To Compare the Anesthetic Effect of Remimazolam and Propofol in Painless Hysteroscopic Minimally Invasive Surgery

Ann. Ital. Chir., 2024 95, 2: 159–165
https://doi.org/10.62713/aic.3291

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Objective: Hysteroscopic surgery will stimulate the autonomic nerves innervating the uterus, causing intense discomfort and pain in the examined person, and in severe cases, it will cause blood pressure drop, heart rate slowing, arrhythmia and even cardiac arrest, so most patients need anesthetic intervention. This study to retrospectively compare the anesthetic effect of remimazolam and propofol in minimally invasive painless hysteroscopic surgery and to explore the safety and efficacy of remimazolam.

Methods: The clinical data of 110 female patients who underwent painless hysteroscopic minimally invasive surgery in our hospital from January 2023 to June 2023 were collected. The patients were divided into the remimazolam group (group R, n = 55) and the propofol group (group P, n = 55) according to the main anesthetic drugs used during the operation. The changes in heart rate (HR), mean arterial pressure (MAP), blood oxygen saturation (SpO_2), and respiratory rate (RR) at the time of entry (T_0), modified vigilance/sedation score (MOAA/S) 0 (T_1), cervical dilation (T_2), end of the operation (T_3) and anesthesia recovery (T_4) were compared between the two groups. Anesthesia induction time, operation time, and anesthesia recovery time were compared between the two groups, and the incidence of intraoperative and postoperative adverse reactions was compared between the two groups.

Results: HR, MAP, and SpO_2 in group R were significantly higher than those in group P at T_1, T_2, T_3, and T_4 ($p < 0.05$), and there was no significant difference in RR between the two groups ($p > 0.05$). HR, MAP, and SpO_2 at T_1 and T_2 were significantly lower than those at T_0 in group R ($p < 0.05$), and RR at different time points in the group had no significant difference ($p > 0.05$). HR, MAP, and SpO_2 at T_1, T_2, T_3, and T_4 were significantly lower than those at T_0 in group P ($p < 0.01$), and RR at different time points in the same group had no significant difference ($p > 0.05$). The anesthesia induction time in group R was more prolonged than in group P, and the anesthesia recovery time in group R was shorter than in group P ($p < 0.05$). The incidences of hypotension, bradycardia, low oxygen saturation, respiratory depression, and injection pain in group R were significantly lower than those in group P ($p < 0.05$).

Conclusion: Intravenous induction of remimazolam at 6 $mg \cdot kg^{-1} \cdot h^{-1}$ and maintenance of anesthesia at 1–2 $mg \cdot kg^{-1} \cdot h^{-1}$ have less effect on hemodynamics, faster recovery time and lower incidence of adverse reactions compared with propofol when used in minimally invasive hysteroscopic surgery. Remimazolam can be safely and effectively used in this kind of surgery.

Keywords: hysteroscopy; painless diagnosis and treatment; remimazolam; propofol; effect of anesthesia

Introduction

Hysteroscopic surgery is a common minimally invasive surgery in gynecological diagnosis and treatment. It has the advantages of small trauma, rapid postoperative recovery, low failure rate, and related complications [1]. Hysteroscopy uses the anterior part of the lens to enter the uterine cavity and visually observe the lesion surface's size, location, appearance, range, and tissue structure. It is of great significance for the diagnosis and treatment of intrauterine adhesions, abnormal uterine bleeding, suspected intrauterine malformations, infertility, and other intrauterine diseases and gynecological bleeding diseases [2]. During the operation, the autonomic nerves innervating the uterus are stimulated, and the traction reaction is caused when the vaginal dilation device is inserted, the cervix is dilated, and the curettage, biopsy, and other intrauterine operations are performed. The main manifestations are body movement, dizziness, or nausea, which will cause intense discomfort and pain in the examined patient. In severe cases, there are risks for decreases in blood pressure and heart rate, arrhythmia, and even cardiac arrest. Therefore, most patients need anesthesia intervention [3, 4]. Analgesia and sedation play a vital role in painless hysteroscopic minimally invasive surgery. At present, propofol is still the most commonly used anesthesia method in minimally invasive hysteroscopic surgery [5]. Still, it has a high incidence of complications such as injection pain and circulatory and respiratory depression [6, 7]. Remazolam is a new type of ultra-short-acting benzodiazepine, which has the characteristics of rapid onset, short maintenance and recovery time, no accumulation in tissues, metabolism's independence of liver and kidney function, and no significant side effects; where

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Table 1. Comparison of general clinical data between the two groups.

