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The Impact of Intraoperative Dexmedetomidine Infusion on Postoperative Delirium Prevention in Intensive Care Unit Patients after Esophagectomy: A Randomized Double-Blind Clinical Trial

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Abstract

Background: Delirium is a significant issue for esophagectomy patients, with dexmedetomidine (Dex) showing promise in alleviating this burden. A randomized trial on Dex's role in post-esophagectomy delirium can enhance care strategies and patient outcomes.

Methods: This randomized, double-blind clinical trial, conducted at Imam Reza Hospital, Tabriz University of Medical Sciences, in Iran in 2022, involved 60 esophagectomy patients. The intervention group received Dex infusion (0.5 µg/kg/h), while the control group received normal saline. Postoperatively, patients received analgesia and were monitored for delirium incidence over 3 days in the intensive care unit (ICU) using the Confusion Assessment Method. This study utilized an independent-sample t test, the Mann-Whitney U test, the $\chi 2$ test, and the Kaplan-Meier survival analysis with a log-rank test for data comparisons.

Results: Delirium in the ICU over 3 days after surgery was significantly lower in the intervention group (10%, n=3) compared with the control group (20%, n=6) (relative risk, 0.62 [95% CI, 0.42-0.98]; *P*=0.036). On the first day, no delirium cases occurred in the intervention group, contrasting with 2 cases in the control group (*P*=0.014). Similarly, on the second day, one case was observed in the intervention group versus 2 in the control group (*P*=0.042). On the third day, 2 cases were recorded in the intervention group versus 3 in the control group (*P*=0.031).

Conclusion: The significant reduction in delirium occurrence observed in patients receiving intraoperative Dex infusion highlights its potential as a preventive strategy for postoperative delirium in ICU patients after esophagectomy.

Keywords: Intraoperative, Dex, Delirium, Esophagectomy, Intensive Care Unit

Conflicts of Interest: *None declared*
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Introduction

Delirium is a prevalent and challenging complication that often occurs in critically ill patients, particularly after major surgical procedures such as esophagectomy (1, 2). Esophagectomy—a complex surgical intervention involving the partial or complete removal of the esophagus—is commonly indicated for conditions like esophageal cancer or severe gastroesophageal reflux disease (3). Despite advancements in surgical techniques and perioperative care, the incidence of postoperative delirium remains a significant concern in this patient population (4).

Delirium is characterized by an acute and fluctuating disturbance in attention, cognition, and awareness, posing a considerable challenge in the management of patients in the intensive care unit (ICU) (2, 5). It is associated with a range of adverse outcomes—including increased mortality rates, extended hospital stays, heightened healthcare costs, and long-term cognitive impairment (6). The pathophysiology of delirium is multifaceted, involving factors such as inflammation, neurotransmitter imbalances, oxidative stress, and alterations in cerebral blood flow (7, 8).

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↑What is "already known" in this topic:
Delirium is a significant issue for esophagectomy patients, with Dex showing promise in alleviating this burden.

→What this article adds:
The significant reduction in delirium occurrence observed in patients receiving intraoperative Dex infusion highlights its potential as a preventive strategy for postoperative delirium in ICU patients after esophagectomy.

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In recent years, there has been a growing interest in utilizing preemptive pharmacological interventions to prevent delirium in high-risk patient groups (9). Dex, a highly selective α2-adrenergic receptor agonist, has emerged as a promising agent for delirium prevention due to its sedative, analgesic, and anxiolytic properties (10, 11). Dex functions by reducing sympathetic outflow, facilitating sedation without respiratory depression, and modulating neurotransmitter release within the central nervous system (11).

The rationale behind employing Dex as a preemptive measure in preventing delirium after esophagectomy lies in its potential to mitigate the neuroinflammatory response elicited by surgical stress (12). Surgical trauma triggers the release of proinflammatory cytokines, such as interleukin-6 and tumor necrosis factor-alpha, which can disrupt the blood-brain barrier and induce neuroinflammation (13). Dex has demonstrated the ability to diminish the production of proinflammatory cytokines and inhibit the activation of microglia and astrocytes in preclinical models, suggesting a neuroprotective effect (14).

