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Effect of propofol combined with remimazolam besylate on blood pressure during general anesthesia induction in patients undergoing gynecological laparoscopic surgery: single-centre randomized controlled trial

Xinmin Zhao[1*], Haigen Xu[1], Shuping Wang[1], Yuanyuan Chen[1] and Shuyu Yue[1]

Abstract

Background Hypotension often occurs during intraoperative anesthesia induction in gynecological laparoscopic surgery. Remimazolam is reportedly associated with lesser intraoperative hypotension than propofol. This trial was conducted to evaluate the effect of propofol combined with remimazolam besylate on post-induction hypotension (PIH) in patients undergoing gynecological laparoscopic surgery.

Methods All enrolled patients were randomly assigned to receive propofol (Group P), remimazolam besylate plus propofol (Group PR), or remimazolam besylate (Group R). Patients in group P received 2.0 mg/kg propofol, Sufentanil 0.4 μg/kg, and rocuronium bromide 0.8 mg/kg; Patients in group PR received remimazolam besylate 0.2 mg/kg, propofol 1.0 mg/kg, Sufentanil 0.4 μg/kg, and rocuronium bromide 0.8 mg/kg; Patients in group R received remimazolam besylate 0.4 mg/kg, Sufentanil 0.4 μg/kg, and rocuronium bromide 0.8 mg/kg; the anesthesia was maintained with propofol 4–10 mg/kg/h and remifentanil 0.1–0.3 μg/kg/min.

The primary outcome was the incidence of hypotension after anesthesia induction. Hypotension was defined as a mean arterial pressure (MAP) reduced 30% or more from the baseline MAP value or MAP < 65 mmHg. Blood pressure was recorded five times during anesthesia. Time points T0, T1, T2, T3 and T4, were base line, before tracheal intubation, 1 min after tracheal intubation, 5 min after intubation, and immediately after surgical skin incision, respectively.

The secondary outcomes were heart rate and bispectral index (BIS). Heart rate and BIS were measured from T0 to T4.

Results One hundred sixty-nine patients were included in this study. A total of 30 patients in the three groups developed hypotension after anesthesia induction, among which the incidence of PIH induced in group P was 31.6% (18/57), the incidence of PIH induced in group PR was 14.3% (8/56), and the incidence of PIH induced group R 7.1% (4/56), and there was a statistical difference in the incidence of PIH between the three groups ($\chi 2 = 12.24$, $p = 0.0022$).

The heart rates in group R (70.53 ± 13.36 bpm, 88.48 ± 13.53 bpm, and 72.68 ± 13.42 bpm) were significantly higher than that in group P (63.68 ± 10.76 bpm, 80.25 ± 12.50 bpm, and 66.35 ± 11.56 bpm) at T1, T2 and T4 ($p < 0.05$, respectively). The heart rate in group R (88.48 ± 13.53 bpm) was significantly higher than that in group PR (80.00 ± 13.42 bpm) at T2 ($p < 0.05$). There was no statistically significant difference between group PR and group P ($p > 0.05$).

*Correspondence:
Xinmin Zhao
zxmfby@163.com

BIS was significantly higher in group R than that in group P and in group PR at T3 and T4 ($p < 0.05$, respectively). There was no statistically significant difference between group PR and group P ($p > 0.05$).

Conclusions Both Propofol plus remimazolam besylate and remimazolam besylate alone can reduce PIH, but propofol plus remimazolam besylate smooths the heart rate after general anesthesia undergoing gynecological laparoscopic.

Trial registration This trial was retrospectively registered at http://www.chictr.org.cn (06/06/2024, ChiCTR-2400085401).

Keywords Propofol, Remimazolam, Post-induction hypotension, General anesthesia

Introduction

Post-induction hypotension (PIH) immediately after general anesthesia induction is a common complication, which is related to poor postoperative outcomes, and propofol is a commonly used induction drug for general anesthesia, with an incidence of about 20%−50% [1, 2]. Propofol, sufentanil, and rocuronium bromide are commonly used sequential induction drugs for general anesthesia, and their cardiovascular inhibition often leads to hypotension after anesthesia induction.

