J. Adv. Med. Pharm. Biomed. Res.; **(2026),** Volume 2, Issue 6, 518-526

Journal of Advanced in Medicinal, Pharmaceutical and Biomedical Research

Journal homepage: https://www.jampbr.com

DOI: https://doi.org/10.5281/zenodo.22059659

Effect of Intraoperative Dexmedetomidine Administration on Postoperative Delirium Scores during the First 72 Hours: A Randomized Controlled Trial

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Article info
Received: 15.06.2026
Accepted: 20.08.2026
Available Online: 20.08.2026
Checked for Plagiarism: Yes

Keywords:
dexmedetomidine; postoperative delirium; randomized controlled trial; postoperative pain

ABSTRACT

Introduction: Postoperative delirium is a frequent complication associated with prolonged recovery, increased morbidity, and higher healthcare costs. Dexmedetomidine may reduce delirium through its sedative, analgesic-sparing, and sympatholytic effects, although evidence remains inconsistent. This randomized controlled trial aimed to evaluate the effect of intraoperative dexmedetomidine administration on postoperative delirium scores during the first 72 hours.

Material and methods: In this double-blind, randomized controlled trial conducted at Imam Reza Hospital, 50 surgical patients were allocated (1:1) to receive either intraoperative dexmedetomidine (0.5 µg/kg bolus, then 0.2-0.5 µg/kg/h infusion) or 0.9% normal saline. Postoperative delirium was evaluated during the first 72 hours using the Confusion Assessment Method (CAM/CAM-S).

Results: Across the first 72 postoperative hours, the dexmedetomidine group showed consistently lower delirium severity and incidence than controls, with the greatest separation at 24-48 hours; delirium scores peaked early and then declined in both groups, but remained lower with dexmedetomidine at every assessment (all time points: $P<0.05$). In parallel, the dexmedetomidine group had lower intraoperative heart rate and slightly lower mean arterial pressure, along with significantly lower postoperative VAS pain scores from 1 to 24 hours (all comparisons: $P<0.05$).

Conclusion: Intraoperative dexmedetomidine appears to reduce early postoperative delirium burden while improving analgesia and maintaining acceptable hemodynamic stability. These findings support its role as a useful perioperative adjunct, likely through attenuation of surgical stress, sympathetic activation, and pain-related neurocognitive disruption.

Introduction

Postoperative delirium is a common and clinically important neuropsychiatric complication following major surgery, particularly in older adults and patients with significant comorbidity. It characterized by an acute disturbance in attention, awareness, and cognition that develops over a short period and tends to fluctuate during the course of the day. Although often transient, delirium is associated with longer hospital stay, increased need for intensive care, higher rates of postoperative complications, functional decline, and greater mortality. In addition, it imposes a substantial burden on families and health care systems because of the need for closer monitoring, additional treatment, and delayed recovery.

As surgical populations continue to age and complex procedures performed in patients with limited physiologic reserve, the prevention of postoperative delirium become an increasingly important issue in perioperative medicine [1].

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The pathophysiology of postoperative delirium is multifactorial and incompletely understood. Proposed mechanisms include neuroinflammation, neurotransmitter imbalance, oxidative stress, stress-response activation, sleep disruption, pain, hypoxemia, and exposure to sedative or anticholinergic medications. Surgical trauma and anesthetic drugs may alter cerebral homeostasis, especially in patients with preexisting cognitive vulnerability. Because delirium is not caused by a single factor, effective prevention requires a multidimensional approach that includes optimization of pain control, avoidance of overly deep sedation, maintenance of hemodynamic stability, and careful selection of anesthetic agents. Despite growing interest in delirium prevention, no universally accepted pharmacologic strategy has yet been established, and many interventions have shown inconsistent results across different patient populations and surgical settings [2].

