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CLINICAL TRIAL REPORT

Addition of Dexmedetomidine to the Anesthesia Regimen Attenuates Pain and Improves Early Recovery After Esophageal Endoscopic Submucosal Dissection: A Randomized Controlled Trial

Xin Luo[1]*, Hai-Jun Hou[2]*, Pei-Shan Chen[1], Xin-Lu Chang[1], Yang Li[1], Li-Xin An[1], Fu-Kun Liu[1], Fu-Shan Xue[1,3]

[1]Department of Anesthesiology, Beijing Friendship Hospital, Capital Medical University, Beijing, People's Republic of China; [2]Department of Pain Medicine, Guanganmen Hospital, China Academy of Chinese Medical Sciences, Beijing, 100053, People's Republic of China; [3]Department of Anesthesiology, Shengli Clinical Medical College of Fujian Medical University, Fujian Provincial Hospital, Fuzhou University Affiliated Provincial Hospital, Fuzhou, People's Republic of China

*These authors contributed equally to this work

Correspondence: Fu-Shan Xue, Department of Anesthesiology, Shengli Clinical Medical College of Fujian Medical University, Fujian Provincial Hospital, Fuzhou University Affiliated Provincial Hospital, Fuzhou, Fujian Province, 350001, People's Republic of China, Tel +86-13911177655, Fax +86-0591-88217841, Email xuefushan@aliyun.com; fushanxue@outlook.com

Objective: Postoperative pain is a common yet often underestimated complication following esophageal endoscopic submucosal dissection (ESD), with limited strategies for effective management. This prospective, double-blind, randomized controlled trial assessed the effects of adding dexmedetomidine (DEX) to the anesthesia regimen on postoperative pain and early recovery in patients undergoing esophageal ESD.

Methods: In total, 60 patients scheduled for elective esophageal ESD under general anesthesia were randomly assigned to the DEX or control group. The DEX group received an intravenous loading dose of DEX at 1 μg/kg for 10 min, followed by a continuous intravenous infusion of 0.6 μg/kg/h, which was stopped 30 min before the end of the procedure. The control group received normal saline as a placebo. The study's primary outcome was the incidence of moderate-to-severe postoperative pain. Secondary outcomes included postoperative pain scores, hemodynamic parameters, the occurrence of postoperative nausea and vomiting (PONV), patient satisfaction, and lengths of stay in the post-anesthesia care unit (PACU) and hospital.

Results: The incidence of moderate-to-severe postoperative pain in the DEX group was significantly lower than that in the control group (absolute difference: −33.4%; OR: 0.250; 95% CI: 0.085–0.731, $P = 0.01$). Pain scores at 1 h postoperatively (0.5[2.0] *vs* 3.0[1.3], $P = 0.003$) were significantly lower in the DEX group. Additionally, morphine dosage in the PACU (0[0] *vs* 1.0[2.0] $P = 0.004$) was significantly reduced in the DEX group compared with the control group. In the DEX group, the incidence and severity of PONV were significantly decreased and the length of PACU stay was shorter than in the control group ($P < 0.01$). However, the rates of intraoperative hypotension, tachycardia, and bradycardia were similar between the two groups. Patient satisfaction and length of hospital stay were also comparable.

Conclusion: Adding DEX to the anesthesia regimen for esophageal ESD significantly attenuates postoperative pain and improves early recovery outcomes.

Keywords: endoscopic submucosal dissection, esophageal neoplasm, dexmedetomidine, postoperative pain, adverse events

Introduction

Endoscopic submucosal dissection (ESD) is a minimally invasive technique used to treat esophageal neoplasms. It is highly valued for its ability to achieve high en-bloc resection rates and minimize local recurrence.[1,2] However, despite these advantages, recent studies have highlighted the frequent complications associated with ESD for early esophageal cancer, such as delayed bleeding, infection, postoperative pain, and stenosis.[3] The ESD-associated complications are often a great concern and can be treated in a timely manner. Postoperative pain, while a significant concern, has often

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been undervalued and inadequately addressed in both clinical practice and research.[2,4] Only a few studies have focused on postoperative pain in patients undergoing esophageal ESD. For example, only two retrospective studies have reported that the incidence of postoperative chest pain or non-cardiac chest pain (NCCP) after esophageal ESD ranges from 35.7%–49.5%. However, no study has reported effective postoperative analgesia strategies for this procedure.[4,5] Even the Chinese expert consensus on sedation and anesthesia in digestive endoscopy[6] recommends only non-steroidal anti-inflammatory drugs as analgesics for pain control after ESD.

