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Comparison of different dosages of propofol combined with its equivalent alfentanil in outpatient abortion: a prospective, double-blinded, randomized trial

L.-D. JIN[1], L. XING[1], S.-F. LIN[1], X.-Q. JIN[1], Y. WANG[1], Y.-H. SHEN[1], J. XU[1], L.-H. SUN[2]

[1]Department of Anesthesiology, Linping District Women and Children Care Hospital, Hangzhou, China
[2]Department of Anesthesiology, Women's Hospital, Zhejiang University School of Medicine, Zhejiang University, China

L.-D. Jin and L. Xing contributed equally to the work

Abstract. – OBJECTIVE: This study aimed at determining the optimal dose combination of alfentanil and propofol for outpatient abortion anesthesia.

PATIENTS AND METHODS: The study was separated into two parts. In the first part, patients were to determine the median effective dose (ED_{50}) and the 95% effective dose (ED_{95}) of alfentanil in combination with 2.5 mg·kg^{-1} propofol to inhibit body movements during the abortion using the Dixon up-and-down sequential allocation method. In the second part, 170 patients were randomly divided into group C (2.0 mg·kg^{-1} propofol with alfentanil 12.16 μg·kg^{-1}) and group E (2.5 mg·kg^{-1} propofol with its ED_{95}) to compare the anesthetic effect. The primary outcome was the sedation level during general anesthesia. The secondary outcomes were circulation, respiratory complications, and postoperative recovery quality.

RESULTS: The ED_{50} and the ED_{95} values of alfentanil were 3.37 μg·kg^{-1} (95% CI: 2.58-3.97 μg·kg^{-1}) and 4.68 μg·kg^{-1} (95% CI: 4.04-9.32 μg·kg^{-1}). The frequency of deep sedation in group E was significantly higher than in group C (76.5% *vs.* 60%). Patients in group C showed more wakefulness even during the surgery (14.3% *vs.* 4.4%). The results of our exploratory analyses did not reveal differences in respiratory depression, circulatory depression, postoperative side effects, or recovery outcomes.

CONCLUSIONS: The combination of 2.5 mg·kg^{-1} propofol and 4.68 μg·kg^{-1} alfentanil produces a better sedative effect than the combination of 2.0 mg·kg^{-1} propofol and 12.16 μg·kg^{-1} alfentanil without increasing additional risks associated with anesthesia.

Key Words:
Alfentanil, Propofol, Outpatient, Abortion, ED_{95}, Sedative, Anesthesia effect.

Abbreviations

ED_{50}, effective dose in 50% of subjects; ED_{95}, effective dose in 95% of subjects; CI, confidence interval; ASA, American Society Anesthesiologists; MAP, mean arterial pressure; HR, heart rate; BP, blood pressure; SpO_2, oxygen saturation; ECG, electrocardiogram syndrome; VAS, visual analog score; SD, standard deviation; BMI, body mass index.

Introduction

Abortion is a surgical option to prevent congenital malformations, genetic conditions, and unwanted pregnancies[1]. Since abortions are typically rapid, inappropriate drugs for anesthesia might cause side effects such as respiratory depression, hypotension, and delayed awakening[2-4]. Therefore, choosing the appropriately matched medication and dosage is crucial to perform accurate anesthesia.

In past outpatient surgeries, drugs like fentanyl or other analgesics were commonly used as pain management options. However, these drugs often trigger a range of side effects, including respiratory depression, dizziness, and nausea[5,6]. In recent years, there has been considerable attention paid to the use of alfentanil in outpatient surgeries due

Corresponding Authors: L.-D. Jin, MD; e-mail: lidanjin@zju.edu.cn; L.-H. Sun, MD; e-mail: sunlihong@zju.edu.cn

to its distinctive pharmacological properties[7]. Alfentanil, an opioid receptor agonist, produces rapid onset of action, mild respiratory depression, a low incidence of choking, and fewer postoperative side effects[8]. Both propofol and alfentanil are short-acting anesthetics indicated for outpatient surgery[9]. However, research[10] regarding the optimal combined dosage of alfentanil and propofol for outpatient surgeries remains scarce. In our previous study[11], the ED_{95} of alfentanil combined with 2.0 mg·kg^{-1} propofol have been determined (12.16 μg·kg^{-1}). However, prior research still found that some patients had wakefulness events during general surgical anesthesia. Therefore, there is a pressing need for further in-depth research into the appropriate dosage combination of alfentanil and propofol in order to provide more precise reference and guidance for the clinical use of anesthesia in outpatient surgeries, thereby promoting its widespread adoption. This study holds the potential to enhance the quality of anesthesia in outpatient surgeries and improve the overall surgical experience for patients.

The purpose of the present study was to determine the ED_{95} of alfentanil combined with 2.5 mg·kg^{-1} of propofol. We aimed to compare the anesthetic and side effects between 2.0 mg·kg^{-1} propofol and 2.5 mg·kg^{-1} propofol combined with each equivalent ED_{95} of alfentanil. We hypothesized that, when alfentanil and propofol are combined for anesthesia of abortion, higher doses of propofol at 2.5 mg·kg^{-1} and the corresponding effective dose of alfentanil may provide a more satisfactory anesthetic effect for anesthesia of abortion.

Patients and Methods

Design and Study Subjects

The study protocol was approved by the Research Ethics Committee of Women and Children Care Hospital in Linping and was registered in the Chinese Clinical Trials Registry on 4 May 2021 (Registry number: ChiCTR2100046111). The first patient was enrolled on 18 June 2021.

