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CLINICAL TRIAL REPORT

Low-Dose Dexmedetomidine Attenuates the Dose Requirement of Propofol for Suppression of Body Movement in Patients Undergoing Operative Hysteroscopy

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Background: Dexmedetomidine is a central α-2 adrenergic agonist characterized by its sedative, analgesic, and sympatholytic properties. We investigated the effect of low dose dexmedetomidine on the dose-response relationship of propofol for sedation in patients undergoing operative hysteroscopy.

Methods: The patients were firstly randomly assigned to receive either propofol and fentanyl (P group, n = 100) or a combination of propofol, dexmedetomidine, and fentanyl (DP group, n = 100). Subsequently, participants were further randomized to receive propofol at doses of 1.0, 1.5, 2.0, and 2.5 mg/kg in P group, and 0.5, 1.0, 1.5, and 2.0 mg/kg in DP group. The primary outcome of this study was the incidence of patients achieving effective propofol dose, defined as the dosage at which a patient exhibited no body movement during cervical dilation and had a BIS value below60. The Probit method was used to calculate the ED50 and ED95 of propofol in the inhibition of body movement reaction to cervical dilation during hysteroscopic surgery.

Results: The ED50 and ED95 values for propofol in the inhibition of body movement reaction to cervical dilation during hysteroscopic surgery were 1.781 (95% CI 1.507~2.118) and 4.670 (95% CI 3.555~7.506) mg/kg, respectively, in P group; while in the DP group, these values were found to be 0.983 (95% CI 0.800~1.173) and 2.578 (95% CI 2.013~3.895) mg/kg.

Conclusion: Low-dose dexmedetomidine (0.5μg/kg) could reduce the requirement of propofol for suppression of body movement in patients undergoing operative hysteroscopy.

Keywords: dexmedetomidine, propofol, cervical dilation, hysteroscopy, dose-response

Background

Hysteroscopy is a widely utilized endoscopic procedure that has emerged as the gold-standard for both diagnosing and treating intrauterine pathological conditions.[1] Monitored anesthesia care (MAC) with propofol administration is frequently utilized for hysteroscopy procedures that require cervical dilation.[2,3] Dilation of the cervix can elicit significant visceral stimulation and pain, which a single administration of a high dose of propofol alone may not adequately address for surgical requirements, while concurrently suppressing respiratory and circulatory systems.[4] To mitigate these concerns, extensive research has been conducted to explore the combination of propofol with other pharmacological agents in order to minimize procedural sedation and analgesia (PSA) complications during MAC for such procedures.[5,6]

Dexmedetomidine has been reported as an optimal sedative with arousable properties and analgesic effects, while avoiding respiratory depression.[7] Intravenous administration of dexmedetomidine during surgery can effectively mitigate the dose requirement for propofol and reduce the occurrence of cardiopulmonary complications.[8] However, the complete

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determination of the effect of dexmedetomidine on the dose-response relationship of propofol in inhibiting reaction to uterine dilation during hysteroscopic surgery remains elusive. Our hypothesis was that a low dose of dexmedetomidine would decrease the requirement for propofol in this setting. Therefore, we conducted a prospective, double-blind, randomized study to investigate the impact of low-dose dexmedetomidine on the dose-response relationship of propofol for sedation in patients undergoing operative hysteroscopy in this study.

Methods

Study Design

This prospective, randomized, placebo-controlled study was registered with the Chinese Clinical Trial Registry (Identifier: ChiCTR-ICR-2000039747) on November 7th, 2020. The study (KY2020SL069-02) was approved by the Research Ethics Committee of Ningbo Medical Centre Lihuili Hospital. Participants were requested to provide informed consent. The study was conducted at a single medical center from November 2020 to July 2022. This study adhered to the principles outlined in the Declaration of Helsinki and followed the guidelines for reporting parallel group randomized trials, specifically complying with the Consolidated Standards for Reporting Trials 2010 (CONSORT).[9]

