Journal of Current Research in Oral Surgery
2025, Volume 5, Page No: 60-69
Copyright CC BY-NC-SA 4.0
Available online at: www.tsdp.net

ISSN: 3062-3480

Original Article

Temporal Patterns of Behavioral Effects Following General Anesthesia in Autistic and Neurotypical Pediatric Dental Patients

Martin P. Novak[1]*, Tesfaye M. Bekele[1], Marco R. Bianchi[1]

[1]Department of Oral Surgery, Faculty of Medicine, Comenius University, Bratislava, Slovakia.

***E-mail** ✉ martin.novak@outlook.com

Received: 18 October 2024; **Revised:** 07 January 2025; **Accepted:** 12 January 2025

ABSTRACT

This study aimed to examine differences in the occurrence of short- and long-term adverse behavioral outcomes following general anesthesia (GA) between neurotypical children and those with moderate to severe autism spectrum disorder (ASD). A total of 40 neurotypical children and 37 children with ASD, aged 3–17 years, who underwent GA for dental procedures were included. Anesthesia records were analyzed, and parental telephone surveys evaluated changes in activity levels, sleep patterns, gastrointestinal symptoms, central nervous system manifestations, and respiratory issues. Assessments were conducted at 8 hours, 24 hours, and 3 months postoperatively. Within the first 8 hours post-surgery, 455 adverse behavioral events were reported. Children with ASD exhibited significantly higher rates of gait instability ($P = 0.016$) and nausea ($P = 0.030$), whereas neurotypical children more frequently displayed snoring during the return journey ($P = 0.036$) and referenced the dental procedure verbally ($P = 0.027$). At 3 months post-discharge, concerning behavioral changes were noted in six children with ASD, compared with none in the neurotypical group ($P = 0.008$). Overall, the incidence of adverse behavioral effects declined significantly between 8 and 24 hours. The majority of postoperative behavioral disturbances manifest within 8 hours of surgery. While children with ASD may experience potential long-term adverse behavioral effects from GA, such occurrences are infrequent and typically transient.

Keywords: Autism spectrum disorder (ASD), General anesthesia, Behavioral outcomes, Long-term follow-up, Short-term follow-up

How to Cite This Article: Novak MP, Bekele TM, Bianchi MR. Temporal Patterns of Behavioral Effects Following General Anesthesia in Autistic and Neurotypical Pediatric Dental Patients. J Curr Res Oral Surg. 2025;5:60-9. https://doi.org/10.51847/BsRqEYWeJW

Introduction

Effective management of child behavior is a cornerstone of pediatric dental care. When required, oral sedation serves as a useful tool. However, in cases where standard guidance techniques and oral sedation fail to secure adequate cooperation for dental procedures, general anesthesia (GA) often becomes the preferred approach. This is particularly true for very young patients or those with significant medical conditions who need comprehensive or invasive treatments.

Extensive literature exists on the post-sedation behavioral changes in typically developing children receiving oral sedatives, yet far less is known about the impacts of GA. For instance, McCormack and colleagues noted that most unfavorable behaviors after oral sedation emerged within the initial 8 hours following discharge [1]. Similarly, Ritwik and colleagues identified lingering effects—such as irritability, nausea, and heightened sleepiness—lasting up to 24 hours [2]. Findings from oral sedation research could help guide explorations into potential parallels with GA.

In contrast, only isolated case reports describe behavioral alterations in children with autism spectrum disorder (ASD) after GA-assisted dental care [3]. One report by Matton *et al*. highlighted two cases involving children with co-occurring ASD and attention deficit hyperactivity disorder (ADHD) who displayed

© 2025 Journal of Current Research in Oral Surgery

postoperative issues like agitation, social withdrawal, appetite reduction, sleep disturbances, and excessive daytime fatigue after oral surgery under GA [3]. Broader estimates from Becker *et al.* suggest that 10–20% of patients in hospital settings may encounter negative responses to anesthetics [4]. As these insights stem from case reports alone, a well-designed prospective cohort study is needed to better understand GA's behavioral implications in this group.

Preclinical studies in animals have fueled worries about early anesthesia exposure potentially causing lasting neurocognitive harm. Domains such as learning, memory, attention, and motor abilities may be compromised [5-7]. Research on rodents and primates has demonstrated anesthesia-induced cell death in neurons, especially within cortical areas [8-12]. Agents like ketamine, propofol, and isoflurane—known for blocking NMDA receptors or enhancing GABA activity—have been implicated in brain degeneration that might contribute to neurodevelopmental issues, including ADHD and ASD [7].

Heightened awareness of these risks in pediatric GA has led to dedicated research efforts. The SmartTots initiative, a joint venture of the International Anesthesia Research Society and the FDA, supports investigations into early anesthesia's effects on children's cognitive growth [10, 13, 14]. Complementing this, the multicenter Pediatric Anesthesia Neurodevelopment Assessment (PANDA) study examines long-term neurodevelopmental outcomes in young GA recipients [15].

Evidence regarding GA's influence on pediatric behavior and cognition remains inconsistent. Factors like preoperative distress, discomfort, or prolonged fasting appear to exacerbate postoperative regression [3]. One study by Camm *et al*. indicated greater stress among children treated dentally under GA [16]. Furthermore, research by Bakri *et al*. linked multiple GA exposures to elevated chances of anxiety, depression, ADHD, and sleep issues, without corresponding increases in aggression, withdrawal, tiredness, or pain [5].

The present study seeks to investigate and contrast the occurrence of both immediate and delayed negative behavioral changes following GA in typically developing children compared to those with moderate-to-severe autism. Assessments of any behavioral shifts will occur during GA delivery and at intervals of 8 hours, 24 hours, and 3 months post-discharge.

