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Comparison of remimazolam versus propofol in combination with remifentanil in hysteroscopic surgery

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Abstract: Objective To compare the anesthesia effect and hemodynamics of remimazolam versus propofol in combination with remifentanil in hysteroscopic surgery. **Methods** A total of 60 patients who underwent elective hysteroscopic endometrial dissection due to abnormal uterine bleeding and endometrial thickening in Qingdao Municipal Hospital from April to December 2022 were randomly divided into observation group (n=30) and control group (n=30). Propofol combined with remifentanil for anesthesia induction and maintenance were given in the control group, and remimazolam combined with remifentanil for anesthesia induction and maintenance were given in the observation group. The hemodynamic indexes, anesthesia effect and adverse reactions of patients were compared between the two groups at the following 6 time points: before anesthesia induction (T_1), when inserting a laryngeal mask (T_2), 5 min before the start of surgery (T_3), immediately after the start of surgery (T_4), 5 min before removing the laryngeal mask (T_5), and immediately after removing the laryngeal mask (T_6). **Results** The mean arterial pressure (MAP) at T_2, T_3, T_4, T_5 and T_6 and heart rate (HR) at T_2 in the observation group were higher than those in the control group, with statistically significant differences (P<0.05). Compared with the control group, the observation group had a longer disappearance time of eyelash reflexes (P<0.05). There was no significant difference in the awakening time between the two groups (P>0.05). The incidences of injection pain (0 *vs* 56.67%, χ^2= 23.721) and hypotension (23.33% *vs* 56.67%, χ^2= 6.944) in the observation group were lower than those in the control group, with statistically significant differences(P<0.01). **Conclusion** Compared with propofol, the induction and maintenance of anesthesia with remimazolam combined with remifentanil during hysteroscopic surgery can reduce the impact on the hemodynamics of patients and reduce the incidence of adverse reactions.

Keywords: Remimazolam; Remifentanil; Propofol; Hysteroscopy; Hemodynamics

Background

Hysteroscopic surgery is one of the most common procedures used to diagnose and treat endometrial and other intrauterine diseases, and is characterized by short operating time, simple operation and mild stimulation. However, most procedures require anesthesia due to the intense pain caused by cervical dilation and uterine scraping [1-2]. Commonly used anesthesia drugs include propofol, sevoflurane, dexmedetomidine combined with opioids, paracervical block and local anesthesia [3-6]. Propofol combined with opioids remains the most common anesthesia methods for hysteroscopic surgery [7]. However, the incidence of injection pain caused by propofol is high in clinical practice. Propofol is also prone to cause respiratory and circulatory depression as the dose increases [8]. The safety and comfort of propofol in clinical use need to be further improved.

As a short-acting benzodiazepine, remimazolam has the advantages of rapid onset of action, short half-life, antagonism, complete awakening, and no injection pain, making it a modern, safe and effective anesthetic sedative [9-10]. Remifentanil is an ultra-short-acting opioid analgesic [11], which can be rapidly hydrolyzed into pharmacologically inactive metabolites by non-specific esterases in the blood and tissues. It has a short duration of action, rapid recovery, independence on hepatic or renal function, and no accumulation by continuous infusion, which is particularly suitable for anesthesia of short-term surgery [12]. Therefore, in this study, remimazolam and propofol were used in combination with remifentanil for hysteroscopic surgery to observe the effects on respiratory circulation, postoperative awakening time and relevant adverse reactions, and to assess the effectiveness and safety of clinical use of remimazolam, aiming to provide a safer, more comfortable and controllable anesthesia option for future hysteroscopic surgery.

1 Material and methods

1.1 General data

A total of 60 patients who underwent elective hysteroscopic endometrial dissection for abnormal uterine bleeding and endometrial thickening in Qingdao Municipal Hospital from April to December 2022 were selected as study subjects. The patients were divided into a control group and an observation group, with 30 cases in each group using the randomized numerical table method.

Control group: aged 18-70 (41.8±1.70) years old and body mass index (BMI) was 18-27 (23.46±0.73) kg/m^2. Observation group: aged 18-70 (41.5±1.96) years old and BMI was 18-27 (24.13±0.76) kg/m^2. There were no statistically significant differences in general characteristics between the two groups (P >0.05) **[Table1]**. All patients signed an informed consent form, and the study was reviewed and approved by the medical ethics committee of the hospital (2022Y No.055).

Tab. 1 Comparison of general data comparison of between two groups (n=30, $\bar{x}\pm s$)

Group	Age (years)	Height (cm)	Weight (kg)	BMI (kg/m^2)	Duration of operation (min)
Control group	41.80±9.29	162.67±5.07	61.83±9.54	23.46±3.99	23.53±9.81
Observation group	41.50±10.77	162.47±4.74	63.73±11.49	24.13±4.15	23.10±10.31
***t* value**	0.116	0.158	0.697	0.644	0.167
***P* value**	0.908	0.875	0.489	0.522	0.868

1.2 Criteria for inclusion and exclusion

Inclusion criteria: (1) patients with American Society of Anesthesiologists (ASA) grade I-II; (2) patients aged 18-70 years old; (3) those who met the indications for hysteroscopic surgical treatment.

Exclusion criteria: (1) patients with severe hypertension, diabetes mellitus and cardiac, pulmonary, hepatic and renal advanced diseases; (2) patients with psychiatric disorders or cognitive dysfunction; (3) patients with a history of hormone therapy, chemotherapy, radiotherapy and immune-assisted therapy; (4) patients with suspected or confirmed history of analgesic and sedative drug abuse and treatment; (5) patients with a history of allergy or contraindications to drugs used in this clinical study.

1.3 Grouping and methods

After the patient was admitted to the operating room, cardiac monitoring was routinely performed to monitor blood pressure, heart rate, and oxygen saturation.

