Intranasal Midazolam Procedural Sedation in the Autistic Patient for Diagnostic Dental Procedures

THESIS

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By

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ABSTRACT

The reported prevalence of Autism Spectrum Disorders (ASD) has increased dramatically over the past three decades. Patients with ASD present with difficulty in social situations and communicative delays. Sensory integration disorders and combative behavior may make collection of diagnostic dental information difficult. Intranasal midazolam offers an approved pharmacologic behavior management technique that requires little patient compliance and increased sedative bioavailability compared to oral regimens. The purpose was to determine the effectiveness of intranasal versed sedation to collect diagnostic dental information on patients with ASD.

A Nationwide Children’s Hospital Institutional Review Board approved post-sedation database was kept from 2009 to present day. Twenty-nine records met inclusion criteria of ASD, age 5-18 years, and scheduled for a diagnostic and preventive visit with intranasal midazolam sedation. All treatment and assessment were done under a single pediatric dentist attending and operator. Caregivers of children were contacted within 48 hours of discharge and recover assessed. IRB expedited protocol reviewed bitewing radiographs with 3 raters calibrated to assess diagnostic yield for caries, periodontal disease, and other pathology.

The operator rated 76% of sedations successful while 96% of caregivers were satisfied with the procedure. Most patients were discharged within 60 minutes and returned to baseline eating and sleeping in 2 hours or less. Seventy-seven percent of
radiographs were moderately to highly diagnostic. Findings support intranasal midazolam as an effective regimen to obtain diagnostic information on ASD patients.
DEDICATION

This document is dedicated to my family.
ACKNOWLEDGEMENTS

This research and thesis were generously supported by the time and expertise of Drs. Casamassimo and Prior, my committee members. Their guidance and patience during this process taught me as much as the research itself. The staff and assistants at Nationwide Children’s Hospital were essential for patient recruitment and data collection. I am especially grateful to my advisor and mentor Dr. Thikkurissy. He navigated me through my studies and teaches me every day how to be a better pediatric dentist and educator.
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INTRODUCTION

EPIDEMIOLOGY & NOMENCLATURE OF AUTISM AND AUTISM SPECTRUM DISORDERS

Autism is the most prevalent syndrome in a spectrum of disorders that are grouped together in the Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition, Text Revision under the rubric of pervasive developmental disorders (PDDs). (1) PDD is currently divided into the following categories in order of decreasing prevalence: pervasive developmental disorder not otherwise specified (PDD-NOS) Autism disorder, Asperger disorder, Rett’s disorder, and childhood disintegrative disorder. (1) (2) These conditions are complex neurological and developmental disorders characterized by the presence of social deficits, abnormalities in communication, the presence of stereotyped, repetitive behaviors, and a characteristic course. (1) A diagnosis requires delays or abnormal functioning in at least one of the following areas: social interaction, language as used in social communication, or symbolic and imaginative play. As a neurodevelopmental disorder, PDDs are present from infancy or early childhood, but may not be detected until later because of minimal social demands and support from parents or caregivers in early years. (3) Autism disorder appeared as a separate entity for the first time in the Diagnostic and Statistical Manual of Mental Disorder, Third Edition (DSM-III) in 1980. (4) The next and unpublished fifth edition of the DSM redefines these disorders and creates a new category: Autism Spectrum Disorder (ASD). The revision
creates a continuum in which a patient may be diagnosed on the Autism Spectrum. ASD will include autistic disorder (autism), Asperger’s disorder, childhood disintegrative disorder, and pervasive developmental disorder not otherwise specified (PDD-NOS). Rett’s disorder was removed altogether due to the brevity of the autistic symptoms in the clinical course and clear etiology. (3)

