ORIGINAL RESEARCH

Effects of Esketamine Combined with Propofol for Hysteroscopy Anesthesia on Patient Hemodynamics and Adverse Reactions

Jianying Wang, BM; Yu Liu, MM; Qiong Xu, BM

ABSTRACT

Objective • To investigate the effect of esketamine combined with propofol on patient hemodynamics and its safety in hysteroscopy anesthesia.

Methods • A total of 186 hysteroscopic patients admitted to our hospital from January 2021 to January 2022 were selected, and the patients were divided into group K and Group P according to a completely random number table, with 93 cases each. In short, all patients are uniformly numbered and adequately intermixed, according to the prescribed sampling starting point and order, the sample unit numbers were successively drawn from the random number table, until the extraction to the required sample size. Group K was given esketamine combined with propofol intravenously, and group P was given sufentanil combined with propofol intravenously. The changes in respiratory circulation [heart rate (HR), mean arterial pressure (MAP) and oxygen saturation (SpO_2)] at the time of entering the operating room (T0), at the beginning of surgery (T1), 10 minutes after surgery(T2), and 10 minutes after the end of surgery (T3) were compared between the two groups, as well as the total time of surgery, the time to wake up after surgery, the amount of propofol used intraoperatively and the proportion of additional propofol were compared. The numerical rating scale (NRS) was used to assess the pain level of patients in both groups at different times after awakening and the occurrence of intraoperative and postoperative adverse reactions such as body movement, respiratory depression, bradycardia, injection site pain, nausea and vomiting, and dizziness were counted in both groups.

Results • There were no significant changes in MAP, HR, and SpO_2 in Group K at all moments compared with T0 ($P > .05$), MAP, HR and SpO_2 in Group P at T1 and T2 were lower than those at T0 ($P < .05$). MAP, HR, and SpO_2 were significantly lower in Group P at T1 and T2 moments compared with Group K, suggesting that circulatory depression was more pronounced in Group P at T1 and T2 moments ($P < .05$) and was not conducive to postoperative recovery. Compared with group P, the postoperative recovery time of group K was significantly shorter, and the dosage of propofol and the proportion of additional propofol were significantly lower ($P < .05$) which was beneficial to the health of patients. The pain level was significantly lower in Group K at 5, 15, and 30 minutes after awakening than in Group P ($P < .05$). The incidence of adverse reactions such as intraoperative motion, respiratory depression, bradycardia, injection site pain, and dizziness was significantly lower in group K than in group P ($P < .05$), and there was no significant difference in the incidence of nausea and vomiting between the two groups ($P > .05$), and prove that esketamine combined with propofol used for anesthesia which have high safety as well as more effective.

Conclusion • The use of esketamine compounded with propofol in hysteroscopy anesthesia has less effect on the patient's circulatory and respiratory systems. This protocol can improve the postoperative analgesic effect of anesthesia in patients, reduce the amount of propofol during surgery, have fewer adverse effects and mild symptoms, is safe and effective, and can be used in clinical practice. (*Altern Ther Health Med.* 2024;30(1):18-23).

Jianying Wang, BM, Associate chief physician; **Yu Liu, MM**, Associate chief physician; Department of Anesthesiology, Yiwu Central Hospital, Zhejiang Province, Yiwu, Zhejiang, China. **Qiong Xu, BM**, Attending doctor; Department of Anesthesia, Zhuji Maternal and Child Health Hospital, Zhuji, Zhejiang, China.

Corresponding author: Qiong Xu, BM
E-mail: xuqiong0511@163.com

INTRODUCTION

As a minimally invasive diagnosis and treatment of gynecology, hysteroscopy has the characteristics of simple operation, high safety, minimally invasive and fast postoperative recovery, which meets the psychological requirements of patients.[1] Currently, hysteroscopy is widely used in China for the diagnosis of endometrial lesions,[2] uterine foreign bodies,[3] intrauterine adhesions[4] and other uterine diseases, as well as for performing abortions[5] and other operations, which plays a pivotal role in the clinical diagnosis and treatment of female gynecological diseases. Although hysteroscopy is a minimally invasive procedure, studies[6,7] have shown that many women experience moderate to severe pain and discomfort during mini-hysteroscopy, which is the main cause of surgical failure and can also cause psychological harm and stress trauma to patients and worsen the doctor-patient relationship. Therefore, a well-developed and effective anesthesia protocol is essential for the smooth performance of the examination during hysteroscopy, so that the patient can maintain a comfortable

state during the process of hysteroscopy, increase the success rate of surgery, and maintain a good doctor-patient relationship. Propofol is a short-acting intravenous anesthetic with a powerful sedative drug, and due to its short half-life, patients can wake up from anesthetic sedation quickly after surgery, which better meets the requirements of rapid awakening for hysteroscopy and is considered an ideal anesthetic drug for hysteroscopy.[8-10] However, due to the poor analgesic effect of propofol, if propofol alone is used for anesthesia, patients may experience motion due to pain when encountering some irritating operations. It is often necessary to increase the dosage of propofol to achieve deeper anesthesia, which not only increases the risk of circulatory and respiratory depression but also is not conducive to the patient's postoperative recovery.[11,12]

