CLINICAL TRIAL REPORT

Cardiopulmonary Adverse Events of Remimazolam versus Propofol During Cervical Conization: A Randomized Controlled Trial

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Purpose: This study aimed to compare the cardiopulmonary safety of remimazolam and propofol in patients undergoing cervical conization.

Methods: This was a single-blind, parallel, randomized controlled study. A total of 204 patients scheduled for day surgery of cold knife cervical conization received either remimazolam-alfentanil anesthesia (remimazolam group) or propofol-alfentanil anesthesia (propofol group). The primary outcome was the incidence of intraoperative cardiopulmonary adverse events (a composite outcome of hypotension, bradycardia and hypoxemia). The occurrence of hypotension, bradycardia, hypoxemia and the degree of body movement were secondary outcomes, as well as the moment at which consciousness was lost, the interval between the end of anesthesia and the operating room's release of the patient, and the overall dosage of alfentanil administered during the procedure.

Results: The incidence of intraoperative cardiopulmonary adverse events was 45 (44.1%) in the remimazolam group and 72 (70.6%) in the propofol group (absolute risk difference [95% CI], −26.47% [−39.55% to −13.39%]; odds ratio (OR) [95% CI], 0.43 [0.28 to 0.65]; $P < 0.001$). The remimazolam group showed lower incidences of hypotension and hypoxemia compared to the propofol group ($P = 0.01$ for both). No significant differences were observed in the overall alfentanil dosages administered, bradycardia, bodily movement, or time to losing consciousness between the two groups.

Conclusion: In patients who underwent cold knife cervical conization, remimazolam-alfentanil anesthesia was associated with a reduced incidence of intraoperative cardiopulmonary adverse events compared with propofol-alfentanil anesthesia.

Keywords: adverse events, alfentanil, cervical conization, general anesthesia, propofol, remimazolam

Introduction

Cervical conization is a crucial procedure for identifying and managing cervical abnormalities. It significantly reduces the risk of relapse and patients mortality before undergoing a severe hysterectomy.[1,2] Therefore, it has become a standard practice before radical hysterectomy,[3] usually performed in an office or as a day surgery due to its short duration. Cervical conization can be performed under various anesthesia types, such as local anesthesia, local/regional block anesthesia, spinal anesthesia or general anesthesia. Among them, general anesthesia is preferred by anesthesiologists and day case surgeons[4] as it provides a superior hypnotic effect without affecting postoperative ambulation. Besides, it is known that the cone depth and volume are higher for loop electrosurgical excision procedure specimens conducted under general anesthesia than local anesthesia.[4,5] Cervical traction and excessive nervousness may cause vagal reflex, further worsening the decrease in venous return to the heart. Reports of cardiac arrest during cervical conization have also been documented.[6] Therefore, general anesthesia is considered the superior approach for cervical knife conization.[7] The general anesthesia regime for typically involves a hypnotic such as propofol and opioid.[8,9] Propofol is a rapid-onset and offset hypnotic suitable for short operations such as gastroenteroscopy, fiberoptic bronchoscopy and hysteroscopy. However, propofol's use carries a dose-dependent risk of hemodynamic and respiratory compromise.[10,11]

Remimazolam, a recently synthesized benzodiazepine sedative, which contains a rapidly hydrolyzed ester linkage,[12] can be used for procedural sedation, induction and maintenance of general anaesthesia, and sedation of patients in the intensive care unit (ICU).[13,14] Compared to propofol, remimazolam demonstrated a lower incidence of hypotensive events and injection site pain.[15] Thus, remimazolam has been suggested as a safer option for inducing drowsiness during minor surgical operations.[16]

Alfentanil has been approved as a supplement to general anaesthesia with a very rapid onset action (5 to 10 min).[17] Its use may prevent respiratory depression following loss of responsiveness within a limited range of safety.[18] For sedation during colonoscopy, gastrointestinal system endoscopy and hip fracture surgery, alfentanil and propofol have been extensively utilized.[19–21] However, there are cardiac side effects associated with a combination of alfentanil and propofol, such as systolic hypotension, bradycardia and hypoxemia,[22] which should not be ignored. A recent published research showed that moderate sedation induced by remimazolam and alfentanil caused less adverse events compared to propofol–alfentanil combination during third molar extraction. It is unknown whether a combination of remimazolam and alfentanil anesthesia would show advantages in terms of reducing cardiopulmonary adverse events compared with the propofol–alfentanil combination.

This study aimed to investigate whether combined alfentanil with remimazolam could reduce cardiopulmonary adverse events during cold knife cervical conization compared to propofol-alfentanil anesthesia.

Materials and Methods
Study Design
This was a single-blind, randomized, parallel-group clinical trial that was approved by the Medicine Ethics Committee of Xijing Hospital (Document number: KF20212105- F-1; Approval data: August 2021) and registered at Chictr.org (ChiCTR2100048855; Registration data: July 2021). The study was conducted in compliance with the Declaration of Helsinki, and the design and report of the study followed the Consolidated Standards of Reporting Trials (CONSORT) principles.

