

ORIGINAL RESEARCH

Anesthetic Effect of Dezocine Combined with Propofol in Laparoscopic Surgery and Its Influence on T Cells and Inflammatory Factors in Patients

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ABSTRACT

Objective • To investigate the anesthetic effects of combining dezocine with propofol during laparoscopic surgeries, particularly its impact on T cells and inflammation.

Methods • A prospective study was conducted on 80 patients undergoing laparoscopy at the Third Hospital of Qiqihar Medical University from January 1, 2021, to August 1, 2022. Patients were randomly divided into two groups of 40 each using the random number table method. The combined group received 0.1mg/kg dezocine and 2.5 mg/kg propofol, while the control group received only 2.5 mg/kg propofol. Postoperative levels of NK cells, T cells, TNF- α , and IL-1 β were analyzed.

Results • Postoperative recovery times, including spontaneous breathing, eye-opening, verbal response, extubation, and orientation, were notably shorter in the combined group

compared to the control. While both groups showed an increase in TNF- α and IL-1 β levels post-surgery, the combined group had significantly lower levels at specific timepoints (T1, T2). This group also showed elevated levels of NK cells, CD4+, and CD4+/CD8+. Additionally, the combined group reported significantly less pain and had fewer patients with a low body condition score after extubation. No significant difference was observed in postoperative adverse reactions between the groups.

Conclusions • Combining dezocine with propofol offers superior anesthesia for laparoscopic procedures. This combination not only enhances recovery speed and reduces postoperative pain but also maintains high safety standards. (*Altern Ther Health Med.* 2023;29(8):447-451).

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INTRODUCTION

Laparoscopic surgery offers benefits like minimal trauma and quicker recovery of gastrointestinal functions when compared to traditional laparotomy. Such procedures lead to reduced postoperative pain intensity and duration. Coupled with the application of nutrients in the perioperative period, patients can experience accelerated postoperative recovery. As a result, laparoscopic surgery has garnered significant attention.¹ However, it remains an invasive procedure requiring anesthesia. Surgical anesthetics, especially in immunocompromised patients, can produce pronounced

adverse effects.² Insufficient anesthesia, especially during the latter part of the surgery, can cause significant postoperative pain, triggering a pronounced stress response detrimental to recovery.³ Traditional opioid analgesics come with severe side effects, necessitating careful dosage control.⁴ Propofol, a prevalent clinical anesthetic, targets central inhibitory receptors. By inhibiting central excitatory conduction, it exerts its anesthetic effects. Yet, its standalone use can result in unstable anesthetic effects and adverse reactions, such as hypotension and hypoxia.⁵ This has led to its combined use with other drugs. Dezocine, characterized as a κ -opioid receptor agonist and μ -receptor antagonist, mainly functions as an analgesic. It boasts minimal addictive properties and a prolonged half-life, ensuring lasting efficacy.⁶ Recent research suggests that variations in serum levels of natural killer (NK) cells and T cells can influence patient prognosis post-treatment.⁷ This study seeks to leverage the benefits of combining dezocine with propofol. The aim is to explore their collective impact on laparoscopic patients, minimize respiratory depression incidence, and ultimately, enhance the outcomes of clinical anesthesia. Through this, the study endeavors to provide a solid theoretical foundation for anesthesia treatments in laparoscopic surgeries.

MATERIALS AND METHODS

Selection of patients

Inclusion criteria in patients. (1) Classified as grade I or II by the American Society of Anesthesiologists (ASA) classification.⁸ (2) Aged between 20-50 years. (3) 40 benign cases and 40 malignant cases. (4) Serological indicators of benign patients within normal range; malignant patients in accordance with corresponding internal medicine and surgery indices. (5) Maintained a normal lifestyle. (6) No contraindications to dezocine and propofol combination anesthesia. (7) Normal liver and kidney function. (8) Patients and their families provided informed consent.