Conservative estimates report the prevalence of autism as 13 per 10,000 children. (5) A large cohort of 9-10-year old children studied in England estimated the total prevalence of ASDs to be 116.1 per 10,000 or approximately 1% of the child population. (6) The prevalence of autism in metropolitan Atlanta in 1996 for children aged 3 to 10 was 3.4 per 1000. This overall rate is 10 times higher than rates from 3 other US studies that used DSM-III or ICD-9. (10) Extending the definition from autism to include all disorders under the term Autism Spectrum Disorder (ASD) yields a prevalence of 1 in every 88 children. (7) This figure has been replicated in studies by Chakrabarti and Fomnonne. (2) (8) (9) The change in diagnostic criteria and increased awareness and understanding of ASD is a factor in the increasing prevalence of the condition. The debate continues whether the overall prevalence of autism has increased or whether past rates underestimated true prevalence.

Males are affected approximately 4 times more frequently than females and increases to 10 times more frequently in some surveys of Asperger’s syndrome. (11) As severity of cognitive impairment increases from mild to profound, the male-female ratio decreases from 4.4 to 1.3. (10) Learning difficulties and lower IQ’s are present in
approximately 70% of cases and autism is associated with medical conditions such as tuberose sclerosis, Rett’s syndrome, and fragile X syndrome. (11)

PATHOPHYSIOLOGY OF ASD

Psychiatric diagnoses are statistically based groupings of symptoms, therefore the etiology of autism is not well understood and likely multifactorial. There is strong support for a genetic component in the etiology. The concordance of autism among monozygotic twins is 36–60% rising to 90% when the whole ASD spectrum is taken into account. (12) Relatives of those diagnosed with an ASD may demonstrate attenuated forms of these conditions, the so-called broader autism phenotype. (12) Linkage studies identify comparatively broad genomic regions co-inherited with a phenotype. In total, 26 non-overlapping regions of the genome have been suggested, reinforcing the complexity of the genetics involved. (13) Candidate gene association analysis for ASD has been an extremely active field with over two hundred genes examined in the last 15 years. (13) These genes are selected for association studies based solely on their known function indicating that they plausibly affect the phenotype. The serotonin transporter gene SLC6A4 is one such example as serotonin levels have been shown to be altered in autism cohorts (14) (15)

On a gross scale, localized failure of cerebellar development, cerebral cortical abnormalities altered amygdala development and decreased corpus callosum size have been reported. (16) (17) (18) (19) Abnormal genesis, migration, shape, arrangement and maturation of neurons are reported, leading to general disorganization of the grey and white matter. (19) Neuroimaging studies have demonstrated a lack of synchronization in
the activation of brain regions in autistic individuals. (20) (21) This led to the Underconnectivity Theory, which postulates that fewer long range connections between different regions are present, leading to decreased synchronization among regions of the brain. (22) This may decrease global information processing and explain the autistic phenotype.

The broad genomic regions co-inherited with the autistic phenotype are relatively common and are present without the phenotype in the general population. (13) The DNA codes for and creates the RNA, which then goes on to code for and create the proteins. Although the template function is largely independent of outside forces, the transcriptional function is highly regulated and responsive to environmental factors (23). Environmental factors can cause developmental disabilities. Obvious examples are fetal alcohol syndrome and phenylketonuria. (24) Kandel suggests certain combinations of normal genes against an environmental background may predispose towards schizophrenia. If this is true, finding any gene by itself may not be helpful because it may be a normal gene. (23)

To date various environmental, therapeutic, and dietary substances have been implicated as modulating causes of Autism. In 2000, Brick Township became a focus for environmental factors related to ASDs. The CDC, using the Autism Diagnostic Observation Schedule-Generic to confirm diagnoses, found that the prevalence for strictly defined autism was 4 per 1,000 and that the prevalence for ASDs was 6.7 per 1,000. These prevalence figures are approximately 4 times higher than the 1 per 1,000 most frequently cited in the literature. (25) At the same time, the Agency for Toxic
Substances and Disease Registry (ATSDR) (Atlanta, GA) studied the township environmentally and found three contaminants in the drinking water at various times. These substances were tetrachloroethylene, trichloroethylene, and trihalomethanes (THMs). (26)

