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Safety and efficacy of remimazolam compared with propofol for general anesthesia during cold knife conization: a single-center, randomized controlled trial

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Abstract

Background Cold knife conization is usually performed under general anesthesia without intubation. This type of anesthesia is more critical in terms of the properties of the sedative drugs. Remimazolam is a novel ultrashort-acting benzodiazepine in which the lipid bond can be rapidly hydrolyzed by nonspecific lipases in the plasma. Therefore, remimazolam can be used for general anesthesia without intubation in patients undergoing short procedures. In this study, we compared the safety and efficacy of remimazolam with those of propofol for cold knife conization.

Methods This single-center, randomized controlled trial screened 104 patients, and 90 were randomly assigned to receive propofol (P, $N=45$) or remimazolam (R, $N=45$) during cold knife conization. All the patients received a 1 μg/kg fentanyl injection. The patients received 1.5 mg/kg propofol or 0.2 mg/kg remimazolam injection, followed by a rate of 4 ~ 12 mg/kg/h or 1.0 ~ 3.0 mg/kg/h continuous intravenous infusion, respectively, to keep the patient state index (PSi) between 35 and 50. The primary outcome was intraoperative hypoxemia. The secondary outcomes were hemodynamic parameters, respiratory parameters, and other adverse events.

Results The incidence of intraoperative hypoxemia in the R group was significantly lower than that in the P group (46.7% vs. 71.1%, $p=0.018$). Compared with patients in the P group, patients in the R group had fewer changes in the respiratory rate, mean arterial pressure and heart rate at some time points during surgery. The incidences of hypotension (15.6% vs. 35.6%, $p=0.030$) and injection pain (42.2% vs. 84.4%, $p<0.001$) were lower in the R group than in the P group; however, patients in the R group required more time to awaken (7.9 ± 4.5 min vs. 4.3 ± 1.7 min, $p<0.001$).

Conclusion In conclusion, patients in the R group had a lower incidence of hypoxemia and fewer hemodynamic changes than did patients in the P group. Thus, remimazolam can be safely used for unintubated general anesthesia in patients undergoing cold knife conization.

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Trial registration The trial registration number is ChiCTR2200065519.

Keywords Remimazolam, Propofol, General anesthesia, Cold knife conization, Safety, Efficacy

Background

Cervical conization, which includes cold knife conization (CKC), laser conization, loop electrosurgical excision procedure (LEEP), and loop excision of the transformation zone (LLETZ), is an excisional surgical procedure used to diagnose and treat premalignant cervical lesions [1–3]. CKC may be preferred over other methods for patients with a high cervical cancer risk in whom the specimen margins must be maintained [1]. This procedure is usually performed under general anesthesia [1, 4], which is induced and maintained with sedatives and analgesics but without muscle relaxants. Thus, patients breathe normally during the procedure. This method of anesthesia is more critical in terms of the properties of the sedative drugs.

Ideal sedatives are water soluble, nonirritating, have a rapid onset of action, allow smooth induction of sedation, are nonanalgesic, and rarely cause cardiovascular and respiratory depression [5]. Currently, the most commonly used sedative in clinical practice is propofol because of its rapid onset with nearly no excitation phenomena, relatively short context-sensitive time, rapid terminal half-life time and low incidence of postoperative nausea and vomiting (PONV) [6]. However, most patients complain of pain during the injection of propofol [7, 8]. In addition, propofol is associated with respiratory and cardiovascular depression [9], and its sedative effect cannot be antagonized. Therefore, propofol is not considered a perfect sedative drug.

Remimazolam is a novel ultrashort-acting benzodiazepine in which the lipid bond can be rapidly hydrolyzed by nonspecific lipases in the plasma, converting it into an inactive metabolite [10]. Studies have shown that remimazolam has good pharmacokinetic and pharmacodynamic characteristics, such as high clearance and therefore a short half-life, a small volume of distribution, and a rapid onset of action and inactivation, and the pharmacokinetics of prolonged infusion of remimazolam are similar to those of intermittent administration [11]; moreover, remimazolam is water soluble and not painful to inject, it does not inhibit adrenocortical function, and the sedative effect can be antagonized [12]. These advantages suggest that remimazolam has promising clinical applications.