Participants

A total of two hundred patients, who were scheduled to undergo operative hysteroscopy, were evaluated for their eligibility to participate in the study. Inclusion criteria: (i) 19 years ≤age ≤60 years; (ii) ASA I–II; (iii) 18kg/m^2-<BMI<30kg/m^2; (iv) patients undergoing hysteroscopy required Monitored Anesthesia Care (MAC). Exclusion criteria: (i) Mallampati III~IV, Interincisor Distance < 3cm; (ii) gastroesophageal reflux history; (iii) chronic obstructive pulmonary disease and recent asthma attacks, or hypoxemia; (iv) Arrhythmia with II- or III-degree atrioventricular block; (v) severe hepatic, or renal dysfunction; (vi) history of dexmedetomidine hypersensitivity; (vii) use of sedatives, sleeping pills or analgesics for>3 months; (viii) central nervous system disease or neuropsychiatric disorders; (ix) refusal to sign the informed consent form.

Randomization and Blinding

The patients were firstly randomly assigned to receive either propofol and fentanyl (P group, n = 100) or a combination of propofol, dexmedetomidine, and fentanyl (DP group, n = 100), using a computer-generated randomized sequence with Microsoft Excel (Microsoft Corporation, Redmond, WA, United States). Subsequently, participants were further randomized to receive propofol at doses of 1.0, 1.5, 2.0, and 2.5 mg/kg in P group, and 0.5, 1.0, 1.5, and 2.0 mg/kg in DP group. Upon finalization of the randomization lists, treatment assignment was determined by revealing concealed envelopes subsequent to obtaining informed consent from study participants. The study drugs were prepared by a research assistant who possessed knowledge of the patients' grouping. All anesthesiologists responsible for anesthesia management and data collection were blinded to patient grouping.

Study Protocol

No premedication was given, and all patients underwent an 8-hour fasting period for solid food and a 2-hour fasting period for water prior to the surgery. In the operating theater, standardized monitoring techniques were employed for all patients, encompassing non-invasive blood pressure (NIBP), electrocardiography (ECG), peripheral oxygen saturation (SpO2), end-tidal carbon dioxide partial pressure (EtCO2), and bispectral index (BIS). Prior to anesthesia induction, all patients were administered oxygen at a flow rate of 5L·min-1 via a face mask. During preoxygenation, patients in the DP group received intravenous dexmedetomidine (0.5μg·kg^{-1}) over a period of 10 minutes, while those in the P group received an isovolumetric infusion of normal saline. The study assistant prepared both dexmedetomidine and saline using identical 20 mL syringes labeled solely with the study serial number. Before propofol administration, all patients were administered a bolus of fentanyl at a dose of 2.0 μg·kg^{-1}, followed by the delivery of propofol based on patient grouping. The anesthesia was maintained by administering a continuous infusion of propofol at a rate ranging from 6 to 8 mg·kg^{-1} per hour, with adjustments made based on patients' heart rate (HR), mean arterial pressure (MAP), BIS. Propofol

administration was terminated upon completion of the surgical procedure, and subsequent patient transfer to the post-anesthesia care unit (PACU) ensued. The administration of MAC anesthesia and data collection was carried out by a team of three highly skilled and experienced anesthesiologists (X.F Zhang, Y.Y Lou, K.W Wu). An effective dose was defined as the propofol dosage at which a patient achieves cervical dilation without any body movement, accompanied by a BIS value below 60 indicating unconsciousness. While, an ineffective dose was defined as the propofol dosage at which a patient exhibited body movement during cervical dilation and/or had a BIS value exceeding 60. In the event of an ineffective dose, we would incrementally increase the propofol dosage by 0.5mg/kg until the patient displayed no response to cervical dilation. Bradycardia was defined as the HR < 50 beats/min and was treated with intravenous atropine 0.5 mg. Hypotension was defined as the MAP < 60 mmHg or 30% lower than the baseline and was treated with intravenous ephedrine 6 mg.

The primary outcome of this study was the incidence of patients achieving effective propofol dose, defined as the dosage at which a patient exhibited no body movement during cervical dilation and had a BIS value below60. Secondary outcomes included assessment of vital signs (MAP, HR, SpO2, and BIS) at multiple time points: before administration (T0), after anesthetic induction (T1), during uterine dilation (T2), 15 minutes post-dilation (T3), and at the end of surgery (T4). Adverse events were recorded along with Ramsay sedation score and visual analog scale (VAS) score in the post-anesthesia care unit following the operation.