Unmanaged postoperative pain not only decreases patient satisfaction but also prolongs hospitalization and increases medical expenses.[2,7,8] Moreover, patients who experience substantial postoperative pain may develop concerns about the success of the ESD procedure and achieving a good long-term outcome of primary disease.[9] This often reduces their willingness to undergo follow-up endoscopies or additional ESD procedures.[9] This underscores the critical need for effective postoperative pain management strategies following esophageal ESD.

Dexmedetomidine (DEX), a selective and potent α_2-receptor agonist, has gained recognition in clinical practice for its sedative, analgesic, and anxiolytic properties, with the advantage of not causing respiratory depression.[10] In addition to pain relief, DEX offers organ protection through its anti-inflammatory, anti-oxidative stress, and immune-modulating effects.[11,12] DEX inhibits gastrointestinal motility and gastric emptying in healthy volunteers,[13] of which gastrointestinal motility is a feature particularly beneficial for successful ESD.[14] DEX alone[15,16] or in combination with other anesthetics such as propofol,[17] midazolam[3,18,] and remifentanil[14] is effective and safe for sedation or general anesthesia in patients undergoing gastrointestinal tumor resection, including ESD.

DEX exerts its analgesic effects by stimulating α_2 receptors in the central nervous system, thereby inhibiting nociceptive stimuli in the peripheral nervous system.[19] As postoperative pain is closely linked to nociceptive stimuli, which are further influenced by inflammation and immunoreaction, DEX's anti-inflammatory and immunoregulatory properties may play a key role in reducing postoperative pain.[11] Adding DEX to anesthesia or sedation regimens for gastric and colorectal ESD effectively reduces both intraoperative and postoperative pain.[20,21] According to a recent study, using enhanced recovery protocols with DEX in the perioperative period in patients undergoing ESD for early gastric cancer is feasible and safe. Moreover, it leads to faster postoperative gastrointestinal recovery, shorter hospital stays, fewer postoperative complications such as nausea and vomiting, lower fever, better pain control, and higher patient satisfaction.[22] Despite the promising results in gastric and colorectal ESD, no study has determined the effects of adding DEX to anesthesia or sedation regimens for esophageal ESD. Thus, this prospective, double-blinded, randomized controlled trial evaluated the effects of adding DEX to the anesthesia regimen on postoperative pain and early recovery in patients undergoing esophageal ESD.

Materials and Methods

This was a single-center, prospective, double-blinded, randomized controlled trial. The study protocols were approved by the Ethics Committee of Beijing Friendship Hospital, Capital Medical University (Approval No: 2021-P2-003-01) and registered at the Chinese Clinical Trial Registry (https://www.chictr.org.cn/; registration number: ChiCTR2100043837). The protocols were published in *Trials* in 2022.[23] This study complies with the Declaration of Helsinki and follows the Consolidated Standard of Reporting Trials guidelines.[24]

Patients

Patients undergoing elective ESD for early esophageal cancer at the endoscopy center from March 20, 2021, to March 31, 2022, were enrolled in this study. The inclusion criteria were an age of 18–65 years and American Society of Anesthesiologists (ASA) physical status classification I–II. The patient exclusion criteria were as follows: (1) sinus bradycardia, (2) sick sinus syndrome, (3) predicted difficulty airway or obesity (body mass index (BMI) > 35 kg/cm^2), (4) mental disorders, (5) allergy to drugs used in the study, (6) history of long-term opioid use, and (7) refusal of analgesic drugs after surgery. Patients who required conversion to open surgery, had an ESD procedure lasting more than 4 h, and needed re-operation or endoscopic examination due to ESD-related complications within 48 h after surgery were also excluded from the final analysis. Patients were informed of their right to withdraw from the study at any time. The written informed consent was obtained from all study participants.

Study Design

Patients were randomly assigned to the DEX or control group using a 1:1 allocation ratio. A computer-generated list of random codes was created, and each code was placed in a sealed, opaque envelope. Before the start of the study, an anesthesia nurse extracted a random code from the envelope, and the patient was assigned to the DEX or control group based on the code. The nurse then prepared the study medications according to the group assignment. In the DEX group, 200 μg DEX was diluted with 50 mL of normal saline to a concentration of 4 μg/mL. In the control group, the same volume of normal saline was prepared. Both groups received the prepared medications by using the same-looking syringes. The anesthesiologists, researchers, and endoscopic physicians participating in the study were all blinded to the group assignments of the patients.

