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ORIGINAL RESEARCH

Transcutaneous Electrical Acupoint Stimulation Combined with Moderate Sedation of Remimazolam Tosilate in Gastrointestinal Endoscopy: A Prospective, Randomized, Double-Blind, Placebo-Controlled Clinical Trial

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ABSTRACT

Introduction: Further clinical validation is required to determine whether transcutaneous electrical acupoint stimulation (TEAS) can replace opioids and be used in combination with remimazolam for sedation during gastrointestinal endoscopy.

Methods: A total of 108 outpatients who underwent diagnostic gastrointestinal endoscopy were randomly divided into three groups: fentanyl plus remimazolam group (group C), TEAS plus remimazolam group (group E), and placebo-TEAS plus remimazolam group (group P). The assessments of patient satisfaction, physician satisfaction, and pain scale score during the examination constituted the primary endpoints of the study. The secondary endpoints were the time of recovery, recovery of normal behavioral function and discharge, incidence of adverse reactions, and dose of remimazolam.

Results: Compared with group C, group E had a greater median score for patient satisfaction at follow-up and a slightly lower median score for physician satisfaction. The pain score of group E was slightly greater than that of group C, but the difference was not significant. However, in group C, the incidence of hypoxemia, the rate of nausea and the severity of vertigo were greater, and the number of patients discharged and resuming normal behavioral function was greater than those in the other two groups. The

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dose of remimazolam in group C and group E was less than that in group P.
Conclusions: TEAS combined with moderate sedation of remimazolam can provide an ideal sedative effect, which preferably suppresses discomfort caused by gastrointestinal endoscopy and has fewer sedation-related complications.
Trial Registration: ID: NCT05485064; First registration (29/07/2022); Last registration (02/11/2022) (Clinical Trials.gov).

Keywords: Transcutaneous electrical acupoint stimulation; Remimazolam tosilate; Moderate sedation; Gastrointestinal endoscopy; Patient satisfaction

Key Summary Points

Since 2020, the annual number of gastrointestinal endoscopies in China has exceeded tens of millions, so research on sedation related to gastrointestinal endoscopy has a great significance. However, the cost of sedation administered by anesthesiologists is relatively high, and the incidence of anesthesia-related complications, such as reflux and aspiration, is also high. Patients often cannot quickly recover normal behavior after undergoing sedation, so finding a new method of analgesia and sedation has become an urgent problem that needs to be solved.

TEAS can replace opioid drugs for safer administration in gastrointestinal endoscopy. Learn from study: As a non-pharmacological analgesic method, TEAS can minimize some adverse reactions after sedation while ensuring the analgesic effect during gastrointestinal endoscopy.

TEAS combined with moderate sedation of remimazolam can provide an ideal sedative effect, which preferably suppresses discomfort caused by gastrointestinal endoscopy and has fewer sedation-related complications.

INTRODUCTION

The advent of a new ultrashort-acting benzodiazepine, remimazolam, is a highly significant development in the field of sedation for gastrointestinal endoscopy procedures [1]. The onset and duration of sedation associated with remimazolam are similar to those associated with propofol, and remimazolam has a mild effect on respiratory depression. These properties make it the most promising sedative agent for replacing propofol and midazolam for safe use by anesthesiologists or endoscopists [1]. Because remimazolam lacks analgesic properties, opioids are still needed, which partially negates rapid recovery and mild respiratory depression and increases the incidence of postoperative nausea and vomiting (PONV) [2, 3].

Acupuncture is a nonpharmaceutical technique that originated in China and has been used for over 3000 years. Acupuncture can produce sedation and analgesia accurately by stimulating specific acupoints and releasing endogenous opioid peptides, such as endorphins [4–6]. The National Institutes of Health (NIH) approved the clinical application of acupuncture in 1997 [7]. TEAS is a modification of traditional acupuncture [8–13], which combines the advantages of acupuncture and percutaneous electrical nerve stimulation (PENS). It is a new noninvasive acupoint stimulation method that is simpler to use and less painful for patients under the premise of ensuring the efficacy of acupuncture [12, 14–17].

We verified whether TEAS can replace opioids and be used in combination with moderate sedation of remimazolam to maximize the pharmacological advantages of remimazolam during gastrointestinal endoscopy.

METHODS

Study Design and Population

We conducted a randomized, double-blind, placebo-controlled prospective clinical trial from August to November 2022 at the Affiliated

Hospital of Qingdao University. The study was conducted in accordance with the principles outlined in the Declaration of Helsinki and adhered to the reporting guidelines provided by the Standards for Reporting Interventions in Clinical Trials of Acupuncture [18] and the Consolidated Standards of Reporting Trials statement [19]. Ethics approval: The ethics committee of the Affiliated Hospital of Qingdao University approved this study (ID: QYFYKYLL916711920), which was also registered on the clinical trial website (NCT05485064). All patients provided informed consent before enrollment.

Inclusion criteria were patients aged 18 years to 80 years who were scheduled for gastrointestinal endoscopy were included. Exclusion criteria were patients with neuropsychiatric disorders, severe anxiety, severe depression, etc., who could not complete this study; those with American Society of Anesthesiologists (ASA) class > III, such as those with severe heart, liver, kidney, brain, or lung diseases; those who did not receive TEAS or who were allergic to acupoint electrodes or benzodiazepines; pregnant or lactating women; those with a history of long-term alcohol or drug abuse; and those who were unable to provide informed consent. Additionally, patients who were aware of or had previously received TEAS treatment were excluded because patients in group P were aware that TEAS was not guaranteed to be included in the grouping, which could lead to the failure of double-blind control [9, 17].

Division of Researchers

The study staff members included three gastroenterologists, three endoscopic nurses, two research assistants, and one anesthesiologist. The gastroenterologists had the same proficiency level (more than 3000 gastrointestinal endoscopies were performed). Research assistant 1 recruited, screened, obtained informed consent, randomized, grouped, collected general information, placed acupuncture electrodes at acupoints, and adjusted the stimulation parameters of the patients. Researcher assistant 1 was the only member who was aware of the study groups. The administration of moderate sedation, monitoring of vital signs, and evaluation of adverse events during the examination were carried out by the anesthesiologist. Research assistant 2 was responsible for performing the behavioral pain scale for non-intubated patients (BPS-NI) [13, 20] assessments at each time point during the examination, documenting adverse events and procedure duration, overseeing patient recovery, conducting satisfaction surveys, and conducting follow-up via telephone.

