ED50 of Propofol Combined with Nalbuphine on the Sedative Effect in Painless Hysteroscopy

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ABSTRACT

Introduction: Nalbuphine has gradually become a commonly used clinical analgesic drug for painless hysteroscopy. The aim of our study was to identify the median effective dose (ED50) of propofol combined with nalbuphine for painless hysteroscopy.
Methods: Sixty-one patients aged 18–60 years were recruited to undergo elective painless hysteroscopy. Patients were administered 0.1 μg/kg nalbuphine (group A) or 0.2 μg/kg nalbuphine (group B) intravenously 3 min before endoscopic placement. The Dixon sequential method was used with an initial intravenous propofol dose of 2 mg/kg, which varied by 0.5 mg per kilogram.
Results: The ED50 of propofol was 1.729 mg/kg (95% confidence interval [CI] 1.526–1.856 mg/ kg) in group A and 1.658 mg/kg (95% CI 1.359–1.799 mg/kg) in group B. The 95% effective dose (ED95) of propofol was 2.051 mg/kg (95% CI 1.899–3.331 mg/kg) in group A and 2.020 mg/kg (95% CI 1.849–3.832 mg/kg) in group B.
Conclusion: For safety and effective painless hysteroscopic, the ED50 values of propofol combined with nalbuphine were 1.729 mg/kg (0.1 mg/kg nalbuphine) and 1.658 mg/kg (0.2 mg/kg nalbuphine). The recommended dose of nalbuphine is therefore 0.1 mg/kg.
Trial Registration: Chinese Clinical Trial Registry: ChiCTR2100042342 (http://www.chictr. org.cn/edit.aspx?pid=66342&htm=4; registration date 19 Jan 2021).

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Key Summary Points

Painless hysteroscopy is usually performed under total intravenous general anaesthesia without tracheal intubation, with propofol as the main anaesthetic drug and opioid analgesics as supplementary analgesics.

Our study aimed to identify the median effective dose (ED50) of propofol combined with nalbuphine for painless hysteroscopy.

During hysteroscopy with intravenous anaesthesia, the ED50 values of propofol combined with nalbuphine were 1.729 mg/kg (0.1 mg/kg nalbuphine) and 1.658 mg/kg (0.2 mg/kg nalbuphine).

Increases in the nalbuphine dose did not achieve additional benefits; consequently, we suggest that 0.1 mg/kg nalbuphine is the appropriate dose for hysteroscopy.

DIGITAL FEATURES

This article is published with digital features, including a summary slide, to facilitate understanding of the article. To view digital features for this article, go to https://doi.org/10.6084/m9.figshare.14744349.

INTRODUCTION

Hysteroscopy is a minimally invasive technique that is widely used to diagnose and treat gynaecological conditions [1]. This procedure can be performed in an outpatient setting in clinics, without any type of anesthesia and need of an operating room. However, painless hysteroscopy, which aims to improve the patient's experience and is performed under intravenous general anaesthesia without tracheal intubation, is becoming increaslingly popular. In painless hysteroscopy, propofol is commonly used as the main anaesthetic drug and opioid analgesics as supplementary analgesics painless hysteroscopy [2, 3].

Nalbuphine is a classical opioid receptor agonist–antagonist that acts on both κ-receptors (agonist) and μ-receptors (antagonist). Due to both its agonist–antagonist effects and good analgesic effects, nalbuphine has gradually become a commonly used clinical analgesic drug, especially for the management of visceral pain [4]. However, the minimum effective dose of propofol is unknown when used in combination with nalbuphine. Therefore, the aim of our study was to identify the median effective dose (ED50) of propofol combined with nalbuphine for painless hysteroscopy.

METHODS

Ethics Approval

This study was approved by the Ethical Committee of The First Affiliated Hospital of Anhui Medical University, Hefei, China (Approval No. PJ2021-01-20) and registered in the Chinese Clinical Trial Registry (www.chictr.org.cn; registration number ChiCTR2100042342). All patients provided written informed consent, and all procedures were conducted according to the Declaration of Helsinki.

Participants

From January to March 2020, we recruited 61 patients aged 18–60 years with American Society of Anaesthesiologists (ASA) physical condition I or II to undergo elective hysteroscopy and therapeutic surgery at the First Affiliated Hospital of Anhui Medical University.