Exclusion criteria in patients. (1) History of severe cardiovascular and cerebrovascular diseases. (2) Acute inflammation symptoms such as fever and infection. (3) Risk of accidental inhalation due to conditions like intestinal obstruction or gestation. (4) Upper respiratory tract infections. (5) Pathological changes in the airway. (6) Conditions causing low lung compliance. (7) History of oral surgery. (8) History of alcohol abuse.

Grouping of patients

Eighty patients undergoing laparoscopy were selected and randomly divided into two groups. Both groups were monitored for comparable post-anesthetic performance. The study was double-blind, with research subjects and researchers unaware of group assignments.

Anesthesia methods

Preanesthetic preparation. Medical history related to anesthesia was reviewed, noting previous anesthetic experiences and drug allergies. Patients fasted for 12 hours and abstained from water for 4 hours before anesthesia.^{9,11} Pre-anesthetic medication was administered to mitigate potential complications.

Anesthesia induction. Upon entering the operating room, vital signs were monitored. Both groups inhaled pure oxygen for 3 minutes before anesthesia. Specific intravenous drugs were administered based on the group. Anesthesia was maintained using remifentanyl and atracurium in both groups.

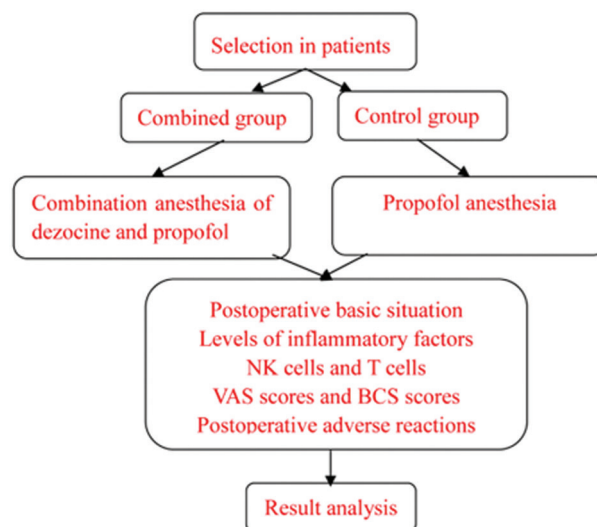
Observation indexes

General information. The indicators such as age, body mass index (BMI), ASA classification, gender, pathological characteristics, educational level and anesthesia time of all research subjects were collected.

Clinical indicators, including spontaneous breathing recovery time, eye-opening time, verbal response time, extubation time, and orientation recovery time, were meticulously documented.

Serum inflammatory cytokines. Blood (2 ml) was drawn from the radial artery at three time points: pre-anesthesia (T0), 10 minutes post-pneumoperitoneum (T1), and 10 minutes post-surgery (T2). Levels of TNF- α and IL-1 β were determined using an enzyme-linked immunosorbent assay (provided by Beijing Kewei Clinical Diagnostic Reagent Inc.; NMPA approval No.: S20060028).

Figure 1. Flow chart of patient selection and grouping



Immune function indexes. 2 ml of fasting venous blood was collected post-surgery. The T cell population (CD4+, CD8+, and CD4+/CD8+) and NK cell levels in the peripheral blood were assessed using flow cytometry.

Evaluation of pain degree and physical condition. The Visual Analog Scale (VAS), a 10-cm sliding scale ranging from 0 (painless) to 10 (most severe pain), was employed to evaluate pain at 4h and 6h post-surgery. The Body Condition Score (BCS) assessed patients' physical condition immediately post-extubation and 1h afterward. In this study, VAS and BCS average scores post-surgery were set at 3 and 2, respectively, which were used as benchmark values.

Adverse reactions. The incidence of adverse reactions, such as nausea, vomiting, drowsiness, and respiratory depression within 6 hours post-surgery, was calculated using the following formula: Total adverse reactions/total cases \times 100%.

Statistical analysis

Data was processed using SPSS 22.0 (IBM) and visualized with GraphPad Prism 7. Enumeration and measurement data were analyzed using the χ^2 and t test, respectively, and are presented as [n (%)] and ($\bar{x} \pm s$). $P < .05$ was considered statistically significant.