Participants
Written informed consent was obtained from patients between September 2021 and October 2022 before their enrollment in the study. Patients who were scheduled to undergo cervical conization under general anesthesia and were aged from 18 to 65 years, with a body mass index (BMI) ranging from 18.5 to 30 kg/m^2, were included in the study. Patients with a history of serious heart, brain, lung, liver, kidney or metabolic diseases, neuromuscular system disease or mental illness, history of narcotic analgesics or tranquilizers abuse, known allergic history of emulsions, benzodiazepines or opioids, and those who were unable to cooperate or communicate with the study team were excluded from the study.

Randomization and Blinding
The patients were assigned randomly to either the propofol or remimazolam groups at 1:1 ratio using permuted blocks of four, through a central web-based system. The anesthesiologists were not blinded, as there were clear visual differences in the packaging of propofol and remimazolam. The remaining participants, including patients, outcome assessors, follow-up staff, and the statistician, were kept blind throughout the study.

Interventions and Assessments
The patients' baseline vital signs were monitored upon their entry into the operating room, and they were provided with pre-oxygen at 100%. If there were no contraindications, dexamethasone was administered to prevent nausea and vomiting. Flurbiprofen axetil was given for pain relief.

Before being disinfected, all the enrolled patients were administered alfentanil (Yichang Humanwell Pharmaceutical CO. Ltd., China) at a dose of 7 μg/kg body weight. In the remimazolam group, a bolus of remimazolam besylate (Yichang Humanwell Pharmaceutical CO. Ltd., China) at a dose of 0.2 mg/kg was administered over a period of 30 s, followed by an infusion at 1 to 1.5 mg/kg/h. For the propofol group, patients were given propofol (Fresenius Kabi AG, Austria) at a dose of 2 mg/kg, followed by an infusion at 6 to 8 mg/kg/h. The operation procedure commenced after

patients had lost consciousness. During operation, patients in both groups received additional doses of alfentanil as required during operations. All patients received an oxygen supplement via masks at a flow rate of 5 L/min.

Vital signs and end-tidal carbon dioxide ($EtCO_2$) levels were continuously monitored and recorded at 1, 3, 6, 9, 12, 15, 20, 25 and 30 min after induction. The initiation of anesthetic induction was considered as the beginning of sedative (remimazolam or propofol) administration. Loss of consciousness was defined as the absence of the eyelash reflex in patients. The time to loss of consciousness is defined as the duration from the initiation of sedative administration and the detection of loss of consciousness symptoms.

If analgesia were insufficient (heart rate >100 beats/min or sudden increase of more than 20 beats/min over baseline), the dose of alfentanil was increased by 2 μg/kg body weight. Sedatives were increased if there were indications of insufficient sedation (facial grimace, body movement of grade 3 or 4, SBP > 140 mmHg) and decreased if there were signs of excessive sedation (respiratory depression, hypotension). The airway maneuver (including jaw lift and bag-mask ventilation) will be implemented if pulse oxygen saturation (SpO_2) remained below 90% for more than 1 min for all subjects. In cases of refractory hypoxemia or continued decline in SpO_2, manual ventilation may be necessary. If the systolic blood pressure drops below 80mmHg and the heart rate falls below 40 bpm, pharmacological interventions such as atropine, vasopressors and/or inotropic agents should be considered.

Outcome Measures

The primary outcome was the incidence of cardiopulmonary adverse events during operation, which included hypotension, bradycardia and hypoxemia. Hypotension was defined as systolic blood pressure (SBP) of less than 90 mmHg or a decrease of more than 20% from baseline. Bradycardia was defined as a heart rate of less than 50 bpm. Hypoxemia was recorded when pulse oxygen saturation (SpO_2) dropped below 90% during the operation.

The secondary outcomes included each of the component of the primary outcome, as well as vital signs during the operation, the time to loss of consciousness, awakening time at the end of surgery, time of discharge from operating room (defined as the time from the end of the procedure to patients discharge from operation room), the total dosage of alfentanil during anesthesia, and body movements. Intraoperative body movement was classified into four categories ranging from 1 to 4 (Grade 1, finger and toe joint mobility; Grade 2, wrist and ankle joint mobility; Grade 3, elbow and knee joint mobility, requiring sedatives to facilitate surgery; Grade 4, hip joint mobility, requiring sedatives to facilitate surgery).

The safety outcomes assessed were upper airway obstruction, which was defined as the presence of snoring with paradoxical breathing, apnea, which was defined as the absence of respiratory effort for 10 s or longer or a flat line shown on the capnography monitor for 10 s or longer, and the use of atropine, vasopressor, and/or inotrope drugs during operation.