Because the study was adjusted for specific criteria, the recommended seven-step crossover rule was used to discontinue the inclusion of participants. Thus, we did not calculate the sample size in advance.

Exclusion Criteria

Patients were excluded from this study for the following reasons: ASA class III or higher; age > 60 years or < 18 years; liver or kidney dysfunction or other systemic complications before the operation; central nervous, respiratory or circulatory system diseases; psychotic disorders; escalation to tracheal intubation and general anaesthesia; a procedure lasting > 30 min; or a lack of desire to comply with the protocol or procedures or an inability to understand the language used.

Anaesthesia

All patients routinely fasted for > 8 h and were not allowed to drink water at least 2 h prior to the operation. No preoperative medication was given. Once the patient was in the operating room, venous access to the left upper limb was obtained. Electrocardiogram, blood pressure and pulse oxygen saturation (SpO2) were monitored regularly (every 3 min), and oxygen was supplied by mask (5 L/min). Patients were randomly divided into group A or group B by the random number table method. Patients in group A were given 0.1 μg/kg nalbuphine intravenously 3 min before endoscopic placement, and those in group B received nalbuphine 0.2 μg/kg intravenously at the same time point. Propofol was slowly injected intravenously for > 1 min. The hysteroscopy procedure was started once the patient lost consciousness. All anaesthesia was administered by the same senior anaesthesiologist, and examinations were performed by the same team of experienced gynaecologists.

The nalbuphine citrate used in this study was manufactured by Ren Fu Rui Jing Pharmaceutical (Henan, China; lot no. 01J09011), and the propofol was manufactured by AstraZeneca (Disoprofol; Cambridge, UK; lot no. RK649.).

The Dixon sequential method was used in this study. The initial dose of intravenous propofol was 2 mg/kg, and 0.5 mg/kg of propofol was added when cervical dilation and hysteroscopic placement were poor or if the previous patient had had a positive response,

which was defined as any physical movement, frowning or Ramsay score < 5 within 5 min. Also, the dosage of propofol for the next patient was increased by 1 dose gradient, and if the hysteroscopic examination was successfully completed, the dose gradient for the next patient was decreased by 1 dose gradient. The difference between the two adjacent doses was 0.1 mg/kg. Ephedrine (5–10 mg) was intravenously injected if the intraoperative systolic blood pressure was < 20% of the baseline value. Atropine (0.5 mg) was intravenously injected in patients with bradycardia. If the SpO2 was < 95%, the lower jaw was propped; if the SpO2 level still did not improve or continued to decline, pressure-assisted ventilation with mask was given. In this study, seven crossovers were considered to be sufficient to identify the ED50 of propofol.

The Ramsay Sedation Scale was measured on a 6-point scale as follows: level 1 awareness: the patient is anxious, restless or irritable; level 2 wakefulness: the patient is cooperative, well oriented or quiet; level 3 wakefulness: the patient responds only to commands; Level 4 sleep: the patient responds quickly to eyebrow tapping or strong sound stimulation; level 5 sleep: the patient is unresponsive to light tapping on the eyebrow or strong sound stimulation; level 6 sleep: the patient does not respond to light tapping on the eyebrow or strong acoustic stimulation.

The recorded measures included the first initial dose of propofol, the time of maintaining the first dose of propofol, the repeated dose of propofol, the total dose of propofol, the examination time (from hysteroscope insertion to hysteroscope removal), the dose per unit time (the ratio of the total dose of propofol to the duration of anaesthesia) and the anaesthesia recovery time (the time from the last administration to the patient's recovery). The visual analogue scale (VAS) pain score at the point of anaesthesia recovery was recorded (scores of 0–10 represent different degrees of pain with 0 = painless and 10 = severe pain). The heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP) and SpO2 were recorded before induction (T1) and at the time of commencement of

hysteroscopy (T2). Adverse reactions recorded were: body movement reaction, hypotension (blood pressure < 20% of baseline), sinus bradycardia (HR < 50 beats/min), hypoxemia (SpO2 < 95%), nausea and vomiting.

