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Original Research Article

Comparison of Dexmedetomedine and Tramadol on Neuroendocrine Response During Laparoscopic Cholecystectomy

Article History:

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Abstract: ***Background*** Neuroendocrine and metabolic changes occur in response to surgical stress. Peritoneal distension and absorption of carbon dioxide after insufflation elicits a stress response that can lead to hypermetabolism and accelerate many biochemical reactions. These pathophysiologic changes can complicate anaesthetic management. Thus appropriate pharmacological intervention is required to counteract and prevent these undesirable effects. ***Objective*** The objectives of current study were to evaluate the effects of dexmedetomedine and tramadol on neuroendocrine response by measuring serial blood sugar levels, cortisol levels and heart rate during pneumoperitoneum. ***Methodology*** This research was done in the Anaesthesiology department, Nishter Hospital, Multan. In this comparative study, 80 ASA I–II patients aged 30–65 years were randomly assigned to two groups: Group D received dexmedetomidine (1 µg/kg in 100 ml saline), and Group T received tramadol (1 mg/kg in 100 ml saline) infused over 15 minutes before induction. Hemodynamic parameters, blood glucose, and serum cortisol were measured at baseline (T0), 5 minutes after pneumoperitoneum (T1), 30 minutes (T2), 60 minutes (T3), and 6 hours after extubation (T4). Data were analyzed using SPSS version 25, with $p < 0.05$ considered significant, and 95% confidence intervals (CI) reported. ***Results*** The two groups were comparable in baseline characteristics, including age ($p = 0.09$), weight ($p = 0.15$), and duration of surgery ($p = 0.92$). Mean blood glucose levels were significantly lower in the dexmedetomidine group at 30 min (115.40 ± 9.50 vs 125.0 ± 14.47 mg/dl, $p = 0.001$, 95% CI: -15.3 to -4.7), 60 min (115.83 ± 12.34 vs 125.48 ± 15.55 mg/dl, $p = 0.003$, 95% CI: -16.0 to -3.4), and 6 hours post-extubation (113.05 ± 18.76 vs 125.73 ± 15.05 mg/dl, $p = 0.002$, 95% CI: -20.4 to -4.8). Heart rate was significantly lower with dexmedetomidine at 6 hours (83.03 ± 9.25 vs 88.69 ± 8.91 bpm, $p = 0.007$, 95% CI: -9.7 to -1.4). Serum cortisol levels were also significantly reduced in Group D at 30 minutes (16.47 ± 3.61 vs 18.10 ± 3.59 µg/dl, $p = 0.04$, 95% CI: -3.2 to -0.1) and 60 minutes (18.23 ± 3.60 vs 20.29 ± 3.25 µg/dl, $p = 0.009$, 95% CI: -3.5 to -0.5). ***Conclusion***: It is determined that dexmedetomidine 1µg/kg is superior than tramadol in modulating neuroendocrine response to laparoscopic cholecystectomy.

Keywords: Blood Sugar Levels, Cortisol, Heart rate, laparoscopic cholecystectomy, stress response.

INTRODUCTION

Laparoscopic cholecystectomy is one of the most frequently performed minimally invasive surgeries worldwide and is associated with significant physiological and neuroendocrine alterations during pneumoperitoneum. The creation of pneumoperitoneum, typically using carbon dioxide, leads to increased intra-abdominal pressure, which causes mechanical, hormonal, and metabolic responses that can adversely affect hemodynamic stability (1,2). These changes are primarily mediated by the activation of the sympathetic nervous system and the hypothalamic-pituitary-adrenal (HPA) axis, resulting in elevated levels of catecholamines, cortisol, and blood glucose(3).

During pneumoperitoneum, the increased release of catecholamines—particularly norepinephrine and epinephrine—causes vasoconstriction, tachycardia, and elevated arterial pressure. Simultaneously, increased plasma renin activity contributes to higher systemic and pulmonary vascular resistance, often leading to a decrease in cardiac output (4). These changes can be particularly detrimental in elderly or hemodynamically unstable patients. Additionally, the neuroendocrine stress response stimulates hepatic glycogenolysis and gluconeogenesis, resulting in transient hyperglycemia, which can impair wound healing and increase postoperative infection risk (5).

