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CLINICAL TRIAL REPORT

Intravenous Lidocaine and Cognitive Recovery After Endoscopic Submucosal Dissection: A Randomized Controlled Trial

Yagui Liang[1,*], Bin Qian[2,*], Yifen Zhuo[3,*], Jingxuan Zhang[4], Weitao Gao[4], Hao Li[4], Xiaohong Zhang[4], Wenjun Lin[4]

[1]Department of Anesthesiology, Mindong Hospital Affiliated to Fujian Medical University, Fuan, Fujian, People's Republic of China; [2]Department of Anesthesiology, People's Hospital Affiliated to Fujian University of Traditional Chinese Medicine, Fuzhou, Fujian, People's Republic of China; [3]Department of Anesthesiology, Xiamen Haicang Hospital, Xiamen, Fujian, People's Republic of China; [4]Department of Anesthesiology, Shengli Clinical Medical College of Fujian Medical University, Fujian Provincial Hospital, Fuzhou, Fujian, People's Republic of China

*These authors contributed equally to this work

Correspondence: Xiaohong Zhang; Wenjun Lin, Department of Anesthesiology, Shengli Clinical Medical College of Fujian Medical University, Fujian Provincial Hospital, No. 134, Dongjie Street, Fuzhou, Fujian, 350001, People's Republic of China, Email zhxh@fjmu.edu.cn; 1231120224@fjmu.edu.cn

Background and Purpose: While intravenous lidocaine reduces propofol requirements during procedures, its effects on postoperative cognitive function remain uncertain. This study evaluated whether lidocaine enhances cognitive recovery in patients undergoing endoscopic submucosal dissection (ESD) with propofol sedation.

Patients and Methods: In this randomized, double-blind, placebo-controlled trial, 234 patients undergoing colorectal ESD received either intravenous lidocaine (1.5 mg/kg bolus followed by 2 mg/kg/h infusion) or a saline placebo. The standard sedation protocol included sufentanil 0.1 μg/kg and propofol for induction, with additional propofol as needed to maintain adequate sedation depth. The primary outcome was cognitive recovery on postoperative day 3 assessed by the PostopQRS cognitive domain. Secondary outcomes included recovery patterns at four timepoints (30 minutes, 1, 3, and 7 days), propofol consumption, injection pain, satisfaction scores, and adverse events.

Results: The lidocaine group demonstrated significantly better cognitive recovery than the placebo group [relative risk 1.15, 95% confidence interval (CI) 1.04–1.28, p=0.008], with benefits lasting through day 7 (p=0.035). Lidocaine administration resulted in a 25% reduction in propofol consumption [230 (208–258) mg compared to 305 (261–354) mg, with a median difference of –71 mg, 95% CI –85 to –57, p<0.001]. Additionally, injection pain scores were significantly lower in the lidocaine group [median score of 0 (0–1) versus 1 (0–3), p<0.001]. The incidence of hypotensive episodes was also reduced with lidocaine administration (12.8% compared to 24.8%, p=0.019). Importantly, no lidocaine toxicity was observed.

Conclusion: Intravenous lidocaine was associated with enhanced cognitive recovery on postoperative day 3, as well as decreased propofol requirements, injection pain, and hypotensive episodes during ESD. These results indicate that lidocaine may serve as an effective adjuvant in endoscopic sedation protocols.

Registration: ClinicalTrials.gov, NCT05750056.

Keywords: lidocaine, postoperative cognitive dysfunction, endoscopic submucosal dissection, propofol, sedation, cognitive recovery

Introduction

Colorectal cancer, the third most common cancer and second leading cause of cancer death globally, resulted in 1.9 million new cases and 930,000 deaths in 2020.[1,2] With incidence projected to double by 2040, screening programs have become critical for early detection and removal of precancerous lesions.[3] Endoscopic submucosal dissection (ESD) has emerged as the preferred removal technique, achieving complete excision with superior outcomes compared to