Studies[13,14] have shown that opioids combined with propofol for painless bore examination reduce propofol dosage and the probability of adverse effects. However, opioids combined with propofol have a relatively large effect on respiration and circulation, which can cause hypotension and hypoxemia, which can have serious consequences if left untreated.[15] Therefore, anesthesiologists have been working to identify an intravenous anesthetic that, when combined with propofol, achieves a more comprehensive and safe anesthetic effect that retains the sedative benefits of propofol while reducing the incidence of adverse effects. Essiac ketamine is a new narcotic sedative and analgesic drug derivative of phencyclidine and ketamine, a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist with strong sedative and analgesic effects.[16,17] Akhondzadeh et al.[18] demonstrated that in patients who are difficult to sedate during endoscopic reverse cholangiopancreatography, propofol-ketamine resulted in a better quality of analgesia and sedation with a higher safety profile. The above studies confirm that esketamine combined with propofol can achieve better anesthesia in various endoscopic examinations, but the application of this protocol in hysteroscopy has been less studied. Therefore, this study aimed to observe the effect of esketamine compounded with propofol used in anesthesia for hysteroscopy to provide a reference for the choice of anesthetic drugs in hysteroscopy. It is of great significance to optimize the anesthesia program in hysteroscopy and help to improve the quality of nursing.

PATIENTS AND METHODS

Research Subjects

A total of 186 patients were selected for hysteroscopy under intravenous anesthesia in our hospital from January 2021 to January 2022. Inclusion criteria: (1) 25-55 years of age (normal menstrual period and perimenopausal women). (2) 1-2 vaginal deliveries (no births in the last 2 years) (hysteroscopy had trauma to the vagina). (3) Patients who had indications for hysteroscopy and no contraindications to hysteroscopy were found in the routine preoperative examination (preoperative examination included blood and urine routine, examination sample of vaginal discharge, coagulation function, pelvic ultrasound, and electrocardiogram) (there were no contraindications to hysteroscopy). (4) Patients without contraindications to the use of esketamine, propofol, sufentanil, and other injection solutions (no contraindications to anesthetic use). Exclusion criteria: (1) Patients with acute infections of the genital tract (hysteroscopy has damaged the genital tract). (2) Those who had used prostaglandin inhibitors in the past month (inhibition of uterine contraction, not conducive to examination). (3) Pregnant women (uterus and fetus were injured by hysteroscopy). (4) Those with serious heart, liver, and kidney diseases (combined diseases have an impact on the results of hysteroscopy). (5) Patients with a history of large month induced abortion (≥24 weeks of gestation) within the last 2 years (induced abortion in older months may cause great damage to the uterus). (6) Patients with a history of miscarriage within the last 3 months (abortion has a large damage to the uterus). (7) Menopausal patients (uterus will gradually shrink and become smaller after menopause). Patients were divided into two groups according to the random number table method: the esketamine combined with the propofol group (n = 93, Group K) and the sufentanil combined with the propofol group (n = 93, Group P). Shortly, all patients are uniformly numbered and adequately intermixed, according to the prescribed sampling starting point and order, the sample unit numbers were successively drawn from the random number table, until the extraction to the required sample size. This study has been in accordance with the relevant ethical regulations of the hospital. IBM SPSS 23.0 software was used for data processing. *t* test was used for quantitative data which satisfying normal distribution ($\bar{x} \pm s$). Qualitative data (%) were tested by χ^2 test. $P < .05$ was considered statistically significant.

Experimental materials

Main instruments: anesthesia machine: Datex-ohemda Aestiva/5, USA. Anesthesia monitor: G60, Shenzhen Jinkowei Industrial Co. Main drug: Sufentanil Hydrochloride Injection, 50 μg/mL, Yichang Renfu Pharmaceutical Co. Essiac Ketamine Hydrochloride Injection, 0.5 mg/mL, Jiangsu Hengrui Medicine Co. Propofol Injection, 0.2 mg / 20 mL, Jiangsu Enhua Pharmaceutical Co. Ephedrine, 30 mg/mL, Northeast Pharmaceutical Group Shenyang First Pharmaceutical Co. Atropine, 0.5 mg / 1 mL, Tianjin Jinyao Pharmaceutical Co.