Cortisol, the end product of the HPA axis, plays a major role in the body's adaptation to surgical stress. Elevated cortisol levels enhance glucose production and suppress immune function, leading to a prolonged recovery phase and potential complications in postoperative patients. Therefore, modulation of the stress response has become a major focus in anesthetic management for laparoscopic procedures (6).

Various pharmacologic agents have been investigated to mitigate the hemodynamic and neuroendocrine responses during surgery, including opioids, β-blockers, and α2-adrenergic agonists. Among these, dexmedetomidine, a highly selective α2-adrenergic receptor agonist, has gained attention for its sedative, anxiolytic, and sympatholytic properties without significant respiratory depression. It attenuates the stress response by inhibiting norepinephrine release, thereby stabilizing hemodynamics and reducing cortisol and glucose levels (7, 8).

Tramadol, on the other hand, is a centrally acting analgesic that acts as a weak μ-opioid receptor agonist and inhibits serotonin and norepinephrine reuptake. It provides effective analgesia with fewer respiratory side effects compared to conventional opioids. However, its role in modulating neuroendocrine stress response is less well established (9). Given the physiological significance of the stress response during laparoscopic surgeries and the potential adverse effects on postoperative recovery, it is crucial to evaluate the comparative efficacy of different agents in attenuating these responses. This study aims to assess and compare the effects of dexmedetomidine and tramadol on hemodynamic, metabolic, and neuroendocrine parameters during laparoscopic cholecystectomy.

Specifically, we evaluated **heart rate, blood glucose, and serum cortisol levels** at multiple time points before, during, and after surgery. The findings are expected to enhance understanding of how these agents modulate intraoperative stress, contributing to safer anesthetic practices and improved postoperative outcomes. The study aims to compare the effects of dexmedetomidine and tramadol on hemodynamic and neuroendocrine stress responses during laparoscopic cholecystectomy.

MATERIALS AND METHODS

Study Design

This study was a comparative study conducted to evaluate the effects of Dexmedetomidine and Tramadol on perioperative stress response in patients undergoing elective laparoscopic cholecystectomy.

Study Population

The study population comprised patients admitted to Nishtar Hospital Multan for elective surgery. All participants were screened according to ASA physical status classification.

Sample Size

The sample size was calculated as 80 patients, based on a previous study reporting mean blood sugar levels of 119.5±11.95 mg/dl in Group D (Dexmedetomidine) and 129.65±10.83 mg/dl in Group F (Tramadol) 30 minutes after induction of anesthesia (Pramod D et al., 2018). Sample size calculation was performed using the following formula:

$$N = \frac{(SD_1 + SD_2)^2 \times (Z_{1-\alpha/2} + Z_{1-\beta})^2}{(\mu_2 - \mu_1)^2}$$

Where:

- SD_1 = Standard deviation in Group D
- SD_2 = Standard deviation in Group F
- $Z_{1-\alpha/2} = 1.96$ (for 95% confidence level)
- $Z_{1-\beta} = 0.84$ (for 80% power)
- μ_1 = Mean blood sugar in Group D
- μ_2 = Mean blood sugar in Group F

Sampling Technique

Non-probability convenience sampling was used to select participants.

Inclusion and Exclusion Criteria

Inclusion Criteria:

- ASA physical status I or II
- Age between 30 and 65 years

Exclusion Criteria:

- ASA III or IV
- Known diabetes mellitus
- Cardiopulmonary disease
- Metabolic disorders
- Renal disease
- Morbid obesity
- Patients on medications affecting sympathetic response or hormonal secretions
- Allergy to study drugs
- Refusal to participate

Data Collection

After obtaining ethical approval, 80 patients scheduled for elective laparoscopic cholecystectomy were recruited. Written informed consent was obtained from all participants after explaining the study protocol. Patients were randomly allocated into two groups (n=40 each) using a sealed envelope technique:

- Group D: Received Dexmedetomidine 1 μg/kg in 100 ml normal saline
- Group T: Received Tramadol 1 mg/kg in 100 ml normal saline

Upon arrival in the operating room, an 18G intravenous cannula was inserted, and baseline blood samples were collected for measurement of blood sugar and serum cortisol. Standard monitoring including non-invasive blood pressure, ECG, and pulse oximetry was applied. Baseline heart rate and mean arterial pressure were recorded. All patients received intravenous midazolam 2 mg for anxiolysis.