Numerous clinical studies have explored the use of Dex for delirium prevention in diverse surgical populations, yielding varying results (15). While some studies have reported a reduction in the incidence and duration of delirium with Dex administration, others have found no significant difference compared with conventional sedatives like propofol or midazolam (16). The disparities in study outcomes may be attributed to variations in patient demographics, surgical procedures, dosing protocols, and outcome assessments (17).

Despite the inconclusiveness of the existing evidence, the potential benefits of preemptive Dex in averting delirium after esophagectomy warrant further investigation (18). Esophagectomy is a high-risk surgical procedure associated with notable postoperative morbidity, including respiratory complications, infections, and cardiac events, all of which can predispose patients to delirium (19). By targeting the underlying mechanisms of delirium with Dex, healthcare providers may potentially reduce the occurrence and severity of this debilitating condition after esophagectomy (20).

In conclusion, delirium represents a formidable challenge that afflicts a significant proportion of patients undergoing esophagectomy and is linked to unfavorable outcomes. Preemptive pharmacological strategies, such as Dex, offer promise in alleviating the burden of delirium in this vulnerable patient cohort. By elucidating the role of Dex in preventing delirium post-esophagectomy through a randomized clinical trial, we can refine perioperative care strategies and enhance outcomes for patients undergoing this intricate surgical procedure.

Methods

Study Design

The study was conducted as a randomized and double-blind clinical trial at Imam Reza Hospital, Tabriz University of Medical Sciences, in Iran, throughout 2022, with participants who were candidates for esophagectomy.

Eligibly Criteria

The study's inclusion criteria encompassed individuals aged between 18 and 75 years, candidates slated for esophagectomy surgery, those voluntarily consenting to participate, and those classified as American Society of Anesthesiologists (ASA) class I, II, or III. Uniformity in anesthesia methodology for all patients and a surgery duration ranging between 3 and 5 hours were also requisite. Conversely, the exclusion criteria involved factors such as a body mass index surpassing 40 kg/m^2, heart ejection fraction below 35, heart rate under 55 beats per minute, and the presence of cardiac arrhythmias. Further exclusions were based on liver enzymes exceeding twice the normal levels, serum creatinine surpassing 1.2, a history of chronic pain disorder or drug addiction, use of specific medications (antidepressants, beta-blockers, anti-arrhythmic drugs, or digoxin), the presence of epidural catheters, known allergy to Dex, and instances of vital sign instability during surgery leading to the discontinuation of Dex infusion. These stringent criteria were implemented to ensure a homogeneous and representative participant cohort while upholding ethical considerations.

Sampling

To determine the sample size based on the primary outcome of delirium scores, we conducted a pilot study involving 10 individuals, with 5 participants in each group. Using the findings from this pilot study and the following formula, incorporating values such as S1 = 3.6, S2 = 9.2, X1 = 5.90, X2 = 88.1, CI = 95%, and a test power of 80%, we calculated that 29 participants were needed in each group. Subsequently, we expanded the study, including 30 participants in each group, resulting in a total of 60 individuals. The inclusion of these 60 participants in the study was facilitated through an available sampling method, ensuring practicality and efficiency in the participant recruitment process for the present research.

$$n_1 = n_2 = \frac{(Z_{1-\frac{\alpha}{2}} + Z_{1-\beta})^2 \times (S_1^2 + S_2^2)}{(\bar{X}_1 - \bar{X}_2)^2}$$

Randomization

In this study, a sample size of 50 participants was employed, and the allocation process utilized the block permutation randomization method. The primary objective of this method was to achieve a balanced distribution of participants between the intervention and control groups. Each block, comprising 4 participants, allowed for 6 possible arrangements: BBAA, AABB, ABAB, BABA, ABBA, and BAAB. A total of 13 blocks were necessary for the 50 participants, and the randomization involved selecting numbers from 1 to 6. For instance, if block 6 was chosen first and block 2 second, participants were assigned the sequence BAABAABB. Subsequently, the participants were divided into 2 groups: Group A (intervention) and Group B (control).

