doi.org/10.36721/PJPS.2026.39.12.344.1

Intravenous lidocaine reduces the propofol EC50 for loss of consciousness and intraoperative anesthetic consumption in gynecological laparoscopy: A randomized controlled trial

Lin Jin[1#], Panpan Pan[2#], Jialin Wang[1], Xiaoping Chen[1], Min Chen[3], Shaobing Dai[1], Lihong Sun[1] and Peng Ying[4]*

[1]Department of Anesthesiology, Women's Hospital, School of Medicine, Zhejiang University, Hangzhou, Zhejiang Province, China
[2]Department of Operating Room, Branch, Women's Hospital, School of Medicine, Zhejiang University, Linhai, Zhejiang Province, China
[3]Department of Anesthesiology, Women and Children's Hospital, Lishui, Zhejiang Province, China
[4]Department of Anesthesiology, Hangzhou Red Cross Hospital, Hangzhou, Zhejiang Province, China

Abstract: **Background**: Intravenous lidocaine reduces propofol requirements and procedure-related adverse events. **Objectives**: The study aimed to test whether intravenous lidocaine would reduce the effect-site concentration of propofol required to achieve loss of consciousness–and decrease propofol consumption during total intravenous anesthesia in gynecological laparoscopy. **Methods**: This was a prospective, randomized, double-blind, placebo-controlled trial. Sixty patients were randomly allocated to receive either intravenous lidocaine (1.5 $mg \cdot kg^{-1}$ bolus) followed by continuous infusion or an equal volume of saline. Propofol was administered via target-controlled infusion starting at an effect-site concentration of 3.5 μg/mL. The concentration was then adjusted in steps of 0.5 μg/mLaccording to Dixon's up-and-down sequential method: decreased if loss of consciousness was achieved, or increased if not. Loss of consciousness was defined as loss of response to verbal commands. The median effective concentration (EC50) of propofol for inducing loss of consciousness was calculated using the Dixon's up-and-down method. General anesthesia was maintained with propofol and remifentanil, guided by state entropy (target 40-60) and surgical pleth index (target 20-50). Drug consumption was normalized to anesthesia duration and body weight. **Results**: The estimated EC50 of propofol for inducing loss of consciousness was significantly lower in the lidocaine group than in the saline group (3.32 μg/mL, 95% Confidence Interval (CI): 3.04-3.59 vs. 3.89 μg/mL, 95% CI: 3.50-4.28). Under the study protocol, the lidocaine group also required less propofol (8.62 $mg \cdot kg^{-1} \cdot h^{-1}$, 95% CI: 8.10-9.15 vs. 9.89 $mg \cdot kg^{-1} \cdot h^{-1}$, 95% CI: 9.05-10.73) and less remifentanil (0.23 $\mu g \cdot kg^{-1} \cdot min^{-1}$, 95% CI: 0.21-0.24 vs. 0.27 $\mu g \cdot kg^{-1} \cdot min^{-1}$, 95% CI: 0.24-0.30) compared with the saline group. **Conclusion**: Intravenous lidocaine reduced the propofol EC50 for Loss of Consciousness (LOC) and decreased intraoperative propofol and remifentanil consumptions in patients undergoing gynecological laparoscopy. These findings suggest a propofol- and opioid-sparing effect of intravenous lidocaine in this setting, although confirmation in larger multicenter trials is needed.

Keywords: Anesthetic depth; Lidocaine; Propofol; Remifentanil; Surgical pleth index.

Submitted on 25-04-2026 – Revised on 13-06-2026 – Accepted on 07-07-2026 – Available online on 27-08-2026 – Published on 01-12-2026

INTRODUCTION

Propofol is a commonly used agent for general anesthesia induction and maintenance, owing to its rapid onset, swift recovery and low incidence of postoperative nausea and vomiting. However, propofol is likely to cause one or more of the following adverse effects to some extent: bradycardia, hypotension and hypoxia (Sahinovic *et al.*, 2018). To decrease propofol dosage and its related adverse effects, adjuvant medications are often administered in combination. Intravenous lidocaine, an amide-type local anesthetic, has been shown to reduce propofol requirements in several clinical settings. For instance, Forster *et al*. (2018) reported that IV lidocaine reduced propofol consumption during colonoscopy under propofol-ketamine anesthesia. Similarly, Weber *et al.* (2015) and Xu *et al.* (2021) demonstrated that lidocaine decreases the propofol dose required to prevent movement in response to surgical stimulation (Weber *et al.*, 2015 , Xu *et al.*, 2021). Beyond its propofol-sparing effect, lidocaine also provides anti-inflammatory and analgesic benefits that may enhance postoperative recovery, including reduced pain and nausea, shortened ileus duration, decreased opioid requirements and reduced hospital stay (Kranke *et al.*, 2015).

Despite these established propofol-sparing effects of lidocaine during the maintenance phase of anesthesia and in response to surgical stimulation, its specific effect on propofol requirements for inducing loss of consciousness (LOC) — an important induction endpoint —has not been well studied. Specifically, few studies have quantified whether lidocaine pretreatment reduces the effect-site concentration of propofol (Ce_{prop}) required to achieve LOC during induction before surgical stimulation.

**Corresponding author:* e-mail: 15168435098@163.com
#These authors contributed equally and are the co-first authors.

Therefore, it was hypothesized that intravenous lidocaine would decrease the propofol requirement for LOC induction. The primary objective of this study was to evaluate the effect of lidocaine on the EC50 of propofol for LOC induction in patients undergoing gynecological laparoscopy. Secondary outcomes included propofol and remifentanil consumption during maintenance of total intravenous anesthesia.