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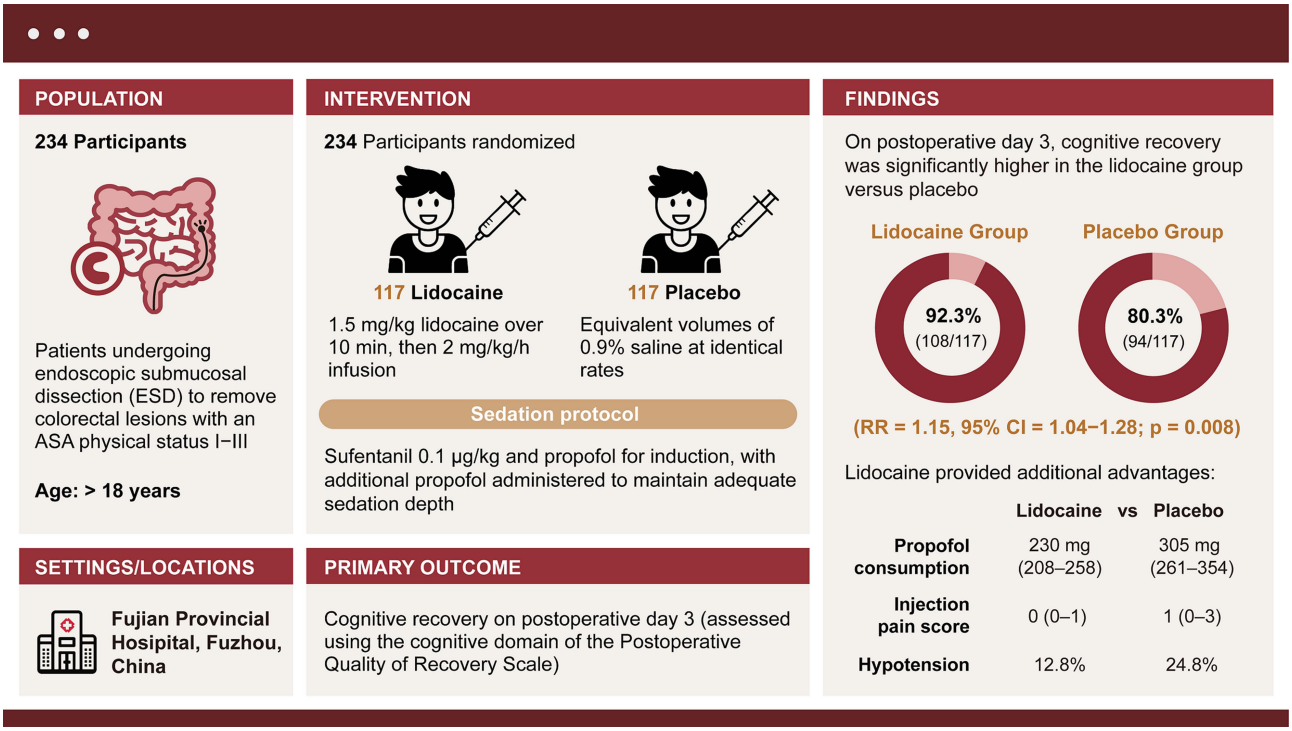
Graphical Abstract



conventional methods.[4] However, the technical complexity of ESD necessitates prolonged procedure times and deep sedation, raising important safety considerations.[5]

Propofol remains the preferred sedative for endoscopic procedures due to its rapid onset and swift recovery.[6,7] However, it can cause dose-dependent cardiovascular depression, potentially compromising cerebral perfusion, a concern that is particularly relevant for ESD procedures which require deep sedation lasting over 60 minutes.[8] Recent studies have highlighted concerns about cognitive safety following endoscopic sedation. An observational study found that approximately 15% of patients exhibited incomplete cognitive recovery extending from days to weeks after endoscopy.[9] Additionally, a study by Padmanabhan et al[10] showed that 18.5% of colonoscopy patients experienced cognitive impairment at discharge, though long-term effects were not assessed. Given the longer duration and more profound sedation requirements of ESD procedures, there is a compelling need to investigate the potential for cognitive impairment in this procedural context.

Intravenous administration of lidocaine has been shown to alleviate complications associated with propofol, including a 25% reduction in propofol consumption and the elimination of injection pain during endoscopic procedures.[11,12] A systematic review conducted by Wang et al encompassing 25 surgical studies demonstrated that lidocaine significantly reduced postoperative cognitive dysfunction, particularly on days 3 and 7, and enhanced cognitive test performance while decreasing markers of neuronal injury.[13] Despite the heterogeneity of studies and issues related to sample size, these clinical observations are corroborated by laboratory evidence indicating lidocaine's role in cytokine suppression, mitochondrial preservation, and reduction of excitotoxicity.[14,15] However, results across trials are inconsistent; for example, Wang et al reported cognitive benefits following cardiac surgery,[16] whereas Klinger et al did not observe such effects.[17] Importantly, the cognitive effects of lidocaine during endoscopic procedures remain unexplored, where sedation and hemodynamic profiles differ from those in general anesthesia.

Building upon the established propofol-sparing effects and potential neuroprotective properties of lidocaine, we hypothesized that intravenous administration of lidocaine would enhance cognitive recovery following ESD compared to a placebo. To test this hypothesis, we conducted a randomized controlled trial to assess whether lidocaine improves cognitive recovery on the third postoperative day, as measured by the cognitive domain of the Postoperative Quality of Recovery Scale (PostopQRS).[18] Secondary objectives included evaluating the effects of lidocaine on propofol consumption, injection pain, emergence time, hemodynamic stability, and adverse events.

Materials and Methods

Study Design and Ethics

We conducted this randomized, double-blind, placebo-controlled trial at the Gastrointestinal Endoscopy Center of Fujian Provincial Hospital, Fuzhou, China. The Institutional Review Board of Fujian Provincial Hospital approved the study (K2020-05-029-02). The trial adhered to the Declaration of Helsinki (2013 version), Good Clinical Practice guidelines, and all applicable local regulations. The study protocol was registered with ClinicalTrials.gov (NCT05750056, https://clinicaltrials.gov/study/NCT05750056) on January 28, 2023, with no subsequent protocol amendments. All participants provided written informed consent prior to enrollment. This report follows the Consolidated Standards of Reporting Trials (CONSORT) guidelines.[19]

Patient Selection

Eligible participants were adults aged ≥18 years with American Society of Anesthesiologists (ASA) physical status I–III scheduled for colorectal ESD. Exclusion criteria included: body mass index >30 kg/m^2, severe cardiac arrhythmia, hepatic or renal impairment, chronic pain requiring daily analgesics, allergy to study medications, pregnancy, cognitive impairment (Mini-Mental State Examination score <24), and inability to communicate in Mandarin Chinese.