Statistical Analysis

The sample size was determined using the Cochran-Armitage test through PASS 15.0 software. Preliminary findings revealed that the proportions of effective doses of propofol in P group were 20%, 40%, 60%, and 70% at induction doses of 1.0 $mg{\cdot}kg^{-1}$, 1.5 $mg{\cdot}kg^{-1}$, 2.0 $mg{\cdot}kg^{-1}$, and 2.5 $mg{\cdot}kg^{-1}$, respectively. To achieve a statistical power of 90% in detecting a linear trend in the number of patients who achieved an effective propofol dose, we employed a continuity-corrected Z-test with a significance threshold of 0.05. Based on our calculations, it was determined that each group would require 17 patients, resulting in a total sample size of 68 patients. Taking into account potential patient dropout, we set the target sample size for each group at 25.

Statistical analysis was performed using IBM SPSS for Windows version 26.0 (IBM Corp, Armonk, NY, USA) and GraphPad Prism version 9.0 (GraphPad Software Inc, San Diego, CA, USA). The Kolmogorov–Smirnov test was utilized to assess the normality of continuous variables. Normally distributed variables were presented as mean ± standard deviation (SD) and analyzed using Student's *t*-test. Non-normally distributed variables were presented as median and interquartile range (IQR) and analyzed using the Mann–Whitney *U*-test. Categorical variables were expressed as number (%) and analyzed using the chi-square test. Probit regression analysis was employed to estimate the ED50 and ED95 values of propofol in suppressing cervical dilation induced body movement among hysteroscopic patients in both groups. The goodness-of-fit of the Probit model was evaluated using the Pearson chi-square test. A significance level of $P < 0.05$ was considered statistically significant.

Results

A total of 216 patients were initially recruited and assessed for eligibility. Among them, 7 declined to participate in the study, and 9 patients were excluded due to not meeting the inclusion criteria. The flowchart illustrating the CONSORT (Consolidated Standards of Reporting Trials) is presented in Figure 1. The demographic characteristics of the two groups did not exhibit any significant differences (all $P > 0.05$, Table 1). The consciousness recovery time in the DP group (8.86 ±2.86 mins) was found to be significantly longer compared to P group (6.76±2.52 mins), with an increase of 2.10 mins (95% CI, 1.31 to 2.89, $p<0.001$, Table 1).

Dose-Response of Propofol

The ED50 and ED95 values for propofol in the inhibition of body movement reaction to cervical dilation during hysteroscopic surgery were 1.781 (95% CI 1.507~2.118) and 4.670 (95% CI 3.555~7.506) mg/kg, respectively, in P group; while in the DP group, these values were found to be 0.983 (95% CI 0.800~1.173) and 2.578 (95% CI 2.013~3.895) mg/kg. The relative median potency in the DP group compared to the P group was 0.552 (95% CI