(1) Control group: anesthesia was induced by propofol combined with remifentanil at an induction dose of 1.5-2 mg/kg of propofol [13-14] and 2 μg/kg of remifentanil. After achieving Modified Observer's Alertness/Sedation (MOAA/S) ⩽ 1, rocuronium bromide 0.3 mg/kg was given to the patients. A standard laryngeal mask was inserted on the patient until the lash reflex disappeared. No air leaks were auscultated, airway pressure was less than 20 mmHg, tidal volume was set at 6-8 mL/kg, with a respiratory rate of 12-16 breaths/min, maintaining end-tidal carbon dioxide pressure at 35-45 mmHg. Anesthesia maintenance utilizes propofol at 4-8 mg/(kg·h) and remifentanil at 0.15 μg/(kg·min). The pumping rate of sedative drugs was adjusted to maintain the patient's BIS value between 40 and 60.

(2) Observation group: anesthesia was induced by propofol combined with remifentanil at an induction dose of 1.5-2 mg/kg of propofol [14-15] and 2 μg/kg of remifentanil. After achieving Modified Observer's Alertness/Sedation (MOAA/S) ⩽1, rocuronium bromide 0.3 mg/kg was given to the patients. A standard laryngeal mask was inserted on the patient until the lash reflex disappeared. No air leaks were auscultated, airway pressure was lower than 20 mmHg, tidal volume was set at 6-8 mL/kg, respiratory rate was 12-16 breaths per minute, and partial pressure of carbon dioxide at the end of expiration was maintained at 35-45 mmHg. Anesthesia was maintained with 0.6-1.2 mg/(kg·h) remimazolam and 0.15 μg/(kg·min) remifentanil. The pumping rate of the sedative drugs was adjusted so that the patient's BIS value was maintained between 40 and 60.

Ten minutes before the operation, 1 g propacetamol injection was given intravenously for analgesic pretreatment. After the operation, the laryngeal mask was removed and the patient was sent to the post-anesthesia care unit after the recovery of spontaneous respiration. Adequate ephedrine was given to regulate blood pressure when MAP was below 65 mmHg, and atropine was given to regulate heart rate (HR) when HR was below 50 beats per minute.

1.4 Observation indexes

(1) Hemodynamic indexes: the HR and MAP of the two groups before anesthesia induction (T_1), when inserting a laryngeal mask (T_2), 5 min before the start of the operation (T_3), immediately after the start of the operation (T_4), 5 min before the removing the laryngeal mask (T_5), and immediately after removing the laryngeal mask (T_6).

(2) Anesthesia effect and quality of awakening: the time for disappearance of eyelash reflex and the awakening time in the two groups.

(3) The occurrence of perioperative adverse reactions in the two groups, such as nausea and vomiting, injection pain, hypotension, etc.

1.5 Statistical analysis

Data were processed using SPSS 25.0 software, and measurement data were expressed as $\bar{x}$ ±s, two-sample

t-test and repeated measures ANOVA were used. Count data were expressed as cases (%), and chi-square test and the adjusted chi-square test were used. $P < 0.05$ indicated a statistically significant difference.

2 Results

2.1 Comparison of changes in hemodynamic indexes

Compared with T_1, MAP and HR at T_2, T_3, T_4 and T_5 were reduced in both groups. MAP level at T_2, T_3, T_4, T_5 and T_6 and HR levels at T_2 were higher in the observation group than in the control group, and the differences were statistically significant ($P < 0.05$) **[Table 2-3]**.

Tab. 2 Comparison of MAP at different time points between two groups (*n*=30，mmHg，$\bar{x}\pm s$)

Group	MAP					
	T_1	T_2	T_3	T_4	T_5	T_6
Control group	97.27±12.62	62.67±7.52[a]	68.73±6.85[a]	68.50±7.23[a]	71.27±11.07[a]	85.90±11.64[a]
Observation group	97.17±14.54	70.30±10.68[ab]	72.77±8.19[ab]	77.13±11.33[ab]	81.83±11.93[ab]	96.53±13.37[b]
F / P_{group} value			10.782/<0.05			
F/ P_{time} value			145.034/<0.05			
F / $P_{interaction}$ value			4.262/<0.05			

Note: Compared with T_1 time, [a]$P<0.05$; compared with control group at the same time point, [b]$P<0.05$.

Tab. 3 Comparison of HR at different time points between two groups (*n*=30，beat/min，$\bar{x}\pm s$)

Group	HR					
	T_1	T_2	T_3	T_4	T_5	T_6
Control group	75.23±11.29	57.87±5.89[a]	58.77±7.70[a]	59.53±7.68[a]	60.30±8.29[a]	71.73±7.74
Observation group	78.17±13.36	64.67±9.11[ab]	61.77±7.98[a]	62.10±8.00[a]	63.00±10.44[a]	76.10±9.24
F / P_{group} value			3.721/>0.05			
F/ P_{time} value			104.249/<0.05			
F/ $P_{interaction}$ value			1.258/>0.05			

Note: Compared with T_1 time, [a]$P<0.05$; compared with control group at the same time point, [b]$P<0.05$.

2.2 Comparison of anesthesia effect and quality of awakening

The time for the disappearance of the eyelash reflex in the observation group was longer than that in the control group, and the difference was statistically significant ($P < 0.05$). There was no statistically significant difference in the awakening time between two groups ($P > 0.05$) **[Table 4].**

Tab. 4 Comparison of disappearance time of the eyelash reflex and duration of awakening between two groups ($\bar{x}\pm s$)

Group	Case	Disappearance time of the eyelash reflex(s)	Duration of awakening (s)
Control group	30	106.00±11.48	490.83±121.76
Observation group	30	113.73±11.85	450.10±111.83
t value		2.568	1.349
P value		0.013	0.182

2.3 Comparison of the incidence of perioperative adverse reactions

Compared with the control group, the incidence of injection pain and hypotension in patients in the observation group were lower than those in the control group, and the differences were statistically significant ($P < 0.01$) **[Table 5].**

Tab. 5 Comparison of perioperative adverse effects between two groups [case(%)]

Group	Case	Injection pain	Bradycardia	Hypotension	Nausea and vomiting
Control group	30	17 (56.67)	6 (20.00)	17 (56.67）	3 (10.00)
Observation group	30	0	4 (13.33)	7 (23.33)	2 (6.67)
χ^2 value		23.721	0.480	6.944	0.000
P value		<0.001	0.488	0.008	1.000

3 Discussion

Hysteroscopic surgery is one of the most common minimally invasive gynecologic surgeries in clinical practice, but the different degrees of pain and discomfort caused to the patient by the dilatation of

the cervical canal and stimuli such as pulling of the tissues during the surgical procedures can seriously affect the course of the procedure. Therefore, a more comfortable, safe, and effective anesthesia method is essential for the smooth progress of hysteroscopic surgery. This study discusses the application of remimazolam and propofol in combination with remifentanil in hysteroscopic surgery.