Randomization and Blindness

After the patients had an appointment for gastrointestinal endoscopy, researcher assistant 1 invited the patients to participate in this clinical trial, obtained their informed consent, and randomized them into the fentanyl plus remimazolam group (group C), TEAS plus remimazolam group (group E), and placebo-TEAS plus remimazolam group (group P) by using a computer-generated random numbers table. To ensure that patients in group E or group P were unaware of the grouping, all patients had no prior experience or knowledge of TEAS and were advised that they may not feel anything in the acupoints where the electrodes were placed [9, 17].

Intervention and Procedure

All patients were required to undergo fasting and water deprivation for more than 8 h and complete routine bowel preparations associated with the colonoscopy. Venous access was established after the patients were hospitalized on the examination day. Subsequently, normal saline was continuously administered.

Before Sedation

Patients were directed by research assistant 1 to enter a dedicated induction room and assume a left lateral position on an examination cart. Acupuncture electrodes were applied to the bilateral Neiguan (LI4), Hegu (PC6), and Zusanli (ST36) acupoints for patients in groups C and P. A Hwato acupuncture therapy device was connected [Specification: SDZ-III, Suzhou

Medical Limited Company, Jiangsu Food and Drug Administration (Approval) No. 2270675, 2017], and the parameters were set at dense wave frequencies of 2 and 100 Hz with automatic shifting, maximum tolerable stimulation intensity of the patient (current within 2–3 mA), and pre-operation stimulation time of group E (30 min)]. Throughout the entire examination, the stimulation parameters remained at their default settings [10, 11]. Patients in group P had acupuncture electrodes attached to them, similar to those in group E, but actual electrical stimulation was not administered [14, 15]. Patients in group C waited 30 min between inductions and were administered 50 μg (fentanyl) intravenously by research assistant 1 before they entered the examination room. Research assistant 1 shielded all patients before they entered the examination room to ensure double blinding [14].

Sedation

After entering the examination room, all patients were administered 10 g of lidocaine hydrochloride mucilage (lidocaine 0.2 g) for adequate local anesthesia of the oral cavity and pharynx; then, they were administered an initial dose of remimazolam (5 mg) [remimazolam tosilate for injection, Jiangsu Hengrui Medicine Co., Ltd., China, national medicine permission number: H20190034] intravenously within 1 min and received top-up doses (2.5 mg/dose) dividedly to reach the Modified Observer's Assessment of Alertness/Sedation (MOAA/S) scale of 3–4 [2]. The MOAA/S scores were assessed at regular intervals of 2 min. Continuous administration of supplemental oxygen at a flow rate of 2–4 l/min was provided through a nasal cannula, while the anesthesiologist administered intravenous normal saline. Vital signs, including electrocardiogram, heart rate (HR), noninvasive blood pressure (NIBP), and oxygen saturation (SpO_2), were continuously monitored. If the patient reached the target depth of sedation and was still unable to tolerate the stimulation of gastrointestinal endoscopy (BPS-NI > 9 points), the case was designated a treatment failure, and 50–100 mg of propofol was administered intravenously as a rescue sedative medication by the anesthesiologist.

Gastrointestinal Endoscopy

After reaching the predetermined depth of sedation, the gastroenterologist performed gastrointestinal endoscopy according to the order of gastroscopy and colonoscopy. The gastrointestinal endoscope used was an Olympus CV-290 [Olympus Corporation, China Food and Drug Administration (Approval) No. 3221606, 2017], and the OD of the gastroscope and colonoscope was 9.8 and 13.2 mm, respectively.

Recovery Process

Following the completion of the gastrointestinal endoscopy, research assistant 1 transferred patients to the induction room to remove acupuncture electrodes and associated equipment. Subsequently, patients were moved to the recovery room for ongoing monitoring of vital signs. The discharge criteria were based on the modified Aldrete score, with a minimum threshold of ≥ 9 [21].

Outcomes

The primary endpoints were patient satisfaction, physician satisfaction, and pain scale score during the examination. The secondary endpoints were time of recovery, recovery of normal behavioral function and discharge, incidence of adverse reactions, and dose of remimazolam.

Satisfaction Survey and Follow-up Questionnaire The content and format of the satisfaction survey and follow-up questionnaire were improved based on Cohen (2004) [22], Megan (2006) [23], and Levitzky (2012) [24]. At the conclusion of procedural sedation, research assistant 2 conducted satisfaction surveys with gastroenterologists using a clinical satisfaction with sedation instrument (CSSI). Similarly, patients were administered satisfaction surveys with a sedation instrument (PSSI) before discharge. Both surveys utilized a 100-mm visual analog scale (VAS) for assessment, with scores ranging from 0 (not at all satisfied) to 100 (com-

pletely satisfied). After completing the surveys, the patients were discharged with paper questionnaires of follow-up surveys. Research assistant 2 also contacted discharged patients by phone within 1 week to complete the follow-up questionnaires. They reported their overall satisfaction with the procedural sedation on the 100-mm VAS of the follow-up questionnaire. In addition, they also reported the time when they returned to normal activities (such as work, swimming, etc.) after the examination, the occurrence of nausea and emesis after discharge (based on a 100-mm VAS), procedure recall, and willingness to undergo procedural sedation again.

Pain Response Scale Research assistant 2 used the BPS-NI to evaluate patients' pain scale at each timepoint of gastrointestinal endoscopy (Table 1) [9]. The scale comprises three components, facial expression, body movement, and vocalization, each assessed on a scale of 1 (no pain) to 4 (most severe pain). The overall score ranged from 3 (no pain) to 12 (most severe pain).