Anesthesia Management

In line with our routine practice, patients underwent standard gastrointestinal endoscopy preparation and fasted for 8 h before undergoing esophageal ESD. After the patients entered the endoscopic room, they were monitored for non-invasive blood pressure, heart rate (HR), pulse oxygen saturation (SpO_2), and bispectral index (BIS), and intravenous access was established. Before anesthesia was induced, the DEX group received a loading dose of DEX at 1 μg/kg intravenously in 10 min, whereas the control group received an equivalent volume of saline intravenously. Anesthesia was then induced using intravenous propofol 1–2 mg/kg, remifentanil 1–2 μg/kg, and rocuronium 0.6–0.8 mg/kg. After achieving loss of consciousness and adequate neuromuscular blockade in the patients, tracheal intubation was performed and mechanical ventilation was initiated. Throughout the procedure, anesthesia was maintained with continuous intravenous infusions of propofol and remifentanil. In addition, the DEX group simultaneously received a continuous intravenous infusion of DEX at 0.6 μg/kg/h, while the control group received normal saline at the same rate. The infusion rates of propofol and remifentanil were adjusted to maintain blood pressure and heart rate (HR) within 20% of baseline values and to keep BIS between 40 and 60.

All esophageal ESD procedures were performed by endoscopic physicians with over 5 years of experience and more than 500 completed ESD procedures. The standard steps for esophageal ESD included marking around the lesion, injecting a submucosal solution, making circumferential mucosal incisions, performing submucosal dissections, and using electrocoagulation for hemostasis.[25] In all patients, carbon dioxide insufflation was applied during the procedures and ceased immediately after ESD was completed.

Intravenous infusions of both DEX and saline were stopped 30 min before the end of the procedures. Upon the completion of the ESD, intravenous infusions of propofol and remifentanil were also discontinued. Postoperative analgesia and antiemesis were managed with intravenous tramadol (50 mg) and ondansetron (4 mg). Extubation was performed once the patient was able to follow commands and spontaneous breathing had adequately resumed. The patient was then transferred to the postanesthesia care unit (PACU) for observation until all discharge criteria were met. After the patient returned to the ward, a single dose of omeprazole (40 mg) was administered intravenously at 2 h after the ESD procedures.

Data Collection

Patient demographic data (age, gender, height, weight, comorbidities, and smoking and drinking status) and clinicopathological characteristics (location, depth, and pathological classification) were collected. We also recorded perioperative data, including durations of anesthesia and ESD procedures, anesthetic and analgesic dosages, intraoperative blood loss and fluid volumes, adverse hemodynamic and respiratory events, times to awakening and extubation, lengths of stay in the PACU and hospital, postoperative nausea and vomiting (PONV), pain levels, and patient satisfaction.

Hemodynamic data were recorded before induction (T0), at 1 min after induction (T1), at intubation (T2), at 5 min after intubation (T3), at the end of the procedure (T4), at extubation (T5), and 5 min after extubation (T6). Perioperative adverse cardiovascular events, including hypotension, hypertension, bradycardia, and tachycardia, were also noted. Hypotension is defined as a mean arterial pressure (MAP) reduction of >20% from baseline, whereas hypertension is defined as a MAP increase of >20% from baseline. Bradycardia is defined as a HR of <45 beats/min, whereas tachycardia

is defined as a HR of >100 beats/min. If hypotension persisted for more than 2 min and did not respond to the treatment with 200 mL lactated Ringer's solution infusion, a bolus dose of ephedrine 6 mg was administered intravenously. For hypertension lasting for more than 2 min, a bolus dose of urapidil (5 mg) was administered intravenously. Tachycardia and bradycardia, if necessary, were treated with intravenous esmolol (10 mg) and atropine 0.5 (mg), respectively.[26]

Anesthesia duration was defined as the time from the start of anesthesia induction to the completion of extubation. The duration of the procedure was measured from the initiation of lesion margin localization with the endoscope to the completion of hemostasis. The time to awakening was defined as the interval from the cessation of anesthetic administration to the patient gaining consciousness. The time to extubation was defined as the interval from the termination of anesthetics to the completion of extubation.

Using a 0- to 10-point visual analog scale (VAS) at 1, 2, 4, 6, 12, 24, and 48 h postoperatively, a specialized investigator, who was blinded to the patient group assignment, assessed pain levels. The VAS scale ranged from "0" (no pain) to "10" (unbearable pain).[27] Based on VAS scores, postoperative pain severity was classified as mild (0–3), moderate (4–6), and severe (7–10).[4] If the VAS score exceeded 3 or the patient required additional analgesia, morphine (1 mg) was intravenously administered. PONV severity was assessed using a 4-point scale (0 = no nausea and vomiting; 1 = mild nausea; 2 = moderate nausea, and 3 = vomiting). If the PONV score was 2 or higher, ondansetron (4 mg) was administered intravenously.[28] Postoperative adverse respiratory events, including hypoxemia(defined as SpO_2 < 92%) and apnea (lasting more than 60s), were also recorded.[29] If hypoxemia or apnea occurred, interventions included auditory or painful stimulation, supplemental oxygen via nasal cannula or facemask, upper airway opening with the jaw thrust maneuver, and other necessary measures.

