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A prospective study comparing perioperative anxiety and post-hospital behavior in children with autism spectrum disorder versus typically developing children undergoing outpatient surgery

Running head: Comparing children with autism spectrum disorder and typically developing children undergoing outpatient surgery

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What is already known:

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Data on the experience of children with autism spectrum disorders in the perioperative period is limited. Case reports and review articles advocate using individualistic approaches, incorporating parent knowledge, and minimizing sensory stimulation. Controlled studies, however, have not been conducted.

What this article adds:

This prospective study compares the experiences of children with autism spectrum disorder and typically developing children in the perioperative setting and examines differences in post-hospital behavior. Findings may be used to offer guidance in the management of this patient population.

Abstract

Background:

Research describing the experience of youth with autism spectrum disorders (ASD) in the perioperative setting is limited. This study compared youth with autism spectrum disorder to typically developing children in the perioperative setting and examined group differences in: child anxiety, parent anxiety, pre-medication patterns, induction compliance, and changes in behavior post-procedure.

Methods:

Participants were 60 youth (32 with autism spectrum disorder, 28 typically developing) ages 2-19 years undergoing outpatient surgery and their parents. Parents and research assistants rated children's anxiety at three time points (waiting room, pre-op holding, separation), and parents rated their own anxiety in the waiting room and at separation. The anesthesiologist rated induction compliance. Post-procedure behavior change was assessed via phone survey one and seven days post-procedure. Analyses examined group differences in anxiety, medication patterns, and behavior.

Results:

Children with autism spectrum disorder had higher research assistant reported anxiety than typically developing youth in the holding room only. There were no group differences in parent report of their own anxiety or their child's anxiety across time points. Compared to typically developing youth, children with autism spectrum disorder were more likely to receive a pre-medication (including non-standard premedication), and had poorer induction compliance. Groups did not differ on post-hospital behavior change 1 or 7 days post-surgery.

Conclusion:

Findings revealed ratings of anxiety in youth with and without autism spectrum disorder facing surgery varied by reporter and setting, highlighting the importance of using multiple reporters in research of youth with autism spectrum disorder in the perioperative period. Further, while results showed group differences in premedication patterns and induction compliance, groups did not differ in level of negative behavior change after surgery. Future research can examine how individual differences in youth with autism impact anxiety in the perioperative setting and degree of behavior change post-procedure.

Keywords: autism spectrum disorder; premedication; anxiety; behavior; postoperative period

Background:

The estimated prevalence of autism spectrum disorders (ASD) in children and adolescents is approximately 1.5 percent (1). Children with ASD are more likely to experience medical complexities as compared to their typically developing peers and more frequently utilize the healthcare system (2). Of interest to the current investigation, symptoms specific to ASD (e.g., difficulties with novel situations; hypersensitivity to sensory input) may make accessing healthcare and surgical procedures anxiety provoking for this population.

Managing patients with autism perioperatively can also be challenging for providers. Data on children diagnosed with ASD in the perioperative period, however, is limited. The few studies that exist indicate youth with ASD are more likely to require general anesthesia for routine dental evaluations, refuse an oral premedication, require restraint during induction, and exhibit behavioral difficulties during common perioperative events as compared to their typically developing peers (3-5).

Although it is expected that anxiety experienced by youth with ASD during the perioperative experience may play a role in these aforementioned behavioral concerns, such associations have not been formally studied. The majority of relevant literature describing patients with ASD is based on case reports and anecdotal accounts. This literature advocates for using individualistic approaches, incorporating parent knowledge, minimizing sensory stimulation, and utilizing premedication to help guide care of children with autism during the perioperative period (6-8). Anxiety during the perioperative experience may impact behavior both perioperatively and post-hospitalization, highlighting the need for further research.

Associations between preoperative parental anxiety, child anxiety and baseline temperament, and child behavior after surgery have been previously investigated in typically developing children (9, 10). These associations are yet to be explored among children with ASD. Furthermore, parents may not be the most accurate reporters of their children's anxiety in a typically developing population (11). As children with ASD often do not display age-typical symptoms of anxiety, assessment of this population should be conducted using multiple informants and modalities (12).

Furthermore, anxiety during the preoperative period has been shown to be a strong predictor of poorer induction compliance in typically developing children (13). Specifically, premedication can reduce the incidence of distress at induction in children with high levels of preoperative distress (13). While data suggest children with ASD are more likely to receive a non-standard premedication as compared to typically developing children (14), associations between premedication and induction compliance in youth with ASD have not been studied.