In recent years, numerous studies have investigated the use of remimazolam for the induction and maintenance of anesthesia. Researchers have studied the use of remimazolam for the induction and maintenance of anesthesia for bronchoscopy [13, 14] and gastrointestinal endoscopy [15–17] and in critically ill [18] and cardiac surgery [19–21] patients, and the results of these studies indicate that, compared with other sedatives, remimazolam is safe and effective. The pharmacokinetic and pharmacodynamic characteristics of remimazolam suggest its suitability for short procedures. We hypothesized that remimazolam could be used in patients receiving unintubated general anesthesia with fewer respiratory and hemodynamic effects. Thus, the main objective of this study was to compare the effects of remimazolam and propofol on perioperative respiratory and circulatory parameters in patients undergoing CKC. The secondary objective of this study was to compare the effects of these two drugs on the incidence of other perioperative complications.

Methods

Study design and patients

This was a single-center, randomized controlled clinical trial. Our study was approved by the Ethics Committee of the National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College (22/278–3480) and registered in the Chinese Clinical Trial Registry (ChiCTR2200065519, 8/11/2022). The protocol of this study adheres to CONSORT guidelines. All methods were carried out in accordance with relevant guidelines and regulations.

Patients who underwent CKC and agreed to participate in the study were enrolled. Informed consent was obtained from all the subjects. Patients aged 18 to 65 years who were scheduled for elective CKC and were classified according to the American Society of Anesthesiologists (ASA) physical status classification system I–II with a body mass index (BMI) ranging from 18.5 to 30 were included in this study. Patients with a history of severe hypertension, coronary artery disease, severe electrocardiogram (ECG) abnormalities, severe hepatic or renal function abnormalities, asthma or chronic obstructive pulmonary disease (COPD), long-term use of benzodiazepines, psychiatric disorders, or hypoproteinemia were excluded.

Randomization and masking

The participants were enrolled and randomly divided into 2 groups, the remimazolam (R) group and the propofol (P) group, via an Excel-generated random number chart. The results of randomization were sealed in envelopes, and one of the envelopes was handed to an anesthesiologist before the patient entered the operating room. Because the two drugs differ in appearance,

the anesthesiologists could not be blinded to the group assignments; however, the follow-up investigators were blinded to the group assignments.

Anesthesia management

All patients underwent standard intraoperative monitoring, including pulse oxygen saturation (SpO_2), noninvasive arterial blood pressure, ECG, and end-tidal carbon dioxide ($EtCO_2$) monitoring. Sedline electroencephalography (Masimo, California, USA) was used to monitor the depth of anesthesia, which provided a patient state index (PSi) value to indicate the depth of sedation. All patients received oxygen by a face mask.

Anesthesia was induced with 1 μg/kg fentanyl via an injection, followed by the investigational product (remimazolam or propofol). Anesthesia was maintained with the investigational product, and the infusion rate was adjusted to maintain the PSi between 35 and 50. During the operation, the patients breathed spontaneously; when the operation began, the patients received an additional 0.5 μg/kg fentanyl via an injection. If the SpO_2 was < 95 and there was no increasing trend, the anesthesiologist applied mask ventilation to the patients; if the patients developed unconscious body movements during the operation, 0.5 μg/kg fentanyl was added; if a patient developed hypotension or bradycardia, vasoactive drugs were administered.

Interventions

In the R group, general anesthesia was induced with an intravenous injection of 0.2 mg/kg remimazolam at a rate of 400 ml/h and then maintained with a continuous infusion of remimazolam (1.0–3.0 mg/kg/h).

In the P group, general anesthesia was induced with an intravenous injection of 1.5 mg/kg propofol at a rate of 400 ml/h and then maintained with a continuous infusion of propofol (4–12 mg/kg/h).

Study outcomes and data collection

Baseline data included demographic data (age, height, weight, and BMI), ASA status, comorbidities, smoking habits, SpO_2 before anesthesia, mean arterial pressure (MAP) in the ward, airway assessment [Mallampati grade, thyromental distance, mouth opening extent, snoring status, status of dyspnea upon awakening, status of obstructive sleep apnea syndrome (OSAS)] and relevant laboratory test results.