Sample Size Calculation

It was hypothesized that remimazolam would be superior to propofol in reducing the incidence of adverse events associated with the respiratory and circulatory systems. Based on previous research, the expected incidence of cardiopulmonary adverse events in patients undergoing colonoscopy or gastroscopy who received alfentanil in combination with either propofol or remimazolam was 45% and 18.5%, respectively. A margin of −10% was chosen as the minimum clinically significant difference. To detect a significant difference between remimazolam and propofol, a minimum sample size of 182 patients with an 80% statistical power at a one-sided 5% significance level was required. To account for potential dropouts, a total of 204 patients were included in the study.

Statistical Analysis

All patients who were randomized in the study were included in the intention-to-treat (ITT) population, and the trial data were analyzed based on the ITT principle. Normality of continuous variables (such as time of loss of consciousness, times of being awake and discharge from the operating room, dosage of alfentanil during the operation) was tested using Shapiro–Wilk test. Continuous variables were reported as mean ± standard deviation or median with interquartile range. Categorical variables (such as hypotension, bradycardia, hypoxemia, body movement, safety outcomes) were reported as count and percentage. To compare differences in continuous variables, either a Mann–Whitney U-test or a Student's t-test

was employed. If necessary, Fisher's correction was applied when comparing categorical outcomes using chi-squared tests.

The main analysis was conducted over the ITT population. The randomized assignments of patients were taken into consideration during analysis, and non-significant protocol infractions were ignored. The unadjusted risk differences were reported with corresponding 95% confidence intervals. The primary outcome was further analysed via logistic regression where odds ratio with 95% confidence interval was reported. The secondary outcomes were analysed in the same manner for binary data. For continuous variables, the mean differences were reported with 95% confidence intervals; transformation of data was done if normality test suggested skewness.

The impact of intervention was further explored as a time-to-event outcome, where the time to primary outcome was analysed via the Cox proportional hazard model. Estimations of hazard ratio (HR)s and 95% confidence interval [CI]s were reported with non-parametric cumulative risks obtained via the Kaplan–Meier curve. The proportionality was governed by the parallel lines in the graph of log(-log(survival)) versus log of survival time. Heterogeneity was tested to gauge the consistency across the three components of the primary outcome. The study was conducted under two-sided tests at a significant level of 5% throughout. SPSS software ver. 26.0 (IBM) and R software were used for all statistical analyses (ver. 4.1.2).

Results
Trial Population and Baseline Characteristics
Between September 22, 2021, and October 26, 2022, a total of 237 patients were screened, and 204 were randomized into two groups with 102 allocated to each group (Figure 1). Two patients in the remimazolam group were sedated with propofol as remediation besides intravenous remimazolam. All patients completed the procedure and 185 of them had full history of postoperative follow-ups (remimazolam group, n = 93; propofol group, n = 92; Figure 1).
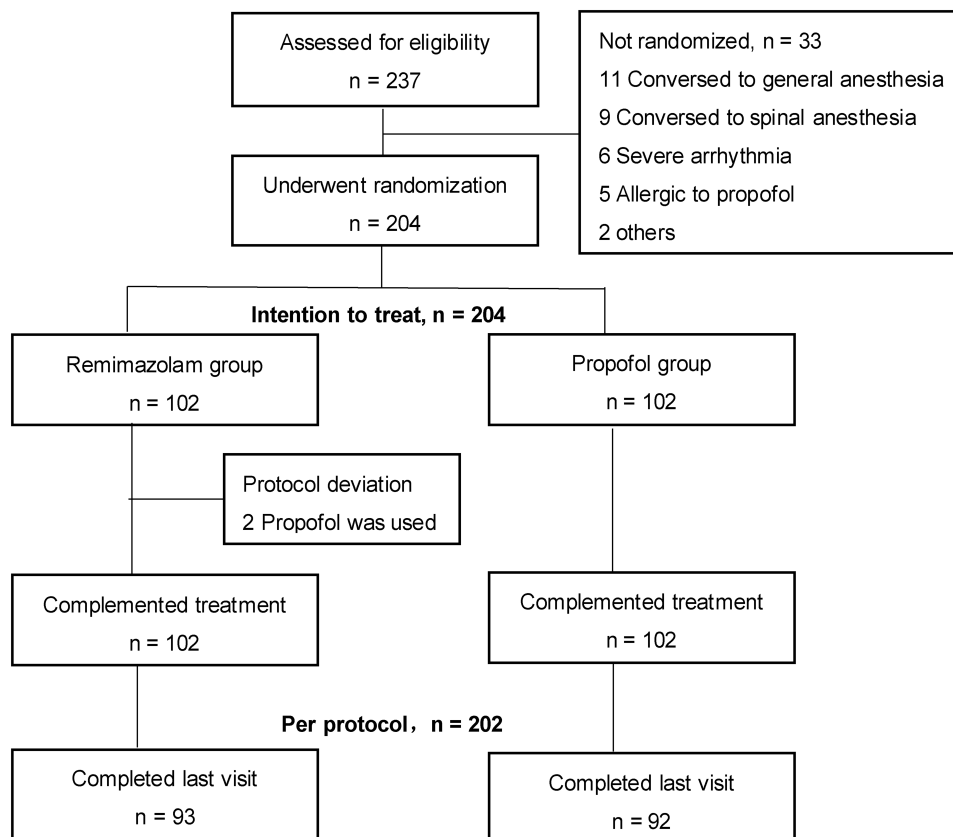

Figure 1 Case screening flow chart. We screened 237 patients undergoing cervical conization, 204 of them were randomized, and 102 in each group. All participants completed the procedure and 185 of them remained after the postoperative follow-up (remimazolam group, n = 93; propofol group, n = 92).

