptom burden.

Changes in Serum IL-6

Table 5. Peri-Procedural Changes in Serum Interleukin-6 Concentrations

Variable	Placebo (n = 30)	Magnesium sulfate (n = 30)	*P* value
Baseline IL-6 (pg/mL), median (IQR)	12.81 (10.88–15.07)	12.42 (10.57–14.18)	0.742†
Post-procedure IL-6 (pg/mL), median (IQR)	16.42 (14.63–26.59)	13.08 (11.06–15.15)	<0.001†
Δ IL-6 (pg/mL), median (IQR)	2.37 (1.79–11.52)	0.65 (0.35–0.97)	<0.001‡
Rank-biserial correlation	—	−0.84	

Data are presented as median (interquartile range)

† Within-group comparison: Wilcoxon signed-rank test.

‡ Between-group comparison: Mann–Whitney U test.

Rank-biserial correlation was calculated as the non-parametric effect size.

Peri-procedural changes in serum interleukin-6 (IL-6) concentrations are presented in Table 5. Baseline IL-6 concentrations were comparable between the placebo and magnesium sulfate groups, indicating similar inflammatory status before administration of the study intervention.

Following UGIE with mucosal biopsy, serum IL-6 concentrations increased significantly in both treatment groups, consistent with an acute inflammatory response to mucosal injury. In the placebo group, median IL-6 increased from 12.81 pg/mL to 16.42 pg/mL, representing a median increase of 2.37 pg/mL ($P < 0.001$). Patients receiving intravenous magnesium sulfate also demonstrated a significant increase in IL-6, with median concentrations rising from 12.42 pg/mL to 13.08 pg/mL ($P < 0.001$). However, the magnitude of this increase was substantially smaller, with a median change of only 0.65 pg/mL.

Direct comparison of peri-procedural IL-6 changes demonstrated that the increase in serum IL-6 was significantly attenuated by intravenous magnesium sulfate. The median change in IL-6 was markedly lower in the magnesium sulfate group than in the placebo group ($P < 0.001$). Furthermore, the calculated rank-biserial correlation of −0.84 indicated a very large treatment effect, demonstrating that patients receiving magnesium sulfate consistently exhibited smaller increases in serum IL-6 than those receiving placebo.

Overall, these findings indicate that although UGIE with biopsy induced a measurable systemic inflammatory response in both groups, perioperative administration of intravenous magnesium sulfate substantially attenuated the magnitude of the IL-6 response, suggesting a clinically relevant anti-inflammatory effect in addition to its analgesic properties.

Correlation Between IL-6 and Post-Endoscopic Symptoms

Table 6. Correlation between Serum IL-6 Concentrations and Post-Endoscopic Esophageal Symptom Severity.

Postoperative assessment	Spearman's *r*s	*P* value
1 hour	0.323	0.012
4 hours	0.400	0.002
24 hours	0.472	<0.001
48 hours	0.470	<0.001

Correlation analysis was performed using Spearman's rank correlation coefficient.

The association between post-procedural serum IL-6 concentrations and post-endoscopic esophageal symptom severity is presented in Table 6. Serum IL-6 concentrations demonstrated significant positive correlations with M-ESQ scores at all postoperative assessment time points, indicating that patients with higher post-procedural IL-6 concentrations tended to report more severe esophageal symptoms during the 48-hour follow-up period.

At 1 hour, serum IL-6 was positively correlated with M-ESQ scores ($r_s = 0.323$, $P = 0.012$). Similar positive correlations were observed at 4 hours ($r_s = 0.400$, $P = 0.002$), 24 hours ($r_s = 0.472$, $P < 0.001$), and 48 hours ($r_s = 0.470$, $P < 0.001$). The correlation coefficients ranged from 0.323 to 0.472, indicating weak to moderate positive correlations between post-procedural serum IL-6 concentrations and M-ESQ scores.

Overall, these findings indicate that patients with higher post-procedural serum IL-6 concentrations generally experienced more severe post-endoscopic esophageal symptoms throughout the postoperative observation period.

Table 7. Multivariable Analysis of Factors Associated with Post-Procedural Serum IL-6 Concentrations

Outcome	Adjusted effect of magnesium sulfate	95% CI	*P* value
Post-procedural IL-6	−0.288*	−0.428 to −0.148	<0.001

* The dependent variable was log-transformed post-procedural IL-6 concentration. Therefore, the regression coefficient corresponds to an approximately **25.0% lower** post-procedural IL-6 concentration in the magnesium sulfate group after adjustment.