RESULTS

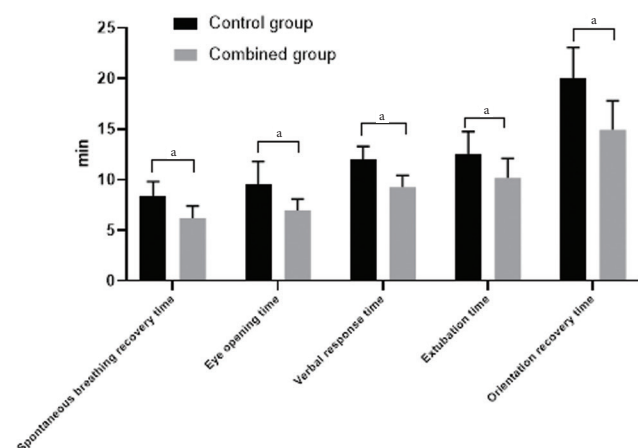
General information

There was no significant difference in patients' general information including age, body mass index (BMI), ASA classification, gender, and pathological characteristics between the two groups ($P < .05$). Refer to Table 1 for detailed patient demographics.

Postoperative basic situation

The postoperative spontaneous breathing recovery time, eye-opening time, verbal response time, extubation time and orientation recovery time of the combined group were obviously shorter compared with the control group, and the

Figure 2. The postoperative basic situation of patients ($n = 40$, min). Notes. The horizontal coordinate represented the observed dimension, and the vertical coordinate represented the time (min). The postoperative spontaneous breathing recovery time, eye-opening time, verbal response time, extubation time, and orientation recovery time in the control group were (8.35 ± 1.48), (9.50 ± 2.29), (11.98 ± 1.33), (12.53 ± 2.22) and (20.05 ± 3.02). The postoperative spontaneous breathing recovery time, eye-opening time, verbal response time, extubation time, and orientation recovery time in the combined group were (6.20 ± 1.21), (6.98 ± 1.11), (9.28 ± 1.16), (10.18 ± 1.95) and (14.95 ± 2.86).



^arepresented a significant difference in postoperative spontaneous breathing recovery time, eye-opening time, verbal response time, extubation time, and orientation recovery time between the two groups from left to right ($t = 7.113, 6.263, 9.676, 5.030$, and 7.755 , all $P < .001$).

difference had a statistical significance ($P < .05$). See postoperative basic situation of patients in Figure 1.

Levels of inflammatory factors

There was no significant difference in the levels of inflammatory factors in both groups at T0 ($P > .05$). In contrast, the levels of TNF- α and IL-1 β in the combined group were distinctly lower compared with the control group at T1 and T2 ($P < .05$). Refer to detailed levels of inflammatory factors in Table 2.

NK cells and T cells in peripheral blood

Compared with the control group, the levels of NK cells, CD4+ and CD4+/CD8+ in the combined group were significantly higher ($P < 0.05$), and there was no significant difference in the CD8+ levels between the two groups ($P > .05$). See NK cells and T cells in peripheral blood through Table 3.

VAS scores and BCS scores

The pain of patients in both groups was assessed at four hours and six hours after surgery, and the proportion of patients with VAS score > 3 in the combined group was 7.5%, which was significantly lower than the control group ($P < .05$). The proportion of patients with BCS score < 2 points in the combined group was markedly lower than that in the

Table 1. Comparison of patients' general information between the two groups ($n = 40$)

Observation indexes	Control group	Combined group	χ^2/t	P value
Age (years)	40.13±3.57	41.03±3.80	1.092	.278
BMI (kg/m ²)	24.11±2.15	24.05±2.13	0.125	.901
ASA classification			0.453	.501
Grade I	23 (57.5%)	20 (50.0%)		
Grade II	17 (42.5%)	20 (50.0%)		
Gender			0.457	.499
Male	24 (60.0%)	21 (52.5%)		
Female	16 (40.0%)	19 (47.5%)		
Pathological characteristics			0.800	.371
Benign	18 (45.0%)	22 (55.0%)		
Malignant	22 (55.0%)	18 (45.0%)		
Educational level			0.208	.648
Below High School	17 (42.5%)	15 (37.5%)		
High school and above	23 (57.5%)	25 (62.5%)		
Anesthesia time (min)	170.50±8.41	172.40±8.66	0.995	.323