Groups	Group R (n = 55)	Group P (n = 55)	Chi square/*t*	*p*
ASA I/II (example)	30/25[a]	32/23	0.148	0.701
Age (years) ($\bar{x} \pm s$)	40.32 ± 8.76[a]	38.97 ± 9.01	0.787	0.433
Height (cm) ($\bar{x} \pm s$)	157.23 ± 5.03[a]	158.96 ± 5.36	1.745	0.083
Weight (kg) ($\bar{x} \pm s$)	55.76 ± 6.24[a]	56.13 ± 6.78	0.289	0.767
BMI (kg/m^2) ($\bar{x} \pm s$)	22.64 ± 2.26[a]	22.15 ± 2.13	1.170	0.245

ASA, American Society of Anesthesiologists; BMI, body mass index. [a]: Comparison of parameters between group R and group P.

Table 2. Details of major drugs used during surgery.

Drug names	Manufacturer	Specifications	Code Number Approved by SFDA of China
Remimazolam besylate for injection	Hubei Yichang Renfu Pharmaceutical Co. LTD	25 mg	H20200006
Propofol emulsion injection	Sichuan Guorui Pharmaceutical Co. LTD	20 mL:0.2 g	H20030115
Alfentanil hydrochloride injection	Hubei Yichang Renfu Pharmaceutical Co. LTD	2 mL:1 mg	H20203054

pharmacokinetics are not affected by chronic kidney disease, age, gender, race or weight, light cardiopulmonary inhibition, low risk of injection pain. It can be quickly reversed by flumazenil and has excellent safety [8, 9]. However, whether remimazolam can be safely and effectively used in hysteroscopic surgery or anesthesia remains to be studied. In this study, remimazolam and propofol were compared in more detail in hysteroscopic surgery, and the differences in hemodynamics, anesthesia induction time, operation time, anesthesia recovery time and incidence of adverse strains between the two were compared, and the purpose of this study was to investigate the efficacy and safety of remimazolam in hysteroscopic surgery.

Clinical Materials and Methods

Clinical Materials

The clinical data of 110 female patients who underwent painless hysteroscopic minimally invasive surgery in our hospital from January 2023 to June 2023 were collected. The patients were divided into the remimazolam group (group R, n = 55) and the propofol group (group P, n = 55) according to the main anesthetic drugs used during the operation. There was no significant difference in general clinical data between the two groups ($p > 0.05$), which was comparable (Table 1). This study was a retrospective study and received approval from the Medical Ethics Committee of Second Children & Women's Healthcare of Jinan City, China and exempt patients from informed consent (approval number: 20220067).

Inclusion Criteria

The inclusion criteria for patients in this study were: (1) Age 18–60 years; (2) Body mass (BMI) 18–25 kg/m^2; (3) patients who can tolerate anesthesia and hysteroscopy; and (4) American Society of Anesthesiologists (ASA) grade i–ii.

Exclusion Criteria

The exclusion criteria for patients in this study were: (1) Patients with severe dysfunction of the liver, kidney, heart, and other vital organs; (2) ASA grade ≥III; (3) Intolerance or allergy to remimazolam, propofol, sufentanil, and other drugs; (4) Poorly controlled preoperative blood pressure, systolic blood pressure >180 mmHg and/or diastolic blood pressure >110 mmHg; (5) Preoperative pulse oxygen saturation (SpO_2) <97%; (6) Long-term use of analgesic and sedative drugs, suspected abuse of drugs, narcotic sedative and analgesic drugs; and (7) Participated in other clinical trials within 4 weeks before surgery.

Major Drugs

Table 2 shows the details of the main drugs used in the operation.