Statistical Analysis

All analyses were conducted using SPSS version 23.0 (IBM Inc., Armonk, NY, USA) provided by the Medical Data Processing Center of the School of Public Health of Anhui Medical University. All quantitative data were tested for normality. Normally distributed variables were summarized using the mean and standard deviation, and they were compared using a t test for demographic data. Non-normally distributed continuous variables were analysed using the non-parametric Mann–Whitney U test. All categorical data were tested using a chi-square test. The ED50, 95% effective dose (ED95) and 95% confidence interval (CI) of propofol were calculated by the probit method (probability unit regression). A P value < 0.05 was considered to be statistically significant.

RESULTS

A total of 61 patients were enrolled and all completed the study. The flowchart of patient enrolment is shown in Fig. 1. There was no significant difference in demographic characteristics between the two groups (Table 1).

There was no significant difference in the duration of examination time between the two groups (10.32 ± 5.17 vs. 9.50 ± 4.08 min; $P > 0.05$) or in the total dosage of propofol administered (158.81 ± 53.13 vs. 144.93 ± 33.76 mg; $P > 0.05$). The ratio of total propofol dose to anaesthesia duration was similar between the two groups (13.57 ± 2.96 vs. 12.82 ± 2.56; $P > 0.05$). There was no significant difference in the first dose of propofol
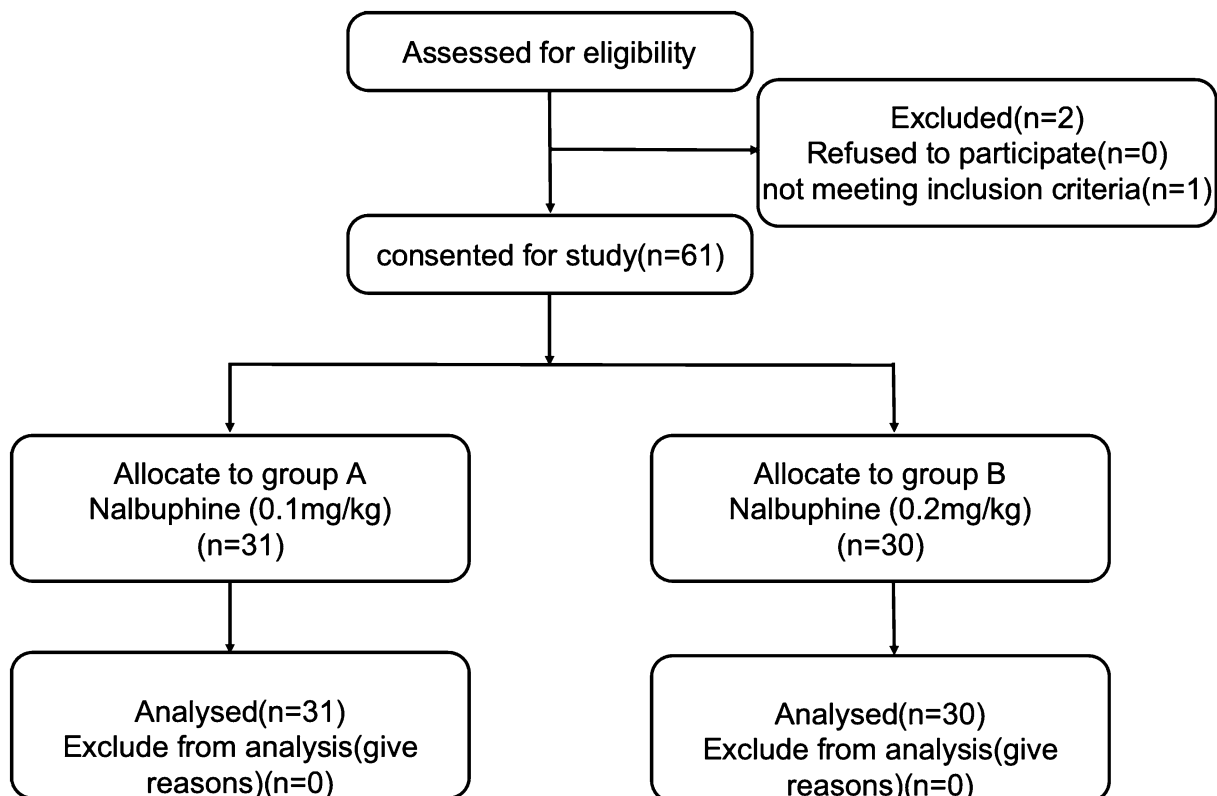