This study showed that both groups' MAP and HR levels were significantly lower after anesthesia. However, the levels in the observation group were significantly higher than the control group. This is because propofol decreases HR and blood pressure more significantly by inhibiting the excitation in the cardiovascular system and damaging the circulatory system in case of drug overdose. Doğanay *et al.* [15] showed that propofol can dilate blood vessels and cause hypotension by directly inhibiting sympathetic nervous system activity and myocardial contractility. At the same time, propofol can interact with calcium channel proteins directly and inhibit the influx of calcium ions by blocking L-type calcium channels, thus delaying atrioventricular (AV) node conduction, even leading to complete AV block. In contrast, remimazolam has a weak inhibitory effect on the respiratory and circulatory systems, which leads to an increase in oxygen saturation level and HR and a decrease in the hemodynamic effects [16].

The results also showed that the disappearance time of eyelash reflexes was longer in the observation group than in the control group. However, the difference in the time of awakening between the two groups was not statistically significant. In a study by Chen *et al.* [17] comparing remimazolam and propofol, the onset of action of remimazolam was significantly slower than that of propofol. However, the time of awakening in the remimazolam group was similar to or faster than that of propofol, suggesting that the distribution of remimazolam may be slower. Its metabolism may be faster than that of propofol.

No serious adverse events occurred in this study, and the incidence of injection pain and hypotension was lower in the observation group than in the control group. Injection pain is one of the most common adverse effects of propofol, which is mainly caused by mediating the off-target interactions of transient receptor potential receptors TRPA1 and TRPV1 on sensory neurons [18]. It has been shown that propofol is more prone to adverse reactions, such as injection site pain, hypotension, dyspnea, etc., during the use of propofol, and the incidence of adverse reactions increases with the increase in the dosage of propofol [19]. Although remimazolam has the same sedative effect as propofol, it can effectively avoid injection pain and improve patient comfort. In a multicenter phase III clinical trial in China, 384 eligible patients undergoing colonoscopy were randomized into the remimazolam and propofol groups. The results showed that patients in the remimazolam group also had a lower hypotension incidence than propofol [17].

Remimazolam is an ultrashort-acting gamma-aminobutyric acid receptor (GABA receptor) agonist that inhibits neuronal activity by opening chloride channels, increasing inward chloride flow, and inducing hyperpolarization of neuronal synaptic cells, resulting in sedative, hypnotic, and amnestic effects [20-21]. At the same time, remimazolam has the advantages of a rapid onset of action, a short elimination half-life, and drug metabolism that is not dependent on hepatic or renal function [22]. Moreover, the sedative effects of remimazolam can be inhibited by pretreatment with flumazenil, an antagonist of benzodiazepine receptors, implying that remimazolam has better effects than propofol [18,23]. Freyer *et al.* [24] showed that the metabolism of remimazolam was stable during a prolonged (5 days) continuous infusion and that the use of remimazolam had no deleterious effects on either hepatocyte integrity or metabolic activity, all of which are characteristics that allow for better controllability and safety.

In conclusion, compared with propofol, the use of remimazolam combined with remifentanil for induction and maintenance of anesthesia in hysteroscopic surgery can alleviate the impact on patients' hemodynamics, reduce the incidence of adverse reactions, and improve the safety and comfort of anesthesia in the perioperative period of hysteroscopic surgery. However, this study has some limitations, and further research is needed to expand the sample size.

Conflict of interest The authors report no conflict of interest

References

[1] Yin Q, Sun SQ, Wu XF, et al. Effect and perioperative stress response of hysteroscopy combined with laparoscopy in the treatment of type III Caesarean scar pregnancy[J]. Chin J Hum Sex, 2022, 31(1): 113-116. **[In Chinese]**

[2] Sutton C. Hysteroscopic surgery[J]. Best Pract Res Clin Obstet Gynaecol, 2006, 20(1): 105-137.

[3] Bingol Tanriverdi T, Koceroglu I, Devrim S, et al. Comparison of sedation with dexmedetomidine vs propofol during hysteroscopic surgery: single-centre randomized controlled trial[J]. J Clin Pharm Ther, 2019, 44(2): 312-317.

[4] Moharram EE, El Attar AM, Kamel MA. The impact of anesthesia on hemodynamic and volume changes in operative hysteroscopy: a bioimpedance randomized study[J]. J Clin Anesth, 2017, 38: 59-67.

[5] Cooper NAM, Khan KS, Clark TJ. Local anaesthesia for pain control during outpatient hysteroscopy: systematic review and meta-analysis[J]. BMJ, 2010, 340: c1130.

[6] Riemma G, Schiattarella A, Colacurci N, et al. Pharmacological and non-pharmacological pain relief for office hysteroscopy: an up-to-date review[J]. Climacteric, 2020, 23(4): 376-383.