MATERIALS AND METHODS

Study subjects

Approval for this study was obtained from the Research Ethics Committee of Women's Hospital, Zhejiang University School of Medicine (IRB-20190001-R), with registration in the Chinese Clinical Trial Registry (ChiCTR2100045063). Patients were recruited between April 2021 and July 2021. The format of the paper is in line with CONSORT 2010.

Eligibility criteria for participants

After providing written informed consent, patients scheduled for elective gynecological laparoscopy under total intravenous anesthesia (TIVA) were consecutively screened for eligibility. All participants underwent routine preoperative blood investigations, including complete blood count, liver and renal function tests, and coagulation profile, together with clinical evaluation to confirm eligibility.

Inclusion criteria

Patients were eligible for inclusion if they met all of the following criteria: (1) scheduled for elective gynecological laparoscopy under TIVA; (2) American Society of Anesthesiologists (ASA) physical status I or II; (3) aged 18–60 years; and (4) body mass index (BMI) of 18–24 $kg \cdot m^{-2}$.

Exclusion criteria

Patients were excluded if they had any of the following: (1) significant cardiopulmonary disease; (2) renal failure; (3) hepatic insufficiency; (4) neurological disorders; (5) arrhythmia; (6) diabetes mellitus; (7) current or recent use of sedatives or opioids; or (8) allergy to lidocaine. Sixty eligible patients were ultimately enrolled in the study.

Randomization and blinding

Patients were randomly allocated to the lidocaine (n=30) or saline (n=30) groups using a computerized randomization scheme. Allocation concealment was ensured using sealed, opaque envelopes. Prior to surgery, an unblinded investigator opened the envelope and prepared the study medication. The bolus injection contained either lidocaine ($1.5\ mg \cdot kg^{-1}$) or saline, with both solutions adjusted to a final volume of 10 mL. For continuous infusion, a 50 ml syringe was filled with either lidocaine (10 mg/ml) or saline. All syringes were labeled only with the study serial number to maintain blinding. One anesthesiologist was responsible for administering the study medication. Other anesthesiologists, blinded to group allocation, performed anesthesia induction, tracheal intubation and intraoperative anesthetic titration. Patients, anesthesiologists and surgeons were all blinded to the group assignments. The unblinding strategy was predefined: the blind would be broken only by the study director (who was not involved in clinical procedures) upon opening the sealed allocation envelope in the event of a serious adverse event requiring urgent knowledge of group assignment.

Primary and secondary outcomes

The primary outcome measure was the EC50 of the propofol effect-site concentration (Ce_{prop}) associated with LOC induction. Secondary outcome indicators were anaesthetic consumption (propofol and remifentanil), mean arterial pressure (MAP), heart rate (HR), peripheral capillary oxygen saturation (SpO_2), response entropy (RE), state entropy (SE) and surgical pleth index (SPI) during surgery. The numerical rating scale (NRS) for pain and the requirement for rescue analgesia in the post-anesthesia care unit (PACU) were also recorded as secondary outcomes. Other indicators of the result include the time of appearance, presence of side effects during and after surgery and conditions in the PACU.

Study protocol

Patients were required to fast for at least 6 hours prior to the procedure and did not receive pre-medication. An IV site was obtained in the operating room. Before induction, each subject was given $10\ mL \cdot kg^{-1}$ Ringer's lactate as a bolus, then infused at $10\ mL \cdot kg^{-1} \cdot h^{-1}$ during the procedure. The following monitors were used for comprehensive patient observation: Electrocardiogram, SpO_2, non-invasive blood pressure (NIBP) and end-tidal carbon dioxide partial pressure ($ETCO_2$). An entropy sensor was placed over the frontotemporal region to monitor the SE and determine whether a hypnotic component of anesthesia had been introduced. SPI—was calculated from the plethysmographic signal of a SpO_2 sensor and the ratio of nociception to antinociception was evaluated (Bonhomme *et al.*, 2011; Huiku *et al.*, 2007).

Patients received an intravenous bolus of $1.5\ mg \cdot kg^{-1}$ lidocaine or matching saline over 2 minutes, followed by continuous infusion of $2\ mg \cdot kg^{-1}$ lidocaine or saline. This dose regimen was selected based on published evidence demonstrating its safety and efficacy in perioperative settings. Specifically, A previous report confirmed that a $1.5\ mg \cdot kg^{-1}$ bolus followed by $2\ mg \cdot kg^{-1} \cdot h^{-1}$ infusion maintains plasma lidocaine concentrations well below the toxic threshold of $5\ \mu g \cdot ml^{-1}$ (Kaba *et al.*, 2007). Additionally, previous studies (Forster *et al.*, 2018; Weber *et al.*, 2015; Xu *et al.*, 2021) have shown that this regimen produces clinically significant propofol-sparing effects without increasing the risk of lidocaine-related adverse

events. Therefore, this regimen was considered both safe and pharmacodynamically appropriate for evaluating lidocaine's impact on propofol EC50 for LOC in the present study. Another anaesthesiologist entered the operating room one minute later and with propofol, a target-controlled infusion (TCI) pump (Injectomat TIVA Agilia RC2, Fresenius Kabi AG, Bad Homburg, Germany) was used for anesthesia induction (Schnider *et al.*, 1998).