Table 1 Baseline Characteristics of Randomized Population

Characteristics		Remimazolam n=102	Propofol n=102	p
Age, mean (SD), years		40.0 (8.8)	40.6 (8.2)	0.81
Body Mass Index, kg/m^2		21.9 (20.3, 23.8)	22.6 (20.8, 24.9)	0.12
ASA, n (%)	I	53 (52.0)	58 (56.9)	0.57
	II	49 (48.0)	44 (43.1)	
Diagnosis, n (%)	Cervical lesion	90 (88.2)	97 (95.1)	0.21
	Cervical cancer	10 (9.8)	4 (3.9)	
	Infection of HPV	2 (2.0)	1 (1.0)	
Surgical History, n (%)		18 (17.6)	23 (22.5)	0.11
History of Nausea and Vomiting, n (%)		3 (2.9)	6 (5.9)	0.25
Motion Sickness, n (%)		19 (18.6)	19 (18.6)	0.56
Abnormal ECG, n (%)		11 (10.8)	13 (12.7)	0.83
Systolic Blood Pressure (SBP)		118 (111, 129)	118 (110, 132)	0.98
Heart Rate (HR)		73 (65, 85)	76 (68, 82)	0.39
Ramsay Sedation Scale score[a]		2 (2,2)	2 (2,2)	0.97
Visual Analog Pain Scale (VAS)[b]		0 (0,0)	0 (0,0)	0.08
Duration of surgery[c], min		18.5 (15.0, 24.0)	17.0 (13.0, 23.0)	0.43
Intravenous dexamethasone, n (%)		84 (82.3)	86 (84.3)	0.49
Intravenous flurbiprofen axetil, n (%)		71 (69.6)	72 (70.6)	0.60

Notes: Values are median (IQR), unless stated otherwise. [a]Ramsay Sedation Scale score: 1 = patient anxiety and restlessness; 2 = patient cooperation, orientation, quiet; 3 = patient responds to instructions; 4 = lethargic, responsive to tapping between the eyebrows or loud auditory stimuli; 5 = lethargic, sluggish response to tapping between the eyebrows or loud auditory stimuli; 6 = lethargic, no response. [b]Visual Analog Pain Scale (VAS): a 0–10 scale with "no pain" at 0 and "worst pain imaginable" at 10. [c]Duration of surgery was the time from skin incision to skin suture.
Abbreviations: IQR, inter quartile range; ASA, American Society of Anesthesiologists.

The baseline traits and surgical information of the patients in the initial analysis did not show statistical difference between the two groups (Table 1). The average age of patients was 40.3±8.7 years. A total of 187 (91.7%) patients were diagnosed with cervical lesions; 38 (18.6%) had history of motion sickness. No diagnoses of bradycardia or tachycardia were seen.

Primary and Secondary Outcomes

The primary outcome was observed in 117 (57.4%) patients, 45 (44.1%) in the remimazolam group and 72 (70.6%) in the propofol group (absolute risk difference, −26.47% [−39.55% to −13.39%]; OR, 0.43 [0.28 to 0.65]; $P < 0.001$; Table 2). The upper limit of the CI for the difference (ie, −13.39%) was below the predetermined superiority margin of −10% with statistical significance, suggesting that remimazolam was superior to propofol in reducing the incidence of cardiopulmonary adverse events.

The incidence of hypotension and hypoxemia in the remimazolam group was significantly lower than the propofol group ($P = 0.01$; Table 2). Tachycardia, body movements, time of loss of consciousness and alfentanil dosage did not significantly differ between groups (Table 2). The time to being awake and discharge from the operating room in the remimazolam group was longer than that in the propofol group ($P < 0.001$, $P = 0.02$, respectively; Table 2). Patients in the remimazolam group