Currently, the internet has become a primary forum of information sharing for parents of youth with ASD. Parent blogs and internet searches reveal a wide range of qualitatively reported surgery experiences. These anecdotal accounts from parents include descriptions of significant regression in behavior following anesthesia. Such behavioral change has not been empirically examined, and

investigation into whether this patient population is indeed more susceptible to peri-procedural anxiety and behavioral changes is needed.

The aims of this study were to examine differences between children with ASD and typically developing youth undergoing outpatient surgical procedures. We tested group differences (ASD versus typically developing) in: 1) parent and observer reports of child anxiety, 2) parent report of their own anxiety, 3) parent report of their child's need for premedication, 4) premedication patterns and induction compliance, and 5) parent report of post-hospital behavioral changes. We hypothesized that children with ASD would be rated as having higher levels of anxiety, and that parents of youth with ASD would report higher anxiety and an increased need for premedication for their child. In addition, we hypothesized that youth with ASD would be more likely to receive non-standard premedication, show poorer induction compliance, and exhibit more negative behavioral changes post-hospitalization as compared to typically developing youth.

Methods:

This study was conducted at an academic medical center in the northwestern United States with Institutional Review Board (IRB00008764) approval. All participants provided consent prior to participating. Enrollment took place between December 2012 and October 2015. Participants were parents of children ages 2-19 years diagnosed with ASD (n=32; M=11.2, SD=4.4) or parents of typically developing youth (n=28; M=6.9, SD=3.2). All participants were presenting for outpatient surgery with general anesthesia, to be discharged the same day. All children had an ASA physical status classification of 1 or 2. Children were selected based on the OR schedule, research assistant availability, and whether they met inclusion criteria via chart review. The majority of procedures were dental, short in duration, and all children were able to go home following recovery of anesthesia.

Children in the ASD group had a pre-existing DSM IV TR diagnosis of autistic disorder, Asperger's disorder, or PDD-NOS or a DSM 5 diagnosis of autism spectrum disorder based on chart review (15); **the majority of patients had a chart diagnosis of "autism spectrum disorder" and the diagnosis was confirmed by parents on the day of surgery.** Children in the typically developing group were otherwise medically healthy without ASD or concern for behavior problems or developmental delay. The preoperative process was similar in children with ASD and typically developing children, such that children with ASD did not receive special preparation prior to surgery. All parents were required to have fluency in reading and writing English.

Procedure:

Parents of eligible children and adolescents were approached in the waiting room prior to their child's surgical procedure by a research assistant. The study was explained verbally and participants were consented in person. A written copy of the study criteria and procedures was given to participants.

Questionnaire Measures:

Demographic Characteristics: Parents completed a questionnaire in the waiting room reporting on demographic characteristics of their child and confirmation of the child's ASD diagnosis.

Parent Report of Child Anxiety: Parents reported on their perceptions of their child's anxiety using the Children's Fear scale (CFS) at three different time points (waiting room, pre-op holding, and separation). The measure is scored with five response options (0 = no anxiety to 4 = extreme anxiety) with higher scores indicating a greater level of anxiety (16).

Parent Report of Their Own Anxiety: Parents reported on their own anxiety using the 20 item State-Trait Anxiety Inventory (STAI) State Anxiety Subscale in the waiting room and at separation. Response options are based on a 4-point scale (1 = "not at all", to 4 = "very much so"). Higher scores are indicative of greater levels of anxiety (17, 18).

Observer Reported Anxiety: Trained research assistants rated child anxiety at three time points (waiting room, pre-op holding, and at separation) using the Modified Yale Preoperative Anxiety Scale (mYPAS), a 27-item observational measure. This measure assesses five categories of behavior indicative of anxiety in children: activity, emotional expressivity, state of arousal, use of parent, and vocalization. Scores range from 0 to 4 in all five categories, with higher scores indicating a higher level of perceived anxiety (19).

Premedication: Parents' response to the question, "Do you think your child will need premedication to help reduce his/her anxiety?" was documented in the waiting room. Research assistants also reviewed each child's medical record and documented whether they actually received a premedication. If the child did receive a premedication, the medication route and drug were recorded. The anesthesiologist chose the medication and route of administration following discussion with the pre-operative nurse and obtaining parent report on their child's perceived need for premedication. Standard premedication was defined as oral midazolam +/- acetaminophen. Non-standard medication included any route other than oral (nasal, rectal, intramuscular) and/or any medication other than midazolam.

Induction Compliance: The anesthesiologist conducting the child's surgery rated induction compliance using the Induction Compliance Checklist (20). The checklist consists of 10 behaviors (i.e., crying, turning head away from mask, verbal refusal, pushing the mask or staff away, hysterical crying/screaming, kicking/flailing/arching of back, requiring physical restraint). The child was given one point for each behavior observed and the score was summed. Induction compliance is rated on an 11-point scale (0-10) with a score of 0 indicating the child exhibited no problematic behaviors and a score of 10 indicating a large number of negative behaviors during induction.