Methods

Pre-anesthesia preparation. All patients were asked to fast for 6 hours, abstain from drinking for 4 hours before surgery, and not to use any medication before surgery. During the preoperative preparation, the patient's pain level was first evaluated by the nurse with a numerical rating scale (NRS), and the upper extremity venous access was opened at the same time, and sodium lactate Ringer's solution was continuously administered intravenously at a rate of 5-10 (ml/kg/h). After admission to the hysteroscopy room,

patients were asked to take a cystotomy position. At the same time, systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), oxygen saturation (SpO_2), and heart rate (HR) were monitored at regular intervals (3-minute interval). Oxygen was routinely administered at 3-4 (L/min) to the patient's face mask during the entire procedure.

Anesthesia method. In group P, propofol 1.5 (mg/kg) was used for induction, followed by intravenous administration of sufentanil 0.1-0.15 (μg/kg). In group K, esketamine 0.5 (mg/kg) was given for induction of anesthesia, and then the operation was started. In both groups, intraoperative propofol 4-6 ($mg \cdot kg^{-1} \cdot h^{-1}$) was pumped to maintain anesthesia.

Anesthesia maintenance. During the operation, the dosage of propofol was adjusted according to whether the patient had a physical reaction. If the patient showed motion, frowning, shrugging, and swallowing, anesthesia is not enough, additional propofol 0.5-1.0 (mg/kg) was added intravenously to maintain the required depth of anesthesia for the operation. After the procedure, the patient was awakened in the hysteroscopic room and sent to the post-anesthesia recovery room for further resuscitation and documentation.

Management of Intraoperative Adverse Reactions. If the patient experienced an intraoperative drop in blood pressure (MAP less than 30% of basal value or less than 60 mmHg), an intravenous bolus of 6 mg of ephedrine was given, and the infusion was accelerated, ephedrine is an adrenocorticotropic drug, it can stimulate sympathetic nerves, relax bronchial smooth muscle contraction, and has a significant central excitatory effect on blood vessels. If HR was <55 (beats/min) intraoperatively, 0.3~0.5 mg of atropine was given intravenously for treatment, atropine is a typical M cholinergic receptor blocker, results in a mild slowing of the heart rate when administered at low doses. If the patient developed respiratory depression or apnea (SpO_2 <90%) during surgery, the anesthesiologist supported the patient's jaw with both hands to assist ventilation in patients and if the patient's oxygen saturation continued to decline and the hypoxia condition did not improve, the mask was changed to positive pressure assisted ventilation.

Observation indexes. General patient status: subject's age, weight, height, body mass index (BMI), American Society of Aneshesiologists (ASA) classification, basal hemodynamic indices (including heart rate, mean arterial pressure, SpO_2), preoperative diagnosis. HR, MAP, and SpO_2 were recorded for each patient at the time of admission to the operating room (T0), at the beginning of surgery (T1), 10 min after the beginning of surgery (T2), and 10 min after surgery (T3). The intraoperative propofol dosage, the number of additional propofol cases, and the postoperative awakening time (time from drug discontinuation to call for eye opening) were recorded in each patient. The numeric rating scale (NRS) was used to evaluate the degree of contraction pain at 5, 15, and 30 min after awakening (A score of 0 indicated no pain; 1 to 3 indicated mild pain; 4 to 6 indicated moderate pain; and 7 to 10 indicated severe pain). The occurrence of adverse reactions such as intraoperative body movements, respiratory depression, bradycardia, injection site pain, nausea and vomiting, and dizziness were recorded in patients within 24 hours after surgery.

Table 1. Comparison of baseline information between the two groups

Indicator	Group P (n = 93)	Group K (n = 93)	t/χ^2 value	*P* value
Age (years)	40.23 ± 5.47	39.02 ± 6.08	1.427	.155
Height (m)	1.57 ± 0.05	1.58 ± 0.03	1.654	.100
Body weight (kg)	53.58 ± 5.21	54.21 ± 6.03	0.762	.447
BMI (kg/m^2)	21.69 ± 1.08	21.66 ± 1.62	0.149	.882
Disease type (n,%)			1.421	.701
Endometrial polyp	42 (45.16)	45 (48.39)		
Vaginal bleeding	38 (40.86)	40 (43.01)		
Infertility	4 (4.30)	2 (2.15)		
Hysteromyoma	9 (9.68)	6 (6.15)		
ASA classification(n,%)			1.022	.312
Grade I	90 (96.77)	92 (98.92)		
Grade II	3 (3.23)	1 (1.08)		
Surgery time (min)	18.19 ± 3.17	18.14 ± 2.79	0.114	.909

Note: BMI is body mass index and ASA is American society of Aneshesiologists.

