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The Effect of Dexmedetomidine on Preventing Postoperative Delirium by Modulating Tumor Necrosis Factor-Alpha (TNF-α) Levels in Patients Undergoing Esophagostomy

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ABSTRACT

Introduction: Esophagectomy-induced systemic inflammation, specifically elevated TNF-α, significantly contributes to postoperative delirium. Dexmedetomidine may mitigate this cognitive decline through its potent anti-inflammatory and neuroprotective effects. This study investigates whether dexmedetomidine prevents postoperative delirium by modulating TNF-α levels in patients undergoing esophagectomy.

Material and methods: This prospective randomized study was conducted in 2023 at Imam Reza Hospital, Tabriz University of Medical Sciences. Fifty patients (25 per group), determined using the two-independent-sample formula, were enrolled. The primary variables included perioperative TNF-α levels and the incidence of postoperative delirium, along with demographic characteristics, intraoperative hemodynamics, anesthetic requirements, and ICU stay duration.

Results: Dexmedetomidine significantly attenuated postoperative TNF-α elevation compared with control, with a significant time-by-group interaction (P=0.002) and lower TNF-α levels at the end of surgery (P=0.003) and 24 hours postoperatively (P<0.001). The incidence of postoperative delirium was reduced (16.00% vs. 40.00%, P=0.048), with delayed onset (P=0.011), shorter duration (P=0.004), and lower CAM-ICU scores (P=0.002). Peak TNF-α levels correlated positively with delirium severity (r=0.79, P<0.001).

Conclusion: Perioperative dexmedetomidine administration reduced postoperative delirium and mitigated its severity following esophagectomy, likely through suppression of TNF-α–mediated inflammatory responses. The observed association between inflammatory burden and delirium severity supports a mechanistic link between systemic inflammation and postoperative neurocognitive dysfunction.

Introduction

The surgical management of esophageal cancer, primarily through esophagostomy, remains one of the most invasive and physiologically taxing procedures in modern thoracic surgery. Despite advancements in minimally invasive techniques and the implementation of enhanced recovery after surgery (ERAS) protocols, the procedure characterized by extensive tissue trauma, prolonged anesthesia, and significant hemodynamic fluctuations. These factors contribute to a disproportionately high rate of postoperative complications, among which neuropsychiatric disturbances are particularly prevalent and debilitating. Patients undergoing esophagostomy are at a heightened risk for systemic inflammatory response syndrome (SIRS) due to the anatomical complexity of the surgery, the necessity of multi-cavitary involvement, and the potential for significant pulmonary and gastrointestinal insults (1, 2). Postoperative delirium (POD) stands out as a critical neuropsychiatric complication following major thoracic interventions, manifesting as an acute and fluctuating decline in cognitive function, altered

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levels of consciousness, and impaired attention. In the specific context of esophagostomy, the incidence of POD has reported to range significantly, often exceeding twenty percent in high-risk cohorts or elderly populations. This condition is not merely a transient postoperative phase but is independently associated with prolonged mechanical ventilation, extended intensive care unit (ICU) stays, and increased thirty-day mortality rates. Furthermore, the development of POD often serves as a precursor to long-term cognitive decline and reduced quality of life, necessitating the development of proactive and effective pharmacological preventative strategies (3, 4).

The underlying pathophysiology of POD is multifactorial and remains a subject of intense investigation, involving a complex interplay between neurotransmitter imbalances, oxidative stress, and blood-brain barrier disruption. However, the "neuroinflammatory hypothesis" has gained substantial traction as a primary driver of cognitive dysfunction following major surgical trauma. This hypothesis posits that peripheral surgical injury triggers a systemic release of pro-inflammatory cytokines, which subsequently penetrate the central nervous system (CNS) through both humoral and neural pathways. Once within the brain, these peripheral signals activate resident microglia, leading to a localized inflammatory cascade that disrupts neuronal signaling and synaptic plasticity, ultimately manifesting as the clinical symptoms of delirium (5, 6).