Among the agents investigated for delirium prevention, dexmedetomidine has attracted considerable attention. Dexmedetomidine is a highly selective alpha-2 adrenergic agonist with sedative, anxiolytic, analgesic-sparing, and sympatholytic properties. Unlike many other sedatives, it produces a state of cooperative sedation that resembles natural sleep and is associated with minimal respiratory depression. These features make dexmedetomidine particularly appealing in the perioperative setting, where preservation of spontaneous ventilation and stable arousal are valuable. In addition, by reducing sympathetic activation and opioid requirements, dexmedetomidine may indirectly lower some of the physiologic stressors that contribute to delirium. For these reasons, it has been studied as a potential neuroprotective adjunct in anesthesia and critical care [3].

Evidence from previous studies suggests that dexmedetomidine may reduce the incidence or severity of postoperative delirium, although findings have not been entirely consistent. Several randomized trials and meta-analyses have reported a beneficial effect, particularly in older surgical patients and in procedures associated with substantial inflammatory and stress responses. However, other investigations have failed to demonstrate a clear reduction in delirium, possibly due to variations in dose, timing, route of administration, patient characteristics, surgical type, and delirium assessment methods. This heterogeneity has limited the ability to draw firm conclusions and has created uncertainty regarding its routine use solely for delirium prevention. Therefore, further well-designed randomized studies are still needed to clarify the role of intraoperative dexmedetomidine in diverse clinical contexts [4].

The timing of dexmedetomidine administration may be especially important. Intraoperative use could theoretically provide greater benefit than postoperative administration by modulating the neuroendocrine stress response during surgery itself, when inflammatory and hemodynamic disturbances begin. By attenuating intraoperative sympathetic surges, reducing anesthetic and opioid consumption, and promoting more stable emergence from anesthesia, dexmedetomidine may influence the early postoperative period when delirium most commonly develops. The first 72 hours after surgery represent a critical window for delirium detection, as many cases emerge shortly after anesthesia and during the initial phase of recovery. Evaluating delirium scores during this period may therefore provide meaningful insight into the early neurocognitive effects of perioperative dexmedetomidine exposure [5].

From a practical standpoint, postoperative delirium remains challenging to diagnose and quantify in routine clinical practice. Delirium is frequently underrecognized, especially hypoactive delirium, which may be mistaken for fatigue, depression, or normal postoperative drowsiness. Using validated scoring systems and structured assessments improves detection and allows comparison across studies. Measuring delirium scores rather than relying only on incidence may also capture changes in severity and clinical trajectory, offering a more nuanced understanding of intervention effects. This is particularly relevant in randomized trials, where even modest reductions in delirium burden may translate into clinically meaningful benefits such as improved patient comfort, fewer complications, and easier postoperative care [6].

Dexmedetomidine is not without potential adverse effects, and its clinical value must be weighed against safety considerations. The most commonly reported hemodynamic effects include bradycardia and hypotension, particularly when higher doses or rapid bolus administration are used. In some patients, excessive sedation may also delay recovery or complicate neurologic assessment. Accordingly, the optimal balance between benefit and harm remains an active area of investigation. A clearer understanding of whether intraoperative dexmedetomidine meaningfully improves delirium outcomes, and under what dosing strategies, is therefore essential before widespread adoption can be recommended. Randomized controlled trials remain the most reliable method for addressing this question because they can minimize confounding and provide stronger evidence of causal association [7].

Given the clinical importance of delirium, the biologic plausibility of dexmedetomidine as a preventive agent, and the existing uncertainty in the literature, further targeted research is warranted. Studies that focus on the immediate postoperative period and apply standardized outcome assessment may help clarify whether intraoperative dexmedetomidine meaningfully alters delirium-

related outcomes after surgery. Therefore, the present randomized controlled trial was designed to evaluate the effect of intraoperative dexmedetomidine administration on postoperative delirium scores during the first 72 hours after surgery.

Material and methods

Study Design

This double-blind, randomized controlled clinical trial was conducted at Imam Reza Hospital, Tabriz, Iran. Eligible participants were randomly allocated in a 1:1 ratio to either the dexmedetomidine intervention group or the control group. Randomization was performed using a computer-generated sequence. To maintain blinding, the study medication and placebo were prepared in identical syringes by an anesthesiologist who was not involved in patient assessment or data analysis. The patients, postoperative assessors, and statistical analyst were unaware of group assignments throughout the study.