Fig. 1 Flowchart of patient enrolment

Table 1 Demographic characteristics of patients

Demographic characteristic	Group A (n = 31)[a]	Group B (n = 30)[a]	t value	P value
Age (years)	35.87 ± 9.10	37.87 ± 10.10	− 0.811	0.420
Height (cm)	161.68 ± 5.26	159.53 ± 4.95	1.640	0.106
Weight (kg)	56.66 ± 6.35	53.92 ± 5.58	1.791	0.078
Body mass ndex	21.66 ± 1.80	21.11 ± 1.67	1.241	0.220

Data are presented as the mean ± standard deviation.(SD). No significant differences were found between the two groups with respect to these characteristics

[a] Patients were administered 0.1 μg/kg nalbuphine (group A) or 0.2 μg/kg nalbuphine (group B) intravenously 3 min before endoscopic placement

Table 2 Comparison of intravenous anaesthesia outcomes between the two groups

Index	Group A (n = 31)	Group B (n = 30)	t value	P value
Initial dose of propofol (mg)	99.79 ± 14.63	92.02 ± 13.63	2.147	0.036*
Total dose of propofol (mg)	158.81 ± 53.13	144.93 ± 33.76	1.213	0.230
Inspection time (min)	10.32 ± 5.17	9.50 ± 4.08	0.688	0.494
Maintenance time of first dose of propofol (min)	4.90 ± 2.10	4.90 ± 2.04	0.006	0.995
Unit time dose of propofol (mg/min)	13.57 ± 2.96	12.82 ± 2.56	1.057	0.295
Time of recovery (min)	5.00 ± 1.97	4.47 ± 2.33	0.967	0.337
Visual analogue scale (VAS) pain score (points)	1.58 ± 0.81	1.17 ± 0.38	2.577	0.013*
Respiratory depression (n)	3	4		0.707
Nausea and vomiting (n)	2	2		1.000

Data are presented as the mean ± SD or as the number of patients, as appropriate

*Significant difference at $P < 0.05$

maintenance time and anaesthesia recovery time between the two groups ($P > 0.05$). Compared with group A, the initial dose of propofol and VAS pain score in group B were significantly lower, and the differences were statistically significant (initial dosage 99.79 ± 14.63 vs. 92.02 ± 13.63 and VAS pain score 1.58 ± 0.81 vs. 1.17 ± 0.38; both $P < 0.05$). There was no statistical significance in the incidence of respiratory depression, nausea and vomiting between the two groups ($P > 0.05$) (Table 2).

At T1, there were no statistically significant differences in haemodynamic indexes between the two groups ($P > 0.05$). In comparison with the values at T1, the SBP in both groups was significantly decreased at T2 ($P < 0.05$), with the SBP in group B significantly lower than that in group A at this same timepoint ($P < 0.05$). Also in comparison with the values at T1, the DBP in both groups was significantly decreased at T2, with the DBP in group B significantly lower than that in group A at this same time point ($P < 0.05$). Similarly, the MAP in both groups was significantly decreased at T2, and the MAP in group B was significantly lower than that in group A at this same time point ($P < 0.05$) (Table 3).

The ED50 of propofol determined by the up-and-down sequential allocation method was 1.729 (95% CI 1.526–1.856) mg/kg in group A

Table 3 Comparison of haemodynamic parameters at different time points

Index	Time points[a]	Group A	Group B
Heart rate (bpm)	T1	82.77 ± 12.60	83.83 ± 15.64
	T2	80.42 ± 12.36	79.33 ± 13.46
Systolic blood pressure (mmHg)	T1	135.45 ± 9.43	134.87 ± 10.02
	T2	$115.06 \pm 11.83^{\#}$	$108.77 \pm 8.92^{*\#}$
Diastolic blood pressure (mmHg)	T1	87.97 ± 11.98	87.77 ± 10.37
	T2	$68.77 \pm 10.34^{\#}$	$63.83 \pm 5.89^{*\#}$
Mean arterial pressure (mmHg)	T1	103.90 ± 10.01	105.43 ± 9.13
	T2	$85.74 \pm 9.91^{\#}$	$81.30 \pm 6.37^{*\#}$

