International Journal of Biology and Life Sciences
ISSN: 2957-9511 | Vol. 8, No. 3, 2024

ED_{50} and ED_{95} of Nalbuphine Combined with Ciprofol in Laryngeal Mask Insertion Responses in Day-Patient Hysteroscopic Surgery

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Abstract: Objective: This study aimed to determine the effective dose (ED_{50} and ED_{95}) of ciprofol combined with nalbuphine in inhibiting laryngeal mask insertion responses in day-patients hysteroscopic surgery using a sequential method. Methods: Patients undergoing general anesthesia hysteroscopic in a daytime surgery center were selected. The age of patients ranged from 18 to 60 years, BMI ranged from 18.0 to 28.0 kg/m ^{2}, and ASA classification ranged from gradeIto gradeII. Nalbuphine was administered via slow intravenous injection at an initial dose of 0.16 mg/kg, followed by intravenous administration of 0.4 mg/kg ciprofol. The laryngeal mask was inserted when the patient's eyelash reflex disappeared and the Narcotrend index reached between 50 and 60. A sequential method was employed to establish the nalbuphine dosage: if a positive response occurred during laryngeal mask insertion, the next patient received a dose one gradient higher; conversely, if no response was observed, a lower dose one gradient down was chosen, with adjacent dose differences of 0.01 mg/kg. The ED_{50} and ED_{95} of ciprofol combined with nalbuphine for inhibiting laryngeal mask insertion responses were calculated along with their respective 95% confidence intervals (CIs). Results: The ED_{50} value of nalbuphine for inhibiting laryngeal mask insertion responses was found to be 0.149 mg/kg (95% CI: 0.142–0.155 mg/kg), while the ED_{95} value was determined to be 0.160 mg/kg (95% CI: 0.154–0.191 mg/kg).Conclusion: When combined with ciprofol, the ED_{50} of nalbuphine for inhibiting laryngeal mask insertion responses in patients undergoing outpatient hysteroscopic surgery is established at 0.149 mg/kg (95% CI: 0.142–0.155 mg/kg), and the ED_{95} is set at 0.160 mg/kg (95% CI: 0.154–0.191 mg/kg).

Keywords: Nalbuphine; Ciprofol; ED_{50}; Laryngeal Mask; ED_{95}.

1. Research Background

In recent years, the development of daytime surgery has progressed rapidly, with laryngeal mask anesthesia being widely applied in daytime hysteroscopic procedures. Anesthesiologists are particularly concerned with avoiding intraoperative respiratory depression while ensuring hemodynamic stability and timely postoperative recovery for patients [1]. As a supraglottic airway device, the laryngeal mask airway has the least stimulation for patients, no need for muscle relaxant and simple operation; However, its insertion can still cause some stimulation. Ciprofol is a novel intravenous anesthetic that acts quickly and smoothly, allowing for rapid and complete recovery with minimal impact on respiration. However, the sole use of ciprofol may not effectively suppress the pharyngeal reflex during laryngeal mask insertion, leading to reactions such as coughing, laryngospasm, and body movement. Nalbuphine is a commonly used sedative analgesic in clinical practice. There are studies that have indicated that nalbuphine can significantly reduce cardiovascular stress responses induced by laryngoscopy or tracheal intubation [2]. Nevertheless, there is currently a lack of relevant research regarding the dose-response relationship of nalbuphine when combined with ciprofol in suppressing reactions associated with laryngeal mask insertion. Therefore, this study aims to investigate the ED_{50}/ED_{95} (median effective dose and 95% effective dose) of nalbuphine and its 95% confidence intervals in suppressing laryngeal mask insertion reactions during outpatient hysteroscopic surgery when administered alongside ciprofol, providing a reference for rational drug use in clinical settings.