The EC50 of LOC was defined as the lowest Ce_{prop} causing loss of consciousness in 50% participants. The EC50 for propofol in LOC was assessed using Dixon's up-down sequential method (Dixon, 1991). For each group,the initial patient received an effect-site concentration (Ce_{prop}) of 3.5 $\mu g \cdot ml^{-1}$ via TCI, which was selected based on previous findings as an estimated concentration sufficient to induce LOC and loss of response to verbal commands in most patient (Fu *et al.*, 2014). LOC was considered achieved when the patient no longer response to verbal commands. The concentration increment of 0.5 $\mu g \cdot mL^{-1}$ was selected based on recommendations for Dixon's up-and-down methodology, in which the step size should approximate 10–20% of the anticipated EC50 to achieve efficient convergence while maintaining adequate precision of the estimate. Given that previous studies reported a propofol effect-site concentration for LOC of approximately 3–4 $\mu g \cdot mL^{-1}$, a step size of 0.5 $\mu g \cdot mL^{-1}$ (approximately 13–17% of the expected EC50) was considered appropriate. The Ce_{prop} for the next patient was decreased by 0.5 $\mu g \cdot mL^{-1}$ if LOC was attained; otherwise, increased in the current patient, or increased by the same increment if LOC was not achieved. If induction failed, Ce_{prop} was increased by 0.5 $\mu g \cdot mL^{-1}$ every 2 minutes until unconsciousness occurred.

Once loss of consciousness was achieved, remifentanil was initiated using target-controlled infusion with an effect-site concentration target of 4 $ng \cdot mL^{-1}$ and cisatracurium 0.15 $mg \cdot kg^{-1}$ was administered to facilitate tracheal intubation. Four minutes later, tracheal intubation was performed and mechanical ventilation was commenced to maintain an end-tidal carbon dioxide partial pressure of 30–40 mmHg.

Anaesthesia was maintained with target-controlled infusions of propofol and remifentanil. Following intubation, the propofol effect-site concentration was adjusted in increments or decrements of 0.5 $\mu g \cdot mL^{-1}$ to maintain a state entropy value between 40 and 60. Simultaneously, the remifentanil effect-site concentration was adjusted in increments or decrements of 1 $ng \cdot mL^{-1}$ to maintain a surgical pleth index between 20 and 50. Cisatracurium was administered in bolus doses of 3-4 mg to maintain muscle relaxation, according to the anesthesiologist's clinical experience during the surgery. For postoperative analgesia, patients were given 0.1 $mg \cdot kg^{-1}$ oxycodone and 50 mg flurbiprofen intravenously 30 minutes preoperatively. Lidocaine, propofol and remifentanil infusions were halted after skin closure. The values of NIBP, HR, SpO_2, RE, SE and SPI were recorded every 5 min during the surgery. Predicted Ce_{prop} and Ceremi were continuously recorded intraoperatively, including key time points: LOC, tracheal intubation, anesthetic cessation, anesthesia emergence and tracheal extubation.

Cumulative propofol and remifentanil consumption was documented. The anesthesia time (from induction to discontinuation of propofol) was recorded. The time interval between induction and the termination of propofol infusion – defined as the anesthesia duration- was also recorded. Furthermore, awakening time, defined as the interval from discontinuation of anesthesia to spontaneous eye opening, was recorded. Adverse events within the PACU were recorded.

All adverse events were managed according to standardized clinical protocols: hypotension was treated with intravenous norepinephrine (4-8 μg bolus), bradycardia with intravenous atropine (0.3-0.5 mg) and hypoxia ($SpO_2 < 92\%$) with supplemental oxygen and jaw thrust. Serious adverse events were defined as those that were life-threatening, required prolonged hospitalization, or resulted in persistent disability and were to be reported to the ethics committee within 24 hours. All adverse events were documented in the case report form, including the time of onset, duration, management, and outcome.

Statistical analysis

Sample size was estimated a priori based on sequential dose-finding design recommendations and prior studies. Based on simulation evidence suggesting that 20–40 patients are sufficient for a stable EC50 estimate, 30 patients per group were enrolled (Pace and Stylianou, 2007). An adequate number of crossover pairs was required for EC50 estimation in each group. The Dixon up-and-down method was used for calculating propofol EC50 for inducing LOC (Dixon, 1991).

Additionally, probit regression analysis was conducted as a sensitivity and additional evaluation, using the pooled counts of successful and unsuccessful responses at each concentration level across both groups. Point estimates of EC50 were obtained using the Dixon up-and-down method, and 95% CIs were estimated using probit regression, as this method provides more reliable interval estimates than the Dixon method under sequential allocation. Probit regression utilizes all individual response data across concentration levels and assumes a sigmoidal dose-response relationship, yielding CIs based on the asymptotic standard errors of the estimated parameters. To compare the EC50 estimates between the lidocaine and saline groups, two complementary statistical approaches were employed. First, group differences in EC50 were

assessed using probit regression and likelihood ratio testing for unequal variances. Second, probit regression analysis was used to generate dose-response curves and 95% CIs for each group; the null hypothesis of equal EC50 between groups was tested using a likelihood ratio test comparing a full model (separate EC50 for each group) with a reduced model (common EC50). Both methods yielded consistent results, supporting the robustness of the findings.

Normality was assessed using the Kolmogorov-Smirnov test. Normally distributed data were compared using an independent-samples t-test, Non-normally distributed data were compared using the Mann-Whitney U test. Categorical data were analyzed using chi-square test or Fisher's exact test (when any expected cell count was <5). The Kaplan-Meier method was used to analyze emergence time, and the log-rank test was used for between-group comparison. Analyses were performed using IBM SPSS Statistics 19.0 and GraphPad Prism 5.0. (GraphPad Software Inc., San Diego, CA, USA). To address multiple comparisons, Bonferroni correction was applied to the prespecified secondary outcomes. The primary outcome (EC50) involved a single pre-specified hypothesis test between the two groups; therefore, no correction for multiple comparisons was required.