Sample Size and Sampling

The sample size was estimated using the two-independent-means sample-size formula, based on the expected difference in postoperative delirium scores between the two groups, a two-sided significance level of 0.05, and a statistical power of 80%. Considering the anticipated effect size and a possible loss to follow-up, the required sample was determined to be 50 participants. Accordingly, 25 patients were assigned to the intervention group and 25 to the control group. Participants were recruited using convenience sampling from eligible patients scheduled for surgery. After providing informed consent, participants were randomly allocated to the study groups using a computer-generated randomization list.

Inclusion and Exclusion Criteria

The inclusion criteria were age ≥18 years; eligibility for elective surgery under general anesthesia; ability to understand the study procedures; ability to communicate adequately with the research team; willingness to participate and sign written informed consent; and availability for postoperative delirium assessment during the first 72 hours after surgery. Patients were excluded if they had a previous diagnosis of delirium, dementia, major neurocognitive disorder, psychosis, severe cognitive impairment, or a documented history of cerebrovascular disease; a preoperative Glasgow Coma Scale score below 15; severe hepatic, renal, cardiac, or respiratory dysfunction; clinically significant bradycardia, hypotension, or conduction abnormality; allergy or contraindication to dexmedetomidine; chronic use of sedatives, antipsychotic medications, or alpha-2 adrenergic agonists; alcohol or substance dependence; inability to cooperate with postoperative assessment; emergency surgery; anticipated postoperative mechanical ventilation; admission to the intensive care unit before surgery; or concurrent participation in another interventional study. Patients were also excluded after enrollment if the surgical procedure was cancelled or postponed, if a major intraoperative complication occurred that required deviation from the study protocol, if the study medication was not administered as planned, or if they or their legally authorized representative requested withdrawal from the study.

Study Procedure: Intervention

After standard preoperative evaluation, demographic and baseline clinical information were recorded, including age, sex, body mass index, educational level, marital status, smoking history, alcohol or substance use, medical comorbidities, previous surgery, preoperative medications, baseline vital signs, and preoperative cognitive status. In the operating room, standard monitoring was applied, including electrocardiography, noninvasive blood pressure measurement, pulse oximetry, capnography, and monitoring of body temperature. Anesthesia was induced and maintained according to the institutional protocol. Following induction of general anesthesia and before surgical incision, participants allocated to the intervention group received dexmedetomidine at a dose of 0.5 µg/kg administered intravenously over 10 minutes, followed by a continuous infusion of 0.2–0.5 µg/kg/h until the completion of surgery. The infusion rate was adjusted or temporarily discontinued in the event of clinically significant bradycardia or hypotension, according to predefined safety criteria. The total dose administered, duration of infusion, intraoperative hemodynamic changes, and any adverse effects were documented.

Study Procedure: Control and Outcome Assessment

Participants in the control group received an equal volume of 0.9% normal saline administered over the same 10-minute period, followed by a continuous saline infusion at a rate and volume corresponding to the intervention protocol. The anesthetic technique, intraoperative monitoring, fluid therapy, analgesic regimen, and criteria for postoperative care were otherwise similar between the two groups. The following perioperative variables were recorded: type and duration of surgery, duration of anesthesia, estimated blood loss, intraoperative fluid administration, use and dose of opioids and other analgesics, use of vasoactive medications, intraoperative oxygen saturation, heart rate, systolic and diastolic blood pressure, mean arterial pressure, episodes of hypotension or bradycardia, recovery time, and time to tracheal extubation. Postoperatively, delirium was assessed at

standardized time points during the first 72 hours using the Confusion Assessment Method (CAM), with delirium severity quantified using the CAM-Severity (CAM-S) score. Assessments were performed at 6, 24, 48, and 72 hours after surgery by a trained investigator who was blinded to treatment allocation. Additional postoperative outcomes included pain intensity, rescue analgesic consumption, nausea and vomiting, level of sedation, sleep disturbance, oxygen saturation, duration of recovery-room stay, length of hospital stay, intensive care admission, and other postoperative complications.

