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Original Article

Does Exposure to General Anesthesia Have Worsening Effects on ADHD Treatment Efficiency?

Genel Anesteziye Maruziyetin DEHB Tedavi Etkinliği Üzerinde Olumsuz Etkileri Var mıdır?

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ABSTRACT

Objective: This study aimed to examine whether exposure to general anesthesia (GA) has impairing effects on the pharmacological treatment efficiency in Attention-Deficit/Hyperactivity Disorder (ADHD), and to compare symptoms of inattention (IN), hyperactivity/impulsivity (HI), Oppositional Defiant Disorder (ODD) and Conduct Disorder (CD) between those exposed, and non-exposed to GA.

Method: A total of 106 children with ADHD, aged 7 to 12 years who received pharmacological treatment with methylphenidate or atomoxetine for ADHD and followed up for 3 months were included in the study. An appropriate and standardized dose titration process was applied to all cases. Parents completed Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Disruptive Behavior Disorders Rating Scale questionnaire items at the beginning and at the end of the follow-up period. Information about the children's exposure to GA, frequency of exposures, and age they received GA was obtained from their parents.

Results: Both at the beginning and at the end of the follow-up period, exposure to GA, the age at the onset of exposure and the number of exposures were detected to have no significant effect on the decreases in any dimensional symptom counts (IN, HI, ODD and CD) (all $p>0.05$). However, the symptom counts of HI were found to be significantly higher in children with a history of exposure to GA, those with multiple exposures to GA and younger than 3 years of age than patients not exposed to GA (all $p<0.006$).

Conclusion: Although exposure to GA is associated with ADHD, neither exposure to GA itself, exposures at earlier ages and multiple exposures do not seem to weaken the response to pharmacological treatment of ADHD. However, particularly symptoms of HI may be more vulnerable to adverse effects of GA and related factors. These preliminary findings need to be confirmed by future studies.

Keywords: Exposure to general anesthesia, ADHD, treatment efficiency, children, environmental factors

ÖZ

Amaç: Bu çalışmanın amacı, genel anestezi (GA) maruziyetinin Dikkat Eksikliği Hiperaktivite Bozukluğu (DEHB) farmakolojik tedavisi etkinliği üzerinde olumsuz etkilerinin olup olmadığını incelemek ve GA maruziyeti olan ve olmayan olgular arasında Dikkat Eksikliği (DE), Hiperaktivite/Impulsivite (HI), Karşıt Olma Karşı Gelme Bozukluğu (KOKGB) ve Davranış Bozukluğu (DB) semptomlarını karşılaştırmaktır.

Yöntem: Yedi ila 12 yaşları arasındaki 106 DEHB'li çocuk DEHB tedavisi (metilfenidat veya atomoksetin) ile tedavi edilmiş ve 3 ay boyunca takip edilmiştir. Tüm olgulara uygun ve standart bir doz titrasyonu uygulanmıştır. Hem takibin başında hem de sonunda ebeveynler Ruhsal Bozuklukların Tanısal ve İstatistiksel El Kitabı, Dördüncü Baskı, Yıkıcı Davranış Bozuklukları Derecelendirme Ölçeği'ni doldurmuştur. Olguların GA alma durumu, kaç kez ve hangi yaşta GA aldıkları hakkında bilgiler ebeveynlerden alınmıştır.

Bulgular: İki dönem arasında, GA maruziyeti durumu, GA maruziyeti yaşı ve GA maruziyeti sayısının herhangi bir alt ölçek semptom sayısındaki (DE, HI, KOKGB, DB) azalmalar üzerinde anlamlı bir etkisi olmadığı tespit edilmiştir (tüm $p>0,05$). Ancak, HI semptom sayısının, GA'ya birden fazla maruz kalan ve üç yaşın altında GA'ya maruz çocuklarda, GA'ya maruz kalmayanlara göre anlamlı derecede daha yüksek olduğu saptanmıştır (tüm $p<0,006$).