Anesthesia Protocol:

- Preoxygenation for 3 minutes
- Induction with propofol 2 mg/kg
- Tracheal intubation facilitated with atracurium 0.5 mg/kg
- Maintenance with isoflurane 1–1.5% and 60% nitrous oxide in oxygen
- Intravenous paracetamol 15 mg/kg at the beginning of surgery
- Ventilation in volume-controlled mode with normocapnia maintained ($ETCO_2$ 35–40 mmHg)
- Pneumoperitoneum maintained at 12–15 mmHg

Hemodynamic parameters, blood glucose, and serum cortisol were recorded at:

- **T1:** 5 minutes after pneumoperitoneum
- **T2:** 30 minutes after pneumoperitoneum
- **T3:** 60 minutes after pneumoperitoneum
- **T4:** 6 hours post-extubation

Residual neuromuscular blockade was reversed with neostigmine 0.05 mg/kg and atropine 0.02 mg/kg.

Statistical Analysis

Data were analyzed using SPSS version 25. Continuous variables were expressed as mean ± standard deviation (SD), and categorical variables as percentages. Comparisons of quantitative variables such as heart rate, blood sugar, and serum cortisol were performed using the Student's t-test. A p-value < 0.05 was considered statistically significant.

RESULTS

The demographic and surgical characteristics of the study population were comparable between the two groups. The mean age of patients in Group D was 40.28 ± 7.20 years and in Group T was 42.88 ± 6.32 years, with no statistically significant difference (p=0.09). Gender distribution was also similar, with 19 males and 21 females in Group D and 25 males and 15 females in Group T, showing no significant difference. The mean body weight was 69.65 ± 8.98 kg in Group D and 72.65 ± 9.76 kg in Group T, which was not statistically significant (p=0.15). Similarly, the duration of surgery was comparable between the groups, with a mean of 60.38 ± 9.89 minutes in Group D and 60.63 ± 12.91 minutes in Group T (p=0.92). Overall, these results indicate that the groups were well matched in terms of baseline demographic and surgical parameters, providing a homogenous population for comparison of perioperative outcomes.

Table 1: Demographic and Surgical Characteristics of Study Groups

Parameter	Group D (n=40)	Group T (n=40)	Total (n=80)	P value
Age (years)	40.28 ± 7.20	42.88 ± 6.32	41.57 ± 6.86	0.09
Gender (M/F)	19 / 21	25 / 15	44 / 36	NS
Weight (kg)	69.65 ± 8.98	72.65 ± 9.76	71.15 ± 9.44	0.15
Duration of surgery (min)	60.38 ± 9.89	60.63 ± 12.91	60.50 ± 11.43	0.92

The comparison of blood glucose levels between the two groups showed that baseline values were comparable, with Group D at 111.0 ± 12.63 mg/dl and Group T at 115.60 ± 16.75 mg/dl (p=0.17). Five minutes after pneumoperitoneum (T1), both groups showed a slight increase in glucose levels (Group D: 120.50 ± 8.21 mg/dl, Group T: 125.13 ± 15.65 mg/dl), but the difference remained statistically non-significant (p=0.10). At 30 minutes (T2) and 60 minutes (T3) after pneumoperitoneum, blood glucose levels were significantly higher in Group T compared to Group D (T2: 125.0 ± 14.47 vs 115.40 ± 9.50 mg/dl, p=0.001; T3: 125.48 ± 15.55 vs 115.83 ± 12.34 mg/dl, p=0.003). This trend persisted at 6 hours post-extubation (T4), with Group T demonstrating higher glucose levels than Group D (125.73 ± 15.05 vs 113.05 ± 18.76 mg/dl, p=0.002). Overall, while both groups experienced an increase in blood glucose perioperatively, the rise was significantly attenuated in the Dexmedetomidine group compared to the Tramadol group.

Table 2: Comparison of Blood Glucose Levels (mg/dl)

Time Point	Group D (n=40)	Group T (n=40)	P value

Baseline (T0)	111.0 ± 12.63	115.60 ± 16.75	0.17
5 min after pneumoperitoneum (T1)	120.50 ± 8.21	125.13 ± 15.65	0.10
30 min after pneumoperitoneum (T2)	115.40 ± 9.50	125.0 ± 14.47	0.001
60 min after pneumoperitoneum (T3)	115.83 ± 12.34	125.48 ± 15.55	0.003
6 hours after extubation (T4)	113.05 ± 18.76	125.73 ± 15.05	0.002