$^{*}P < 0.05$, compared with group A

$^{\#}$ $P < 0.05$, compared with T1

^{a} T1 is before induction; T2 is at the time of commencement of hysteroscopy
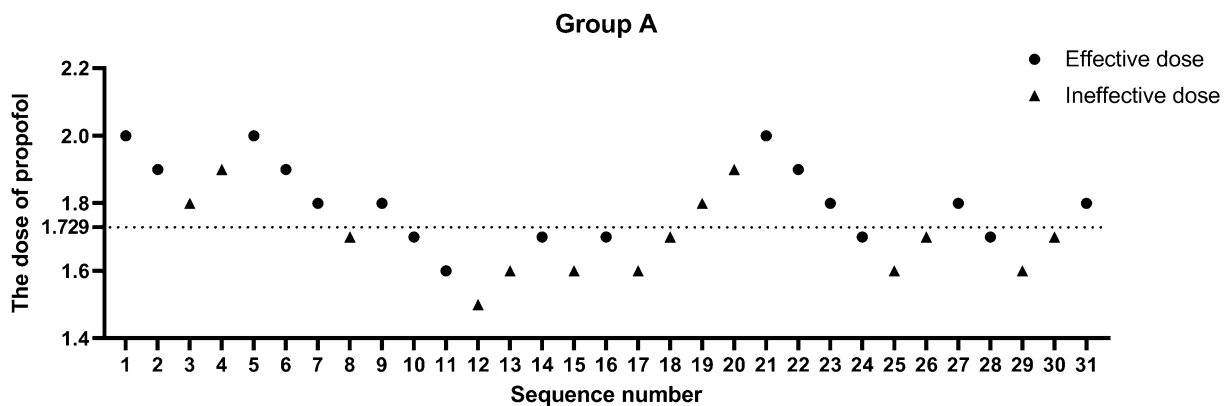
Fig. 2 Stepwise dose adjustment of propofol with nalbuphine (0.1 mg/kg) (group A) using the Dixon sequential method. Filled circle represents an effective dose; filled triangle represents an ineffective dose

and 1.658 (95% CI 1.359–1.799) mg/kg in group B. The ED95 of propofol determined by the up-and-down sequential allocation method was 2.051 (95% CI 1.899–3.331) mg/kg in group A and 2.020 (95% CI 1.849–3.832) mg/kg in group B. There was a significant difference in ED50 and ED95 between the two groups ($P < 0.05$). The sequential doses of propofol coadministered with nalbuphine for intravenous anaesthesia in hysteroscopy are shown in Figs. 2 and 3.

DISCUSSION

Hysteroscopy is an important method for the diagnosis and treatment of uterine diseases. Painless hysteroscopy with propofol alone or combined with a pure μ-receptor agonist (such as fentanyl and sufentanil) has become a popular procedure due to the favourable sedative effect and rapid onset and short duration of action of propofol [2]. Propofol has a weak analgesic effect, while opioids, such as fentanyl and sufentanil, are prone to cause adverse
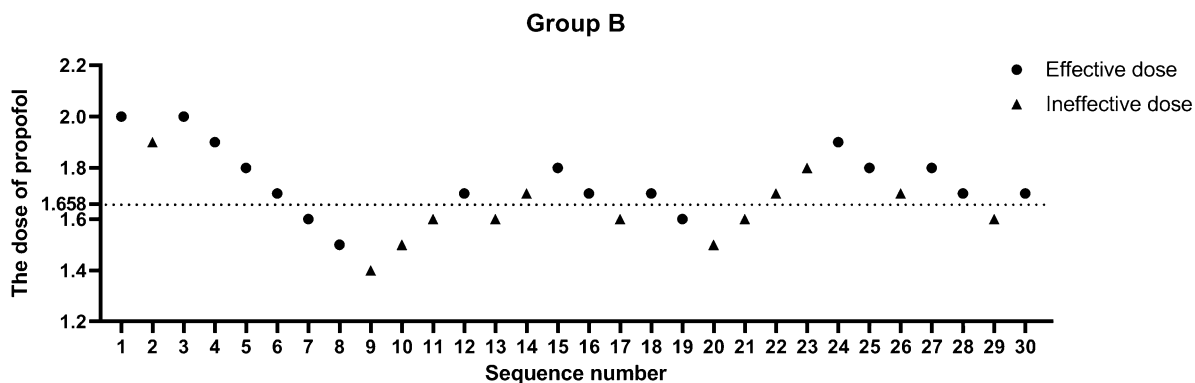
Fig. 3 Stepwise dose adjustment of propofol with nalbuphine (0.2 mg/kg) (group B) using the Dixon sequential method. Filled circle represents an effective dose; filled triangle represents an ineffective dose

