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Original Article

Effect of Penehyclidine on Dreaming Occurrence and Plasma Acetylcholine Variation During Propofol Anesthesia for Minor Gynecological Surgery

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ABSTRACT

Background: Dreaming often occurs during anesthesia especially with using propofol, which is a poorly understood phenomenon on the basis of current available data. The present study aimed to determine whether penehyclidine can inhibit propofol anesthesia-related dreaming and evaluate the relationship between acetylcholine and propofol-induced dreaming.

Methods: Healthy women undergoing elective minor gynecological surgery were randomized to receive penehyclidine hydrochloride 0.01 mg/kg (penehyclidine group, n = 200) or the same volume of saline (saline group, n = 200) at 10 min before propofol injection. Immediately after surgery, blood samples of the women were collected to determine the plasma acetylcholine concentrations. Interviews concerning dreaming incidence, contents, as well as how she felt her dream (pleasant, neutral, or unpleasant) were conducted 3-5 minutes after she could speak out her name and take appropriate action according to the observer's instruction.

Results: Penehyclidine did not affect dreaming incidences when compared with saline (39.0% vs. 47.5%, P = 0.086). There was no significant difference with respect to the age, weight, propofol dose, or surgery duration between penehyclidine group and saline group, as well as between dreamers and non-dreamers in the saline group. There was no significant difference with respect to the plasma acetylcholine concentrations between dreamers and non-dreamers in the saline group. Sixty-five women (68.0%) recalled the contents of dreams among which 39 (60.0%) were pleasant. Women who recalled dream contents had higher plasma concentrations of acetylcholine than women who did not (P = 0.000).

Conclusions: Penehyclidine cannot reduce the dreaming incidence in women during propofol anesthesia. But, the dreamers who can recall the dreaming contents during propofol anesthesia have higher plasma levels of acetylcholine. (Funded by the National Natural Science Foundation of China; Chinese Clinical Trial Registry number, ChiCTR-TRC-14005033.)

Dreaming is a common but poorly understood phenomenon on the basis of current available data. One study conducted by Leslie et al. has demonstrated that 22% of the population undergoing general anesthesia have dreams, with a higher incidence in young, healthy, and with propofol maintenance (1). The incidence of dreaming during propofol anesthesia supplemented with midazolam and/or fentanyl sedation for colonoscopy is reported to be 25.5% (2). A multicenter research has shown that dreaming during general anesthesia displayed a high risk of awareness ranging from 1.1% to 10.7% (3). However, there is no research about dreaming during simple propofol anesthesia.

The mechanisms underlying the dreaming during anesthesia are still unknown. Anesthesia-related dreaming is related with a rapid eye movement (REM)- like electroencephalographic pattern and it seems that dreaming just occurs before awakening (4). Propofol has a potential relationship with dreaming probably because propofol satisfies REM sleep homeostasis (5), which is not found with isoflurane or sevoflurane anesthesia (6, 7).

Cholinergic neurotransmission plays an important role in the general anesthetic actions (8, 9) and in the physiology of dreaming activity (10-12). Moreover, an enhanced central cholinergic neurotransmission is observed in the mental experience of dreaming during the REM sleep (11). The activation of the cholinergic neurons may contribute to dreaming during propofol- based anesthesia since propofol affects the central cholinergic neurons (10, 12-14). However, whether acetylcholine may serve as one of plasma biomarkers for anesthesia-related dreaming still remains unknown.

In additional, Toscano et al. have found that intramuscular injection of scopolamine prevents dreams during propofol-nitrous oxide anesthesia (10). Currently, penehyclidine is a more widely used anticholinergic drug before anesthesia than scopolamine in China, which can easily pass through the blood-brain barrier (15). However, there is no available information regarding penehyclidine on dreaming during anesthesia.

On the basis of aforementioned points, we hypothesized that penehyclidine can affect propofol anesthesia- related dreaming and acetylcholine are involved in the development of propofol-induced dreaming. Therefore, we hereby determined whether penehyclidine can reduce the occurrence of propofol- induced dreaming and evaluated the relationship between acetylcholine and this kind of dreaming.