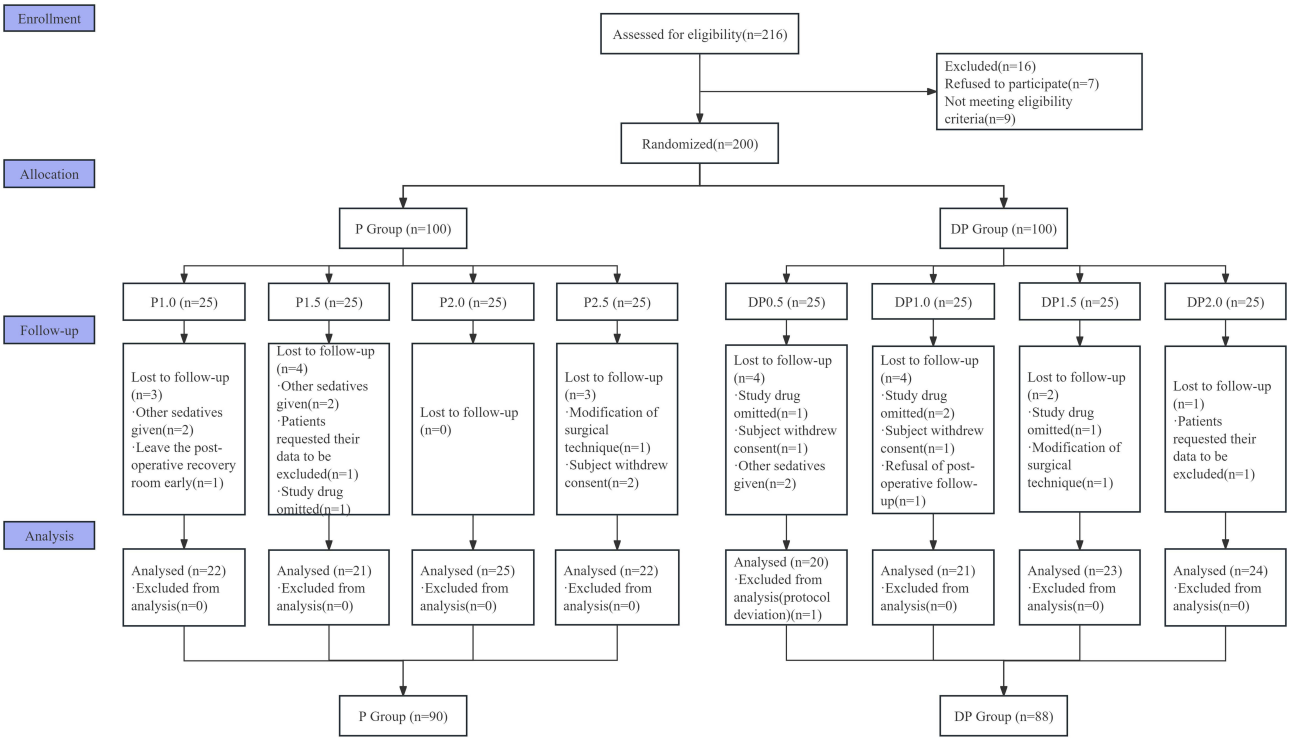

Figure 1 Consolidated Standards of Reporting Trials (CONSORT) flow diagram defining patient assessment and enrollment numbers in the study.

0.327~0.759), indicating a statistically significant disparity. The Pearson goodness-of-fit test ($\chi 2$= 1.114, P= 0.953) indicated a strong alignment between the observed data and the proposed model. The dose-response curves obtained through probit regression analysis are presented in Figure 2.

Consumption of Propofol

The total amount of propofol administered for cervical dilation in the DP group (91.84 ± 27.52 mg) was significantly reduced by 38.86 mg (95% CI 29.83 to 47.89) compared to the P group (130.70 ± 33.72 mg, Table 1), with a statistically significant difference observed (P <0.001). Furthermore, the total propofol dosage in the DP group (254.40 ± 70.82mg) exhibited a significant reduction of 67.38mg (95% CI 45.85 to 88.91) compared to the P group (321.78 ± 75.68mg, Table 1), *P*< 0.001.

Table 1 Patient Characteristics and Propofol Consumption at Different Phases

	P Group (n=90)	DP Group(n=88)	*P* value
Age (yr)	38.8±10.8	39.9±10.0	0.463
BMI (kg/m^2)	21.9±2.7	21.9±2.8	0.912
ASA I/II	71/19	69/19	0.938
Duration of anesthesia (min)	36.69±6.04	35.09±6.17	0.083
Duration of surgery (min)	26.08±6.39	25.18±6.65	0.361
Recovery time (min)	6.76±2.52	8.86±2.86	<0.001
Propofol induction dose (mg)	130.70±33.72	91.84±27.52	<0.001
Propofol total dose (mg)	321.78±75.68	254.40±70.82	<0.001

Notes: Data are presented as numbers or mean ± SD.
Abbreviations: BMI, Body mass index (kg/m^2); ASA, American Society of Anesthesiologists.

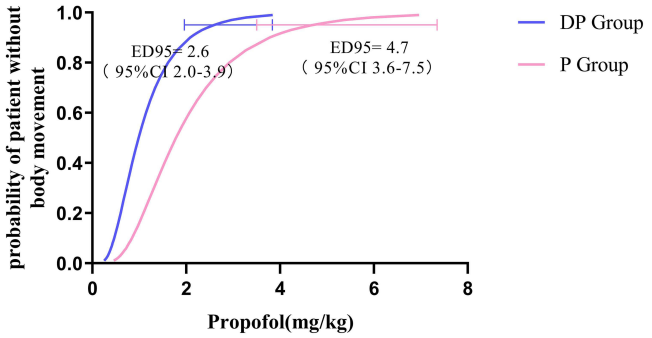

Figure 2 The dose-response curve of the probability of patient without body movement versus propofol dose. The ED95 of propofol for the DP and P groups, calculated using probit logistic regression, was 2.6 (95% CI: 2.0–3.9) and 4.7 (95% CI: 3.6–7.5) mg/kg, respectively.