Statistical Analysis

Data analysis was performed using SPSS version 26. Continuous variables were evaluated for normality using the Shapiro-Wilk test, together with histograms and Q-Q plots. Normally distributed continuous variables were summarized as mean ± standard deviation, whereas non-normally distributed variables were reported as median and interquartile range. Categorical variables were presented as frequencies and percentages. Baseline characteristics were compared using the independent-samples t test or the Mann-Whitney U test for continuous variables, as appropriate, and the chi-square test or Fisher's exact test for categorical variables. Changes in delirium scores over time were examined using repeated-measures analysis of variance or a linear mixed-effects model, according to the distribution of the data and the presence of missing observations. The interaction between treatment group and assessment time was also evaluated. Between-group comparisons of delirium scores at each time point were performed using the independent-samples t test or Mann–Whitney U test. Within-group changes were assessed using paired-samples t tests or the Wilcoxon signed-rank test. The incidence of delirium and categorical postoperative outcomes were compared using the chi-square or Fisher's exact test. Multivariable logistic or linear regression analysis was used, when appropriate, to adjust for clinically relevant covariates, including age, sex, baseline cognitive status, type and duration of surgery, comorbidities, opioid consumption, and intraoperative hypotension. Effect estimates were reported with 95% confidence intervals. All tests were two-sided, and a P value <0.05 was considered statistically significant.

Ethical Considerations

The study protocol was reviewed and approved by the Ethics Committee of Tabriz University of Medical Sciences under approval code IR.TBZMED.REC.1401.859. The study was conducted in accordance with the principles of the Declaration of Helsinki and applicable national ethical regulations. Before enrollment, the study objectives, procedures, potential benefits, possible risks, confidentiality measures, and voluntary nature of participation were explained to all eligible patients. Written informed consent was obtained from each participant before data collection. Participants were informed that they could withdraw from the study at any time without affecting the quality or continuity of their medical care. Personal information was kept confidential, and the collected data were analyzed and reported anonymously. Rescue treatment and appropriate clinical management were provided whenever clinically indicated.

Results

The line graph illustrates the comparative longitudinal changes in delirium severity scores between the dexmedetomidine and control groups at four standardized postoperative intervals: 6, 24, 48, and 72 hours. Patients in the dexmedetomidine group consistently exhibited lower mean delirium scores across all assessment points compared to the control group, suggesting a beneficial neurocognitive effect of the intraoperative intervention. Both groups demonstrated a peak in delirium scores within the first 24 hours, followed by a gradual decline in severity by the 72-hour mark. The persistent downward shift of the dexmedetomidine curve relative to the control curve highlights the potential efficacy of alpha-2 adrenergic agonists in mitigating the intensity of early postoperative cognitive fluctuations, thereby promoting a more stable neurocognitive recovery profile in the immediate surgical aftermath (figure1).