All study subjects provided written, signed, informed consent. Study subjects who met the following inclusion criteria were considered: American Society of Anesthesiologists (ASA) II, aged between 18 and 40 years old, gestational age 60 days, scheduled to have an abortion, and required general anesthesia. Exclusion criteria included: a history of chronic pain or psychiatric condition, hepatitis and renal failure, regular use of sedatives or analgesics, severe anemia, malnutrition, cardiovascular diseases, and history of allergy to alfentanil or propofol.

The study was divided into two parts: first, we used an up-and-down sequential allocation methodology to calculate the ED_{95} of alfentanil in 2.5 mg·kg^{-1} of propofol, and then we compared the anesthesia quality between group C (2.0 mg·kg^{-1} propofol with 12.16 μg·kg^{-1} alfentanil) and group E (2.5 mg·kg^{-1} propofol with its ED_{95}).

Study Protocol-Part I

We performed a prospective, single-blind, up-down sequential allocation study to determine the ED_{95} of alfentanil combined with 2.5 mg·kg^{-1} of propofol during the painless abortion. Based on the results of previous studies and clinical pre-trials[11], we set the dose of alfentanil in gradients (1:1.2 ratio) to 10 levels: 2.5, 3.0, 3.6, 4.3, 5.2, 6.5, 7.5, 9.0, 10.8, and 13.0 (μg·kg^{-1}). Referring to the upper dose of the instructions and considering patient satisfaction during the surgery, the dose of alfentanil for the first patient was set as 13.0 (μg·kg^{-1}). According to the up-down sequential allocation method, for the next patient, the dose of alfentanil was determined by the previous patient's response to the dose of alfentanil. If the previous patient's response was effective, the dose of alfentanil for the next was decreased by 20%. If the previous patient's response was ineffective, the dose of alfentanil for the next was increased by 20%. The effective response was defined as no body movement when the uterine probe entered the uterine cervix. The ineffective response was defined as any body movement response when the uterine probe entered the uterine cervix. The process ended when eight pairs of reversals of sequence were obtained[12,13] (Reversal pair was defined as an effective response followed by an ineffective response).

Patients were routinely fasted from solids for 6 h and liquids for 2 h before surgery, and misoprostol (Misoprostol tablets, 0.2 mg per tablet, Zhejiang Xianju Pharmaceutical Co., Ltd., China) was administered sublingually for 0.5 h before entering the operating room. After admission to the operating room, the patient was inserted with a 20-gauge intravenous indwelling needle (Safety IV Catheter, Penang, Malaysia), and connected with a three-way stopcock; a monitor (Goldway, model UT4000A, American General Universal Co., USA) was connected; an electrocardiogram (ECG), blood pressure (BP), heart rate (HR), and

Table I. The Richmond Agitation-Sedation Scale (RASS).

Sedation lever	Target RASS	RASS Description
Poor sedation	+4	Combative, violent, danger to staff
	+3	Pulls or removes tube (s) or catheters; aggressive
	+2	Frequent nonpurposeful movement, fight ventilator
	+1	Anxious, apprehensive, but not aggressive
Moderate sedation	0	Alert and calm
	-1	Awakens to voice (eye-opening/contact) >10 sec
	-2	Light sedation, movement or eye opening. No eye contact
	-3	Moderate sedation, movement or eye opening. No eye contact
Deep sedation	-4	Deep sedation, no response to voice, but movement or eye opening to physical stimulation
	-5	Unarousable, no response to voice or physical stimulation

Sedation level classification in terms of the Richmond Agitation-Sedation Scale (RASS).

pulse oxygen (SpO_2) were monitored, and basal values were recorded. Then, the patients were set in the lithotomy position, with skin preparation and draping. All the patients were supported with oxygen by nasal cannula (Disposable nasal oxygen tube, Hangzhou, China) (3 ml·min^{-1}). For anesthesia, 2.5 mg·kg^{-1} of propofol (Propofol Injectable Emulsion, 20 ml:200 mg, Xi'an Lipan Pharmaceutical Co., Ltd., China) and alfentanil (Alfentanil Hydrochloride Injection, 2 ml:1 mg, Hubei Yichang Renfu Pharmaceutical Co., Ltd., China) was administered intravenously. The procedure was started when the patient's eyelash reflex and consciousness were lost. 4 mg of Ondansetron (Ondansetron Hydrochloride Injection, 2 ml:4 mg, Qilu Pharmaceutical, Co., Ltd., China) were applied intravenously to prevent nausea after surgery. The patient's body movement response was observed during the surgery. An investigator not involved in subsequent anesthetic management or collection prepared the study solutions. Additional bolus propofol 0.5 mg·kg^{-1} was applied if the patient's body moved during the operation. Any episode of hypotension, defined as BP<90 mmHg or mean arterial pressure (MAP) <60 mmHg, was treated with a bolus of 6 mg of intravenous ephedrine, repeatedly if needed. Bradycardia, defined as a heart rate of less than 50 beats per minute, was treated with 0.5 mg of atropine intravenously. Respiratory depression was defined as SpO_2<90% and was treated with a face mask, oxygen inhalation, and respiratory support, if required.

Study Protocol-Part II

The preoperative preparation and anesthesia methods were the same as in the first part. Pregnant women were randomly assigned to Group C (general anesthesia with 2.0 mg·kg^{-1} propofol + 12.16 μg·kg^{-1} alfentanil) or Group E (general anesthesia with 2.5 mg·kg^{-1} propofol + 4.68 μg·kg^{-1} alfentanil), based on prior research and the findings of the first part[11]. A randomization scheme was generated using Microsoft Excel 2017 (Redmond, WA, UAS). The randomization sequence was generated before the enrollment of the first participant. The group allocation codes were placed in sealed envelopes, which were opened at the time of randomization. An investigator who was not involved in subsequent anesthetic management or data collection prepared the study solutions according to the group allocation code number.