Among the various inflammatory mediators involved in this process, Tumor Necrosis Factor-alpha (TNF-α) is recognized as a pivotal orchestrator of the early inflammatory response and a key biomarker of surgical stress. TNF-α is a potent pro-inflammatory cytokine primarily produced by activated macrophages and monocytes in response to tissue injury, hypoxia, or end toxemia. In the surgical setting, elevated plasma levels of TNF-α are frequently observed immediately following incision and tend to peak throughout the early postoperative period. Research suggests that high perioperative concentrations of TNF-α correlate strongly with the severity of the systemic inflammatory response and the subsequent development of multi-organ dysfunction, including acute cerebral impairment (7, 8).

The specific role of TNF-α in the pathogenesis of POD is mediated through its ability to significantly increase the permeability of the blood-brain barrier (BBB). By upregulating adhesion molecules and activating matrix metalloproteinase, TNF-α facilitates the transmigration of peripheral immune cells and the leakage of neurotoxic substances into the brain parenchyma. Furthermore, TNF-α directly stimulates the production of other downstream interleukins, such as IL-1β and IL-6, within the CNS, creating a self-sustaining inflammatory environment that is toxic to neurons. This neuroinflammation interferes with the cholinergic system, which is essential for maintaining attention and cognitive focus, thereby providing a direct mechanistic link between systemic cytokine levels and behavioral manifestations (9, 10).

Given the severe clinical and economic implications of POD, pharmacological interventions aimed at mitigating the inflammatory cascade have become a focal point of perioperative research. Dexmedetomidine, a highly selective alpha-2 adrenoceptor agonist, has emerged as a promising agent due to its unique sedative, analgesic, and sympatholytic properties. Unlike traditional sedatives such as benzodiazepines, which known to increase the risk of delirium, dexmedetomidine provides a form of "cooperative sedation" where patients remain easily arousable and interactive. Beyond its primary sedative effects, a growing body of evidence highlights its significant immunomodulatory and neuroprotective capabilities, making it a candidate of primary interest for delirium prevention in high-stress surgeries (11, 12).

The anti-inflammatory effects of dexmedetomidine are believed to be mediated through several molecular pathways, including the inhibition of the toll-like receptor 4 (TLR4) signaling pathway and the activation of the vagus nerve-mediated cholinergic anti-inflammatory pathway. By suppressing the activation of nuclear factor-kappa B (NF-κB), dexmedetomidine effectively reduces the transcription and subsequent systemic release of pro-inflammatory cytokines, specifically TNF-α. This reduction in the systemic inflammatory burden potentially limits the secondary neuroinflammatory response that occurs following esophagostomy. Clinical studies in various surgical settings have shown that patients receiving dexmedetomidine infusions exhibit lower circulating levels of TNF-α compared to those receiving standard anesthetic care (13, 14).

Moreover, dexmedetomidine's ability to preserve the integrity of the blood-brain barrier may offer an additional layer of protection against the development of POD. By attenuating the surge of TNF-α, the drug limits the cytokine-induced degradation of tight junction proteins in the cerebral vasculature, thereby maintaining the brain's internal environment. Furthermore, dexmedetomidine has shown to reduce oxidative stress and inhibit apoptosis in hippocampal neurons, which are critical areas for memory and cognitive processing. These multifaceted neuroprotective mechanisms suggest that the benefits of dexmedetomidine extend far beyond simple sedation, providing a biological shield against the rigors of major thoracic surgery (15,16).

In the specific population of patients undergoing esophagostomy, the use of dexmedetomidine is

particularly relevant due to the high baseline risk of delirium and the necessity for early postoperative mobilization. The drug's lack of significant respiratory depression makes it an ideal sedative for patients who require close monitoring of pulmonary function and rapid weaning from mechanical ventilation. While several clinical trials have investigated the impact of dexmedetomidine on POD in cardiac and general abdominal surgery, its specific role in modulating the TNF-α pathway to prevent delirium in esophageal cancer patients remains an area requiring further empirical validation. Identifying a clear correlation between cytokine suppression and clinical cognitive outcomes could refine anesthetic protocols for this vulnerable group (17,18).