Blood volume is an important factor influencing blood pressure [3]. However, ultrasound-derived IVC parameters showed poor diagnostic accuracy in predicting hypotension after induction in healthy adult patients [4]. Hypersympathetic activity in patients before surgery often masks volume depletion [5], Moreover, moderate fluid infusion before anesthesia cannot clearly prevent hypotension after anesthesia induction [6]. Therefore, we need to take the necessary and effective interventions to stop the occurrence of hypotension after anesthesia induction. Remimazolam has been reported to be associated with lesser hypotension than propofol [7–9].

Gynecological laparoscopic surgery has requirements for mechanical bowel preparation (MBP), and hypotension often occurs during intraoperative anesthesia induction, while remimazolam besylate is rarely studied in anesthesia induction in gynecological laparoscopic surgery. This study intends to evaluate the effect of propofol combined with remimazolam besylate on blood pressure after general anesthesia induction in patients undergoing gynecological laparoscopic surgery, and provide a reference for the rational use of induction drugs under general anesthesia in such patients.

Methods

Patients

This study was designed as a prospective, randomized, parallel-controlled trial. The trial protocol was approved by the consent of the Medical Ethics Committee of Yancheng Maternal and Child Health Care Hospital Affiliated to Yangzhou University, the patient herself signed an informed consent form to select patients with elective gynecological laparoscopic surgery under tracheal intubation under general anesthesia, with American Society of Anesthesiologists (ASA) grade I or II, aged 19–65 years old. Exclusion criteria: those who participated in other clinical trials at the same time, refused to participate in this trial, body mass index (BMI) > 35, Non-lithotomy surgery, hypertension, and those who were allergic to fat emulsion or remimazolam besylate. This study complied with the 1964 Helsinki Declaration and its subsequent amendments.

Grouping and intraoperative intervention

After the patient was admitted to the operating room, the peripheral vein was opened for continuous intravenous infusion, An arterial catheter was inserted into the right radial artery under ultrasound guidance for hemodynamic monitoring of blood pressure (MAP), and the heart rate (HR), pulse oximetry (SpO_2) and bispectral index (BIS) (BIS Complete Monitoring system, Covidien Ire land Limited, Dublin, Ireland) were monitored at the same time during the operation.

Patients in group P received 2.0 mg/kg propofol (Liaoning Haisike Biopharmaceutical Co., Ltd., China. LOT No., 20,221,213), Sufentanil 0.4 μg/kg (Yichang Humanwell Biopharmaceutical Co., Ltd., China. LOT No., 21 A11271), and rocuronium bromide 0.8 mg/kg (guangdong Xinghao Pharmaceutical Co., Ltd., China. LOT No., 139,231,101).

Patients in group PR received remimazolam besylate 0.2 mg/kg (Yichang Humanwell Biopharmaceutical Co., Ltd., China. LOT No., 30 T10151), propofol 1.0 mg/kg (Liaoning Haisike Biopharmaceutical Co., Ltd., China. LOT No., 20,221,213), Sufentanil 0.4 μg/kg (Yichang Humanwell Biopharmaceutical Co., Ltd., China. LOT No., 21 A11271), and rocuronium bromide 0.8 mg/kg (guangdong Xinghao Pharmaceutical Co., Ltd., China. LOT No., 139,231,101).

Patients in group R received remimazolam besylate 0.4 mg/kg (Yichang Humanwell Biopharmaceutical Co., Ltd., China. LOT No., 30 T10151), Sufentanil 0.4 μg/kg (Yichang Humanwell Biopharmaceutical Co., Ltd., China. LOT No., 21 A11271), and rocuronium bromide 0.8 mg/

kg (guangdong Xinghao Pharmaceutical Co., Ltd., China. LOT No., 139,231,101).