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Sonuç: GA maruziyetinin DEHB ile ilişkisi olmasına rağmen, GA'ya maruz kalmanın kendisi, erken yaşlarda maruz kalma ve de birden fazla kez maruz kalma DEHB farmakolojik tedavi yanıtını zayıflatıyor gibi görünmemektedir. Ancak, özellikle HI semptomları GA'ya ve ilişkili faktörlere karşı daha duyarlı olabilir. Bu ön bulgular gelecekteki çalışmalarla mutlaka tekrarlanmalı ve doğrulanmalıdır.

Anahtar kelimeler: Genel anestezi maruziyeti, DEHB, tedavi etkinliği, çocuklar, çevresel faktörler

INTRODUCTION

Attention-Deficit/Hyperactivity Disorder (ADHD) is a childhood-onset neurodevelopmental disorder with the symptoms of Inattention (IN), hyperactivity/impulsivity (HI),[1]. The etiology of ADHD has always been an interesting field of research. Although ADHD has a high level of heritability and multiple genes play a substantial role on its pathogenesis, growing evidence suggests that, environmental factors have also a non-negligible role on its etiopathogenesis. It has been reported that environmental factors exert their effects either independently of genetic factors, or through gene-environment interaction or epigenetic mechanisms[2]. Despite the existing evidence indicating associations with the development of ADHD, and an environmental factor ie. Exposure to general anesthesia (GA), its developmental process at early ages is still debatable.

GA is described as a state of unconsciousness and painlessness maintained during unpleasant and painful surgical and invasive interventions. Experimental animal studiessuggestthatanestheticagents,especiallyN-methyl D-aspartate (NMDA) antagonists and gamma-amino butyric acid (GABA) agonists exert long-term adverse effects on developing brain by provoking widespread apoptotic neurodegeneration and emergence of deficits in hippocampal synaptic function[3]. Growing evidence claims that multiple rather than a single exposure to GA before 2 or 3 years of age may facilitate the development of behavioral-learning difficulties and also ADHD[4,5]. On the other hand, some studies have not detected a possible association between exposure to GA and later development of ADHD[6,7]. Supportively, an animal study suggests that early exposure to sevoflurane does not cause impairments in attentional processes in rats[8]. In fact, the literature findings are contradictory and do not indicate the presence of an explicit relationship between exposure to GA and ADHD. Indeed, a recent meta-analysis of cohort studies documents that the degree of association between exposure to GA and ADHD depends on the dose of the general anesthetic agent and duration of GA[9].

Given the hypothesis that general anesthetic agents contribute to the development of ADHD in the long term by damaging neural structures, the question of whether exposures to GA at an early age complicate the pharmacological treatment of ADHD conveys critical importance. A recent study has investigated the association between exposure to GA and subsequent use of medications for the treatment of ADHD and found that children only exposed to GA were 37% times more likely to need subsequent and persistent drug treatment for ADHD when compared to non-exposed children[10]. Although this study revealed that children exposed to GA persistently require drug treatment for ADHD, the dilemma whether GA exerts adverse effects on the pharmacological treatment process of ADHD has not been clearly elucidated yet. Moreover, does early exposure to GA have a negative effect on psychotropic treatment efficiency in terms of oppositional defiant disorder (ODD) and conduct disorder (CD) symptoms-that often accompany ADHD- as well as ADHD symptoms? To our knowledge,these conflicting issues have not been resolved yet.

To fulfill these gaps, we primarily aimed to investigate if exposure to GA per se , the age of exposure to GA and the number of exposures have complicating effects on drug treatment efficiency of ADHD, ODD and CD symptoms. We secondarily aimed to compare ADHD, ODD and CD symptoms of children with ADHD by categorizing them in terms of exposure to GA (if any) , age of exposure to GA and the number of exposures.

MATERIALS and METHODS

Participants

This was a multi-centered study conducted in child and adolescent psychiatry outpatient clinics of Ege University and University of Health Sciences Turkey, Dr. Behçet Uz Training and Research Hospital of Pediatrics. The sample was derived from medical files of both hospitals which are located in the third-largest Turkish city of İzmir. The ethics committee approval for this study was obtained from University of Health Sciences Turkey, Dr. Behçet Uz Training and Research Hospital of Pediatrics (approval number: 405, dated: 18.06.2020). Before recruiting to the study, the study participants and their parents were informed of the study protocol , and written informed consent was obtained from the parents/guardians of the children.