Post-operative behavioral changes: Parents were called via telephone on days one and seven post-procedure and verbally administered the Post Hospital Behavior Questionnaire (PHBQ) by the research assistant. We elected to eliminate one item regarding the need for a pacifier given the age range of our population, leaving 26 items. Questions pertained to observed activities and behaviors in the child following surgery in relation to baseline activity. Parents were asked to answer each question with one of five responses ranging from: 1= much less to 5 = "much more". The measure was scored using the revised PHBQ scoring system. Specifically, if the child demonstrated negative behavioral changes in six or more of the items, they were characterized as having maladaptive behavioral change. If parents

endorsed 5 or fewer items youth were classified as having "no" maladaptive behavioral change (21, 22). Scores on behavior change were calculated separately for days 1 and 7 post procedure.

Statistical Analysis

Data was analyzed using SPSS v.20 and Stata/IC v.13. Summary statistics were used to describe characteristics of the sample, and are reported separately for each group (Table 1). Means and standard deviations were used for continuous data, and categorical items were described using frequency statistics. T-tests were used to examine age differences by group. To examine group differences on child and parent anxiety in the perioperative setting, three regression analyses were conducted using Generalized Estimating Equations (GEE) to account for repeated measures correlation. Robust linear regression was used to examine group mean differences in induction compliance and relative risk regression was used to analyze the pre-medication outcomes. GEE models were also used to compare groups post-hospital behavior change at days 1 and 7. All models included age, ethnicity, surgery type, and sex as covariates.

Results:

Descriptives

A total of 60 child-parent dyads participated in this study, 32 children with ASD (M=11.2 years, SD=4.4) and 28 typically developing children (M=6.9 years, SD=3.2). Demographic characteristics of the participants are presented in Table 1. Groups differed by age, ethnicity, surgery type and sex, with the youth with autism being more likely to be older, non-Hispanic, male, and to undergo dental surgery. Youth in both groups were presenting for outpatient surgical procedures that included a range of surgical specialties, including dentistry, otolaryngology, orthopedic surgery, and urology (Table 1).

Group Differences on Child and Parent Anxiety

Three separate GEE regression models were fitted to evaluate group differences on 1) parent report of child anxiety, 2) observer report of child anxiety, and 3) parent self-reported anxiety. All models included age, ethnicity, surgery type, and sex as covariates.

Findings from the first analysis evaluating group differences between the children with ASD and typically developing children on parent report of child anxiety across the three settings (waiting room, holding room, separation) revealed no significant differences by group (Wald $\chi 2$ (3) = 4.23, p = .24) (Table 2).

In the second analysis evaluating group differences on observer report of child anxiety across settings (waiting room, holding room, separation), the results indicated significant group differences, (Wald $\chi 2$ (3) = 18.01, $p < .001$; see Table 2). The pairwise comparisons indicated there were significant differences in observer report of child anxiety in the holding room with the adjusted mean for children with autism 7.0 points higher (95% CI=[3.7, 10.2], $p < .001$) than that of typically developing youth.

In the third analysis evaluating group differences on parent report of their own anxiety across settings (STAI waiting room, separation), the multivariate model indicated no significant group differences (Wald $\chi 2$ (2) = 1.75, p = .42) (Table 2).

Group Differences in Premedication Patterns

In accordance with our hypothesis, significantly more parents of children with autism said their child would need a premedication as compared to parents of typically developing youth (adjusted RR = 4.9, 95% CI=[2.0, 11.7], p < 0.001). 87.5% of youth with ASD received a premedication as compared to 64.3% of typically developing youth. Similarly, children with ASD were more likely to receive a non-standard premedication than typically developing youth (RR = 4.9, 95% CI=[2.0, 11.7], p < 0.001), with 34.4% of children in the ASD group received a non-standard premedication as compared to no children in the typically developing group. **The most frequently used non-standard medication was intramuscular ketamine.**

Group Differences in Induction Compliance

A robust linear regression was fitted to evaluate group differences in induction compliance. Results revealed that children with ASD had poorer anesthesiologist-rated induction compliance as compared to their typically developing peers (adjusted mean difference = 2.0, 95% CI=[0.9, 3.1], p = 0.001).