The demographic and medical data, including the subject's age, Body mass index (BMI), days of menopause (gestational age), and pain of propofol injection (during propofol injection, patients with an infusion-side arm pain score of more than 3 scores were recorded as having intravenous pain) were recorded[14]. The score of sedation [using Richmond Agitation-Sedation Scale (RASS) (as shown in Table I)[15], the score was divided into three levels: deep sedation = (-5 to -4 score), moderate sedation = (-3 to 0 score), poor sedation (+1 to +4 score)][16], frequency of body movement, wakefulness events, respiratory depression, circulatory depression (hypotension, bradycardia), duration of surgery and awakening time (with MOAA/S the time it takes for a patient to reach a wakefulness score of 4 or more at the end of the surgery, using the MOAA/S score standard as the wakefulness index[17]) were recorded. The criteria for discharge were performed according to the PADSS (Post Anaesthetic Discharge Scoring System)[18], with a total score no lower than 9 at the time of discharge.

In addition, the scores of visual analog score (VAS: the VAS consisted of a 100-mm horizontal line anchored at one end with the words "no pain" (defined as 0 points) and at the other end with the words "worst pain imaginable" (defined as 10 points). The VAS score marked by the patient) was assessed and recorded at 30 min, 90 min, and discharge after surgery. The number of patients who experienced dizziness, nausea, vomiting, and other adverse effects after awakening was also recorded. We also documented the first time out of bed, the time of discharge, and patient satisfaction with the anesthesia, as well as unscheduled health services within 30 days of discharge and the days of taking leave following surgery.

Statistical Analysis

Published research[19,20] suggests that 20-40 study subjects are required to estimate the ED_{50} using the up-down allocation method and that the sample size is sufficient when six pairs of reversals of sequence are obtained[19,20]. Therefore, for part I, we estimated that about 30 study subjects would be needed to observe more than six pairs of reversal of sequence at least. This process was repeated until eight pairs of reversal were in the first part of the study. The values of the median effective dose (ED_{50}), the values of ED_{95}, and the 95% CI of alfentanil were determined by Probit regression analysis[21].

The sample size of part II was evaluated by the formula method.

$$(n = \frac{2\bar{p}\bar{q}(z_\alpha + z_\beta)^2}{(p_1 - p_2)^2})$$

The primary indicator of sample size was the rate of deep sedation during the surgery. The preliminary experiment had 30 cases in each group; the rate of deep sedation in Group E and Group C was 67% and 40%, respectively. Therefore, a sample size of 72 in each group was determined to be required for value of 0.10 and value of 0.05. Assuming a 10% dropout rate and considering the possibility of data loss, a sample size of at least 80 was needed in each group.

Normally distributed statistics data were analyzed using Student's *t*-test, nominal data were analyzed using the Chi-square test, nonparametric data were further analyzed using the median (Q1, Q3) or ratio, and the nonparametric Mann-Whitney U test were used to evaluate the differences between the two groups in this condition. GraphPad Prism version 9.0 (GraphPad Software Inc., San Diego, CA, USA) and IBM SPSS Statistics for Windows version 26.0 (IBM Corp., Armonk, NY, USA) were used for data analysis. p-value<0.05 was considered statistically significant.

Results

Sequential Results and ED_{95} for Part I

In the first part, a total of 32 early-pregnancy women accomplished the trial, and the up-down sequential allocation results are shown in Figure 1. The ED_{50} and the ED_{95} values of alfentanil were 3.37 μg·kg^{-1} (95% CI: 2.58-3.97) and 4.68 μg·kg^{-1} (95% CI: 4.04-9.32). Probit regression was Probit (p) = - 4.23 + 1.26 (alfentanil dose), and the Pearson model goodness-of-fit test ^{2} = 1.001 (p=0.999). Dose-response curves, estimating the ED_{50} and ED_{95} values for alfentanil, as calculated by Probit analysis, are shown in Figure 2.

Participants and Clinical Characteristics for Part II

Out of 170 patients who were involved and assessed for suitability for this clinical trial, 160 patients were randomly assigned to the two groups, and finally, 138 subjects were analyzed. (Figure 3). There were no significant differences between the two groups in demographic data, including age, height, weight, BMI, gestation period, and duration of surgery (p>0.05) (Table II).

Sedative Effect

Concerning sedation effects, most patients were at moderate or deep sedation levels, and there was no statistically significant difference in the incidence of poorly sedated patients in both groups (p>0.05). However, the occurrence of deep sedation in group E was significantly higher than in group C (76.5% *vs.* 60%, p=0.038), and the frequency of moderate sedation was lower in group E than in group C (16.2% *vs.* 31.4%, p=0.036), as shown in Figure 4.

Side Effects During the Surgery

Results of secondary outcomes are presented in Table III. Notably, group C showed more cases of wakefulness events during the surgery than group E (4.4% *vs.* 14.3%, p=0.047). There was no statistical significance in terms of adverse effects such as respiratory depression, circulatory depression, pain from propofol injection, and body movement between the two groups (p>0.05).

Table II. Demographic data.