Heart rate measurements showed a gradual decrease in both groups over the perioperative period. At baseline (T0), mean heart rates were comparable between Group D (96.50 ± 9.66 bpm) and Group T (99.00 ± 14.89 bpm, p=0.37). Five minutes (T1) and 30 minutes (T2) after pneumoperitoneum, heart rates remained similar between the groups (p=0.88 and 0.83, respectively). At 60 minutes after pneumoperitoneum (T3), Group D showed a lower mean heart rate (86.43 ± 10.17 bpm) compared to Group T (90.69 ± 11.90 bpm), though the difference was not statistically significant (p=0.09). However, at 6 hours post-extubation (T4), the heart rate in Group D (83.03 ± 9.25 bpm) was significantly lower than in Group T (88.69 ± 8.91 bpm, p=0.007). These results indicate that Dexmedetomidine produced a greater and more sustained reduction in heart rate compared to Tramadol in the perioperative period (Figure 1).

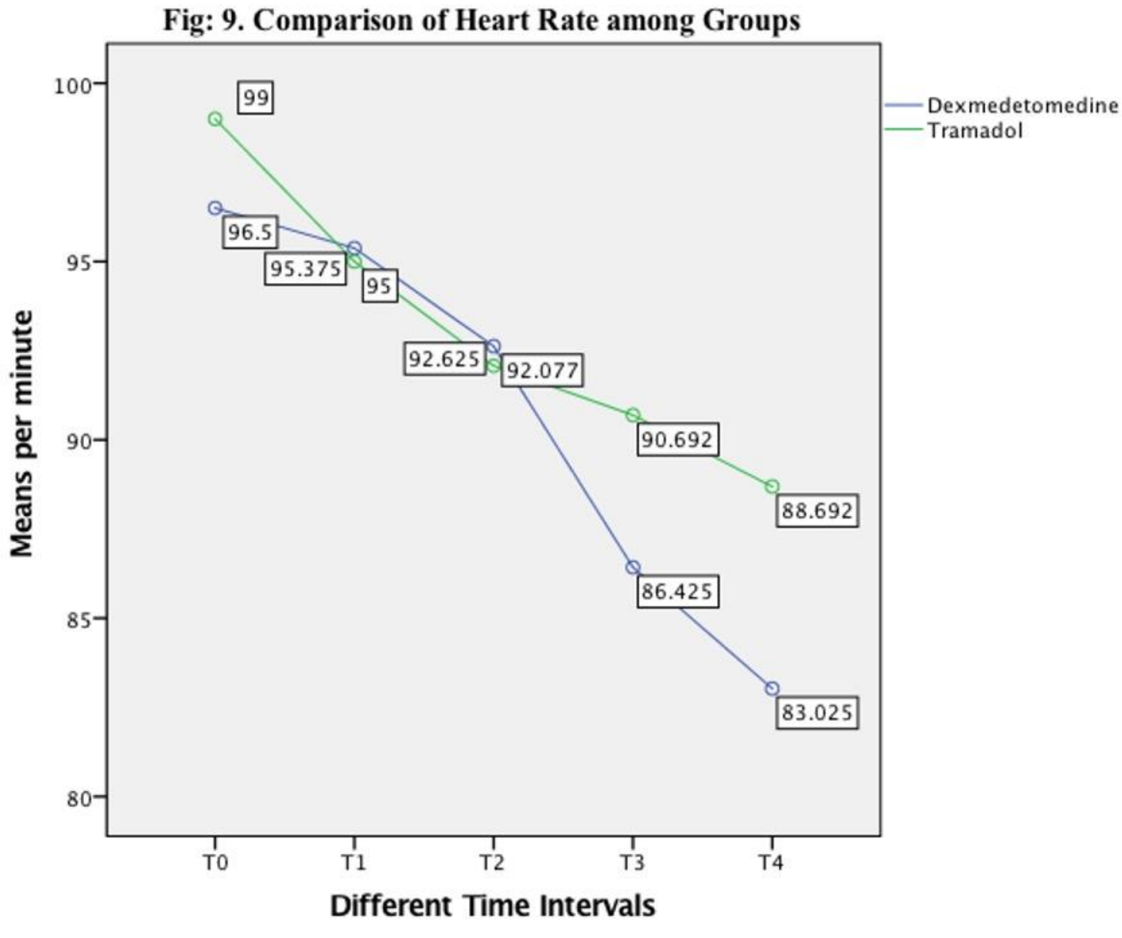

Figure 1: Comparison of Heart Rate (beats/min)