Methods

Preoperative Preparation

All subjects were routinely fasted for 6 to 8 hours before surgery, and water was forbidden for 2 hours. No sedative, analgesic, anxiolytic, or antipruritic drugs were given to the patients 24 hours before surgery. All patients completed routine examinations before entering the hospital. After entering the room, the venous channels of the upper limbs were opened, and the electrocardiogram (ECG), heart rate (HR), mean arterial pressure (MAP), blood oxygen saturation (SpO_2), and respiratory rate (RR) were routinely monitored. The patients in both groups were placed in lithotomy position, and given oxygen inhalation by nasal oxygen tube with 4 L/min flow rate and intravenous injection of opioid analgesic drug alfentanil 10 μg/kg for preanalgesic treatment. According to the group, each drug was given respectively two minutes later.

Table 3. Comparison of heart rate (HR) between the two groups [beats/min, ($\bar{x} \pm s$)].

Groups	Number of cases	T_0	T_1	T_2	T_3	T_4
Group R	55	78.35 ± 5.01	73.13 ± 6.13^a	74.25± 5.72^a	76.88 ± 6.01	76.45 ± 5.78
Group P	55	78.44 ± 4.65	69.26 ± 7.21^b	71.33 ± 6.17^b	70.25 ± 6.24^b	71.44 ± 5.72^b
t		0.098	3.033	2.574	5.675	4.569
p		0.922	0.003	0.011	0.000	0.000

Note: Compared with T_0 in group R, $^a p < 0.01$; group P compared with T_0 time point within the group, $^b p < 0.01$.

Table 4. Comparison of mean arterial pressure (MAP) between the two groups [mmHg, ($\bar{x} \pm s$)].

Groups	Number of cases	T_0	T_1	T_2	T_3	T_4
Group R	55	95.22 ± 5.63	91.65 ± 6.12^a	92.36± 5.13^a	93.26 ± 5.58	93.78 ± 5.76
Group P	55	95.39 ± 4.69	89.47 ± 4.25^b	90.44 ± 4.25^b	91.01 ± 6.23^b	91.49 ± 6.12^b
t		0.172	2.170	2.137	1.995	2.021
p		0.864	0.032	0.035	0.049	0.046

Note: Compared with T_0 in group R, $^a p < 0.01$; group P compared with T_0 time point within the group, $^b p < 0.01$.

Induction and Maintenance of Anesthesia

(1) The Remimazolam Group (group R). Anesthesia was induced by intravenous pump injection of remimazolam besylate 6 mg·kg^{-1}·h^{-1} [10] and a revised observer Alertness/sedation assessment (MOAA/S) score of 0. The anesthesia maintenance dose of remimazolam besylate was adjusted to 1–2 mg·kg^{-1}·h^{-1}. If the MOAA/S score $\geq$1 or body movement occurred during the operation, 2.5 mg/time of remimazolam could be added as rescue sedation according to the need for anesthesia. If the MOAA/S score was still $\geq$1 or body movement occurred after the continuous addition of drugs more than 5 times, the MOAA/S score was still $\geq$1 or body movement occurred. If the number of consecutive additional drugs was more than 5 times, the MOAA/S score was still $\geq$1, or a body movement reaction occurred. The anesthesia was recorded as a failure, and propofol emulsion injection was recorded as a rescue drug to complete the operation.

(2) The Propofol Group (group P). Anesthesia was induced by intravenous injection of propofol 1.5 mg/kg, and the operation began when the MOAA/S was 0, and the maintenance dose of propofol was adjusted to 2–5 mg·kg^{-1}·h^{-1} by pump injection. If the MOAA/S score $\geq$1 or body movement occurred during the operation, If the MOAA/S score $\geq$1 or body movement happened during the operation, propofol 0.5 mg/kg could be added for rescue sedation. At the end of the operation, the drug was stopped, and the patient was sent to the postanesthesia care unit (PACU) for recovery.

Observation Indicators

① The changes of HR, MAP, SpO_2, and RR in the two groups were recorded at the time points of admission (T_0), MOAA/S = 0 (T_1), cervical dilatation (T_2), the end of operation (T_3) and anesthesia recovery (T_4). ② The time to induction of anesthesia (from the start of the injection until the eyelash reflex disappeared), the time to surgery (from the placement of the vaginal dilator to the withdrawal of the drug), and the time to recovery from anesthesia (from the withdrawal of the drug to the MOAA/S score of 5) were recorded. ③ Occurrence of adverse reactions.