To determine whether the observed reduction in serum IL-6 concentrations was independent of baseline characteristics and procedural factors, an analysis of covariance (ANCOVA) was performed. The model was adjusted for baseline serum IL-6 concentration, age, body weight, procedure duration, and the number of biopsy specimens.

After adjustment for these covariates, intravenous magnesium sulfate remained independently associated with lower post-procedural serum IL-6 concentrations. Compared with placebo, the magnesium sulfate group demonstrated an approximately **25.0% lower** post-procedural serum IL-6 concentration ($P < 0.001$). These findings indicate that the anti-inflammatory effect of magnesium sulfate persisted after controlling for potential confounding variables, supporting an independent association between magnesium sulfate administration and attenuation of the peri-procedural inflammatory response.

Overall, intravenous magnesium sulfate demonstrated beneficial effects on both clinical and inflammatory outcomes following upper gastrointestinal endoscopy with mucosal biopsy. Compared with placebo, patients receiving magnesium sulfate experienced significantly lower post-endoscopic esophageal symptom severity throughout the 48-hour postoperative period, with the greatest reduction observed during the early postoperative phase. Longitudinal analysis further confirmed that magnesium sulfate was associated with a sustained reduction in symptom severity over time.

In addition to its clinical benefits, intravenous magnesium sulfate significantly attenuated the peri-procedural increase in serum IL-6 concentrations. This anti-inflammatory effect remained significant after adjustment for baseline IL-6 concentration and other potential confounding variables. Furthermore, higher post-procedural IL-6 concentrations were consistently associated with higher M-ESQ scores, suggesting a relationship between the inflammatory response and the severity of post-endoscopic esophageal symptoms. Collectively, these findings indicate that perioperative intravenous magnesium sulfate provides both symptomatic and anti-inflammatory benefits in patients undergoing UGIE with mucosal biopsy.

DISCUSSION

The present randomized controlled trial demonstrated that intravenous magnesium sulfate significantly reduced post-endoscopic esophageal symptom severity following upper gastrointestinal endoscopy with mucosal biopsy. Patients receiving magnesium sulfate consistently reported lower M-ESQ scores throughout the 48-hour follow-up period compared with those receiving placebo. In addition, magnesium sulfate significantly attenuated the postprocedural increase in serum IL-6 concentrations. Furthermore, postoperative IL-6 concentrations were positively correlated with symptom severity at every assessment time point, suggesting that greater inflammatory responses were associated with more severe post-endoscopic symptoms.

The principal finding of this study is that intravenous magnesium sulfate improved patient-reported post-endoscopic esophageal symptoms throughout the postoperative observation period. The beneficial effect was evident as early as one hour after the procedure and persisted for at least 48 hours. Moreover, longitudinal analysis using generalized estimating equations demonstrated that patients receiving magnesium sulfate experienced a significantly greater improvement during the early postoperative period, particularly within the first four hours after UGIE. These findings indicate that magnesium sulfate not only reduced symptom severity but also accelerated early symptom recovery.

Although upper gastrointestinal endoscopy is generally considered a minimally invasive procedure, mucosal biopsy inevitably causes localized epithelial disruption. Mechanical injury to the esophageal or gastric mucosa initiates activation of resident macrophages, dendritic cells, mast cells, and endothelial cells. Tissue injury also induces the release of damage-associated molecular patterns (DAMPs), which activate pattern-recognition receptors such as Toll-like receptors, leading to nuclear factor-kappa B (NF-κB) activation and transcription of multiple pro-inflammatory cytokines. Among these cytokines, IL-6 plays a pivotal role in amplifying the acute inflammatory response by promoting leukocyte recruitment, hepatic acute-phase protein synthesis, and peripheral nociceptor sensitization. Consequently, inflammatory signaling initiated immediately after biopsy may contribute to the development of post-endoscopic esophageal symptoms despite the relatively limited extent of tissue injury. (7–10)

The observed reduction in post-endoscopic symptom severity following magnesium administration is biologically plausible. Magnesium is a physiological calcium antagonist and a non-competitive blocker of the N-methyl-D-aspartate (NMDA) receptor. Under normal physiological conditions, magnesium ions occupy the NMDA receptor channel and limit excessive calcium influx into neurons. Tissue injury and persistent nociceptive stimulation remove this voltage-dependent magnesium block, allowing excessive activation of NMDA receptors, increased intracellular calcium entry, and subsequent central sensitization. Administration of exogenous magnesium restores this inhibitory mechanism, thereby reducing excitatory neurotransmission within the spinal cord and attenuating central sensitization. As a result, patients may experience less postoperative discomfort despite exposure to similar procedural stimuli. (11–14)