Randomization and Allocation

Participants were allocated in a 1:1 ratio to either the lidocaine or placebo group through computer-generated block randomization (blocks of four and six). An independent researcher employed R statistical software to generate the randomization sequence. To ensure allocation concealment, treatment codes were placed in opaque envelopes and stored securely in the pharmacy. A designated pharmacy nurse, who was not involved in patient care, prepared the study medication in identical 50-mL syringes on each procedure day. Throughout the study, all study personnel, including anesthesiologists, endoscopists, nurses, and outcome assessors, as well as the patients, remained blinded to the treatment allocation.

Study Procedures

All patients underwent standardized bowel preparation with a low-residue diet for three days and polyethylene glycol solution (2–4 liters) the evening before ESD. Continuous monitoring included heart rhythm, oxygen saturation, and blood pressure throughout the procedure. Supplemental oxygen was delivered at 3 L/min via nasal cannulas. Following baseline monitoring, the lidocaine group received intravenous lidocaine 1.5 mg/kg over 10 minutes (based on ideal body weight), followed by continuous infusion at 2 mg/kg/h. This dosing regimen was based on established protocols.[20,21] The placebo group received equivalent volumes of saline. A single anesthetist blinded to group allocation performed all sedation procedures.

Sedation was induced with sufentanil 0.1 μg/kg and propofol 1 mg/kg, with additional propofol boluses of 0.5 mg/kg titrated to maintain Modified Observer's Assessment of Alertness/Sedation (MOAA/S) scores of 1–2.[22] A single experienced endoscopist (>200 ESDs annually) performed all procedures. Once target sedation was achieved, the endoscopist performed standardized ESD: marking 5 mm beyond lesion margins; submucosal injection with sodium hyaluronate and blue dye; circumferential incision and dissection; and vessel cauterization. Hypotension (mean arterial pressure <65 mmHg or >30% below baseline) was treated with ephedrine 3 mg;

bradycardia (<50 bpm) with atropine 0.2 mg. Post-procedure, patients recovered until achieving a Modified Aldrete Score ≥9.

Study Outcomes

The primary endpoint was cognitive recovery on postoperative day 3, assessed using the PostopQRS cognitive domain. This time point allowed complete sedative clearance while capturing early cognitive changes. The PostopQRS evaluates five domains: physiological (9 items), nociceptive (2 items), emotional (2 items), functional (4 items), and cognitive (5 items). While four domains define recovery as returning to baseline, the cognitive domain incorporates tolerance thresholds for normal performance variation. Cognitive recovery requires meeting all five criteria: orientation at baseline, digits forward within 2 points, digits backward within 1 point, and word recall and generation, each within 3 points of baseline.[23]

Secondary endpoints comprised PostopQRS recovery at four timepoints (30 minutes, 1, 3, and 7 days), propofol consumption, injection pain, emergence time, and satisfaction ratings. Satisfaction was assessed using 5-point Likert scales (1 = very dissatisfied; 5 = very satisfied) for patients and endoscopists.[24] Emergence time was defined as the interval from procedure completion to full alertness (MOAA/S score 5).[25]

Safety monitoring included assessment of: hypotension (mean arterial pressure <65 mmHg or ≥30% decrease from baseline), bradycardia (heart rate <50 beats/min), hypoxemia (SpO_2 <90% despite supplemental oxygen), postoperative nausea and vomiting, and lidocaine toxicity symptoms (perioral numbness, metallic taste, tinnitus, dizziness, slurred speech, and tremor).

Sample Size Calculation

Sample size was calculated based on anticipated differences in cognitive recovery rates between the study groups. Prior research indicates that approximately 80% of patients experience cognitive recovery by the third day post-endoscopic procedures.[26] We considered a 15% absolute improvement in recovery rates (from 80% to 95%) to be of clinical significance. To achieve this, with a two-sided alpha level of 0.05 and a statistical power of 90%, we determined that 105 participants per group were required. Accounting for a potential attrition rate of 10%, a total of 234 participants were recruited for the study.

Statistical Analysis

All analyses adhered to the intention-to-treat principles, incorporating every randomized participant irrespective of protocol adherence. Sensitivity analyses conducted on a per-protocol basis corroborated the primary findings. Missing data were addressed using multiple imputation via chained equations, resulting in 20 imputed datasets. Data are reported as mean (standard deviation) for normally distributed variables and as median (interquartile range) for non-parametric data. The normality of the data was evaluated using the Shapiro–Wilk test. Categorical variables are presented as frequencies and percentages. Recovery patterns across all time points were examined using generalized linear mixed models (GLMM) with a binomial distribution and a logit link function. For analytical purposes, all recovery outcomes were dichotomized into "recovered" versus "not recovered". The models incorporated treatment group, time (as a categorical variable), and the interaction between time and treatment as fixed effects, with patient-specific random intercepts to account for within-patient correlation. Results from the GLMM are expressed as odds ratios (OR) with 95% confidence intervals (CIs). Between-group comparisons were conducted using independent t-tests or Mann–Whitney *U*-tests for continuous data, and chi-square or Fisher's exact tests for categorical data, as appropriate. Statistical significance was set at $p<0.05$ (two-tailed). All analyses used R software (version 4.3.1).