All patients were intubated by a skilled anesthesiologist 90 s after rocuronium injection. After fixing the endotracheal tube, it was connected to the anesthesia machine for controlled breathing, the inhaled oxygen concentration was 60%−70%, the oxygen flow rate was 2 L/min, the tidal volume was 6–8 mL/kg, the inhalation-exhalation ratio was 1:1.5–1:2.0, the respiratory rate was 12 times/min, the partial pressure of end-tidal carbon dioxide (PET CO_2) was maintained at 35–45 mmHg during the operation, and the anesthesia was maintained with propofol 4–10 mg/kg/h and remifentanil 0.1–0.3 μg/kg/min.

Variables and assessments

The primary outcome was the incidence of hypotension after anesthesia induction. Hypotension was defined as a mean arterial pressure (MAP) reduced 30% or more from the baseline MAP value or MAP < 65 mmHg.

Blood pressure was recorded five times during anesthesia. Time points T0, T1, T2, T3 and T4, were base line, before tracheal intubation, 1 min after tracheal intubation, 5 min after intubation, and immediately after surgical skin insection, respectively.

The secondary outcomes were heart rate and BIS. Heart rate and BIS were measured from T0 to T4.

Management of adverse events

In the case of PIH, one phenylephrine bolus(50 μg) or dopamine 1 mg was given intravenously and urapidil 15 mg was used when blood pressure was more than 30% above the basal value; Atropine 0.3 mg intravenous bolus when heart rate was below 50 beats per minute, and esmolol 30 mg when heart rate was above 120 beats per minute, which can be used repeatedly.

Sample size

According to the references and the previous observation of 50 patients with endotracheal intubation in our hospital, the probability of post-induction hypotension was 50% in group P, 20% in group PR and 8% in group R, and the level of hypothesis testing was determined: $\alpha = 0.05$, $\beta = 0.1$, and the sample size required for each group was about 51 cases by pass11.0 software, and the sample size required for each group was 57 cases considering the dropout rate of 10%.

Randomization and masking

All enrolled patients were randomly assigned to receive propofol (Group P), remimazolam besylate plus propofol (Group PR), or remimazolam besylate (Group R). A randomization scheme was generated by SPSS 26.0 software (SPSS Inc., Chicago, IL, USA). Randomized results were sealed in sequentially numbered envelopes until the end of the study.

The anesthesia induction drug was drawn by the anesthetist nurse who did not participate in the study with a syringe in the pre-anesthetic room, and the outside of the syringe was wrapped in opaque tin foil and handed over to the anesthesiologist (Dr. Xu) for general anesthesia induction; The patient did not know which group she was in, and the trial data was recorded by another anesthesiologist (Dr. Wang) who did not know the group. Postoperative follow-up visits were also recorded by another anesthesiologist (Dr. Chen) who was unaware of the grouping.

Statistical analysis

The Kolmogorov–Smirnov test was performed on the quantitative data to determine their normal distribution assumptions, and the results were expressed as the mean ± standard deviation ($\bar{x} \pm s$) where the normal distribution was conformed, otherwise in the median and quartile ranges. One-way analysis of variance (ANOVA) was used for comparison between groups, and Tukey method was used for comparison between two groups. If the variance is uneven, the Welch test is used, and the Games-Howell method is used for pairwise comparison. ANOVA of repeated measures data was used for comparison of different time points within groups, and the Dunnett method was used. Count data were expressed in cases (%), and comparisons were made using the chi-square test or Fisher's exact test. All statistical analyses were performed using SPSS (version 26.0 IBM, USA) and graphing was performed using GraphPad prism 8.0 (GraphPad Software, La Jolla, CA, USA), A $P < 0.05$ was considered statistically significant. For the significant results, multiple comparisons of the enumeration data (group P to group R, group P to group PR, group R to group PR) were performed, and the α lever was set at 0.017.