Materials and Methods

This prospective study received approval from the Loma Linda University Institutional Review Board (IRB #5180244). Participants were recruited from the Koppel Special Care Dentistry Surgery Center. Written informed consent was secured from each patient's legal guardian during the preoperative visit.

A total of 77 children aged 3 to 17 years were enrolled, with no exclusions based on gender, race, or ethnicity. All participants required full-mouth dental rehabilitation under general anesthesia (GA) because of uncooperative behavior that prevented routine dental care in a standard clinic setting. The sample also included children for whom oral sedation had proven ineffective or was deemed unsuitable, leading to referral to the special care center.

The cohort was divided into two groups: Group 1 comprised 40 typically developing healthy children serving as controls, while Group 2 included 37 children diagnosed with moderate to severe autism spectrum disorder (ASD) and no additional medical comorbidities. ASD severity in Group 2 corresponded to levels 2 and 3 according to the Diagnostic and Statistical Manual of Mental Disorders [17]. Level 2 ("requiring substantial support") involves marked deficits in verbal and nonverbal communication, social difficulties persisting despite assistance, reduced social initiation, atypical responses to social cues, rigid adherence to routines, repetitive actions, and challenges adapting to changes [17]. Level 3 ("requiring very substantial support") reflects more profound impairments across these domains, often resulting in significantly limited daily functioning [17].

Dental procedures under GA adhered to established protocols at the surgery center and followed guidelines from the American Dental Association (ADA) and American Academy of Pediatric Dentistry (AAPD). Induction was achieved with either intramuscular ketamine or inhaled sevoflurane, while maintenance relied on intravenous propofol. Additional medications, such as opioids or non-steroidal anti-inflammatory drugs, were administered as clinically indicated. Continuous monitoring included pulse oximetry, end-tidal CO2, electrocardiography, and precordial stethoscope. Airway support was provided via intubation or non-intubation methods as appropriate.

A comprehensive treatment plan was developed and discussed with the guardian, after which all required dental interventions were completed. Local anesthesia, when needed, consisted of 2% lidocaine with 1:100,000 epinephrine, with dosage capped at 4 mg/kg of lidocaine. Following surgery, patients recovered in a dedicated area under ongoing observation until meeting ADA and AAPD discharge criteria, including stable vital signs, return of protective reflexes, age-appropriate ability to communicate and sit

independently, adequate hydration, and maintained cardiovascular and airway stability [18, 19]. Guardians received detailed postoperative instructions prior to leaving.

Data collection involved structured interviews conducted by the principal investigator and a trained research assistant using a standardized script to minimize bias. The assistant underwent calibration for consistent survey delivery. A professional Spanish interpreter assisted with consent and questionnaires for non-English-speaking families when required.

On the surgery day, guardians completed a baseline survey covering pre- and postoperative behavior, supplemented by anesthesia records for intraoperative details. Follow-up telephone surveys were administered to guardians at 8 hours, 24 hours, and 3 months after discharge. These intervals were chosen based on prior research indicating that negative behavioral changes after sedation often appear within the first 8–24 hours [1, 2].

The survey evaluated potential adverse changes in activity levels, sleep patterns, gastrointestinal function, central nervous system effects, and respiratory issues. Paradoxical responses were captured through items addressing excessive aggression, inconsolable crying, hyperactivity, or self-injurious actions like biting/scratching. Answers were binary (yes/no), with open-ended prompts for elaboration on affirmative responses.

Data were recorded in Microsoft Excel 2016 (Microsoft Corporation, Redmond, WA, USA) and analyzed using IBM SPSS Statistics version 25 (IBM Corporation, Armonk, NY, USA). Descriptive and inferential statistics were generated. Chi-square tests assessed differences in the frequency of behavioral changes between groups and across time points. Independent t-tests compared anesthetic drug quantities and overall adverse effect rates between groups. Pearson correlation coefficients explored relationships between age, gender, body mass index, anesthetic agents, and the total number of adverse effects.

Results and Discussion

Seventy-seven patients were enrolled in the study, with demographic details presented in **Table 1**. Induction of anesthesia was performed via mask with sevoflurane in 57 cases (74%) and via intramuscular ketamine in 20 cases (26%).

Compared to the healthy control group, children with autism spectrum disorder (ASD) showed several notable differences: a higher proportion of males ($P = 0.002$), greater use of regular medications ($P < 0.001$), elevated body mass index ($P < 0.001$), and more frequent use of intramuscular ketamine for induction ($P < 0.001$). The ASD group also received lower amounts of lidocaine during treatment ($P = 0.01$). No significant group difference was observed in postoperative recovery duration ($P = 0.117$).

The anesthetic regimen commonly included ketamine, propofol, ketorolac, ondansetron (Zofran), meperidine (Demerol), alfentanil, dexamethasone (Decadron), midazolam (Versed), succinylcholine, atropine, remifentanil, and diphenhydramine (Benadryl). The healthy children received significantly higher doses of meperidine ($P = 0.001$), midazolam ($P = 0.021$), and remifentanil ($P = 0.001$) **(Table 1)**.

Table 1. Demographic data summary.