Table 2 Clinical Outcomes Between Two Groups

Outcomes	Remimazolam n = 102	Propofol n = 102	Absolute Risk Difference[a] (95% CI), %	Remimazolam vs Propofol OR (95% CI)[b]	p
Primary outcome					
Composite end point consisting of hypotension[f], bradycardia[g], hypoxemia[h], n (%)	45 (44.1)	72 (70.6)	−26.47 (−39.55 to −13.39)	0.43 (0.28 to 0.65)	< 0.001[c]
Secondary outcome					
Hypotension, n (%)[f]	31 (30.4)	51 (50.0)	−19.61 (−32.79 to −6.42)	0.44 (0.24 to 0.81)	0.01[d]
Bradycardia, n (%)[g]	4 (3.9)	6 (5.9)	−1.96 (−8.86 to 4.94)	0.65 (0.13 to 2.86)	0.75[d]
Hypoxemia, n (%)[h]	14 (13.7)	31 (30.4)	−16.67 (−27.81 to −5.52)	0.37 (0.17 to 0.77)	0.01[d]
Body movement, n(%)	33 (32.4)	36 (35.3)	−2.9 (−15.9 to 10.0)	1.14 (0.64 to 2.04)	0.65[d]
Time of loss of consciousness, min[i]	1.4 (2.6)	1.3 (0.7)	0.27 (−0.43 to 0.61)[n]		0.45[e]
Time of awake, min[j]	5.0 (3.3)	3.00 (2.)	2.01 (1.25 to 2.77)[n]		< 0.001[e]
Time of discharge from operating room[k]	15.5 (6.71)	12.3 (4.7)	3.25 (1.65 to 4.86)[n]		0.02[e]
Dosage of alfentanil during operation, mg	0.8 (0.2)	0.9 (0.3)	−0.33 (−0.36 to 0.10)[n]		0.09[e]
Safety outcomes					
Vasoactive drugs, n (%)	9 (8.8)	24 (23.5)	−14.71 (−24.61 to −4.80)	0.33 (0.14 to 0.72)	< 0.01[d]
Atropine, n (%)	0 (0)	3 (2.9)	−2.94 (−6.22 to 3.38)	0.49 (0.43 to 0.56)	0.12[d]
Tachycardia, n (%)	4 (3.9)	2 (2.0)	1.96 (−2.67 to 6.60)	2.04 (0.37 to 11.40)	0.41
Pain at injection site, n (%)	1 (1.0)	36 (35.3)	−34.31(−43.78 to −24.84)	0.02 (0.00 to 0.14)	< 0.001
Respiratory Rate less than 8 beat per min, n (%)	22 (21.6)	43 (42.2)	−20.59 (−33.06 to −8.12)	0.38 (0.20 to 0.70)	< 0.01[d]
Apnea, n (%)[l]	7 (6.9)	24 (23.5)	−16.7(−26.25 to −7.08)	0.24 (0.10 to 0.59)	< 0.01[d]
Upper respiratory obstruction, n (%)[m]	24 (23.5)	23 (22.6)	0.98 (−10.58 to 12.54)	1.06 (0.55 to 2.03)	0.87[d]
Need for airway manuever, n (%)	34 (33.3)	50 (49.0)	−15.69 (−29.02 to 2.35)	0.51 (0.29 to 0.90)	0.02[d]

Notes: [a]Absolute risk difference < 0 indicates an effect in favor of remimazolam group compared to propofol group. [b]OR less than 1 indicates an effect in favor of handover remimazolam group compared with propofol group. [c]χ^2 test. [d]Fisher exact test. [e]Student's t-test. [f]Hypotension was defined as systolic blood pressure (SBP) less than 90 mm Hg or 20% lower than baseline. [g]Bradycardia was defined as heart rate less than 50 beat per minutes (bpm). [h]Hypoxemia was defined as saturation of peripheral oxygen (SpO$_2$) less than 90% during operation. [i]Time of loss of consciousness was defined as time from induction to the loss of eyelash reflex. [j]Time of awake was defined as the time from the end of the procedure to patients answering their name accurately. [k]Time of discharge from operating room was defined as the time from the end of the procedure to patients discharge from operation room. [l]Apnea was defined as the absence of respiratory effort for ≥10 s, a flat line for ≥10 s shown on the capnography monitor. [m]Upper respiratory obstruction was defined as presence of snoring with paradoxical breathing. [n]Mean difference for continuous variables.
Abbreviation: OR, odds ratio.

were given fewer vasoactive drugs ($P < 0.01$), and less injection site pain was reported ($P < 0.001$; Table 2). The incidence of apnea (a respiratory rate <8 breaths per min), manual assisted ventilation, and tachycardia in the remimazolam group was also observed to be comparably less than the propofol group. No significant between-group difference was observed between the proportion of atropine used and the incidence of upper respiratory obstruction.