For the pre-specified secondary outcomes (propofol dose, remifentanil dose, recovery Ce_{prop} and NRS pain score), a sensitivity analysis using the Bonferroni correction was performed, with a corrected alpha level of 0.0125 (0.05/4). All other secondary outcomes (hemodynamic variables, SPI values, PACU outcomes, recovery time, etc.) were considered exploratory analyses without adjustment for multiple comparisons and their results should be interpreted as hypothesis-generating rather than confirmatory. A two-tailed p value < 0.05 was considered statistically significant for the primary outcome; corrected thresholds were applied to prespecified secondary outcomes.

RESULTS

Patient characteristics

A total of 83 subjects met the criteria for inclusion. Among them, 60 were randomized and successfully participated in the study (Fig. 1). No protocol deviations, blinding failures, or missing data occurred during the trial. Table 1 presents the demographic and baseline information of the subjects. Age, weight, height, BMI, and ASA physical status distribution did not differ significantly in the lidocaine and saline groups.

EC50 of propofol

The lidocaine group had a markedly lower propofol EC50 for LOC induction than the saline group, as determined by probit regression analysis (3.32, 95%CI 3.04-3.59 μg/mL vs 3.89, 95% CI 3.50-4.28 μg/mL; p=0.018 for the comparison of EC50 between groups, derived from the likelihood ratio test). The individual responses to propofol for the corresponding Ce_{prop} are presented in figure 2. Dose-response curves resulting from probit regression analysis are presented in figure 3. This reduction corresponds to an approximately 14.7% decrease in the propofol effect-site concentration required to induce loss of consciousness. From a clinical perspective, such a reduction may allow induction of anaesthesia with lower propofol exposure, potentially decreasing the risk of dose-dependent adverse effects such as hypotension and respiratory depression.

Propofol or remifentanil requirements

Maintenance doses of propofol and remifentanil were calculated as total drug consumption divided by anesthesia duration and body weight. As presented in table 2, the lidocaine group required less propofol than the saline group (8.62, 95% CI 8.10-9.15 vs 9.89, 95% CI 9.05-10.73 $mg \cdot kg^{-1} \cdot h^{-1}$, p=0.012). Its remifentanil dosage was also obviously decreased (0.23, 95% CI 0.21-0.24 vs 0.27, 95% CI 0.24-0.30 $\mu g \cdot kg^{-1} \cdot min^{-1}$, p=0.01). After applying Bonferroni correction for multiple comparisons (corrected $\alpha = 0.0125$), the differences in propofol dose (p=0.012) and remifentanil dose (p=0.01) remained statistically significant. Meanwhile, intraoperative target effect-site concentrations of both agents were lower in the lidocaine group (Fig. S1). Compared with the saline group, lidocaine reduced propofol consumption by approximately 12.8% and remifentanil consumption by approximately 14.8%. Although the study was not powered to detect differences in clinical outcomes, these reductions suggest a potentially meaningful anesthetic-sparing effect that may contribute to improved hemodynamic stability and reduced exposure to anaesthetic agents during surgery.

Perioperative data

The recovery time was comparable between the lidocaine group (16.0 min [95% CI: 13.63-18.30]) and the saline group (14.5 min [95% CI: 12.79-16.28]) (p=0.319). The accumulated percentages of patients who have not regained consciousness at different times are shown in figure 4. Regarding hemodynamic parameters, the MAP during surgery was 82.5 ± 8.3 mmHg in the lidocaine group and 81.9 ± 9.1 mmHg in the saline group (p=0.782); the HR was 78.6 ± 10.2 bpm in the lidocaine group and 79.3 ± 11.4 bpm in the saline group (p=0.803). The MAP, HR and hypnotic depth (as shown by SE) of the two groups were all the same. The SPI values were higher in the saline group than in the lidocaine group at several time points after surgery (Fig. S2). No significant differences were observed in intraoperative anesthetic conditions or adverse reactions between the two groups.