Outcomes

The primary outcome of this study was the incidence of moderate-to-severe pain within the first 48 h postoperatively. Secondary outcomes were pain VAS scores at 1, 2, 4, 6, 12, 24, and 48 h after surgery, the occurrence of perioperative adverse respiratory and cardiovascular events, incidence and severity of PONV, the proportion of patients with a PONV score of 2 or higher, and dosages of postoperative analgesia and antiemetics, lengths of stay in the PACU and hospital, and patient satisfaction.

Sample Size Calculation

The sample size calculation was based on the findings from a preliminary experiment, where the incidence of moderate-to-severe postoperative pain was 30% in the DEX group and 70% in the control group. The difference was used to calculate the required sample size to detect a clinically significant difference between the groups using PASS.2021 software. With a type 1 error probability of 0.05 ($\alpha = 0.05$), a type 2 error probability of 0.1 ($\beta = 0.1$), and a power of 0.90 for a two-sided comparison and based on the aforementioned between-group difference in the incidence of moderate-to-severe postoperative pain, we determined that 25 patients were required in each group. Accounting for a 10% lost-to-follow-up rate and a 1:1 enrollment ratio, a total sample size of 60 patients (30 in each group) was included in the study.

Statistical Analysis

All data were analyzed using SPSS version 22.0 (SPSS Inc., Chicago, IL, USA) by the specialized statisticians from the Clinical Research Institute of Beijing Friendship Hospital, who were blinded to the patient group assignments. For all continuous variables, the Shapiro–Wilk test was used to assess data distribution. Continuous variables with a normal distribution were presented as means ± standard deviations, and between-group comparisons were performed using an independent Student's *t*-test. Continuous variables with a non-normal distribution were presented as medians (interquartile range, IQR), and their between-group comparisons were performed using the Mann–Whitney test. Categorical data were presented as numbers and/or percentages and analyzed using the Chi-square test. If the expected frequency of events was less than 5, Fisher's exact test was used for between-group comparisons. $P < 0.05$ was considered statistically significant.

Results

Study Population

From March 2021 to March 2022, 166 patients undergoing esophageal ESD procedures were screened for eligibility. In total, 88 patients were excluded based on the exclusion criteria. Additionally, 11 patients declined to sign the informed consent, and 4 refused to participate in follow-up, leading to their exclusion before randomization. Ultimately, 63 patients were randomly assigned to two groups: 32 patients in the DEX group and 31 patients in the control group. However, two patients in the DEX group and one in the control group were further excluded due to conversion to open thoracotomy. Finally, 30 patients in each group completed the study and were included in the final data analysis (Figure 1). The two groups were comparable in terms of general demographics, clinicopathological features, en bloc resection rate, and gastric tube insertion (Table 1).

Primary Outcome

The incidence of moderate-to-severe postoperative pain was significantly lower in the DEX group [33.3% (10/30)] than in the control group [66.7% (20/30)] (absolute difference: −33.4%, OR: 0.250, 95% CI: 0.085–0.731, $P < 0.05$).

Secondary Outcomes

Postoperative Pain Levels and Morphine Consumption

Figure 2 presents the postoperative VAS scores at different time points. The VAS score at 1 h postoperatively was significantly lower in the DEX group than in the control group ($P < 0.05$). However, VAS scores at other time points postoperatively exhibited no significant difference between the groups ($P>0.05$). Morphine consumption in the PACU and total morphine consumption within the first 24 h after operation were significantly lower in the DEX group than in the control group ($P = 0.004$). However, morphine consumption in the ward did not differ significantly between the groups ($P>0.05$) (Table 2).

Intraoperative Data

Supplement Figure 1 presents the MAP and HR at different time points. HRs at all time points, except for baseline values before induction, significantly decreased in the DEX group compared with the control group ($P<0.05$ or $P < 0.01$). MAP values at 1 min after induction, 1 min after intubation, and the beginning of the ESD procedure were significantly higher in the DEX group than in the control group. However, MAP at extubation was significantly lower in the DEX group than