Table 2. Levels of inflammatory factors in patients ($n = 40$)

Observation indexes	Points of time	Control group	Combined group	t	P value
TNF- α (pg/ml)	T0	21.44±3.25	21.59±3.30	0.205	.838
	T1	40.06±4.81	30.02±3.18	11.012	<.001
	T2	48.11±6.55	34.82±4.38	14.577	<.001
IL-1 β (pg/ml)	T0	14.79±3.10	14.88±3.14	0.129	.898
	T1	27.75±5.10	18.97±4.13	8.462	<.001
	T2	32.53±4.19	24.62±3.83	8.813	<.001

Table 3. NK cells and T cells in the peripheral blood of patients ($n = 40$)

Groups	NK cells	CD4+	CD8+	CD4+/CD8+
Control group	19.84±3.71	33.74±4.20	26.13±2.71	1.15±0.16
Combined group	26.15±3.25	39.56±5.01	25.95±2.83	1.50±0.26
t	8.091	5.630	0.291	7.250
P value	<.001	<.001	.772	<.001

Table 4. Postoperative VAS scores and BCS scores of patients [n(%)]

Groups	VAS score > 3 points		BCS score < 2 points	
	4 h after surgery	6 h after surgery	At Extubation	1 h after extubation
Control group (n = 40)	17 (42.5)	28 (70.0)	24 (60.0)	9 (22.5)
Combined group (n = 40)	3 (7.5)	4 (10.0)	5 (12.5)	3 (7.5)
χ^2	13.067	30.00	19.527	3.529
P value	<.001	<.001	<.001	.060

Table 5. Condition of postoperative adverse reactions in patients [n(%)]

Groups	Nausea and vomiting	Drowsiness	Respiratory depression
Control group (n = 40)	8 (20.0)	7 (17.5)	5 (12.5)
Combined group (n = 40)	5 (12.5)	2 (5.0)	1 (2.5)
χ^2	0.827	3.130	2.882
P value	.363	.077	.090

control group by assessing the body condition of patients at extubation ($P < .05$), with no significant difference at an hour after extubation ($P > .05$). See the specific scores of VAS and BCS in Table 4.

Postoperative adverse reactions

The postoperative complications such as nausea and vomiting, drowsiness, and respiratory depression occurred in both groups. Compared with the control group, the incidence of postoperative adverse reactions was lower, with no significant difference in both groups ($P > .05$). Refer to Table 5 for specific postoperative adverse reactions.

DISCUSSION

With the continuous development of medical technology, laparoscopy has been widely used in clinical practice in recent years. This technology has fewer incisions and less trauma to the body, and patients recovers faster after surgery compared with traditional open surgery. However, the surgery stimulation and trauma in laparoscopic technology inevitably lead to stress response to the body. The carbon dioxide pneumoperitoneum established during the surgery also results in hemodynamic and neuroendocrine changes in patients, causing adverse effects on the respiratory system and circulatory system. Therefore, intraoperative anesthesia is of great significance for the smooth operation of laparoscopy and postoperative recovery of the body. Anesthesia is an important part of surgical operation, and the type of anesthetic drugs will affect the degree of stress response during and after surgery. Some studies have found that propofol is the main anesthetic for laparoscopic surgery.^{12,13} Propofol, is a class of alkyl-phenol short-acting intravenous anesthetics with the function of sedation and hypnosis, which is commonly used in anesthesia and induction clinically.^{14,15} Propofol is widely used in laparoscopic surgery due to the advantages of low price, stable physicochemical properties, strong anesthetic efficacy, muscle-relaxing effect, inconspicuous damage to the liver and kidney, and rapid absorption and exclusion. However, intravenous anesthesia by propofol alone has a large amount of consumption, and the adverse effects might be greatly increased during the recovery period of general anesthesia.^{16,17} According to the report, dezocine is an opioid agonist and antagonist that can reduce anesthetic requirement by 50% and reduce adverse reactions in combination with propofol.^{18,19} However, there is no effective, comprehensive report of this treatment method (dezocine combined with propofol) due to the particularity of pneumoperitoneum in laparoscopic patients. Our study highlights the advantages of combining dezocine with propofol in laparoscopic surgery, particularly concerning reduced inflammatory response and better postoperative recovery.