Lower hazard of risk in seeing the primary outcome was found in the remimazolam group relative to the propofol group (HR 0.56, 95% CI: 0.39 to 0.81; $P < 0.001$; Figure 2). This difference was characterized by lower instantaneous rate of hypotension and hypoxemia in the remimazolam group (HR 0.54, 95% CI: 0.35 to 0.84, $P < 0.01$; HR 0.42, 95% CI: 0.23 to 0.76, $P < 0.01$; Figure 2). Remimazolam did not affect the incidence of bradycardia (HR 0.68, 95% CI: 0.30 to 2.34; $P = 0.54$; Figure 2). The trends of vital signs detected during surgery are illustrated in Figure 3, but no further comparison was made.
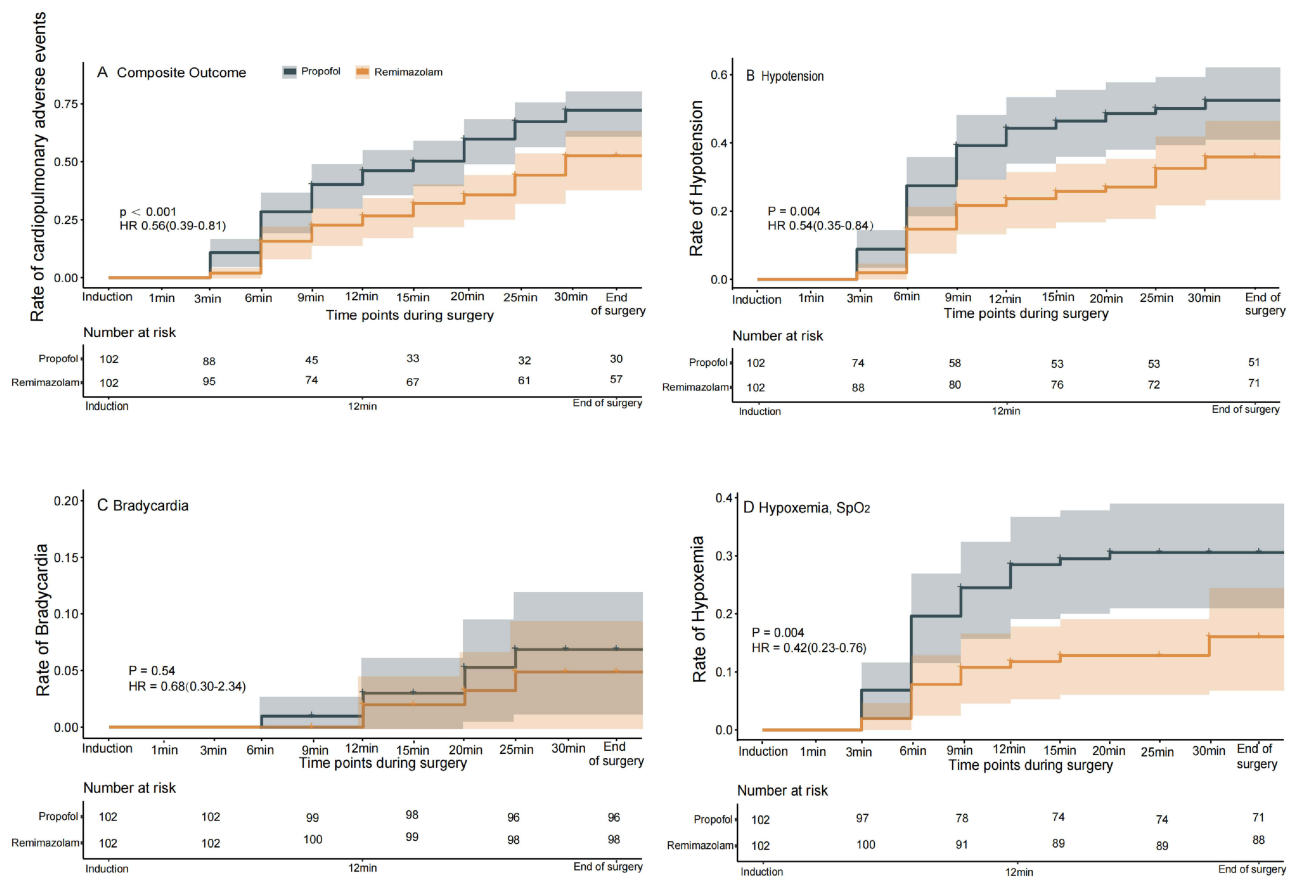
Figure 2 The cumulative incidence of cardiopulmonary adverse events via Kaplan–Meier curve between two group. Lower hazard of risk was found in the remimazolam group (orange line) relative to the propofol group (gray line), HR 0.56 (0.39 to 0.81), *P* < 0.001, plot (**A**) lower rates of hypotension and hypoxemia in the remimazolam group were observed in remimazolam (orange line), compared to the propofol group (gray line), plot (**B** and **C**) remimazolam did not affect the incidence of bradycardia, plot (**D**).

Postoperative Outcomes

No significant difference was observed between groups over the postoperative outcomes (Table 3), including the Ramsay sedation scale and VSA scores in PACU, the satisfaction scores of doctors and patients, postoperative nausea and vomiting, dizziness and pruritus.

Discussion

Patients who underwent cold knife cervical conization under remimazolam-alfentanil anesthesia experienced fewer cardiopulmonary adverse events than those who received propofol-alfentanil. Compared to the propofol group, patients in the remimazolam group demonstrated a significant reduction in the incidence of hypotension and hypoxemia. However, the percentage of patients who experienced bradycardia was virtually identical in both groups.