	Group E (n = 68)	Group C (n = 70)	*p*-value
Age (years)	30.2 ± 5.6	28.9 ± 4.9	0.146
Height (cm)	160.7 ± 4.7	160.1 ± 4.7	0.425
Weight (kg)	54.5 ± 6.2	53.1 ± 6.7	0.185
Body mass index	21.1 ± 2.3	20.7 ± 2.2	0.256
Gestation (days)	47.7 ± 6.9	47.9 ± 6.5	0.895
Operation time (min)	4.1 ± 1.5	4.4 ± 1.0	0.198

Data are mean ± standard deviation (SD). The *t*-test was used for counting data. Statistical significance was defined as $p < 0.05$.

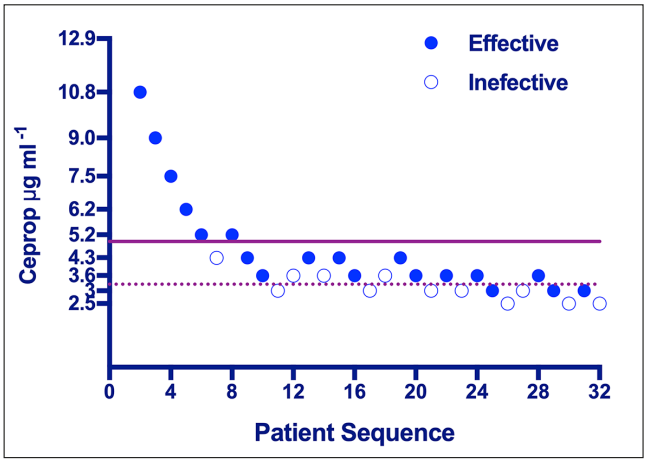

Figure 1. Responses (inhibiting body movement) of 32 consecutive patients who received alfentanil and 2.5 mg·kg-1 propofol anesthetic during the outpatient abortion.

Postoperative and Recovery

The incidence of side effects and recovery after surgery are shown in Table IV. VAS scores at 30 minutes, 90 minutes, and discharge revealed no significant difference between the two groups ($p>0.05$). There were no statistically significant differences in nausea and vomiting, dizziness, the first time out of bed, the time of discharge, and patient satisfaction ($p>0.05$). Of the 138 patients, 3 received unscheduled health services within 30 days following the procedure, including 1 patient in group E (post-abortion bleeding) and 2 patients in group C (post-abortion bleeding and sleeplessness, respectively). After distant follow-up, the three patients were cured, and no major complications associated with surgery were noted in the remaining patients ($p>0.05$). The days of taking leave following surgery showed no difference between the two groups ($p>0.05$).

Table III. Adverse events of anesthesia during the surgery.

	Group E (n = 68)	Group C (n = 70)	*p*-value
Respiratory depression (n)	14 (20.1%)	17 (24.3%)	0.603
Low blood pressure (n)	8 (11.8%)	9 (12.9%)	0.845
Bradycardia (n)	0 (0.0%)	2 (2.9%)	0.160
Pain of propofol injection (n)	28 (41.2%)	26 (37.2%)	0.627
Wakefulness (n)	3 (4.4%)	10 (14.3%)	0.047*
Body movement (n)	5(7.4%)	5(7.1%)	0.962
Wake-up time (min)	1.6 ± 0.9	1.5 ± 0.7	0.242

Data are presented as a number (rate) or mean ± standard deviation (SD). The Chi-square test and *t*-test were used for counting data, $^{*}p < 0.05$ between groups.

Table IV. Postoperative and recovery.

	Group E (n = 68)	Group C (n = 70)	*p*-value
VAS score			
30 min after surgery	1 (1, 2)	2 (1, 2)	0.418
90 min after surgery	1 (1, 2)	1 (1, 1)	0.217
At discharge	0 (0, 1)	0 (0, 1)	0.154
Nausea and vomiting (n)	1(1.5%)	0 (0%)	0.309
Dizziness (n)	3 (4.4%)	4 (5.7%)	0.727
First time out of bed (min)	56.6 ± 10.2	54.9 ± 10.9	0.361
Time of discharge (min)	71.8 ± 9.3	70.0 ± 10.4	0.300
Patient satisfaction (%)	94.8 ± 4.0	93.7 ± 4.6	0.133
Unscheduled health services (n)	1 (1.5%)	2 (2.9%)	0.577
Days of taking leave following surgery (n)			
≤ 7	50 (73.5%)	49 (70.0%)	0.645
7 < ~ ≤ 14	13 (19.1%)	15 (21.4%)	0.736
> 14 days	5 (7.4%)	6 (8.6%)	0.792

Data are presented as a number (rate), mean ± SD, or median (Q1, Q3). The Mann-Whitney U-test was used to evaluate the differences.

Discussion

In this prospective, randomly assigned study, the ED_{50} of alfentanil to inhibit the body movement response combined with 2.5 mg·kg^{-1} propofol anesthesia was 3.37 μg·kg^{-1} (95% CI: 2.58-3.97 μg·kg^{-1}) and the ED_{95} was 4.68 μg·kg^{-1} (95% CI: 4.04-9.32 μg·kg^{-1}). Under the anesthetic regimen of two different doses of propofol combined with equivalent alfentanil, the "2.5 mg·kg^{-1} propofol" group had a higher quality of sedative effect than the "2.0 mg·kg^{-1} propofol" group.