2. Materials and Methods

2.1. General Information

This study received approval from the Medical Ethics Committee of our hospital (YJ202365), was registered with the Chinese Clinical Trial Center (ChiCTR2400079340), and informed consent was obtained from all participants. Patients undergoing hysteroscopic surgery at our hospital's outpatient surgical center in February 2024 were selected based on the following inclusion criteria: age between 18-60 years; ASA physical status I-II; BMI between 18.0-28.0 kg/m²; Mallampati classification I or II; mouth opening greater than 2.5 cm; no airway abnormalities; no history of long-term use of sedatives or hypnotics; no alcohol dependence history. Exclusion criteria included: Patients whose Narcotrend index did not decrease to 50-60 within five minutes after intravenous administration of all medications; those who required two attempts for successful placement of the laryngeal mask; or those whose insertion time exceeded three minutes.

2.2. Anesthesia Methodology

Patients were routinely instructed to fast for eight hours prior to surgery and refrain from drinking fluids for two hours without preoperative medication. Upon entering the operating room, peripheral venous access was established, and vital signs were monitored using a multi-functional monitor connected to a Narcotrend monitoring device (Narcotrend-

Compact, MT Monitor Technik GmbH & Co.KG) to assess sedation depth. According to trial protocols, nalbuphine (produced by Yichang Renfu Pharmaceutical Co., Ltd., batch number is 31j060812) was administered intravenously over at least ten seconds at predetermined doses followed by an intravenous injection of ciprofol at a dosage of 0.4 mg/kg (produced by Liaoning Haisike Pharmaceutical Co., Ltd., batch number is 20230777). When eyelash reflexes ceased and the Narcotrend index reached between 50-60, an experienced anesthesiologist inserted the laryngeal mask (produced by Guangzhou Weili Medical Device Co., Ltd., batch number is 20231030) using standardized techniques based on patient weight—choosing size three or four—and applying paraffin oil evenly on its posterior side before confirming correct positioning through mechanical ventilation via an anesthesia machine while maintaining anesthesia with sevoflurane at concentrations ranging from 1% to 2%. If SBP<85 mmHg is monitored twice in a row or the decrease is greater than 30% of the basic value, it is defined as hypotension and ephedrine injection 6 ~ 10 mg is given intravenously. If SBP<85 mmHg is monitored twice in a row or the decrease is greater than 30% of the basic value, it is defined as hypotension and ephedrine injection ranging from 6 to 10 mg is given intravenously.

The sequential method was employed to determine the dosage of nalbuphine. Based on preliminary pilot studies and previous literature, an initial dose of 0.16 mg/kg was established for nalbuphine, with a dosage increment of 0.01 mg/kg for adjacent patients. If a positive response occurred during laryngeal mask insertion, the dosage for the subsequent patient would be increased by one gradient; conversely, if no response was observed, the dosage would be decreased by one gradient. The criteria for a positive laryngeal mask insertion response were defined as follows [3]: coughing, laryngospasm, or body movement occurring either immediately upon initial insertion or within one minute thereafter. Jaw relaxation was assessed using the Muzi scoring system: 1 point indicated complete relaxation; 2 points denoted mild relaxation; 3 points signified closure but with the ability to open; and 4 points represented tight closure requiring additional sedative medication. In cases of a positive response, ciprofol at a dose of 0.1 mg/kg would be administered intravenously to deepen anesthesia as a corrective measure, with repetition permitted if necessary. This sequential testing procedure continued until a positive response was recorded in the last patient prior to entering the trial phase or until at least seven turning points had been reached, at which point the trial could be terminated.

2.3. Observational Indicators

Primary observational indicators included systematically recording each patient's corresponding nalbuphine dosage resulting in either positive (+) or negative (-) responses during trials undertaken sequentially whereas secondary indicators encompassed baseline values measured pre-administration (T0), one minute post-administration (T1), one minute following laryngeal mask placement (T2), five minutes post-placement (T3), upon hysteroscope entry into uterine cavity(T4), concluding assessments performed post-procedure completion(T5)—focusing primarily on heart rate(HR), mean arterial pressure(MAP), oxygen saturation(SpO_2) alongside Narcotrend indices recorded across these intervals assessed further against rescue measures enacted concerning intraoperative complications such as hypotension, myoclonus, coughing bradycardia, tachycardia etc.; additionally involving postoperative follow-ups gauging occurrences related towards intraoperative awareness, pain severity rated via VAS scores along incidences pertaining nausea/vomiting episodes observed subsequently afterwards accordingly documented comprehensively throughout analyses pursued henceforth.