According to the power analysis performed for the study, the minimum sample size was calculated to be 100 children, with a 12,4% frequency of ADHD, a 4% variance level, and a 95% confidence level. Initially, there were 110 registered participants. Four participants dropped out during the study period, primarily due to scheduling conflicts faced by their families and their unwillingness to participate in the study. These drop-outs were random and unrelated to clinical or demographic variables, minimizing the risk of selection bias. Therefore, final sample consisted of 106 participants. Participants from each center were selected from among patients who met the study inclusion criteria, and had a designated outpatient clinic application order on the specified days.

Among 7-12 year-old patients not receiving any medication for at least one year before their first admissions to the clinic, those having a clinically determined normal cognitive capacity with a diagnosis of ADHD without any comorbid bipolar disorder, psychotic disorder, or autism spectrum disorder were included in the study.

Procedures and Materials

Participants for the current study were determined at their first admissions to the child and adolescent psychiatry outpatient clinic. At the first admission, clinicians gathered information regarding children's demographic profile, psychopathologies, their previous exposures to GA (if any), the age at which they had received GA, and surgeries they had undergone. The clinicians performed a mental status examination to make an accurate diagnosis based on the criteria established by both Fifth Edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) and the Schedule for Affective Disorders and Schizophrenia for School-Age Children Present and Lifetime Version, which is a commonly used, and conducted a semi-structured diagnostic interview to scan present and previous psychiatric diagnoses[11]. The validity and reliability study of its Turkish version was realized in 2004[12].

Patients were followed up for 3 months. Both at the beginning (T1) and at the end (T2), of the follow-up period, parents completed Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) Disruptive Behavior Disorders Rating Scale-IV (ADHD-RS-IV). ADHD-RS-IV is an assessment tool using the DSM-IV diagnostic criteria for symptoms of disruptive behavior disorders[13]. The scale is comprised of 41 items. Nine items inquire about IN; but also contains items inquiring HI (n=9); ODD (n=8), and CD (n=15). The scale is rated by a 4-point Likert-type scale with scores ranging from 0 to 3 (ie. 0= not at all; 1= just a little; 2= much; and 3= very much). If a case gets 2 or 3 points on any symptom item, it is considered that the symptom is present in the case. In 2001, the study on the reliability and validity of the Turkish version of the scale was performed[14]. In this study, pre- and post-treatment sub-dimensional symptom counts of the samples were compared.

To provide optimal standardization in pharmacological treatment procedures, psychostimulant treatment was initiated at doses appropriate for the age and weight of the participants, as indicated in the guidelines[15]. For immediate release-methylphenidate (MPH) users, MPH dose was started at 5-10 mg/d and increased by 5-10 mg/d every 2 weeks, whereas for extended release-MPH users initial daily MPH dose of 10-18 mg was increased up to 30-36 mg within 3 months. For atomoxetine (ATX) users, initial ATX dose of 0.5 mg/kg/d was increased to 1.2 mg/kg/d every 2 weeks.

Statistical Analysis

The resulting data were transferred into 26th version of the SPSS. A p-value below 0.05 was considered as statistically significant. To compare categorical variables, Pearson's chi-square test was performed. Fitness of variables to normal distribution was evaluated via Kolmogorov-Smirnov test for continuous variables. For intergroup comparisons of continuous variables with normal, and non-normal distribution independent samples t-test, and Mann-Whitney U test were used, respectively.

The repeated measures analysis of variance (ANOVA) test was used to compare the scale scores of the same sample estimated at two different time periods. IN, HI, ODD and CD dimensional symptom counts at both T1 and T2 time periods were determined as within-subject factors. Exposure to GA (if any), the number of exposures to GA and the age at which GA was received were determined as between-subject factors in separate models. After potentially confounding factors that may affect dimensional symptom counts were eliminated, gender was determined as a covariate in the models in which 'IN symptom count was determined as a within-subject factor. In each between-subject model, the main effects of between-subject factors and (if present) covariates were analyzed. Type III sum of squares were used for between-subject tests. If the between-subject factor is a categorical variable consisting of more than two categories, pairwise main effect comparisons among the categories were performed using Bonferonni

correction. When sphericity assumption could not be provided in Mauchly's test of sphericity, Greenhouse-Geisser test, which measures within-subject effects, was taken into consideration.