METHODS

Study Design

The present randomized controlled study carried out in Jinling Hospital, which conformed to the principles enumerated in the Helsinki Declaration and was approved by the Ethics Committee of Jinling Hospital, Nanjing University. All the participants signed the written informed consents. Healthy women undergoing elective minor gynecological surgery were equally randomized to receive penehyclidine or saline at 10 min before propofol injection. Immediately after surgery, blood samples of the women were collected to determine the plasma acetylcholine concentrations. Interviews concerning dreaming incidence, contents, as well as how she felt her dream (pleasant, neutral, or unpleasant) were conducted 3-5 minutes after she could speak out her name and take appropriate action according to the observer's instruction.

Inclusion and Exclusion Criteria

Inclusion criteria were Han nationality, age 18-60 yr, weight 40-80 kg, ASA I or II, undergoing elective minor gynecological surgery (including complete curettage of uterine cavity, hysteroscopy, extraction of contraceptive device) in Jinling Hospital, were enrolled in this?prospective parallel study. Women with a language barrier to understand or communicate, glaucoma, psychotic disorders, central nervous diseases, or chronic alcohol, benzodiazepine, or opioid intake before the surgery were excluded in the present study.

Data Collection

Dreaming scores were evaluated as follows: 0 = never dreamed, 1 = less than once a week, 2 = more than once a week, and 3 = dreamed every day. The consumption of propofol, the duration of operation and the baseline characteristics of the women were also recorded. Whether the

Table 1. Baseline Characteristics and Operation Information of the Patients (mean ± SD).

Group	N	Age (yr)	Weight (kg)	Propofol consumption (mg)	Operation duration (min)
Saline	200	31±7	55±6	181±26	4.2±1.5
Penehyclidine	200	29±6	53±7	172±30	4.5±1.3
P Value		0.44	0.87	0.74	0.76

There was no difference in baseline characteristics of the patients and operation information between saline and penehyclidine groups.

Table 2. Dreaming Incidence of the Patients.

Pretreatment	N	Dreamers (%)	Non-dreamers (%)
Control	200	95 (47.5%)	105 (52.5%)
Penehyclidine	200	78 (39.0%)	122 (61.0%)

There was no statistical difference in dreaming incidence between the two groups (P=0.086).

woman dreamed, what content she dreamed, and how she felt her dream (pleasant, neutral or unpleasant) were asked by the two observers (Drs. Zhang and Yang). We defined " Non-dreamer" as the patient who cannot remember whether she dreamed during anesthesia; "Dreamer" as the patient who remembers she dreamed during anesthesia, which is further divided into "Recall patient" and "Non-recall patient" according to whether she recalled the dream content. All the women and Drs. Xu, Zhang, and Yang were blinded to the grouping.

Procedures

All the women were fasting for 8 h or more before the operation. The brachial vein was cannulated and oxygen with a flow rate of 2-3 L/min was supplied via a nasal catheter. Pulse oximetry and heart rate were continuously monitored when the women entered the operating room. The anesthesia procedure was performed by the same anesthesiologist (Dr. Xu) with 2.0-2.2 mg/kg propofol as a bolus injection in 30-40 seconds for anesthesia induction, followed by intermittent injection 0.6-0.7 mg/kg propofol for anesthesia maintenance. Women were randomly divided into two groups by computer allocation: penehyclidine group (penehyclidine hydrochloride 0.01 mg/kg 10 min before propofol injection, n = 200) and saline group (a same volume of saline 10 min before propofol injection, n = 200). Dr. Sun completed the randomization and prepared the injected drugs. Immediately after the operation, the venous blood samples of women were obtained by Dr. Xu and then stored at 4 ° C for later use. When the pulse oximetry of patient is less than 90%, manually-assisted mask ventilation with pure oxygen will be applied. When the heart rate is less than 45 times per minute, isoprenaline 2 μg will be intravenously injected.

