Original Research

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Propofol and Seizure-Like Activity

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ABSTRACT

Objective: In this study, seizure-like activity, injection pain, and the presence of dreams after propofol injection were assessed.

Material and Method: One hundred women scheduled for obstetric and gynecologic procedures were evaluated. Patients were anesthetized with 1 mg/kg propofol. Seizure-like activity was described as "only left arm." "started from left arm and involved whole body," or "face only," etc. The intensity of seizure-like activity (a brief and involuntary twitching of a muscle or a group of muscles) (SLA) was graded as 0=no SLA, 1=mild SLA – Local Group (only mild fasciculation involving face and/or distal upper and/or lower extremity, focal, or involving a part of the body) and 2=severe SLA – Generalized Group (marked movements involving limbs or trunk, generalized to the whole body). Operation time, additional doses of anesthetic given, time to eye-opening, the presence of dreams, injection-induced pain, and if present, seizure-like activity descriptions were analyzed.

Statistical analysis: Baseline characteristics were described with mean, standard deviation, rate, and frequency. The distribution of variables was controlled with Kolmogorov Smirnov test. Quantitative data were compared with ANOVA (Tukey), independent sample t test and Mann Whitney U test. Qualitative data were analyzed using Chi-square test and Fisher test. Statistical analysis was performed using SPSS 21.0 software. A value of $p<0.05$ was considered significant.

Results: The patients in the generalized seizure-like activity group were statistically significantly younger than those in the group with no seizures. Intrinsically, the additional dose in the generalized group was lower than in the group with no seizures and the localized seizure group. In the localized seizure group, there was statistically significant lower injection-induced pain compared to the no-seizure group.

Conclusion: Seizure-like activity could be related with the patients' age.

Keywords: Seizure-Like Activity, propofol, seizures, GABA, injection induced pain

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ÖZ

Propofol ve epileptiform aktivite

Amaç: Bu çalışmada propofol enjeksiyonunun epileptiform aktivite, enjeksiyon ağrısı, işlem sırasında rüya görmeyle olan ilişkisi incelendi.

Gereç ve Yöntem: Obstetrik ve jinekolojik nedenlerle opere olan 100 hasta çalışmaya alındı. Hastalar1 mg/kg propofol ile uyutuldu. Epileptiform aktivite olup olmadığı, olduğunda, örneğin tek kolda ya da yüzde lokalize olduğu veya tüm vücuda yayıldığı gibi gözlemler not edildi. Bu istemsiz hareketler 0=Yok, 1=Lokalize, 2=Generalize olarak sınıflandırıldı.Operasyon süresi, ilave doz ilaç yapılıp yapılmadığı, göz açma süresi, hastanın işlem sırasında rüya görüp görmediğini hatırlaması, enjeksiyon ağrısı olup olmadığı kaydedildi.

İstatistik: Temel değerlendirmede ortalama ve standart sapma kullanıldı.Değişkenlerin dağılımında Kolmogorov Smirnov testi, kantitatif değerlendirmelerde ANOVA (Tukey), independent t test ve Mann Whitney U, kalitatif değerlendirmelerde Ki-kare ve Fisher testi kullanıldı.

Bulgular: Generalize epileptiform aktivite görülen grup diğer gruplara göre daha gençti. Bu grupta ilave doz uygulaması daha az yapılmıştı. Lokalize epileptiform aktivite görülen grupta enjeksiyon ağrısı diğer gruplardan daha azdı.

Sonuç: Propofole bağlı epileptiform aktivite genç yaşta daha sıktır.

Anahtar kelimeler: Epileptiform aktivite, propofol, nöbet, GABA , enjeksiyon ağrısı

Introduction

Since 1986, propofol has been a popular anesthetic agent in the outpatient clinic setting due to its low level of side effects and short on- and off-times. Potential adverse effects include injection-induced pain, arterial hypotension, bradycardia, and respiratory depression (1-3). Central nervous system (CNS) side effects are rare, but some of them, such as generalized tonic-clonic convulsions or opisthotonus are very important complications after propofol injection (4-8). Involuntary muscle contractions not precisely confirmed with EEG changes are not rare in obstetric or gynecologic outpatient procedures, where propofol is especially preferred (9,10). In this study, we discuss seizure-like activity, injection pain, and the presence of dreams after propofol injection and its relation with involuntary muscle contractions.