RESULTS

The final sample was comprised 106 cases, including 82 (77.4%) boys, and 24 (22.6%) girls. The mean age of the study participants was 9.67±1.67 years and 41.5% (n=44) of them had at least one comorbidity in addition to ADHD, while 58 (54.6%) patients had previously received GA. All the cases used stimulant and/or non-stimulant medications for the treatment of ADHD (Table 1).

Our male study population received GA at significantly higher proportion than girls (χ^2=11.057; df=1; p=0.001). The number of exposures to GA were significantly higher in boys than in girls (χ^2=12.784; df=2; p=0.002). Boys also received GA at an significantly earlier age than girls (χ^2=13.069; df=2; p=0.001). Among the cases who had received GA, the most common surgery types were circumcision (n=37; 63.7%) and adenoidectomy (n=18; 31.0%). Besides, age did not significantly differ between the cases with and without exposure to GA (p=0.124).

Mean IN symptom counts at T1 were significantly different between male and female (t=-2.271, p=0.025) participants, however other dimensional symptom counts estimated at T1 and T2 were not significantly different between both genders (all p>0.05). Any dimensional symptom counts were not significantly associated with age (all p>0.05). Thus, gender was determined as a confounding factor for IN symptom counts.

The Effect of GA Exposure Status

Symptom counts related to the sub-dimensions of IN, HI, ODD and CD at T1 and T2 time periods were compared. In all ADHD sub-dimensions and ODD and CD dimensions, symptom counts of the sample significantly reduced within 3 months [all p<0.01; (Table 2)]. However, GA exposure status had no significant effect on the decreases in any dimensional symptom counts [all p>0.05; (Table 2)]. At both T1 and T2 periods, IN and HI symptom counts of cases exposed to GA were significantly greater than those of the non-exposed cases (F=4.289, p=0.041; F=9.537, p=0.003, respectively). However, after making adjustments for gender, significant difference regarding IN symptom counts between the cases with and without exposure to GA was eliminated.

Table 1. Descriptive statistics of participants

	n	%
Gender		
Female	24	22.6
Male	82	77.4
Diagnoses		
ADHD	62	58.5
ADHD + SLD	11	10.3
ADHD + ODD	21	19.8
ADHD + AD	1	0.9
ADHD + SD	1	0.9
ADHD + SLD + ODD	2	1.9
ADHD + SLD + SD	2	1.9
ADHD + ODD + CD	2	1.9
ADHD + ODD + MDD	4	3.8
Medications		
MPH	76	71.7
ATX	6	5.7
MPH + AP	16	15.1
MPH + SSRI	2	1.9
MPH + ATX	2	1.9
ATX + AP	1	0.9
MPH + AP + SSRI	3	2.8
GAE status		
No	48	45.3
Yes	58	54.6
The age at exposure to GA		
< 3 years	21	19.8
> 3 years	37	34.9
Not exposed to GA	48	45.3
The number of exposures to GA		
None	48	45.3
Once	39	36.8
>2	19	17.9
Types of surgeries performed		
Circumcision	37	63.7
Adenoidectomy	18	31.0
Tonsillectomy	7	12.0
Inguinal hernia	6	10.3
Others	15	25.5
	M	SD
Age	9.67	1.67

Values are shown as number (n) and percentage (%) or mean (M) and standard deviation (SD). ADHD: Attention-Deficit/Hyperactivity Disorder, SLD: Specific Learning Disability, ODD: Oppositional Defiant Disorder, AD: Anxiety Disorder, SD: Speech Disorder, CD: Conduct Disorder, MDD: Major Depressive Disorder, MPH: Methylphenidate, ATX: Atomoxetine, AP: Antipsychotics, SSRI: Serotonin-specific reuptake inhibitor, GA: General anesthesia

Table 2. The effects of exposure to general anesthesia on changes in symptom coumts in IN, HI, ODD and CD dimensions within two periods