Statistical Analysis

Statistical Product and Service Solutions (SPSS) 25.0 statistical software (IBM, Armonk, NY, USA) was used for data analysis. All measures (height, weight, age, body mass index, hemodynamic indices, etc.) that obeyed normal distribution were expressed as mean ± standard deviation (Mean ± SD). The measures of skewed distribution were described using median (interquartile spacing), and the counts were expressed as frequencies and percentages (n, %). Depending on the nature and characteristics of the data, comparisons were made using independent sample *t* tests or repeated measures analysis of variance and rank sum tests. $P < .05$ was considered a statistically significant difference.

RESULTS

Comparison of baseline information between the two groups

There were no statistically significant differences in age, weight, height, BMI, ASA classification, preoperative diagnosis (type of disease), and time to surgery between the two groups of subjects ($P > .05$). See Table 1

Comparison of MAP, HR, and SpO2 levels in the two groups at different moments

MAP, HR and SpO2 did not change significantly in Group K at any time compared with T0 ($P > .05$); MAP, HR, and SpO_2 in Group P at T1 and T2 were lower than those at T0 ($P < .05$). MAP, HR, and SpO2 were significantly lower in Group P at T1 and T2 moments compared with Group K ($P < .05$), suggesting that circulatory depression was more pronounced in Group P at T1 and T2 moments. See Figures 1~3.

Comparison of anesthesia-related indexes between the two groups

Compared with Group P, Group K had a significantly

Figure 1. Comparison of MAP levels between the two groups at different times

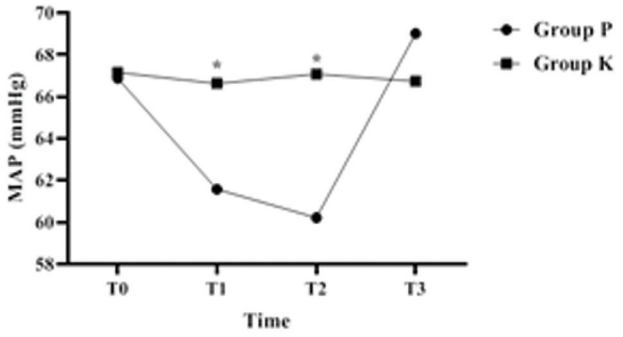


Figure 2. Comparison of HR levels between the two groups at different times

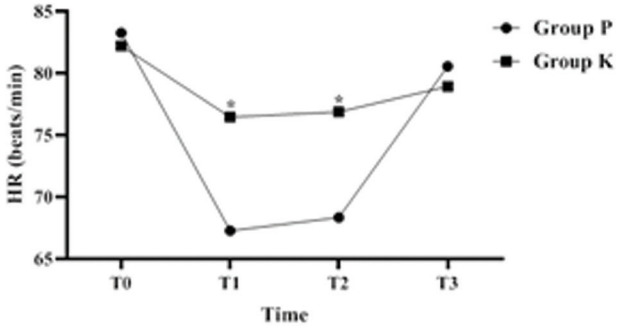
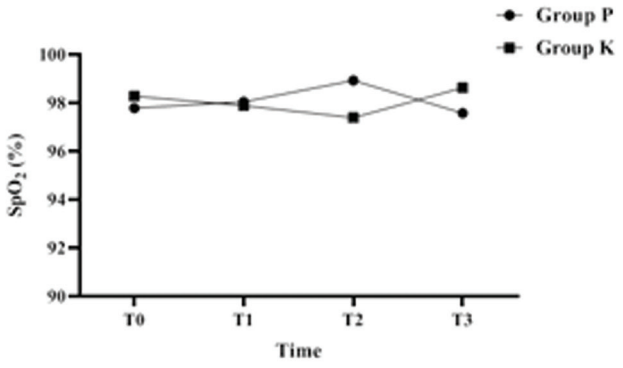


Figure 3. Comparison of SpO_2 levels between the two groups at different times.



[a]$P < .05$ compared with the same moment in the Group P.

Abbreviations: MAP, mean arterial pressure; HR, heart rate; SpO_2, oxygen saturation.

shorter postoperative awakening time, a significantly lower propofol dosage, and a significantly lower proportion of additional propofol ($P < .05$). See Table 2.