At present, laparoscopic surgery is mature with a stable source of patients in our hospital, and it has been widely used in the clinic because of the small injury, light pain, less postoperative complications, and short hospitalization period. Hospital departments can provide the research sites and advanced anesthesia equipment and meet the needs of surgical anesthesia. The headquarter of the medical university can detect and analyze the data provided by departments so that the project is feasible in theoretical instruction and clinical practice. The results of this study were as follows.

Clinical indicators

The postoperative spontaneous breathing recovery time, eye-opening time, verbal response time, extubation time, and orientation recovery time compared with the control group were significantly shorter ($P < .05$), consistent with foreign scholars' reports.²⁰ This further confirms that the combination of dezocine and propofol has a significant anesthetic effect in laparoscopic surgery, which can significantly reduce the

postoperative awake time and promote postoperative recovery.

Inflammatory cytokines.

The levels of TNF- α and IL-1 β were increased gradually in both groups subsequently, with no significant difference in the levels of inflammatory factors in both groups at T0 ($P > .05$), but the levels of TNF- α and IL-1 β in the combined group were significantly lower than those in the control group at T1 and T2 ($P < .05$). The pro-inflammatory and anti-inflammatory factors are in a dynamic balance state in healthy individuals, but surgery, trauma, infection, and perioperative medication can disrupt the balance. TNF- α and IL-1 β are important inflammatory mediators. TNF- α is produced mainly by the activated monocytes and macrophages, while IL-1 β is widely involved in pathological damage, such as tissue damage and edema of the human body, both of which are essential in postoperative environment.

Immune system and NK cells

Compared with the control group, the levels of postoperative NK cells, CD4+ and CD4+/CD8+, were significantly higher ($P < .05$), with no significant difference in the CD8+ level in both groups ($P > .05$), showing a central role in immunity, and this is consistent with the related literature.²¹ NK cell, a non-specific immune cell, plays a major role in tumor surveillance, identification and lethality and infection control. CD4+, an immune T cell, exerts a regulatory role on the human immune to scarring, and CD8+ has a negative regulatory effect. CD4+/CD8+ reflects the immune function. The results suggested that dezocine combined with propofol could effectively reduce the effects of laparoscopic surgery on immune function, which was conducive to the postoperative recovery of patients.

Pain and postoperative complication

The pain of patients was assessed at 4 h and 6 h after surgery, and the proportion of patients with VAS score >3 compared with the control group was significantly lower ($P < .05$). The proportion of patients with BCS score <2 points was significantly lower in the combined group than in the control group by assessing the body condition of patients at extubation ($P < .05$), with no significant difference after an hour ($P > .05$). Postoperative complications such as nausea and vomiting, drowsiness, and respiratory depression occurred in both groups, and the incidence of postoperative adverse reactions was lower in the combined group than in the control group, with no significant difference between the two groups ($P > .05$). The main reason is that dezocine plays an important role in propofol sedation and postoperative pain management. Dezocine is similar to other opioids with a strong analgesic effect but has a long half-life and higher average blood concentration. The combination of propofol and dezocine has a better sedative and analgesic effect and longtime of pharmacodynamic effect, and it could reduce the

occurrence of postoperative adverse reactions. This synergy between propofol and dezocine underscores the potential for improved patient outcomes in laparoscopic procedures.

The statistical difference in postoperative adverse reactions is not reflected due to the small sample size in this study. The contributions of this study are as follows. Dezocine combined with propofol is an effective scheme to reduce the inflammatory response in patients undergoing laparoscopic surgery. Its introduction can promote the postoperative rehabilitation of patients and provide a new direction for the formulation and selection of subsequent anesthesia schemes.