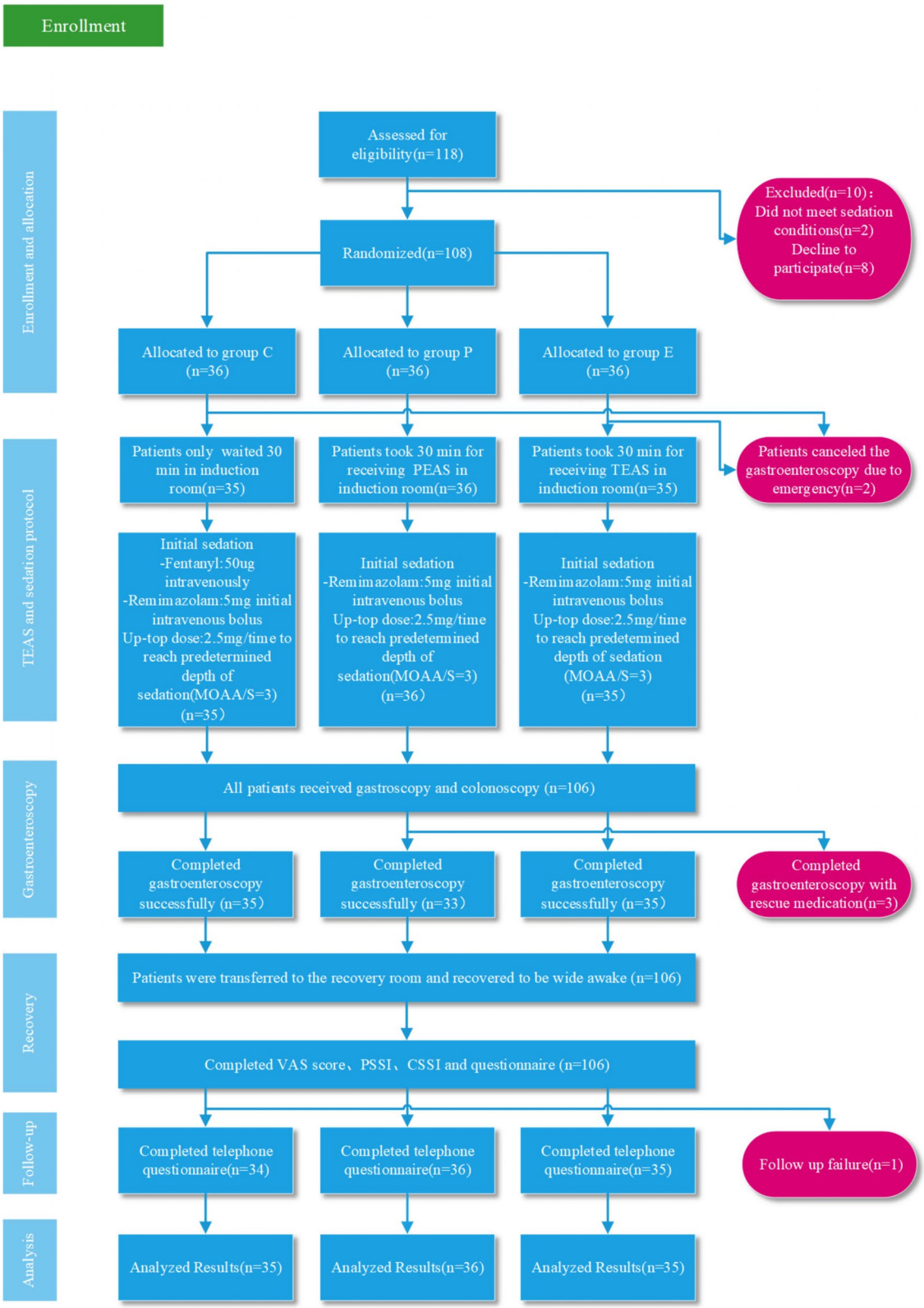
Indicators Related to Time The recovery time was the time from gastrointestinal endoscopy to MOAA/S = 5 (evaluated three times consecutively). The discharge time was the time from full alertness to discharge. The time to resume normal behavioral function was the time from discharge to return to normal (patients resuming work, swimming, driving, etc.), which was obtained through the follow-up questionnaire.

The induction time referred to the duration from the commencement of the intravenous administration of remimazolam by the anesthesiologist to the attainment of a pre-established level of sedation. The procedure time is the total time to complete gastrointestinal endoscopy (from the insertion of the gastroscope to the withdrawal of the colonoscope from the anus).

Adverse Reactions During Examination and Recovery The anesthesiologist monitored and recorded adverse events, such as respiratory depression, hypoxemia, abnormal blood pressure, reflux or aspiration, sedation failure, and the use of rescue sedative medication [2, 22]. Hypoxemia and severe hypoxemia were defined as $SpO_2 < 90\%$ and $< 85\%$, respectively. Hypotension and bradycardia were defined as a decrease in mean arterial pressure and a heart rate $\geq 25\%$ from the baseline value, respectively. Apnea was defined as an adverse event of respiratory arrest lasting ≥ 30 s or < 6 bpm. Adverse events (nausea, emesis, or dizziness) were observed and recorded by research assistant 2 in the recovery room.

Table 1 Timepoints of gastrointestinal endoscopy

Notation	Timepoint	Notation	Timepoint
T	Before all processes	T6	Withdraw gastroscope
T'	After 30 min, before sedation	T7	Begin colonoscopy
T0	After sedation, before operation	T8	Arrive at sigmoid colon
T1	Arrive at pharyngeal cavity	T9	Arrive at splenic flexure
T2	Arrive at esophagus	T10	Arrive at hepatic flexure
T3	Arrive at cardia	T11	Arrive at ileocecum
T4	Arrive at stomach	T12	Withdraw colonoscope
T5	Arrive at duodenum		


Enrollment
Enrollment and allocation
Assessed for eligibility(n=118)
Excluded(n=10): Did not meet sedation conditions(n=2) Decline to participate(n=8)
Randomized(n=108)
Allocated to group C (n=36)
Allocated to group P (n=36)
Allocated to group E (n=36)
TEAS and sedation protocol
Patients only waited 30 min in induction room(n=35)
Patients took 30 min for receiving PEAS in induction room(n=36)
Patients took 30 min for receiving TEAS in induction room(n=35)
Patients canceled the gastroenteroscopy due to emergency(n=2)
Initial sedation -Fentanyl:50ug intravenously -Remimazolam:5mg initial intravenous bolus Up-top dose:2.5mg/time to reach predetermined depth of sedation(MOAA/S=3) (n=35)
Initial sedation -Remimazolam:5mg initial intravenous bolus Up-top dose:2.5mg/time to reach predetermined depth of sedation(MOAA/S=3) (n=36)
Initial sedation -Remimazolam:5mg initial intravenous bolus Up-top dose:2.5mg/time to reach predetermined depth of sedation (MOAA/S=3) (n=35)
Gastroenteroscopy
All patients received gastroscopy and colonoscopy (n=106)
Completed gastroenteroscopy successfully (n=35)
Completed gastroenteroscopy successfully (n=33)
Completed gastroenteroscopy successfully (n=35)
Completed gastroenteroscopy with rescue medication(n=3)
Recovery
Patients were transferred to the recovery room and recovered to be wide awake (n=106)
Completed VAS score、PSSI、CSSI and questionnaire (n=106)
Follow-up
Completed telephone questionnaire(n=34)
Completed telephone questionnaire(n=36)
Completed telephone questionnaire(n=35)
Follow up failure(n=1)
Analysis
Analyzed Results(n=35)
Analyzed Results(n=36)
Analyzed Results(n=35)