In the anesthetic protocol and management of outpatient surgery, we expected drugs to be productive and safe. We compared the anesthetic and side effects between 2.0 mg·kg^{-1} propofol and 2.5 mg·kg^{-1} propofol combined with each equivalent ED_{95} of alfentanil and found no significant difference in effectiveness, safety, and advantages. In the second part of the study, we found no significant difference in the body movement response between the two groups. However, a higher incidence of intra-operative wakefulness events in the 2.0 mg·kg^{-1} propofol group was observed. In contrast, the 2.5 mg·kg^{-1} propofol group had a higher quality depth of sedation. Those pieces of evidence point to similar analgesic efficacy in both groups, but the 2.5 mg·kg^{-1} propofol group

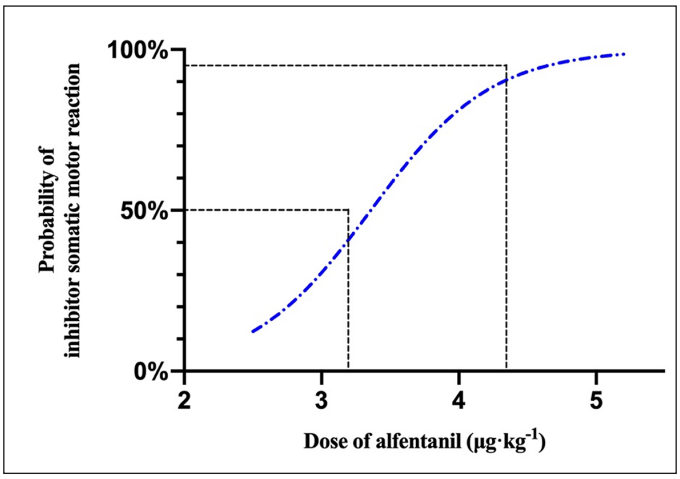

Figure 2. The dose-response curve of alfentanil for inhibiting body movement during outpatient abortion. The ED50 and ED95 values were 3.37 μg·kg-1 (95% CI: 2.58-3.97 μg·kg-1) and 4.68 μg·kg-1 (95%: CI: 4.04-9.32 μg·kg-1) of alfentanil for inhibiting body movement during the outpatient abortion.

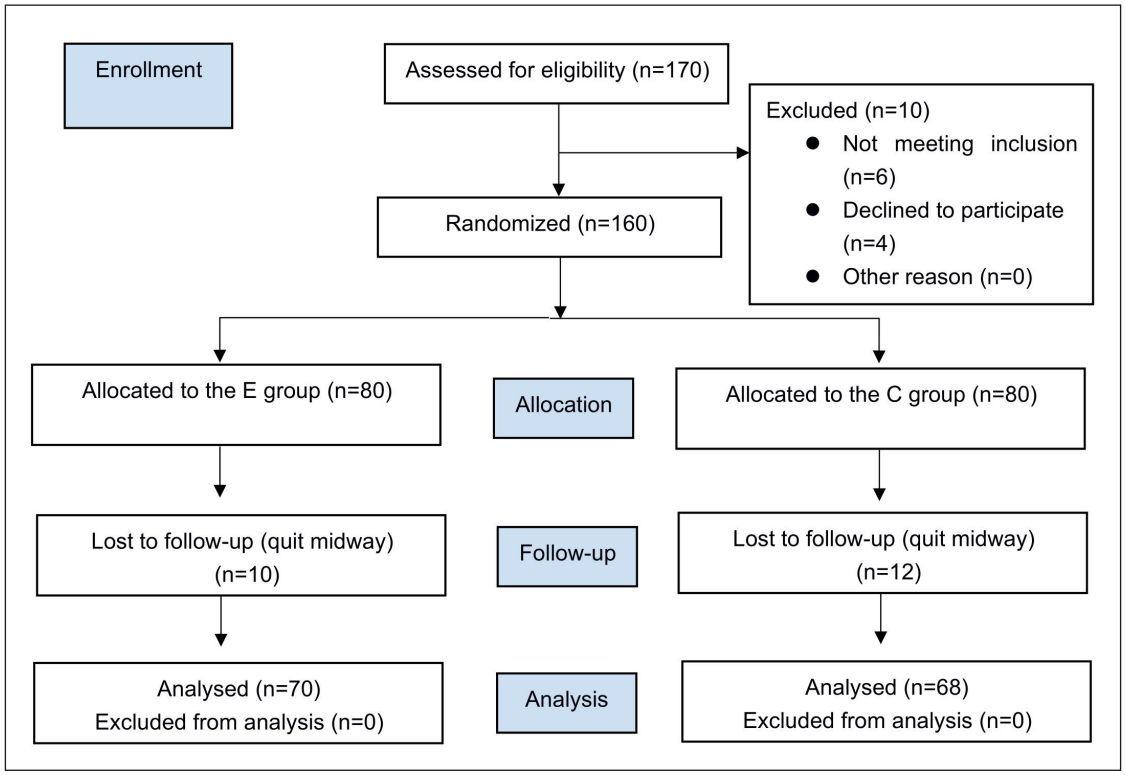

Figure 3. Flow diagram of study.

produced a better sedation effect than the low-dose propofol group. Although in the 2.0 mg·kg-1 propofol group we used a sufficient dose of alfentanil to ensure analgesia, the sedation effect was mediocre. Conversely, in the 2.5 mg·kg^{-1} propofol group, even though the dose of alfentanil used was small, it still provided adequate analgesia and satisfactory depth of sedation.