Results

From April 2023 to December 2023, 202 patients were assessed for eligibility and 169 patients were enrolled. 33 patients were excluded due to not meeting the recruitment criteria, refusing to participate, or combining hypertension. Finally, 169 patients were enrolled and randomly assigned to group P ($n = 57$), group R ($n = 56$) or group PR ($n = 56$) (Fig. 1).

The baseline characteristics, including age, height, weight, body mass index (BMI), ASA classification, basal blood pressure, basal heart rate, preoperative red blood cells, preoperative hemoglobin and preoperative albumin were of no significant difference among the three groups ($p > 0.05$, respectively) (Table 1). During anesthesia

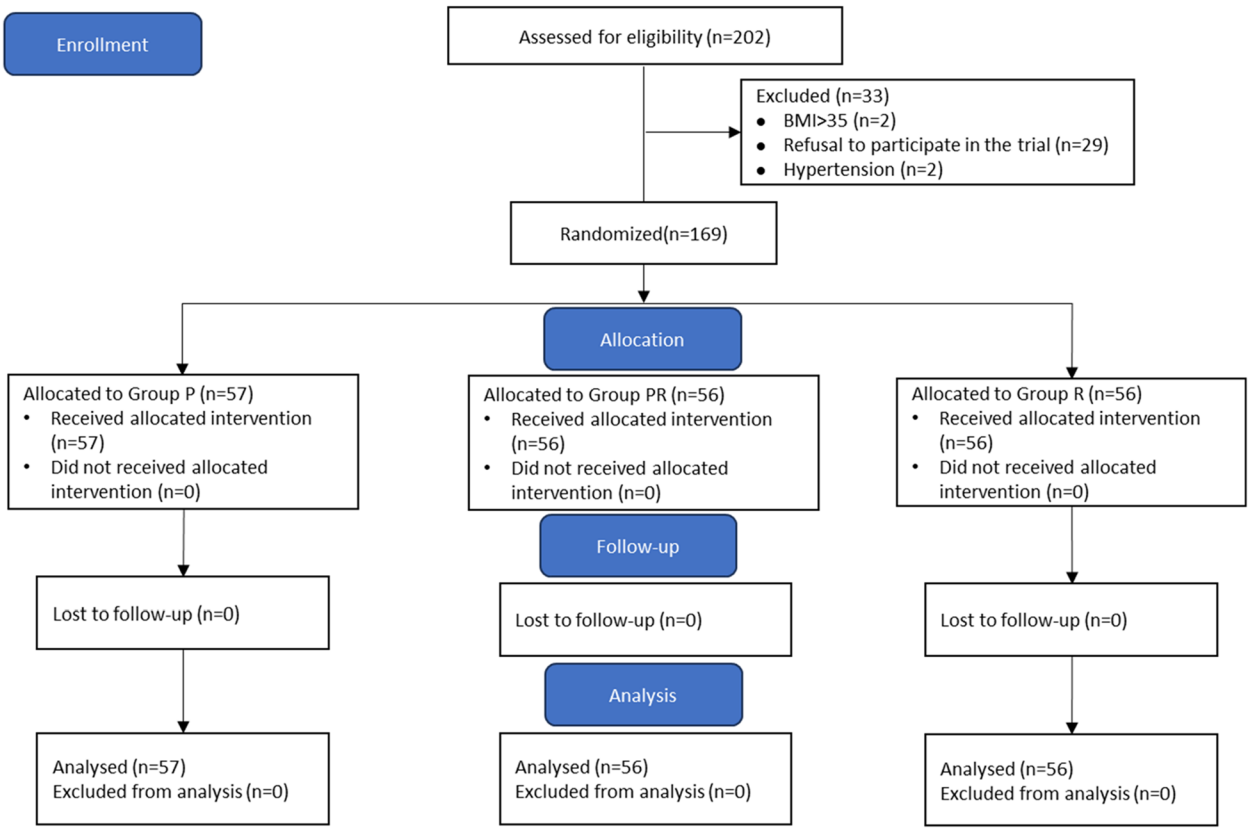

Fig. 1 Consolidated standards of reporting trials (CONSORT) 2010 flow diagram of patient's distribution