◂**Fig. 1** Patient enrollment and allocation of this study. *VAS* visual analogue scale, *TEAS* transcutaneous electrical acupoint stimulation, *PEAS* placebo electrical acupoint stimulation, *CSSI* clinical satisfaction with sedation instrument, *PSSI* patient satisfaction with sedation instrument

Dose of Remimazolam The dose of remimazolam used during gastrointestinal endoscopy in the three groups was recorded separately by researcher assistant 2.

Statistical Methods

SPSS (version 26.0) software was used to statistically analyze all the data. The Kolmogorov test was used to analyze the normal distribution of all the data. Analysis of variance was used to analyze normally distributed measurement data, and the data are expressed as the mean ± standard deviation ($\bar{x} \pm SD$). Pairwise comparisons between the three groups were conducted using the least significant difference *t* test (LSD-t). The Kruskal–Wallis rank-sum test was employed to analyze nonnormally distributed measurement data, with the results presented as medians (ranges). For pairwise comparisons between the three groups, the Bonferroni correction was utilized. Qualitative data were analyzed using either a chi-square test or Fisher's exact test, and the data are reported as frequencies or percentages. A nonparametric rank-sum test was used to analyze multiple sets of hierarchical data, and the data are expressed as quantities or percentages. Statistical significance was determined at $P<0.05$. We incorporated Bonferroni adjustments for multiple testing. There were three pairwise comparisons in this study, so the adjusted **α** was 0.05/3 = 0.017.

Sample Size Calculation

PASS (version 15) was used to calculate the sample size. The mean score of satisfaction was based on the data of the phase III study evaluating the efficacy and safety of remimazolam (CNS 7056) compared with placebo and midazolam in colonoscopy, which was 9.6 (Brice VAS satisfaction questionnaire) [2]. A 5-mm difference in the PSSI was detected with 90% power at a significance level of $\alpha = 0.05$, so approximately 30 patients were required in each group. Considering a loss to follow-up and dropout rate of 15%, the sample size increased by 15%, and the final target sample size was 35 patients per group. Therefore, this study required 105 participants.

RESULTS

Figure 1 shows the enrollment and allocation of patients. This trial invited 118 patients, 110 of whom agreed and eight of whom declined. Two patients were excluded because one patient had a history of alcohol abuse, and the other had an acute upper gastrointestinal hemorrhage. The remaining 108 patients were subsequently randomized into three groups. In addition, due to unforeseen emergencies, two patients had to cancel their appointments on the examination day. As a result, gastrointestinal endoscopy was successful for only 106 patients. Among them, three patients in group P required rescue sedative medication due to their inability to tolerate the stimulation associated with gastrointestinal endoscopy under moderate sedation. Furthermore, one patient in group C was lost to follow-up. The primary indicators of these four patients were analyzed, and other secondary indicators, such as procedure time, recovery time, or dose of remimazolam, were not measured for three patients considered to have treatment failure.

The general characteristics of the three groups were not significantly different (Table 2). Table 3 shows the MOAA/S scores of 103 patients who underwent gastrointestinal endoscopy under moderate sedation, and the differences among the three groups were not statistically significant ($P=0.49$).

Satisfaction Survey and Follow-up Questionnaire

According to the PSSI scores before discharge, the median patient satisfaction scores in both groups C and E were greater than those in group P (96 vs. 87, $P<0.001$; 96 vs. 87, $P<0.001$), and the differences between groups C and E were not significant ($P>0.05$).

Table 2 Baseline characteristics of the patients

	Group			*F*/*H* value	*P* value
	C (*n* = 35)	P (*n* = 36)	E (*n* = 35)		
Age (years)	50.11 ± 9.59 (33,71)	52.25 ± 11.25 (33,72)	49.69 ± 12.52 (26,74)	0.54	0.59
BMI (kg/m^2)	23.93 ± 3.12 (17.8,31)	24.21 ± 3.51 (17.6,35.9)	23.13 ± 3.12 (17.7,31.8)	1.05	0.35
Gender					0.94
Male	18 (51.43%)	18 (50%)	19 (54.29%)		
Female	17 (48.57%)	18 (50%)	16 (45.71%)		
Outpatient narcotics use	6 (17.14%)	7 (19.44%)	5 (14.2%)		0.95
History of gastrointestinal					0.77
Endoscope	11 (31.43%)				
Mallampati classification				0.89	0.64
I	15 (42.86%)	16 (44.46%)	13 (37.14%)		
II	18 (51.43%)	17 (47.22%)	17 (48.57%)		
III	2 (5.71%)	3 (8.33%)	5 (12.9%)		
ASA classification				0.097	0.95
I	1 (2.86%)	3 (8.33%)	2 (5.71%)		
II	30 (85.71%)	28 (77.78%)	29 (82.86%)		
III	4 (11.43%)	5 (13.89%)	4 (11.43%)		
Education				0.46	0.79
Primary	5 (14.29%)	4 (13.89%)	3 (8.57%)		
Secondary	11 (31.42%)	16 (44.44%)	14 (40%)		
College or above	19 (54.29%)	16 (44.44%)	18 (51.43%)		

Date were presented as mean ± SD or *n* (%)

BMI body mass index, *ASA Classification* American Society of Anesthesiologists physical status classification

Regarding the CSSI, the median score for physician satisfaction in group C was greater than that in groups E and P (95 vs. 92, $P = 0.0052$; 95 vs. 85, $P < 0.001$), with group E demonstrating a greater median satisfaction score than did group P (92 vs. 85, $P < 0.001$). According to the intent-to-treat analysis, patients who required rescue sedative medication had the highest satisfaction scores, while physicians had the lowest satisfaction scores. No significant changes were observed between the two groups (Figs. 2, 3).