A largest meta-analysis of randomized trials has shown that propofol has no detrimental effects on survival and it remains one of the most commonly used hypnotics.[23] To the best of our knowledge, remimazolam is a well-tolerated sedative with superior hemodynamic stability and less injection site pain in comparison to propofol.[23–27] Whereas previous studies mainly focused on its efficacy, while safety was generally considered as a secondary outcome.[16,25,28] In this study, the combination of cardiopulmonary adverse events were treated as a composite endpoint, which we believe is of great concern when administering propofol-based intravenous anesthesia during clinical practices. Instead of intermittent bolus injection, the continuous infusion of sedative after bolus administration was adapted in this study as it provides a more convenient alternative especially for a 30 min procedure, ie cold knife cervical conization. Alfentanil was given as a bolus to cope with the painful stimulus in addition. The incidence of hypotension in the propofol group was similar to that of two previously published studies with similar doses for sedation and general anesthesia
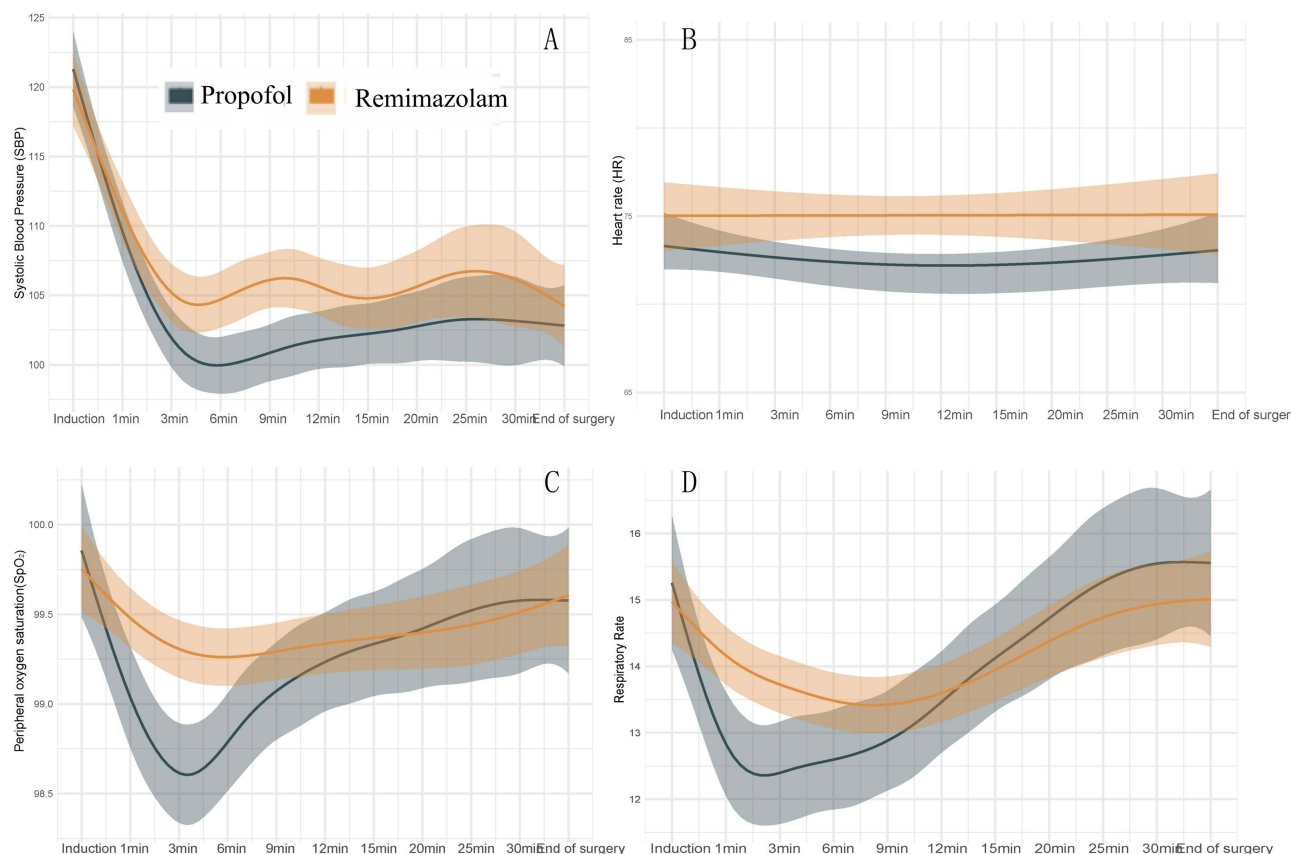
Figure 3 Intraoperative vital signs of two groups. The trends of systolic blood pressure (plot (**A**)), heart rate (plot (**B**)) SpO$_2$ (plot (**C**)) and respiratory rate (plot (**D**)) were detected between remimazolam group (orange line) and propofol group (gray line). No further comparison was made between the two groups. The respiratory rate declined most between 1 to 3 minutes after administration of propofol, and systolic blood pressure and SpO$_2$ decreased most significantly during 3–6 minutes after propofol induction.