To sum up, the present findings advocate for the combined use of dezocine and propofol in laparoscopic surgeries. This combination not only promises better postoperative recovery but also hints at the potential to redefine anesthesia strategies in the future.

CONCLUSION

In summary, the combined use of dezocine and propofol offers an effective anesthetic solution for laparoscopic surgeries. This combination not only facilitates quicker post-operative consciousness recovery and diminishes pain but also maintains high safety standards. These findings serve as a theoretical foundation for enhancing clinical anesthesia practices, especially in the context of laparoscopic surgeries.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

AUTHOR CONTRIBUTIONS

LiS and HZ conceptualized and executed the study. HZ and YZ were responsible for data collection, while FG and LeiS undertook the data analysis. LiS drafted the manuscript. All authors have reviewed and approved the final version of the manuscript.

FUNDING

This research received financial support from the Basic Scientific Research Business Expenses and Scientific Research Projects of Provincial Colleges and Universities in Heilongjiang Province under grant number 2021-KYYWF-0351.

REFERENCES

1. Buote NJ; Updates in Laparoscopy. *Vet Clin N Am-Small*. 2022;52(2):513-529. doi:10.1016/j.cysm.2021.12.007
2. Macías AA, Finneran JJ. Regional Anesthesia Techniques for Pain Management for Laparoscopic Surgery: a Review of the Current Literature. *Curr Pain Headache Rep*. 2022;26(1):33-42. doi:10.1007/s11916-022-01000-6
3. Chen Y, Liu S, Liang J, Zhu H. Evaluating the effect of anti-nausea drugs in IDO enzyme gene expression and preventing postoperative vomiting and nausea in patients undergoing general anesthesia: A Meta-analysis. *Cell Mol Biol*. 2022;68(9):186-191. doi:10.14715/cmb/2022.68.9.29
4. Lavonas EJ, Dezfulian C. Impact of the Opioid Epidemic. *Crit Care Clin*. 2020;36(4):753-769. doi:10.1016/j.ccc.2020.07.006
5. Dai G, Pei L, Duan F, et al. Safety and efficacy of remimazolam compared with propofol in induction of general anesthesia. *Minerva Anesthesiol*. 2021;87(10):1073-1079. doi:10.23736/S0375-9393.21.15517-8
6. Hu X, Luo B, Wu Q, et al. Effects of Dezocine and Sufentanil on Th1/Th2 Balance in Breast Cancer Patients Undergoing Surgery. [J]. *Drug Des Devel Ther*. 2021;15:4925-4938. doi:10.2147/DDDT.S326891
7. Zhao P, Cui Y, Sun L, Sun X. Inhalation of low-dose desflurane prevents the hemodynamic instability caused by target-controlled infusion of remifentanyl and propofol during laparoscopic gynecological surgery: A randomized controlled trial. *Exp Ther Med*. 2021;21(1):54. doi:10.3892/etm.2020.9486
8. Horvath B, Kloesel B, Todd MM, Cole DJ, Prielipp RC; The Evolution, Current Value, and Future of the American Society of Anesthesiologists Physical Status Classification System. The Evolution, Current Value, and Future of the American Society of Anesthesiologists Physical Status Classification System. *Anesthesiology*. 2021;135(5):904-919. doi:10.1097/ALN.0000000000003947
9. An G, Wang G, Zhao B, et al. Opioid-free anesthesia compared to opioid anesthesia for laparoscopic radical colectomy with pain threshold index monitoring: a randomized controlled study. *BMC Anesthesiol*. 2022;22(1):241. doi:10.1186/s12871-022-01747-w
10. Kaya C, Cebeci H, Tomak L, Ozbalki GS; KAYA. Prospective Randomized Trial Between Propofol Intravenous and Sevoflurane Inhaled Anesthesia on Cerebral Oximetry. *Bariatric Surg Pract Patient Care*. 2020;15(3):160-168. doi:10.1089/bari.2019.0038
11. Sujata N, Tobin R, Tamhankar A, Gautam G, Yattoo AH. A randomised trial to compare the increase in intracranial pressure as correlated with the optic nerve sheath diameter during propofol versus sevoflurane-maintained anesthesia in robot-assisted laparoscopic pelvic surgery. *J Robot Surg*. 2019;13(2):267-273. doi:10.1007/s11701-018-0849-7
12. Yang X, Wu X, Qin B, Wang Z, Zhu X, Huang S. Effects of Propofol anesthesia combined with remifentanyl on inflammation, stress response and immune function in children undergoing tonsil and adenoid surgery. *Cell Mol Biol*. 2022;68(2):87-93. doi:10.14715/cmb/2022.68.2.13