Results

Figure 1 presents the CONSORT flow diagram detailing participant recruitment and retention. Between February 2023 and April 2024, we screened 245 patients and enrolled 234 who met the inclusion criteria. Participants were randomized equally between the lidocaine and placebo groups (n=117 each). Of 11 exclusions, 4 patients declined participation and 7 did not meet eligibility criteria. Retention rates were similar between groups: 110 (94.0%) lidocaine and 111 (94.9%)

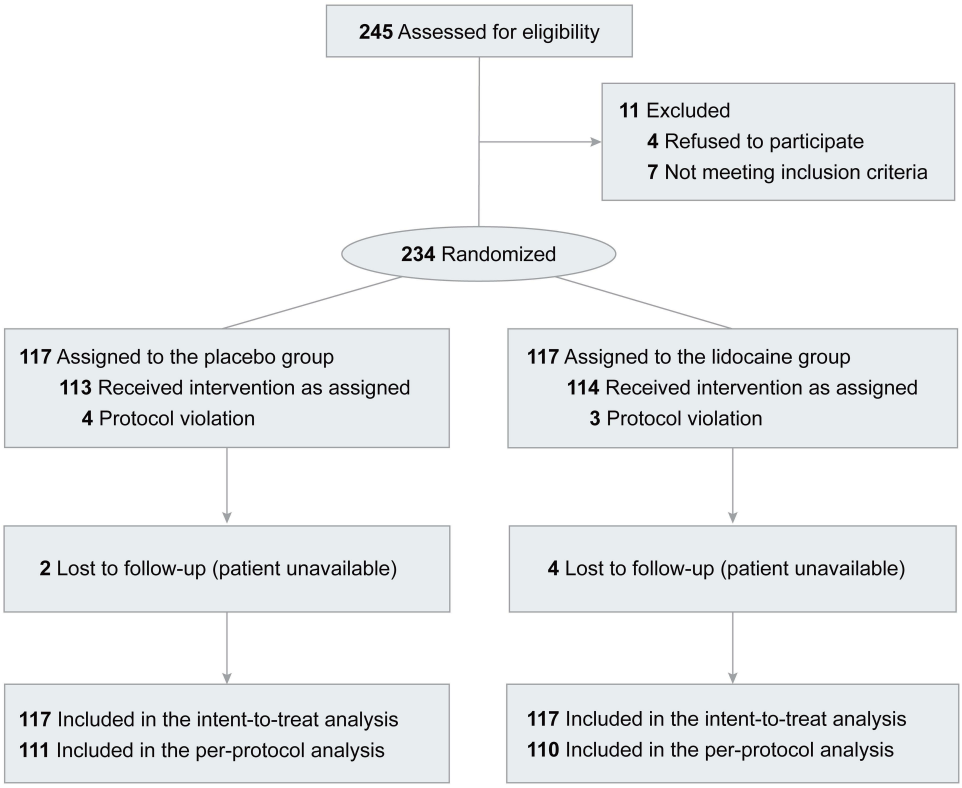


Figure 1 CONSORT flow diagram. Participant flow through trial phases. Of 245 patients screened between February 2023 and April 2024, 234 were randomized 1:1 to lidocaine (n=117) or placebo (n=117). Protocol completion rates were 94.0% (110/117) in the lidocaine group and 94.9% (111/117) in the placebo group (p=0.775). All 234 randomized participants were included in intention-to-treat analysis; 221 completed per-protocol analysis.

placebo patients completed the study per protocol. Protocol violations occurred in 3 lidocaine and 4 placebo patients; loss to follow-up occurred in 4 and 2 patients, respectively. This difference in completion rates was not statistically significant (p=0.775). Baseline characteristics were well-balanced between groups (Table 1).

Primary Outcome

Cognitive recovery on postoperative day 3 was significantly higher in the lidocaine group: 92.3% (108/117) versus 80.3% (94/117) in the placebo group [relative risk (RR) 1.15, 95% CI 1.04–1.28; p=0.008]. Per-protocol sensitivity analysis confirmed these findings (RR 1.11, 95% CI 1.08–1.19; p=0.003). The GLMM analysis revealed a significant treatment-by-time interaction (p=0.019), indicating that the treatment effect varied across timepoints (Figure 2A). While cognitive recovery was similar between groups at 30 minutes (58.1% vs 50.4%; OR 1.37, 95% CI 0.81–2.29; p=0.238), the lidocaine group showed significantly higher recovery at day 3 (92.3% vs 80.3%; OR 2.94, 95% CI 1.30–6.66; p=0.027) and day 7 (98.3% vs 90.6%; OR 5.97, 95% CI 1.31–27.14; p=0.035).