Despite the promising biological rationale, there remains a notable gap in the literature regarding the exact dose-response relationship of dexmedetomidine and its efficacy in inhibiting the TNF-α-mediated inflammatory surge specifically during the critical first twenty-four hours after esophagostomy. Some studies suggest that the timing of administration whether initiated intraoperatively or continued into the early postoperative period in the ICU is crucial for maximizing the anti-inflammatory benefit. Furthermore, the variability in individual patient responses to surgical stress means that a standardized approach to immunomodulation is still being sought. Investigating these temporal dynamics and molecular interactions is essential for moving toward personalized perioperative medicine and improving the neurological recovery of thoracic surgical patients (19, 20).

The current study designed to address these research gaps by rigorously evaluating the influence of dexmedetomidine on postoperative TNF-α levels and the subsequent incidence of delirium in patients undergoing esophagostomy. By quantifying the changes in cytokine concentrations at multiple perioperative time points, we aim to provide robust biochemical evidence for the drug's anti-inflammatory mechanism in a clinical setting. We hypothesize that dexmedetomidine will significantly attenuate the postoperative rise in TNF-α, thereby reducing the neuroinflammatory burden and lowering the frequency and severity of POD. This investigation seeks to contribute to a deeper understanding of the molecular links between systemic inflammation and acute cognitive dysfunction, potentially shifting the paradigm of anesthetic management (21,22).

In conclusion, the intersection of surgical oncology, immunology, and neocritical care highlights the urgent need for integrated strategies that protect the brain during periods of major physiological stress. The potential for dexmedetomidine to act as a bridge between anesthesia and immune modulation offers a compelling avenue for improving patient outcomes after esophagostomy. As we strive to reduce the morbidity associated with esophageal resection, understanding the role of TNF-α as both a biomarker and a therapeutic target becomes paramount. This research serves as a critical step in establishing evidence-based practices that prioritize both the physical and cognitive recovery of patients, ensuring that the success of the surgical intervention not undermined by avoidable neuropsychiatric complications.

Material and methods

Study Design

This investigation conducted as a prospective, randomized, parallel-group clinical study at Imam Reza Hospital, affiliated with Tabriz University of Medical Sciences, throughout the year 2023. The study included two independent groups receiving either dexmedetomidine or standard care, and all perioperative assessments performed under uniform institutional protocols to ensure methodological consistency.

Sampling Method and Sample Size Determination

Participants recruited using a convenience sampling strategy from eligible patients scheduled for elective esophagostomy. Sample size was calculated using the standard formula for comparing means between two independent groups (Two-Independent-Sample Formula), based on assumptions of type I error (α=0.05), statistical power (80%), expected effect size in postoperative TNF-α levels, and estimated variability from prior pilot data. Using these assumptions, the calculation yielded a requirement of 25 patients per group, resulting in a total sample size of 50 participants.

Eligibility Criteria

Inclusion criteria were adult patients aged 18-75 years, candidates for elective esophagostomy under general anesthesia, ASA physical status II–III, and the ability to provide informed consent. Exclusion criteria included pre-existing cognitive impairment or delirium, neurological or psychiatric disorders, chronic use of sedatives or opioids, severe hepatic or renal dysfunction, cardiac conduction abnormalities, known hypersensitivity to dexmedetomidine, alcohol or substance abuse, active infection or sepsis, autoimmune or inflammatory diseases that could alter cytokine profiles, hemodynamic instability before surgery, and refusal to participate.