Propofol, 2,6-diisopropyl phenol, includes fast onset and rapid elimination, short duration of action, and rapid recovery from anesthesia, all of which make propofol an ideal sedative agent[22]. Apart from this, propofol had a somewhat analgesic effect, as confirmed by the significant difference in ED_{50} in the first part of this study compared to previous studies[11] (12.16 μg·kg^{-1}). This result was similarly evidenced in other experiments[23]. The mechanism of propofol analgesia may be due to its action on gamma-aminobutyric acid (GABA), the type A receptor, and suppression of the N-methyl-D-aspartate (NMDA) receptor subunit[24-26]. As with propofol, alfentanil is especially useful for outpatient surgery anesthesia because of its potent analgesia, rapid onset of action, and rapid metabolism. According to previous research, alfentanil showed negligible impact on mid-latency auditory evoked potentials and bispectral index (BIS)[27-29]. As there is a parallel between the perception of auditory stimuli and consciousness, it can be related to a higher incidence of intraoperative awareness when opioids are the primary anesthetic[30,31]. In addition, opioids had no dose-dependent effects on mid-latency auditory evoked potentials[32]. Studies[33,34] have shown that the optimal induction dose of propofol for improving the most excellent anesthesia effect without significant side effects in general anesthesia, when coupled with alfentanil, is 2.5 mg·kg^{-1}, similar to the findings of the current investigation.

Despite the dosage variations between the two groups, it is heartening to observe that the 2.5 mg·kg^{-1} propofol group was not associated with an increased risk of respiratory-related problems (respiratory depression) or hemodynamic instability (hypotension and bradycardia). It neither prolongs postoperative awakening time nor increases postoperative pain levels, and there is no statistically significant difference between the two groups in terms of digestive problems (nausea and vomiting) and intravenous injection pain. Moreover, a higher dose of propofol was not associated with more severe injection pain when it came to intra-

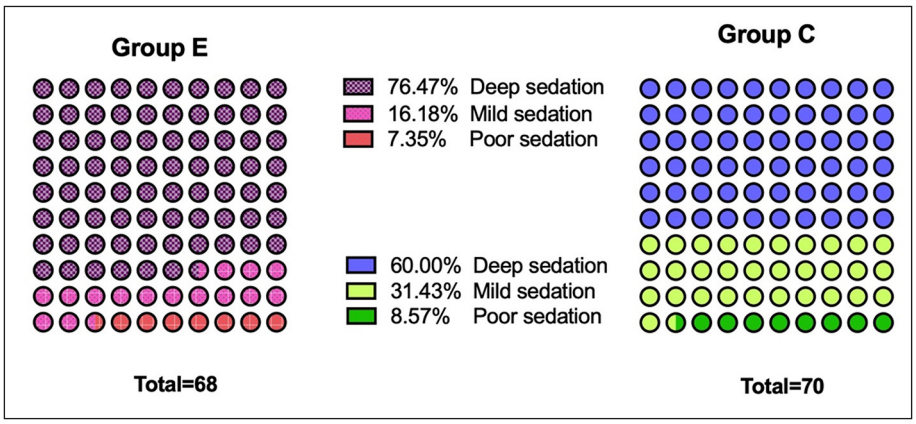

Figure 4. Percentage depth of sedation.

venous injection pain. This is consistent with the findings of Picard and Tramèr[35], who concluded that propofol injection pain was not directly related to the injection rate or intravenous needle size. Therefore, under the circumstance of the current study, taking into account the sedation effect and the complications (no difference in cardiopulmonary-related side effects), the "2.5 mg·kg^{-1} propofol and 4.68 μg·kg^{-1} alfentanil" group provides better sedation than the "2.0 mg·kg^{-1} propofol and 12.16 μg·kg^{-1} alfentanil" group.

Limitations

To the best of our knowledge, this study is the first paper to compare the depth of sedation effect during outpatient abortion under different equivalent anesthesia doses. However, it has several limitations. First, we did not utilize a more objective BIS as an evaluation indicator, which could not provide an accurate evaluation indicator of sedation level. Research[36-38] has demonstrated that the BIS value correlates strongly with the RASS score under sedation, which is routinely used to evaluate the depth of sedation in outpatients. Moreover, the intraoperative wakefulness events supported that utilizing a RASS scorer to assess the depth of sedation did not have an impact on the results. Second, because the subjects are outpatients, we could not track the recovery quality of patients during the first 48 hours after surgery, which would have allowed for a more visual examination of the influence of these two anesthetic regimens on postoperative quality of life. Thus, we investigated unscheduled health services after surgery and the duration of leave following discharge to provide a comprehensive perspective of the treatment effects as completely as possible.

Conclusions

The ED_{50} and ED_{95} values for alfentanil to inhibition of the body movement response were 3.37 μg·kg^{-1} (95% CI: 2.58-3.97 μg·kg^{-1}) and 4.68 μg·kg^{-1} (95% CI: 4.04-9.32 μg·kg^{-1}) under the induction of 2.5 mg·kg^{-1} propofol. For anesthesia in outpatient abortion, the combination of 2.5 mg·kg^{-1} propofol and 4.68 μg·kg^{-1} alfentanil produces a better sedative effect than the combination of 2.0 mg·kg^{-1} propofol and 12.16 μg·kg^{-1} alfentanil, without increasing additional risks associated with anesthesia.

Conflict of Interest

The authors declare that they have no conflict of interests.

Authors' Contributions

Conceptualization: L.-D Jin, L.-H Sun; Methodology: L.-D Jin, L.-H Sun; Software: Y.-H Shen; Validation: S.-F Lin, Y. Wang, X.-Q Jin; Formal analysis: L.-D Jin, L. Xing; Investigation: J. Xu, L. Xing, Y.-H Shen, S.-F Lin; Data curation: L.-H Sun, L. Xing; Writing—original draft preparation: L.-D Jin; Writing—review and editing: L.-H Sun; Visualization: J. Xu; Supervision: L.-H Sun. All authors have read and agreed to the published version of the manuscript.