Blinding

The anesthesiologist conducting the procedure was not blinded due to the study's nature. However, to ensure the

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integrity of the research, the analyst assessing the thesis results and the individual collecting information remained unaware of the specific procedural interventions. This approach was implemented to maintain a double-blind study design, enhancing the reliability and objectivity of the study outcomes.

Anesthesia Induction and Maintenance

Anesthesia was induced using intravenous propofol and fentanyl, and maintained with intravenous propofol and remifentanil, along with inhalation of a 1 to 1 nitrous oxide: oxygen mixture. The target anesthesia depth aimed to maintain a Bispectral Index value between 40 and 60. Muscle relaxation was achieved through the administration of atracurium and/or cisatracurium. Fluid infusion and blood transfusion were performed in accordance with routine practice. Blood pressure was maintained within 20% of baseline, and nasopharyngeal temperature was sustained between 36°C and 37°C.

Intervention

Patients in the intervention group received a loading dose of Dex (0.6 µg/kg), administered as a 0.15-mL/kg infusion over 10 minutes before the induction of anesthesia. Following the loading dose, a continuous infusion of Dex was maintained at a rate of 0.125 mL per kg per hour (0.5 µg/kg/hour) until 1 hour before the completion of the surgery. The administration was facilitated using a specially designed injection pump for Dex. Patients in the control group received volume-matched normal saline at the same infusion rate and duration as the intervention group. The administration process was identical, utilizing the same injection pump. Drug infusion continued until the end of the surgery, with interruptions for heart rates less than 50 beats per minute or significant blood pressure drops. Bradycardia and hypotension were managed using atropine and vasopressor drugs as needed.

Postoperative Care

After surgery, all patients were transferred to the postanesthesia care unit (PACU) and moved to ICU for 3 days. Postoperative analgesia was managed through patient-controlled intravenous analgesia (PCIA) with morphine 0.5 mg/mL. The PCIA system was programmed to deliver a background infusion rate of 0.5 mg/h, with a 1-mg bolus and an 8-minute lock-out interval. Additional morphine could be administered at 10-minute intervals for patients with a numerical rating scale pain score of ≥4. Intravenous nonsteroidal anti-inflammatory drugs and/or oral tramadol were also available for supplemental pain management.

Outcome Assessment

The primary endpoint was the incidence of delirium within the first 3 days after surgery. Delirium assessments were conducted twice daily using the Confusion Assessment Method (CAM) for nonventilated patients or the CAM for the Intensive Care Unit (CAM-ICU) for ventilated patients. Assessments were scheduled from 8 to 9 AM and 7 to 8 PM . In cases where patients were discharged or deceased within 5 days of surgery, the last delirium assessment findings were considered for any missing data. Trained investigators, who underwent periodic training intervals, performed delirium assessments and postoperative follow-ups. The training program included lectures on delirium symptoms, diagnosis, and treatment by a psychiatrist, instructions on using CAM and CAM-ICU, and simulation training with patient-actors until a 100% consensus on delirium diagnosis was achieved with the psychiatrist.

Data Analysis

Continuous data with normal distribution were compared using an independent-sample t test, while continuous data with non-normal distribution were analyzed using an independent-sample Mann-Whitney U test. Categorical data underwent comparison using the $\chi 2$ test or continuity correction $\chi 2$ test. Time-to-event data were assessed through Kaplan-Meier survival analysis, with group differences evaluated by the log-rank test. Relative risk (RR) or odds ratio (OR) was reported for binary outcomes, hazard ratio (HR) for time-to-event data, and mean or median difference for continuous data, with 95% confidence intervals (CI). The Hodges-Lehmann estimator calculated the difference and 95% CI between the 2 medians. Analyses were conducted on the intention-to-treat population, with per-protocol analysis performed for the primary endpoint. Statistical tests were executed using SPSS version 21.0 and SAS Version 9.3, with significance set at $P < 0.050$ (2-tailed).

Results

During the specified period, 101 patients were referred for esophagectomy surgery. Due to reasons such as sensitivity to Dex, meeting exclusion criteria (body mass index >40 (n = 6), heart ejection fraction below 35 (n = 9), a history of drug addiction (n = 3), use of beta-blockers (n = 4), use of anti-arrhythmic drugs (n = 1), and a history of previous hospitalizations in the ICU (n = 18), 41 patients were not included in the study. Ultimately, 60 patients were included in this study (Figure 1).