Procedures and Measurements

On the day of surgery, eligible patients randomly assigned to either the dexmedetomidine group or the control group using a computer-generated sequence. Patients in the dexmedetomidine group received an infusion of dexmedetomidine at a loading dose of 0.5 µg/kg over 10 minutes, followed by a continuous

infusion of 0.4 μg/kg/h maintained until the completion of surgery. The control group received standard anesthetic management without dexmedetomidine. Venous blood samples collected at three predefined time points: baseline before induction of anesthesia, immediately at the end of surgery, and 24 hours postoperatively. Serum TNF-α levels measured using a validated enzyme-linked immunosorbent assay (ELISA) kit with standardized laboratory procedures. Postoperative delirium assessed twice daily for 48 hours using the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU), administered by trained researchers blinded to group allocation. Additional variables included demographic characteristics, intraoperative hemodynamic data, anesthetic drug requirements, duration of surgery, length of ICU stay, and postoperative complications.

Statistical Analysis

Data were analyzed using standard statistical software. Continuous variables tested for normality using the Shapiro–Wilk test, then compared using independent-sample t-tests or Mann-Whitney U tests as appropriate. Categorical variables analyzed with chi-square or Fisher's exact tests. Repeated measures of TNF-α levels were evaluated using repeated-measures ANOVA or mixed-effects modeling. Logistic regression used to assess the association between dexmedetomidine exposure and the occurrence of postoperative delirium, adjusting for potential confounders. A two-tailed P-value <0.05 was considered statistically significant.

Ethical Considerations

The study approved by the Ethics Committee of Tabriz University of Medical Sciences under protocol number IR.TBZMED.REC.1401.859. Written informed consent obtained from all participants prior to enrollment, and all procedures adhered to the principles of the Declaration of Helsinki.

Results

The baseline demographic and clinical characteristics of the participants analyzed to confirm the adequacy of randomization and comparability between groups prior to intervention. There were no statistically significant differences between the dexmedetomidine and control groups in terms of age (62.48 ± 7.12 vs. 61.96 ± 8.04 years, P=0.812), gender distribution (P=0.772), or body mass index (24.83 ± 3.14 vs. 24.47 ± 3.29 kg/m², P=0.693). The distribution of ASA physical status was comparable between groups (P=0.741), and no significant differences were observed in the prevalence of hypertension (P=0.781), diabetes mellitus (P = 0.758), or coronary artery disease (P=0.532). In addition, the duration of surgery (298.64 ± 41.52 vs. 306.12 ± 43.18 minutes, P=0.521), type of esophagostomy (P=0.773), baseline cognitive function measured by MMSE (28.16±1.25 vs. 28.08±1.41, P=0.834), and baseline serum TNF-α levels (8.42 ± 1.67 vs. 8.48±1.49 pg/mL, P=0.892) were statistically similar, indicating successful group homogeneity at baseline (table 1).

Table 1. Baseline Demographic and Clinical Characteristics of Patients Undergoing Esophagostomy

Variable	Dexmedetomidine Group (n = 25)	Control Group (n = 25)	P-value
Age (years), mean ± SD	62.48 ± 7.12	61.96 ± 8.04	0.812
Gender (Male/Female), n (%)	18 (72.00%) / 7 (28.00%)	17 (68.00%) / 8 (32.00%)	0.772
BMI (kg/m²), mean ± SD	24.83 ± 3.14	24.47 ± 3.29	0.693
ASA Physical Status, n (%)	-	-	0.741
─ Class II	14 (56.00%)	15 (60.00%)	-
─ Class III	11 (44.00%)	10 (40.00%)	-
Hypertension, n (%)	9 (36.00%)	10 (40.00%)	0.781
Diabetes Mellitus, n (%)	5 (20.00%)	6 (24.00%)	0.758
Coronary Artery Disease, n (%)	3 (12.00%)	5 (20.00%)	0.532
Duration of Surgery (min), mean ± SD	298.64 ± 41.52	306.12 ± 43.18	0.521
Surgical Approach, n (%)	-	-	0.773
─ McKeown	16 (64.00%)	15 (60.00%)	-
─ Ivor Lewis	9 (36.00%)	10 (40.00%)	-
Baseline MMSE Score, mean ± SD	28.16 ± 1.25	28.08 ± 1.41	0.834
Baseline TNF-α (pg/mL), mean ± SD	8.42 ± 1.67	8.48 ± 1.49	0.892

Note: Continuous variables analyzed using the independent-samples t-test. Categorical variables were analyzed using the chi-square test. Data presented as mean ± standard deviation or number (percentage). A P-value <0.050 was considered statistically significant.