Statistical Methods

The data were analyzed by SPSS23.0 software (IBM Corp, Chicago, IL, USA). Measurement data was confirmed to conform to a normal distribution and expressed as mean ± standard deviation ($\bar{x} \pm s$). An independent sample *t*-test was used to compare the data between the two groups. Count data were expressed as examples (%), and comparison between groups was analyzed by chi-square test. $p < 0.05$ was considered statistically significant.

Results

Hemodynamic and Respiratory Changes

Comparison of HR Changes at Different Time Points between the Two Groups

The HR of group R was significantly higher than that of group P at T_1, T_2, T_3, and T_4 time points ($p < 0.05$). In group R, HR at T_1 and T_2 was significantly lower than that at T_0 (t = 4.890, 3.999, p = 0.000, 0.000) ($p < 0.01$); There was no significant difference in HR between T_3, T_4 and T_0 (t = 1.391.842, p = 0.166, 0.068) ($p > 0.05$). HR at T_1, T_2, T_3, T_4 was significantly lower than that at T_0 in group P (t = 7.935, 6.825, 7.805, 6.710, p = 0.000, 0.000, 0.000, 0.000) ($p < 0.01$) (Table 3).

Comparison of MAP Changes at Different Time Points between the Two Groups

The MAP in group R was significantly higher than in group P at T_1, T_2, T_3, and T_4 ($p < 0.05$). For intra-group comparisons, the MAP at T_1 and T_2 was significantly lower than that at T_0 in group R (t = 4.967, 2.544, p = 0.000, 0.012) ($p < 0.05$). There was no significant difference in MAP be-

Table 5. Blood oxygen saturation (SpO_2) comparison between the two groups [%, ($\bar{x} \pm s$)].

Groups	Number of cases	T_0	T_1	T_2	T_3	T_4
Group R	55	98.23 ± 1.15	94.26 ± 2.36^a	95.32 ± 2.67^a	97.52 ± 2.89	97.65 ± 2.21
Group P	55	98.42 ± 1.09	93.15 ± 2.45^b	94.12 ± 3.01^b	95.99 ± 3.52^b	96.32 ± 3.25^b
t		0.889	2.420	2.212	2.491	2.506
p		0.376	0.017	0.029	0.014	0.013

Note: Compared with T_0 in group R, $^a p < 0.01$; group P compared with T_0 time point within the group, $^b p < 0.01$.

Table 6. Comparison of respiratory rate (RR) between the two groups [(times/min), ($\bar{x} \pm s$)].

Groups	Number of cases	T_0	T_1	T_2	T_3	T_4
Group R	55	17.21 ± 1.02	16.84 ± 0.98	16.97 ± 1.22	16.86 ± 0.98	16.88 ± 0.97
Group P	55	17.33 ± 0.93	17.12 ± 1.06	16.99 ± 1.13	16.96 ± 1.06	17.01 ± 0.87
t		0.645	1.438	0.089	0.513	0.740
p		0.521	0.153	0.929	0.609	0.461

tween T_3, T_4 at T_0 (t = 1.834, 1.326, p = 0.069, 0.188) ($p > 0.05$). MAP at T_1, T_2, T_3, T_4 was significantly lower than that at T_0 in group P (t = 6.937, 5.800, 4.166, 3.751, p = 0.000, 0.000, 0.000, 0.000) ($p < 0.01$) (Table 4).

Comparison of SpO_2 Changes at Different Time Points between the Two Groups

The SpO2 in group R was significantly higher than in group P at T_1, T_2, T_3, and T_4 ($p < 0.05$). For intra-group comparisons, the SpO_2 at T_1 and T_2 in group R was significantly lower than that at T_0 (t = 11.210, 7.424, p = 0.000, 0.000) ($p < 0.01$). There was no significant difference in SpO_2 between T_3, T_4 and T_0 (t = 1.693, 1.727, p = 0.093, 0.067) ($p > 0.05$). In group P, SpO_2 at T_1, T_2, T_3 and T_4 was significantly lower than that at T_0 (t = 14.580, 9.962, 4.891, 4.543, p = 0.000, 0.000, 0.000, 0.000) ($p < 0.01$) (Table 5).