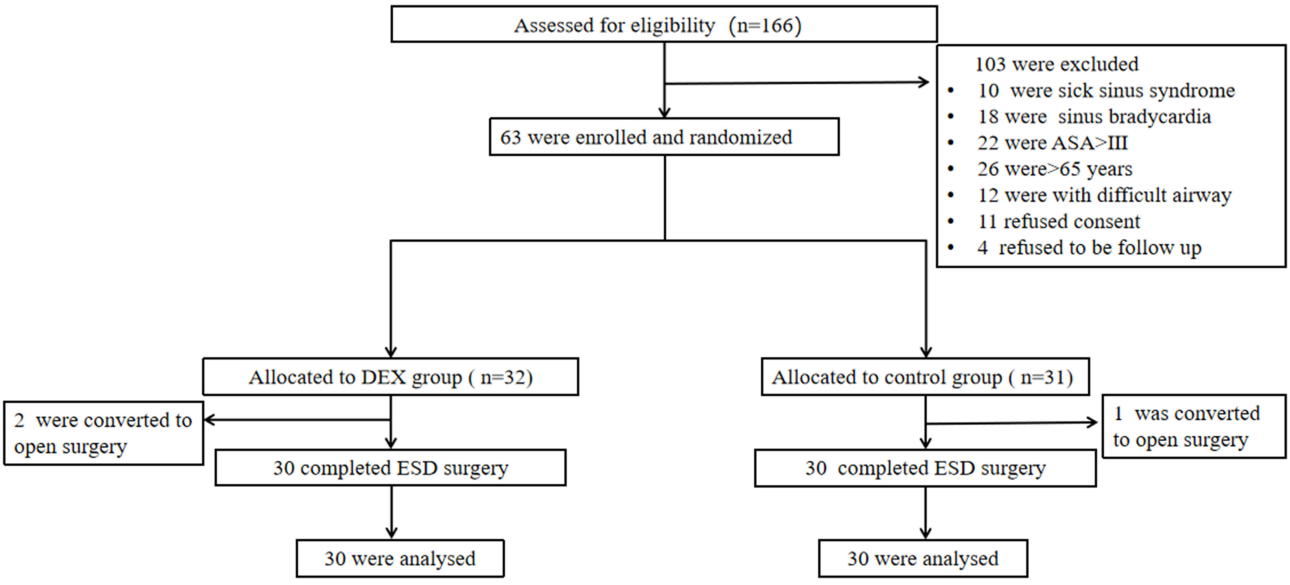

Figure 1 The flow chart of included and excluded patients.

Table 1 General Data, Clinicopathological Features, En Bloc Resection Rate and Gastric tube insertion of Patients

Variables	DEX Group (n=30)	Control Group (n=30)	*P* values
Age (years)	57.5 (50.8, 64.0)	58.0 (52.8, 62.3)	0.786
Sex (Male/ female)	22/8	23/7	0.766
BMI (kg/cm^2)	22.5 (21.4, 24.8)	24.8 (22.7, 26.6)	0.077
ASA (I/II)	10/20	9/21	0.781
Smoking	15 (50.0%)	15 (50.0%)	1
Alcohol use	12 (40.0%)	15 (50.0%)	0.436
Comorbidities			
Hypertension	6 (20.0%)	13 (43.3%)	0.052
Diabetes	3 (10.0%)	2 (6.7%)	1
Coronary heart disease	1 (3.3%)	0 (0%)	1
Hyperlipidemia	13 (43.3%)	12 (40.0%)	0.793
General anesthesia history	11 (36.7%)	12 (40.0%)	0.791
Repeated ESD procedure history	3 (10.0%)	5 (16.7%)	0.706
Specimen size (cm)	2.9 (2.1, 4.6)	2.9 (2.2, 4.1)	0.677
Tumor invasion depth			
Mucosa	15 (50.0%)	22 (73.3%)	0.063
Submucosa	15 (50.0%)	8 (26.7%)	
Localized site			
Upper third	6 (20.0%)	3 (10.0%)	0.519
Middle third	11 (36.7%)	11 (36.7%)	
Lower third	13 (43.3%)	16 (53.3%)	
Histopathology			
Squamous Cell Carcinoma	18 (60.0%)	18 (60.0%)	0.072
Dysplasia	3 (10.0%)	5 (16.7%)	
Leiomyoma	9 (30.0%)	7 (23.3%)	
En bloc resection rate	28 (93.3%)	30 (100%)	0.492
***Gastric tube* insertion** (Y/N)	20/10	21/9	0.781

Notes: Values are present as number of patients (%), median (IQR).
Abbreviation: Dex, dexmedetomidine; BMI, body mass index; ASA, American Society of Anesthesiologists; ESD, endoscopic submucosal dissection.

in the control group ($P<0.05$). The incidences of intraoperative hypotension, tachycardia, and bradycardia; dosages of atropine and remifentanil; volumes of bleeding and fluid; times to awakening and extubation, and durations of anesthesia and the procedure did not differ significantly between the groups ($P>0.05$). However, propofol and ephedrine dosages during surgery were significantly higher in the control group than in the DEX group (Supplement Table 1).