Group	Male *N* (%)	Female *N* (%)	Mean age (years)	Mean BMI	Mean surgery time (min)	Mean recovery time (min)	Mean xylocaine amount (mL)
				Demographics			
Healthy	20 (50.0)	20 (50.0)	4.5 ± 0.9	16.1 ± 1.4	68.4 ± 21.0	35.6 ± 16.0	1.3 ± 0.7
ASD	31 (83.8)	6 (16.2)	9.0 ± 3.9	19.8 ± 4.67	58.1 ± 24.7	41.4 ± 15.7	0.8 ± 0.8
Total	51 (66.2)	26 (33.8)	6.7 ± 3.5	17.9 ± 3.8	63.4 ± 23.3	38.4 ± 16.0	1.0 ± 0.7
Group	**NKDA *N* (%)**	**Antibiotic *N* (%)**	**Seasonal *N* (%)**	**Multiple *N* (%)**	**Other *N* (%)**		
				Allergies			
Healthy	30 (75.0)	1 (2.5)	5 (12.5)	2 (5.0)	2 (5.0)		
ASD	26 (70.3)	3 (8.1)	6 (43.2)	1 (2.7)	1 (2.7)		
Total	56 (72.7)	4 (5.2)	11 (14.3)	3 (3.9)	3 (3.9)		
Group	**None *N* (%)**	**Albuterol *N* (%)**	**OTC allergy *N* (%)**	**Multi-vitamins *N* (%)**	**Melatonin *N (%)***	**Valproic *N* (%)**	**Multiple *N* (%)**
				Medications			
Healthy	23 (57.5)	5 (12.5)	4 (10.0)	7 (17.5)	0 (0)	0 (0)	1 (2.5)
ASD	13 (35.1)	1 (2.7)	3 (8.1)	2 (5.4)	2 (5.4)	1 (2.7)	13 (35.1)
Total	36 (46.8)	6 (7.8)	7 (9.1)	9 (11.7)	2 (2.6)	1 (1.3)	14 (18.2)

Drug	Healthy number (%)	ASD number (%)	Dose for Healthy (mean ± SD mg/kg)	Dose for ASD (mean ± SD mg/kg)	*P* -value
Drugs used during surgery					
Propofol	40 (100.0)	37 (100.0)	9.3 ± 7.8	7.6 ± 5.0	0.243
Ketamine	14 (35.0)	27 (73.0)	2.2 ± 1.4	2.7 ± 1.4	0.275
Ketorolac	39 (97.5)	33 (89.2)	0.5 ± 0.1	0.5 ± 0.3	0.777
Zofran	38 (95.0)	31 (83.8)	0.4 ± 1.6	0.1 ± 0.2	0.430
Demerol	32 (80.0)	23 (62.2)	1.6 ± 0.6	1.0 ± 0.5	**0.001***
Alfentanil	21 (52.5)	16 (43.2)	40.9 ± 18.0	29.3 ± 16.0	0.050
Decadron	27 (67.5)	27 (73.0)	0.4 ± 0.7	0.2 ± 0.1	0.089
Versed	6 (15.0)	22 (59.5)	0.1 ± 0.01	0.04 ± 0.01	**0.021***
Succinylcholine	2 (5.0)	4 (10.8)	0.5 ± 0.1	0.4 ± 0.2	0.840
Atropine	4 (10.0)	1 (2.7)	0.01 ± 0.0	0.004 (no sd)	N/A
Remifentanil	1 (2.5)	3 (8.1)	32.2 (no sd)	4.0 ± 0.9	**0.001***
Benadryl	4 (10.0)	8 (21.6)	0.7 ± 0.1	0.5 ± 0.2	0.164

*P < 0.05 using t-test to indicate difference in average dose of each drug used between Healthy and ASD groups. Bold values mean they are statistically significant.

In total, the surveys comprised 77 questions, generating 5,929 responses across all participants. Of these, 700 (11.8%) were affirmative ("Yes") answers signifying the presence of adverse behavioral effects **(Table 2)**.

The baseline survey (Survey 1, administered on the day of surgery) included 15 questions, yielding 1,155 responses overall and only 5 (0.43%) "Yes" responses indicative of adverse effects occurring during GA.

The 8-hour post-discharge survey (Survey 2) consisted of 29 questions, with 2,233 responses and 455 (20.4%) affirmative answers.

The 24-hour follow-up (Survey 3) featured 27 questions, producing 2,079 responses and 194 (9.3%) "Yes" responses.

Finally, the 3-month survey (Survey 4) contained 6 questions, resulting in 462 responses and 46 (10.0%) affirmative replies.

Table 2. Survey questions comparing incidence of adverse behavioral events after GA.

Question	Yes N (%)	Healthy N (%)	ASD N (%)	P-value (Chi-square)
Survey 1: Initial survey				
Prior to GA induction, did the patient:				
1P. Cry or scream inconsolably?	8 (10.4)	3 (7.5)	5 (13.5)	0.388
2P. Exhibit any aggressive behavior?	7 (9.1)	0 (0)	7 (18.9)	0.004*
3P. Bite or scratch anyone?	2 (2.6)	0 (0)	2 (5.4)	0.136
4P. Seem hyperactive?	8 (10.4)	3 (7.5)	5 (13.5)	0.107
5. Speak age-appropriately?	43 (55.8)	38 (95.0)	5 (13.5)	<0.001*
6. Walk on their own, if age appropriate?	76 (98.7)	39 (97.5)	37 (100)	0.333
7. Does your child snore?	21 (27.3)	13 (32.5)	8 (21.6)	0.113
During GA surgery, did the patient:				
8A. Require the use of reversal agents?	4 (5.2)	1 (2.5)	3 (8.1)	0.268
9A. Saturation level ever drop below 90%?	1 (1.3)	0 (0)	1 (2.7)	0.295
10A. Require head repositioning? (> five times per hour)	0 (0)	0 (0)	0 (0)	N/A
11A. Have any abnormal rash?	0 (0)	0 (0)	0 (0)	N/A
12A. At any point was treatment aborted? (if yes, why?)	0 (0)	0 (0)	0 (0)	N/A
At discharge, could the patient:				
13. Sit unaided?	77 (100)	40 (100)	37 (100)	N/A
14. Hold their head up on their own?	77 (100)	40 (100)	37 (100)	N/A
15. Speak age-appropriately?	43 (55.8)	38 (95.0)	5 (13.5)	<0.001*
Survey 2: 8-hour post-GA follow-up phone survey				
After leaving the surgery clinic, did your child:				
1P. Cry or scream inconsolably?	12 (15.6)	8 (20.0)	4 (10.8)	0.267
2P. Exhibit any abnormally aggressive behavior?	4 (5.2)	4 (10.0)	0 (0)	0.048*