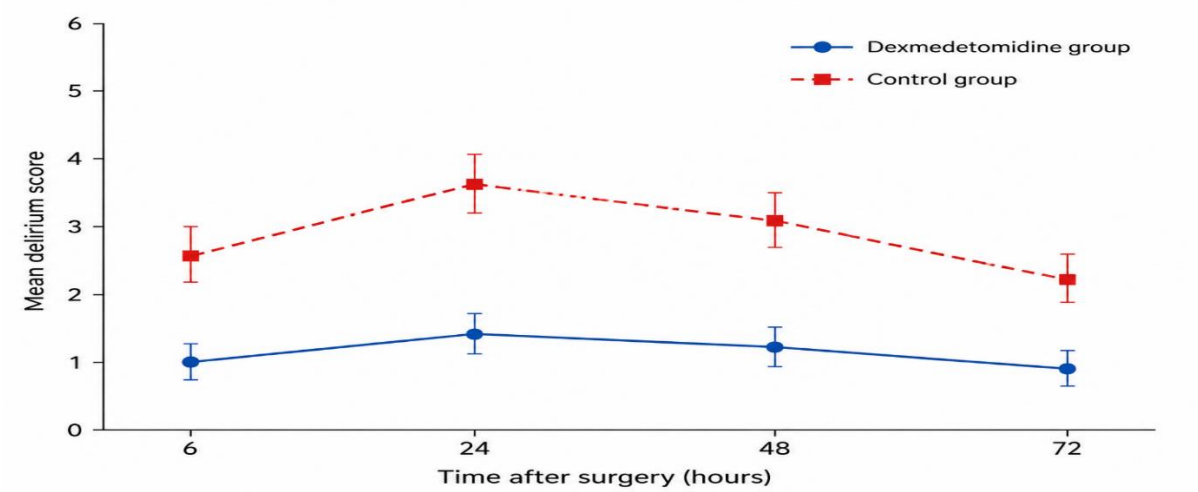

Figure 1. Temporal trajectory of mean postoperative delirium scores during the first 72 hours in patients receiving intraoperative dexmedetomidine versus control

This bar chart compares the incidence of postoperative delirium between the dexmedetomidine and control groups at 6, 24, 48, and 72 hours after surgery. Across all time points, the dexmedetomidine group showed a lower delirium incidence than the control group, indicating a potential protective effect of intraoperative dexmedetomidine on early postoperative neurocognitive outcomes. The between-group difference appears most pronounced at 24 and 48 hours, when delirium was more frequent in the control group, while the lowest incidence was observed by 72 hours in both groups. Overall, the pattern suggests that dexmedetomidine may reduce the likelihood and burden of postoperative delirium during the critical early recovery period (figure 2).

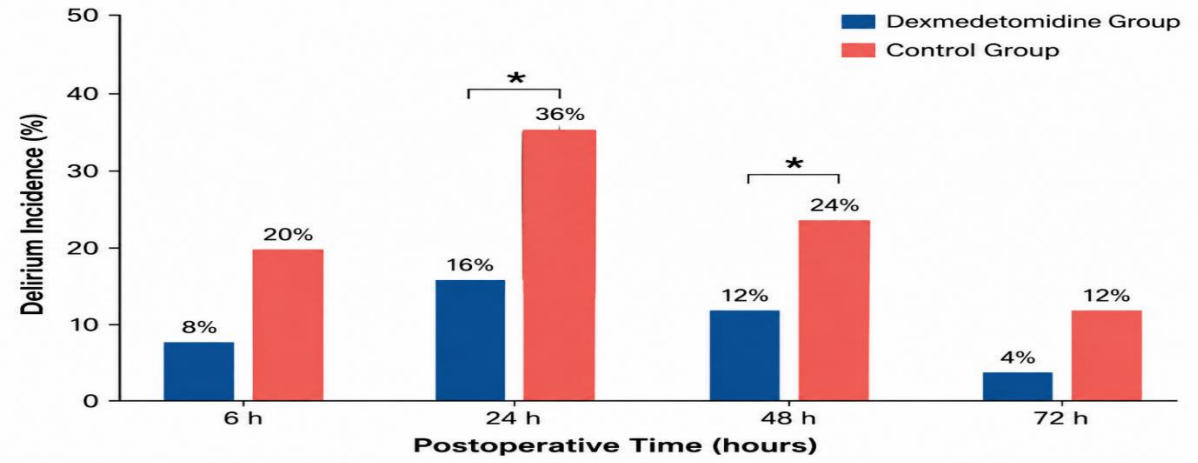

Figure 2. Incidence of postoperative delirium in the dexmedetomidine and control groups across the first 72 hours after surgery

This figure compares the temporal trends in heart rate and means arterial pressure between patients receiving intraoperative dexmedetomidine and those receiving control treatment. The dexmedetomidine group maintained a consistently lower heart rate throughout the surgical period, whereas the control group showed relatively higher values. Mean arterial pressure was also modestly lower in the dexmedetomidine group during the early intraoperative period, followed by comparable values between the groups later in surgery. Overall, these findings suggest that intraoperative dexmedetomidine may attenuate sympathetic cardiovascular responses while maintaining an acceptable degree of hemodynamic stability (figure3).