Postoperative Data

Postoperative data are shown in Supplement Table 2. The incidence of PONV throughout the observation period and PONV scores at PACU arrival, 15 min after PACU arrival, and at PACU discharge were significantly lower in the DEX group. However, the proportion of patients with a PONV score of 2 or higher; incidences of hypotension and bradycardia; and dosages of ondansetron, atropine, and ephedrine in the PACU did not differ significantly between the groups ($P > 0.05$). The length of stay in the PACU was significantly shorter in the DEX group, although no significant differences in patient satisfaction and the overall length of hospital stay were observed between the groups ($P > 0.05$). During the postoperative period, no hypoxemia or apnea occurred in any patient.

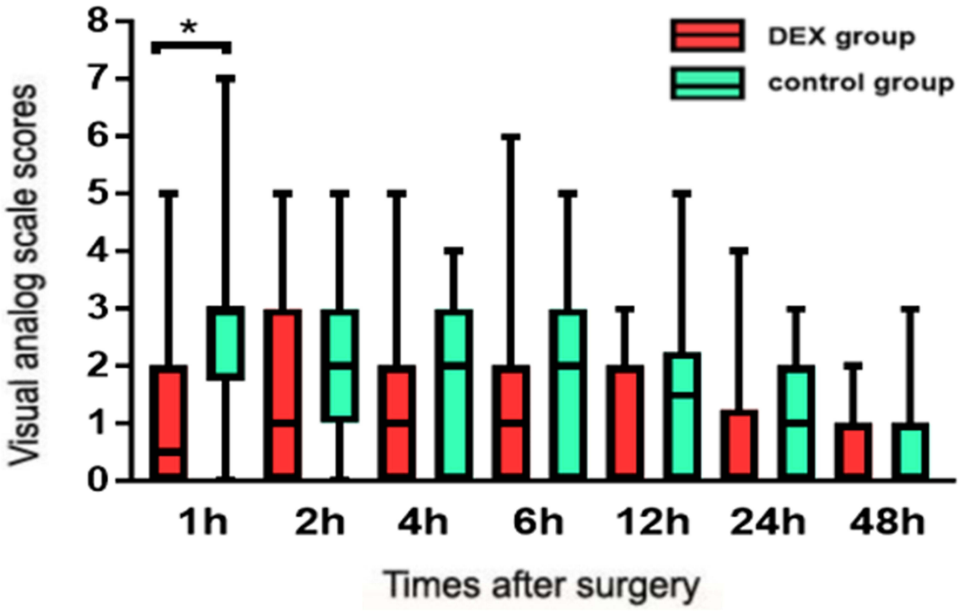

Figure 2 Postoperative pain scores.
Notes: Values are present as mean ± SD. *P<0.05, intergroup comparisons.
Abbreviation: DEX, dexmedetomidine.

Discussion

The study results demonstrated that DEX addition significantly reduced the incidence of moderate-to-severe postoperative pain by half of that noted in the control group (33.3% vs 66.7%) and postoperative morphine consumption. Additionally, the DEX group had a lower incidence of PONV and a shorter length of stay in the PACU. These findings suggest that adding DEX to the anesthesia regimen significantly reduces postoperative pain and improves early postoperative outcomes, confirming the study's initial hypothesis.

Esophageal ESD can be performed under general anesthesia or sedation, but general anesthesia has been associated with a lower risk of acute procedure-related complications than sedation.[30,31] Consequently, general anesthesia is commonly used for esophageal ESD in our hospital. Consensus on the optimal dosing regimen of intravenous DEX for various procedures is lacking. When DEX is combined with other drugs for anesthesia in gastrointestinal and esophageal surgeries, the reported dosing protocols vary. Studies have suggested administering a loading dose of 0.5–1.0 μg/kg over 10–20 min before anesthesia induction, followed by a continuous infusion of 0.2–1.0 μg/kg/h during maintenance.[32–34] Based on these studies and our clinical experience,[21] we selected a dosing regimen of 1 μg/kg DEX administered intravenously over 10 min before induction and a continuous infusion rate of 0.6 μg/kg/h during anesthesia maintenance for this study.