Plasma Preparation and Enzyme- Linked Immune Sorbent Assay (ELISA)

Venous blood of the patient was centrifuged at 4,000 rpm at 4 °C for 10 min. After centrifugation, the concentrations of acetylcholine were measured according to the manufacturer instructions (Chemicon, USA). The concentrations of acetylcholine were determined by absorbencies in 550 nm. Total amounts of the biomarkers were measured by Lowry' s method using bovine serum albumin as a standard.

Statistical Analysis

Statistical analysis was performed by the SPSS 16.0 software. Measurement data are presented as mean ± standard deviation (SD), and independent sample t test was used to compare the differences between groups. Enumeration data are expressed as number or percentage, and chi-square test was used to compare the differences between groups. A P value < 0.05 was regarded as statistically difference.

RESULTS

This prospective parallel study was conducted from June 2014 to April 2016 and 400 women were enrolled with each group of 200 women. No significant difference was observed with respect to age, weight, propofol consumption, and operation duration between the two groups (Table 1).

The primary outcome measures showed that 95 in 200 women (47.5%) dreamed in the saline group, while 78 in 200 women (39.0%) dreamed in the penehyclidine group. The penehyclidine group and saline group had no statistical significance in the dreaming incidence (Table 2), therefore the present study did not go any further in the branch of the penehyclidine group (Figure 1). The women with penehyclidine hydrochloride administration were observed for