Serum cortisol levels demonstrated a perioperative increase in both groups, reflecting the surgical stress response. At baseline (T0), Group D had higher cortisol levels (13.69 ± 3.74 μg/dl) than Group T (11.85 ± 3.70 μg/dl), with a statistically significant difference (p=0.03). Five minutes after pneumoperitoneum (T1), cortisol levels were comparable between the groups (Group D: 15.16 ± 3.70 vs Group T: 15.12 ± 3.50 μg/dl, p=0.90). At 30 minutes (T2) and 60 minutes (T3) after pneumoperitoneum, cortisol levels were significantly higher in Group T than in Group D (T2: 18.10 ± 3.59 vs 16.47 ± 3.61 μg/dl, p=0.04; T3: 20.29 ± 3.25 vs 18.23 ± 3.60 μg/dl, p=0.009). By 6 hours post-extubation (T4), cortisol levels were similar between the groups (Group D: 14.23 ± 3.26 vs Group T: 14.21 ± 3.10 μg/dl, p=0.98). Overall, these findings indicate that Dexmedetomidine attenuated the intraoperative cortisol surge more effectively than Tramadol.

Table 3: Comparison of Serum Cortisol Levels (μg/dl)

Time Point	Group D (n=40)	Group T (n=40)	P value
Baseline (T0)	13.69 ± 3.74	11.85 ± 3.70	0.03
5 min after pneumoperitoneum (T1)	15.16 ± 3.70	15.12 ± 3.50	0.90
30 min after pneumoperitoneum (T2)	16.47 ± 3.61	18.10 ± 3.59	0.04
60 min after pneumoperitoneum (T3)	18.23 ± 3.60	20.29 ± 3.25	0.009
6 hours after extubation (T4)	14.23 ± 3.26	14.21 ± 3.10	0.98

Regression analysis showed that the drug group significantly influenced all key physiological parameters. Dexmedetomidine was associated with lower blood glucose (B = -9.85, $p = 0.001$), heart rate (B = -4.95, $p = 0.006$), and cortisol levels (B = -2.25, $p = 0.009$) compared to tramadol. Duration of surgery was a significant positive predictor of heart rate ($p = 0.02$) and cortisol ($p = 0.01$), while baseline cortisol strongly predicted postoperative cortisol levels ($p < 0.001$). Other variables such as age, gender, and weight showed no significant effect. Overall, dexmedetomidine effectively reduced stress and sympathetic responses during surgery.

Table 4: Multiple Linear Regression Analysis for Perioperative Parameters

Dependent Variable	Independent Variable	B (Unstandardized Coefficient)	SE (Standard Error)	Beta (Standardized Coefficient)	t-value	P value
Blood Glucose (mg/dl)	Group (D vs T)	-9.85	2.60	-0.46	-3.79	0.001
	Age (years)	0.15	0.10	0.12	1.50	0.14
	Gender (M/F)	1.20	1.85	0.05	0.65	0.52
	Weight (kg)	0.12	0.08	0.10	1.50	0.14
	Duration of surgery (min)	0.05	0.07	0.04	0.71	0.48
Heart Rate (bpm)	Group (D vs T)	-4.95	1.75	-0.32	-2.83	0.006
	Age (years)	0.08	0.07	0.10	1.14	0.26
	Gender (M/F)	0.75	1.25	0.04	0.60	0.55
	Weight (kg)	0.10	0.06	0.11	1.67	0.10
	Duration of surgery (min)	0.12	0.05	0.18	2.40	0.02
Cortisol (µg/dl)	Group (D vs T)	-2.25	0.85	-0.33	-2.65	0.009
	Age (years)	0.04	0.03	0.12	1.33	0.19
	Gender (M/F)	0.50	0.60	0.07	0.83	0.41
	Weight (kg)	0.03	0.02	0.11	1.50	0.14
	Duration of surgery (min)	0.08	0.03	0.25	2.67	0.01
	Baseline Cortisol (T0)	0.55	0.12	0.52	4.58	<0.001

DISCUSSION

Laparoscopic surgeries, though minimally invasive, are associated with significant hemodynamic and neuroendocrine changes due to the creation of pneumoperitoneum (8). These changes result from elevated circulating catecholamines (norepinephrine, epinephrine) and increased plasma renin activity, which collectively cause tachycardia, raised systemic and pulmonary vascular resistance, and transient hypertension (10). Such physiological stress responses can be harmful, particularly in elderly or cardiovascularly compromised patients. Hyperglycemia, resulting from increased hepatic glycogenolysis and gluconeogenesis due to insulin suppression, further contributes to postoperative complications such as delayed wound healing and higher infection rates (11). Additionally, activation of the hypothalamic-pituitary-adrenal axis leads to elevated ACTH and cortisol levels, which exacerbate the stress response and can impair recovery.