[7] Yu J, Xiang B, Song Y, et al. ED50 of propofol in combination with low-dose sufentanil for intravenous anaesthesia in hysteroscopy[J]. Basic Clin

Pharmacol Toxicol, 2019, 125(5): 460-465.
[8]Lundström S, Twycross R, Mihalyo M, et al. Propofol[J].J Pain Symptom Manage，2010，40(3):466-470.
[9] Xie TH,Su G,Zhang WW,et al.Sedative effect of remimazolam used during and after mitral valve replacement[J]. J Clin Pract Diagn Ther, 2023,37(4):422-425. **[In Chinese]**
[10] Sneyd JR, Rigby-Jones AE. Remimazolam for anaesthesia or sedation[J].Curr Opin Anaesthesiol，2020，33(4):506-511.
[11] Liu L, Liang SR, Pan ZL,et al. Huan-hang. Intravenous optimization effect of dexmedetomidine combined with low dose remifentanil on elderly patients undergoing hip arthroplasty[J]. Chinese Journal of General Practice, 2022, 20(4): 606-610. **[In Chinese]**
[12] Zhu RY, Zhu XL, Wu SX. Effects of low-dose ketamine combined with remifentanil anesthesia on hemodynamics and pain medium level in patients undergoing myomectomy[J]. China Med, 2021, 16(7): 1074-1077. **[In Chinese]**
[13] Sheng XY, Liang Y, Yang XY, et al. Safety, pharmacokinetic and pharmacodynamic properties of single ascending dose and continuous infusion of remimazolam besylate in healthy Chinese volunteers[J]. Eur J Clin Pharmacol, 2020, 76(3): 383-391.
[14] Doi M, Morita K, Takeda J, et al. 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.
[15] Doğanay F, Ak R, Alışkan H, et al. The effects of intravenous lipid emulsion therapy in the prevention of depressive effects of propofol on cardiovascular and respiratory systems: an experimental animal study[J]. Medicina (Kaunas) 2018, 55(1): 1.
[16] Hu QH, Zhou WJ, Hou MY, et al. Preliminary study on the application of ramazolam benzenesulfonic acid in painless gastroenteroscopy in obese patients[J]. Drug Eval, 2020, 17(24): 55-58.
[17] Chen SH, Wang J, Xu XH, et al. The efficacy and safety of remimazolam tosylate versus propofol in patients undergoing colonoscopy: a multicentered, randomized, positive-controlled, phase III clinical trial[J]. Am J Transl Res, 2020, 12(8): 4594-4603.
[18] Kilpatrick GJ. Remimazolam: non-clinical and clinical profile of a new sedative/anesthetic agent[J]. Front Pharmacol, 2021, 12: 690875. **[In Chinese]**
[19] Zhao J, Lou LL. Application of remizolam and propofol combined with sufentanil in painless gastroscopy of patients[J]. Chin Remedies Clin, 2021, 21(12): 2143-2144.
[20] Yang YC,Shuai SC,Han J,et al.Sedative effect of low-dose remidazolam combined with propofol in elderly patients received gastrointestinal endoscopy[J].Chin J Clin Res, 2023,36(8):1205-1209. [In Chinese]
[21] Wei L, Li JQ, Hong TH, et al. Safety and efficacy of different doses of remimazolam in hysteroscopic surgery[J]. J Clin Anesthesiol, 2022, 38(4): 346-350.
[22] Schüttler J, Eisenried A, Lerch M, et al. Pharmacokinetics and pharmacodynamics of remimazolam (CNS 7056) after continuous infusion in healthy male volunteers: part I. pharmacokinetics and clinical pharmacodynamics[J]. Anesthesiology, 2020, 132(4): 636-651.
[23] Chen X, Sang NE, Song KC, et al. Psychomotor recovery following remimazolam-induced sedation and the effectiveness of flumazenil as an antidote[J]. Clin Ther, 2020, 42(4): 614-624.
[24] Freyer N, Knöspel F, Damm G, et al. Metabolism of remimazolam in primary human hepatocytes during continuous long-term infusion in a 3-D bioreactor system[J]. Drug Des Dev Ther, 2019, 13: 1033-1047.

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·论　著·

瑞马唑仑与丙泊酚分别联合瑞芬太尼在宫腔镜手术中的比较

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摘要：目的　比较瑞马唑仑与丙泊酚分别联合瑞芬太尼在宫腔镜手术中的麻醉效果和血流动力学情况。**方法**　选取 2022 年 4 月至 12 月在青岛市市立医院因异常子宫出血、子宫内膜增厚择期行宫腔镜下子宫内膜剥离术的 60 例患者作为研究对象，随机分为观察组（$n=30$）和对照组（$n=30$）。对照组给予丙泊酚联合瑞芬太尼进行麻醉诱导与维持，观察组给予瑞马唑仑联合瑞芬太尼进行麻醉诱导与维持。比较两组患者麻醉诱导前（T_1）、置入喉罩时（T_2）、手术开始前 5 min（T_3）、手术开始即刻（T_4）、拔出喉罩前 5 min（T_5）、拔出喉罩后即刻（T_6）的血流动力学指标、麻醉效果及不良反应发生情况。**结果**　观察组血流动力学指标平均动脉压在 T_2、T_3、T_4、T_5、T_6 时刻和心率在 T_2 时刻均高于对照组，差异有统计学意义（$P<0.01$）。观察组患者睫毛反射消失时间长于对照组（$P<0.05$）；两组苏醒时间差异无统计学意义（$P>0.05$）。观察组注射痛（0 *vs* 56.67%，$\chi^2=23.721$）、低血压发生率（23.33% *vs* 56.67%，$\chi^2=6.944$）低于对照组，差异有统计学意义（$P<0.01$）。**结论**　与丙泊酚相比，宫腔镜手术中使用瑞马唑仑联合瑞芬太尼进行麻醉诱导与维持，能够减轻对患者血流动力学的影响，降低不良反应发生率。

关键词：瑞马唑仑；瑞芬太尼；丙泊酚；宫腔镜；血流动力学

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Abstract: Objective　To compare the anesthesia effect and hemodynamics of remimazolam versus propofol in combination with remifentanil in hysteroscopic surgery. **Methods**　A total of 60 patients who underwent elective hysteroscopic endometrial dissection due to abnormal uterine bleeding and endometrial thickening in Qingdao Municipal Hospital from April to December 2022 were randomly divided into observation group ($n=30$) and control group ($n=30$). Propofol combined with remifentanil for anesthesia induction and maintenance was given in the control group, and remimazolam combined with remifentanil for anesthesia induction and maintenance was given in the observation group. The hemodynamic indexes, anesthesia effect and adverse reactions of patients were compared between the two groups at the following 6 time points: before anesthesia induction (T_1), when inserting a laryngeal mask (T_2), 5 min before the start of surgery (T_3), immediately after the start of surgery (T_4), 5 min before removing the laryngeal mask (T_5), and immediately after removing the laryngeal mask (T_6). **Results**　The mean arterial pressure at T_2, T_3, T_4, T_5 and T_6 and heart rate at T_2 in the observation group were higher than those in the control group, with statistically significant differences ($P<0.05$). Compared with the control group, the observation group had a longer time for disappearance of eyelash reflexes ($P<0.05$). There was no significant difference in the anesthesia recovery time between the two groups ($P>0.05$). The incidences of injection pain (0 *vs* 56.67%, $\chi^2=23.721$) and hypotension (23.33% *vs* 56.67%, $\chi^2=$