Comparison of the pain level of contractions at different times after surgery between the two groups

Compared with group P, the pain level was significantly lower in Group K at 5, 15, and 30 minutes after awakening ($P < .05$). See Table 3.

Table 2. Comparison of anesthesia-related indexes between the two groups

Indicator	Group P (n = 93)	Group K (n = 93)	t/χ^2 value	*P* value
Postoperative awakening time (min)	6.84 ± 2.36	5.14 ± 2.27	5.007	.000
Propofol dosage (mg)	320.00 ± 30.00	230.00 ± 40.00	17.359	.000
Supplementary propofol (n,%)	30 (32.26)	7 (7.53)	17.848	.000

Table 3. Comparison of the pain level of contractions at different times after surgery between the two groups

Time point	Group	Number of cases	Mild	Moderate	Severe
5 minutes after awakening	Group P	93	65 (69.89)	28 (30.11)	0 (0.00)
	Group K[a]	93	81 (87.10)	7 (7.53)	0 (0.00)
15 minutes after awakening	Group P	93	37 (39.78)	51 (54.84)	5 (5.38)
	Group K[a]	93	74 (78.57)	19 (20.43)	0 (0.00)
30 minutes after awakening	Group P	93	56 (60.22)	37 (39.78)	0 (0.00)
	Group K[a]	93	76 (81.72)	17 (18.28)	0 (0.00)

[a]$P < .05$ compared with the Group P.

Table 4. Comparison of the occurrence of complications between the two groups

Complications	Group P (n = 93)	Group K (n = 93)	χ^2 value	*P* value
Intraoperative motion	16 (17.20)	7 (7.53)	4.019	.045
Respiratory depression	10 (10.75)	0 (0.00)	10.568	.001
Bradycardia	30 (32.26)	10 (10.75)	12.740	.000
Injection site pain	31 (33.33)	3 (3.23)	28.217	.000
Nausea and vomiting	2 (2.15)	0 (0.00)	2.022	0.155
Dizziness	50 (53.76)	18 (19.35)	23.737	0.000

Comparison of the occurrence of complications between the two groups

The incidence of adverse reactions such as intraoperative motion, respiratory depression, bradycardia, injection site pain, and dizziness was significantly lower in group K than in group P ($P < .05$); the difference in the incidence of nausea and vomiting between the two groups was not statistically significant ($P > .05$). See Table 4.

DISCUSSION

Currently, hysteroscopy has become an important tool to assess the pathological condition of the female uterine cavity, and advances in such techniques have enabled a shift from relying on the experience of the gynecologist to operating under direct visualization in outpatient gynecological surgery.[19,20] Hysteroscopy procedures are usually short, which means that the patient has to be able to recover quickly after the procedure. Stimulation from intraoperative dilation, pulling of the cervix, and intrauterine manipulation can cause a stress reaction in patients and can be a tremendously painful experience for non-sedated patients.[21] In the process of dilation and traction of the cervix, if the patient produces nausea and physical movement due to insufficient sedation depth, which is not conducive to the smooth progress of the operation, it is more likely to cause damage to the tissue of the operation part, causing adverse reactions such as tissue rupture and bleeding.[22] Therefore, how to perform hysteroscopy under systematic anesthesia, manage intraoperative analgesia and sedation levels, and maintain the hemodynamic stability of patients is the direction that needs to be paid attention to and studied in clinical anesthesia.

Traditionally, hysteroscopy is mostly performed using intravenous anesthesia, and opioids are the commonly used

anesthetic drugs in clinical practice. Opioid agonists, represented by propofol, are widely used in intravenous anesthesia because of their rapid onset of action, precise effect, and rapid postoperative awakening.[23] However, in hysteroscopy with breathing-sparing, its obvious respiratory and cardiovascular inhibitory effects cannot be ignored. Sufentanil is one of the analgesics that can be used in combination with propofol, and it is also the most powerful opioid analgesic. and has a short half-life, which can greatly shorten the awakening time of patients, and is one of the drugs commonly used in hysteroscopic anesthesia.[24,25] However, sufentanil also has a dose-related effect in respiratory depression, and this adverse effect lies in the increased risk of anesthesia when used in combination with propofol.[26] Esketamine is a new anesthetic sedative and analgesic drug that combines anesthetic, analgesic, and sympathomimetic properties and causes less cardiopulmonary depression than other sedative anesthetic drugs, making it a more desirable adjunct to propofol.[27] Esketamine blocks the sodium channel of the parasympathetic nerve in the brain stem, inhibits the electrical activity of the parasympathetic nerve in the heart, and increases cardiac output.[28] Esketamine can also inhibit the uptake of norepinephrine by neurons, increase the concentration of norepinephrine, produce sympathetic nerve excitation and increase peripheral vascular resistance.[29] Vagus excitation during hysteroscopy can be antagonized by utilizing the parasympathetic inhibition of esketamine. In addition, when esketamine acts on the NMDA receptor, a large number of Ca^{2+} into the nerve cells, activate the secondary messenger, produce nitric oxide, prostaglandins and so on, can be directly restrain activity of GABA receptors, reduce the presynaptic inhibition.[30] Esketamine can also act on voltage-gated sodium channel and cyclic nucleotide-gated channel through NMDA receptor to produce analgesic and sedative effects.[31] Intravenous infusion of ketamine combined with propofol has been shown to be safe and effective in pediatric patients after years of clinical practice and exploration,[32]. Still, it has not been widely accepted in adult anesthesia, especially outside the operating room.