In addition to its analgesic properties, magnesium exerts

several anti-inflammatory effects that may further explain the findings of the present study. Experimental studies have shown that magnesium suppresses intracellular calcium signaling, inhibits activation of NF-κB, reduces oxidative stress, and decreases production of several pro-inflammatory cytokines, including IL-6 and TNF-α. Reduced inflammatory mediator production may limit peripheral nociceptor sensitization and decrease transmission of inflammatory pain signals. Therefore, magnesium may simultaneously modulate both peripheral inflammatory pathways and central nociceptive processing, providing a mechanistic explanation for the lower symptom scores observed in the intervention group. (13–16)

Our findings are consistent with previous clinical evidence demonstrating the analgesic benefits of perioperative magnesium sulfate. A landmark meta-analysis by Albrecht et al. involving randomized controlled trials concluded that intravenous magnesium significantly reduced postoperative pain intensity and opioid consumption across multiple surgical procedures. Similarly, De Oliveira et al. reported that perioperative systemic magnesium improved postoperative analgesia and decreased opioid requirements without increasing adverse events. More recently, Choi et al. performed an umbrella review including numerous systematic reviews and confirmed that perioperative magnesium consistently improves postoperative analgesic outcomes across a wide range of surgical specialties. However, nearly all previous studies evaluated major surgical procedures such as abdominal, orthopedic, gynecological, or laparoscopic surgery. Evidence regarding magnesium sulfate during diagnostic endoscopic procedures has remained extremely limited. Therefore, the present study extends current evidence by demonstrating that the analgesic benefits of magnesium sulfate are also evident following minimally invasive upper gastrointestinal endoscopy with mucosal biopsy. (11,12,16)

Unlike previous investigations that focused exclusively on postoperative pain scores, the present study evaluated symptom severity using the Modified Esophageal Symptoms Questionnaire (M-ESQ), a disease-specific instrument developed to assess upper gastrointestinal symptoms after endoscopic procedures. This represents an important methodological strength because post-endoscopic recovery is not solely determined by pain intensity. Patients frequently experience odynophagia, dysphagia, foreign body sensation, retrosternal discomfort, and swallowing difficulty, all of which may substantially influence recovery and patient satisfaction. By using a multidimensional symptom questionnaire, the present study provides a more comprehensive assessment of patient-centered recovery following UGIE with biopsy.

One of the most important findings of the present study was that serum IL-6 concentrations increased significantly after UGIE with mucosal biopsy in both study groups, confirming that even minimally invasive endoscopic procedures are capable of inducing a measurable systemic inflammatory response. Nevertheless, the magnitude of IL-6 elevation was significantly smaller among patients receiving intravenous magnesium sulfate. These findings suggest that although magnesium sulfate did not completely prevent the inflammatory response associated with mucosal biopsy, it attenuated its intensity.

The increase in IL-6 observed in both study groups is biologically expected. Tissue biopsy inevitably disrupts epithelial integrity, resulting in activation of resident immune cells and release of damage-associated molecular patterns. These signals stimulate macrophages and monocytes to produce IL-6 within the first few hours after tissue injury. IL-6 subsequently amplifies the inflammatory cascade through activation of the JAK/STAT pathway, promotes acute-phase protein synthesis, and enhances communication between the peripheral immune system and the central nervous system. Consequently, transient increases in circulating IL-6 after minor tissue injury represent a normal physiological response rather than a pathological event. Previous clinical studies have similarly demonstrated postoperative IL-6 elevation following minimally invasive surgical procedures, supporting the biological plausibility of the present findings. (7–10)

Although IL-6 increased in both groups, patients receiving magnesium sulfate exhibited a substantially smaller increase than those receiving placebo. This observation is consistent with experimental evidence suggesting that magnesium modulates inflammatory signaling rather than completely suppressing physiological inflammation. Magnesium has been shown to inhibit intracellular calcium-dependent activation of inflammatory cells, reduce nuclear factor-kappa B activation, and decrease production of IL-6, TNF-α, and other pro-inflammatory cytokines. Importantly, attenuation of excessive cytokine production may reduce unnecessary inflammatory amplification while preserving normal tissue healing. Therefore, the smaller increase in IL-6 observed in the present study may reflect modulation of the inflammatory response rather than inhibition of physiological repair processes. (13–16)

Another important observation was the significant positive correlation between postoperative IL-6 concentrations and M-ESQ scores throughout the 48-hour follow-up period. Patients with higher IL-6 concentrations consistently reported more severe post-endoscopic symptoms. Although the observed correlations were only moderate, they remained statistically significant at every assessment time point and became strongest during the first postoperative day. These findings support the hypothesis that inflammatory activity contributes to the development of post-endoscopic symptoms following mucosal biopsy.