Table 1 Baseline characteristics and dopamine usage

	Group P($n=57$)	Group PR($n=56$)	Group R($n=56$)
Age (y)	44.9 ± 12.0	42.0 ± 10.3	43.6 ± 11.3
Height (cm)	159.5 ± 5.0	160.2 ± 4.7	159.2 ± 5.6
Body weight (kg)	61.5 ± 7.2	61.2 ± 10.1	61.7 ± 11.0
Body mass index (BMI)	24.3 ± 2.8	23.8 ± 4.5	24.3 ± 3.5
ASA classification			
I	29 (50.9%)	28 (50.0%)	30 (53.6%)
II	28 (49.1%)	28 (50.0%)	26 (46.4%)
Basal blood pressure (mmHg)	96.1 ± 13.3	95.9 ± 11.7	96.8 ± 12.8
Basal heart rate (bpm)	85.3 ± 15.2	86.0 ± 14.9	85.2 ± 13.7
Preoperative red blood cells ($\times 10^{12}$)	4.2 ± 0.4	4.1 ± 0.4	4.2 ± 0.3
Preoperative hemoglobin (g)	123.1 ± 15.3	121.1 ± 15.6	126.0 ± 15.5
Preoperative albumin (g)	44.6 ± 3.9	46.0 ± 3.5	45.3 ± 3.6
Dopamine usage (mg)	0.25 ± 0.45	0.09 ± 0.28*	0.06 ± 0.16*

Compared to group P, * $P < 0.017$, Tukey's multiple comparisons test was done

There were no significant differences in the other baseline characteristics. *ASA* American Society of Anesthesiologists

induction, the total dose of dopamine in group PR (0.09 ± 0.28 mg) and group R (0.06 ± 0.16 mg) were lower than that in group P (0.25 ± 0.45 mg; $p < 0.01$) (Table 1).

A total of 30 patients in the three groups developed hypotension after anesthesia induction, among which the incidence of PIH induced by propofol general anesthesia was 31.6% (18/57), the incidence of PIH induced

by propofol combined with remimazolam besylate was 14.3% (8/56), and the incidence of PIH induced by remimazolam general anesthesia was 7.1% (4/56), and there was a statistical difference in the incidence of PIH between the three groups ($\chi 2 = 12.24$, $p = 0.0022$) (Table 2). There was no statistically significant difference in the incidence of PIH induced by propofol combined with remimazolam besylate general anesthesia and remimazolam besylate general anesthesia ($p = 0.3602$). There were statistically significant differences in the incidence of PIH induced by propofol general anesthesia induced by propofol combined with remimazolam besylate and remimazolam besylate general anesthesia ($p < 0.017$).

The blood pressure decreased after anesthesia induction and increased following placement of the endotracheal tube decreased again in groups. The MAPs in group R (80.56 ± 7.82 mmHg, 95.66 ± 12.54 mmHg) were significantly higher than that in group P (64.86 ± 8.53 mmHg, 86.30 ± 11.48 mmHg) at T1 and T2 ($p < 0.001$, respectively). MAP in group PR (70.29 ± 9.56 mmHg) was significantly higher than that in group P (64.86 ± 8.53 mmHg) at T1 ($p = 0.003$) (Fig. 2). In group P, compared to T0 the MAPs at T1, T2, T3 and T4 were significantly lower ($p < 0.017$, respectively). Similarly, in group PR, compared to T0 the MAPs at T1, T2, T3 and T4 were significantly lower ($p < 0.017$, respectively). In group R, compared to T0, MAP at T2 had not significant difference ($p > 0.05$), but the MAPs at T1, T3 and T4 were significantly lower ($p < 0.017$, respectively).