We scrutinized the baseline variables among blood patients and noted that these variables were evenly distributed between the 2 wrist groups. The assessed variables encompassed age, weight, sex, underlying diseases, ASA class, Charlson Co-morbidity Index (CCI) score, Mini-Mental State Examination (MMSE) score, and the occurrence of delirium. The comparative analysis of baseline data between the study groups is detailed in Table 1.

We conducted a comparison of data both during and after surgery in our patient cohort. It was observed that the mean levels of propofol and remifentanil in the group receiving Dex were significantly lower than those in the control group. Interestingly, the duration of surgery between the 2 groups was nearly identical, showing no statistically significant differences. Furthermore, no statistically significant variances were noted in the administration of nonsteroidal anti-inflammatory drugs and glucocorticoids in the duration of the study, volume of bleeding, fluid intake during surgery, morphine usage in PCIA, or the dosage of sedative

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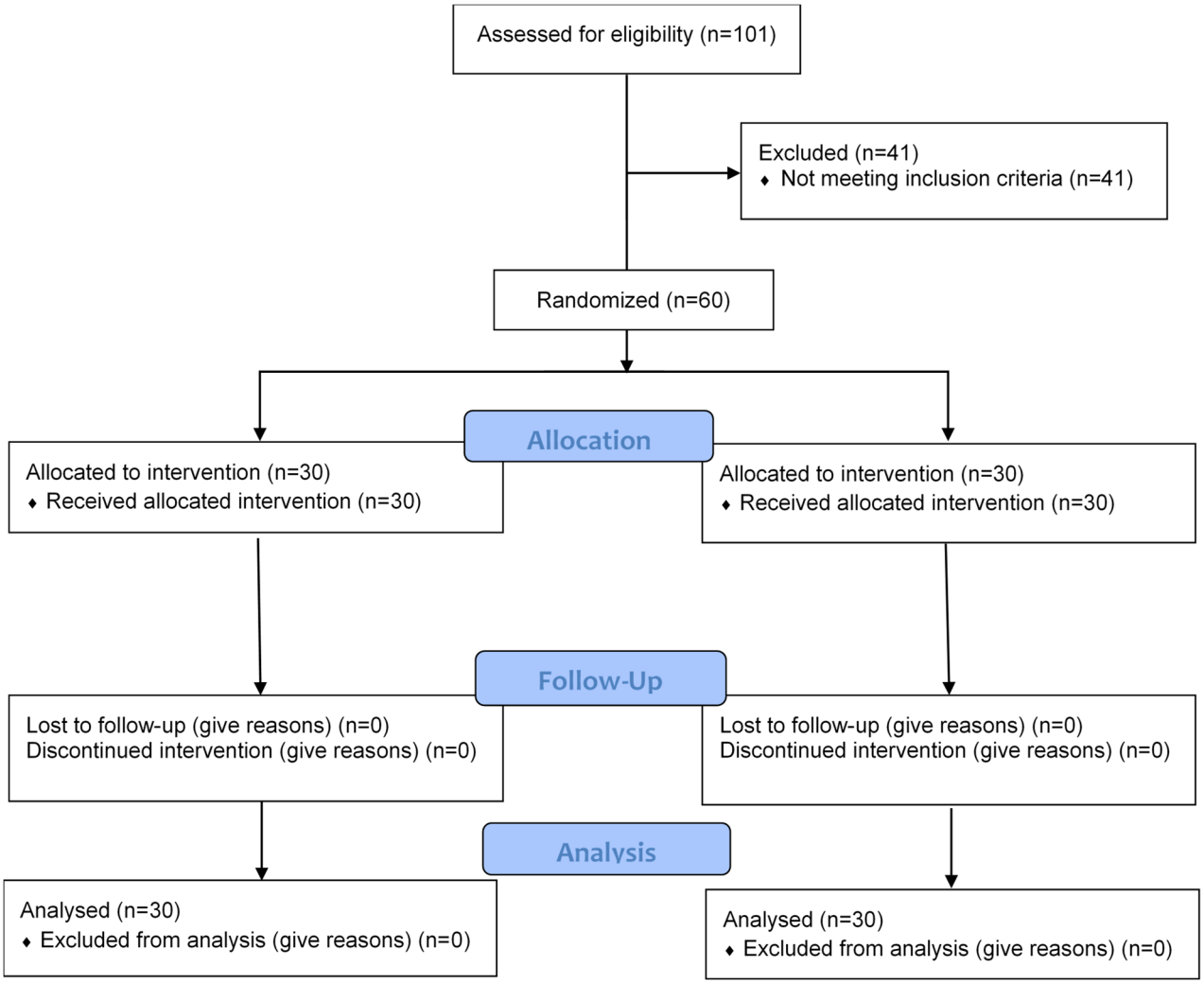