3P. Bite or scratch anyone?	1 (1.3)	0 (0)	1 (2.7)	0.295
4P. Seem hyperactive?	7 (9.1)	4 (10.0)	3 (8.1)	0.773
5S. Fall asleep on the car ride home?	66 (85.7)	37 (92.5)	29 (78.4)	0.077
5a. Does your child normally sleep in the car?	36 (46.8)	26 (65.0)	10 (27.0)	0.001*
5bR. Did your child snore?	21 (27.3)	15 (37.5)	6 (16.2)	0.036*
5c. Does your child usually snore?	19 (24.7)	13 (32.5)	6 (16.2)	0.098
5dS. Was it difficult to awaken your child when you arrived home?	11 (14.3)	4 (10.0)	7 (18.9)	0.264
6U. Act in a way that made you concerned and caused you to pull the car over?	2 (2.6)	1 (2.5)	1 (2.7)	0.955
7S. Sleep soon after arriving home?	48 (62.3)	24 (60.0)	24 (64.9)	0.660
7aS. Did your child complain of bad dreams?	3 (3.9)	1 (2.5)	2 (5.4)	0.510
8L. Need help to sit up?	18 (23.4)	7 (17.5)	11 (29.7)	0.205
9L. Have difficulty walking?	27 (35.1)	9 (22.5)	18 (48.6)	0.016*
10L. Seem lethargic?	46 (59.7)	26 (65.0)	20 (54.1)	0.328
11L. Play immediately after arriving home?	19 (24.7)	12 (30.0)	7 (18.9)	0.260
12C. Talk less than normal or refuse to talk?	32 (41.6)	17 (42.5)	15 (40.5)	0.862
13C. Talk more than normal?	0 (0)	0 (0)	0 (0)	N/A
14C. Slur or speak incoherently?	5 (6.5)	2 (5.0)	3 (8.1)	0.573
15C. Complain of or seem dizzy?	23 (29.9)	8 (20.0)	15 (40.5)	0.070
16. Have any memory of what happened at the surgery clinic?	26 (33.8)	14 (35.0)	12 (32.4)	0.101
17. Talk about the dental surgery?	32 (41.6)	19 (47.5)	13 (35.1)	0.027*
18C. Have or complain of a headache?	4 (5.2)	1 (2.5)	3 (8.1)	0.167
19G. Complain of nausea?	10 (13.0)	2 (5.0)	8 (21.6)	0.030*
20G. Vomit?	9 (11.7)	3 (7.5)	6 (16.2)	0.234
21G. Have an upset stomach?	3 (3.9)	2 (5.0)	1 (2.7)	0.603
22G. Have diarrhea?	1 (1.3)	0 (0)	1 (2.7)	0.295
23U. Take any medication?	33 (42.9)	18 (45.0)	15 (40.5)	0.693
24U. Have any abnormal rash?	3 (3.9)	2 (5.0)	1 (2.7)	0.603
Survey 3: 24-hour post-GA follow-up phone survey				
After leaving the surgery clinic, did your child:				
1P. Cry or scream inconsolably?	5 (6.5)	3 (7.5)	2 (5.4)	0.709
2P. Exhibit any abnormally aggressive behavior?	1 (1.3)	1 (2.5)	0 (0)	0.333
3P. Bite or scratch anyone?	0 (0)	0 (0)	0 (0)	N/A
4P. Seem hyperactive?	10 (13.0)	5 (12.5)	5 (13.5)	0.895
5S. Sleep more or less than normal?	19 (24.7)	9 (22.5)	10 (27.0)	0.645
5aR. Did your child snore?	17 (22.1)	12 (30.0)	5 (13.5)	0.081
5b. Does your child usually snore?	18 (23.4)	12 (30.0)	6 (16.2)	0.153
5cS. Was it difficult to awaken your child?	4 (5.2)	1 (2.5)	3 (8.1)	0.303
5dS. Did your child complain of bad dreams?	2 (2.6)	0 (0)	2 (5.4)	0.185
6L. Need help to sit up?	2 (2.6)	2 (5.0)	0 (0)	0.168
7L. Have difficulty walking?	3 (3.9)	2 (5.0)	1 (2.7)	0.603
8L. Seem lethargic?	17 (22.1)	9 (22.5)	8 (21.6)	0.926
9L. Play more or less than normal?	16 (20.8)	6 (15.0)	10 (27.0)	0.194
10C. Talk less than normal or refuse to talk?	6 (7.8)	2 (5.0)	4 (10.8)	0.342
11C. Talk more than normal?	6 (7.8)	3 (7.5)	3 (8.1)	0.921
12C. Slur or speak incoherently?	3 (3.9)	2 (5.0)	1 (2.7)	0.511
13C. Complain of or seem dizzy?	4 (5.2)	3 (7.5)	1 (2.7)	0.343
14. Have any memory of what happened at the surgery clinic?	17 (22.1)	8 (20.0)	9 (24.3)	0.078
15. Talk about the dental surgery?	25 (32.5)	15 (37.5)	10 (27.0)	0.048*
16C. Have or complain of a headache?	1 (1.3)	0 (0)	1 (2.7)	0.185
17G. Complain of nausea?	0 (0)	0 (0)	0 (0)	N/A