induction.[24,29] Hypotension occurred in slightly more patients in our remimazolam group than in the remimazolam groups of the two studies mentioned above. In explanation to this difference, we postulate that the loading alfentanil bolus might have contributed to the higher incidence of hypotension. As for hypoxia, Nilsson observed that two-thirds of patients suffered from hypoxia (oxygen saturation <90%) in gynecological outpatient surgery when alfentanil was administered together with propofol.[30] Propofol is a derivative of short-acting alkylphenols widely in use for over

Table 3 Postoperative Outcomes

Observed Indicator	Remimazolam n=102	Propofol n=102	Absolute Risk Difference (95% CI), %	*p*
Ramsay Sedation Scale score in PACU	2 (2, 2)	2 (2, 2)	0.20 (−0.18 to 0.22)	0.71
VAS in PACU	0 (0, 3)	0 (0, 2)	0.25 (−0.47 to 0.50)	0.88
Satisfaction score[a] of Doctor	8.7 (1.7)	8.8 (1.6)	0.17 (−0.4 to 0.75)	0.45
Satisfaction score[a] of Patient	9.1 (0.8)	8.7 (0.7)	0.46 (0.6 to 0.77)	0.54
Nausea and Vomiting, n (%)	6 (6.5)	9 (9.8)	−3.33 (−11.19 to 4.53)	0.16
Dizziness, n (%)	5 (5.4)	1 (1.1)	4.29 (−0.76 to 9.34)	0.22

Notes: Values are median (IQR), unless stated otherwise. [a]Satisfaction scores: from 0 to 10, the higher the score, the more satisfied.
Abbreviations: PACU, post anesthesia care unit; VAS, Visual Analog Pain Scale.

a decade. Comparing with ketamine/propofol mixture, propofol alone has more respiratory adverse effects in procedural sedation.[31]

In the presented study, 13% of patients experienced hypoxia in the remimazolam group, reduced by about 39% in comparison to a third in the propofol group. The incidence of bradycardia was comparable between the propofol and remimazolam groups, a result similar to earlier published findings.[24,32] One study had suggested that the administration of remimazolam and propofol had lowered autonomic nerve activity judging by hemodynamic measurements and heart rate variability before and after anesthesia.[33] In patients undergoing cervical conization, bradycardia is a common concern because of the vagal reflex.[6,34] In this research, the analgesic used was alfentanil, which did not quantitatively or clinically significantly affect the QT distance of patients' ECGs.[35] And comparing fentanyl and sufentanil, alfentanil had no appreciable statistical differences with regard to hemodynamic parameters.[36] According to our outcomes, remimazolam did not increase the rate of bradycardia and it can be safely used in this patient population.

The awakening time and the time from the end of surgery to discharge from the operating room were longer in the remimazolam group, which was consistent with a previous report.[37] In a randomized controlled study,[25] the awakening time in the remimazolam combination with alfentanil group was slightly less than in the propofol combination with alfentanil group. In the present study, the period of time from the end of surgery to leaving the operating room for patients assigned to the remimazolam group was 15.5 ± 6.7 min. The time for full alertness to be regained was 19 ± 7 min after stopping the remimazolam continuous infusion in healthy male volunteers.[38] All subjects stayed in the PACU and were observed for 30 min before they left the operating room.

The findings of our study have important implications for clinical practice. Based on the safety profile demonstrated by the remimazolam-alfentanil anesthesia in patients undergoing cold knife cervical conization, this combination may be a superior choice compared to propofol-alfentanil. Additionally, the non-intubation anesthesia we utilized may be a more cost-effective option compared to laryngeal or tracheal intubation general anesthesia. These results may inform clinical decision-making and improve patient care in this population.

Limitations

The study had some limitations, including the fact that it was an open-label trial and that anesthesiologists were not blinded to treatment randomization. While our outcome assessor and follow-up staff were unaware of patient group information, there was still potential for bias because the anesthesiologist could influence the dosage of sedative and alfentanil. In addition, the patients who underwent day surgery were in good health. Therefore, it may not be possible to generalize the results to more diverse patient populations and other types of surgical procedures. Further research is needed to determine if the findings are applicable to different patient groups. Finally, some outcomes, such as post-operative nausea, vomiting and dizziness, were missing due to early discharge before follow-up.

Conclusion

Among patients undergoing cold knife cervical conization under non-intubation general anesthesia, remimazolam combination with alfentanil reduced the incidence of cardiopulmonary adverse events comparing to the propofol–alfentanil combination.

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Disclosure

The authors report no conflicts of interest in this work.

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