2.4. Statistical Analysis

Statistical analyses were conducted using SPSS version 25.0. Continuous data are presented as means ± standard deviations, while intergroup comparisons were performed using t-tests. Categorical data were analyzed with either the chi-square test or Fisher's exact probability method, with a significance level set at $P < 0.05$ indicating statistical relevance. The probit method was employed to calculate the ED_{50} and ED_{95} values of nalbuphine along with their corresponding 95% confidence intervals (CIs). Additionally, sequential plots and dose-response curves for nalbuphine were generated to illustrate the relationship between dosage and response outcomes.

3. Results

A total of 23 patients were included in the study, and the experimental flow is illustrated in Figure 1. The demographic and clinical characteristics of the patients are presented in Table 1. The mean age was 43.65 ± 9.43 years, with a body mass index (BMI) of 22.34 ± 2.34 kg/m². Among the participants, 14 were classified as ASA I and 9 as ASA II; Mallampati classification revealed that 16 patients were categorized as class I and 7 as class II. Positive responses to laryngeal mask insertion were observed in 11 cases, while negative responses occurred in 12 cases. All patients achieved Muzi scores between 1 and 2 upon induction, and successful placement of the laryngeal mask was accomplished when the Narcotrend index ranged from 50 to 60, with no instances requiring tracheal intubation.

According to Dixon's sequential method, a laryngeal mask insertion reaction was noted when the nalbuphine dosage decreased to 0.15 mg/kg; this patient's previous nalbuphine dosage was recorded at 0.16 mg/kg, which served as the first case for analysis. Following an alternating pattern of seven positive and negative responses, the trial was terminated prematurely. The reactions of patients to various dosages of nalbuphine are depicted in Figure 2. When combined with intravenous administration of ciprofol, the ED_{50} for nalbuphine in suppressing laryngeal mask insertion reactions during hysteroscopic procedures was determined to be 0.149 mg/kg (95% CI: 0.142–0.155 mg/kg), while the ED_{95} was found to be 0.160 mg/kg (95% CI: 0.154–0.191 mg/kg). The dose-response curve for nalbuphine is shown in Figure 3.

As shown in Table 2, HR, MAP, and Narcotrend index decreased following the completion of anesthesia induction, subsequently stabilizing at consistent levels. Three patients experienced hypotension, which was corrected with an appropriate dose of ephedrine. There were no significant adverse reactions observed during the procedure. The average awakening time was recorded as 7.8 ± 2.4 minutes. Postoperative follow-up revealed that all visual analog scale (VAS) scores remained below 3, with no instances of intraoperative awareness or episodes of nausea and vomiting reported. The average length of hospital stay was one day, with the average hospitalization cost amounting to 4586 ± 312 yuan.