13. Pan T, Lei Y, Lei Z, et al; Clinical Study on Anesthesia with Remifentanyl and Propofol in Patients with High Hemodynamics. *Clinical Study on Anesthesia with Remifentanyl and Propofol in Patients with High Hemodynamics*. *Altern Ther Health Med*. 2022;28(4):44-49.
14. Söderström CM, Borregaard Medici R, Assadzadeh S, et al. Deep neuromuscular blockade and surgical conditions during laparoscopic ventral hernia repair: A randomised, blinded study. *Eur J Anaesthesiol*. 2018;35(11):876-882. doi:10.1097/EJA.0000000000000833
15. Kitamura S, Takechi K, Nishihara T, Konishi A, Takasaki Y, Yorozuya T. Effect of dexmedetomidine on intraocular pressure in patients undergoing robot-assisted laparoscopic radical prostatectomy under total intravenous anesthesia: A randomized, double blinded placebo controlled clinical trial. *J Clin Anesth*. 2018;49:30-35. doi:10.1016/j.jclinane.2018.06.006
16. Nam JH, Jang DK, Lee JK, Kang HW, Kim BW, Jang BI; Committees of Quality Management and Conscious Sedation of Korean Society of Gastrointestinal Endoscopy. Propofol Alone versus Propofol in Combination with Midazolam for Sedative Endoscopy in Patients with Paradoxical Reactions to Midazolam. [J]. *Clin Endosc*. 2022;55(2):234-239. doi:10.5946/ce.2021.126
17. Ollenschläger G, Jansen S, Schindler J, Rasokat H, Schrappe-Bäcker M, Roth E. Plasma amino acid pattern of patients with HIV infection. *Clin Chem*. 1988;34(9):1787-1789. doi:10.1093/clinchem/34.9.1781
18. Doi M, Morita K, Takeda J, Sakamoto A, Yamakage M, Suzuki T. Efficacy and safety of remimazolam versus propofol for general anesthesia: a multicenter, single-blind, randomized, parallel-group, phase IIb/III trial. [J]. *J Anesth*. 2020;34(4):543-553. doi:10.1007/s00540-020-02788-6
19. Bonavia A, Verbeek T, Adhikary S, et al. A randomized controlled trial comparing methohexital and propofol for induction in patients receiving angiotensin axis blockade. *Medicine (Baltimore)*. 2019;98(5):e14374. doi:10.1097/MD.00000000000014374
20. Kateliya R, Madhukant DM, Dubey M, Chandra S, Sahay N. Comparison of recovery profiles in target-controlled infusions (TCI) versus manually controlled infusions for total intravenous anesthesia (TIVA) in laparoscopic surgeries. A randomized controlled trial. [J]. *J Anaesthesiol Clin Pharmacol*. 2023;39(2):258-263. doi:10.4103/joacp.joacp_396_21
21. Subramaniam B, Shankar P, Shaei S, et al. Effect of Intravenous Acetaminophen vs Placebo Combined With Propofol or Dexmedetomidine on Postoperative Delirium Among Older Patients Following Cardiac Surgery: The DEXACET Randomized Clinical Trial. [J]. *JAMA*. 2019;321(7):686-696. doi:10.1001/jama.2019.0234