Except for one patient in group C, 105 patients were successfully contacted by phone within 1 week after gastrointestinal endoscopy. However, this patient and three patients who were considered to have sedation failure were included in the follow-up intent-to-treat analysis based on the optimal results. The median PSSI score at follow-up was greater in group E than

Table 3 Sedation level of patients

	Group			*H* value	*P* value
	C ($n=35$)	P ($n=36$)	E ($n=35$)		
MOAA/S score				1.45	0.49
1	2	6	1		
2	10	16	11		
3	279	297	282		
4	67	70	72		

MOAA/S score Modified Observer's Assessment of Alertness/Sedation score

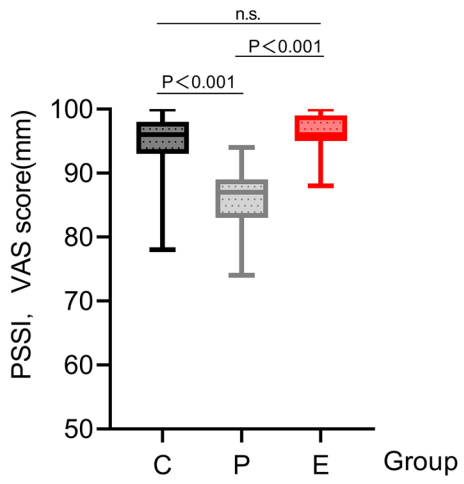


Fig. 2 PSSI of sedation procedure. *PSSI* patient satisfaction with sedation instrument, *VAS* visual analog score

in groups C and P, with group C showing greater satisfaction than group P. Compared with the PSSI score before discharge, the follow-up PSSI score was lower in group C (96 vs. 92). Moreover, the incidence of dizziness and nausea in group P after discharge was similar to that in group E, and the differences were not statistically significant. The median scores in both groups were significantly lower than the scores in group C. Approximately 60% of patients in group C reported that the time to complete recovery of normal behavior function was > 2 h, which was significantly longer than that of approximately 90% of patients in groups P and E within 2 h

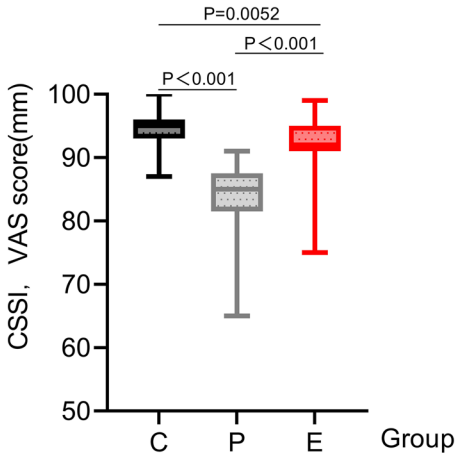


Fig. 3 CSSI of sedation procedure. *CSSI* clinical satisfaction with sedation instrument, *VAS* visual analog score

($P<0.001$, $P<0.001$). The incidence of intraoperative recall was comparable among the three groups, as more than 90% of patients reported having either no recollection or partial memory. However, 91.18, 75.76, and 97.14% of patients reported that they would undergo the same sedation again ($P<0.017$). After the intent-to-treat analysis, the statistical analysis results were unchanged (Table 4).

INTRAOPERATIVE PAIN RESPONSE SCALE

Figure 4 shows the trend in the BPS-NI scores of 103 patients who were successfully sedated during gastrointestinal endoscopy. The Scheirer–Ray–Hare test was employed to analyze repeated measurement data that did not adhere to a normal distribution. However, the analysis did not include the assessment of BPS-NI at each time point following propofol administration. The mean BPS-NI of group E was slightly greater than that of group C during gastrointestinal endoscopy, but the difference was not significant ($P=0.020$). However, the mean BPS-NI of group P was significantly greater than that of the other two groups ($P<0.001$, $P<0.001$) (Table 5).

The BPS-NI scores of the three patients who experienced sedation failure were ≥ 9 at

Table 4 Results of follow-up telephone questionnaire

	Group			*H* value	P^a	P^b	P^c	*P* value
	C (*n* = 34)	P (*n* = 33)	E (*n* = 35)					
Q1: On a scale of 0–100, how would you rate this sedation procedure?								
	92 (83,100)	87 (74,94)	96 (88,100)	54.88	< 0.001	< 0.001	< 0.001	< 0.001
Q2: On a scale of 0–10, how would you rate the scale of discomfort?								
Vertigo	3 (1,5)	1 (0,2)	1 (0,2)	42.18	< 0.001	0.09	< 0.001	< 0.001
Nausea	4 (0,6)	1 (0,2)	1 (0,1)	53.55	< 0.001	0.21	< 0.001	< 0.001
Q3: When did you resume your normal daily activities after procedure?								
< 2 h	14 (41.18%)	29 (87.88%)	32 (91.43%)	26.25	< 0.001	0.64	< 0.001	< 0.001
2–4 h	16 (47.10%)	3 (9.10%)	2 (5.71%)					
> 4 h	4 (11.77%)	1 (3.03%)	1 (2.86%)					
Q4: Do you remember this procedure?								
No	25 (70.59%)	20 (60.61%)	23 (65.71%)	1.34				0.51
Part	8 (26.47%)	11 (33.33%)	11 (31.43%)					
All	1 (2.94%)	2 (6.06%)	1 (2.86%)					
Q5: Can you choose to receive this sedation procedure again?								
Yes	31 (91.18%)	25 (75.76%)	34 (97.14%)		> 0.017	< 0.017	> 0.017	0.023
No	3 (8.82%)	8 (24.24%)	1 (2.86%)					
Intent-to-treat analysis								
Q1: On a scale of 0–100, how would you rate this sedation procedure?								
	92 (83,100)	87 (74,94)	96 (88,100)	51.38	< 0.001	< 0.001	0.0014	< 0.001
Q2: On a scale of 0–10, how would you rate the scale of discomfort?								
Vertigo	3 (1,5)	1 (0,2)	1 (0,2)	40.36	< 0.001	0.23	< 0.001	< 0.001
Nausea	4 (0,6)	1 (0,2)	1 (0,1)	49.17	< 0.001	0.40	< 0.001	< 0.001
Q3: When did you resume your normal daily activities after procedure?								
< 2 h	15 (42.86%)	32 (86.11%)	32 (91.43%)	26.45	< 0.001	0.73	< 0.001	< 0.001
2–4 h	16 (45.71%)	3 (11.11%)	2 (5.71%)					
> 4 h	4 (11.43%)	1 (2.78%)	1 (2.86%)					
Q4: Do you remember this procedure?								
No	26 (74.29%)	23 (63.89%)	23 (65.71%)	1.02				0.60
Part	8 (22.86%)	11 (30.56%)	11 (31.43%)					
All	1 (2.86%)	2 (5.55%)	1 (2.86%)					
Q5: Can you choose to receive this sedation procedure again?								
Yes	32 (91.42%)	28 (77.78%)	34 (97.14%)		> 0.017	< 0.017	> 0.017	0.038
No	3 (8.58%)	8 (22.22%)	1 (2.86%)					