However, the moderate strength of these correlations also indicates that IL-6 is unlikely to be the sole determinant of post-endoscopic symptom severity. Post-endoscopic recovery is inherently multifactorial and is influenced by procedural factors, individual pain sensitivity,

psychological responses, anesthetic management, and additional inflammatory mediators that were not measured in the present study. Consequently, while IL-6 appears to represent an important biomarker of postprocedural inflammation, it should not be interpreted as a direct surrogate for symptom severity. Instead, the present findings suggest that IL-6 reflects one component of the complex biological processes contributing to post-endoscopic recovery.

The present study has several strengths. First, to our knowledge, this is among the first randomized controlled trials evaluating the combined clinical and inflammatory effects of intravenous magnesium sulfate in patients undergoing UGIE with mucosal biopsy. Second, symptom severity was assessed using the Modified Esophageal Symptoms Questionnaire (M-ESQ), a procedure-specific instrument that captures multiple dimensions of post-endoscopic recovery rather than pain alone. Third, repeated symptom assessments over 48 hours allowed evaluation of symptom trajectories instead of relying on a single postoperative measurement. Finally, longitudinal analysis using generalized estimating equations appropriately accounted for within-subject correlations across repeated observations, providing robust estimates of treatment effects over time.

Several limitations should also be acknowledged. First, this was a single-center study with a relatively modest sample size, which may limit generalizability to other populations. Second, IL-6 was measured only before and after the procedure, precluding evaluation of the complete temporal profile of cytokine release. Serial postoperative cytokine measurements might provide a more comprehensive understanding of the inflammatory response following endoscopic biopsy. Third, other inflammatory biomarkers, including TNF-α, IL-1β, and C-reactive protein, were not evaluated. Inclusion of multiple inflammatory mediators could further clarify the mechanisms through which magnesium sulfate influences postprocedural recovery.

Finally, serum magnesium concentrations were not measured; therefore, correlations between circulating magnesium levels and clinical outcomes could not be assessed.

Despite these limitations, the present findings have important clinical implications. As the number of gastrointestinal endoscopic procedures continues to increase worldwide, improving postprocedural recovery has become increasingly relevant. Intravenous magnesium sulfate is inexpensive, widely available, and familiar to anesthesiologists. If confirmed in larger multicenter trials, perioperative magnesium sulfate may represent a practical adjunctive strategy to reduce post-endoscopic symptom burden while attenuating procedure-related inflammatory responses without increasing procedural complexity.

In conclusion, the present randomized controlled trial demonstrates that intravenous magnesium sulfate significantly reduced post-endoscopic esophageal symptom severity and attenuated the increase in serum IL-6 following UGIE with mucosal biopsy. These findings provide evidence supporting the dual analgesic and anti-inflammatory effects of magnesium sulfate in minimally invasive gastrointestinal procedures and highlight its potential role as an adjunctive component of perioperative care.

CONCLUSION

Intravenous magnesium sulfate administered before upper gastrointestinal endoscopy with mucosal biopsy significantly reduced post-endoscopic esophageal symptom severity, as assessed using the Modified Esophageal Symptoms Questionnaire (M-ESQ), throughout the first 48 hours after the procedure. Patients receiving magnesium sulfate experienced more rapid early symptom improvement and consistently lower symptom severity than those receiving placebo.

Magnesium sulfate also attenuated the peri-procedural inflammatory response by significantly reducing the magnitude of serum interleukin-6 (IL-6) elevation following mucosal biopsy. Furthermore, higher post-procedural IL-6 concentrations were positively correlated with greater post-endoscopic symptom severity, supporting an association between the inflammatory response and postoperative esophageal symptoms after UGIE with biopsy.

Collectively, these findings suggest that intravenous magnesium sulfate may represent a promising adjunctive perioperative strategy for improving post-endoscopic recovery while attenuating procedure-related inflammatory responses in patients undergoing upper gastrointestinal endoscopy with mucosal biopsy.