As illustrated in Figure 1 (TNF_alpha_boxplot.png, /mnt/data), serum TNF-α levels increased significantly over time in both groups following esophagostomy; however, the magnitude of elevation was markedly attenuated in the dexmedetomidine group. Repeated-measures ANOVA demonstrated a significant within-group time effect (P<0.001), confirming postoperative inflammatory activation. Importantly, the between-group comparison revealed significantly lower TNF-α concentrations in the dexmedetomidine group at the end of surgery (P=0.003) and at 24 hours postoperatively (P<0.001). The time-by-group interaction effect was statistically significant (P=0.002), indicating that dexmedetomidine significantly modified the trajectory of perioperative TNF-α changes. These findings support a clinically meaningful anti-inflammatory effect of dexmedetomidine in patients undergoing esophagostomy.

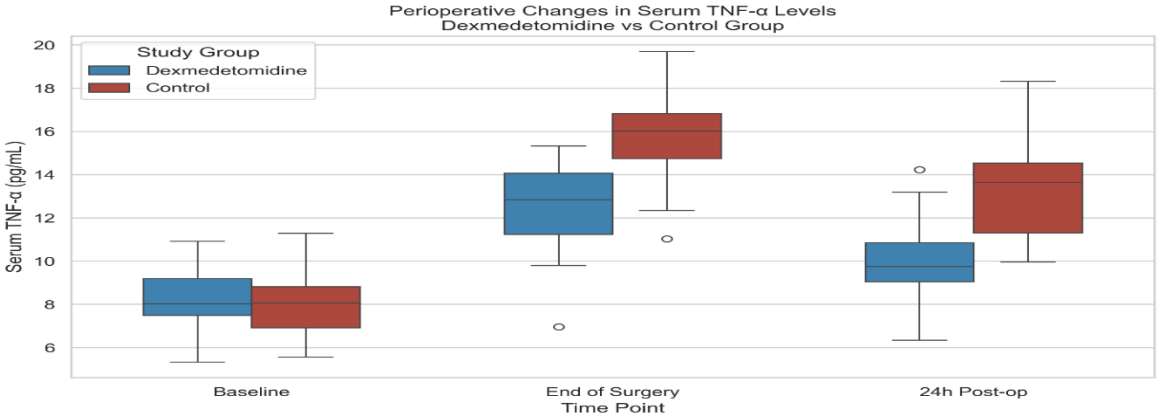

Figure 1. Effect of Dexmedetomidine on Perioperative TNF-α Dynamics

Postoperative delirium occurred less frequently in patients receiving dexmedetomidine compared with the control group (16.00% vs. 40.00%, P=0.048). In addition to the reduced incidence, patients in the dexmedetomidine group demonstrated a delayed onset of delirium (30.75 ± 6.42 vs. 18.60 ± 5.87 hours, P=0.011) and a significantly shorter duration of symptoms (14.80 ± 4.36 vs. 26.35 ± 7.18 hours, P=0.004). Moreover, delirium severity assessed using the CAM-ICU score was lower in the intervention group (4.60 ± 1.12 vs. 6.15 ± 1.48, P=0.002). These findings indicate both a protective and mitigating effect of dexmedetomidine on postoperative cognitive dysfunction following esophagostomy (table 2).