18G. Vomit?	0 (0)	0 (0)	0 (0)	N/A
19G. Have an upset stomach?	2 (2.6)	1 (2.5)	1 (2.7)	0.955
20G. Have diarrhea?	1 (1.3)	0 (0)	1 (2.7)	0.295
21U. Take any medication?	29 (37.7)	14 (35.0)	15 (40.5)	0.616
22U. Have any abnormal rash?	1 (1.3)	1 (2.5)	0 (0)	0.333
23U. Act in a way that made you concerned?	3 (3.9)	1 (2.5)	2 (5.4)	0.510
Survey 4: 3-month post-GA follow-up phone survey				
Since the 24-hour follow-up, did your child exhibit any:				
1C. Psychological problems (aggressive behavior, crying or screaming, insomnia, nightmares)?	8 (10.4)	2 (5.0)	6 (16.2)	0.107
2G. Gastrointestinal problems (nausea, vomiting, diarrhea, constipation, upset stomach, loss of appetite)?	8 (10.4)	3 (7.5)	5 (13.5)	0.388
3C. Neurological problems (relapse in behavior, dizziness, or headaches)?	3 (3.9)	1 (2.5)	2 (5.4)	0.510
4P. Seem hyperactive?	14 (18.2)	4 (10.0)	10 (27.0)	0.053
5U. Act in a way that made you concerned?	6 (7.8)	0 (0)	6 (16.2)	0.008*
6U. Any changes in medications after surgery?	7 (9.1)	2 (5.0)	5 (12.5)	0.194

N, Number of Responders; %, Frequency,

*P < 0.05 using chi-square test to indicate differences between Healthy and ASD who answered "Yes." P, Paradoxical Reaction; S, Sleep Disturbance; R, Respiratory Effects; L, Activity Level; C, CNS Effects; G, GI Disturbance; A, Adverse Reaction During Surgery; U, Unusual Occurrence. Bold values mean they are statistically significant.

At the preoperative assessment (Survey 1, **Figure 1**), notable behavioral differences were observed between the groups. A higher proportion of ASD patients displayed aggressive behavior (P = 0.004), whereas more healthy children demonstrated age-appropriate speech both prior to GA induction and at discharge (P < 0.001 for both). Eight hours post-discharge, healthy patients were more likely to sleep normally in the car (P < 0.001), snore during the car ride home (P = 0.036), and discuss the dental procedure (P = 0.027). In contrast, ASD patients more frequently experienced difficulty walking (P = 0.016) and nausea (P = 0.030) during this period **(Table 2)**. At 24 hours post-discharge, healthy patients continued to discuss the dental procedure more often (P = 0.048). Three months post-surgery **(Figure 2)**, ASD patients were significantly more likely to exhibit behaviors concerning to their caregivers (P = 0.008), with increased hyperactivity observed in the ASD group (P = 0.05). No other survey items demonstrated significant differences between the groups.

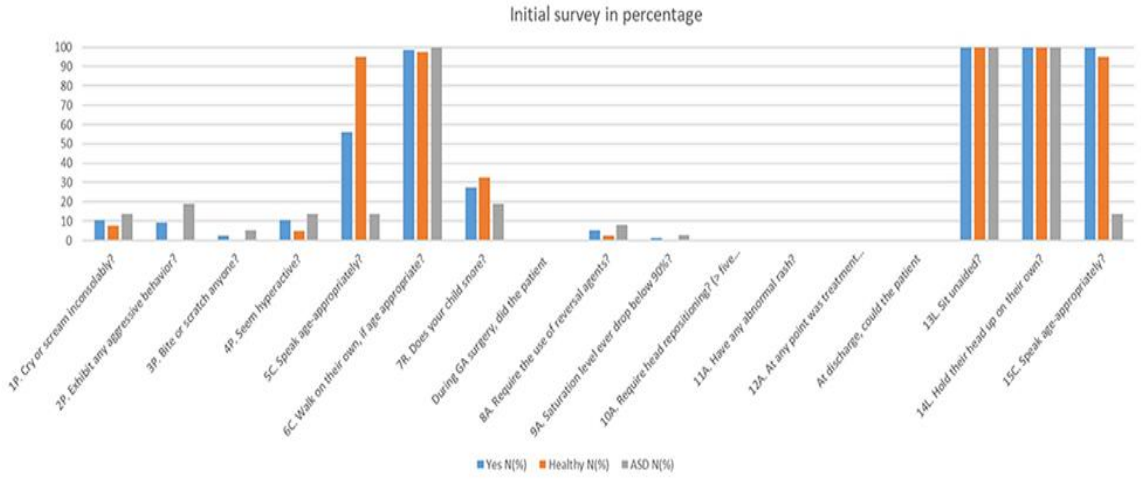

Figure 1. Initial survey in percentage.