Date were presented as median ± range or *n* (%). For intent-to-treat analysis, results for patients who had an event of sedation failure or did not complete the follow-up questionnaire were considered to be treatment failures. P^a = group C vs. group P; P^b = group E vs. group P; P^c = group C vs. group E

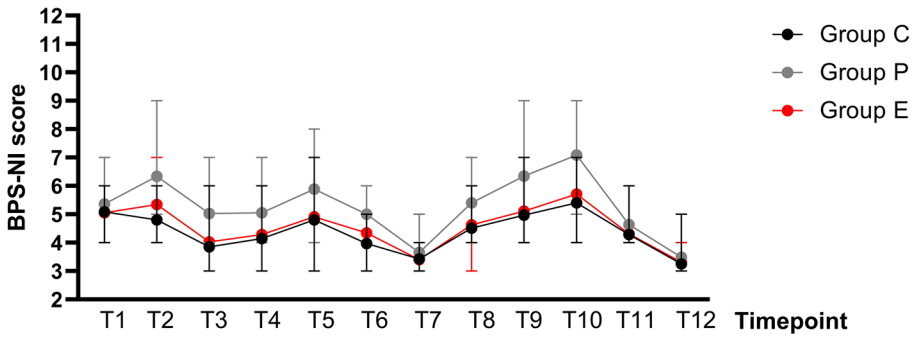


Fig. 4 Trend of the BPS-NI of three groups. *BPS-NI* the behavioral pain scale for non-intubated patients

Table 5 Repeated measures analysis of BPS-NI score

Factor	*Df*	SS	*H* value	P^a	P^b	P^c	*P* value
Group	2	7,739,436.32	63.44	< 0.001	< 0.001	0.020	< 0.001
Timepoint	11	6,721,638.99	55.09				< 0.001
Group:Timepoint	22	172,899.72	1.42				0.99
Residuals	1221	48,985.90					
Intent-to-treat analysis							
Group	2	9,295,967.46	74.20	< 0.001	< 0.001	0.021	< 0.001
Timepoint	11	6,488,925.72	51.79				< 0.001
Group:Timepoint	22	143,641.26	1.15				0.99
Residuals	1236	53,372.50					

"Group:Timepoint" represents interaction effect between group and timepoint, P^a = group C vs. group P; P^b = group E vs. group P; P^c = group C vs. group E

T2, T9, and T10, and the BPS-NI scores at the time points after propofol administration were statistically analyzed based on the intent-to-treat analysis; these scores were defined as 12 (the highest scale). The significant differences remained unchanged after the intent-to-treat analysis (Table 5).

Induction, Procedure, Recovery, and Discharge Time

The induction, procedure, and recovery time did not significantly differ among the three groups ($P>0.05$). The mean discharge time of patients in group C (12.03 min) was longer than that in groups P (8.14 min) and E (7.64 min), and the differences between groups E and P were not statistically significant ($P<0.001$, $P<0.001$) (Table 6). The recovery times for the three patients categorized as having sedation failure were 9, 8, and 7 min, respectively. Similarly, their discharge times were 13, 13, and 15 min, respectively.

Adverse Reactions

Regarding adverse cardiovascular reactions, one patient in each of the three groups experienced bradycardia (HR: 48–52 bpm) during colonoscopy, but the bradycardia was

Table 6 Patients' treatment information

	Group			*F*/*H* value	P^a	P^b	P^c	*P* value
	C	P	E					
Treatment time (min)	23.17 ± 1.48	23.40 ± 1.15	22.97 ± 1.02	1.01				0.37
Induction time (min)	0.42 ± 0.063	0.43 ± 0.052	0.42 ± 0.052	0.52				0.60
Recovery time (min)	4.73 ± 1.00	4.56 ± 0.94	4.34 ± 0.78	1.66				0.20
Discharge time (min)	12.03 ± 2.33	8.14 ± 1.37	7.64 ± 1.47	63.27	< 0.001	0.25	< 0.001	< 0.001
Dose of remimazolam (mg)	15 (11.5,20)	17.5 (15,22.5)	17.5 (12.5,22.5)	31.22	< 0.001	0.13	< 0.001	< 0.001
Times of top up (time)	4(3,6)	5(4,7)	5(3,7)	32.52	< 0.001	0.08	< 0.001	< 0.001

Date was presented as mean ± SD, median ± range or *n* (%). P^a = group C vs. group P; P^b = group E vs. group P; P^c = group C vs. group E

transient and not treated. Regarding adverse respiratory reactions, hypoxemia primarily occurred at time points T1, T2, and T3 (Fig. 5). The incidence of hypoxemia during the examination was 17.14% in group C and 8.33% in group P. In contrast, patients in group E did not demonstrate any indications of respiratory depression during gastrointestinal endoscopy, distinguishing them from the other groups. Hypoxemia was treated by calling patients or tapping patients to breathe deeply, but one patient who received rescue sedation medication received supplemental oxygen from a pressurized mask. The situations of three patients with sedation failure were previously mentioned. Other serious adverse events were not experienced by any of the patients.

Dose of Remimazolam

The mean doses of remimazolam administered to the three groups were 15.23 ± 1.86, 18.56 ± 2.17, and 17.54 ± 2.57 mg, respectively. The mean top-up doses of remimazolam were 4.09 ± 0.70, 5.42 ± 0.87, and 4.97 ± 1.01 mg, respectively. The mean and top-up doses of group C were lower than those of groups E and P ($P < 0.001$, $P < 0.001$). The differences between groups E and P were not significant ($P > 0.017$).