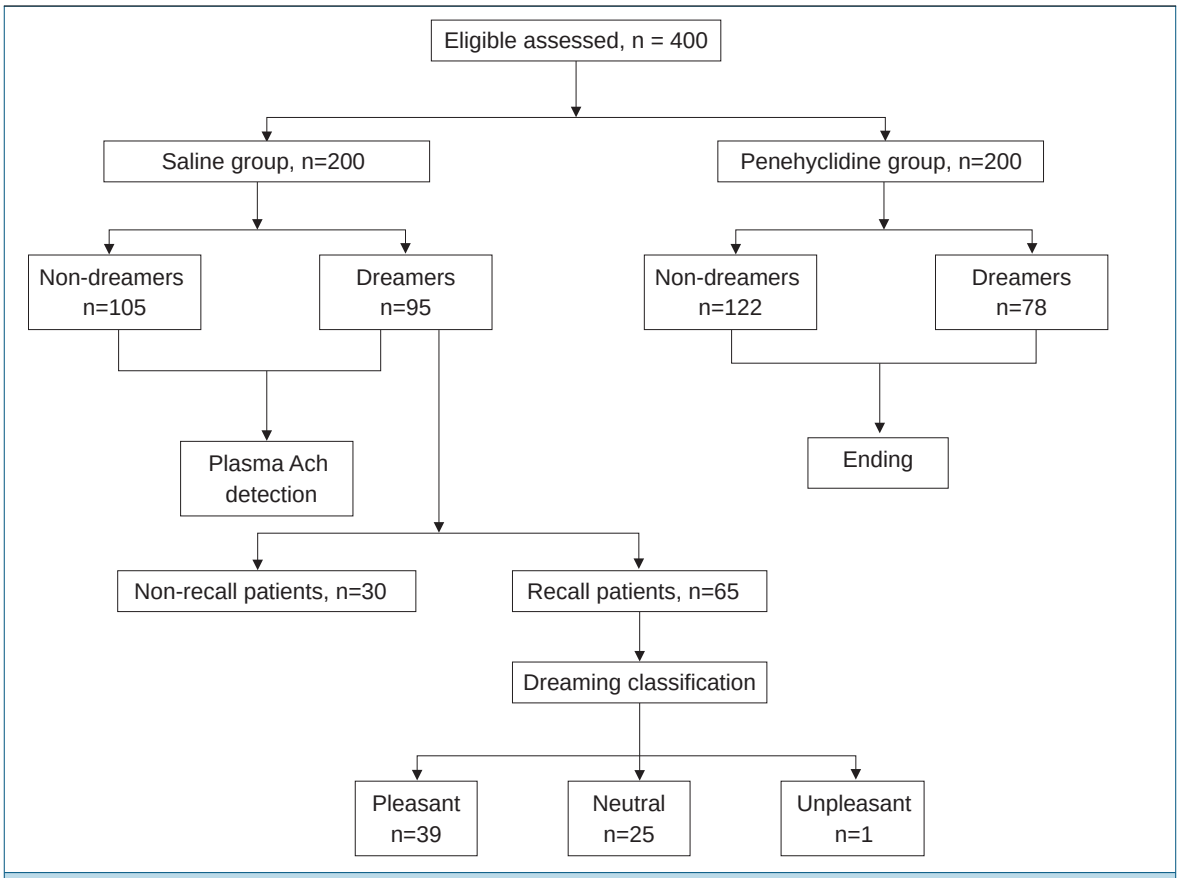

Figure 1. Flow Diagarm of the Present Study.

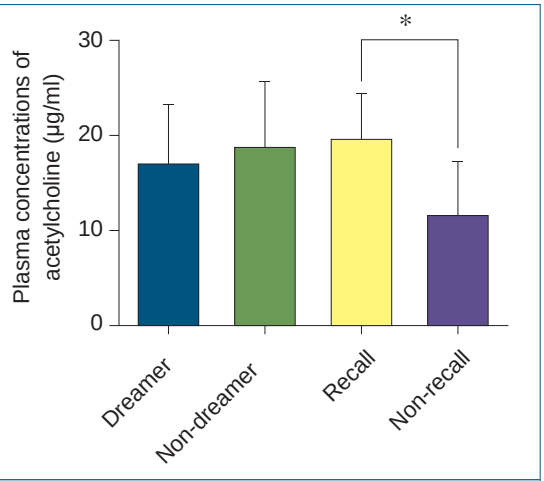

Figure 2. Plasma Concentrations of Acetylcholine in the Saline Group.
There was no significant difference in plasma concentrations of acetylcholine between dreamers and non- dreamers (P = 0.081). However, the plasma concentrations of acetylcholine were higher in the patients who could recall their dream contents compared with those did not recall their dreams (* P = 0.000).

30 min after the operation, and except for dryness of the mouth, no other drug-related side effect was observed.

The secondary outcome measures demonstrated that there was no significant difference in plasma concentrations of acetylcholine between dreamers and non-dreamers (P = 0.081). However, acetylcholine levels were higher in the women who could recall their dream contents compared with those did not recall their dreams (P=0.000) (Figure 2).

No significant difference was observed with respect to age, weight, propofol consumption, and operation duration between dreamers (n = 95) and non- dreamers (n = 105) in the saline group (Table 3). The distribution of dreaming scores in non-dreamers were mainly distributed at scores 0 and 1, while dreaming scores of dreamers were mainly scores 2 and 3. There were significant higher dreaming scores in dreamers compared with non- dreamers in the last 1 month (P =0.000) (Table 4).

Table 3. Baseline Characteristics and Operation Information of the Patients in the Saline Group (mean±SD).

Patients	N	Age (yr)	Weight (kg)	Propofol dose (mg)	Operation duration (min)
Dreamers	95	32±7	56±7	179±24	4.4±1.6
Non-dreamers	105	30±7	54±5	183±28	4.0±1.40.8
P Value		0.54	0.36	0.49	0.89

There was no difference in baseline characteristics of the patients and operation information between dreamers and non- dreamers in the saline group (P>0.05).

Table 4. Dreaming Scores of the Patients in the Last 1 Month in the Saline Group.

	Total	0	1	2	3
Dreamers /Patients	95/200 (47.5%)	20/68 (29.4%)	5/13 (38.5%)	27/48 (56.3%)	43/71 60.6%)

The distribution of dreaming scores in non-dreamers were mainly distributed at scores 0 and 1, while dreaming scores of dreamers were mainly scores 2 and 3. There were significant higher dreaming scores in dreamers compared with non-dreamers in the last 1 month (P=0.000).

Table 5. Dream Contents of the Patients in the Saline Group.