Table 2. Incidence and Severity of Postoperative Delirium Following Esophagostomy

Variable	Dexmedetomidine Group (n=25)	Control Group (n=25)	P-value
Incidence of POD, n (%)	4 (16.00%)	10 (40.00%)	0.048
Time to Onset (hours), mean ± SD	30.75 ± 6.42	18.60 ± 5.87	0.011
Duration of Delirium (hours), mean ± SD	14.80 ± 4.36	26.35 ± 7.18	0.004
Peak CAM-ICU Score, mean ± SD	4.60 ± 1.12	6.15 ± 1.48	0.002

Note: Incidence of postoperative delirium (POD) analyzed using the chi-square test. Continuous variables compared using the independent-samples t-test. Data presented as mean ± standard deviation or number (percentage). Statistical significance defined as P < 0.050.

A Pearson correlation analysis performed to examine the association between perioperative inflammatory response and the severity of postoperative delirium. The analysis demonstrated a statistically significant positive correlation between peak postoperative serum TNF-α levels and peak CAM-ICU scores (r=0.79, P<0.001, 95% CI:0.49-0.81). This finding indicates that higher systemic TNF-α concentrations were associated with greater delirium severity among patients undergoing esophagostomy. The observed relationship supports the neuroinflammatory hypothesis of postoperative delirium and suggests that attenuation of TNF-α through dexmedetomidine administration may contribute to the reduction of delirium severity in the postoperative period (figure 2).

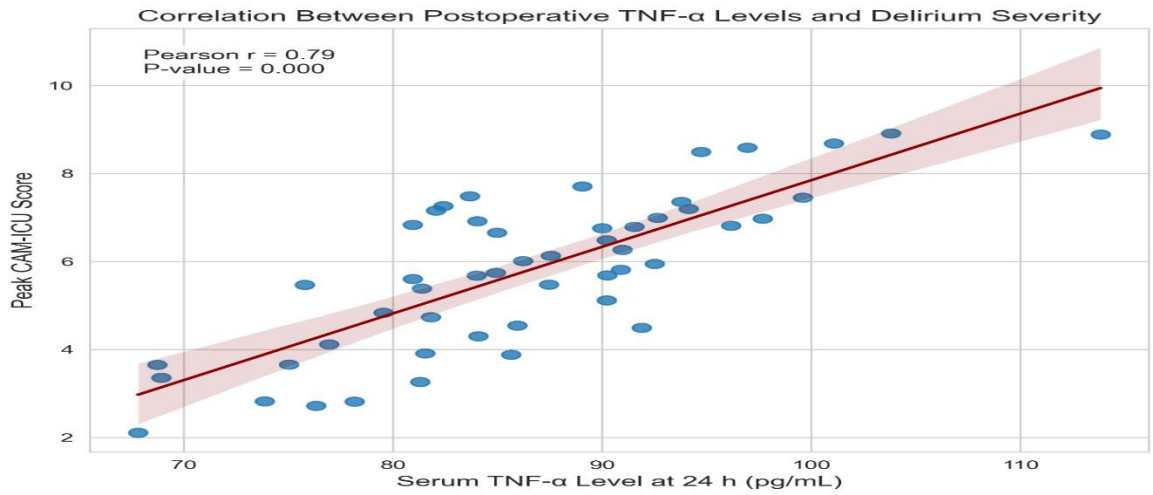

Figure 2. Correlation between Peak Postoperative Tumor Necrosis Factor-Alpha (TNF-α) and Delirium Severity

Discussion

The findings of this prospective clinical trial demonstrate that perioperative dexmedetomidine administration reduced both the occurrence and clinical burden of postoperative delirium in patients undergoing esophagostomy. In qualitative terms, patients who received dexmedetomidine experienced a more favorable postoperative neurocognitive course, with less frequent delirium, milder symptom expression, and a less pronounced inflammatory response. The results also suggest that the relationship between inflammation and delirium is not merely associative but biologically coherent, as higher postoperative TNF-α levels accompanied by greater delirium severity. Taken together, these findings support the concept that dexmedetomidine exerts a protective effect in this setting through modulation of the perioperative inflammatory cascade and preservation of neurocognitive stability after major thoracic surgery (23).