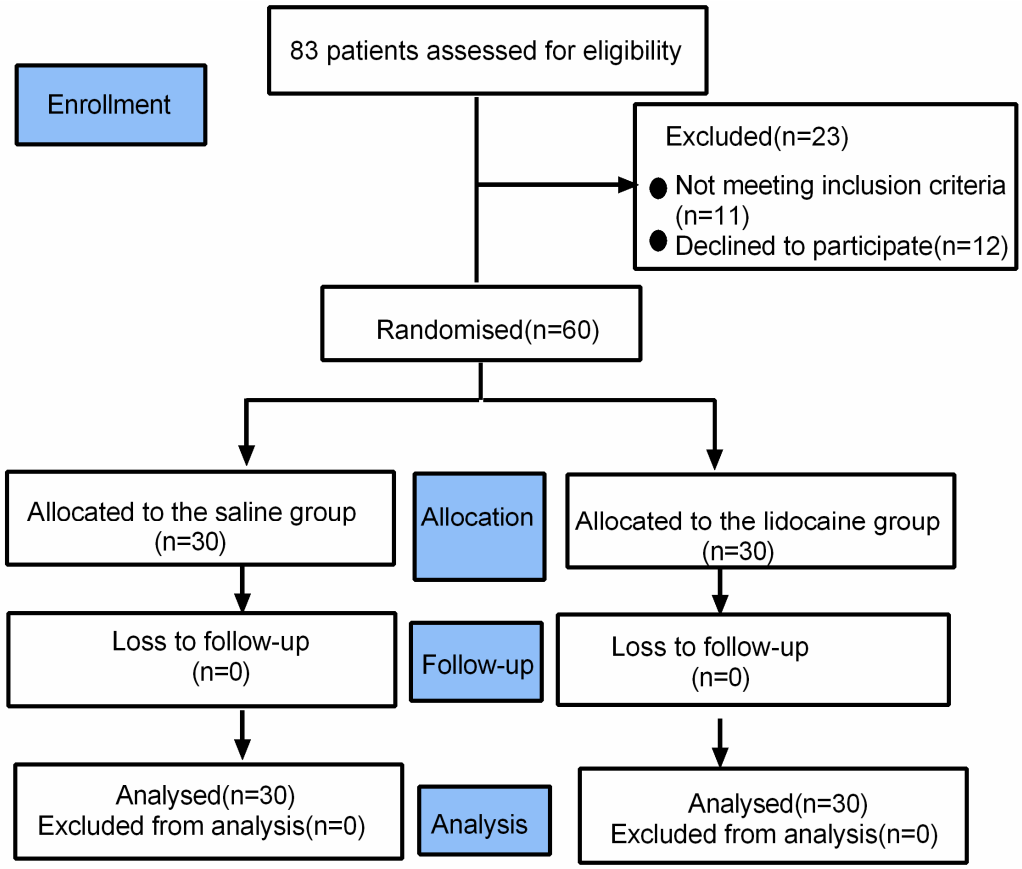

Fig. 1: CONSORT flow diagram of this study.

Table 1: Patient characteristics.

Variable	Lidocaine group (n=30)	Saline group (n=30)	*p* value
Age (yr)	31 ± 7.4	31 ± 6.3	0.999[a]
Height (cm)	159.7 ± 4.0	159.7 ± 5.3	0.978[a]
Weight (kg)	54.3 ± 5.5	53.4 ± 6.3	0.555[a]
BMI ($kg \cdot m^{-2}$)	21.3 ± 1.97	20.9 ± 2.39	0.529[a]
ASA I (n%)	29 (96.7%)	28 (93.3%)	0.999[b]
ASA II (n%)	1 (3.3%)	2 (6.7%)	

Data are presented as mean ± SD or number (%); [a] Independent-samples t-test; [b] Fisher's exact test.

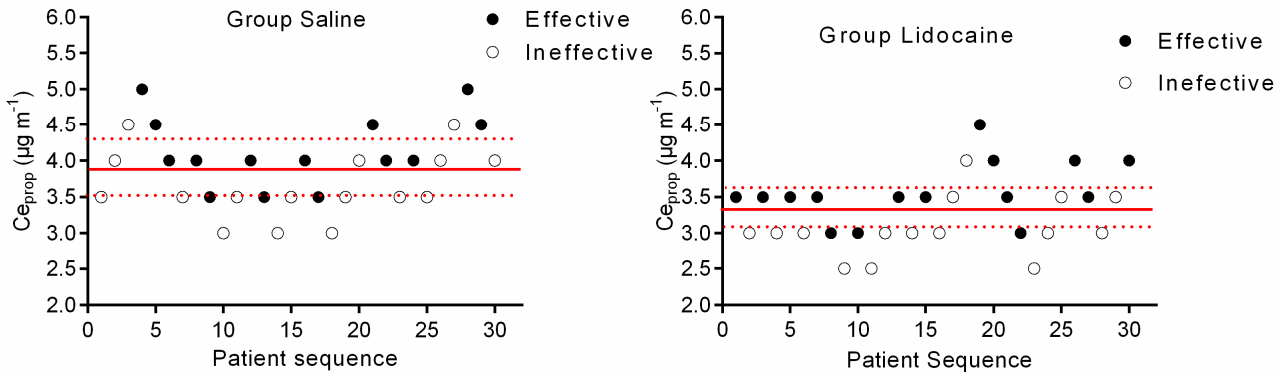

Fig. 2: Individual responses to popofol at corresponding effect-concentrations (Ce_{prop}). Unifilled circles represent a failure to the corresponding for Ce_{prop} achieving LOC. Filled circles represent a success to the corresponding for Ce_{prop} achieving LOC. The EC50 of propofol for LOC is represented by horizontal line.