The primary outcome of this study was the incidence of intraoperative hypoxemia. Hypoxemia was defined as a decrease in SpO_2 to 95 or lower with no increasing trend. Because peripheral SpO_2 values are more delayed than central SpO_2 values are, all these patients' SpO_2 values continued to fall below 90 even if mask ventilation was initiated at an SpO_2 of 95. Other intraoperative data, including respiratory parameters [respiratory rate (RR) and $EtCO_2$] and their changes, hemodynamic parameters [heart rate (HR) and MAP] and their changes, total dose of anesthetic drugs, time to loss of consciousness (PSi < 50), time from the discontinuation of medication to awakening and following commands (recovery time), and use of vasoactive medications, were collected. Respiratory and hemodynamic parameters and their changes were recorded at the following 5 time points: before the induction of anesthesia (T0), after the induction of anesthesia (T1), at the beginning of surgery (T2), 15 min after the beginning of surgery (T3), and at the end of surgery (T4). To compare the variability of these parameters at each time point (T1-T4) relative to the baseline value (T0), we obtain ΔT1 – ΔT4 by subtracting the data of T0 from the data of each time point (T1-T4). After the operation, patients were transferred to the postanesthesia care unit (PACU) for further monitoring. Half an hour after the completion of the procedure, postoperative pain was evaluated using the visual analog scale (VAS), and possible scores ranged from 0 to 10 (0 = no pain, 10 = worst pain imaginable). We explained the VAS score to the patient before the procedure and again half an hour after the procedure. All adverse events [including hypotension (defined as a systolic blood pressure of less than 90 mmHg or a decrease of more than 20% of the baseline value), bradycardia (defined as a heart rate of less than 50 beats/min), injection pain, body movement, shivering, hiccups, PONV, and intraoperative awareness] observed by the investigators or reported spontaneously by the patients were recorded.

Statistical analysis

The sample size was calculated on the basis of the primary outcome. We referenced the published literature concerning the incidence of hypoxemia in both groups of patients [22] (P group: 51.2%, R group: 9.8%) and hypothesized that patients in the R group would have a significantly lower incidence of hypoxemia than those in the P group; we defined the significance level (α) as 0.025, the power of a test (1-β) as 80%, and the margin (Δ) as -0.15. The sample size calculated was 45 for each group.

SPSS 19.0 (IBM SPSS Inc., USA) was used for all the statistical analyses. The Shapiro–Wilk test was used to test whether the data were normally distributed. Levene's test was used for equality of variances. Continuous variables are presented as the means ± standard deviations (SDs) and were analyzed using independent sample t tests. Categorical variables are presented as percentages and were analyzed using the chi-square test or Fisher's exact test. A p value < 0.05 indicated statistical significance.

Results

Patient recruitment and baseline characteristics

One hundred and four patients who were enrolled in the study from January 2023 to April 2024 were randomly divided into two groups, as shown in the CONSORT flow diagram (Fig. 1). Thirteen patients were excluded because their BMI or age was out of the range. One patient in the R group was excluded because of conversion to general anesthesia for tracheal intubation. A total of 45 patients were ultimately included in each group. The baseline characteristics, including ASA status, age, height, weight, BMI, smoking habits, SpO_2 before anesthesia, MAP in the ward, comorbidities and airway assessment, did not differ significantly between the two groups, as shown in Table 1.

Anesthesia characteristics

The characteristics of anesthesia management in both groups of patients are presented in Table 2. Fentanyl consumption was not significantly different between the two groups of patients. The time to loss of consciousness after the induction of anesthesia was similar in both groups of patients; however, patients in the R group took significantly more time to awaken than those in the P group did. The duration of the procedure and the number of vasoactive drugs used did not differ significantly between the two groups of patients.