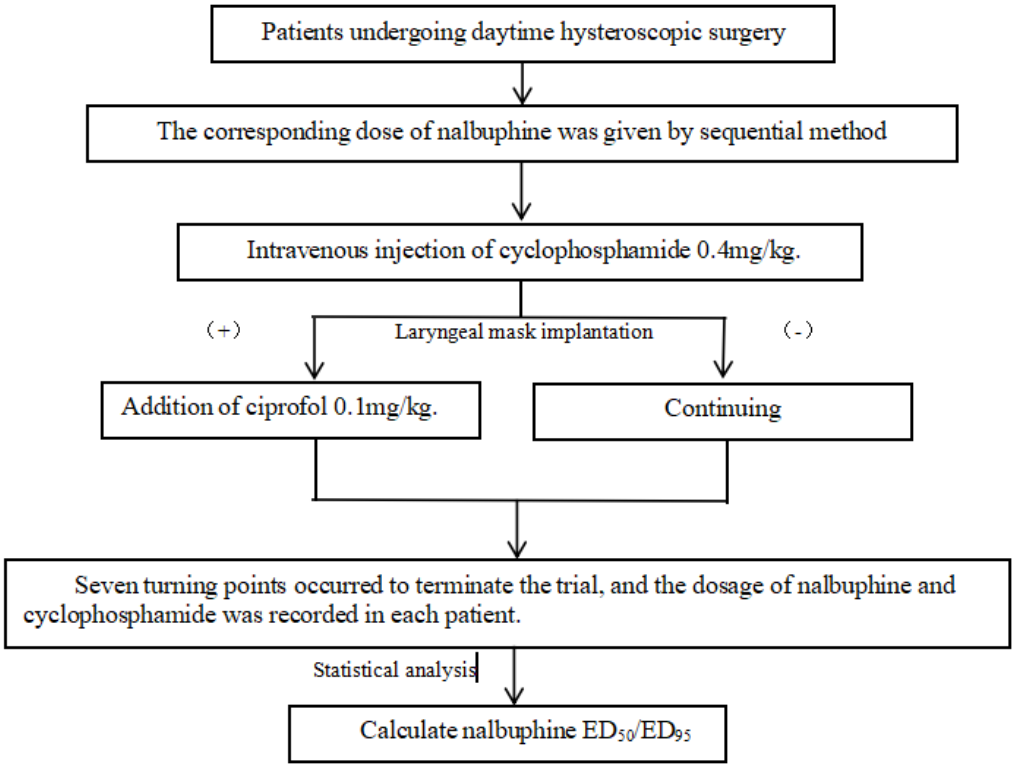

Fig 1. Test Flow Chart

Table 1. General Information of Patients

Project	*n*=23
Age/years	43.65±9.43
BMI (kg/㎡)	23.34±2.33
ASA classification	
I	14(60.87)
II	9(39.13)
Mallampati classification	
I	16(69.56)
II	7(30.44)
Type of surgery	
Excision of endometrial polyp	12 (52.17)
Excision of submucous myoma of uterus	6(26.09)
Diagnostic curettage of endometrium	5(21.74)
Surgery time(min)	38.32±6.76
Intraoperative blood loss(ml)	10.42±4.84
Intraoperative fluid replacement(ml)	584.25±42.19

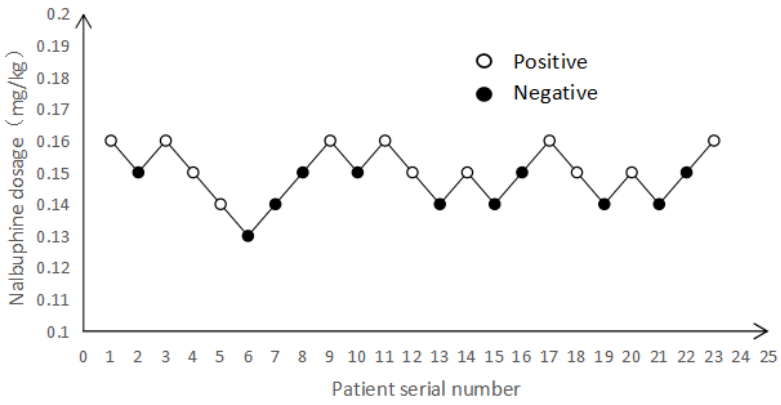

Fig 2. Sequence diagram of ciprofol combined with nalbuphine inhibiting laryngeal mask laryngeal mask insertion responses