These findings are biologically plausible in light of the profound inflammatory and neuroendocrine stress provoked by esophagostomy. This procedure is among the most invasive oncologic operations and is typically associated with extensive tissue injury, prolonged operative exposure, one-lung ventilation, hemodynamic fluctuations, and postoperative intensive care admission. Each of these factors contributes to activation of the innate immune system and release of proinflammatory mediators, among which TNF-α has a central role. TNF-α rapidly produced after tissue injury and amplifies the inflammatory response through endothelial activation, leukocyte recruitment, induction of downstream cytokine pathways. In the perioperative setting, excessive TNF-α release has implicated not only in systemic inflammatory dysregulation but also in postoperative organ dysfunction and impaired neurological recovery. The lower postoperative TNF-α profile observed in the dexmedetomidine group therefore provides a mechanistic basis for the lower burden of delirium seen in these patients (24).

The present findings also support the neuroinflammatory model of postoperative delirium. According to this framework, peripheral inflammatory signals generated by surgical trauma communicate with the central nervous system through humoral, neural, and cellular pathways, ultimately leading to microglial activation, synaptic dysfunction, altered neurotransmission, and acute disturbances in attention and cognition. TNF-α is particularly relevant in this process because it can disrupt blood-brain barrier integrity, facilitate entry of inflammatory mediators into the cerebral milieu, and intensify local neuroinflammatory signaling. In vulnerable postoperative patients, this sequence may manifest clinically as delirium. The marked attenuation of TNF-α elevation in the dexmedetomidine group, together with the lower incidence and severity of delirium, suggests that suppression of early systemic inflammation may interrupt this cascade before it evolves into clinically significant neurocognitive dysfunction. This interpretation is consistent with experimental and clinical literature indicating that reduction of proinflammatory cytokine activity may lessen delirium risk after major surgery (25).

Another important aspect of our results is the positive correlation between peak TNF-α concentrations and CAM-ICU scores. This relationship reinforces the view that inflammatory burden is linked not only to whether delirium occurs, but also to how severe it becomes when present. The finding suggests a dose-response pattern in which greater cytokine activation is associated with more pronounced neurocognitive disturbance. Such an observation strengthens the mechanistic coherence of the study and argues against the reduction in delirium explained solely by nonspecific sedative effects. It also raises the possibility that TNF-α may serve as a clinically informative biomarker for

identifying patients at heightened risk of severe postoperative delirium. Although this concept requires validation in larger cohorts, it underscores the translational relevance of inflammatory monitoring in perioperative neuroprotection research (26).

The beneficial effect of dexmedetomidine in this study is likely multifactorial. Its anti-inflammatory properties are increasingly recognized, but its sedative and sympatholytic characteristics may also contribute substantially to the observed outcomes. Dexmedetomidine acts selectively on central alpha-2 adrenoceptors, reducing sympathetic outflow and catecholamine release. By attenuating the neuroendocrine stress response to surgery, it may indirectly limit cytokine production and reduce physiological perturbations that predispose patients to delirium. In addition, dexmedetomidine produces a form of sedation that resembles natural sleep more closely than GABAergic sedatives, preserving reusability and potentially supporting more normal sleep architecture. Sleep disruption is a well-established contributor to delirium in critically ill and postoperative patients; therefore, preservation of circadian and sleep-related neurophysiology may represent another pathway through which dexmedetomidine lowers delirium risk. The combined anti-inflammatory, autonomic, and neurophysiological effects of this agent offer a persuasive explanation for the overall pattern observed in our trial (27).