The heart rate decreased after anesthesia induction, increased and then decreased again during endotracheal intubation in three groups. The heart rates in group R (70.53 ± 13.36 bpm, 88.48 ± 13.53 bpm, and 72.68 ± 13.42 bpm) were significantly higher than that in group P (63.68 ± 10.76 bpm, 80.25 ± 12.50 bpm, and 66.35 ± 11.56 bpm) at T1, T2 and T4 ($p < 0.05$, respectively). The heart rate in group R (88.48 ± 13.53 bpm) was significantly higher than that in group PR (80.00 ± 13.42 bpm) at T2 ($p < 0.05$). There was no statistically significant difference between group PR and group P ($p > 0.05$) (Fig. 3).

The bispectral index (BIS) maintained between 40–60 after anesthesia induction. They were significantly higher in group R than that in group P and in group PR at T3 and T4 ($p < 0.05$, respectively). There was no statistically significant difference between group PR and group P ($p > 0.05$) (Fig. 4).

Table 2 The incidences of PIH between the three groups

Groups	PIH	Non-PIH	χ2 test	
	[n (%)]	[n (%)]	χ2 value	*P-value*
Group P($n = 57$)	18 (31.6)	39 (68.4)	12.24	0.0022
Group PR($n = 56$)	8 (14.3)	48 (85.7) *		
Group R($n = 56$)	4 (7.1)	52 (92.9) *		

PIH post-induction hypotension. Compared to group P, * $P < 0.017$; χ2 test or Fisher's exact test was applied for each variable

Discussion

Hypotensive events in the early stages of anesthesia can lead to serious complications in patients after surgery, which can be fatal, and post-induction hypotension (PIH) is prevalent in patients with general anesthesia and is associated with poor perioperative outcomes [10]. Furthermore, with intravenous use of the general anesthetic drugs propofol and sufentanil, sympathetic activity and vascular baroreflex are suppressed, resulting in hypotension most likely to occur 4 min to 1 min before endotracheal intubation and between

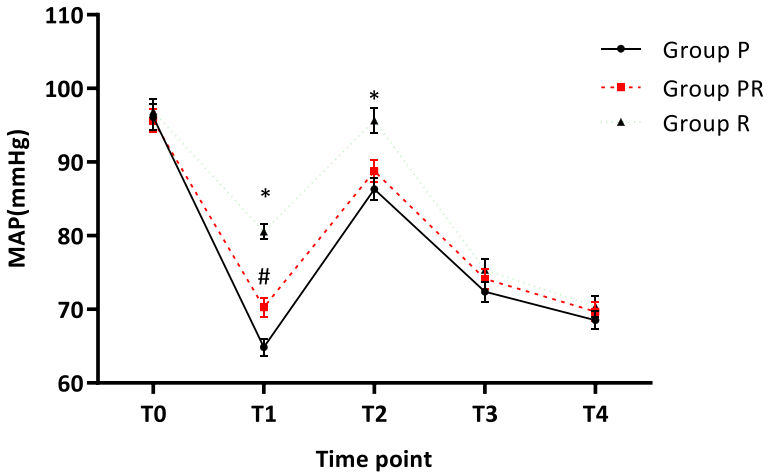

Fig. 2 Mean arterial pressure at each time point. MAP, Mean arterial pressure. Tukey's multiple comparisons test was done, Group R compared to group P at T1 and T2, *$P < 0.001$.Group PR compared to group P at T1, #$P = 0.003$