Dream contents	N (%)	Dream contents
Pleasant	39(60%)	
	13	With families and/or friends (feel happy)
	9	Shopping (car, clothes, or luxuries etc.)
	4	Signing a contract, admission to a graduate school
	4	Eating food or watching TV
	3	Singing, playing cards, or driving
	3	Playing in the parks
	1	Her husband becomes the Hong Kong CEO
	1	Pregnant
	1	Sex
Neutral	25(38%)	
	18	Working
	7	With families and/or friends (feel normal)
Unpleasant	1(2%)	
	1	Quarreling with her boyfriend

Among the 95 patients who dreamed in the first trial, 65 (68%) patients could recall their dream contents, with 39 (60%) patients had pleasant dreams, 25 (38%) patients had neutral dreams, and only 1 (2%) patient had an unpleasant dream.

Among the 95 women who dreamed in the saline group, 65 (68%) women could recall their dream contents, with 39 (60%) women had pleasant dreams, 25 (38%) women had neutral dreams, and only 1 (2%) patient had an unpleasant dream (Table 5).

There were total 34 (8.50%) and 3 (0.75%) patients receiving assisted?respiration and isoprenaline injection, respectively, during anesthesia in the two groups, which had no significant difference between the two groups. All the women were satisfied with the anesthesia procedure, and none of them had intra-operative awareness.

DISCUSSION

In the present study, the incidence of dreaming during propofol anesthesia was 47.5% , which was higher than the previously reported data (1-3). Two reasons might be responsible for this discrepancy. First, the participants included in the present study were only women. Studies find that woman is more likely to report dreams than man (3, 16). Second, we used simple propofol anesthesia without any adjuvant drugs, which has been associated with higher incidence of dreams with propofol maintenance compared with other anesthetics.

It has been reported that intramuscular scopolamine (2.5 μg/kg) prevents dreams or dream recalls in women during propofol–nitrous oxide anesthesia, whereas intramuscular atropine (10 μg/kg) does not have such effects (10). Penehyclidine, a new anticholinergic drug, acts both on muscarinic acetylcholine receptors and nicotinic acetylcholine receptors (17), and can easily pass through the blood-brain barrier (15). However, penehyclidine (0.01 mg/kg) did not prevent dreams or dreams recall. The main reason for this discrepancy with previous study may be that scopolamine could delay the REM sleep onset (10), however there was no report about whether penehyclidine had any effect on the REM sleep as far as I know; another reason may because of a shorter surgery duration the present study took. Still, this result was consistent with our finding that plasma concentrations of acetylcholine did not differ between dreamers and non-dreamers. On the other hand, plasma concentrations of acetylcholine were higher in women who could recall the dream contents, suggesting increased concentrations of acetylcholine enhance the memories of the dreaming contents. Indeed, dreaming is a conscious manifestation of sleep-dependent learning and memory reprocessing (11), which is enhanced by acetylcholine (18).

From the results of this present study, we could see that dreaming habit (scores in the last 1 month) are closely related to dreaming during propofol anesthesia. Furthermore, 68% of the dreamers could recall their dream contents, among which 60% of the dream contents were pleasant. A review carried out by Balasubramaniam and Park (19) suggested that anesthetics cause sexual dreams, especially for propofol and benzodiazepine. Surprisingly, there was only one patient reporting her dream was related to sex, the reason may be that Chinese women are traditional and thus are embarrassing to talk about sex.

Although studies suggested that dreaming patient was less satisfied with anesthetic care (3, 20), whereas other researchers found that dreaming had no effect or even improved women′ satisfaction (1, 2, 21). Consistently, our data indicated that the dreaming women were more pleasant, and satisfied with the anesthetic care.

In the present study, there were still some limitations. First, although the anesthesia and surgical procedure was carried out by the same team, there was no anesthesia depth monitoring, which cannot establish the relationship between depths of anesthesia and dreaming in the present study. Second, it is the best method to detect the concentration of central acetylcholine to decide its role, however it is difficult to detect, so we detected the peripheral acetylcholine. Third, we did not adopt other time-points to observe dreaming.

Our results demonstrated that penehyclidine cannot prevent the occurrence of dreaming in women during propofol anesthesia for minor gynecological surgery. The plasma concentrations of acetylcholine were higher in the women who could recall their dream contents compared with those did not recall their dreams.

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The authors have no potential conflicts of interest.

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