The delayed onset and shorter duration of delirium in the dexmedetomidine group deserve specific consideration. These findings suggest that the intervention did not merely reduce the number of cases but also altered the clinical trajectory of delirium among affected patients. A delayed onset may reflect postponement of the inflammatory and neurochemical threshold required for overt cognitive dysfunction, while shorter duration may indicate faster resolution of the underlying pathophysiological insult. From a practical standpoint, these effects are highly relevant. Even when delirium not fully prevented, reducing its duration and intensity may lessen patient distress, facilitate communication and rehabilitation, decrease the need for rescue sedatives or antipsychotics, and reduce caregiver burden in the postoperative setting. In this respect, dexmedetomidine appears to offer both preventive and mitigating benefits, which is particularly valuable in esophagostomy patients, who are often physiologically fragile and exposed to prolonged postoperative stress (28).

Our findings are also in agreement with prior studies reporting that dexmedetomidine may reduce postoperative delirium in elderly and high-risk surgical populations. However, the present study extends this evidence by focusing specifically on esophagostomy and by linking the observed clinical benefit to perioperative TNF-α dynamics. This is important because esophagostomy patients represent a distinct population with a particularly intense inflammatory insult and a high baseline susceptibility to pulmonary complications, intensive care exposure, and postoperative neurocognitive instability. By showing, that dexmedetomidine modifies both biological and clinical endpoints in this setting; the study contributes a more integrated account of how this agent may work. Rather than demonstrating only symptomatic benefit, the results indicate that dexmedetomidine may influence an upstream pathogenic pathway that is directly relevant to delirium development (29).

Despite these strengths, several limitations acknowledged. The study conducted at a single center with a relatively modest sample size, and this may limit the external validity of the findings. Although randomization and baseline homogeneity support internal validity, larger multicenter studies needed to determine whether the observed effects are reproducible across different perioperative protocols, surgical teams, and patient populations. In addition, TNF-α selected as the principal inflammatory marker, but postoperative delirium is a multifaceted syndrome involving a broad network of cytokines, endothelial mediators, neurotransmitter disturbances, and patient-specific vulnerability factors. Measurement of additional biomarkers such as IL-6, IL-1β, S100B, or C-reactive protein might have offered a more comprehensive characterization of the inflammatory response. Furthermore, the present study focused on early postoperative outcomes and did not include long-term neurocognitive follow-up, so it remains uncertain whether the reduction in delirium translates into sustained cognitive benefit beyond the immediate perioperative period (30).

In summary, this study supports the view that dexmedetomidine provides meaningful neuroprotection in patients undergoing esophagostomy, most plausibly through attenuation of perioperative inflammation and consequent reduction of neuroinflammatory signaling. The overall pattern of results a blunted postoperative TNF-α response, reduced delirium incidence, delayed onset, shorter duration, lower severity, and a positive correlation between cytokine burden and clinical score forms a coherent and biologically credible narrative. These findings strengthen the rationale for considering dexmedetomidine not simply as a sedative adjunct, but as a targeted perioperative strategy for reducing delirium risk in major thoracic surgery. Future investigations with larger samples, broader biomarker panels, and extended follow-up will be essential to refine patient selection, optimize dosing strategies, and clarify the long-term neurocognitive implications of this approach (31).

Conclusion

This study demonstrates that dexmedetomidine exerts clinically meaningful neuroprotective effects in patients undergoing esophagostomy by modulating perioperative inflammatory dynamics. Attenuation of TNF-α release accompanied by a lower incidence, delayed onset, shorter duration, and reduced severity of postoperative delirium. The strong positive correlation between TNF-α levels and CAM-ICU scores reinforces the neuroinflammatory hypothesis of delirium and suggests that targeting inflammatory pathways may represent an effective strategy for preventing postoperative cognitive complications in high-risk surgical populations.

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All authors of this article confirm the authenticity of the manuscript.

Conflicts of interest

The authors declare that they have no competing interests.

Disclosure Statement

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Authors' Contributions

All authors contributed to data analysis, drafting, and revising of the paper and agreed to be responsible for all the aspects of this work.

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