In this study, propofol compounded with esketamine was applied in hysteroscopy anesthesia, and the results showed that there were no patients with respiratory depression in group K. It was considered to be related to the sympathomimetic effect of esketamine, which not only had no respiratory depressant effect but also accelerated the respiratory rate, weakening the respiratory depressant effect of propofol.[33] In addition, the percentage of bradycardia was significantly lower in group K patients compared to group P. This may be due to the central sympathomimetic activity of esketamine antagonizing the circulatory depressant effect of propofol and the vagal reflex effect during the surgical operation.[34] In this study, patients in group K had a lower incidence of intraoperative somatic movements, fewer additional cases of propofol, and less pain at 5, 15, and 30 min after awakening, suggesting a good analgesic effect of esketamine. This may be due to the ability of esketamine not only to reduce the peripheral and central NMDA receptor-related injurious sensations but also to enhance the action of the pain inhibitory system, thus providing good analgesic effects. Trimmel et al.[35] showed that in vitro esketamine increased its affinity for NMDA receptors by about 4-fold compared to levocetamine, had up to 3-fold the analgesic effect of levocetamine alone, produced higher anesthetic potency, and had 1.5 to 3.0 times the hypnotic effect of levocetamine.

However, this study has several limitations. First of all, the sample size of this study is small, and a further increase in sample size is needed to verify the results of this study in the future. Secondly, this study was targeted, so it is unclear whether it applies to patients with other comorbidities, and sufficient experiments are needed to explore it in the future.

In conclusion, esketamine compounded with propofol used in hysteroscopy anesthesia has less effect on the patient's circulatory and respiratory system. This protocol can improve the anesthetic analgesic effect of patients, reduce the intraoperative propofol dosage, has fewer adverse effects and mild symptoms, is safe and effective, and can be used in clinical practice.

DATA AVAILABILITY STATEMENT

The data material in this study is available from the corresponding author upon reasonable request.

CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTIONS

JW and QX designed the study and performed the experiments, QX and YL collected the data, JW and YL analyzed the data, JW and QX prepared the manuscript. All authors read and approved the final manuscript.

FUNDING

This study did not receive any funding in any form.