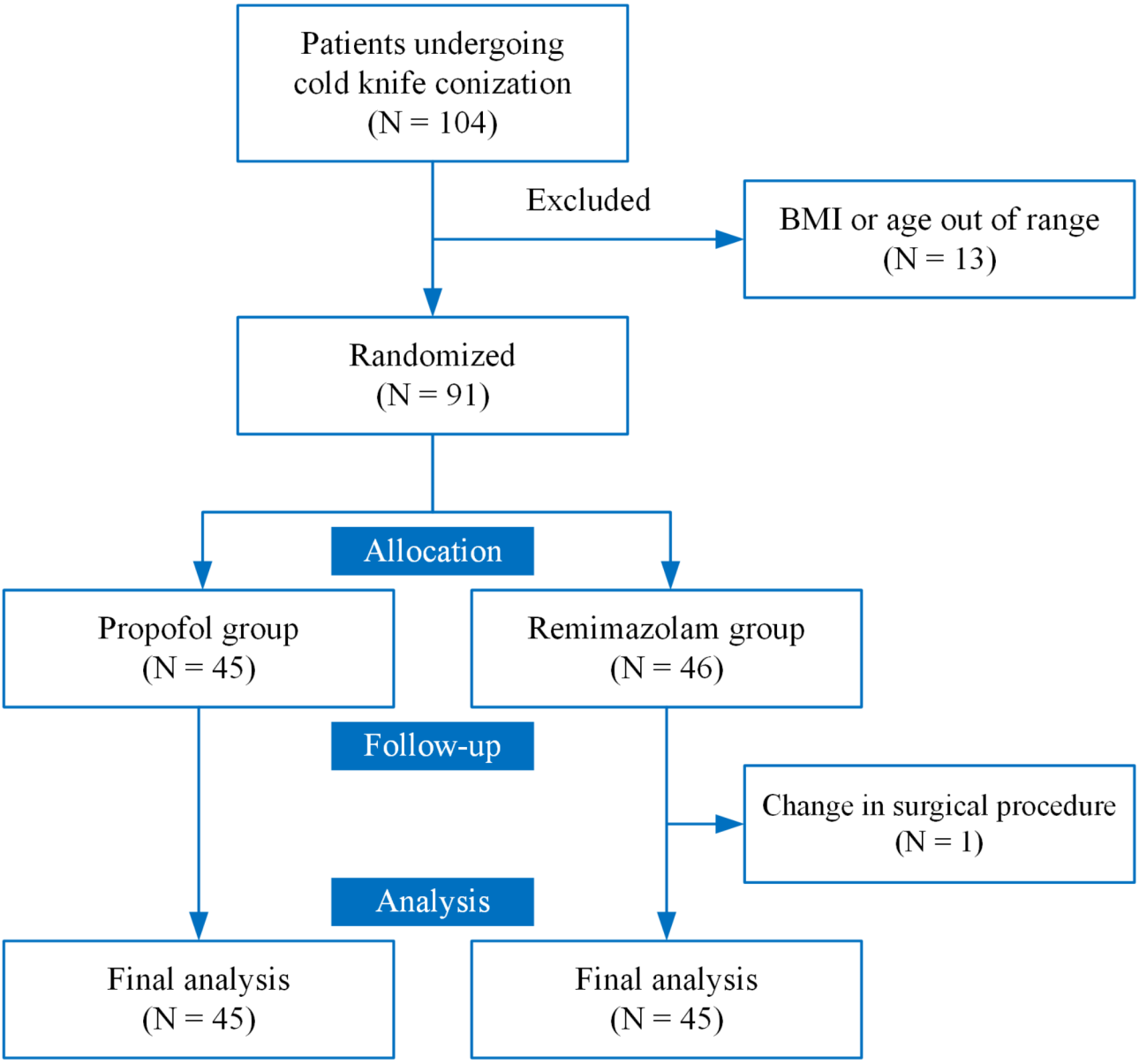

Fig. 1 Flow diagram of patient enrollment

Table 1 Basic characteristics of the patients in the two groups

	***P* Group (*N* = 45)**	***R* Group (*N* = 45)**	***p* value**
ASA I-II (%)	100	100	-
Age (years, mean ± SD)	43.2 ± 10.4	41.7 ± 8.2	0.452
Height (cm, mean ± SD)	162.9 ± 6.3	163.8 ± 4.6	0.448
Weight (kg, mean ± SD)	61.9 ± 9.3	60.4 ± 6.8	0.376
BMI (kg/m^2, mean ± SD)	23.3 ± 3.2	22.5 ± 2.5	0.182
Smoking (%)	0	0	-
SpO_2 before anesthesia (mean ± SD)	99.0 ± 1.2	99.1 ± 1.2	0.671
MAP in the ward (mean ± SD)	85.6 ± 10.1	87.0 ± 10.6	0.536
Preoperative complications (%)			
Cardiovascular comorbidity	13.3	6.7	0.485
Respiratory comorbidity	2.2	2.2	1.000
Neurological comorbidity	2.2	0	1.000
Diabetes mellitus	4.4	0	0.494
Airway assessment			
Mallampati III/IV (%)	2.2	4.4	1.000
Thyromental distance (cm, mean ± SD)	7.5 ± 1.2	7.4 ± 0.9	0.827
Mouth opening (cm, mean ± SD)	4.1 ± 0.9	4.0 ± 0.6	0.752
Snoring (%)	37.8	33.3	0.660
Dyspnea on awakening (%)	4.4	4.4	1.000
OSAS (%)	0	0	-