Dimension	Exposure to GA	Symptom counts				Tests of within-subjects effects				Tests of between subjects effects	
		T1		T2		Time		Time * GAE status			
		M	SD	M	SD	F	p*	F	p*	F	p
IN	No	4.89	2.56	2.16	2.65	8.158	**0.005**†	0.189	0.664†	2.077	0.153†
	Yes	5.70	2.82	3.10	3.04						
HI	No	3.62	2.95	1.70	2.27	31.138	**<0.001**	0.007	0.936	9.537	**0.003**
	Yes	4.93	3.10	3.06	2.78						
ODD	No	2.10	2.40	0.89	1.43	15.886	**<0.001**	0.641	0.425	2.918	0.091
	Yes	2.49	2.36	1.68	2.26						
CD	No	0.32	0.92	0.06	0.32	11.109	**<0.001**	0.120	0.730	0.106	0.745
	Yes	0.39	0.98	0.07	0.32						

Bold values mark statistically significant differences. Values are shown as mean (M) and standard deviation (SD).

*Repeated measures test was performed. Since sphericity criteria were not met, the assessments were made according to Greenhouse-Geisser test. †The effects were calculated after controlling for gender. IN: Inattention, HI: Hyperactivity-Impulsivity, ODD: Oppositional Defiant Disorder, CD: Conduct Disorder, GA: General anesthesia

The Effect of the Age at Exposure to GA

When the interaction of the age at exposure to GA and time interval between T1 and T2 was applied to the repeated measures ANOVA model, patient's age at exposure to GA had no significant effect on the reductions in any dimensional symptom count [all p>0.05; (Table 3)]. The symptom counts of almost all ADHD, ODD and CD dimensions in both T1 and T2 periods were found to be highest in patients exposed to GA under 3 years of age when compared with older patients, and lowest in patients who did not receive any GA. However, the only statistically significant change was detected in the symptom counts of HI dimension [F=5.738, p=0.004; see (Table 3)]. The children exposed to GA under 3 years of age had significantly higher HI symptom counts relative to the non-exposed children (p=0.005).

The Effect of the Number of Exposures to GA

When the interaction of the number of exposures to GA and time interval between T1 and T2 was applied to the repeated measures ANOVA model, the number of exposures had no significant effect on the decreases in any dimensional symptom count [all p>0.05; (Table 4)]. Participants exposed to GA for two or more times had the highest symptom counts, compared to those with single exposures, and patients without exposure to GA had the lowest symptom counts on nearly all ADHD, ODD and CD dimensions in both T1 and T2 time periods. Similarly the only statistically significant difference was observed in HI dimension (F=5.995, p=0.003). The cases with multiple exposures to GA had significantly higher HI symptom counts than those without [p=0.004; (Table 4)].

DISCUSSION

The present study has documented that neither exposure to GA itself, nor the age at exposure to GA or the number of exposures to GA had significantly worsening effects on efficiency of the drug treatment for ADHD, ODD and CD symptoms. It was also found that, among all the symptom dimensions, particularly hyperactive-impulsive symptoms were significantly more frequently detected in those who categorically had been exposed to GA, those who had exposures to GA more than 2 times, and those who had received GA before the age of 3 years compared to those who had not.

Deficits in prefrontal cortex (PFC) which regulates attention, executive functions, behaviors, and emotions play a substantial role in the neurobiology of ADHD[16]. Psychostimulants (MPH and amphetamine) work as reuptake inhibitors by inhibiting dopamine and norepinephrine transporters and increasing neurotransmission in the PFC and corpus striatum[17] while ATX inhibits norepinephrine reuptake in all brain regions and dopamine reuptake selectively in the PFC[18]. Whereas the histopathological changes caused by GA in the animal brain are listed as apoptosis, pathological neurogenesis, and dendritic formation[19]. The findings of our study indicate that even earlier exposure to GA and receiving GA multiple times might

Table 3. The effects of the age of the patients at the time of exposure to general anesthesia on symptom counts in IN, HI, ODD and CD dimensions within two periods