Figure 1. Flow diagram of the trial

Table 1. Baseline Characters

Variable		Study Groups		*P* Value
		Intervention group	Control group	
Age (years)*		56.03±12.89	54.41±12.85	0.896
Height (cm)*		162.63±15.28	174.12±18.30	0.569
Bodyweight (kg)*		81.54±6.41	83.57±8.33	0.632
Sex ratio (F : M)**		12:18	10:20	0.775
co-morbidity **	Hypertension	6(20%)	8(26.66%)	0.842
	Diabetes	3(10%)	4 (13.33 %)	
	Coronary artery disease	1(3.33 %)	0 (0%)	
	Previous stroke	1(3.33 %)	1(3.33 %)	
	COPD	2 (6.66%)	2 (6.66%)	
ASA **	I	19	19	0.956
	II	10	9	
	III	1	2	
CCI score ***		4(4-5)	4 (4-5)	0.999
MMSE score*		27.45±3.11	26.12±2.89	0.912
Delirium **		0 (0%)	0 (0%)	0.999

*Mean±SD- ** N(%) ***: Median COPD, chronic obstructive pulmonary disease; CCI, Charlson Co-morbidity Index; MMSE, Mini-Mental State Examination

drugs between the 2 groups. However, notably, the volume of urinary excretion in patients within the Dex group demonstrated a significantly lower level compared with those in the control group (Table 2).

Delirium after surgery was assessed during the initial 3 days of hospitalization in the ICU. Analysis of the data revealed that within the intervention group, only 3 patients (10%) were diagnosed with delirium, contrasting with 6 patients (20%) diagnosed within the control group (RR, 0.62 [95 CI%, 0.42-0.98]; P = 0.036). The findings indicated that on the first day, no instances of delirium were observed

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Table 2. Intra- and Postoperative Data

Variable		Study Groups		P Value
		Intervention group	Control group	
Propofol (mg)*		740(650-840)	960(780-1090)	0.014
Remifentanyl (µg)*		190(160-230)	275(250-400)	0.001
Use of NSAID **		12 (40%)	15 (50%)	0.114
Use of glucocorticoids **		6 (20%)	9 (30%)	0.256
Surgery duration (h) *		4.1(3.8-4.9)	4.3(4-5.1)	0.411
Bleeding (ml) *		890(740-100)	950(800-1150)	0.199
Fluid intake (ml) *		2550(2350-2800)	2700(2500-3100)	0.077
PCIA morphine *		52.5(47.0-65.5)	59.0(50.5-71.5)	0.086
Sedative **	Midazolam	2 (6.66%)	2 (6.66%)	0.215
	Dexmedetomidine	1 (1.33%)	2 (6.66%)	
	Propofol	0 (0%)	1 (1.33%)	
Urinary excretion *		550(450-650)	750(600-1050)	0.003

* Median - ** N(%)