reactions, including respiratory depression, nausea, vomiting and prolonged awakening [5]. Therefore, maintaining the stable respiratory function of patients and reducing the incidence of adverse reactions during hysteroscopy have always been two difficulties that anaesthesiologists encounter in painless hysteroscopy.

Nalbuphine is a classic opioid receptor agonist–antagonist, and it is not only a kappa receptor agonist but also a μ-receptor antagonist. Nalbuphine can therefore function as an agonist–antagonist and concomitantly provide good analgesic effects, especially for visceral pain. In comparison with other nalgesic drugs, patients receiving nalbuphine have fewer adverse reactions and a lower incidence of respiratory depression; it also has a "capping effect" and rarely involves the cardiovascular system [6]. Studies have shown that the analgesic effect of nalbuphine on women is significantly stronger than that on men [7], resulting in nalbuphine being favoured by obstetricians and gynaecologists due to the gender analgesic advantage. However, there are few reports on propofol being used in combination with nalbuphine for hysteroscopy. Therefore, it is necessary to determine the ED50 and ED95 of propofol when combined with nalbuphine to provide a reference for rational clinical drug use. The induced dose of fentanyl commonly used in clinical anaesthesia is 1 μg/kg, and 1 mL (10 mg) of nalbuphine is considered to be equipotent to 1 mL (100 μg) of fentanyl [8]. Moreover, some studies have also shown that

the recommended dose of nalbuphine in endoscopic examination is 0.1–0.2 mg/kg [9]. Therefore, in this study, two different doses of nalbuphine were administered to patients, namely 0.1 mg/kg (group A) and 0.2 mg/kg (group B). Because the onset time of nalbuphine is 2–3 min [10], propofol should be injected 3 min after the intravenous injection of nalbuphine to maximize the analgesic effect of nalbuphine during painless hysteroscopy.

The initial dose of propofol was signficantly higher when combined with 0.1 mg/kg nalbuphine than when combined with 0.2 mg/kg nalbuphine, suggesting that any reduction of the nalbuphine dose requires increased use of propofol at the beginning of the procedure. However, the total dose of propofol and the ratio of total propofol dosage to anaesthesia time were similar in both groups. In addition, there was no difference in the initial dose action time and recovery time between the two groups. Although the VAS score was higher in group A than in group B, both the patients' need for analgesia and the conditions for comfortable diagnosis and treatment were satisfied, indicating that both combined regimens obtain good anaesthesia and meet the needs of hysteroscopic surgery.

The results of this study also showed that propofol combined with nalbuphine is safe for patients undergoing hysteroscopy. The incidence of respiratory depression was 13.33% when using 0.2 mg/kg nalbuphine and 9.68% when using 0.1 mg/kg nalbuphine. The

incidence of nausea and vomiting was 6.45% when using 0.2 mg/kg nalbuphine and 6.66% when using 0.1 mg/kg nalbuphine with no significant differences. As nalbuphine antagonizes the action of μ-receptors and has a capping effect on respiratory depression, the incidences of respiratory depression, nausea and vomiting are reduced [11, 12].

There was no significant difference in the HR between the two groups at the T1 and T2 time points, but the SBP, DBP and MAP of the two groups were significantly decreased at T2 compared to T1. The degree of decrease was greater when using 0.2 mg/kg nalbuphine in comparison to 0.1 mg/kg nalbuphine, which contradicted what we originally hypothesized. Previous studies have shown that nalbuphine has no direct effect on the cardiovascular system and has little effect on haemodynamics [13–15]. These results may have been due to nalbuphine itself inducing mast cells to release histamine, which further dilates blood vessels and lowers blood pressure, or failure to mask the cardiovascular effects of propofol.