Dimension	The age of GA	Symptom counts				Pairwise comparisons among age categories (p-values**)			Tests of within-subjects effects				Tests of between subjects effects	
		T1		T2					Time		Time* The age of GA			
		M	SD	M	SD	1 vs. 2	1 vs. 3	2 vs. 3	F	p*	F	p*	F	p
IN	Below 3 years	5.80	2.97	3.28	3.30	1.000	0.230	0.294	6.249	**0.014**†	0.125	0.883†	1.038	0.358†
	Above 3 years	5.64	2.77	3.00	2.93									
	Not exposed to GA	4.89	2.56	2.16	2.65									
HI	< 3 years	6.09	3.19	2.95	3.04	0.527	**0.005**	0.102	34.538	**<0.001**	2.324	0.103	5.738	**0.004**
	>3 years	4.27	2.89	3.13	2.66									
	Not exposed to GA	3.62	2.95	1.70	2.27									
ODD	<3 years	2.95	2.56	2.10	2.78	0.497	0.088	1.000	12.339	**0.001**	0.322	0.726	2.447	0.092
	> 3 years	2.24	2.24	1.45	1.92									
	Not exposed to GA	2.10	2.40	0.89	1.43									
CD	<3 years	0.35	0.81	0.05	0.22	0.946	1.000	0.902	10.321	**0.002**	0.069	0.934	0.103	0.902
	>3 years	0.41	1.07	0.08	0.36									
	Not exposed to GA	0.32	0.92	0.06	0.32									

Bold values mark statistically significant differences. Numbers indicated in the columns of pairwise comparisons refer to the paiens that did not receive general anesthesia (1), or received anesthesia twice (2) or more than two times (3), respectively. *Repeated measures test was performed. Since sphericity criteria were not met, the assessments were made acclording to Greenhouse-Geisser test results. **Adjustment for multiple comparisons was performed via Bonferonni correction. †The effects were calculated after adjustments were made for the gender of the patients. M: Mean, SD: Standard deviation, IN: Inattention, HI: Hyperactivity-Impulsivity, ODD: Oppositional Defiant Disorder, CD: Conduct Disorder, GA: General anesthesia

not cause a significant attenuation in response to drug treatment of ADHD.

This condition reveals that despite the micro and macro morphological changes in the brain caused by GA, psychostimulants and ATX might not be affected by these structural deficits and continue to exert their effects mostly through the dopamine/norepinephrine transporter system The general anesthetic agents, and usually GABA agonists (e.g., volatile anesthetics, midazolam, and propofol) or NMDA antagonists (e.g., ketamine, isoflurane, and nitrous oxide), -which affect the brain through glutamate/GABA system supposed to have associations with behavioral deficits and cognitive abnormalities by leading to the development of neurotoxicity[19]. However, the targets for psychostimulants and ATX are dopamine/norepinephrine reuptake systems. The differences in target systems might explain the mechanism by which ADHD drugs might continue to show their own mechanism of action without being adversely affected by the neurotoxicity of general anesthetics.

Experimental animal studies also support the fact that psychostimulants ameliorate hyperactivity symptoms of the animals whose brains had been exposed to neural injury by general anesthetics. A study reported that hyperactivity symptoms of neonatal rodents exposed to NMDA antagonists were reversed with the use of dextroamphetamine[20]. Another study has documented that 6-hydroxydopamine-induced hyperactivity in neonates was improved by the acute use of dextroamphetamine[21]. Although animal studies cannot be extrapolated to human beings, these findings indicate that exposure to GA does not irreversibly impair efficiency of psychostimulant treatment.

Another reason for non-significant effects of GA on treatment efficiency may be related to the higher effectiveness of drugs used for the treatment of ADHD. There is a wide consensus that psychostimulants have the best treatment efficiency in treating ADHD. A network meta-analysis has indicated that the estimated effect sizes of MPH and amphetamine are greater than 0.8, while of ATX is between 0.5 and 0.8[22]. Given the high effect sizes and considering the relationship between ADHD and exposure to GA

Table 4. The effects of the number of exposures to general anesthesia on symptom counts in IN, HI, ODD and CD dimensions both at the beginning and at the end of the follow-up period