ASA: American Society of Anesthesiologists; BMI: body massindex; MAP: mean arterial pressure; OSAS: obstructive sleep apnea syndrome

Table 2 Intraoperative data and postoperative analgesia of the patients in the two groups

	P Group (*N* = 45)	**R Group (*N* = 45)**	***p* value**
Procedure medication			
Fentanyl (μg, mean ± SD)	111.9 ± 26.7	111.2 ± 32.4	0.910
Propofol (mg, mean ± SD)	421.6 ± 133.1	-	-
Remimazolam (mg, mean ± SD)	-	60.5 ± 14.9	-
Time to PSi<50 (min, mean ± SD)	3.2 ± 1.1	3.9 ± 2.0	0.050
Recovery time (min, mean ± SD)	4.3 ± 1.7	7.9 ± 4.5	< 0.001
Duration of procedure (min, mean ± SD)	39.9 ± 15.2	38.9 ± 14.4	0.744
Use of vasoactive drug (%)	35.6	17.8	0.057

PSi: patient state index

Intraoperative hypoxemia and adverse events

As shown in Table 3, the incidence of intraoperative hypoxemia in the R group was significantly lower than that in the P group. The proportion of patients who developed hypotension and experienced pain during injection was significantly lower in the R group than in the P group. There was no significant difference in the incidence of bradycardia, body movement, moderate to severe postoperative pain, shivering or hiccups between the two groups of patients. None of the patients in either group experienced intraoperative awareness or PONV.

Intraoperative respiratory and hemodynamic parameters

The RR, $EtCO_2$, MAP, and HR were compared between the two groups of patients treated via the two approaches.

The RR of patients in the R group was significantly greater than that of patients in the P group at the T2 and T3 time points (Additional file 1). Compared with that in the P group, the change in RR in the R group was less significant at the T1, T2, T3, and T4 time points (Table 4).

$EtCO_2$ and the change in $EtCO_2$ were not significantly different between the two groups at any time point (Additional file 1, Table 4).

The MAP of patients in the R group was significantly greater than that of patients in the P group only at the T3 time point (Additional file 1). However, the changes in MAP were significantly lower in the R group than in the P group at the T1, T3 and T4 time points (Table 4).

The HRs of patients in the R group were significantly greater than those of patients in the P group at the T1 and T3 time points (Additional file 1). The variations in HR were less significant in the R group than in the P group at the T1, T2 and T3 time points (Table 4).

Table 3 Intraoperative hypoxemia and adverse events of the patients in the two groups

	P Group (*N* = 45)	R Group (*N* = 45)	*p* value
Hypoxemia (%)	71.1	46.7	0.018
Adverse events			
Hypotension (%)	35.6	15.6	0.030
Bradycardia (%)	0	2.2	1.000
Injection pain (%)	84.4	42.2	< 0.001
Body movement (%)	53.3	40.0	0.205
Moderate to severe postoperative pain (VAS>3, %)	15.6	6.7	0.180
Shivering (%)	0	6.7	0.242
Hiccups (%)	0	6.7	0.242
PONV (%)	0	0	-
Intraoperative awareness (%)	0	0	-

VAS: visual analog scale; PONV: postoperative nausea and vomiting;

Table 4 Change of respiratory and hemodynamic parameters of the patients in the perioperative period