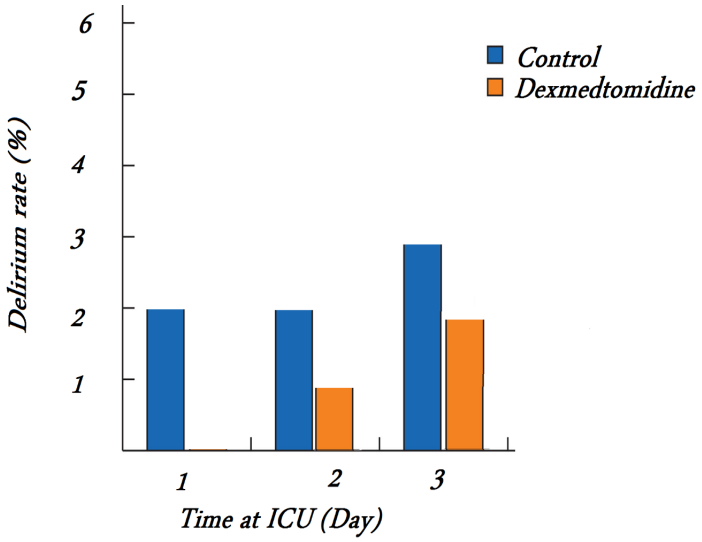

Figure 2. Delirium rate in the intensive care unit

Table 3. Postoperative Complication

Variable		Study Groups		*P* Value
		Intervention group	Control group	
Surgical complication *	Gastrointestinal hemorrhage	0 (0%)	1 (3.33%)	0.035
	ileus	1 (3.33%)	4 (13.33 %)	
	anastomotic leak	2 (6.66%)	3 (10%)	
	surgical-site infection	0 (0%)	1 (3.33%)	
ICU Duration (day) **		4(3-4)	6(4-7)	0.039
Hemodynamic instability *		3 (10%)	2 (6.66%)	0.259
Pain at movement *	At 12 h	2 (6.66%)	4 (13.33 %)	
	At 24 h	1 (3.33%)	3 (10%)	
	At 36 h	1 (3.33%)	4 (13.33 %)	0.041
	At 48 h	0 (0%)	2 (6.66%)	
	At 60 h	0 (0%)	1(3.33%)	
	At 72 h	0 (0%)	1(3.33%)	

*:N(%) **:Median

within the intervention group, whereas 2 patients in the control group experienced delirium (P = 0.014). Conversely, on the second day, 1 patient from the intervention group and 2 patients from the control group exhibited delirium (P = 0.042). Similarly, on the third day, 2 patients from the intervention group and 3 from the control group were diagnosed with delirium (P = 0.031) (Figure 2).

The incidence of postsurgical complications among patients in the intervention group was notably lower compared with those in the control group (P = 0.035). Conversely, the duration of ICU stay among patients in the control group was significantly prolonged in comparison with that of the intervention group (P = 0.039). Additionally, hemodynamic instability showed a nonsignificant trend toward higher occurrence in the intervention group compared with the control group (P = 0.259) (Table 3).

Furthermore, the intensity of pain was assessed every 12 hours using the visual analog scale. The analysis revealed

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that a greater number of patients in the control group reported experiencing more pain during movement compared with those in the intervention group ($P = 0.041$).

Discussion

The purpose of the study was to investigate the impact of intraoperative Dex infusion on the prevention of postoperative delirium in ICU patients after esophagectomy. The results of the study revealed a notable difference in the incidence of delirium between the intervention and control groups. Specifically, within the intervention group, only 10% of patients were diagnosed with delirium, whereas in the control group, the prevalence was higher at 20%.

Esophagectomy is a complex surgical procedure associated with a high risk of postoperative delirium, particularly in critically ill patients admitted to the ICU (21). Delirium in this context can lead to adverse outcomes—including prolonged hospitalization, increased morbidity and mortality, and diminished quality of life for patients. Therefore, identifying effective preventive measures is of paramount importance in optimizing patient care and outcomes (22, 23).

Dex, a highly selective alpha-2 adrenergic agonist, exerts its preventive effects on delirium through various pharmacological mechanisms (24). Firstly, Dex acts centrally by binding to presynaptic alpha-2 receptors in the locus coeruleus, leading to inhibition of norepinephrine release (25). By modulating the sympathetic nervous system activity, Dex induces sedation, analgesia, and anxiolysis, thereby promoting a calmer and more stable mental state in patients undergoing esophagectomy (17).