Sedation-Related Adverse Effects

No statistically significant differences were observed between P group and DP group in terms of sedation-related adverse events, including hypotension, bradycardia, dizziness, lethargy, nausea, and vomiting (all $P > 0.05$, Table 2). No instances of arrhythmia were observed in the DP group. Compared to the P group, the DP group exhibited a significant reduction of 14.0% in the occurrence of respiratory depression (32.2% vs 18.2%, $P = 0.031$), as well as a notable decrease of 9.9% in postoperative abdominal pain incidence (14.4% vs 4.5%, $P = 0.046$) (Table 2).

MAP, HR, SpO2 and Ramsay Sedation Score

The MAP in the DP group was significantly higher than that in the P group at time points T1, T2, T3, and T4 (all $P < 0.05$, Figure 3A). Conversely, the HR was lower at times T1, T2, and T3 in the DP group compared to the P group (all $P<0.05$, Figure 3B). Additionally, the SpO2 in the DP group was significantly higher than that in the P group at time point T1 ($P < 0.05$, Figure 3C). After surgery, the Ramsay sedation score was significantly higher in DP group compared to P group ($P < 0.05$, Figure 4), whereas there was a significant decrease observed in the VAS score ($P < 0.05$, Table 2).

Table 2 Sedation-Related Adverse Events

	P Group (n=90)	DP Group (n=88)	P value
Hypoxemia (SpO2<95%) (n)	29	16	0.031
Induction (n)	23	13	0.073
Maintenance (n)	6	3	0.516
Increase the flow of oxygen(n)	27	11	0.004
Jaw thrust(n)	19	6	0.006
Mask-assisted ventilation(n)	10	8	0.655
Intubation(n)	0	0	0.000
Hypotension (n)	14	10	0.349
Bradycardia (n)	3	2	>0.999
Nausea and vomiting in PACU (n)	2	2	>0.999
Dizziness and lethargy in PACU (n)	8	10	0.584
Pain in PACU (n)	10	4	0.046

Notes: Data are presented as numbers.

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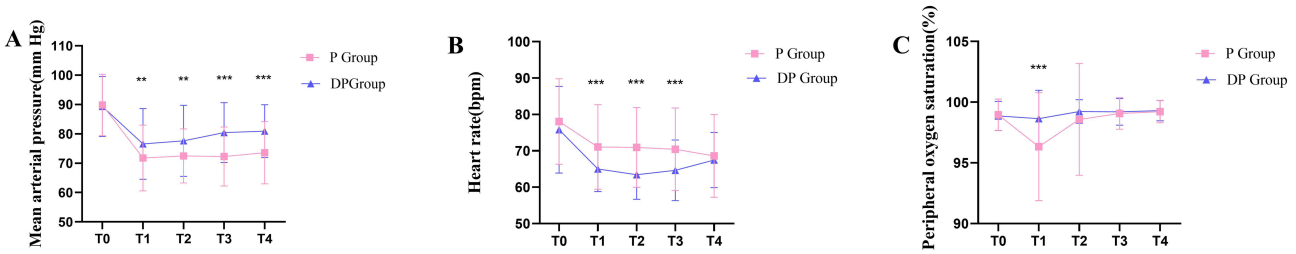

Figure 3 Hemodynamic parameters of patients. Data are presented as mean ± SD. ***P* <0.01 vs P Group, ****P* <0.001 vs P Group. (**A**) mean arterial pressure; (**B**) heart rate; (**C**) peripheral oxygen saturation. T0=Before the induction of sedation; T1= After anesthetic induction; T2= During uterine dilation; T3= 15 minutes post-dilation; T4= At the end of surgery.