Change relative to T0	T0-T0	T1-T0	T2-T0	T3-T0	T4-T0
ΔRR (times/min, mean ± SD)					
P Group (*N* = 45)	0	-4.7 ± 4.1	-5.6 ± 3.1	-3.9 ± 3.6	-2.7 ± 3.4
R Group (*N* = 45)	0	-3.0 ± 3.3	-3.6 ± 3.8	-2.1 ± 3.5	-1.3 ± 3.3
p value	-	0.044	0.006	0.019	0.046
Δ$EtCO_2$(mmHg, mean ± SD)					
P Group (*N* = 45)	0	4.0 ± 4.1	5.3 ± 4.5	6.6 ± 4.3	5.3 ± 4.1
R Group (*N* = 45)	0	3.2 ± 2.5	4.5 ± 3.2	5.8 ± 3.7	4.7 ± 3.4
p value	-	0.270	0.373	0.333	0.437
ΔMAP (mmHg, mean ± SD)					
P Group (*N* = 45)	0	-16.7 ± 8.7	-19.2 ± 9.8	-24.4 ± 11.4	-30.4 ± 12.7
R Group (*N* = 45)	0	-12.2 ± 9.0	-15.2 ± 9.7	-17.1 ± 10.7	-25.3 ± 11.7
p value	-	0.016	0.056	0.002	0.048
ΔHR (times/min, mean ± SD)					
P Group (*N* = 45)	0	-9.6 ± 9.2	-11.7 ± 10.7	-8.4 ± 9.9	-5.8 ± 12.2
R Group (*N* = 45)	0	-2.2 ± 10.5	-5.3 ± 11.1	-0.8 ± 12.7	-2.0 ± 12.7
p value	-	0.001	0.007	0.002	0.148

RR: respiratory rate; $EtCO_2$: end tidal carbon dioxide; MAP: mean arterial pressure; HR: heart rate

Discussion

In this study, we compared the safety and efficacy of remimazolam with those of propofol in patients undergoing CKC. To improve the patients' experience, we performed the procedure under general anesthesia without intubation, and only sedative and analgesic drugs were administered. Furthermore, the notable aspects of this anesthetic protocol are that the airway remains unobstructed and that patients can breathe normally during the procedure. Intraoperative hypoxemia was selected as the primary outcome because its occurrence represents the effect of the anesthesia method on the patient's respiration and airway status. The incidence of intraoperative hypoxemia was lower in the R group than in the P group.

Ahmer et al. performed a meta-analysis comparing remimazolam with propofol for sedation in elderly patients undergoing gastrointestinal endoscopy and colonoscopy and reported that, compared with propofol, remimazolam was less likely to cause hypoxemia; however, the incidence of respiratory depression was not significantly different between the two drugs [23]. Moreover, our research findings support the findings of the study mentioned above. Although the incidence of hypoxemia was significantly lower in the R group than in the P group, hypoxemia still occurred in 46.7% of patients and should be intensively monitored by anesthesiologists during the operation. The incidence of hypoxemia in patients in the R group was greater in this study than in other studies, probably because of differences in surgeries and administration protocols. To suppress the stress response, we administered fentanyl both at the induction of anesthesia and before the start of surgery, which may have contributed to the higher incidence of hypoxemia than that reported in other studies.

In addition to the incidence of intraoperative hypoxemia, we also recorded the RR and $EtCO_2$ to assess the patient's respiratory status. Wang et al. reported that the incidence of apnea in the remimazolam group (21.6%) was also lower than that in the propofol group (42.2%) during CKC [24]. We recorded the RRs for both groups

of patients at five time points. As shown in Additional file 1 and Table 4, the RR was greater and the change in RR was less significant in the R group than in the P group at the T2 and T3 time points; from the start of the procedure to 15 min after the start of the procedure, the drug had a full effect and had a greater effect on the patient's RR, and our data indicate that the effect of remimazolam on the patient's RR was less significant than that of propofol during this period. To our surprise, even though the RRs of the two groups of patients were significantly different at some time points, the $EtCO_2$ values and changes in the $EtCO_2$ of the two groups were not significantly different at any of the five time points, suggesting that the effects of the two drugs on carbon dioxide clearance are relatively similar. Considering that the incidence of hypoxemia significantly differed between the two groups of patients, we may infer that the exchange of carbon dioxide in the human body is more fault tolerant than the exchange of oxygen.