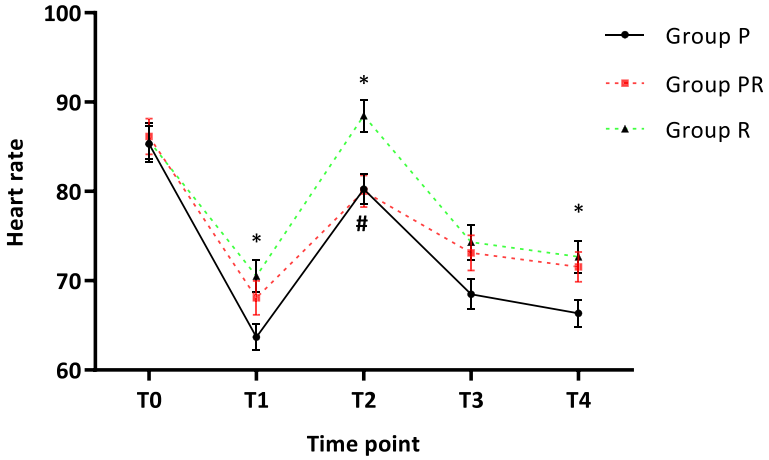

Fig. 3 Heart rate at each time point. Tukey's multiple comparisons test was done, Group R compared to group P at T1, T2 and T4, *$P < 0.05$. Group R compared to group PR at T2, #$P < 0.05$. There was no statistically significant difference between group PR and group P

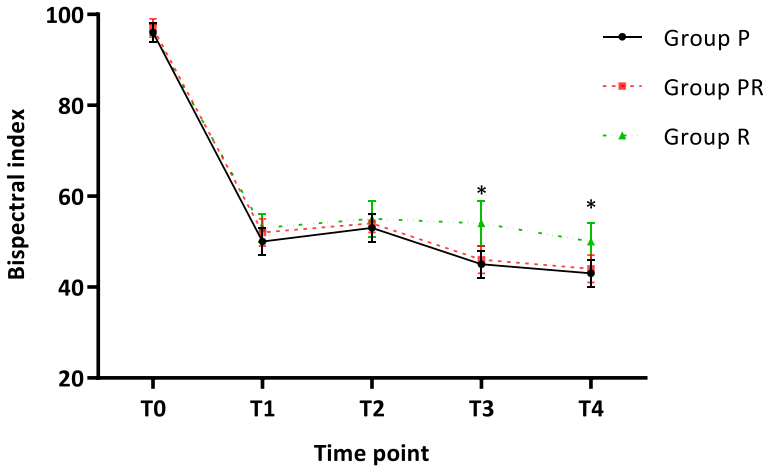

Fig. 4 Bispectral index at each time point. Tukey's multiple comparisons test was done,Group R compared to group P and group PR at T3 and T4, *$P < 0.001$. There was no statistically significant difference between group PR and group P ($P > 0.05$)

endotracheal intubation and skin incision [11, 12]. As the most commonly used intravenous general anesthesia induction drug, the main mechanisms of propofol inducing blood pressure drop are decreased myocardial contractility, venous dilation with decreased venous return, and arterial dilation with decreased systemic vascular resistance [13, 14]. As an intravenous benzodiazepine, remimazolam besylate has a mild cardiovascular inhibitory effect [15]. The heart rate increased to a certain extent during anesthesia induction alone, and this study showed that the heart rate in the remimazolam group was higher than that in the other two groups after anesthesia induction. The use of remimazolam besylate combined with propofol can not only moderately reduce the dose of propofol, thereby reducing its inhibitory effect on the cardiovascular system, but also maintain a certain depth of anesthesia, so that the blood pressure and heart rate are not too high during tracheal intubation. The results of this study showed that the BIS values of the P group and the PR group were similar, but the count of hypotension after anesthesia induction in the remimazolam combined with propofol group was significantly less than that in the propofol group alone, and the amount of dopamine used in the propofol group was significantly higher than that in the remimazolam combined with propofol group. The incidence of PIH in group R was also significantly lower than that in group P, but the heart rate was fast during endotracheal intubation, and the subsequent BIS was also high, proving that remimazolam

combined with propofol anesthesia induction made the patient's blood pressure and heart rate more stable under the same degree of sedation.