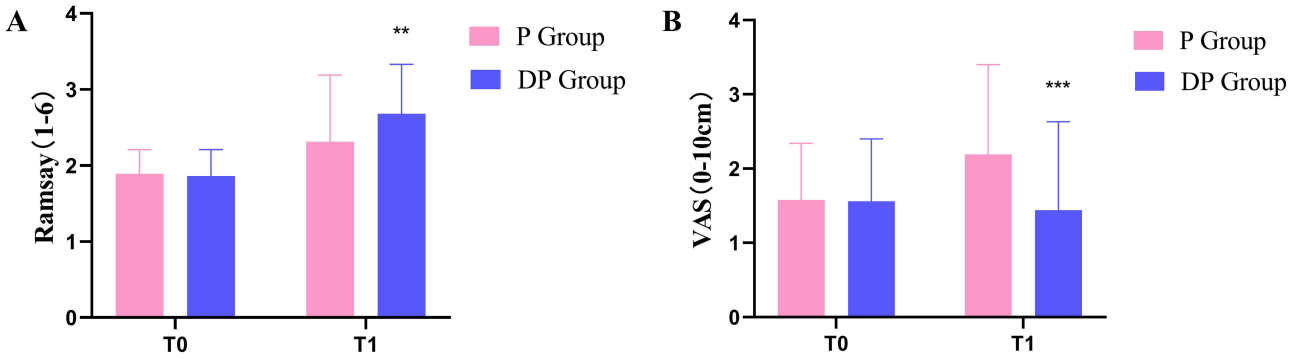

Figure 4 Postoperative sedation and pain scores. Data are presented as mean ± SD. ***P* <0.01 vs P Group, ****P* <0.001 vs P Group. (**A**) Ramsay sedation scores; (**B**) VAS pain scores. T0 = Before the induction of sedation; T1 = Enter recovery room immediately (**A**); T1=At the time of consciousness recovery (**B**). VAS, visual analogue scale, scaled from 0 to 10 (0 means no pain and 10 means the maximum intensity of pain).

Discussion

In this current randomized, double-blind study, we observed a significant decrease in the ED50 and ED95 of propofol required to maintain patient comfort during hysteroscopy at cervical dilation following pre-induction administration of an intravenous dexmedetomidine bolus at a dose of 0.5 μg/kg. These findings suggest that the combined use of dexmedetomidine reduced the dosage requirement of propofol in patients undergoing cervical dilation. The intravenous administration of dexmedetomidine also resulted in a reduction in total propofol consumption during hysteroscopy, as well as a decrease in the incidence of hypoxia and postoperative pain. Furthermore, no additional adverse effects were observed with the use of dexmedetomidine.

The combination of propofol with opioids is a commonly employed anesthetic technique known as MAC for operative hysteroscopic procedures.[10,11] However, the administration of high-dose boluses of opioids can exacerbate respiratory depression, making it unsuitable for implementation in the MAC technique. Therefore, we utilized a relatively low dose of fentanyl (2 μg/kg) for MAC in this study. According to reports, dexmedetomidine possesses sedative, analgesic, anxiolytic, and opioid-sparing properties, making it advantageous for clinical application.[12] In addition to these properties, several clinical reports have demonstrated that dexmedetomidine effectively reduces the propofol dosage required for sedation. Edokpolo et al[8] observed a reduction in propofol consumption among patients undergoing colonoscopy when administered with 0.3 μg/kg dexmedetomidine, compared to those without dexmedetomidine administration. Li et al identified a dose-dependent propofol-sparing effect of dexmedetomidine when combined with target-controlled infusion of propofol during hysteroscopic submucosal myomectomy, and proposed an optimal dosage of 0.5 μg/kg for dexmedetomidine administration.[13] This propofol sparing-effect was also observed in elderly patients undergoing endoscopic retrograde cholangiopancreatography, with a starting dose of 0.4 $\mu g \cdot kg^{-1} \cdot h^{-1}$ administered 15 minutes prior to surgery and continued until completion.[14] Notably, the comprehensive quantification of this impact and the complete elucidation of the dose-response relationship for guiding clinical practice remain to be determined. This study provides a comprehensive dose-response curve of propofol with dexmedetomidine for clinical reference, including the

minimum effective dose (ED50: 0.983 mg/kg) and guiding dose (ED95: 2.578), and demonstrates that administering 0.5 μg/kg of dexmedetomidine can reduce the required propofol dosage by approximately 45% to suppress body movement in patients undergoing operative hysteroscopy. To the best of our knowledge, this study represents the first attempt to quantitatively assess the impact of dexmedetomidine on propofol dosage.