Our results unveiled that the overall incidence of moderate-to-severe pain after esophageal ESD was 50% (30 of 60 patients), indicating that postoperative pain is a common and significant concern that warrants high attention for improving patient comfort and surgical outcomes. This finding contrasts with the findings of previous studies, such as

Table 2 Morphine Consumption for Postoperative Pain Control

Variables	DEX Group (n=30)	Control Group (n=30)	*P* values
Dosage of morphine in PACU (mg)	0 (0, 0)	1.0 (0, 2.0)	0.004
Dosage of morphine in ward (mg)	0 (0, 1.0)	0 (0, 2.0)	0.302
Total dosage of morphine within 24 h (mg)	0 (0, 1.0)	1.0 (0, 3.0)	0.005

Notes: Values are present as number of patients (%) or median (IQR).
Abbreviations: Dex, dexmedetomidine; PACU, postanesthesia care unit.

a single-center retrospective study by Zhao et al,[4] where only 10% of the 309 patients experienced moderate-to-severe NCCP following esophageal ESD under general anesthesia with propofol, remifentanil, and DEX. They reported that the incidence of moderate-to-severe NCCP after esophageal ESD was only 10%, which is significantly lower than the 33.3% observed in the DEX group. Similarly, in another retrospective study by Sakai et al[5] involving 42 patients undergoing ESD with general anesthesia for early thoracic esophageal cancer, the incidence of postoperative NCCP was reported at 35.7%, which is also significantly lower than the overall incidence of moderate-to-severe pain (50%) observed in our study. Several factors could explain these discrepancies in the reported incidence of postoperative pain. First, both Zhao et al[4] and Sakai et al[5] studies are retrospective, which may inevitably introduce some potential confounders that affect postoperative pain assessment. For instance, neither study provided the detailed information about postoperative pain management, while our study used intravenous tramadol (50 mg) alone as a postoperative analgesic. This variation in pain management approaches makes direct comparisons of results between studies challenging. Second, the primary outcome in the Zhao et al[4] and Sakai et al[5] studies focused on NCCP after esophageal ESD. By contrast, epigastric pain and discomfort are also common after esophageal ESD, especially in patients with middle and lower esophageal cancer.[35] These types of pain might not have been fully captured in those studies but are relevant in our patient population. Third, differences in the tumor site, size, depth of invasion, the proportion of the esophageal circumference resected, and the duration of the ESD procedure may also contribute significantly to variations in pain incidence between studies. Factors such as the esophageal wound size, procedural time, and exposure of the muscle layer are the independent risk factors for electrocoagulation syndrome after esophageal ESD, which is a primary cause of postoperative discomfort and pain.[36,37]

Our results indicate that adding DEX to the anesthesia regimen significantly reduced the incidence of moderate-to-severe postoperative pain, early postoperative pain levels, and morphine consumption. These findings suggest that DEX is effective for early postoperative pain control, aligning with our previous work on gastric ESD patients[21] and other studies involving endoscopic surgeries, such as bariatric surgery, cholecystectomy, and gynecological surgeries.[38,39] DEX is generally believed to act as an analgesic by activating α_2 receptors in the brain and spinal cord's anterior horn. Moreover, DEX may exert non-opioid analgesic effects through other possible mechanisms, such as inhibiting nociceptive neurons related to Aδ and C fibers in the peripheral nervous system, as well as having systemic immunoregulatory and anti-inflammatory properties.[19]

In this study, the dosage of propofol was significantly lower in the DEX group, consistent with the findings of Ashikari et al,[40] who reported a reduction in propofol maintenance doses and fewer rescue injections for sedation during esophageal ESD when combined with DEX. Evidence suggests that adding DEX at a loading dose of 0.6–1 μg/kg, with or without a continuous infusion, is beneficial in maintaining perioperative hemodynamic stability.[41] Despite the reduction in propofol dosage, no significant differences in the incidences of intraoperative adverse cardiovascular events, including hypotension, tachycardia, and bradycardia, were observed between the groups. However, the intraoperative use of ephedrine was significantly lower in the DEX group, which indicated that adding DEX made intraoperative cardiovascular function more stable This finding is consistent with previous findings in surgical patients receiving general anesthesia.[41] Propofol is known for its peripheral vasodilatory and negative inotropic effects, which can lead to hypotension during propofol sedation or anesthesia for gastrointestinal endoscopy.[42] The reduced severity and duration of hypotension associated with lower propofol dose suggest that adding DEX likely contribute to more stable cardiovascular function by decreasing the required propofol dosage through a synergistic effect.[43]