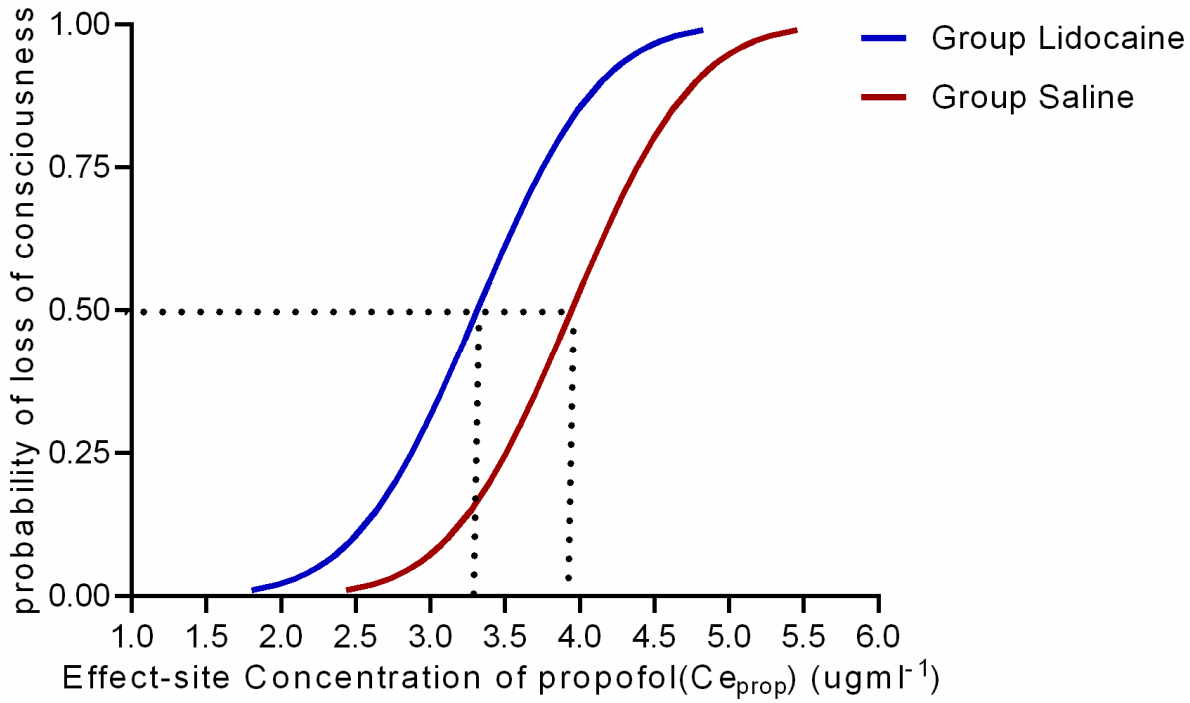

Fig. 3: Dose-response curve of propofol infusions for loss of consciousness plotted estimated probabilities of success (1%-100%) versus the corresponding effect-site concentrations of propofol (Ce_{prop}) using probit regression analysis.

Table 2: Intraoperative anesthetic data values. Adverse events in the PACU.

Variable	Lidocaine group (n=30)	Saline group (n=30)	*p* value
Intraoperative data			
Anesthesia time (min)	114.4 ± 42.6	99.4 ±35.8	0.145[a]
Propofol dose ($mg \cdot kg^{-1} \cdot h^{-1}$)	8.62 ± 1.4	9.89 ± 2.25	0.012[a]
Remifentanil dose ($\mu g \cdot kg^{-1} \cdot min^{-1}$)	0.23 ± 0.04	0.27 ± 0.07	0.01[a]
MAP during surgery (mmHg)	82.5 ± 8.3	81.9 ± 9.1	0.782[a]
HR during surgery (bpm)	78.6 ± 10.2	79.3 ± 11.4	0.803[a]
Recovery time from propofol cessation to eye opening (min)	16.0 ± 6.3	14.5 ± 4.7	0.319[a]
Recovery Ce_{prop} ($\mu g \cdot mL^{-1}$)	0.94 ± 0.20	1.09 ± 0.22	0.006[a]
Recovery Ce_{remi} ($ng \cdot mL^{-1}$)	0.76 ± 0.58	0.79 ± 0.33	0.845[a]
Atropine(n%)	9 (30) / 21 (70)	6 (20) / 24 (80)	0.371[b]
norepinephrine(n%)	2 (6.67) / 28 (93.33)	1 (3.33) / 29 (96.67)	0.999[c]
PACU time (min)	35(30-55)	35(30-50)	0.935[d]
Adverse events in PACU			
Hypotension (n%)	0 (0) / 30 (100)	1 (3.33) / 29 (96.66)	1.0[c]
Bradycardia	4 (13.33) / 26 (86.67)	3 (10) / 27 (90)	0.687[c]
Hypoxia/ oxygen desaturation	0 (0) / 30 (100)	0 (0) / 30 (100)	NA
Nausea	1 (3.33) / 29 (96.66)	2 (6.67) / 28 (93.33)	1.0[c]
Vomiting	0 (0) / 30 (100)	0 (0) / 30 (100)	NA
Postoperative pain outcomes in PACU			
NRS pain score at 30 min (0-10)	2.5 ± 0.4	2.7 ± 0.5	0.092[a]
Rescue analgesia (tramadol 50 mg) (n%)	3 (10)	5 (16.67)	0.456[c]

Data are presented as mean ± SD or number (%); Recovery Ce_{prop}: Predicted propofol effect-site concentrations at consciousness recovery; Ceremi: predicted remifentanil effect-site concentrations at consciousness recovery; Oxygen desaturation was defined as peripheral capillary oxygen saturation (SpO_2) < 92%.
[a] Independent-samples t-test; [b] Chi-square test; [c] Fisher's exact test; [d] Mann-Whitney U test