Different doses of propofol have an effect on the depth of sedation [16], the higher the dose to achieve the deeper the depth of sedation, and the shorter the time required, 2.0 mg/kg propofol anesthesia induces a BIS value of 60, it takes about 70 s, at this time the body's arteries are dilated, vagus nerve is excited, and blood pressure drops. Thinking that a certain amount of propofol induction should be able to inhibit the stress response during endotracheal intubation, we chose 0.5 mg/kg, 1.0 mg/kg and 1.5 mg/kg of propofol combined anesthesia induction, in which remimazolam 0.2 mg/kg combined with propofol 1.0 mg/kg was induced, and the time required for the BIS value to reach 60 was about 70 s. This is consistent with the time required for the control group to reach 60 for propofol 2.0 mg/kg anesthesia induction BIS value, where the depth of sedation is assumed to be the same. Therefore, remimazolam 0.2 mg/kg combined with propofol 1.0 mg/kg was selected as the test group.

The correlation between propofol and BIS is clear, while the association between BIS and remimazolam needs further research [17]. Tracheal intubation is performed when all patients'BIS values were below 60. This aligns with the established BIS threshold of 40–60 for adequate general anesthesia [18]. However, our data showed Group R maintained higher BIS values at T3 and T4, coinciding with the exaggerated hemodynamic response to intubation. This suggesting Group R patients were at the borderline of consciousness. Furthermore, indices produced by the different commercial monitors can give highly discordant results when analysing changes in the frontal EEG [19]. Our findings suggest the need for multimodal depth assessment combining BIS with hemodynamic trend analysis.

Prolonged hypotension (defined as MAP < 65 mmHg for > 10 min) may contribute to metabolic acidosis, particularly when accompanied by serum lactate > 2 mmol/L [20], and a decrease in pH often leads to serious postoperative complications [21]. No deaths occurred during the hospitalization period in either study group of patients in the 30-day follow-up, which may be that the subjects of this study were young and middle-aged patients with ASA grade I or II, and there were no elderly patients with poor compensatory ability, and serious postoperative complications were not only related to hypotension after anesthesia induction, but also related to prolonged intraoperative hypotension [21]. Anesthesiologists should be actively involved in perioperative management, especially to ensure the stability of the cardiovascular system during surgery, so as to improve the postoperative mortality rate of patients [22].

This study has several limitations. First, the exclusive focus on female patients undergoing gynecologic laparoscopic surgery limits the generalizability of our findings to other populations (e.g., males, non-gynecologic procedures). Second, as a single-center study with a relatively small sample size ($n = 57$), the results may be influenced by institutional-specific practices and lack the statistical power to detect rare outcomes. Third, vasopressors should prioritize the first-line vasopressor drugs listed in the guidelines, such as ephedrine or norepinephrine. Dopamine should be used as a second-line vasopressor. While these constraints are typical for early-stage investigations, future multicenter studies with larger, more diverse cohorts are needed to validate our conclusions.

In summary, Propofol combined with remimazolam not only reduces PIH but also stabilizes the heart rate after general anesthesia induction in patients undergoing gynecological laparoscopic surgery, which is worthy of clinical application.

Acknowledgements
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Authors' contributions
Xinmin Zhao, Shuyu Yue and Yuanyuan Chen designed the study. Haigen Xu and Shuping Wang recruited patients and collected data. Xinmin Zhao performed statistical processing and wrote the manuscript. All authors reviewed the manuscript.

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This study was self-financed.

Data availability
The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
The trial protocol was approved by the consent of the Medical Ethics Committee of Yancheng Maternal and Child Health Care Hospital Affiliated to Yangzhou University (2023-LW-003, approval date: January 15, 2023). This trial was retrospectively registered at http://www.chictr.org.cn (06/06/2024, ChiCTR-2400085401). The study protocol followed the CONSORT guidelines. The study protocol was performed in the relevant guidelines. Written informed consent was obtained from all patients.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]Department of Anesthesiology, Yancheng Maternal and Child Health Care Hospital Affiliated to Yangzhou University, Yancheng, Jiangsu Province 224000, P. R. China.

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