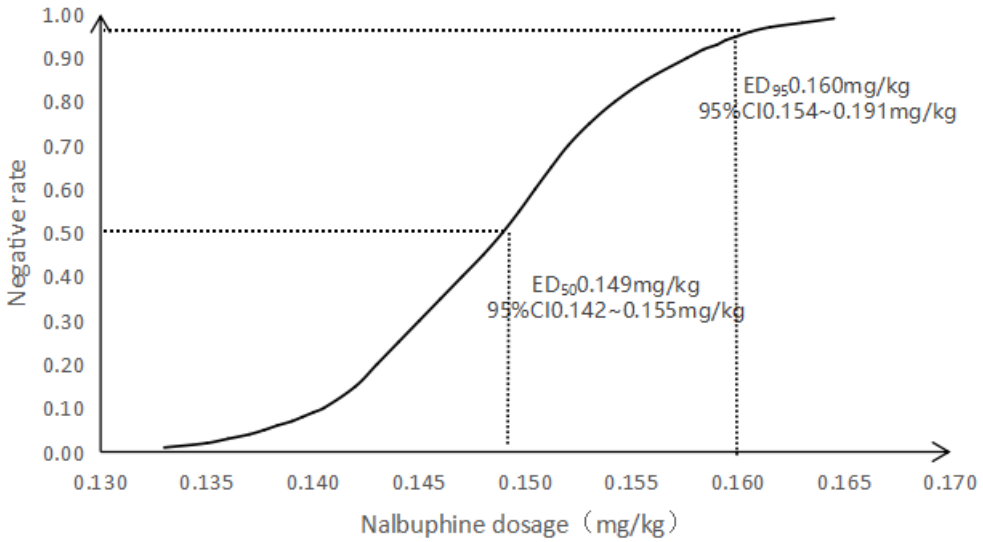

Fig 3. Dose-effect curve of ciprofol combined with nalbuphine inhibiting laryngeal mask laryngeal mask insertion responses

Table 2. Basic vital signs of patients（$\bar{x} \pm s$,n=23)

Index	T_0	T_1	T_2	T_3	T_4	T_5
HR/min	75.91±9.53	64.48±6.29[a]	67.70±10.43[a]	60.43±6.30[a]	60.13±6.13[a]	59.78±6.21[a]
MAP(mmHg)	80.04±12.02	70.17±8.79[a]	70.96±8.96[a]	63.65±7.00[a,b]	65.17±6.20[a]	64.48±5.80[a]
Narcotrend index	99.39±0.58	41.96±6.08a	54.26±10.92[a,b]	49.78±6.51[a,b]	52.96±5.87[a,b]	52.52±8.26[a,b]
SpO_2(%)	99.74±0.69	100.00±0.00	100.00±0.00	100.00±0.00	100.00±0.00	100.00±0.00

Note: Compared with T0, [a]P<0.05; Compared with T_1, [b]P<0.05

4. Discussion

Hysteroscopic surgery is commonly utilized for diagnosing and treating uterine conditions in gynecological patients due to its advantages, including rapid recovery, safety, efficacy, minimal invasiveness, and reduced hospital stay. It has been classified as one of the first procedures suitable for outpatient surgery by national guidelines, providing both cost and time benefits. Although hysteroscopic surgery is generally regarded as a safe and well-tolerated minimally invasive procedure, manipulation of the cervix and fluid distension during the operation can stimulate pelvic nerve endings distributed throughout the uterus, potentially causing severe pain or discomfort in patients [4]. Intraoperative involuntary movements such as hip twisting or leg kicking may adversely affect surgical operations and increase the risk of complications such as bleeding or endometrial injury [5]. Therefore, effective analgesia and sedation are essential during hysteroscopic procedures to ensure patient comfort and satisfaction. According to expert consensus on anesthesia management for accelerated recovery in adult outpatient surgeries [6], general anesthesia can be widely applied in outpatient settings, with recommendations to select agents that have rapid onset, short duration of action, quick elimination times, and minimal impact on liver and kidney function.