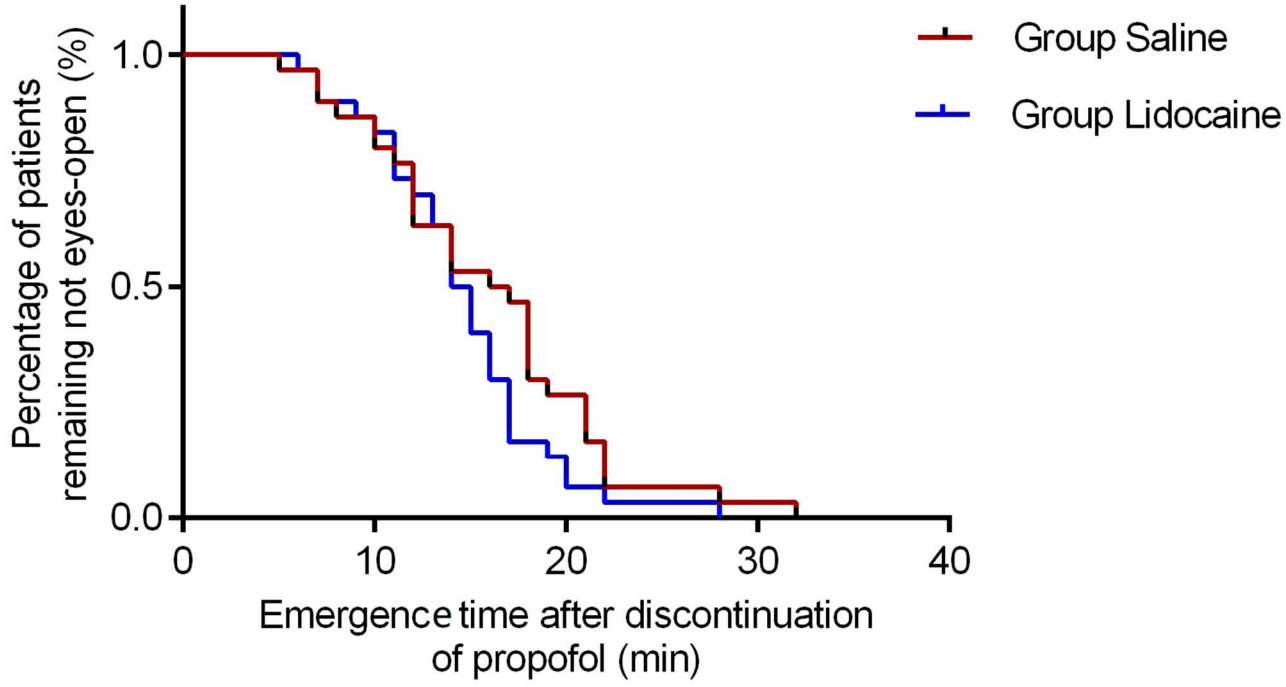

Fig. 4: Cumulative percentages of patients a remaining unconscious after discontinuation of propofol in the lidocaine group and saline group. Log-rank differences between the two groups were not significant. (p=0.123).

A detailed recording of adverse events was performed: In the lidocaine group, 4 patients (13.33%) developed bradycardia, 9 patients (30.0%) received atropine, and 2 patients (6.67%) received norepinephrine; in the saline group, 3 patients (10.0%) developed bradycardia and 1 patient (3.33%) received norepinephrine ($p > 0.05$ for all comparisons). All adverse events were transient and resolved without sequelae. Moreover, no obvious difference was observed in the incidence of postoperative adverse events in PACU (Table 2). In the PACU, pain scores (NRS) at 30 min after admission were 2.5 ± 0.4 in the lidocaine group and 2.7 ± 0.5 in the saline group (p=0.092); rescue analgesia (intravenous tramadol 50 mg) was required in 3 patients (10%) in the lidocaine group and 5 patients (16.67%) in the saline group (p=0.456). For the prespecified secondary outcomes, after Bonferroni correction (corrected $\alpha = 0.0125$), recovery Ce_{prop} remained statistically significant ($p = 0.006$), whereas the difference in NRS pain score did not reach statistical significance. All other secondary outcomes were considered exploratory and are reported without adjustment.

DISCUSSION

This study demonstrated that intravenous lidocaine significantly reduced the propofol effect-site concentration required to induce loss of consciousness (LOC) and decreased intraoperative propofol and remifentanil consumption in patients undergoing gynecological laparoscopy, without increasing perioperative adverse events. The observed reduction in propofol EC50 from 3.89 μg/mL to 3.32 μg/mL (approximately 14.7%) suggests that lidocaine pretreatment may meaningfully enhance anesthetic sensitivity during induction. Importantly, this effect was observed under conditions free of surgical stimulation, indicating that the influence of lidocaine may extend beyond nociceptive modulation to include effects on hypnotic requirements.

Previous studies have consistently reported that intravenous lidocaine reduces anesthetic requirements in various surgical settings (Forster *et al.*, 2018; Weber *et al.*, 2015; Xu *et al.*, 2021). However, these studies primarily evaluated anesthetic-sparing effects during maintenance anesthesia or in response to surgical stimulation, where reduced nociceptive input is a major confounding factor. In contrast, the present study isolates the induction phase and specifically evaluates propofol requirements for LOC prior to any nociceptive input. This distinction is clinically important because it suggests that lidocaine may influence central anesthetic sensitivity rather than acting solely through peripheral analgesia. Nevertheless, differences in study design, endpoints and anesthetic depth monitoring may also explain variability among findings, particularly regarding the magnitude of anesthetic-sparing effects reported across studies.

Lidocaine is an amide-type local anesthetic with established perioperative applications, including reduction of propofol injection pain (Xing *et al.*, 2018), attenuation of hemodynamic responses to airway manipulation (Jain and Khan, 2015) and facilitation of postoperative recovery through anti-inflammatory and analgesic effects (Beaussier

et al., (2018). Although its central hypnotic-modulating mechanisms remain incompletely understood, several hypotheses may explain the current findings. Lidocaine has been shown to modulate sodium channel activity and suppress cortical excitability, which may synergistically enhance propofol-induced GABAergic inhibition. This could explain why LOC occurred at lower propofol concentrations in the lidocaine group even before surgical stimulation. Furthermore, the observed reduction in both propofol and remifentanil consumption during maintenance anesthesia is consistent with previously reported anesthetic-sparing effects of lidocaine (Altermatt *et al.*, 2012), although the magnitude of the reduction may depend on anesthetic depth-monitoring strategies and intraoperative titration protocols.

Notably, differences across prior studies may also be explained by heterogeneity in analgesic and nociception-monitoring techniques. Most earlier studies relied on conventional hemodynamic variables to guide opioid administration, which are relatively insensitive to nociceptive balance. In contrast, the present study utilized the Surgical Pleth Index (SPI), a more specific surrogate of nociception-antinociception equilibrium (Bonhomme *et al.*, 2011). SPI-guided titration has been shown to improve the precision of intraoperative analgesic delivery and may reduce variability in opioid administration (Chen *et al.*, 2010). Therefore, the use of SPI monitoring may partially explain the observed reduction in remifentanil consumption and represents a methodological strength of the present trial. These findings suggest that lidocaine may exert clinically relevant opioid-sparing effects when nociception monitoring is optimized, although this requires confirmation in larger multicenter studies.