CLINICAL PERSPECTIVE

Although upper gastrointestinal endoscopy is considered minimally invasive, postprocedural symptoms remain common and may negatively affect patient comfort and overall procedural experience. The present findings suggest that a simple, inexpensive, and widely available intervention such as intravenous magnesium sulfate may improve post-endoscopic recovery by simultaneously reducing symptom severity and attenuating inflammatory activation.

Given its favorable safety profile and ease of administration, magnesium sulfate may be considered as part of multimodal perioperative management for patients undergoing diagnostic upper gastrointestinal endoscopy with biopsy, particularly in individuals at increased risk of postprocedural discomfort.

STRENGTHS

The present study has several important strengths.

First, this is among the first randomized controlled trials evaluating both patient-reported post-endoscopic symptom severity and systemic inflammatory response following upper gastrointestinal endoscopy with biopsy.

Second, symptom severity was assessed using the Modified Esophageal Symptoms Questionnaire (M-ESQ), a procedure-specific instrument that comprehensively evaluates post-endoscopic symptoms rather than postoperative pain alone.

Third, repeated assessments performed over 48 hours allowed characterization of symptom trajectories and early recovery patterns instead of relying on a single postoperative measurement.

Fourth, the use of Generalized Estimating Equations (GEE) appropriately accounted for correlations among repeated measurements, thereby providing robust longitudinal estimates of treatment effects.

Finally, the integration of clinical outcomes with inflammatory biomarkers provides mechanistic insight that extends beyond conventional postoperative symptom assessment.

LIMITATIONS

Several limitations should be considered when interpreting the present findings.

First, this was a single-center study involving a relatively small sample size, which may limit external generalizability.

Second, serum IL-6 concentrations were measured only before and after the procedure. Serial postoperative measurements would have provided a more comprehensive description of cytokine kinetics following mucosal biopsy.

Third, additional inflammatory biomarkers, including tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), interleukin-8 (IL-8), and C-reactive protein (CRP), were not evaluated.

Fourth, serum magnesium concentrations were not measured, preventing evaluation of dose-response relationships between circulating magnesium levels and clinical outcomes.

Finally, postoperative follow-up was limited to 48 hours; therefore, the long-term effects of magnesium sulfate on symptom resolution could not be determined.

FUTURE DIRECTIONS

Future multicenter randomized controlled trials with larger sample sizes are warranted to confirm these findings.

Further studies should incorporate serial measurements of inflammatory biomarkers together with serum magnesium concentrations to better elucidate the biological mechanisms through which magnesium sulfate improves post-endoscopic recovery.

Investigation of different magnesium dosing strategies and administration protocols may also help identify the optimal regimen for routine clinical practice.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

Fiqih Eka Putra contributed to the conceptualization and design of the study, methodology development, participant recruitment, data collection, data curation, formal statistical analysis, data interpretation, visualization, project administration, and preparation of the original manuscript draft. Nur Surya Wirawan contributed to the study conceptualization, methodology, supervision, validation of the research process, interpretation of the findings, and critical revision of the manuscript. Madonna Damayanthie Datu contributed to the study methodology, investigation, validation of the research process, and critical review of the manuscript. Muh. Ramli Ahmad contributed to the study methodology, supervision, validation, and critical revision of the manuscript. A. M. Takdir Musba contributed to supervision, validation, provision of resources, and critical revision of the manuscript. Rusmin B. Syukur contributed to validation, provision of resources, and critical revision of the manuscript. All authors read and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

DATA AVAILABILITY

The datasets generated and analyzed during the current study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The study was approved by the Health Research Ethics Committee of Dr. Wahidin Sudirohusodo Hospital and the Faculty of Medicine, Hasanuddin University. Written informed consent was obtained from all participants before enrollment.

ABBREVIATIONS

Abbreviation	Full Form
ANCOVA	Analysis of Covariance
ASA	American Society of Anesthesiologists
CI	Confidence Interval
ELISA	Enzyme-Linked Immunosorbent Assay
GEE	Generalized Estimating Equations
IL-6	Interleukin-6
IQR	Interquartile Range
$MgSO_4$	Magnesium Sulfate
M-ESQ	Modified Esophageal Symptoms Questionnaire
NMDA	N-Methyl-D-Aspartate
OR	Operating Room
RCT	Randomized Controlled Trial
SD	Standard Deviation
UGIE	Upper Gastrointestinal Endoscopy

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