Ciprofol is a novel intravenous anesthetic agent belonging to the class of short-acting γ gamma-aminobutyric acid receptor agonists. It offers several advantages including high potency, minimal respiratory and circulatory depression, low incidence of adverse drug reactions, and reduced injection pain compared to traditional agents like propofol. Ciprofol shares a similar chemical structure with propofol but exhibits tighter binding affinity for short-acting γ gamma-aminobutyric acid _A receptors while possessing lower lipophilicity and more favorable spatial volume than propofol [7]. Some studies have reported that ciprofol provides comparable induction effects to propofol during general anesthesia for gynecological outpatient surgeries but demonstrates improved safety profiles with lower incidences of injection pain [8]. However, when used alone, ciprofol may not achieve optimal conditions for laryngeal mask insertion; therefore, it is often combined with other analgesic agents in clinical practice to maintain hemodynamic stability conducive to successful laryngeal mask placement.

Nalbuphine is an opioid analgesic that acts as a κ and μ1 receptor agonist while antagonizing μ2 receptors. It exerts minimal effects on respiratory and cardiovascular systems with fewer side effects at clinically relevant doses [9], offering rapid onset coupled with prolonged action. At equivalent dosages, nalbuphine produces analgesic effects is similar to those of morphine but demonstrates superior efficacy against visceral traction pain and uterine contraction pain associated with hysteroscopic procedures. Furthermore, research indicates that nalbuphine exhibits “gender dimorphism,” suggesting enhanced pharmacological effectiveness in female patients along with lower required dosages [10]. Studies have shown that nalbuphine improves postoperative analgesia by reducing perioperative inflammation and oxidative stress responses [11]; moreover, when compared to sufentanil combined with propofol for hysteroscopic surgeries, nalbuphine was found to provide better anesthetic outcomes alongside fewer adverse reactions such as nausea and vomiting [12, 13].

Postoperative pain along with nausea and vomiting are among the most common anesthetic-related reasons for

delayed discharge following outpatient hysteroscopy [10]. Thus, optimizing drug combinations for anesthesia in hysteroscopic procedures is crucial not only for providing adequate perioperative analgesia but also for minimizing postoperative nausea and vomiting rates—factors that significantly contribute to accelerating patient recovery times and enhancing overall quality of care [14].

Currently, there is limited research investigating the combination of nalbuphine with ciprofol specifically for hysteroscopic surgery. This study explored this drug combination during anesthesia induction using Dixon's sequential method to determine the ED_{50} and ED_{95} values of nalbuphine; this approach is straightforward yet effective while requiring a smaller sample size. Literature reports indicate that under target-controlled infusion of propofol background conditions, the ED_{95} value for nalbuphine inhibiting laryngeal mask insertion response was found to be 0.163 mg/kg; thus, our initial dosage was set at 0.16 mg/kg based on this information [15]. Considering the differing onset times between these two drugs—ciprofol achieving successful induction within 34.8 ± 15.5 seconds [7] while intravenous administration of nalbuphine takes approximately 2–3 minutes before effect onset [16]—nalbuphine was administered slowly prior to ciprofol infusion so that both agents would take effect simultaneously during laryngeal mask insertion attempts. This strategy effectively minimized stress responses: all patients exhibited relaxed mandibles facilitating optimal conditions for laryngeal mask placement without any significant adverse reactions occurring during induction.

While this study presents promising results regarding this drug combination's potential benefits—including stable hemodynamics during anesthesia induction along with short awakening times—it does possess certain limitations. Due to objective constraints preventing multicenter trials from being conducted as well as lacking stratified analyses across different age groups or varying doses of ciprofol employed within our cohort necessitates further exploration in future studies aimed at providing additional evidence supporting rational clinical medication use.

5. Conclusion

In conclusion, the sequential method was employed to determine that the ED_{50} of nalbuphine for inhibiting laryngeal mask insertion in patients undergoing outpatient hysteroscopic surgery in combination with ciprofol was found to be 0.149 mg/kg (95% CI: 0.142–0.155 mg/kg), while the ED_{95} value was determined to be 0.160 mg/kg (95% CI: 0.154–0.191 mg/kg).

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