Secondary Outcomes

Recovery in other PostopQRS domains is shown in Table 2 and Figure 2B–F. The GLMM analysis revealed a significant treatment-by-time interaction for overall recovery (p<0.001). Overall recovery improved significantly with lidocaine at days 3 (91.5% vs 79.5%, OR=2.76, 95% CI 1.28–5.95, p=0.009) and 7 (97.4% vs 89.7%, OR=4.34, 95% CI 1.20–15.71, p=0.043). The physiological domain showed early benefit with lidocaine at 10 minutes post-procedure (76.9% vs 64.1%, OR=1.87, 95% CI 1.06–3.28, p=0.030). No significant differences were observed between groups for the nociceptive, emotional, or activities-of-daily-living domains at any time (all p>0.05, Table 2).

Lidocaine provided significant procedural benefits (Table 3). Propofol consumption decreased by 25% with lidocaine [median 230 (IQR 208–258) vs 305 (261–354) mg, difference –71 mg, 95% CI –85 to –57, p<0.001]. Emergence time

Table 1 Patient Characteristics

Characteristic	Lidocaine (n = 117)	Placebo (n = 117)	p-value[a,b]
Age, median (IQR), year	65 (54–70)	66 (55–70)	0.687
Sex, n (%)			0.356
Male	47 (40.2)	54 (46.2)	
Female	70 (59.8)	63 (53.8)	
Height, mean (SD), cm	166.3 (6.3)	166.1 (6.3)	0.892
Weight, median (IQR), kg	64.0 (58.0–68.5)	65.0 (59.5–68.0)	0.435
BMI, median (IQR), kg/m^2	23.0 (21.8–24.1)	23.0 (21.8–24.3)	0.459
ASA physical status, n (%)			0.383
I	18 (15.4)	25 (21.4)	
II	86 (73.5)	83 (70.9)	
III	13 (11.1)	9 (7.7)	
Comorbidities, n (%)			
Coronary artery disease	13 (11.1)	10 (8.5)	0.510
Diabetes mellitus	17 (14.5)	21 (17.9)	0.478
Hypertension	28 (23.9)	22 (18.8)	0.339
Duration of procedure, mean (SD), min	65.9 (9.1)	64.4 (8.7)	0.203

Notes: Data presented as n (%), mean (SD), or median (IQR) as appropriate. Groups were well-balanced at baseline with no significant differences. [a]p-value compares lidocaine versus placebo; [b]Independent *t*-test for means, Mann–Whitney *U*-test for medians, chi-square test for proportions.

Abbreviations: ASA, American Society of Anesthesiologists; BMI, body mass index; IQR, interquartile range; SD, standard deviation.

was shorter in the lidocaine group [median difference –3 min, 95% CI –3 to –2, p<0.001]. Injection pain was nearly eliminated with lidocaine [median score 0 (0–1) vs 1 (0–3), p<0.001]. Both patient and endoscopist satisfaction scores were significantly higher with lidocaine (p=0.003 and p<0.001, respectively).

Safety Outcomes

Both treatments were well-tolerated with comparable adverse event rates (Table 3). Hypotension occurred less frequently in the lidocaine group (12.8% vs 24.8%; RR 0.52, 95% CI 0.29–0.91, p=0.019), consistent with lidocaine's hemodynamic-stabilizing effects. No serious adverse events or lidocaine toxicity were observed.

Discussion

This randomized controlled trial demonstrated that intravenous administration of lidocaine enhanced cognitive recovery on the third postoperative day in patients undergoing ESD. As the first study to investigate the cognitive effects of lidocaine in endoscopic procedures, we address an important gap in the existing literature. Additionally, the lidocaine group exhibited reduced propofol consumption, lower pain scores associated with injection, and fewer episodes of hypotension, thereby supporting the role of lidocaine as an effective adjuvant for sedation during endoscopy.

Several factors informed the design and interpretation of our study. Cognitive function was assessed on the third postoperative day to ensure the clearance of sedatives while still capturing early cognitive changes. A significant strength of our study was the employment of the PostopQRS, which evaluates recovery in relation to each patient's baseline rather than relying on absolute scores. This individualized approach accounts for pre-existing cognitive differences and