Furthermore, Dex has been shown to possess neuroprotective properties, which may contribute to its preventive effects on delirium. Studies suggest that Dex can attenuate neuroinflammation and oxidative stress, both of which are implicated in the pathogenesis of delirium (18, 19). By reducing neuroinflammation and oxidative stress, Dex may help preserve cognitive function and prevent the development of delirium in vulnerable patient populations (26).

Moreover, Dex's ability to promote natural sleep patterns and enhance sleep quality may also play a role in delirium prevention. Sleep disturbances are common in ICU patients and are associated with an increased risk of delirium (27). Dex has been shown to increase nonrapid eye movement (NREM) sleep and preserve rapid eye movement (REM) sleep, thereby facilitating restorative sleep and mitigating factors contributing to delirium development, such as sleep deprivation and disruption of circadian rhythms (28, 29).

The results revealed a notable disparity in delirium occurrence between the intervention and control groups over the initial 3 days after surgery. Specifically, no instances of delirium were observed within the intervention group on the first day, whereas 2 patients in the control group experienced delirium ($P = 0.014$). Similarly, on the subsequent days, the occurrence of delirium remained significantly lower in the intervention group compared with the control group, with 1 patient from the intervention group and 2 patients from the control group exhibiting delirium on the second day ($P = 0.042$), and 2 patients from the intervention group and 3 patients from the control group diagnosed with delirium on the third day ($P = 0.031$).

Furthermore, the administration of Dex during surgery has been shown to reduce the requirement for other anesthetic agents such as propofol and remifentanil (30). This decrease in anesthetic dosage may contribute to the lower incidence of delirium observed in the intervention group, as excessive sedation and analgesia are recognized risk factors for delirium development. By minimizing the use of propofol and remifentanil, Dex infusion promotes a more balanced and controlled level of sedation, reducing the likelihood of oversedation and subsequent delirium (31, 32).

While our study on the impact of intraoperative Dex infusion on postoperative delirium prevention in ICU patients after esophagectomy provides valuable insights, it is important to acknowledge several limitations. First, our sample size was relatively small, potentially limiting the generalizability of our findings to broader patient populations. Additionally, our study was conducted at a single center, which may introduce biases related to patient demographics, surgical practices, and perioperative care protocols. Furthermore, the follow-up duration was limited to 3 days after surgery, which may not capture longer-term outcomes or the full spectrum of delirium occurrences. To address these limitations and further advance our understanding of Dex's role in delirium prevention following esophagectomy, future research endeavors should consider the following suggestions. First, conducting multicenter studies with larger sample sizes would enhance the external validity of our findings and allow for subgroup analyses to explore potential differences across diverse patient populations. Additionally, extending the follow-up duration beyond the immediate postoperative period would provide insights into the long-term efficacy and safety of Dex infusion. Implementing a double-blinded design throughout the entire study period would help mitigate observer bias and enhance the robustness of delirium assessments. Furthermore, investigating the optimal dosing regimen and duration of Dex infusion, as well as exploring potential synergistic effects with other pharmacological agents or non-pharmacological interventions, would provide valuable insights for optimizing delirium prevention strategies in this patient population. Finally, incorporating patient-reported outcomes and qualitative assessments to complement quantitative measures would offer a more comprehensive understanding of the impact of Dex infusion on patients' overall well-being and postoperative recovery experience.

Conclusion

The significant reduction in delirium occurrence observed in patients receiving intraoperative Dex infusion highlights its potential as a preventive strategy for postoperative delirium in ICU patients after esophagectomy. The pharmacological actions of Dex, particularly its modulation of neurotransmitter release and ability to decrease anesthetic requirements, contribute to its effectiveness in delirium prevention. Incorporating Dex into anesthesia protocols may therefore offer clinical benefits in terms of improved patient outcomes and enhanced perioperative care in this patient population.

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Authors' Contributions

All authors played an effective role in every stage of this study.

Ethical Considerations

This study was conducted following approval from the ethics committee of Tabriz University of Medical Sciences (ethic NO: IR.TBZMED.REC.1401.859) and registration in the clinical trial system of Iran (IRCT20190325043107N42). Before surgery, participants provided informed consent. Patients incurred no costs and received treatment from the research team promptly.

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Conflict of Interests

The authors declare that they have no competing interests.

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