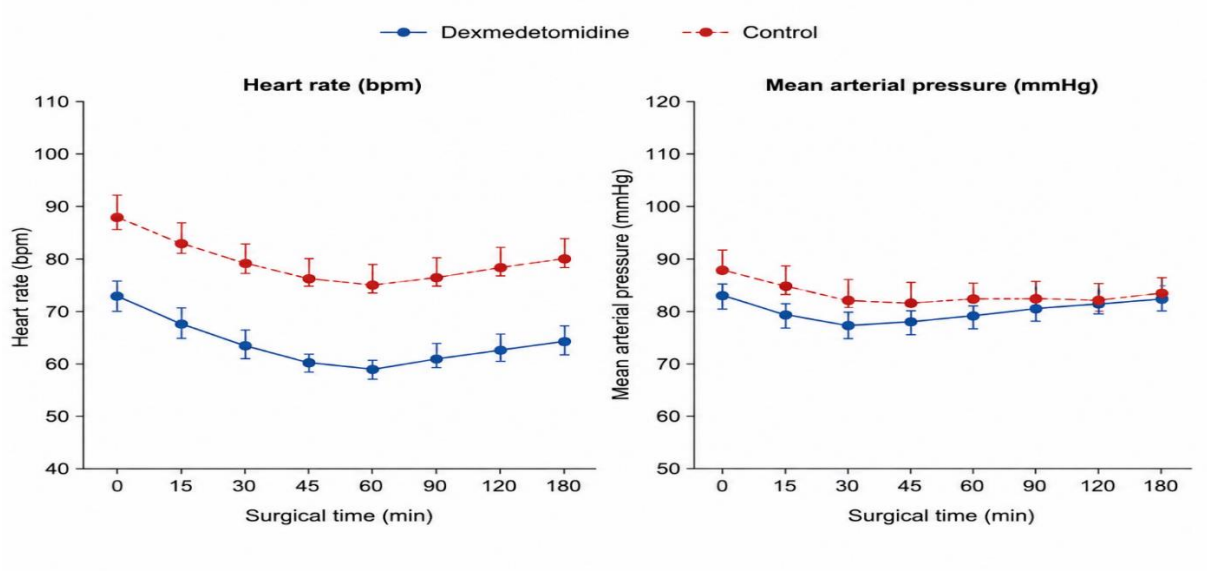

Figure 3. Perioperative changes in heart rate and mean arterial pressure in the dexmedetomidine and control groups.

The box-and-whisker plot illustrates the distribution of postoperative visual analogue scale (VAS) pain scores between the dexmedetomidine and control groups at 1, 2, 4, 6, 12, and 24 hours following surgery. Patients in the dexmedetomidine group demonstrated consistently lower median pain scores and narrower interquartile ranges throughout the early postoperative period compared with controls. This analgesic-sparing benefit was most pronounced during the first 6 hours postoperatively, reflecting substantial early pain suppression following intraoperative administration. Although pain intensity gradually declined in both cohorts by 24 hours, the persistently attenuated pain profiles in the intervention group highlight the opioid-sparing and adjunctive analgesic efficacy of intraoperative dexmedetomidine in optimizing acute postoperative recovery (figure 4).