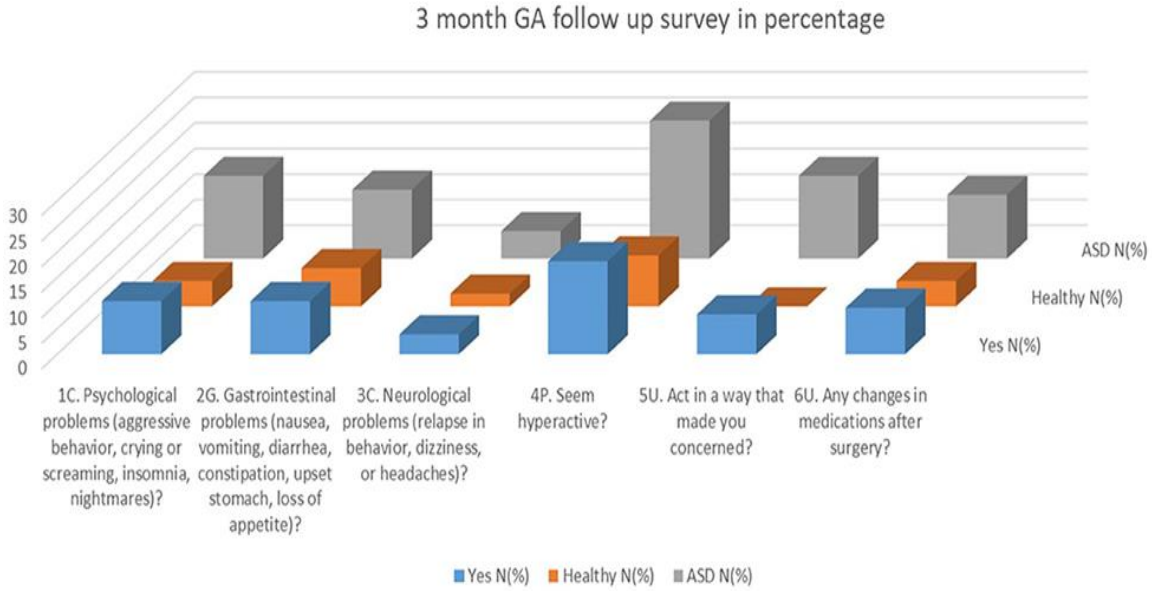

Figure 2. Three months FA follow up in percentage.

Survey questions were categorized to facilitate comparison of various types of adverse behavioral effects between the healthy and ASD groups **(Table 2)**. No significant difference was found in the rate of adverse reactions occurring during the surgical procedure (P = 0.143).

In preoperative assessments, children with ASD exhibited significantly higher rates of aggressive behavior and inconsolable crying or screaming (P = 0.008), as well as age-inappropriate speech (P < 0.001). The incidence of paradoxical reactions showed no significant group differences at 8 hours (P = 0.174) or 24 hours (P = 0.189) post-discharge. However, at the 3-month follow-up, Fisher's exact test revealed that the ASD group experienced significantly more paradoxical reactions (P = 0.05), primarily manifesting as increased hyperactivity.

At 8 hours post-discharge, healthy children displayed significantly more respiratory-related effects (P = 0.032), particularly snoring during the car ride home and habitual snoring; this group difference was not present at 24 hours.

At 3 months following surgery, the ASD group reported significantly higher rates of gastrointestinal disturbances (P = 0.008) and concerning unusual behaviors that alarmed parents or caregivers (P = 0.013).

No significant intergroup differences were observed in central nervous system effects, activity levels, or sleep disturbances across any survey time points. Nonetheless, a notable trend emerged in the 24-hour survey, where children with ASD were more likely to have difficulty awakening and to report bad dreams (P = 0.062).

Paired t-tests were employed to evaluate changes in specific adverse effects between the 8-hour and 24-hour post-discharge periods **(Table 3)**.

Pearson correlation analyses identified significant positive associations between certain categories of adverse behavioral effects **(Table 4)**. All correlated pairs listed in **Table 4** demonstrated positive relationships.

Table 3. Paired *t*-test statistics for adverse behavioral effects over time.

Survey questions	Standard error	Significance	Mean	Standard deviation
Paradoxical reaction 8 h	0.07	*P* = 0.219	0.31	0.59
Paradoxical reaction 24 h	0.06	Not significant	0.21	0.5
Sleep disturbance 8 h	0.05	***P* = 0.034***	0.17	0.45
Sleep disturbance 24 h	0.03	**Significant decrease**	0.08	0.27
Level of activity 8 h	0.11	***P* < 0.001***	1.43	0.98
Level of activity 24 h	0.1	**Significant decrease**	0.49	0.9
CNS effects 8 h	0.15	***P* < 0.001***	1.71	1.24
CNS effects 24 h	0.12	**Significant decrease**	0.87	0.97

GI discomfort 8 h	0.07	***P* = 0.001***	0.3	0.62
GI discomfort 24 h	0.03	**Significant decrease**	0.04	0.25
Respiratory effects 8 h	0.09	*P* = 0.228	0.52	0.77
Respiratory effects 24 h	0.09	Not significant	0.45	0.79
Unusual occurrence 8 h	0.06	*P* = 0.581	0.45	0.53
Unusual occurrence 24 h	0.06	Not significant	0.42	0.57
Unusual occurrence 24 h	0.06	***P* = 0.001***	0.41	0.57
Unusual occurrence 3 months	0.05	**Significant decrease**	0.17	0.44
Unusual occurrence 8 h	0.06	***P* < 0.001***	0.45	0.52
Unusual occurrence 3 months	0.05	**Significant decrease**	0.17	0.44

N = 77 patients.

*P < 0.05 using paired t-test to indicate significant change in incidence of effects between time points. Reported are significant decreases from earlier time point to later time point. Bold values mean they are statistically significant.

Table 4. Correlation between adverse behavioral effect type.