Bradycardia is a known concern with intravenous DEX, as evidenced by Nonaka et al[44] who found a significantly higher incidence of bradycardia (HR ≤ 45 bpm) when DEX was combined with propofol than when propofol was used alone (37.9% vs 10.3%, $P = 0.029$) in patients undergoing gastric ESD with deep sedation. In our study, throughout the observation period, the average HR percent change from baseline was greater in the DEX group, indicating a tendency toward lower HR values. However, no significant difference was observed in the incidences of intraoperative and postoperative bradycardia (HR ≤ 45 bpm) between the groups. The discrepancy between our findings and those of Nonaka et al[44] could be attributed to several factors. First, the median age of patients in Nonaka et al's study[44] was more than 70 years, which is greater than the median age in our study. Second, Nonaka et al[44] evaluated the effectiveness and safety of a deep sedation protocol using propofol combined with DEX for gastric ESD, whereas our study focused on

anesthesia with DEX addition for esophageal ESD. Third, Nonaka et al[44] did not specify if their observation period included the early postoperative period in the PACU. When comparing the total incidence of intraoperative and postoperative bradycardia in our study, we found a statistically significant between-group difference (40.0% in the DEX group vs 16.7% in the control group, absolute difference: 23.3%, OR: 3.333, 95% CI: 0.998–11.139, $P = 0.045$).

PONV can negatively impact patient satisfaction, delay functional recovery, and extend hospital stays.[45–47] Furthermore, adding DEX to the surgical anesthesia regimen has been shown to improve patient satisfaction and enhance functional recovery after surgery.[26,47] However, only a few studies have assessed the effect of adding DEX to anesthesia or sedation regimens on PONV occurrence following gastrointestinal endoscopy or endoscopic procedures. The present study demonstrated that adding DEX significantly reduced both the incidence of PONV and PONV scores in the PACU. These results agree with previous findings in surgical patients,[26,48] indicating that the antiemetic and opioid-sparing effects of DEX contribute to reduced PONV.[19,49]

Our study results also revealed that the length of stay in the PACU was significantly reduced in the DEX group, which may be ascribed to decreased intraoperative propofol dosage, improved postoperative pain control, reduced opioid consumption, and lower PONV incidence in the PACU. However, unlike the findings in surgical patients,[26,48] our study found no significant differences in patient satisfaction and length of hospital stay between the groups, despite the beneficial effects of DEX on postoperative pain control and PONV occurrence. The difference in recovery outcomes between patients undergoing esophageal ESD and surgical patients could be explained by the following factors. First, esophageal ESD leads to less tissue damage than surgical procedures, causing milder postoperative pain that can be effectively managed. Thus, both groups reported high patient satisfaction, with a median score of 10. Second, postoperative pain and PONV after esophageal ESD tend to be most significant in the early postoperative period, especially for the first 6 h postoperatively, after which they subside. Third, while the incidence of PONV was significantly lower in the DEX group, the proportion of patients with a PONV score of 2 or higher did not differ significantly between the groups. This suggests that most PONV episodes after esophageal ESD were mild and did not require rescue antiemetics. The aforementioned characteristics of pain and PONV after esophageal ESD might explain why adding DEX to the anesthesia regimen did not significantly affect the length of hospital stay in this study.

Our study design has several limitations. First, adding DEX to the anesthesia regimen improved postoperative pain control after esophageal ESD, but the exact mechanisms underlying the improved analgesia were not investigated. Second, the sample size was calculated based on the incidence of moderate-to-severe postoperative pain. Therefore, this study may be not sufficiently powered to detect significant differences in secondary outcomes, such as the incidence of adverse cardiovascular events. Third, a single DEX dosing protocol was designed and tested in our study. Thus, this study cannot determine whether different DEX dosing regimens might further affect postoperative pain, recovery outcomes, or adverse events in patients undergoing esophageal ESD. Fourth, our study specifically included patients aged 18–65 years with an ASA physical status I or II and a BMI of <35 kg/cm^2. These inclusion criteria limit the generalizability of our findings to older patients, those with a BMI of >35 kg/cm^2, or those with higher ASA classifications. Thus, the study findings should not be extrapolated to these populations. To address the aforementioned issues, further studies are warranted.

Conclusions

This study demonstrates that addition of DEX to the anesthesia regimen can significantly reduce postoperative pain and improve early postoperative outcomes for patients undergoing esophageal ESD. The findings highlight the clinical values of intraoperative DEX in enhancing postoperative pain control after esophageal ESD and improving early postoperative outcomes with fewer adverse events. These findings suggest that DEX should be integrated into the routine anesthesia scheme in clinical practice. Furthermore, additional clinical studies should be conducted to determine the possible postoperative analgesic effect and potential benefits of intraoperative DEX for elderly patients with multiple comorbidities undergoing esophageal ESD.

Clinical Trial

Chinese Clinical Trial Registry (https://www.chictr.org.cn/); registration number: ChiCTR2100043837; Type of study: Prospective, randomized, single center study.

Data Sharing Statement

The original contributions presented in the study are included in the article, further inquiries can be directed to the corresponding author.

Disclosure

The authors declare that they have no competing interests in this work.

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