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6.944) in the observation group was lower than that in the control group, with statistically significant differences (P< 0.01). **Conclusion** Compared with propofol, the induction and maintenance of anesthesia with remimazolam combined with remifentanil during hysteroscopic surgery can reduce the impact on the hemodynamics of patients and reduce the incidence of adverse reactions.

Keywords: Remimazolam; Remifentanil; Propofol; Hysteroscopy; Hemodynamics

宫腔镜手术是诊断、治疗子宫内膜和其他宫内疾病常见的手术之一，具有手术时间短、操作相对简单和刺激相对较轻等特点。手术时因患者无法耐受宫颈扩张和刮宫时的剧烈疼痛[1-2]，大多数需要麻醉。常用麻醉药物和方法包括丙泊酚、七氟烷或右美托咪定联合阿片类药物、宫颈旁阻滞和局部麻醉等[3-6]。其中，丙泊酚与阿片类药物联用仍是宫腔镜手术最常见的麻醉方法[7]。但临床工作中，丙泊酚引起注射痛发生率高，随剂量增加，其还易引起呼吸、循环抑制[8]，临床使用安全性及舒适性有待进一步改善。

瑞马唑仑作为短效苯二氮䓬类药物，具有起效快、半衰期短、可拮抗、苏醒完全，且无注射痛的优点，是一种新型、安全有效的麻醉镇静药物[9-10]。而瑞芬太尼是一种超短效阿片类镇痛药[11]，可被存在于血液和组织中的非特异酯酶迅速水解为无药理活性的代谢产物，因此作用时间短，恢复迅速，代谢不依赖肝肾功能，且持续输注无蓄积，特别适合短时间手术的麻醉[12]。因此本研究采用瑞马唑仑和丙泊酚两种药物分别联合瑞芬太尼用于宫腔镜手术，观察其对呼吸循环、术后苏醒时间及相关不良反应的影响，评估瑞马唑仑临床使用的有效性和安全性，为日后宫腔镜手术提供一种更为安全、舒适、可控的麻醉方案。

1　资料与方法

1.1　一般资料　选取 2022 年 4 月至 12 月在青岛市市立医院因异常子宫出血、子宫内膜增厚择期行宫腔镜下子宫内膜剥离术的患者 60 例作为研究对象。采用随机数字表法，将患者分为对照组和观察组，各 30 例。对照组：年龄 18～70（41.80±9.29）岁；身体质量指数（BMI）为 18～27（23.46±3.99）kg/m^2。观察组：年龄 18～70（41.50±10.77）岁；BMI 为 18～27（24.13±4.15）kg/m^2。两组患者一般资料比较差异无统计学意义（P>0.05）。见表 1。所有患者均签署知情同意书，且本研究通过医院医学伦理委员审核批准［2022 临审字第 055 号］。

1.2　纳入与排除标准　纳入标准：（1）美国麻醉医师协会（American Society of Anesthesiologists，ASA）分级为Ⅰ～Ⅱ级的患者；（2）年龄 18～70 岁的患者；（3）符合宫腔镜手术治疗指征者。排除标准：（1）合并严重高血压，糖尿病以及心、肺、肝、肾等疾病者；（2）有精神疾病或认知功能障碍者；（3）有激素、放化疗及免疫辅助治疗史；（4）怀疑或确有镇痛、镇静类药物滥用病史及治疗的患者；（5）对本临床研究所使用的药物有过敏史或禁忌证的患者。

表 1　两组患者一般资料比较　（n=30，$\bar{x}\pm s$）

Tab. 1　Comparison of general data between two groups　（n=30，$\bar{x}\pm s$）

组别	年龄（岁）	身高（cm）	体重（kg）	BMI（kg/m^2）	手术时长（min）
对照组	41.80±9.29	162.67±5.07	61.83±9.54	23.46±3.99	23.53±9.81
观察组	41.50±10.77	162.47±4.74	63.73±11.49	24.13±4.15	23.10±10.31
t 值	0.116	0.158	0.697	0.644	0.167
P 值	0.908	0.875	0.489	0.522	0.868

1.3　分组与方法　患者入手术室后，常规予以心电监护，监测血压、心率（HR）、血氧饱和度。（1）对照组：采用丙泊酚联合瑞芬太尼进行麻醉诱导，诱导剂量为丙泊酚 1.5～2 mg/kg[13-14]、瑞芬太尼 2 μg/kg，患者改良警觉/镇静评分（MOAA/S）≤1 分后给予罗库溴铵0.3 mg/kg，当睫毛反射消失后置入标准型喉罩，听诊无漏气，气道压低于 20 mmHg，设置潮气量 6～8 mL/kg，呼吸频率 12～16 次/min，维持呼气末二氧化碳分压 35～45 mmHg。麻醉维持采用丙泊酚 4～8 mg/（kg·h）与瑞芬太尼0.15 μg/（kg·min），调整镇静药物泵注速度，使患者的脑电双频指数（BIS）值维持在 40～60。（2）观察组：采用瑞马唑仑联合瑞芬太尼进行麻醉诱导，诱导剂量为瑞马唑仑 0.2 mg/kg[13-14]、瑞芬太尼 2 μg/kg，患者 MOAA/S≤1 分后给予罗库溴铵 0.3 mg/kg，当睫毛反射消失后置入标准型喉罩，听诊无漏气，气道压低于 20 mmHg，设置潮气量 6～8 mL/kg，呼吸频率 12～16 次/min，维持呼气末二氧化碳分压 35～45 mmHg。麻醉维持采用瑞马唑仑 0.6～1.2 mg/（kg·h）与瑞芬太尼 0.15 μg/（kg·min），调整镇静药物泵注速度，使患者的 BIS 值维持在 40～60。手术开始前 10 min 予丙帕他莫注射液 1 g 静脉滴注进行镇痛预处理，术毕待恢复自主呼吸后拔出喉罩并送至麻醉复苏室。当平均动脉压（MAP）低于65 mmHg 时，给予适量麻黄碱调节血压；HR 低于 50 次/min 时，给予适量阿托品调节 HR。