Hypoxemia is a prevalent adverse effect of propofol administration for the purpose of inducing or maintaining sedation in patients during specific clinical procedures. Moreover, the prevalence of hypoxemia may be linked to an increased risk of brain injury, myocardial ischemia, and the need for mechanical ventilation, thereby contributing to higher mortality rates. To mitigate potential adverse effects in this context, dexmedetomidine has been extensively investigated and demonstrated a lower incidence of respiratory depression compared to propofol.[15,16] In the present study, we observed a significantly lower incidence of respiratory depression in patients who received a combination of dexmedetomidine and propofol compared to those who received propofol alone. Accordingly, patients in P group frequently exhibited retrolingual collapse during the procedure, necessitating increased intervention by anesthesiologists. This suggests that the combined technique offers potential benefits in mitigating the workload of anesthesiologists. The possible reasons are as follows: first, the administration of dexmedetomidine rarely leads to respiratory depression and does not enhance the respiratory depressive effects of opioid analgesics;[17,18] second, the administration of dexmedetomidine resulted in a reduction in propofol dosage, leading to a subsequent decrease in the incidence of respiratory depression. Additionally, the study observed a higher incidence of respiratory depression during the dilation phase, potentially attributed to an increased short-term propofol dosage in response to stimulation during dilation, thereby suggesting a dose-dependent relationship between propofol administration and respiratory depression.

The incidence of postoperative uterine pain was lower in patients who received dexmedetomidine, possibly attributed to its analgesic effect mediated by α2-A receptors located on the presynaptic and postsynaptic membranes of spinal cord interneurons. This mechanism facilitates cellular hyperpolarization and inhibits bidirectional transmission of pain signals[19–21].The stability of the mean arterial pressure (MAP) is enhanced when dexmedetomidine is used, possibly due to the predominant localization of α2-B receptors in vascular smooth muscle.[22] These receptors mediate the modulation of MAP, indicating that the combined technique confers hemodynamic benefits. Although the recovery time was prolonged in patients who received dexmedetomidine, potentially due to the agonistic action on α2-C receptors,[21,23] both groups of patients met the discharge criteria within 30 minutes upon arrival at the post-anesthesia care unit, with no observed delay in recovery. Therefore, the higher incidence of postoperative lethargy holds limited clinical significance in the context of this study.

We acknowledged several limitations. First, although we implemented a randomized double-blinded protocol, it is possible that the observers were aware of the patients' grouping due to some patients experiencing somnolence after dexmedetomidine infusion. However, considering the objective nature of our study's primary outcome measure, we contend that any potential limitations in blinding would have minimal impact on our findings. Second, variations in drug combinations protocols across different institutions, encompassing the presence or absence of opioids and varying dosage regimens, may contribute to divergent ED95 values for propofol. Therefore, the generalizability and applicability of the findings from this study are constrained. Third, the limited generalizability of this single-center study is attributed to its stringent inclusion and exclusion criteria as well as the specific population under investigation. Therefore, further investigations encompassing diverse settings are warranted.

Conclusion

Under the condition of this study, we found that low-dose dexmedetomidine (0.5 μg/kg) could reduce the requirement for propofol to suppress body movement in patients undergoing operative hysteroscopy without adding any undesirable side effects.

Abbreviations

MAC, Monitored anesthesia care; PSA, procedural sedation and analgesia; ASA, American Society of Anesthesiologists; NIBP, non-invasive blood pressure; ECG, electrocardiography; SpO2, peripheral oxygen saturation; EtCO2, end-tidal carbon dioxide partial pressure; BIS, bispectral index; HR, heart rate; MAP, mean arterial pressure; VAS, visual analog scale.

Data Sharing Statement

The datasets generated during and/or analyzed during the current study are not publicly available due to the privacy policy but are available from the corresponding authors on reasonable requests.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors did not report any potential conflict of interests.

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