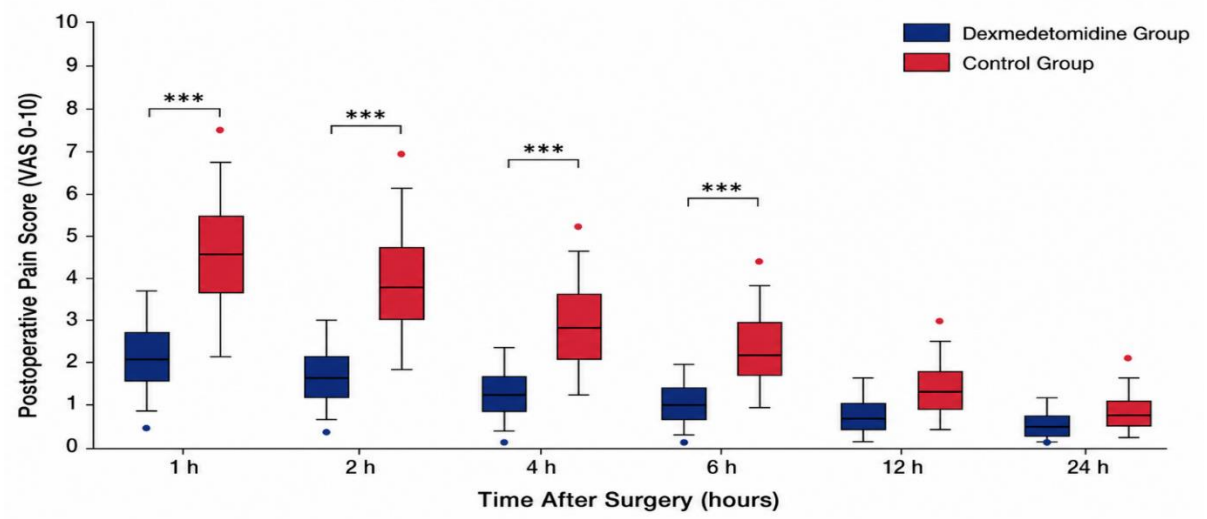

Figure 4. Comparative distribution of postoperative pain scores at serial time points within the first 24 hours in the dexmedetomidine and control groups

Discussion

In this randomized controlled trial, intraoperative dexmedetomidine was associated with lower postoperative delirium scores and a lower incidence of delirium during the first 72 hours after surgery compared with the control group. The benefit was most apparent in the early postoperative period, particularly within the first 24 to 48 hours, when delirium typically peaks. In parallel, the dexmedetomidine group showed lower heart rate and modestly lower mean arterial pressure intraoperatively, suggesting attenuation of the surgical stress response, and also experienced lower postoperative pain scores during the first 24 hours. Taken together, these findings indicate that intraoperative dexmedetomidine may confer both

neurocognitive and analgesic advantages while maintaining acceptable hemodynamic stability [8,9].

One plausible explanation for the lower delirium scores observed in the dexmedetomidine group is its unique pharmacologic profile. As a selective alpha-2 adrenergic agonist, dexmedetomidine reduces central sympathetic outflow, decreases catecholamine release, and provides sedative effects that more closely resemble physiologic sleep than do conventional sedatives. This sleep-like sedation may be particularly important in the early postoperative phase, when disruption of sleep-wake cycles contributes to delirium pathogenesis. Unlike benzodiazepines and several other sedative agents, dexmedetomidine is less likely to produce deep cortical suppression, respiratory depression, or prolonged psychomotor impairment, all of which may worsen postoperative confusion. Therefore, the observed reduction in delirium severity may reflect a more favorable neuro-sedative environment during and after surgery [10,11].

Another important mechanism is the attenuation of perioperative stress and inflammation. Surgical trauma activates the hypothalamic-pituitary-adrenal axis and the sympathetic nervous system, leading to increased circulating catecholamines, inflammatory mediators, and metabolic stress. These physiologic responses can disrupt cerebral homeostasis and increase vulnerability to acute cognitive dysfunction. The lower heart rate and slightly lower mean arterial pressure in the dexmedetomidine group suggest that the drug effectively blunted the sympathetic surge associated with surgery and anesthesia. By reducing autonomic hyperactivity, dexmedetomidine may have limited downstream neuroinflammatory cascades and helped preserve cerebral perfusion stability, both of which are thought to be relevant to delirium prevention [12,13].

The timing of the benefit also deserves attention. Delirium is often most common in the first 24 to 48 hours after surgery, when patients are recovering from anesthesia, experiencing pain, sleep disruption, and fluctuating hemodynamics. In the present study, the greatest separation between groups occurred during this vulnerable window, which supports the idea that intraoperative administration may exert its strongest protective effect when the brain is most susceptible to acute stressors. A single intraoperative exposure may not eliminate delirium risk entirely, but it may reduce the intensity of early cognitive fluctuation enough to improve the overall postoperative course. This pattern is clinically meaningful because even modest reductions in delirium severity may translate into better cooperation, shorter recovery, fewer complications, and easier nursing care [14,15].