Propofol and remifentanil remain the cornerstone agents for total intravenous anesthesia due to their favorable pharmacokinetic profiles. However, both agents exhibit dose-dependent adverse effects, including hypotension, bradycardia and respiratory depression (Noseir *et al.*, 2003; Sneyd *et al.*, 2022) which have been associated with adverse perioperative outcomes (Sahinovic *et al.*, 2018; Sessler *et al.*, 2012). From this perspective, even modest reductions in anesthetic requirements may have clinical relevance. In the present study, lidocaine administration was associated with lower intraoperative anesthetic consumption without prolonging recovery or increasing adverse events. However, as the trial was not powered to detect safety endpoints or differences in clinical outcomes, it remains uncertain whether these pharmacological advantages translate into improved postoperative recovery or reduced complication rates.

The present findings also differ from some reports suggesting that intravenous lidocaine primarily reduces postoperative analgesic requirements rather than intraoperative opioid consumption (Andjelković *et al.*, 2018; De Oliveira *et al.*, 2014). In contrast, a significant reduction in intraoperative opioid requirements in ambulatory surgery patients (McKay *et al.*, 2009). Differences in surgical stimulation intensity, anesthetic techniques and opioid titration strategies may explain these discrepancies. Importantly, nociception monitoring methods likely play a central role in these differences. Studies relying solely on hemodynamic variables may underestimate opioid-sparing effects due to poor sensitivity, whereas more structured monitoring approaches may reveal clearer differences.

A further consideration is the safety of systemic lidocaine administration. Although toxicity remains a theoretical concern, previous pharmacokinetic data have demonstrated that perioperative lidocaine infusions at clinically used doses remain below toxic plasma concentrations (Kaba *et al.*, 2007). In the present study, the lidocaine regimen (1.5 $mg \cdot kg^{-1}$ bolus followed by 2 $mg \cdot kg^{-1} \cdot h^{-1}$ infusion) was well tolerated, with no increase in adverse events or delayed emergence. These findings support the safety of short-term intraoperative lidocaine administration in appropriately selected patients.

This study has several limitations that should be acknowledged. First, as a single-center trial in a relatively homogeneous population of healthy female patients (ASA I–II, BMI 18–24 $kg \cdot m^{-2}$), the external validity is limited, particularly to male patients, patients with significant comorbidities, or those outside the studied age and BMI ranges. Second, although the sample size was adequate for the primary endpoint (EC50 estimation), it may have been insufficient to detect differences in secondary clinical outcomes. Third, plasma lidocaine concentrations were not measured, limiting pharmacokinetic-pharmacodynamic correlationand limiting mechanistic interpretation. Although prior studies suggest that plasma levels below 5 $\mu g \cdot mL^{-1}$ may still exert anesthetic-sparing effects, this cannot be confirmed in the present dataset. Fourth, follow-up was limited to the intraoperative and PACU periods and longer-term recovery outcomes were not assessed. Fifth, only a single lidocaine dosing regimen was evaluated, precluding formal assessment of dose–response relationships. Finally, although probit regression was used to estimate EC50 with confidence intervals, bootstrap validation was not performed, which could have strengthened robustness. Future studies should validate these findings in larger, multicenter trials involving more diverse patient populations, including patients with broader age and BMI ranges and different comorbidity profiles. Evaluation of multiple lidocaine dosing regimens, together with measurement of plasma lidocaine concentrations, would help clarify dose–response and pharmacokinetic–pharmacodynamic relationships. In addition, longer-term postoperative follow-up and assessment of clinically relevant outcomes, such as postoperative pain, opioid consumption, recovery quality, and complications, are

warranted to determine whether the observed anesthetic-sparing effects translate into meaningful clinical benefits.

CONCLUSION

Intravenous lidocaine was associated with a lower propofol EC50 required for loss of consciousness and decreases intraoperative propofol and remifentanil consumption during total intravenous anesthesia in gynecological laparoscopy. These findings suggest an anesthetic-sparing effect of lidocaine. Clinically, this anesthetic-sparing effect may improve intraoperative anesthetic efficiency. Future studies should include multicenter designs, broader patient populations, pharmacokinetic measurements and mechanistic investigations to clarify the interaction between lidocaine and propofol requirements during induction and maintenance of anesthesia.

Acknowledgements
ChatGPT (version 5.0) was used in language improvement. The authors thank the colleagues in the Department of Anesthesiology, Women's Hospital, Zhejiang University School of Medicine, Hangzhou, China.

Author's contributions
Lin Jin and Xiaoping Chen designed the work. Jialin wang and Shaobing Dai did the acquisition of the data. Panpan Pan made contributions to data analysis. Min Chen did the interpretation of data. Lin Jin, Xiaoping Chen and Lihong Sun had drafted the work. Peng Ying provided the conception of the work and revised it.

Funding
This work was supported by Lishui Science and Technology Project (2023SJZC005 to Dr. Min Chen).

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

Ethical approval
The study was approved by the Ethical Committee of Women's Hospital, Zhejiang University School of Medicine (Hangzhou, China) (No. IRB-20190001-R) and was registered at the Chinese Clinical Trials.gov (No. ChiCTR2100045063). Written informed consent was obtained from all participants prior to enrollment. The consent process included a detailed explanation of the study purpose, procedures, potential risks and benefits and the right to withdraw at any time without affecting their medical care. The study complies with the Declaration of Helsinki. This study was conducted in accordance with the CONSORT reporting guideline for randomized controlled trials. This study was performed in adherence with the CONSORT guidelines. See supplementary file for the CONSORT checklist.

Conflict of interest
The authors declare that they have no competing interests.

Supplementary data
https://pjps.pk/uploads/2026/08/SUP1787836851.pdf

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