Comparison of RR Changes at Different Time Points between the Two Groups

There was no significant difference in RR at T_1, T_2, T_3, and T_4 between the two groups ($p > 0.05$). There was no significant difference in RR between T_1, T_2, T_3, T_4 and T_0 in group R (t = 1.940, 1.119, 1.835, 1.826, p = 0.055, 0.266, 0.069, 0.070) ($p > 0.05$). There was no significant difference in RR between T_1, T_2, T_3, T_4, and T_0 in group P (t = 1.104, 1.273, 1.946, 1.864, p = 0.272, 0.826, 0.543, 0.065) ($p > 0.05$) (Table 6).

The Anesthesia Induction Time, Operation Time, and Anesthesia Recovery Time were Compared between the Two Groups

The anesthesia induction time in group R was significantly longer than that in group P ($p < 0.05$), and the anesthesia recovery time was considerably shorter than that in group P ($p < 0.05$). There was no significant difference in operation time between the two groups ($p > 0.05$) (Table 7).

Comparison of the Incidence of Adverse Reactions between the Two Groups

The incidences of hypotension, bradycardia, low oxygen saturation, respiratory depression, and injection pain in group R were significantly lower than those in group P ($p < 0.05$) (Table 8).

Discussion

Hysteroscopy is the gold standard for diagnosing intrauterine lesions, and using an endoscope to enter the uterine cavity can allow minimally invasive diagnosis and surgical treatment of cervical and intrauterine lesions [11]. Although this kind of surgery is minimally invasive, the implantation of instruments and intrauterine operation will still cause pain in patients. Hence, the choice of anesthesia is of great significance in reducing patients' pain and ensuring a smooth operation [12]. The choice of anesthetic drug is related to the success of painless hysteroscopic surgery and the possibility of complications.

At present, propofol is the most commonly used intravenous anesthetic for hysteroscopic noninvasive surgery, which has the advantages of fast onset, short time, and good recovery effect [13]. It is the most commonly used intravenous anesthetic for hysteroscopic noninvasive surgery. However, it has the risks of injection pain, falling tongue, respiratory depression, and circulatory depression, thus increasing the difficulty of intraoperative management [14]. Remimazolam is a new benzodiazepine sedative, whose main advantages include rapid onset/failure, predictable duration of action, metabolism's independence of organ function, availability of reversal drugs, and maintenance of stable hemodynamics [15]. It is an ideal sedative and anesthetic drug for procedural sedation and outpatient short surgery. The safety and effectiveness of remimazolam for endoscopic sedation have been internationally recognized, but there are relatively few observational studies on using remimazolam for non-invasive hysteroscopic surgery [16].

Table 7. Comparison of anesthesia induction time, operation time, and anesthesia recovery time between the two groups ($\bar{x} \pm s$).

Groups	Number of cases	Anesthesia induction time (s)	Operation time (min)	Anesthesia recovery time (min)
Group R	55	94.12 ± 8.15	18.09 ± 2.85	7.25 ± 2.01
Group P	55	88.96 ± 8.79	17.88 ± 3.01	8.64 ± 1.87
t		3.192	0.376	3.755
p		0.002	0.708	0.0003

Table 8. Comparison of incidence of adverse reactions between the two groups [n (%)].

Adverse reactions	Group R (n = 55)	Group P (n = 55)	χ^2	*p*
Low blood pressure	3 (5.45)	10 (18.18)	4.274	0.039
Bradycardia	2 (3.64)	8 (14.55)	3.960	0.047
Low oxygen saturation	3 (5.45)	12 (21.82)	6.253	0.012
Respiratory depression	4 (7.27)	12 (21.82)	4.681	0.031
Pain on injection	4 (7.27)	14 (25.45)	6.643	0.010
Body movement during surgery	2 (3.64)	5 (9.09)	1.373	0.241
Cough	2 (3.64)	4 (7.27)	0.705	0.401
Postoperative nausea and vomiting	3 (5.45)	6 (10.91)	1.089	0.297