THMs within the same range as found in Brick Township have been associated with a 2-fold increase in neural tube defects. (27) This follows the research which hypothesizes that autism may be caused by interfering with neural tube closure during the gestation day 20 to 24. (28) This research originally implicates excess retinoid use during pregnancy. Animal models using retinoic acid have been developed and share many of the specific brain lesions associated with autism including cerebellar malformations, cranial nerve abnormalities, and abnormalities of the dopaminergic system. (24)

In 1998, a British researcher identified an association between gastrointestinal disease and developmental regression in a group of previously normal children. The parents of the subjects associated onset of symptoms with measles, mumps, and rubella vaccination in eight of the 12 children, with measles infection in one child, and otitis media in another. (32) Subsequently, autistic entero-colitis, has been a central tenet of the “MMR-causes-autism” belief. It is hypothesized that MMR vaccine damages the bowel; this allows dietary ‘opioid peptides’ to leak into the system, which leads to brain damage, regression of development and autism. (11)

High doses of mercuric compounds are nephrotoxic and neurotoxic. (29) One study found an association between more severe autism and the number of mothers’ dental amalgam restorations. Geier and colleagues did not adjust for the age of the
mother when her child was born, and although it was titled a prospective study, the
design was a cohort because all the subjects were from a population already diagnosed
with ASD. (30) A randomized clinical trial in older children did not see an increase in
neuropsychological problems associated with the use of dental amalgam in children. (31)

Multiple studies by Geier group reported an association of thimerosal with
neurodevelopmental disorders, including autism. These studies used the Vaccine Adverse
Events Reporting System (VAERS) as their data source which is unsuitable for this
purpose because most reports to the VAERS system in recent years regarding thimerosal
were influenced by litigation. (33) Wakefield’s seminal paper was retracted by the
Lancet in February 2010 because “several elements are incorrect, contrary to the findings
of an earlier investigation (2004).” Recent studies by other researchers, including three
cohort studies, (34) (35) (36) a case-control study, (37) a cross-sectional study, (38) and
an ecologic study, (39) report no association of thimerosal with autism.

The hypothesis of an association between thimerosal and autism has primarily
been based on biological plausibility through analogies with methylmercury. (40)
Ethylmercury, however, is thought to have a shorter half-life in the human body than
methylmercury, and no controlled studies of low-dose ethylmercury toxicity in humans
have been conducted. (41) Autism prevalence, however, continues to increase even after
thimerosal was effectively removed from childhood vaccines according to reports from
Canada (8)
SCREENING FOR ASD

Multiple screening tools have been devised to try to standardize screening for potential autism spectrum disorder prospectively. (see Table 1) The most common tools designed for use with children as young as 18 months are the Checklist for Autism in Toddlers (CHAT), Pervasive Developmental Disorders Screening Test (PDDST), Screening Tool for Autism in Two Year Olds (STAT), Checklist for Autism in Toddlers-23 (CHAT-23), and the Modified Checklist for Autism in Toddlers (M-CHAT). (42) (43) A positive score on a screening test can support referral to a specialist team for comprehensive evaluation, but a negative score does not rule out autism. (44) The primary care clinician should order a hearing assessment to rule out hearing loss as a contributory factor. If the child has pica with frequent mouthing of items, measurement of hemoglobin and lead will identify anemia or a raised lead concentration. (44) Then a referral is made to a neurobehavioral specialist or multidisciplinary team for fine testing, assessment, and counseling.