1.4　观察指标　（1）血流动力学指标：对比两组患者麻醉诱导前（T_1）、置入喉罩时（T_2）、手术开始前 5 min（T_3）、手术开始即刻（T_4）、拔出喉罩前 5 min（T_5）、拔出喉罩后即刻（T_6）的 HR、MAP。（2）麻醉效果及苏醒质量：比较两组患者的睫毛反射消失时间和麻醉苏醒时间。（3）比较两组患者围术期不良反应发生情况，如恶心呕吐、注射痛、低血压等。

1.5　统计学方法　使用 SPSS 25.0 软件处理数据。计量资料以 $\bar{x}\pm s$ 表示，两组间比较采用成组 t 检验；两组多个时点的比较采用两因素重复测量方差分析，多重比较采用 LSD-t 检验；计数资料以例（%）表示，组间比较采用 χ^2 检验和校正 χ^2 检验。$P<0.05$ 为差异有统计学意义。

2　结　果

2.1　血流动力学指标变化比较　与 T_1 相比，两组患者 T_2、T_3、T_4、T_5 时的 MAP、HR 均降低，且观察组患者 MAP 在 T_2、T_3、T_4、T_5、T_6 时和 HR 在 T_2 时均高于对照组，差异有统计学意义（$P<0.05$）。见表 2、表 3。

2.2　麻醉效果及苏醒质量比较　观察组患者睫毛反射消失时间长于对照组（$P<0.05$）。两组患者苏醒时间差异无统计学意义（$P>0.05$）。见表 4。

2.3　围术期不良反应发生情况比较　与对照组相比较，观察组患者注射痛、低血压发生率低于对照组，差异有统计学意义（$P<0.01$）。见表 5。

表 2　两组患者不同时间点的 MAP 比较　（$n=30$，mmHg，$\bar{x}\pm s$）

Tab. 2　Comparison of MAP at different time points between two groups　（$n=30$，mmHg，$\bar{x}\pm s$）

组别	MAP					
	T_1	T_2	T_3	T_4	T_5	T_6
对照组	97.27±12.62	62.67±7.52[a]	68.73±6.85[a]	68.50±7.23[a]	71.27±11.07[a]	85.90±11.64[a]
观察组	97.17±14.54	70.30±10.68[ab]	72.77±8.19[ab]	77.13±11.33[ab]	81.83±11.93[ab]	96.53±13.37[b]
$F_{组间}/P_{组间}$ 值	10.782/<0.05					
$F_{时间}/P_{时间}$ 值	145.034/<0.05					
$F_{交互}/P_{交互}$ 值	4.262/<0.05					

注：与 T_1 时比较，[a]$P<0.05$；与同时点对照组比较，[b]$P<0.05$。

表 3　两组患者不同时间点的 HR 比较　（$n=30$，次/min，$\bar{x}\pm s$）

Tab. 3　Comparison of HR at different time points between two groups　（$n=30$，beat/min，$\bar{x}\pm s$）

组别	HR					
	T_1	T_2	T_3	T_4	T_5	T_6
对照组	75.23±11.29	57.87±5.89[a]	58.77±7.70[a]	59.53±7.68[a]	60.30±8.29[a]	71.73±7.74
观察组	78.17±13.36	64.67±9.11[ab]	61.77±7.98[a]	62.10±8.00[a]	63.00±10.44[a]	76.10±9.24
$F_{组间}/P_{组间}$ 值	3.721/>0.05					
$F_{时间}/P_{时间}$ 值	104.249/<0.05					
$F_{交互}/P_{交互}$ 值	1.258/>0.05					

注：与 T_1 时比较，[a]$P<0.05$；与同时点对照组比较，[b]$P<0.05$。

表 4　两组患者的睫毛反射消失时间和麻醉苏醒时间比较　（$\bar{x}\pm s$）

Tab. 4　Comparison of the eyelash disapperance time and anesthesia recovery time between two groups　（$\bar{x}\pm s$）

组别	例数	睫毛反射消失时间（s）	苏醒时间（s）
对照组	30	106.00±11.48	490.83±121.76
观察组	30	113.73±11.85	450.10±111.83
t 值		2.568	1.349
P 值		0.013	0.182

表 5　两组患者围术期不良反应比较　［例（%）］

Tab. 5　Comparison of perioperative adverse effects between two groups　［case（%）］

组别	例数	注射痛	心动过缓	低血压	恶心呕吐
对照组	30	17（56.67）	6（20.00）	17（56.67）	3（10.00）
观察组	30	0	4（13.33）	7（23.33）	2（6.67）
χ^2 值		23.721	0.480	6.944	0.000
P 值		<0.001	0.488	0.008	1.000

3　讨　论

宫腔镜手术是临床工作中最常见的一种妇科微创手术，但手术操作过程中宫颈管扩张以及组织牵拉等刺激会给患者带来不同程度的疼痛和不适感，严重影响手术的进程。因此，更为舒适、安全、有效的麻醉方法对宫腔镜手术的顺利进行至关重要。本研究对瑞马唑仑与丙泊酚分别联合瑞芬太尼在宫腔镜手术中的应用进行讨论。

本研究结果显示，两组患者麻醉后的 MAP、HR 水平明显降低，但观察组明显高于对照组，是由于丙泊酚通过抑制心血管系统兴奋，使 HR、血压等降低更显著，且过量使用时会对循环系统造成影响。Doğanay 等[15]研究表明，丙泊酚可以通过直接抑制交感