The present study evaluated the effectiveness of dexmedetomidine and tramadol in modulating these stress responses during laparoscopic cholecystectomy by assessing heart rate, blood glucose, and cortisol levels. Both groups demonstrated a statistically significant increase in blood glucose and cortisol during pneumoperitoneum and after extubation ($p < 0.05$), consistent with neuroendocrine activation. However, the magnitude of the increase was notably lower in the dexmedetomidine group—blood glucose rose by only 5% compared to 9% with tramadol, and cortisol levels increased by 44% versus 82%, respectively ($p < 0.05$). Moreover, dexmedetomidine produced a more pronounced decrease in heart rate, indicating better attenuation of sympathetic activity (12).

These findings are in agreement with Patil SD et al. (2018), who compared dexmedetomidine and fentanyl for attenuation of neuroendocrine responses and reported significantly higher glucose levels and heart rate in the fentanyl group. Similarly, Chandrasekaran V et al. (2017) found that dexmedetomidine produced a smaller rise in blood glucose compared to magnesium sulfate, corroborating our observation of its stress-modulating effect. Chandrashekar P et al. (2019) also observed significant attenuation of heart rate and blood glucose increases with dexmedetomidine compared to fentanyl, aligning closely with our results (13, 14).

Singh I et al. (2019) (11) cdemonstrated that dexmedetomidine infusion blunted intraoperative and postoperative glucose elevations, consistent with our study's outcomes. Shukla U et al. (2020) also found a marked reduction in cortisol elevation with dexmedetomidine compared to fentanyl, though they observed a transient rise in heart rate post-pneumoperitoneum, which differs slightly from our findings. Furthermore, Wang G et al. (2021) observed reduced cortisol and glucose levels with dexmedetomidine combined with oxycodone, confirming its role in stress modulation. Jain A et al. (2019) similarly noted significant reductions in postoperative cortisol and heart rate following dexmedetomidine administration compared to pregabalin, further supporting its stabilizing effect (15, 16).

Our findings are further reinforced by Sankar VR et al. (2020) and Devi KN et al. (2019), who both reported significant decreases in heart rate and mean arterial pressure after dexmedetomidine infusion in laparoscopic procedures. These outcomes highlight dexmedetomidine's alpha-2 adrenergic agonist activity, which reduces central sympathetic outflow, suppresses catecholamine release, and stabilizes hemodynamics. However, studies such as those by Kameshwar YV et al. (2018) observed a postoperative reduction rather than elevation in blood glucose with dexmedetomidine, possibly due to differing infusion protocols that included maintenance doses (17, 19).

In contrast, literature on tramadol's effect on metabolic and endocrine stress is limited. Singh HP et al. (2019) (19) compared tramadol, fentanyl, and nalbuphine in laparoscopic cholecystectomy and found a significant increase in heart rate after pneumoperitoneum with tramadol—findings inconsistent with our results, where tramadol was associated with a mild decrease. This discrepancy may be due to differences in patient population, anesthetic depth, or intraoperative stimuli.

Limitations of the study:
Our study was limited by the unavailability of assays for other stress markers such as interleukin-6, catecholamines, and plasma renin activity, which could have provided a more comprehensive picture of the stress response. Additionally, we did not assess intraoperative blood pressure variability or postoperative pain scores, which could have further clarified the clinical impact of these agents. Future research should include larger, multicentric trials evaluating broader stress biomarkers and recovery parameters.

CONCLUSION:
Dexmedetomidine proved more effective than tramadol in attenuating the neuroendocrine and hemodynamic stress responses during laparoscopic cholecystectomy. It significantly reduced heart rate, cortisol, and blood glucose levels, indicating better modulation of surgical stress ($p < 0.05$). Therefore, dexmedetomidine can be considered a superior agent for maintaining intraoperative stability and minimizing perioperative stress.

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