Adverse effect	Correlated with (r, *P*-value)
CNS at 8 h	Paradoxical at 24 h (r = +0.290, *P* = 0.015) CNS at 24 h (r = +0.512, *P* < 0.001) Sleep at 8 h (r = +0.290, *P* = 0.016) Sleep at 24 h (r = +0.491, *P* < 0.001) Activity level at 8 h (r = +0.570, *P* < 0.001) Activity level at 24 h (r = +0.510, *P* < 0.001) GI discomfort at 8 h (r = +0.433, *P* < 0.001) Unusual occurrence at 8 h (r = +0.281, *P* = 0.017) Unusual occurrence at 3 months (r = +0.278, *P* = 0.021)
CNS at 24 h	Paradoxical reaction at 24 h (r = +0.336, *P* = 0.004) Sleep disturbance at 8 h (r = +0.358, *P* = 0.002) Sleep disturbance at 24 h (r = +0.363, *P* = 0.002) Activity level at 24 h (r = +0.426, *P* < 0.001) Unusual occurrence at 8 h (r = +0.275, *P* = 0.021) Unusual occurrence at 24 h (r = +0.305, *P* = 0.010) Unusual occurrence at 3 months (r = +0.451, *P* < 0.001)
CNS at 3 months	Paradoxical reaction at 8 h (r = +0.246, *P* = 0.031) Paradoxical reaction at 24 h (r = +0.254, *P* = 0.026) Unusual occurrence at 3 months (r = +0.395, *P* < 0.001)
GI discomfort at 8 h	Pre-op behavioral issue (r = +0.346, *P* = 0.002) Sleep disturbance at 24 h (r = +0.271, *P* = 0.010) Activity level at 8 h (r = +0.259, *P* = 0.023) Activity level at 24 h (r = +0.411, *P* < 0.001)
Unusual occurrence at 24 h	Sleep disturbance at 24 h (r = +0.439, *P* < 0.001) GI discomfort at 24 h (r = +0.246, *P* = 0.031) Unusual occurrence at 8 h (r = +0.404, *P* < 0.001) Unusual occurrence at 24 h (r = +0.231, *P* = 0.043)
Sleep disturbance at 24 h	Pre-op behavioral issue (r = +0.294, *P* = 0.010) Paradoxical reaction at 24 h (r = +0.281, *P* = 0.015) Activity level at 8 h (r = +0.272, *P* = 0.018)
Respiratory effect at 8 h	Respiratory effect at 24 h (r = +0.518, *P* < 0.001)
Activity level at 8 h	Activity level at 24 h (r = +0.295, *P* = 0.009)

Statistical significance was defined as P < 0.05. The significant correlations identified between specific categories of adverse behavioral effects are presented.

Certain medications administered during surgery were associated with higher rates of particular adverse effects. Ketorolac showed a borderline association with

increased neurological issues (P = 0.054). Demerol was linked to a significantly greater occurrence of behaviors that worried parents/caregivers (P = 0.031) and a marginally higher rate of gastrointestinal discomfort (P = 0.051). Versed was associated with elevated psychological problems (P = 0.016) and postoperative medication changes (P = 0.043). Atropine correlated with more psychological issues (P = 0.025). Remifentanil was tied to higher gastrointestinal discomfort (P = 0.008) and changes in medications post-surgery (P = 0.003). In contrast, Benadryl use was significantly associated with no postoperative medication adjustments (P = 0.039).

The ASD group exhibited a broader age distribution: 11 patients younger than 6 years, 18 aged 6 to <12 years, and 8 aged 12 years or older. The 6 to <12-year age group received significantly higher doses of ketamine (P = 0.048), ketorolac (P = 0.021), and midazolam (Versed) (P = 0.021). This group also had a higher proportion reporting habitual snoring (P = 0.023). In the 8-hour survey, fewer patients in this age bracket typically slept in the car (P = 0.003) or experienced gastrointestinal issues (P = 0.044), though more showed central nervous system effects. At 24 hours, this group had lower rates of inconsolable crying/screaming (P = 0.022) and recall of the dental procedure (P = 0.047), but higher snoring (P = 0.047). At 3 months, hyperactivity was reported less frequently in this age group (P = 0.005). No other categories showed significant age-related differences.

Findings from this study align with prior literature on children with autism spectrum disorder (ASD), including a higher male predominance and elevated body mass index in the ASD cohort [15]. As anticipated from the inclusion criteria—requiring marked deficits in verbal and nonverbal communication—significantly fewer ASD patients demonstrated age-appropriate speech. Baseline aggressive behavior was also more prevalent in the ASD group, which frequently necessitated intramuscular ketamine for induction due to poor cooperation with mask delivery, consistent with our observations. The wider age range in the ASD group reflected the patient population available at the Special Care Dentistry center. Age-stratified analyses revealed limited significant differences, likely attributable to the concentration of ASD patients in the 6–12-year range.

Healthy children more frequently reported snoring during the car ride home, consistent with their higher baseline reports of habitual snoring. They also discussed the dental procedure more often, probably due to better verbal abilities compared to the ASD group. At 8 hours post-discharge, ASD patients experienced more nausea and walking difficulties, indicating greater impact on gastrointestinal function and mobility in this population.

Children exhibiting central nervous system effects at 8 hours tended to show persistent sleep disturbances, reduced activity, and ongoing CNS issues at 24 hours, suggesting that early CNS involvement predicts prolonged effects at the next time point. The low 6.57% rate of adverse effects at 3 months indicates that most were transient. In general, the frequency of adverse behavioral changes declined markedly over time **(Table 2)**.

Consistent with McCormack *et al*., who identified peak adverse effects within 8 hours post-discharge [1]—including prolonged sleep, impaired activity (e.g., walking difficulty, reduced talking), and CNS manifestations (e.g., slurred speech)—our results showed the highest incidence at 8 hours, followed by 24 hours. Significant reductions occurred between 8 and 24 hours in sleep disturbances, activity level impairments, CNS effects, and gastrointestinal issues. Unusual events (e.g., rashes, medication changes, concerning behaviors) also decreased substantially from 8 hours to 3 months and from 24 hours to 3 months, reinforcing their short-term nature **(Table 3)**.

Acknowledgments: None

Conflict of Interest: None

Financial Support: The authors wish to thank the Center for Dental Research at Loma Linda University for funding the research project.