Dimension	The number of exposures to general anesthesia	Symptom counts				Pairwise comparisons among age categories (p values**)			Tests of within-subjects effects				Tests of between subjects effects	
		T1		T2					Time		Time* The number of exposures to GA			
		M	SD	M	SD	1 vs. 2	1 vs. 3	2 vs. 3	F	p*	F	p*	F	p
IN	None	4.89	2.56	2.16	2.65	0.432	0.103	1.000	7.038	**0.009**†	0.177	0.838†	1.303	0.276†
	Once	5.43	2.92	3.00	2.75									
	≥2	6.26	2.57	3.31	3.65									
HI	None	3.62	2.95	1.70	2.27	0.098	**0.004**	0.389	31.308	**<0.001**	0.908	0.407	5.995	**0.003**
	Once	4.41	3.15	2.97	2.55									
	≥2	6.00	2.76	3.26	3.26									
ODD	None	2.10	2.40	0.89	1.43	0.797	0.161	0.891	12.565	**0.001**	0.391	0.677	2.010	0.139
	Once	2.28	2.37	1.56	2.17									
	≥2	2.94	2.33	1.94	2.48									
CD	None	0.32	0.92	0.06	0.32	1.000	1.000	1.000	13.324	**<0.001**	1.012	0.367	0.139	0.870
	Once	0.31	0.87	0.10	0.38									
	≥2	0.55	1.19	0.00	0.00									

Bold numbers mark statistically significant differences. Numbers indicated in the columns of pairwise comparisons refer to the paiens that did not receive general anesthesia (1), or received anesthesia twice (2) or more than two times (3), respectively. *Repeated measures test was performed. Since sphericity criteria were not met, the assessments were made acclording to Greenhouse-Geisser test results. **Adjustment for multiple comparisons was performed via Bonferonni correction test. †The effects were calculated after adjustments were made for the gender of the patients. M: Mean, SD: Standard deviation, IN: Inattention, HI: Hyperactivity-Impulsivity, ODD: Oppositional Defiant Disorder, CD: Conduct Disorder

is dose-, developmental stage-, duration- and repetition-dependent[4,9], it is not surprising that a negative effect of receiving GA on the ADHD treatment response has not been determined in our study.

The findings also indicate that the improvements in the symptomatology of ODD, CD and also ADHD provided by ADHD medication were not adversely affected by generasl anesthesia-related factors. The etiological roots of disruptive behavioral disorders such as ODD and CD more likely stem from psychological, social issues and intra-familial conflicts[23] and less likely depend on neurobiological underpinnings when compared to ADHD. This might be a reason why the anesthetic agents had not adversely affected improvements in the symptomatology of ODD/CD. To our knowledge, these are the first estimates documenting that exposure to GA and related features have no significant effect leading to restrictions in both ADHD treatment response and improvements in the symptomatology of ODD/CD.

Another important advantage of our study is the comparison of HI symptoms in pediatric patients with ADHD. Existing studies are usually case-control studies and aim to comparatively evaluate the risk of ADHD in later life in children that had been exposed and not exposed to GA. Tsai et al.[4] concluded that children exposed to GA on more than one occasion or below 3 years of age had an increased risk for the development of ADHD. Sprung et al.[5] also found an association between repeated procedures requiring GA performed before 2 years of age and a later development of ADHD. However, the current study sample consisted of ADHD subjects, not of controls. Since the methodology was determined in this way, it was concluded that HI symptoms were more frequently detected in children with ADHD who had been exposed to GA categorically, who had multiple exposures to GA or received GA before 3 years of age compared to those with ADHD not exposed to GA. Although these outcomes are consistent with the literature, they

also expand literature knowledge by suggesting that exposure to GA at earlier ages and multiple exposures might increase especially the severity of HI symptoms in children with ADHD even in comparisons among themselves. A study documented that inguinal hernia repair had a significant association with ADHD. Supportive of our study results, it was suggested that this relationship may arise since inguinal hernia repair, which requires GA, is usually performed at very early ages[24].