DISCUSSION

Recently, the advent of remimazolam has become an important event in the field of procedural sedation, especially for gastrointestinal endoscopy [1]. Patients can recover quickly because tissue carboxylesterases can rapidly hydrolyze their side chains, and the resulting metabolites have no pharmacological activity, making them comparable to that of propofol. Furthermore, its adverse effect on slight cardiopulmonary depression is better than that of propofol [25]; thus, it can potentially be applied in procedural sedation.

Nevertheless, benzodiazepines do not possess analgesic properties, necessitating the use of remimazolam in combination with opioids. Remimazolam alone is insufficient to fully alleviate the discomfort associated with gastrointestinal endoscopy, resulting in a low procedure success rate, as validated by premarketing clinical trials of remimazolam. In a phase II clinical trial of remimazolam, the procedure success rate of using remimazolam alone was only 32–64%, and 36–68% of patients required the use of rescue sedatives [26]. In subsequent clinical trials, the success rate of procedural sedation increased to more than 92% [2, 27]. However, in addition to the social factor of drug abuse, those using opioids are prone to respiratory depression, and more importantly, opioids are the most significant predisposing factor for PONV. Thus, the concept of being

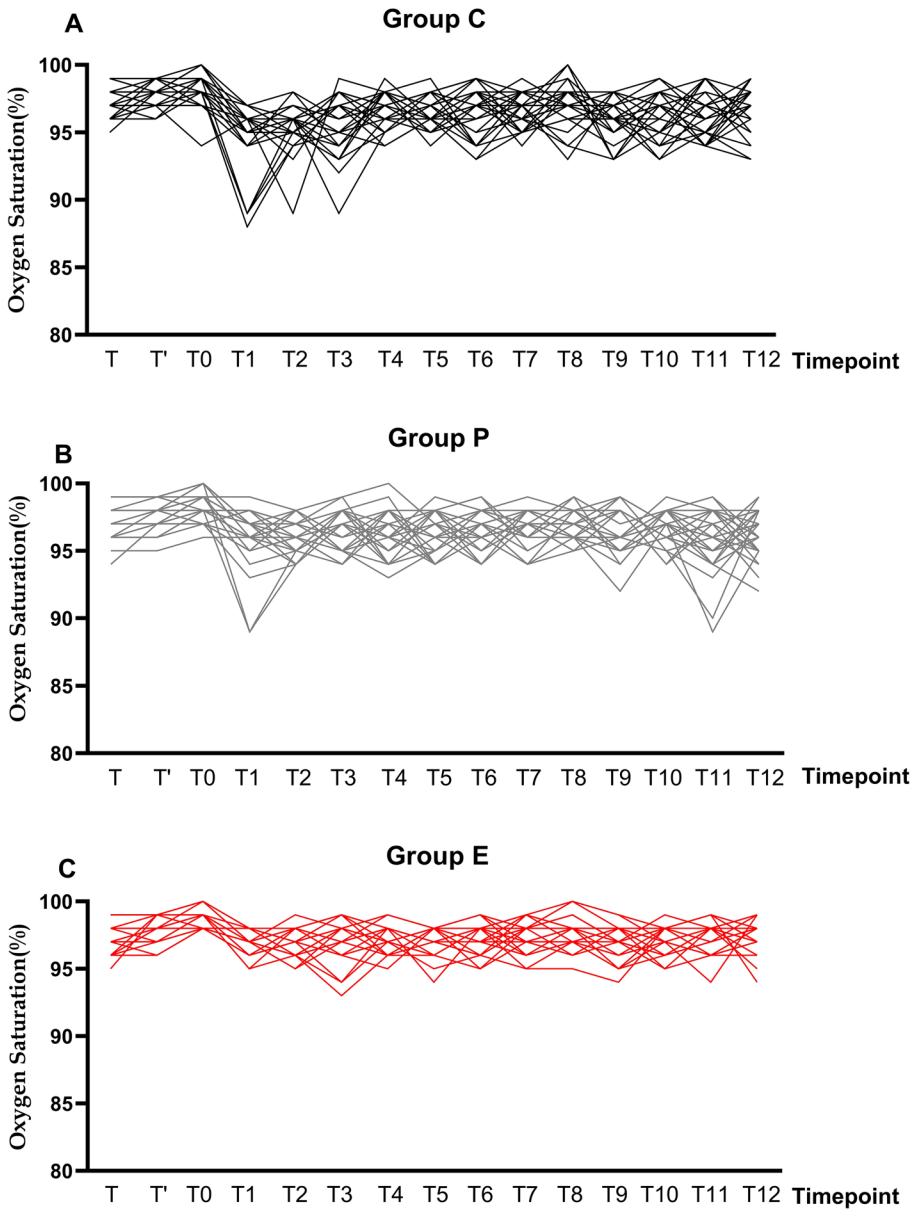


Fig. 5 Trend of oxygen saturation of three groups during each timepoint

opioid free has recently been advocated for anesthesia and enhanced recovery after surgery (ERAS) [28, 29]. The incidence of nausea and vomiting in patients who undergo gastrointestinal endoscopy is already high due to underlying gastrointestinal disease, dietary abstinence, or gastrointestinal inflation. The use of opioids may exacerbate these symptoms, leading to a notable impact on both the quality of recovery and patient satisfaction [30]. Furthermore, the majority of opioids currently employed in clinical practice have prolonged durations of action. Consequently, combining remimazolam with opioids can substantially prolong patient recovery time, partially diminishing the pharmacological benefits associated with the ultrashort-acting nature of remimazolam. An ideal analgesic drug or method that can be combined with remimazolam for procedural sedation is urgently needed.

Acupuncture has been used in China for over 3000 years. It is applied to treat acute and chronic pain, nausea, and vomiting caused by pregnancy, chemotherapy, or surgery. Since the 1950s, acupuncture has been used clinically as an anesthetic method by stimulating specific acupoints. In summary, acupuncture anesthesia (AA) is used in approximately 2 million surgeries [31, 32]. Subsequently, with studies of the mechanism of AA, the attitude toward acupuncture gradually became objective, especially when endorphins were found to play an essential role in mediating the analgesic effect of acupuncture. Acupuncture alone cannot solve clinical problems; it can only be used as an auxiliary measure of anesthesia. Chinese researchers have introduced the concepts of acupuncture-assisted anesthesia (AAA) and acupuncture–drug balanced anesthesia (ABA) and have predominantly employed acupuncture as a supplementary approach to general anesthesia in clinical settings [31–33].