Ethics Approval

The study was conducted in accordance with the ethical standards of the institution and national research committees and approved by the Ethical Committee of Linping District

Women and Children Care Hospital (No. LLSC-KYKT-2021-0003-A; April 2021).

Informed Consent
Informed consent was obtained from all the subjects involved in the study.

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None.

Data Availability Statement
The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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ORCID ID
L.-D. Jin: 0000-0001-6583-2746
L. Xing: 0009-0003-6400-7367
S.-F. Lin: 0009-0005-6998-4778
X.-Q. Jin: 0009-0002-9647-2856
Y. Wang: 0009-0007-0534-7395
Y.-H. Shen: 0009-0006-1824-0995
J. Xu: 0009-0001-6246-9774
L.-H. Sun: 0009-0008-5382-2792

References

1) Fiala C, Agostini A, Bombas T, Lertxundi R, Lubusky M, Parachini M, Gemzell-Danielsson, K. Abortion: Legislation and statistics in Europe. Eur J Contracept Reprod Health Care 2022; 27: 345-352.
2) Jiang J, Jiao Y, Gao P, Yin W, Zhou W, Zhang Y, Liu Y, Wen D, Wang Y, Zhou L, Yu T, Yu W. Propofol differentially induces unconsciousness and respiratory depression through distinct interactions between GABAA receptor and GABAergic neuron in corresponding nuclei. Acta Biochim Biophys Sin (Shanghai) 2021; 53: 1076-1087.
3) Wang LL, Guan ZY, Wang CM, Zhang YW, Zhang J, Zhao P. A comparative study on the efficacy and safety of propofol combined with different doses of alfentanil in gastroscopy: a randomized controlled trial. J Anesth 2023; 37: 201-209.
4) Chen B, Pang QY, An R, Liu HL. A systematic review of risk factors for postinduction hypotension in surgical patients undergoing general anesthesia. Eur Rev Med Pharmacol Sci 2021; 25: 7044-7050.
5) Furdui A, Da SSC, Montandon G. Fentanyl-Induced Respiratory Depression and Locomotor Hyperactivity Are Mediated by μ-Opioid Receptors Expressed in Somatostatin-Negative Neurons. eNeuro 2023; 10: 0035-0023.
6) Chen H, Ding X, Xiang G, Xu L, Liu Q, Fu Q, Li P. Analysis of the efficacy of subclinical doses of esketamine in combination with propofol in non-intubated general anesthesia procedures - a systematic review and meta-analysis. BMC Anesthesiol 2023; 23: 245.
7) Dong SA, Guo Y, Liu SS, Wu LL, Wu LN, Song K, Wang JH, Chen HR, Li WZ, Li HX, Zhang L, Yu JB. A randomized, controlled clinical trial comparing remimazolam to propofol when combined with alfentanil for sedation during ERCP procedures. J Clin Anesth 2023; 86: 111077.
8) Zhang L, Yu L, Xu L, Wang JF, Li JY, Chen ZJ. Effectiveness of remimazolam besylate combined with alfentanil for fiberoptic bronchoscopy with preserved spontaneous breathing: a prospective, randomized, controlled clinical trial. Eur Rev Med Pharmacol Sci 2023; 27: 6071-6080.
9) Practice Guidelines for Moderate Procedural Sedation and Analgesia 2018: A Report by the American Society of Anesthesiologists Task Force on Moderate Procedural Sedation and Analgesia, the American Association of Oral and Maxillofacial Surgeons, American College of Radiology, American Dental Association, American Society of Dentist Anesthesiologists, and Society of Interventional Radiology. Anesthesiology 2018; 128: 437-479.
10) De IF, Mannaioni G, Serra S, Finco G, Sartori S, Gandolfo E, Sansone P, Marinangeli F. Equianalgesia, opioid switch and opioid association in different clinical settings: a narrative review. Eur Rev Med Pharmacol Sci 2022; 26: 2000-2017.
11) Jin LD, Lin SF, Xing L, Shen YH, Lang HJ, Xie JR. Effect of Intravenous Lidocaine on the Half Effective Dose of Alfentanil in Propofol Anesthesia to Suppress the Somatic Motor Response of Patients Undergoing Artificial Abortion Surgery. Chin J Mod Appl Pharm 2022; 39: 1744-1749.
12) Liu L, Drzymalski D, Xu W, Zhang W, Wang L, Xiao F. Dose dependent reduction in median effective concentration (EC50) of ropivacaine with adjuvant dexmedetomidine in labor epidural analgesia: An up-down sequential allocation study. J Clin Anesth 2021; 68: 110115.
13) Song Y, Zou XJ. Remimazolam dosing for intraoperative sedation in elderly patients undergoing hip replacement with combined spinal-epidural anesthesia. Eur Rev Med Pharmacol Sci 2023; 27: 7485-7491.
14) Xing J, Liang L, Zhou S, Luo C, Cai J, Hei Z. Intravenous Lidocaine Alleviates the Pain of Propofol

Injection by Local Anesthetic and Central Analgesic Effects. Pain Med 2018; 19: 598-607.

15) Rasheed AM, Amirah MF, Abdallah M, Parameaswari JP, Issa M, Alharthy A. Ramsay Sedation Scale and Richmond Agitation Sedation Scale: A Cross-sectional Study. Dimens Crit Care Nurs 2019; 38: 90-95.