神经活动和心肌收缩力,从而舒张血管,引起低血压。同时,丙泊酚还可以直接作用于钙通道蛋白,通过阻滞 L 型钙通道,抑制钙离子的流入,延迟房室结的传导,甚至导致完全性房室传导阻滞。而瑞马唑仑对呼吸、循环系统抑制作用较小,可使血氧饱和度提升,提高 HR,降低对血流动力学的影响[16]。

本研究结果还显示,观察组患者睫毛反射消失时间长于对照组,但两组患者苏醒时间差异无统计学意义。Chen 等[17]的研究中,瑞马唑仑组的起效时间明显慢于丙泊酚,但瑞马唑仑组的苏醒时间与丙泊酚相似或更快,表明瑞马唑仑的分布速度可能比丙泊酚更慢,其代谢速度可能比丙泊酚更快。

本研究结果示,两组患者均未发生严重不良反应事件,且观察组的注射痛、低血压发生率低于对照组。注射痛是丙泊酚最为常见的不良反应,主要是通过介导感觉神经元上的瞬时受体电位受体 TRPA1 和 TRPV1 的非靶向互相作用而产生[18]。丙泊酚在使用过程中较易发生注射部位疼痛、低血压、呼吸困难等不良反应,且随着用量的增加,其发生率也随之升高[19]。而瑞马唑仑拥有与丙泊酚相同的镇静作用,却可以有效避免注射痛,提高患者的舒适度。我国一项多中心Ⅲ期临床试验中,384 例结肠镜检查患者麻醉结果表明,与丙泊酚相比,瑞马唑仑组患者的低血压发生率更低[17]。

瑞马唑仑是一种超短效的 γ-氨基丁酸受体激动剂,可通过开放氯离子通道,增加氯离子内流,引起神经突触细胞超极化而抑制神经元活动,从而产生镇静、催眠和遗忘作用[20-21]。同时其具有起效快、消除半衰期短、药物代谢不依赖肝肾功能的优点[22];此外,通过苯二氮䓬类受体拮抗剂氟马西尼的预处理,瑞马唑仑的镇静作用可以被抑制,表明瑞马唑仑优于丙泊酚[8,23]。Freyer 等[24]研究表明,在长期(5 d)连续输注期间,瑞马唑仑的代谢稳定,其使用对肝细胞的完整性和代谢活性都未产生有害影响,这些特点都使其具有更好的可控性和安全性。

综上所述,与丙泊酚相比,宫腔镜手术中使用瑞马唑仑联合瑞芬太尼进行麻醉诱导与维持,能够减轻对患者血流动力学的影响,降低不良反应发生率,提高宫腔镜手术围术期的麻醉安全性与舒适性。但本研究也存在局限性,需要扩大样本量进一步探讨。

利益冲突　无

参考文献

[1] 殷倩,孙时清,吴晓风,等.宫腹腔镜联合手术与腹腔镜手术治疗Ⅲ型剖宫产瘢痕妊娠的效果及围术期应激反应分析[J].中国性科学,2022,31(1):113-116.
Yin Q, Sun SQ, Wu XF, et al. Effect and perioperative stress response of hysteroscopy combined with laparoscopy in the treatment of type Ⅲ Caesarean scar pregnancy[J]. Chin J Hum Sex, 2022, 31(1): 113-116.

[2] Sutton C. Hysteroscopic surgery[J]. Best Pract Res Clin Obstet Gynaecol, 2006, 20(1): 105-137.

[3] Bingol Tanriverdi T, Koceroglu I, Devrim S, et al. Comparison of sedation with dexmedetomidine vs propofol during hysteroscopic surgery: single-centre randomized controlled trial[J]. J Clin Pharm Ther, 2019, 44(2): 312-317.

[4] Moharram EE, El Attar AM, Kamel MA. The impact of anesthesia on hemodynamic and volume changes in operative hysteroscopy: a bioimpedance randomized study[J]. J Clin Anesth, 2017, 38: 59-67.

[5] Cooper NAM, Khan KS, Clark TJ. Local anaesthesia for pain control during outpatient hysteroscopy: systematic review and meta-analysis[J]. BMJ, 2010, 340: c1130.

[6] Riemma G, Schiattarella A, Colacurci N, et al. Pharmacological and non-pharmacological pain relief for office hysteroscopy: an up-to-date review[J]. Climacteric, 2020, 23(4): 376-383.

[7] Yu J, Xiang B, Song Y, et al. ED50 of propofol in combination with low-dose sufentanil for intravenous anaesthesia in hysteroscopy[J]. Basic Clin Pharmacol Toxicol, 2019, 125(5): 460-465.

[8] Lundström S, Twycross R, Mihalyo M, et al. Propofol[J].J Pain Symptom Manage,2010,40(3):466-470.

[9] 谢添华,苏刚,张伟卫,等.行二尖瓣置换术患者术中及术后应用瑞马唑仑镇静效果观察[J].中华实用诊断与治疗杂志,2023,37(4):422-425.
Xie TH, Su G, Zhang WW, et al. Sedative effect of remimazolam used during and after mitral valve replacement[J]. J Clin Pract Diagn Ther, 2023, 37(4): 422-425.

[10] Sneyd JR, Rigby-Jones AE. Remimazolam for anaesthesia or sedation[J].Curr Opin Anaesthesiol,2020,33(4):506-511.

[11] 刘卢,梁苏荣,潘在礼,等.右美托咪定复合小剂量瑞芬太尼在老年患者髋关节置换术中的静脉优化效应[J].中华全科医学,2022,20(4):606-610.
Liu L, Liang SR, Pan ZL, et al. Huan-hang. Intravenous optimization effect of dexmedetomidine combined with low dose remifentanil on elderly patients undergoing hip arthroplasty[J]. Chinese Journal of General Practice, 2022, 20(4): 606-610.

[12] 李璐宏,罗艳.术中瑞芬太尼持续泵注对胃肠术后镇痛的影响[J].上海交通大学学报(医学版),2021,41(4):509-513.
Li LH, Luo Y. Impact of intraoperative continuous pumping of remifentanil on postoperative analgesia after gastrointestinal surgery[J]. J Shanghai Jiao Tong Univ Med Sci, 2021, 41(4): 509-513.