In our study, in addition to HI symptoms, IN, ODD and CD symptoms were also highly, but not statistically significantly more frequent in those who were exposed to GA before the age of 3 and those experienced multiple exposeures to GA. HI symptoms might be more vulnerable to environmental factors such as GA compared to other symptom dimensions. In a study, elevated HI symptoms but not IN symptoms were associated with surgical history of the patients[24]. Although the effects of GA on ADHD symptoms were not directly measured in that study, the positive association between surgery and increased frequency of HI symptoms are in line with the current findings. Supportively, it was established that propofol induces hyperactivity in adolescent rats through its neurotoxic effects on the neurons of the corpus striatum, thalamus and medial PFC[25].

Strengths and Limitations of the Study

As one of the strengths of our research, this study has focused on the possible effects of GA and related factors on the efficiency of drug treatment of ADHD which has been investigated for the first time in the literature. Besides, whether or not GA has adversely affected the treatment efficiency against ODD, CD as well as ADHD symptoms has been evaluated for the first time. Apart from that, symptomatological changes at the beginning, and end of the follow-up period could be observed accurately and objectively.

Study Limitations

However, some limitations of our study must be taken into consideration. Small sample size restricted the generalizability of the findings to the community. Besides, the sample had heterogenous characteristics in terms of different comorbidities and medication regimens. It is important to consider the influence of comorbidities and diverse medication regimens when interpreting the findings. For instance, comorbid ODD or CD may exacerbate symptom severity, potentially impacting the treatment response. A Turkish study suggested that the parents, and the teachers of the pediatric patients with ADHD + ODD reported IN and HI symptoms at a significantly higher rate when compared to those with only ADHD[26]. Therefore, comorbid conditions may constitute a handicap in terms of the reliability of the findings. In addition, although administration of medication for each participant was tried to be standardized as much as possible, additional medications other than psychostimulants and ATX and additional comorbidities other than ADHD might have prevented us from observing the unique effects of exposure to GA on ADHD treatment efficiency. For instance, it was reported that atypical antipsychotics such as risperidone had improved HI symptoms in ADHD + ODD/CD patients[27]. Furthermore, certain selective serotonin re-uptake inhibitors were also shown to control IN or HI symptoms of ADHD[28]. Hence, the outcomes of this study might not reflect the unique effects of exposure to GA on pharmacological efficiency of specific drugs used for the treatment of ADHD in children using multiple psychotropic drugs. Finally, since we could not know the duration of exposure to GA for each participant, the effect of duration of exposure to GA ob treatment efficiency could not be estimated.

CONCLUSION

Although the association between exposure to GA and ADHD has not been fully clarified, growing evidence indicates the presence of such a relationship. However, neither exposure to GA itself, nor earlier ages to exposures or multiple exposures do not seem to attenuate pharmacological treatment response to ADHD. Although general anesthetics cause neurodegeneration in the developing brain, the pharmacological effects of psychostimulants, and ATX might not be altered by these structural deficits and these drugs continue to show their own mechanism of action without being adversely affected by the neurotoxicity of general anesthetic agents. Besides, exposure to GA before 3 years of age and more than one exposure might even comparatively increase especially the severity of HI symptoms in children with ADHD. This condition indicates that HI symptoms may be more vulnerable to the adverse effects of GA and related factors. As a clinical implication, fortunately exposure to GA and anesthesia-related factors had not complicated the treatment process of ADHD. Nonetheless, this study reveals preliminary findings and larger scale future studies performed with homogenous samples should replicate the current findings.

Ethics

Ethics Committee Approval: The ethics committee approval for this study was obtained from University of Health Sciences Turkey, Dr. Behçet Uz Training and Research Hospital of Pediatrics (approval number: 405, dated: 18.06.2020).

Informed Consent: The participants and their parents were informed of the study and written inform consent was obtained from the parents/guardians of the children.

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Footnotes

Author Contributions

Surgical and Medical Practices: Concept: A.E.Y., S.F.D., S.G.S., E.S.E., Design: A.E.Y., S.F.D., S.G.S., E.S.E., Data Collection or Processing: Z.İ.E., A.T., S.F.D., Analysis or Interpretation: A.T., S.F.D., Literature Search: A.E.Y., A.T., S.G.S., Writing: A.E.Y., A.T., E.S.E.

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