16) Karamchandani K, Rewari V, Trikha A, Batra RK. Bispectral index correlates well with Richmond agitation sedation scale in mechanically ventilated critically ill patients. J Anesth 2010; 24: 394-398.

17) Kim KM, Seo KH, Lee JM, Park EY, Park J. Target-controlled infusion of dexmedetomidine effect-site concentration for sedation in patients undergoing spinal anaesthesia. J Clin Pharm Ther 2020; 45: 347-353.

18) Phillips NM, Street M, Kent B, Haesler E, Cadeddu M. Post-anaesthetic discharge scoring criteria: key findings from a systematic review. Int J Evid Based Healthc 2013; 11: 275-284.

19) Tang Y, Yang M, Fu F, Huang X, Feng Y, Chen X. Comparison of the ED50 of intrathecal hyperbaric ropivacaine co-administered with or without intrathecal dexmedetomidine for cesarean section: A prospective, double-blinded, randomized dose-response trial using up-down sequential allocation method. J Clin Anesth 2020; 62: 109725.

20) Kang S, Chae YJ, Bae SY, Song JY, Joe HB. Remifentanil requirement for acceptable intubation conditions with two different doses of ketamine without a neuromuscular blocking agent in pediatric patients. Eur Rev Med Pharmacol Sci 2022; 26: 1632-1639.

21) Ni JX, Feng JL, Yao SJ, Ni LF, Song SB, Song CZ, Qian XW, Mei Z, Yu J. Determination of the Dose-Response Relationship of Epidural Dexmedetomidine Combined with Ropivacaine for Labor Analgesia. Drug Des Devel Ther 2022; 16: 609-618.

22) Trapani G, Altomare C, Liso G, Sanna E, Biggio G. Propofol in anesthesia. Mechanism of action, structure-activity relationships, and drug delivery. Curr Med Chem 2000; 7: 249-271.

23) Wong SSC, Chan WS, Irwin MG, Cheung CW. Total Intravenous Anesthesia (TIVA) With Propofol for Acute Postoperative Pain: A Scoping Review of Randomized Controlled Trials. Asian J Anesthesiol 2020; 58: 79-93.

24) Fassoulaki A. Is propofol an analgesic? Eur J Anaesthesiol 2011; 28: 481-482.

25) Krasowski MD, Jenkins A, Flood P, Kung AY, Hopfinger AJ, Harrison NL. General anesthetic potencies of a series of propofol analogs correlate with potency for potentiation of gamma-aminobutyric acid (GABA) current at the GABA(A) receptor but not with lipid solubility. J Pharmacol Exp Ther 2001; 297: 338-351.

26) Kingston S, Mao L, Yang L, Arora A, Fibuch EE, Wang JQ. Propofol inhibits phosphorylation of N-methyl-D-aspartate receptor NR1 subunits in neurons. Anesthesiology 2006; 104: 763-769.

27) Iselin-Chaves IA, El MHE, Gan TJ, Ginsberg B, Glass PS. Changes in the auditory evoked potentials and the bispectral index following propofol or propofol and alfentanil. Anesthesiology 2000; 92: 1300-1310.

28) Iselin-Chaves IA, Flaishon R, Sebel PS, Howell S, Gan TJ, Sigl J, Ginsberg B, Glass PS. The effect of the interaction of propofol and alfentanil on recall, loss of consciousness, and the Bispectral Index. Anesth Analg 1998; 87: 949-955.

29) Jung D, Yang S, Lee MS, Lee Y. Remifentanil Alleviates Propofol-Induced Burst Suppression without Affecting Bispectral Index in Female Patients: A Randomized Controlled Trial. J Clin Med 2019; 8: 1186.

30) Brown EN, Lydic R, Schiff ND. General anesthesia, sleep, and coma. N Engl J Med 2010; 363: 2638-2650.

31) Hilgenberg JC. Intraoperative awareness during high-dose fentanyl--oxygen anesthesia. Anesthesiology 1981; 54: 341-343.

32) Schwender D, Rimkus T, Haessler R, Klasing S, Pöppel E, Peter K. Effects of increasing doses of alfentanil, fentanyl and morphine on mid-latency auditory evoked potentials. Br J Anaesth 1993; 71: 622-628.

33) Yu AL, Critchley LA, Lee A, Gin T. Alfentanil dosage when inserting the classic laryngeal mask airway. Anesthesiology 2006; 105: 684-688.

34) Bartolek D, Lajtman Z, Zdravcević-Sakić K, Jakobović J, Bartolek F, Cavrić G. The optimal pediatric induction dose of propofol in combination with reduced-dose rocuronium and alfentanil for day-case tonsillectomy in children. Int J Pediatr Otorhinolaryngol 2007; 71: 1873-1881.

35) Picard P, Tramèr MR. Prevention of pain on injection with propofol: a quantitative systematic review. Anesth Analg 2000; 90: 963-969.

36) Yaman F, Ozcan N, Ozcan A, Kaymak C, Basar H. Assesment of correlation between bispectral index and four common sedation scales used in mechanically ventilated patients in ICU. Eur Rev Med Pharmacol Sci 2012; 16: 660-666.

37) Bal BS, Crowell MD, Kohli DR, Menendez J, Rashti F, Kumar AS, Olden KW. What factors are associated with the difficult-to-sedate endoscopy patient? Dig Dis Sci 2012; 57: 2527-2534.

38) Grimaldi M, Quadrini F, Caporusso N, Troisi F, Vitulano N, Delmonte V, Di Monaco A. Deep sedation protocol during atrial fibrillation ablation using a novel variable-loop biphasic pulsed field ablation catheter. Europace 2023; 25: euad222.