Ethics Statement: None

References

1. McCormack L, Chen J-W, Trapp L, Job A. A comparison of sedation-related events for two multiagent oral sedation regimens in pediatric dental patients. Pediatr Dent. (2014);36:302–8. [PubMed] [Google Scholar]
2. Ritwik P, Cao LT, Curran R, Musselman RJ. Post-sedation events in children sedated for dental care. Anesth Prog. (2013) 60:54–9. 10.2344/0003-3006-60.2.54 [DOI] [PMC free article] [PubMed] [Google Scholar]
3. Matton S, Romeo GP. Behavioral regression in 2 patients with autism spectrum disorder and attention-deficit/hyperactivity disorder after oral surgery performed with a general anesthetic. J Am Dent Assoc. (2017) 148:519–24. 10.1016/j.adaj.2017.05.006 [DOI] [PubMed] [Google Scholar]

4. Becker DE. Adverse drug reactions in dental practice. Anesth Prog. (2014) 61:26–34. 10.2344/0003-3006-61.1.26 [DOI] [PMC free article] [PubMed] [Google Scholar]
5. Bakri MH, Ismail EA, Ali MS, Elsedfy GO, Sayed TA, Ibrahim A. Behavioral and emotional effects of repeated general anesthesia in young children. Saudi J Anaesth. (2015) 9:161–66. 10.4103/1658-354X.152843 [DOI] [PMC free article] [PubMed] [Google Scholar]
6. DiMaggio C, Sun L, Li G. Early childhood exposure to anesthesia and risk of developmental and behavioral disorders in a sibling birth cohort. Anesth Analg. (2011) 113:1143–51. 10.1213/ANE.0b013e3182147f42 [DOI] [PMC free article] [PubMed] [Google Scholar]
7. Sprung J, Flick RP, Katusic SK, Colligan RC, Barbaresi WJ, Bojanić K, et al. Attention-deficit/hyperactivity disorder after early exposure to procedures requiring general anesthesia. Mayo Clin Proc. (2012) 87:120–9. 10.1016/j.mayocp.2011.11.008 [DOI] [PMC free article] [PubMed] [Google Scholar]
8. Brambrink AM, Evers AS, Avidan MS, Farber NB, Smith DJ, Zhang X, et al. Isoflurane-induced neuroapoptosis in the neonatal rhesus macaque brain. Anesthesiology. (2010) 112:834–41. 10.1097/ALN.0b013e3181d049cd [DOI] [PMC free article] [PubMed] [Google Scholar]
9. Creeley C, Dikranian K, Dissen G, Martin L, Olney J, Brambrink A. Propofol-induced apoptosis of neurones and oligodendrocytes in fetal and neonatal rhesus macaque brain. Br J Anaesth. (2013) 110 (Suppl. 1):i29–i38. 10.1093/bja/aet173 [DOI] [PMC free article] [PubMed] [Google Scholar]
10. Jevtovic-Todorovic V. Pediatric anesthesia neurotoxicity: an overview of the 2011 SmartTots panel. Anesth Analg. (2011) 113:965–8. 10.1213/ANE.0b013e3182326622 [DOI] [PubMed] [Google Scholar]
11. Loepke AW, Soriano SG. An assessment of the effects of general anesthetics on developing brain structure and neurocognitive function. Anesth Analg. (2008) 106:1681–707. 10.1213/ane.0b013e318167ad77 [DOI] [PubMed] [Google Scholar]
12. Slikker W, Jr, Zou X, Hotchkiss CE, Divine RL, Sadovova N, Twaddle NC, et al. Ketamine-induced neuronal cell death in the perinatal rhesus monkey. Toxicol Sci. (2007) 98:145–58. 10.1093/toxsci/kfm084 [DOI] [PubMed] [Google Scholar]
13. Orser BA, Suresh S, Evers AS. SmartTots update regarding anesthetic neurotoxicity in the developing brain. Anesth Analg. (2018) 126:1393–6. 10.1213/ANE.0000000000002833 [DOI] [PubMed] [Google Scholar]
14. Sun LS, Li G, DiMaggio C, Byrne M, Rauh V, Brooks-Gunn J, et al. Anesthesia and neurodevelopment in children: time for an answer? Anesthesiology. (2008) 109:757–61. 10.1097/ALN.0b013e31818a37fd [DOI] [PubMed] [Google Scholar]
15. McDonald RE, Avery DR, Dean JA. Pharmacologic management of patient behavior. In: Dean JA, Avery DR, McDonald RE. editors. McDonald and Avery's Dentistry for the Child and Adolescent. 9th ed. Maryland Heights, Mo.: Mosby Elsevier; (2011). p. 1–18. 10.1016/B978-0-323-05724-0.50005-9 [DOI] [Google Scholar]
16. Camm JH, Mourino A, Cobb E, Doyle T. Behavioral changes of children undergoing dental treatment using sedation vs. general anesthesia. Pediatr Dent. (1987) 9:111–7. [PubMed] [Google Scholar]
17. Autism Speaks. DSM-5 Criteria. Available online at: https://www.autismspeaks.org/dsm-5-criteria (accessed July 17, 2018).
18. Coté CJ, Wilson S. Guidelines for monitoring and management of pediatric patients during and after sedation for diagnostic and therapeutic procedures: an update. Pediatr Dent. (2016) 38:13–39. 10.1542/peds.2016-1212 [DOI] [PubMed] [Google Scholar]
19. American Dental Association . Guidelines for the Use of Sedation and General Anesthesia by Dentists. Available online at: www.ada.org/sectiona/about/pdfs/anesthesia)guidelines.pdf (accessed June 10, 2019).