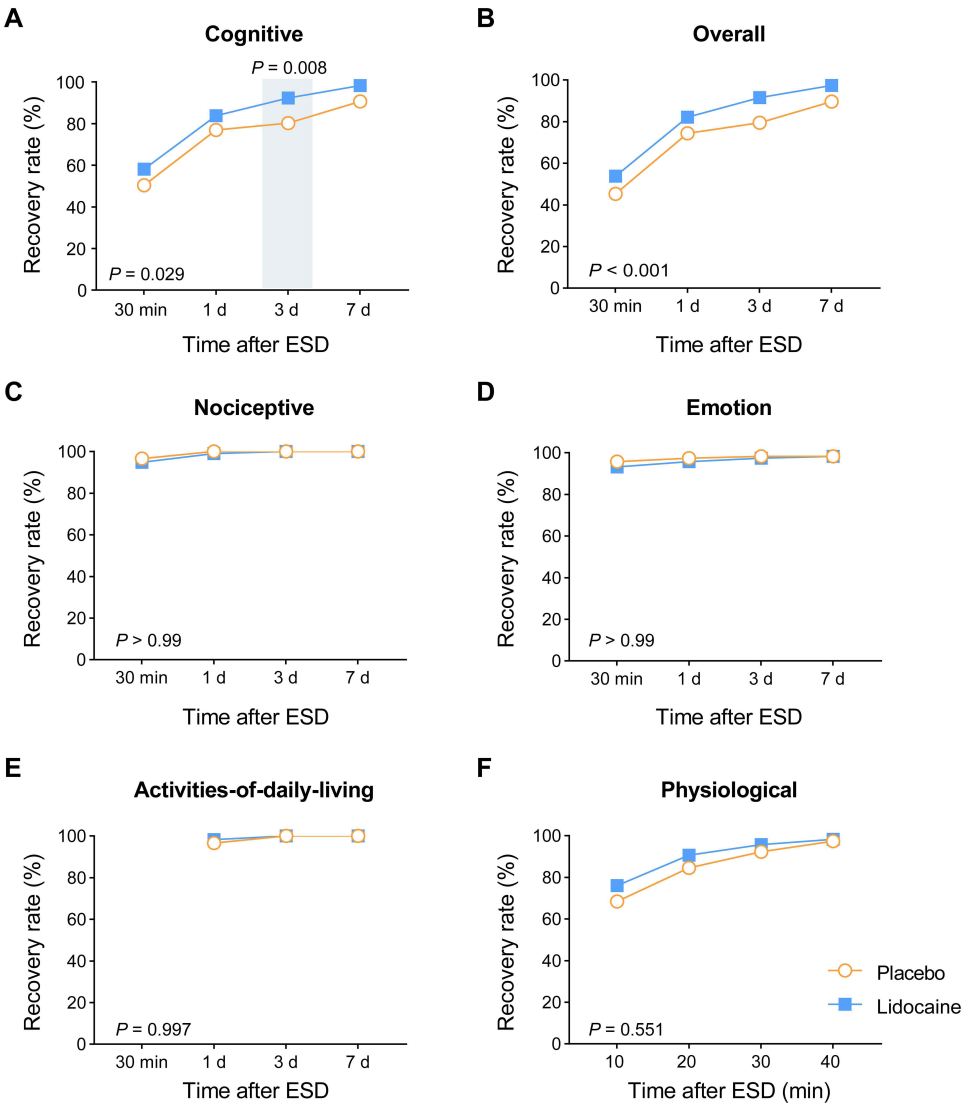


Figure 2 Postoperative Quality of Recovery Scale (PostopQRS) recovery rates over time by domain. Recovery rates shown as percentage meeting domain criteria at specified timepoints. Blue squares: lidocaine (n=117); Orange circles: placebo (n=117). (**A**) Cognitive Domain: Primary outcome at day 3 (gray shading): 92.3% vs 80.3%, p=0.008. Treatment-by-time interaction p=0.029. (**B**) Overall Recovery: Combined all five domains. Treatment-by-time interaction p<0.001. (**C**) Nociceptive Domain: Pain and nausea. Treatment-by-time interaction p>0.99. (**D**) Emotional Domain: Anxiety and depression. Treatment-by-time interaction p>0.99. (**E**) Activities of Daily Living: Functional capacity from day 1. Treatment-by-time interaction p=0.997. (**F**) Physiological Domain: Nine parameters at 10-minute intervals. Treatment-by-time interaction p=0.551. P-values from generalized linear mixed models with binomial distribution, logit link, and random intercepts for repeated measures (all two-sided).

enhances the sensitivity to detect meaningful changes. Furthermore, the validation of the tool for both face-to-face and telephone administration facilitated comprehensive follow-up.

Our findings demonstrate that intravenous lidocaine facilitates cognitive recovery following ESD. However, evidence from diverse surgical contexts reveals mixed outcomes. A meta-analysis by Geng et al, encompassing 10 studies, demonstrated that lidocaine significantly mitigates postoperative cognitive dysfunction, particularly in the short term (less than 30 days).[27] Chen et al observed a reduction in cognitive dysfunction three days post-spine surgery,[28] while Wang et al demonstrated cognitive benefits following coronary artery bypass surgery.[16] In contrast, several rigorously designed trials reported no cognitive benefits. Klinger et al observed no improvement in cognitive outcomes post-cardiac surgery, despite using similar dosing protocols,[17] and Mathew et al found no cognitive enhancement in cardiac surgery patients at six weeks post-operation.[29] Similarly, Peng et al reported no improvement at six months following neurosurgery,[30] and the 2025 ALLEGRO trial, a large multicenter study involving 590 patients undergoing minimally

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Table 2 Recovery Rates Overall and by Individual Domains for Patients Undergoing Endoscopic Submucosal Dissection