TEAS is a modified version of traditional acupuncture techniques that is simple, non-invasive, and more acceptable to patients [12, 14–17]. Several studies have reported that the effectiveness of acupuncture or TEAS for surgical sedation is inconclusive, and some studies have even yielded contradictory results [8–15, 17]. In the first systematic review of acupuncture applied in gastrointestinal endoscopy in 2003 [10], only two high-quality studies (sham acupuncture-controlled, double-blind to patients and assessors) were available. Furthermore, studies have indicated that the clinical efficacy of acupuncture is primarily influenced by various factors, including the selection of acupoints, the mode or frequency of stimulation, and the duration of stimulation, compared to other techniques. The inconclusive validity of acupuncture may be due to the lack of rigorous double-blind and placebo-controlled studies, small sample sizes, single evaluation indicators, and publishers' inclination to publish studies with positive results. Because acupuncture is mainly affected by several parameters, it has different effects. To the best of our knowledge, Hegu, Neiguan, and Zusanli are the most commonly selected acupoints for acupuncture anesthesia, and studies have confirmed that endorphins are mostly produced under a frequency of 2/100 Hz and stimulation for > 20 min [34, 35]. Therefore, in addition to learning from previous research, using strict methods of placebo needle and double-blinding, we also combined clinical experience and evidence-based medical results, selected three classic acupoints (Hegu, Neiguan, and Zusanli), and stimulated for 30 min at a frequency of 2/100 Hz. Additionally, our study extended beyond previous research by evaluating the effects of sedation in patients undergoing gastrointestinal endoscopy, encompassing procedures beyond gastroscopy or colonoscopy alone.

The PSSI scores of groups C and E were greater than that of group P according to both questionnaires. Compared with patients in group C, patients in group E were discharged faster and had a lower incidence of dizziness and nausea after examination; thus, satisfaction during follow-up was greater. In addition to preventing opioid-induced nausea and vomiting, acupuncture or TEAS also prevent nausea and vomiting by stimulating specific acupoints, such as Neiguan [36].

A vital index of sedation quality was the time to complete the recovery of normal behavioral function (including driving, swimming, etc.). Most previous studies have focused less on this index than on discharge time because it relates to the turnover of patients and endoscopy units [8–13, 22, 23]. A considerable number of patients reported impaired orientation, abnormal judgment, and persistent nausea and vomiting following discharge, hindering their ability to resume normal activities or necessitating additional care. Within this study, three patients in group C did not fully regain normal functioning within 8 h after discharge, whereas the majority of patients in groups E and P returned to their pre-sedation state within 2 h, indicating that opioids were the primary contributing factor. The theoretical pharmacokinetic advantages of remimazolam include complete recovery within 2 h. Reducing or avoiding the use of opioids may make Dr. Vargo JJ's dream of driving home after an endoscopy occurs [37].

Due to the amnesiac effect of sedatives, inquiring patients about subjective feelings

after gastrointestinal endoscopy was inaccurate in evaluating patients' response to stimuli during gastrointestinal endoscopy, as has been practiced in many similar studies [21–23]. The assessments conducted by gastroenterologists were relatively objective, albeit primarily centered around the endoscopy procedure. Therefore, the observations and evaluations made by a third party (the sedation practitioner) were deemed more accurate. The assessment of BPS-NI at each time point demonstrated that TEAS effectively mitigated a significant portion of adverse stimuli encountered during gastrointestinal endoscopy, producing an effect comparable to that of fentanyl. Although the mean pain score of patients in group E was slightly greater than that of patients in group C at some time points, postoperative recall did not significantly differ, which may be related to the anterograde amnesia induced by remimazolam. The results showed that a low degree of discomfort did not affect patient satisfaction; thus, completely inhibiting discomfort with remimazolam is unnecessary.

In this study, remimazolam dosing in group C was lower than that in the other groups, the difference in the remimazolam dosing between groups P and E was not significant, and the initial remimazolam dose in the three groups was similar. To achieve the target sedation depth, a higher remimazolam dose was required in groups P and T; thus, similar to fentanyl, TEAS did not reduce the dose of remimazolam, which was consistent with the results of Eberl [13].

Although sedation was performed by an anesthesiologist, no patients in group E experienced any unexpected complications, such as artificial ventilation, tracheal intubation, or unplanned hospitalization, and their vital signs remained stable. In comparison to group C, there was a greater incidence of respiratory depression or a temporary reduction in oxygen saturation. TEAS was found to effectively maintain stable oxygen saturation levels in patients during the examination [15]. Although safety was not the primary endpoint of this study, we can conclude that non-anesthesiologist administration of remimazolam plus TEAS was safer than the administration of remimazolam plus fentanyl under moderate sedation.

The limitations of our study include the small sample size and lack of multicenter studies. We did not use low-dose fentanyl or TEAS plus remimazolam in the experimental group; thus, verifying whether the combination of these three factors exhibited better efficacy is impossible. Furthermore, the unique characteristics of acupuncture dictate that its clinical effectiveness is influenced by various parameters, including acupoint selection, stimulation frequency, and stimulation duration. Different combinations of these parameters can yield distinct clinical outcomes. Consequently, employing an orthogonal design to systematically evaluate diverse acupuncture parameter combinations becomes essential.

CONCLUSIONS

Our results showed that TEAS can provide adjunct sedation in combination with remimazolam, which can effectively inhibit adverse reactions caused by gastrointestinal endoscopy and has obvious advantages in reducing postoperative discomfort, such as dizziness or nausea, and recovering normal behavioral function. Those who received TEAS had greater median satisfaction after discharge. Moreover, the incidence of sedation complications, such as hypoxemia, was lower during the examination; thus, non-anesthesiologists can safely perform this procedure.

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Declarations

Conflict of Interest. All authors (Jian-Han Xu,, Hai-Ling Tan, Li-Na Zhang, Zan-Gong Zhou, Li Yuan, Ling-Xin Kong, Ming-Quan Song, Li-Jie Qi and Xiang-Yu Ji) declare that they have nothing to disclose.

Ethical Approval. The ethics committee of the Affiliated Hospital of Qingdao University approved this study (ID: QYFYKYLL916711920), which was also registered on the clinical trial website (NCT05485064). All patients provided informed consent before enrollment.

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