Group Differences in Post-Hospital Behavior

Using the revised PHBQ scoring system (21, 22), participants were identified as having significant post-hospitalization behavior changes if their parent endorsed negative behavior change on 6 or more measure items. GEE analyses accounting for covariates were then used to compare the number of youth in each group who exhibited negative behavior changes at 1 day and 7 days post-hospital stay. Contrary to the hypotheses, results revealed no group differences in negative behavior changes at 1 day (adjusted RR=9.6, 95% CI=[0.7, 132.1], p = 0.09) or 7 days (RR 1.2, 95% CI=[0.1, 14.1], p=0.85) post procedure.

Discussion:

This study examined differences in perioperative anxiety among youth with ASD and typically developing youth and their parents. Significant group differences in observer report of child anxiety in the holding area emerged with youth with ASD rated by observers as displaying more behaviors indicating anxiety. Contrary to our hypotheses, this difference was not found in all settings; no group differences were found between observer and parent report of child anxiety in waiting room or at separation. Similarly, parents' of youth with and without ASD reports of their child's anxiety were not significantly different. This data suggests that reports of anxiety in youth with and without ASD facing surgery vary according to setting, reporter, and measure used. The difference in observer rating of perceived anxiety in the holding room could be related to difficulties following a change in routine displayed by children with ASD. The transition to the holding room involves many novel stimuli including being in a new place, changing into a hospital gown, being in a noisy pre-op area, and interacting with multiple healthcare providers. Seeking to understand the differences between parent report of their child's anxiety and observer report, it is possible that the observer may have interpreted certain behaviors as a sign of distress, whereas the parent did not.

We found that parents of youth with ASD reported their children were more likely to need a premedication than parents of youth without ASD. Similarly, youth with ASD were more likely to receive a non-standard premedication despite parents reporting similar anxiety in their children in both groups. Differences between reports of anxiety and need for premedication calls for further investigation as it is possible that parents of youth with ASD were more concerned about their child's behavior requiring restraint during the induction of anesthesia (and subsequent stress related to that restraint) and not elevated anxiety more broadly.

Premedication patterns differed significantly such that 34% of youth with ASD received a non-standard premedication compared to none of the typically developing youth. Children with ASD may be less tolerant of standard premedication and/or clinicians may have had limited insight into the child's baseline temperament and ability to tolerate standard oral premedication. Taken together, this data suggests that considering a behavioral intervention as a first line treatment to increase medication compliance for youth with ASD (e.g., asking parents to administer medication) could be useful and decrease the need for alternative administration patterns that could negatively impact both child and parent.

Furthermore, anesthesiologist rated induction compliance was different between groups, with the children in the ASD group displaying poorer induction compliance. Poorer induction compliance could be related to change in environment (from holding room to OR) and/or exposure to new sensory experiences (e.g., sights, sounds, the smell of the plastic face mask and inhalational anesthetics, and the increasing tactile stimulation such as being moved by strangers to the OR table and placement of monitors). Parental presence is not the standard approach to anxiety at our institution, but could have a role in improvement of induction compliance in youth with ASD.

Difficulty with compliance at induction in youth with ASD points to an area for future research and intervention. Over the past decade, clinicians have begun to develop programs to improve the experience of their patients with ASD and help clinicians tailor management to account for characteristics specific to the ASD patient population (6, 7). For example, including a way to familiarize patients to anesthesia equipment and the process of induction prior to surgery may help with compliance.

Our examination of post-hospital behavior is an important contribution to the literature, as this study is the first to formally investigate these changes. Contrary to hypotheses, parents of youth with ASD did not report significantly more negative behavior changes following the procedure as compared to typically developing youth. The lack of group differences in behavior changes post-surgery is counter to anecdotal evidence that surgery has a lasting impact on behaviors in youth with ASD.

Given that this study is a small investigation initiating a novel domain of research, there are several limitations that should be considered. First, no measures pertaining to perioperative anxiety have been validated for youth with ASD and reliable measures specific to this population are needed (23-24). Given the dearth of existing assessment instruments normed on youth with ASD, we elected to use the mYPAS and PHBQ. While regularly used in the examination of perioperative experiences in typically

developing children, these tools have significant limitations including lack of validation in youth with ASD, which should be accounted for when interpreting results. An important future direction includes the development of improved and validated tools for assessing anxiety and behavior in children with ASD in the peri-operative setting and post-discharge. **Also, the variability in terms of communication, social and cognitive abilities in youth with ASD may have impacted the results. A follow-up study further characterizing differences in the level of functioning of the ASD population and the role of these factors on the perioperative experience is imperative.**

An additional limitation is use of proxy-report for anxiety symptoms. Given limited verbal abilities and that many measures validated for use with non-verbal individuals with ASD rely on parent, teacher, or clinician report (23), we elected to use parent and observer report of anxiety. In this study, we were unable to blind observers to patients' diagnostic status, and reports may therefore have been biased. A follow-up study in which youth with ASD report on their own anxiety while limiting participation to high functioning youth with ASD, and utilization of the multi-dimensional anxiety scale for children (MASC) could be one solution (23).