CO-MORBIDITIES OF AUTISM SPECTRUM DISORDERS

There are common comorbidities not included in the diagnosis that clinicians should anticipate. The rate of epilepsy in ASDs is typically defined as 30%. (45) Most studies show that ‘syndromic’ (nonidiopathic autism), intellectual deficits, and female sex all increase the risk of epilepsy in ASDs. (46) Motor impairments include stereotypies, motor delays, and deficits, such as dyspraxia, incoordination, and gait problems. (46) Stereotypies, or repetitive behaviors, were once thought ‘self-stimulatory’ but recently there is a growing appreciation that they are an involuntary movement disorder associated
with lower IQ and more severe phenotype of ASD. (46) One study demonstrated that social skills intervention actually improves repetitive behaviors. (47) A meta-analysis of 41 studies investigating coordination, gait, arm movements, and postural stability in ASDs found that, despite the tremendous heterogeneity across studies, individuals with ASDs exhibited significantly more motor incoordination and postural instability than controls. (48) As motor deficits are present in early childhood, they are being investigated as tools for earlier diagnosis and screening. Individuals with ASDs also have a high incidence of sleep dysfunction presenting as difficulty with sleep onset and prolonged awakenings during the night. (46)

**BEHAVIORAL THERAPIES**

Although autism is a medical diagnosis, occupational intervention is typically delivered in the educational setting. (44) The Institute of Medicine’s National Research Council recommends year round, systematically planned intervention of at least 25 hours a week and therapists recommend intensive intervention should start as soon as the diagnosis is seriously considered. (44) The curriculum promotes academic skills as appropriate for the child’s developmental level. Disruptive behaviors are best targeted with functional behavioral assessment, which identifies potentially modifiable factors or triggers. Appropriate treatment targets include the development of functional communication, as well as social and adaptive skills to maximize independence. (31) Reviews of early interventions show specific parent-training approaches yield gains in short-term language function and some challenging behaviors. Data suggest that
subgroups of children displayed more prominent gains across studies, but participant characteristics associated with greater gains are not well understood. (49)

There is no true drug therapy to treat autism, but many psychiatric drugs are used to treat the common comorbidities associated with autism that lead to challenging behaviors. There is evidence that riperidone, aripiprazole, and methylphenidate are effective treatments for hyperactivity, maladaptive behaviors, and irritability. (45) Although there is only marginal evidence for the practice, norepinephrine reuptake inhibitors and selective serotonin reuptake inhibitors are also prescribed. When a new difficult behavior emerges, a thorough search must be undertaken for underlying treatable medical causes such as otitis media, dental pain, constipation, gastro-esophageal reflux. (44)

Complementary Alternative Medicine (CAM) is another common therapy pursued by caregivers for children with ASDs. Vitamin supplementation, light therapy, and diet restriction are frequent therapeutic adjuncts. (44) Melatonin is efficacious in the management of sleep disorders associated with autism, particularly in improving sleep onset. (50) Although not readily harmful to the children, studies show little direct benefit and the studies lack sample size and rigor. (51) Chelation therapy, a less common therapy, has demonstrated itself as directly harmful, with case reports of deaths in children with autism receiving treatment. (44)

Small longitudinal studies have found that children who have absence of language by age 5 and low cognitive functioning have poorer outcomes in adolescence and adulthood on measures of self-sufficiency and adaptive functioning. (52) Higher
cumulative early intervention hours were associated with better outcome. (53) In spite of effort and therapy, many people with autism require supportive living arrangements into adulthood and relatively few are independently employed without support as young adults. (54)