REFERENCES

1. Fagioli R, Vitagliano A, Carugno J, Castellano G, De Angelis MC, Di Spiezio Sardo A. Hysteroscopy in postmenopause: from diagnosis to the management of intrauterine pathologies. *Climacteric*. 2020;23(4):360-368. doi:10.1080/13697137.2020.1754387
2. Zhang Y, Wang Z, Zhang J, et al. Deep learning model for classifying endometrial lesions. *J Transl Med*. 2021;19(1):10. doi:10.1186/s12967-020-02660-x
3. Grigore M, Blidaru I, Iordache F. Intrauterine foreign bodies, other than contraceptive devices and systems, may affect fertility - report of two very different cases. *Eur J Contracept Reprod Health Care*. 2014;19(2):141-143. doi:10.3109/13625187.2013.856406
4. Qu S, Zhou P. Post-hysteroscopy Duration of the Cook Balloon Uterine Stent Effect on the Re-adhesion Formation. *J Coll Physicians Surg Pak*. 2021;31(10):1163-1167. doi:10.29271/jcpsp.2021.10.1163
5. Ryu S, Baek HW, Lee I, et al. Operative hysteroscopy-assisted pregnancy termination after failed surgical abortion in missed abortion of woman with complete septate uterus. *Obstet Gynecol Sci*. 2020;63(1):102-106. doi:10.5468/ogs.2020.63.1.102
6. Riemma G, Schiattarella A, Colacurci N, et al. Pharmacological and non-pharmacological pain relief for office hysteroscopy: an up-to-date review. *Climacteric*. 2020;23(4):376-383. doi:10.1080/13697137.2020.1754388
7. De Silva PM, Stevenson H, Smith PP, Justin Clark T. A Systematic Review of the Effect of Type, Pressure, and Temperature of the Distension Medium on Pain During Office Hysteroscopy. *J Minim Invasive Gynecol*. 2021;28(6):1148-1159.e2. doi:10.1016/j.jmig.2021.01.003
8. Zhang X, Li S, Liu J. Efficacy and safety of remimazolam besylate versus propofol during hysteroscopy: single-centre randomized controlled trial. *BMC Anesthesiol*. 2021;21(1):156. doi:10.1186/s12871-021-01373-y
9. Park S, Choi SL, Nahm FS, Ryu JH, Do SH. Dexmedetomidine-remifentanil vs propofol-remifentanil for monitored anesthesia care during hysteroscopy: Randomized, single-blind, controlled trial. *Medicine (Baltimore)*. 2020;99(43):e22712. doi:10.1097/MD.0000000000022712
10. Zhang S, Wang J, Ran R, Peng Y, Xiao Y. Efficacy and safety of remimazolam tosylate in hysteroscopy: A randomized, single-blind, parallel controlled trial. *J Clin Pharm Ther*. 2022;47(1):55-60. doi:10.1111/jcpt.13525
11. Liang H, Hou Y, Sun L, Li Q, Wei H, Feng Y. Supraglottic jet oxygenation and ventilation for obese patients under intravenous anesthesia during hysteroscopy: a randomized controlled clinical trial. *BMC Anesthesiol*. 2019;19(1):151. doi:10.1186/s12871-019-0821-8
12. Guo YX, Luo K, Jiang PP, Wang D, Wang YZ, Yang XL. Minimal alveolar concentration of sevoflurane in combination with dexmedetomidine in patients with hysteroscopy: an up-down sequential allocation study. *Basic Clin Pharmacol Toxicol*. 2022;131(5):364-371. doi:10.1111/bcpt.13777
13. Yu J, Xiang B, Song Y, Chen H, Li Y, Liu C. ED50 of propofol in combination with low-dose sufentanil for intravenous anaesthesia in hysteroscopy. *Basic Clin Pharmacol Toxicol*. 2019;125(5):460-465. doi:10.1111/bcpt.13280