The analgesic findings further strengthen the interpretation of the delirium results. Patients in the dexmedetomidine group had lower postoperative pain scores across the first 24 hours, especially in the earliest time points. Pain itself is a recognized precipitant of delirium because it increases stress hormone release, interferes with sleep, and often leads to greater opioid exposure. By lowering pain intensity, dexmedetomidine may have indirectly reduced delirium burden through multiple pathways at once. Its opioid-sparing effect is especially relevant, since higher opioid doses can contribute to sedation, nausea, respiratory compromise, and neurocognitive instability. In this sense, dexmedetomidine may have acted not only as a sedative adjunct but also as part of a broader multimodal strategy that improved both comfort and cognitive recovery [16,17].

The hemodynamic profile observed in this study is also consistent with prior knowledge about dexmedetomidine. The drug commonly lowers heart rate and can reduce blood pressure, particularly during loading and early infusion periods. In the present trial, these changes appear to have remained within a clinically acceptable range, suggesting that the hemodynamic effects were manageable rather than harmful. This is important because excessive hypotension or bradycardia could theoretically counteract any neuroprotective advantage by compromising cerebral perfusion. The fact that delirium scores improved despite modest cardiovascular suppression implies that the balance of effect favored benefit in this cohort. However, the finding also underscores the need for careful dose selection and monitoring, especially in patients with limited cardiovascular reserve [18,19].

From a broader clinical perspective, these findings support the growing view that postoperative delirium is best addressed through multifaceted perioperative optimization rather than a single intervention alone. Dexmedetomidine may contribute by improving sedation quality, reducing pain, limiting opioid exposure, and moderating autonomic activation. The convergence of these effects is particularly valuable in the immediate postoperative period, when multiple delirium triggers tend to occur simultaneously. The present results therefore align with a biologically coherent model in which intraoperative dexmedetomidine lowers the burden of early postoperative stress and facilitates a more stable neurocognitive trajectory. This integrated effect may explain why the intervention group consistently performed better across delirium severity, delirium incidence, pain, and hemodynamic measures [20,21].

At the same time, several considerations should temper interpretation. Delirium is a clinically heterogeneous syndrome, and its severity can be influenced by age, baseline cognition, comorbid illness, type of surgery, anesthetic technique, sleep quality, and perioperative medications. Even in a randomized trial, some residual confounding may

persist if these factors are not fully balanced or adjusted. In addition, delirium assessment during the first 72 hours captures an important but incomplete part of the postoperative course; some patients may develop later cognitive complications that were not captured in the current window. The observed reduction in scores should therefore be interpreted as evidence of early benefit rather than definitive proof of long-term neurocognitive protection [22,23].

Another point is that delirium scores and delirium incidence, while related, are not identical outcomes. A lower incidence suggests fewer patients met the threshold for delirium, whereas a lower severity score indicates a reduction in the burden among those affected. The present study showed improvement in both dimensions, which strengthens confidence in the clinical relevance of the findings. Still, future studies with larger sample sizes and longer follow-up would be useful to determine whether intraoperative dexmedetomidine also improves outcomes such as length of hospital stay, discharge readiness, readmission, and persistent cognitive dysfunction. It would also be helpful to identify which subgroups derive the greatest benefit, such as older adults, patients undergoing more painful operations, or those with higher baseline delirium risk [24,25].

Overall, the present trial suggests that intraoperative dexmedetomidine may be a valuable adjunct in reducing early postoperative delirium burden while also improving pain control and preserving acceptable hemodynamic stability. The consistency of the findings across several outcome domains strengthens the plausibility of a true treatment effect. By blunting the perioperative stress response, reducing pain, and providing a more physiologic sedative profile, dexmedetomidine may create conditions that are less favorable for delirium development during the critical first 72 hours after surgery [26,27].

Disclosure Statement

No potential conflict of interest reported by the authors.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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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