[13] Sheng XY, Liang Y, Yang XY, et al. Safety, pharmacokinetic and pharmacodynamic properties of single ascending dose and continuous infusion of remimazolam besylate in healthy Chinese volunteers[J]. Eur J Clin Pharmacol, 2020, 76(3): 383-391.

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者胃肠镜诊疗中的镇静效果[J].中国临床研究,2023,36(8):1205.
Yang YC, Shuai SC, Han J, et al.Sedative effect of low-dose remidazolam combined with propofol in elderly patients received gastrointestinal endoscopy[J]. Chin J Clin Res, 2023, 36(8): 1205.
[12] Yamamoto T, Kurabe M, Kamiya Y. Re-sleeping after reversal of remimazolam by flumazenil[J]. J Anesth, 2021, 35(2): 322.
[13] Masui K. Caution!! Reappearance of remimazolam effect after a flumazenil bolus: a larger bolus of flumazenil and a lower total remimazolam clearance are higher risks[J]. J Anesth, 2023, 37(1): 1-5.
[14] Vanlinthout LEH, Mesfin SH, Hens N, et al. A systematic review and meta-regression analysis of mivacurium for tracheal intubation [J]. Anaesthesia, 2014, 69(12): 1377-1387.
[15] 丰浩荣,廖强,王成寿,等.全麻患者米库氯铵组胺释放程度的评价[J].中华麻醉学杂志,2014, 34(8): 953-955.
Feng HR, Liao Q, Wang CS, et al. Evaluation of mivacurium-induced release of histamine in patients undergoing general anesthesia [J]. Chin J Anesthesiol, 2014, 34(8): 953-955.
[16] Nakanishi T, Sento Y, Kamimura Y, et al. Remimazolam for induction of anesthesia in elderly patients with severe aortic stenosis: a prospective, observational pilot study[J]. BMC Anesthesiol, 2021, 21(1): 306.
[17] Doi M, Hirata N, Suzuki T, et al. Safety and efficacy of remimazolam in induction and maintenance of general anesthesia in high-risk surgical patients (ASA Class Ⅲ): results of a multicenter, randomized, double-blind, parallel-group comparative trial[J]. J Anesth, 2020, 34(4): 491-501.
[18] 姚文壮,刘苏漫,贺小玲,等.瑞马唑仑对老年患者腹腔镜术后苏醒质量的影响[J].临床麻醉学杂志,2023,39(10):1031-1035.
Yao WZ, Liu SM, He XL, et al. Effects of remimazolam on awakening quality in elderly patients undergoing laparoscopic surgery[J]. J Clin Anesthesiol, 2023, 39(10): 1031-1035.
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[14] Doi M, Morita K, Takeda J, et al. 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.
[15] Doğanay F, Ak R, Alışkan H, et al. The effects of intravenous lipid emulsion therapy in the prevention of depressive effects of propofol on cardiovascular and respiratory systems: an experimental animal study[J]. Medicina (Kaunas), 2018, 55(1): 1.
[16] 胡千华,周文娟,侯鸣宇,等.静脉注射苯磺酸瑞马唑仑在肥胖患者无痛胃肠镜检查中的应用分析[J].药品评价,2020,17(24):55-58.
Hu QH, Zhou WJ, Hou MY, et al. Preliminary study on the application of ramazolam benzenesulfonic acid in painless gastroenteroscopy in obese patients[J]. Drug Eval, 2020, 17(24): 55-58.
[17] Chen SH, Wang J, Xu XH, et al. The efficacy and safety of remimazolam tosylate versus propofol in patients undergoing colonoscopy: a multicentered, randomized, positive-controlled, phase Ⅲ clinical trial[J]. Am J Transl Res, 2020, 12(8): 4594-4603.
[18] Kilpatrick GJ. Remimazolam: non-clinical and clinical profile of a new sedative/anesthetic agent [J]. Front Pharmacol, 2021, 12: 690875.
[19] 赵俊,娄丽丽.瑞马唑仑与丙泊酚分别联合舒芬太尼在患者无痛胃镜检查中的应用[J].中国药物与临床,2021,21(12):2143-2144.
Zhao J, Lou LL. Application of remizolam and propofol combined with sufentanil in painless gastroscopy of patients [J]. Chin Remedies Clin, 2021, 21(12): 2143-2144.
[20] 杨亚崇,帅世超,韩静,等.小剂量瑞马唑仑复合丙泊酚在老年患者胃肠镜诊疗中的镇静效果[J].中国临床研究,2023,36(8):1205.
Yang YC, Shuai SC, Han J, et al. Sedative effect of low-dose remidazolam combined with propofol in elderly patients received gastrointestinal endoscopy[J]. Chin J Clin Res, 2023, 36(8): 1205.
[21] 魏来,李洁琼,洪谭浩,等.不同剂量瑞马唑仑用于宫腔镜手术的安全性和有效性[J].临床麻醉学杂志,2022,38(4):346-350.
Wei L, Li JQ, Hong TH, et al. Safety and efficacy of different doses of remimazolam in hysteroscopic surgery[J]. J Clin Anesthesiol, 2022, 38(4): 346-350.
[22] Schüttler J, Eisenried A, Lerch M, et al. Pharmacokinetics and pharmacodynamics of remimazolam (CNS 7056) after continuous infusion in healthy male volunteers: part Ⅰ. pharmacokinetics and clinical pharmacodynamics[J]. Anesthesiology, 2020, 132(4): 636-651.
[23] Chen X, Sang NE, Song KC, et al. Psychomotor recovery following remimazolam-induced sedation and the effectiveness of flumazenil as an antidote[J]. Clin Ther, 2020, 42(4): 614-624.
[24] Freyer N, Knöspel F, Damm G, et al. Metabolism of remimazolam in primary human hepatocytes during continuous long-term infusion in a 3-D bioreactor system[J]. Drug Des Dev Ther, 2019, 13: 1033-1047.
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