Because increases in the nalbuphine dose did not achieve additional benefits, we suggest that the appropriate dose of nalbuphine for hysteroscopy is 0.1 mg/kg.

One limitation to this study is that the combination of propofol and nalbuphine in painless hysteroscopic fouind to be safe and effective may only work in relatively healthier patients (ASA I or II) as no elderly or patients with other health conditions (ASA III or IV) were recruited to this study.

CONCLUSION

For safety and effective painless hysteroscopic, the ED50 values of propofol combined with nalbuphine were 1.729 mg/kg (0.1 mg/kg nalbuphine) and 1.658 mg/kg (0.2 mg/kg nalbuphine), and the recommended dose of nalbuphine is 0.1 mg/kg.

ACKNOWLEDGEMENTS

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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REFERENCES

1. Vitale SG, Bruni S, Chiofalo B, Riemma G, Lasmar RB. Updates in office hysteroscopy: a practical decalogue to perform a correct procedure. Updates Surg. 2020;72(4):967–76.

2. Yu J, Xiang B, Song Y, Chen H, Li Y, Liu C. ED50 of propofol in combination with low-dose sufentanil for intravenous anaesthesia in hysteroscopy. Basic Clin Pharmacol Toxicol. 2019;125(5):460–5.

3. Ryu JH, Kim JH, Park KS, Do SH. Remifentanil-propofol versus fentanyl-propofol for monitored anaesthesia care during hysteroscopy. J Clin Anesth. 2008;20(5):328–32.

4. Huang CY, Li SX, Yang MJ, Xu LL, Chen XZ. A comparative study of three concentrations of intravenous nalbuphine combined with hydromorphone for post-cesarean delivery analgesia. Chin Med J (Engl). 2020;133(5):523–9.

5. Lazzaroni M, Bianchi PG. Preparation, premedication and surveillance. Endoscopy. 2005;37(2):101–9.

6. Zeng Z, Lu J, Shu C, et al. A comparision of nalbuphine with morphine for analgesic effects and safety: meta-analysis of randomized controlled trials. Sci Rep. 2015;3(5):10927.

7. Gear RW, Miaskowski C, Gordon NC, Paul SM, Heller PH, Levine JD. Kappa-opioids produce significantly greater analgesia in women than in men. Nat Med. 1996;2:1248–50.

8. Rawal N, Wennhager M. Influence of perioperative nalbuphine and fentanyl on postoperative respiration and analgesia. Acta Anaesthesiol Scand. 1990;34(3):197–202.

9. Chaoyi D, Xiao W, Qianmei Z, et al. Comparison of nalbuphine and sufentanil for colonoscopy: a randomized controlled trial. PLoS ONE. 2017;12(12):e0188901.

10. Amin SM, Amr YM, Fathy SM, et al. Maternal and neonatal effects of nalbuphine given immediately before induction of general anesthesia for elective cesarean section. Saudi J Anaesth. 2011;5(4):371–5.

11 Zhang Y, Jiang Q, Li T. Nalbuphine analgesic and anti-inflammatory effects on patients undergoing thoracoscopic lobectomy during the perioperative period. Exp Ther Med. 2017;14(4):3117–21.

12. Anna KC, Marzena Z. The use of nalbuphine in paediatric anaesthesia. Anaesthesiol Intensive Ther. 2015;47(3):252–6.

13 Bressolle F, Khier S, Rochette A, et al. Population pharmacokinetics of nalbuphine after surgery in children. Br J Anaesth. 2011;106(4):558–65.

14. Zsigmond EK, Winnie AP, Raza SM, et al. Nalbuphine as an analgesic component in balanced anesthesia for cardiac surgery. Anesth Analg. 1987;66(11):1155–64.

15. Chawda PM, Pareek MK, Mehta KD. Effect of nalbuphine on haemodynamic response to orotracheal intubation. J Anaesthesiol Clin Pharmacol. 2010;26(4):458–60.