Material and Methods

The study was performed at Bakirkoy Obstetric and Pediatric Education and Research Hospital and Istanbul ERH. After obtaining approval of the Ethics Committee of Istanbul ERH (number 712, dated September 18, 2015) and receiving patients' written consents, a total of 100 healthy women about to undergo gynecologic outpatient procedures were enrolled in the study. Their American Society of Anesthesiologists (ASA) physical status was I, ages were between 18 and 57 years, and body weights were in the range of 49-105 kg. Patients with diabetes mellitus, cigarette smokers, or those with a previous history of epilepsy, neurologic disease, febrile convulsion, or cranial injury were excluded; the remaining 88 patients were included into the study.

During the operation, all patients were monitored by noninvasive blood pressure measurement, pulse oximetry, and standard electrocardiogram. A standard dose of intravenous bolus of 1% propofol (Pofol, 200 mg/20 ml ampoule Dong Kook Pharm Co. Ltd. Korea) of 1 mg/kg was administered over a period of 60 s via a vein in the dorsum of the patient's hand. The patients were asked a standard question about the presence or absence of pain during injection. If the answer was "yes," the injection rate was reduced and isotonic sodium chloride was injected. If necessary, the patient's ventilation was assisted with mask and anesthesia circuit. After induction, the operation was immediately started. If there was spontaneous movement of the patient that hampered the execution of the procedure, 2-3 ml 1% propofol were added as bolus. During operation, about 200 mL isotonic sodium chloride solution were given intravenously and 20 IU of oxytocin intramuscularly if the surgeon requested.

The type of surgical procedure and the time from speculum insertion to removal were recorded. Seizure-like activities (SLA) such as brief involuntary twitching of a muscle or a muscle group were observed and their intensities (SLA) were graded as follows:

0=No SLA group,

1=mild SLA – Local group (only mild fasciculation involving face and/or distal upper and/or lower extremity, focal, or involved a part of the body) and

2=severe SLA – Generalized group (marked movements involving limbs or trunk, generalized to whole body).

Recovery time was described as the time from end of anesthesia to the time of the patient's ability to obey commands such as 'open your eyes' and to answer Yes/No to questions such as "Did you dream?". After each patient had become fully awake, she was transferred to the post-anesthesia care unit (PACU) for 2 h.

Statistical Analysis

Baseline characteristics were described as mean, standard deviation, rate and frequency. The distribution of variables was controlled with the Kolmogorov-Smirnov test. Quantitative data were compared with ANOVA (Tukey), independent sample t test, and Mann Whitney U test. Qualitative data was analyzed with Chi-square test and Fisher test. Statistical analysis was performed using SPSS 21.0 software. A value of $p<0.05$ was considered significant.

Results

None of the women developed excessive bleeding, and all of them were discharged in good health after 2 h. The characteristics of the study population are presented in Table 1. No hemodynamic alterations or severe respiratory depression were observed. Neither opisthotonus nor late epileptic activity were seen in PACU.

There was no statistically significant relation between the presence of seizure-like activity and its type with weight, the presence of dreams, or the time to eye-opening. The patients' age in the Generalized group was statistically significantly lower than in the No seizure group and the Local group. The additional dose in the Generalized group was lower than in the

Table 1: Patient and group dynamics of the study

	Subgroups	n		Mean±SD
Age				34.9±11.1
Weight				66.0±14.0
İnjection İnduced Pain	+	68	77.3%	
	-	20	22.7%	
Additional dose	+	59	67%	
	-	29	33%	
Seizure Like Activity	None	55	62.5%	
	Local	23	26.1%	
	Generalize	10	11.4%	
Dream	+	49	54.5%	
	-	39	45.5%	
Time to eye opening (min)				3.66±2.12
	<2 min.	41	46.6%	
	2 min. ≤	47	53.4%	
Operative time (min)				2.44±1.62
	<5 min	72	81.8%	
	5 min≤	16	18.2%	