Remimazolam has the structural characteristics of its parent compounds, midazolam, and remifentanil. Remimazolam specifically acts on γ-aminobutyric acid (GABA) receptors through the benzodiazepine binding site, thereby enhancing the activity of the inhibitory neurotransmitter GABA in the central nervous system and producing sedative and hypnotic effects. Therefore, it has the sedative effect of midazolam and the pharmacokinetic characteristics of remifentanil [17]. Other studies on the pharmacodynamics of remimazolam have also confirmed that remimazolam has an exact sedative effect, which is not inferior to midazolam or propofol, and its sedative effect has a rapid onset, short duration, rapid recovery, and good tolerance and safety [18, 19]. More importantly, flumazenil can reverse the sedative effect of remimazolam, but it cannot reverse propofol [20]. A study of remimazolam used in fiberoptic bronchoscopy found that the probability of respiratory depression with remimazolam was very low, and no patients experienced choking [21]. In another multicenter study, remimazolam was used for induction and maintenance, and it was found that remimazolam had less impact on the cardiovascular system compared to propofol, which was manifested as no significant reduction in heart rate, little change in blood pressure, and less use of vasoactive drugs [22]. Several studies have also confirmed that remazolam has a better safety for sedation and general anesthesia than propofol, including a lower incidence of hypotension, fewer bradycardia treatment requirements, and no pain during injection [10, 23].

In the results of this study, several advantages of remimazolam and propofol were found: (1) Remimazolam improved perioperative hemodynamics of hysteroscopy. HR, MAP, and SpO_2 in group R were significantly higher than those in group P at T_1, T_2, T_3, and T_4, and the decreased amplitude was significantly lower than in group P ($p < 0.05$). There was no significant difference in RR between the two groups ($p > 0.05$). HR, MAP, and SpO_2 are essential indicators for evaluating human hemodynamics and vital signs. Drastic fluctuations of these indicators during anesthesia will lead to severe patient stress responses, affecting their safety. The hemodynamic changes at each time point during operation in group R were more stable, which proved that the degree of inhibition of hemodynamics by remimazolam was less, which may be related to the stable respiratory function of remimazolam, the slight inhibition of cardiac function, and no significant changes in cardiac output within the safe range, which was also consistent with the research results of Fan *et al*. [24]. (2) Remimazolam increased the time of anesthesia induction but significantly shortened the time of anesthesia recovery during hysteroscopy. In terms of anesthesia onset and emergence, this study showed that the anesthesia induction time in group R was longer than in group P, and the emergence time of anesthesia was significantly shorter than that in group P, without increasing the operation time, indicating that the R group was superior to the P group in terms of emergence from anesthesia. (3) In terms of the incidence of adverse reactions, the incidence of hypotension, bradycardia, low oxygen saturation, respiratory depression, and injection pain in group R was significantly lower than that in group P; the difference was statistically significant ($p < 0.05$), and group R was better than group P. The analysis may be that compared with propofol; remimazolam can be metabolized *in vivo* through esterase, which has the advantages of short recovery time and good recovery. If patients have delayed recovery, flumazenil, a specific antagonist of benzodiazepines, can be used for antagonism in clinical practice to shorten patients' recovery time further and significantly reduce the incidence of adverse reactions [25].

Compared with other literature, this study studied in detail the differences in hemodynamics, anesthesia induction time, operation time, anesthesia recovery time and adverse

incidence rate between remimazolam and propofol in hysteroscopic surgery, proving the efficacy and safety of remimazolam in hysteroscopic surgery.
Limited by objective factors such as single-center and insufficient sample size, this study has certain limitations, and the application effect of the drug combination in obesity and the elderly group was not discussed in this study, which needs to be further supplemented in follow-up studies to improve the research conclusions.

Conclusion

Remimazolam can be safely and effectively used in the anesthesia of painless hysteroscopic surgery, and its safety and patient comfort are better than those of propofol anesthesia, which is worthy of popularization and application. Limited by objective factors such as a single center and insufficient sample size, this study has certain limitations, and the effect of this drug combination in the obese and elderly population has not been discussed in this study, which needs to be supplemented in further follow-up studies to improve the study conclusion. More extensive multi-center studies will be conducted in the future to improve the reliability and extensibility of the study.

Availability of Data and Materials

All experimental data included in this study can be obtained by contacting the first author if needed.

Author Contributions

FG and YJX designed the retrospective research. HWZ, CC and HYF performed the research and analyzed all the data gleaned. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

This retrospective study was approved by the Medical Ethics Committee of Second Children & Women's Healthcare of Jinan City, China (approval number: 20220067), ensuring the subject's privacy and confidentiality of identity information and waiving the requirement for patient's informed consent.

Acknowledgment

Not applicable.

Funding

This research received no external funding.

Conflict of Interest

The authors declare no conflict of interest.

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