Sedatives generally have an effect on perioperative hemodynamics; therefore, MAP, HR and their variability in both groups of patients at five time points were recorded to evaluate the effects of the two drugs on patients' hemodynamics. During the induction period, after propofol was administered, most patients presented with a transient increase in HR followed by a decrease, a phenomenon reported in the literature to be due to the predominance of sympathetic innervation by propofol [25]. This study revealed that there was no significant difference in HR or MAP between the two groups of patients at most time points. However, the changes in HR and MAP at most time points were less significant in the R group than in the P group, suggesting that intraoperative hemodynamics were more stable in the R group than in the P group.

In some patients, such as those who are elderly or have cardiovascular disease, blood pressure and respiration are relatively susceptible to the effects of sedative drugs. Guo et al. [26] and Hu et al. [27] used remimazolam or propofol for gastrointestinal endoscopy in elderly patients, and the results revealed that hemodynamic changes and respiratory depression were less common in the R group than in the P group; similar results were found in elderly patients who underwent carotid endarterectomy [28]. Choi et al. reported that, compared with anesthesia induction with propofol, anesthesia induction with remimazolam was more stable, preserved normal hemodynamics and was associated with a relatively lower incidence of hypotension [29]. Kotani et al. reported that, compared with propofol-based total intravenous anesthesia, remimazolam-based total intravenous anesthesia was associated with a lower hypotension rate in patients who underwent transcatheter aortic valve replacement [21]. Our study revealed similar results in patients who underwent CKC. All of the studies mentioned above suggest that, compared with propofol, remimazolam has fewer negative effects on circulation and respiration in patients.

Although the incidence of injection pain was lower in the R group (42.2%) than in the P group (84.4%), it was still much greater than the incidence of injection pain previously reported in the literature [22, 24, 30]. We searched the databases and found no articles explaining the phlebo-irritative mechanism by which remimazolam produces pain during injection. We speculate that the concentration of remimazolam administered (2 mg/mL) may have contributed to the increased incidence of injection pain; however, this finding should be verified in a larger study.

Patients in the R group required significantly more time to awaken than those in the P group did, implying that the offset rates of remimazolam were slower than those of propofol. However, most patients in the remimazolam group recovered within 10 min, and their recovery time could be further reduced if flumazenil was used [31].

The incidences of shivering and hiccups were not significantly different between the two groups. However, we found that all the patients with shivering and hiccups were in the R group; thus, a larger sample size is needed to confirm whether the incidence of shivering and hiccups is greater in patients in the R group than in those in the P group.

There are several limitations in this study. First, remimazolam and propofol differ in appearance, and the anesthesiologists could not be blinded to the group assignments. Second, some outcomes in the two groups of patients were seemingly different but not significantly different; however, these outcomes may significantly differ across large-sample studies. Third, the wide range of propofol used referred to the drug instructions because of the lack of related published literature before this study began. However, in clinical practice, the actual range of propofol is 4–9 mg/kg/h. Finally, the primary analyses in this study excluded individuals who were lost to follow-up, as their final outcome data were unavailable. Compared with traditional intention-to-treat analyses, this approach may slightly overestimate our findings. However, there was only one excluded individual, which had a minimal impact on our main results.

Conclusion

Compared with propofol, remimazolam is associated with a lower incidence of hypoxemia and fewer hemodynamic effects; therefore, remimazolam is considered a safe and effective sedative that can be used during the induction and maintenance of general anesthesia without intubation for CKC.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12871-025-03066-2.

Additional file 1: The table shows the intraoperative respiratory and hemodynamic parameters of the patients in the two groups

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Author contributions
X.Z., H.Z., T.Y. and YR.C. designed the study; X.Z., HX.L. and BN.W. conducted the clinical study and analysed the data; H.Z., T.Y. and YR.C. conducted quality control during the research process; X.Z. wrote the manuscript; HX.L. constructed the figures and tables; and H.Z. and T.Y. revised the manuscript.

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Data availability
The data of this study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
This study was approved by the Ethics Committee of the National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College (22/278–3480) and registered in the Chinese Clinical Trial Registry (ChiCTR2200065519, 8/11/2022). The protocol of this study adheres to CONSORT guidelines. Informed consent was obtained from all the subjects. This study was conducted in accordance with the Declaration of Helsinki. All methods were carried out in accordance with relevant guidelines and regulations.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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