Furthermore, our study is limited by a small sample size and having two imperfectly matched cohorts, specifically group differences in ethnicity, sex and age. The small sample size may have decreased the likelihood of detecting significant effects. Of note, demographic differences are likely an accurate representation of those seen in a typical dental clinic (older children with ASD present for procedures due to inability to tolerate routine care that similarly aged typically developing children tolerate as outpatients). However, as more children with ASD present for procedures, the ability to study this unique population with an age-matched cohort of typically developing children may be possible.

Youth's behavior during anesthesia induction and post-hospital behavior could have been impacted by various factors. Firstly, the type and dose of premedication may have impacted the induction compliance checklist scores. Also, the lack of standardization of anesthetic and controlling PACU medications could impact evaluation of post-hospital behavior. However, evaluating the patients 24 hours and 7 days after the anesthetic would minimize the impact of most medications administered during the anesthetic. Future research standardizing the anesthetic management would be an important next step in better understanding this patient population. Finally, we exclusively investigated patient populations presenting for elective, outpatient surgery. Parent and child anxiety as well as post-hospital behavior may differ in patients presenting for more invasive and complex procedures or in any emergency surgery.

Conclusion:

Our data suggests that there are differences in observer reports of anxiety in youth with ASD compared to typically developing youth that may impact perioperative management. Altering the approach to management in for children with ASD could reduce anxiety and challenging behaviors. While we did not show group differences in post-hospital behavior, additional research on behavioral regression, and the best management approach for patients with ASD is warranted, particularly with a sample who received more invasive surgeries or had a longer hospital stay. Future directions include

consideration of a more structured, pre-operative experience (e.g., exposure to facility and processes in advance) with individualized approaches based on individual patient characteristics (e.g., severity of ASD) (25), assessing whether parental presence decreases anxiety and improves behavior at the time of induction, and neurocognitive testing to better assess how patient characteristics relate to the perioperative experience, anxiety responses and postoperative behavioral change for children with ASD.

Disclosures:
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Table 1. Descriptive characteristics of the sample

Variable	ASD N=32	Typically Developing N=28
	M(SD)/N(%)	M(SD)/N(%)

Age in years (2-19)*	11.3 (4.4)	6.9 (3.2)
Gender[#]		
Female	1 (3.1)	15 (53.6)
Male	31 (96.9)	13 (46.4)
Ethnicity[#]		
Hispanic or Latino	3 (9.4)	11 (39.3)
Not Hispanic or Latino	29 (90.6)	17 (60.7)
Race[#]		
Caucasian/White	26 (83.9)	21 (75.0)
Other [1]	5 (16.1)	7 (25.0)
Type of Surgery[#]		
Dental	28 (87.5)	16 (57.1)
Other[+2]	4 (12.5)	12 (42.9)

*Statistical analysis using T-test

[#] Statistical analysis using Pearson Chi-Square

[1] Includes African American/Black, Asian, American Indian/Alaskan, and not reported

[2] Includes otolaryngology, orthopedic, urologic and gastrointestinal surgery

Table 2. Adjusted Mean Estimates and GEE pairwise test results (z-statistics and p-values) of child anxiety (parent and observer report) at three time points and parent anxiety at two time points.

Child Anxiety (Parent Report)				
	ASD *M* (*SE*)	Typically Developing *M* (*SE*)	Z	p
Waiting Room	2.82 (.31)	2.21 (.24)	1.57	.116
Holding Room	2.54 (.29)	2.02 (.22)	1.40	.163
Separation	2.32 (.27)	2.42 (.26)	-0.24	.810
Child Anxiety (Observer Report)				
	ASD *M* (*SE*)	Typically Developing *M* (*SE*)	Z	p
Waiting Room	12.7 (1.23)	9.9 (.86)	1.73	.084
Holding Room	16.4 (1.18)	9.4 (.79)	4.23	<.001
Separation	13.7 (1.12)	11.2 (.93)	1.63	.103
Parent Anxiety				
	ASD *M* (*SE*)	Typically Developing *M* (*SE*)	Z	p
Waiting Room	46.7 (1.3)	44.5 (1.3)	1.07	.287
Separation	46.3 (1.2)	46.1 (.96)	.11	.916

*Statistical analysis using Generalized Estimating Equation (GEE) regression