14. Ryu JH, Kim JH, Park KS, Do SH. Remifentanil-propofol versus fentanyl-propofol for monitored anesthesia care during hysteroscopy. *J Clin Anesth*. 2008;20(5):328-332. doi:10.1016/j.jclinane.2007.12.015
15. Novac MB, Boldeanu L, Rotaru LT, et al. The perioperative effect of anesthetic drugs on the immune response in total intravenous anesthesia in patients undergoing minimally invasive gynecological surgery. *Rom J Morphol Embryol*. 2021;62(4):961-969. doi:10.47162/RJME.62.4.08
16. McIntyre RS, Rosenblat JD, Nemeroff CB, et al. Synthesizing the Evidence for Ketamine and Esketamine in Treatment-Resistant Depression: An International Expert Opinion on the Available Evidence and Implementation. *Am J Psychiatry*. 2021;178(5):383-399. doi:10.1176/appi.ajp.2020.20081251
17. Sapkota A, Khurshid H, Qureshi IA, et al. Efficacy and Safety of Intranasal Esketamine in Treatment-Resistant Depression in Adults: A Systematic Review. *Cureus*. 2021;13(8):e17352. doi:10.7759/cureus.17352
18. Akhondzadeh R, Ghomeishi A, Nesioonpour S, Nourizade S. A comparison between the effects of propofol-fentanyl with propofol-ketamine for sedation in patients undergoing endoscopic retrograde cholangiopancreatography outside the operating room. *Biomed J*. 2016;39(2):145-149. doi:10.1016/j.bj.2015.11.002
19. Giampaolino P, Della Corte L, Di Filippo C, Mercorio A, Vitale SG, Bifulco G. Office hysteroscopy in the management of women with postmenopausal bleeding. *Climacteric*. 2020;23(4):369-375. doi:10.1080/13697137.2020.1754389
20. Kamath MS, Rikken JFW, Bosteels J. Does Laparoscopy and Hysteroscopy Have a Place in the Diagnosis of Unexplained Infertility? *Semin Reprod Med*. 2020;38(1):29-35. doi:10.1055/s-0040-1718942
21. Vitale SG, Carugno J, Riemma G, et al. Hysteroscopy for Assessing Fallopian Tubal Obstruction: A Systematic Review and Diagnostic Test Accuracy Meta-analysis. *J Minim Invasive Gynecol*. 2021;28(4):769-778. doi:10.1016/j.jmig.2020.11.013
22. Zargar M, Ghafourian M, Nikbakht R, Mir Hosseini V, Moradi Choghakabodi P. Evaluating Chronic Endometritis in Women with Recurrent Implantation Failure and Recurrent Pregnancy Loss by Hysteroscopy and Immunohistochemistry. *J Minim Invasive Gynecol*. 2020;27(1):116-121. doi:10.1016/j.jmig.2019.02.016
23. Chen C, Tang W, Ye W, Zhong W, Li Y. ED50 of Propofol Combined with Nalbuphine on the Sedative Effect in Painless Hysteroscopy. *Pain Ther*. 2021;10(2):1235-1243. doi:10.1007/s40122-021-00280-x
24. Lv Y, He H, Xie J, et al. Effects of transcutaneous acupoint electrical stimulation combined with low-dose sufentanil pretreatment on the incidence and severity of etomidate-induced myoclonus: A randomized controlled trial. *Medicine (Baltimore)*. 2018;97(23):e10969. doi:10.1097/MD.0000000000010969
25. Chen G, Gong M, Liu Y. Comparison of ropivacaine plus sufentanil and ropivacaine plus dexmedetomidine for labor epidural analgesia: A randomized controlled trial protocol. *Medicine (Baltimore)*. 2020;99(36):e22113. doi:10.1097/MD.0000000000022113
26. Kowalski G, Zawadzki M, Leppert W, et al. Analgesic efficacy of sufentanil in dressings after surgical treatment of burn wounds. *Burns*. 2021;47(4):880-887. doi:10.1016/j.burns.2020.10.006
27. Ng J, Rosenblat JD, Lui LMW, et al. Efficacy of ketamine and esketamine on functional outcomes in treatment-resistant depression: A systematic review. *J Affect Disord*. 2021;293:285-294. doi:10.1016/j.jad.2021.06.032
28. Jang Y, Kim M, Hwang SW; Molecular mechanisms underlying the actions of arachidonic acid-derived prostaglandins on peripheral nociception. *J Neuroinflammation*. 2020;22;17(1):30. doi:10.1186/s12974-020-1703-1
29. Xue M, Han L, Qian W, et al; Nitric Oxide Stimulates Acute Pancreatitis Pain via Activating the NF-kB Signaling Pathway and Inhibiting the Kappa Opioid Receptor. *Oxid Med Cell Longev*. 2020;7;2020:9230958. doi:10.1155/2020/9230958
30. Lei Y, Liu H, Xia F, et al; Effects of Esketamine on Acute and Chronic Pain After Thoracoscopy Pulmonary Surgery Under General Anesthesia: A Multicenter-Prospective, Randomized, Double-Blind, and Controlled Trial. *Front Med (Lausanne)*. 2021;8;8:693594. doi:10.3389/fmed.2021.693594
31. Li J, Wang Z, Wang A, Wang Z. Clinical effects of low-dose esketamine for anaesthesia induction in the elderly: A randomized controlled trial. *J Clin Pharm Ther*. 2022;47(6):759-766. doi:10.1111/jcpt.13604
32. Vázquez GH, Bahji A, Undurraga J, Tondo L, Baldessarini RJ. Efficacy and Tolerability of Combination Treatments for Major Depression: antidepressants plus Second-Generation Antipsychotics vs. Esketamine vs. Lithium. *J Psychopharmacol*. 2021;35(8):890-900. doi:10.1177/02698811211013579
33. Eberl S, Koers L, van Hooft JE, et al. Sedation with propofol during ERCP: is the combination with esketamine more effective and safer than with alfentanil? Study protocol for a randomized controlled trial. *Trials*. 2017;18(1):472. doi:10.1186/s13063-017-2197-8
34. Yang H, Zhao Q, Chen HY, et al. The median effective concentration of propofol with different doses of esketamine during gastrointestinal endoscopy in elderly patients: A randomized controlled trial. *Br J Clin Pharmacol*. 2022;88(3):1279-1287. doi:10.1111/bcp.15072
35. Trimmel H, Helbok R, Staudinger T, et al. S(+)-ketamine : current trends in emergency and intensive care medicine. *Wien Klin Wochenschr*. 2018;130(9-10):356-366. doi:10.1007/s00508-017-1299-3