	n (%)		Odd Ratio (95% CI)	p-value[a,b]
	Lidocaine (n = 117)	Placebo (n = 117)		
Cognitive				
30 min	68 (58.1)	59 (50.4)	1.36 (0.81 to 2.30)	0.256
1 day	98 (83.8)	90 (76.9)	1.55 (0.82 to 1.97)	0.177
3 day	108 (92.3)	94 (80.3)	2.94 (1.30 to 6.67)	0.027
7 day	115 (98.3)	106 (90.6)	5.97 (1.31 to 27.14)	0.035
Overall				
30 min	63 (53.8)	53 (45.3)	1.41 (0.84 to 2.36)	0.188
1 day	96 (82.1)	87 (74.4)	1.58 (0.86 to 2.89)	0.145
3 day	107 (91.5)	93 (79.5)	2.76 (1.28 to 5.95)	0.009
7 day	114 (97.4)	105 (89.7)	4.34 (1.20 to 15.71)	0.043
Nociceptive				
30 min	111 (94.9)	113 (96.6)	0.65 (0.18 to 2.38)	0.518
1 day	116 (99.1)	116 (99.1)	1.00 (0.00 to ∞)	>0.99
3 day	117 (100.0)	117 (100.0)	1.00 (0.00 to ∞)	>0.99
7 day	117 (100.0)	117 (100.0)	1.00 (0.00 to ∞)	>0.99
Emotion				
30 min	109 (93.2)	112 (95.7)	0.61 (0.20 to 1.90)	0.399
1 day	112 (95.7)	114 (97.4)	0.59 (0.14 to 2.52)	0.472
3 day	114 (97.4)	115 (98.3)	0.66 (0.11 to 4.02)	0.651
7 day	115 (98.3)	115 (98.3)	1.00 (0.14 to 7.15)	>0.99
Activities of daily living				
1 day	115 (98.3)	113 (96.6)	2.04 (0.37 to 11.35)	0.683
3 day	117 (100.0)	117 (100.0)	1.00 (0.00 to ∞)	>0.99
7 day	117 (100.0)	117 (100.0)	1.00 (0.00 to ∞)	>0.99
Physiological				
10 min	90 (76.9)	75 (64.1)	1.87 (1.06 to 3.28)	0.030
20 min	106 (90.6)	99 (84.6)	1.75 (0.79 to 3.88)	0.164
30 min	112 (95.7)	108 (92.3)	1.87 (0.61 to 5.70)	0.282
40 min	115 (98.3)	114 (97.4)	1.51 (0.25 to 9.18)	0.651

Notes: Data presented as n (%) meeting recovery criteria. Statistical analysis used generalized linear mixed models with binomial distribution and logit link function, accounting for repeated measures. [a]p-value compares lidocaine versus placebo; [b]Chi-square test.

Abbreviations: OR, odds ratio; CI, confidence interval.

Table 3 Secondary Outcomes

Characteristic	Lidocaine (n = 117)	Placebo (n = 117)	p-value[a,b]
Injection pain score, median (IQR)	0 (0–1)	1 (0–3)	<0.001
Propofol consumption, median (IQR), mg	230 (208–258)	305 (261–354)	<0.001
Emergence time, median (IQR), min	10 (8–12)	12 (10–14)	<0.001
Patient satisfaction, n (%)			0.003
Very satisfied	84 (71.8)	59 (50.4)	
Satisfied	30 (25.6)	45 (38.5)	
Neutral	3 (2.6)	9 (7.7)	
Dissatisfied	0	4 (3.4)	
Very dissatisfied	0	0	
Endoscopist satisfaction, n (%)			<0.001
Very satisfied	89 (76.1)	58 (49.6)	
Satisfied	26 (22.2)	54 (46.2)	
Neutral	2 (1.7)	5 (4.3)	
Dissatisfied	0	0	
Very dissatisfied	0	0	
Adverse events, n (%)			
Hypotension	15 (12.8)	29 (24.8)	0.019
Bradycardia	9 (7.7)	6 (5.1)	0.423
Hypoxemia	2 (1.7)	5 (4.3)	0.446
Postoperative nausea or vomiting	1 (0.9)	2 (1.7)	>0.99
Systemic lidocaine toxicity	0	0	>0.99

Notes: Data presented as n (%) or median (IQR). IQR, interquartile range. [a]p-value compares lidocaine versus placebo; [b]mann–Whitney *U*-test for medians, chi-square test for proportions.

invasive colorectal surgery, detected no differences in cognitive outcomes.[31] Notably, none of these studies assessed plasma lidocaine concentrations, precluding definitive conclusions regarding therapeutic drug levels.

This variability in findings can be attributed to methodological differences and procedural contexts. Key variations include lidocaine dosing regimens (bolus doses of 1–2 mg/kg and infusion rates of 1–3 mg/kg/h), cognitive assessment tools (ranging from brief screenings to comprehensive neuropsychological batteries), anesthesia type (comparing volatile agents with total intravenous anesthesia), surgical stress responses (contrasting major open procedures with minimally invasive ones), and patient populations. The procedural context appears particularly significant. For instance, cardiac surgery involves cardiopulmonary bypass, cerebral microemboli, and reperfusion injury—stressors absent in endoscopic procedures. Conversely, endoscopic procedures typically involve moderate sedation with spontaneous respiration, whereas general anesthesia necessitates mechanical ventilation, thereby imposing greater physiological stress. Whether lidocaine's protective mechanisms—such as its anti-inflammatory effects, cellular energy preservation, and reduction of neuronal damage—remain consistent across various surgical contexts remains uncertain, warranting further investigation with standardized outcome measures and pharmacokinetic monitoring.