Table 2: Seizure Like Activity Characteristics

		Seizure Like Activity						
		None		Local		Generalized		p
		Mean±SD/n-%		Mean±SD/n-%		Mean±SD/n-%		
Age		36.3±11.8		34.8±8.4		27.0±9.4		0.042
Weight		67.8±13.5		64.7±12.6		59±8.6		0.123
IIP	+	47	85.5%	13	56.5%	8	80%	0.020
	-	8	14.5%	10	43.5%	2	20%	
AD	+	39	70.9%	18	78.3%	2	20%	0.003
	-	16	29.1%	5	21.7%	8	80%	
Dream	+	29	52.7%	14	60.9%	5	50%	0.796
	-	25	47.3%	9	39.1%	5	50%	
TEO								0.900
(min)	<2 min	24	43.6%	12	52.2%	5	50%	0.768
	2 min≤	31	56.4%	11	47.8%	5	50%	

ANOVA(Tukey)/Ki-square test, p<0.05 Statistically significant, IIP:Injection induced pain, AD:Additional dose, TEO:Time to eye opening

No seizure group and the Local group. In the Local group, there was statistically significantly lower injection-induced pain than in the No seizure group and the Generalized group (Table 2).

Regarding the time to eye-opening being longer or shorter than two minutes, there was no statistically significant relation with age, weight, and the use of an additional dose of anesthetic.

The presence of dreams was not found statistically significantly related with age, weight, the use of an additional dose of anesthetic, injection-induced pain, operation time, and time to eye-opening.

Between the groups with operation time being longer or shorter than five minutes, respectively, the presence of injection-induced pain, the presence of dreams, and time to eye-opening did not differ statistically significantly. The use of an additional dose of anesthetic was statistically significantly higher in the group with a longer operation time.

Discussion

In the emergence of involuntary movements related to propofol, different mechanisms of action can play a role. The most important pathway is that of GABA-A (gamma-aminobutyric acid) receptors. Propofol potentiates GABA-mediated pre- and postsynaptic inhibition. These effects lead to an inhibition of the release of excitatory neurotransmitters. In the central nervous system, glycine is the major inhibitory neurotransmitter in the subcortical areas. Borgeat et al. showed that the drug has paradoxical effects at different doses; it is a glycine antagonist at low doses and a glycine agonist at higher doses (11) The

authors thought that this low-level glycine antagonism may be responsible for spontaneous involuntary movement. Another suggestion by Borgeat et al. was that propofol might stimulate the dopaminergic subcortical areas that cause myoclonic movements (11). Recent research suggests that propofol interacts with the endocannabinoid system. Patel showed that a cannabinoid receptor (CB1) antagonist reduced the action of propofol, while a CB1 receptor agonist resulted in the potentiation of its effects (12). Other theories of propofol toxicity are related with its metabolites. Van den Berg et al. suggested that the delayed neuro-excitatory effects of propofol may be related to the presence of its metabolized phenolic by-products (2,6-diisopropylphenol I, 4-quinol 1) (13).

In the literature, Wang et al. reported one epileptic patient who had an EEG-recorded and clinical grand mal seizure when they administered propofol 1 mg/kg; after giving an additional dose (0.5 mg/kg bolus), the seizure disappeared. In our study, when practitioners noticed the onset of a seizure or if the operation time became longer, an additional dose of anesthetic was administered. This maneuver changed the cumulative doses of propofol, thus the proconvulsant effect turn into an anticonvulsant property, similar to the results of Wang et al. (14).

But neither the time to eye-opening nor the presence of dreams changed. These results can be easily explained with propofol's quick on- and off-times.

Makela et al. indicated that most of the cases reported were women; hence, gender differences cannot be excluded (15-17). The authors tried to explain this observation assuming that "women may undergo more small operations and thus be exposed more to potential side effects of propofol" (18). Table 2 clearly shows that generalized seizures were seen in young women. In our opinion, these results may be explained in a dose-dependent manner; age may play an important role in seizure-like activities caused by propofol.

Conclusion

According to our results, propofol alone is a safe anesthetic drug for gynecologic and obstetric anesthesiology. Major concerns about its central nervous system adverse effect – seizure-like activity – could be related with the patients' age.

Contribution Categories	Name of Author
Development of study idea	Y.C.A., A.G.
Methodological design of the study	S.V., Y.C.A., T.A.
Data acquisition and processing	A.G., S.V.
Data analysis and interpretation	Y.C.A., A.K.S., S.V.
Literature review	Y.C.A., S.V., A.G.
Manuscript write-up	Y.C.A., T.A., A.G., A.K.S.
Manuscript review and revision	Y.C.A., T.A., A.K.S.

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