In contrast to the variable cognitive findings, our procedural outcomes demonstrated remarkable consistency. The observed 25% reduction in propofol usage is consistent with previous meta-analyses that report reductions ranging from 20% to 30%.[32] Additionally, our data on injection pain corroborates the number needed to treat of 4 to 5, as identified in systematic reviews.[33,34] This reproducibility is noteworthy. From a practical perspective, the reduced use of propofol addresses increasing environmental concerns and potential neurotoxicity, while pain-free injections enhance patient comfort, which is particularly important for patients requiring repeated colonoscopies. Our safety data were generally reassuring, with similar adverse events between groups; however, hypotension was significantly less common with lidocaine (12.8% vs 24.8%, p=0.019). Nevertheless, caution is warranted in generalizing these findings. With a sample size of only 234 patients, the study was not powered to detect rare events such as lidocaine toxicity. More critically, we excluded patients at the highest risk—those with hepatic, renal, or cardiac disease, or those taking CYP3A4 inhibitors.[35] These exclusions are significant, as such patients are frequently encountered in clinical practice. The operational benefits observed, including reduced emergence time and decreased propofol consumption, can potentially enhance the efficiency of endoscopy units.

When interpreting our findings, several limitations should be considered. We used the PostopQRS tool to assess cognitive function, which only evaluates basic domains and may miss subtle deficits detectable by comprehensive neuropsychological tests. We did not include molecular biomarkers, such as neuronal injury markers or inflammatory cytokines, which could have provided objective evidence of lidocaine's neuroprotective effects. Additionally, advanced neuroimaging techniques might have identified subclinical brain connectivity or structure changes. Future studies should incorporate these biomarkers and imaging methods to understand lidocaine's neuroprotective mechanisms better.

Our exclusion criteria critically restrict generalizability. By excluding patients with hepatic dysfunction, renal impairment, chronic pain, and baseline cognitive impairment—populations at highest risk for postoperative cognitive dysfunction—we eliminated those who might benefit most from preventive strategies. While justified by lidocaine toxicity concerns in patients with altered drug metabolism, these exclusions yielded a sample poorly representative of routine endoscopic practice. Our single-center design and homogeneous population further limit applicability. Future multicenter trials must enroll patients with organ dysfunction using therapeutic drug monitoring, stratify by baseline cognitive status and comorbidities, and evaluate dose-response relationships to optimize regimens for altered pharmacokinetics. We tested only one lidocaine regimen (1.5 mg/kg bolus, 2 mg/kg/h infusion) without measuring plasma concentrations, precluding pharmacokinetic-pharmacodynamic correlations. Our seven-day follow-up captured early recovery but not long-term effects requiring 3- to 6-month assessment. Clinicians should exercise caution when extrapolating these findings to patients with significant comorbidities, organ dysfunction, or baseline cognitive impairment.

Our findings support incorporating lidocaine into endoscopic sedation protocols in relatively healthy populations. Future research should prioritize several key areas. These recommendations include the following: (1) conducting multicenter trials that enroll patients with hepatic or renal dysfunction while implementing therapeutic drug monitoring and adjusted dosing protocols; (2) performing studies in patients with baseline cognitive impairment or chronic pain who may benefit most from neuroprotective interventions; (3) conducting dose-response evaluations to optimize regimens for patients with altered pharmacokinetics; and (4) incorporating comprehensive neuropsychological testing, biomarkers, and neuroimaging to better characterize neuroprotective mechanisms.

Additionally, head-to-head comparisons with alternatives such as dexmedetomidine would provide valuable comparative effectiveness data. Pharmacokinetic-pharmacodynamic modeling should optimize dosing across populations with varying metabolic capacities, while economic analyses should assess cost-effectiveness across healthcare settings. Such investigations will enable precision sedation strategies matched to individual patient risk profiles and procedural complexity, ensuring benefits extend to high-risk populations who need cognitive protection most.

Conclusion

This trial shows intravenous lidocaine improves cognitive recovery after ESD, with a 12% improvement in cognitive function by day 3. Treating eight patients can prevent one case of delayed cognitive recovery, making lidocaine a practical option for this common issue. Lidocaine also enhances procedural outcomes, reducing propofol use by 25%, which suggests cost savings and fewer anesthetic risks. It halves hypotensive episodes (12.8% vs 24.8%),

improving cardiovascular stability. Reduced injection pain and higher satisfaction scores suggest a better patient experience, potentially boosting compliance with surveillance programs.

The dosing protocol (1.5 mg/kg loading, 2 mg/kg/hour infusion) is straightforward and aligns with clinical practices, showing no toxicity and ensuring safety. However, our study excluded patients with liver or kidney disease, obesity, and those on drugs affecting lidocaine metabolism, limiting the scope of recommendations. Future research should address remaining questions before routine use, including dose-finding studies to identify the minimum effective dose and studies in high-risk populations like the elderly and those with comorbidities. Economic analyses should evaluate cost-effectiveness by considering drug costs, reduced propofol use, and improved recovery times. Lidocaine enhances cognitive outcomes, procedural safety, and patient satisfaction during ESD, supporting its potential as a standard adjuvant for complex endoscopic procedures.

Data Sharing Statement

De-identified participant data, the study protocol, and the complete statistical analysis plan will be available upon reasonable request to the corresponding author (Wenjun Lin, 1231120224@fjmu.edu.cn). This includes individual participant data underlying the published findings, with appropriate confidentiality safeguards in line with research ethics guidelines.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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