DENTISTRY AND AUTISM SPECTRUM DISORDERS

Most studies of dental disease in patients with ASDs lack controls or rigorous study design to be strong evidence. In an early case series the autistic patients revealed a lower oral hygiene status than the controls, but a comparable caries index. (55) A cohort study in Turkey compared children with ASDs to typically developing children and found children with autism disorder had better caries status than children without autism disorder at younger ages. (56) The study showed the better DMFT was related to young age, high income, less sugar consumption rather than suggesting that ASDs are protective from caries. (56) A chart review in Boston showed a higher percentage of patients in the ASD group (51.6 %) than patients in the unaffected group (38.1 %) required restorative or surgical dental treatment (P = .0001), but when controlled for age and sex, they noted a statistically insignificant association between ASD and dental caries prevalence. (57) A Swedish study showed cases and controls had a similar prevalence of fillings, caries, gingivitis and degree of oral hygiene. However, the need of orthodontic treatment seemed to be greater among the autistic children. (58) A report from a hygiene clinic compared patients with ASDs to patients with non-ASD developmental disabilities and assessed their oral health. They found young children with an ASD who resided with parents showed significantly more signs of bruxism than the comparison groups of
developmentally disabled non-ASD patients. (59) Older children who lived at the residential school manifested significantly more gingivitis. Children with an ASD displayed the following percentages for clinically visible conditions: plaque (85%), gingivitis (62%), and caries (21%). (59) Although children with ASD appear to have oral conditions that increase the risk of developing dental disease, they are at or below the caries rate of their peers.

One readily recognized barrier to dental care for patients with ASD is their behavior related to their condition. A survey shows two-thirds of the individuals reportedly exhibited a normal eating pattern, while 14% pouched food. (60) In one study, approximately half of the children with ASD were orally defensive. (59) This is related to the various levels of sensory integration disorders. Successful initial oral examination and bite-wing radiographs were achieved on 50% of the autistic patients examined. (55) Within both groups, younger patients were more uncooperative. Patients with core autism were more uncooperative than patients with PDD-NOS; patients with an additional diagnosis were also more uncooperative. (61)

Cooperation is possibly predictable, but valid instruments do not exist yet. Parents are reliable sources of information about a patient’s potential for cooperation. They most accurately predicted if their child would permit an examination in the dental chair (≥88%) and would cooperate for radiographs (≥84%). Five questions readily answered by a caregiver may indicate a child’s cooperative potential. Pre-appointment inquiry about toilet training, tooth brushing, haircuts, academic achievement and language can give the dentist insight into the child’s ability to respond positively to
behavior guidance techniques based on communication. (62) The need for corporal physical restriction to perform oral examination and dental panoramic radiography during the first dental visit can be an indicator of the degree of collaboration that ASD patients may present. (71) Use of protective stabilization was associated with lower caries severity, presence of seizure disorder, uncooperative behavior, male gender, or residency in a group home or institution. (61)

Compared with other children with special health care needs without emotional, developmental, or behavioral problems, children with ASD were more likely to have unmet needs for specific health care services, family support services, delayed or foregone care, difficulty receiving referrals, and care that is not family centered. Their families were more likely to report financial problems, need additional income for the child’s medical care, reduce or stop work because of the child’s condition, spend 10 hours per week providing or coordinating care, and paid more than $1000 in the previous year for the child’s care. (63) The public health burden, reflected in annual costs, was recently estimated at $35 billion in the United States alone. (64) Dental care is the most prevalent unmet health care need for Children with Special Health Care Needs (CSHCN), affecting substantially more children than any other health care need category. Of those who reported a dental care need, an estimated 755,581 or 10.4% of CSHCN did not receive all of the dental care they needed. (65) The financial impacts of autism spectrum disorder were significantly more burdensome when children with special health care needs did not have a medical home. (63) This relates to unmet dental need and cost of care without a dental home. Examination of Public Dental Service in Sweden reports that
satisfactory care is provided without specialization provided access to a pediatric dentist is available when necessary, which in their survey was approximately 30% of the cases. (58) A survey of US dentists showed that 89% of pediatric dentists and 32% of general dentists treat patients with ASD. The better they felt prepared, the more likely they were to provide care for these patients. (66) The more a provider liked to treat children with ASD, the more patients with ASD they treated \( (r = .313; p = .018) \), and the more accommodations to overcome problems with communication, social interactions and aversion to change they made. Providers' attitudes concerning patients with ASD were positive and correlated with professional behavior concerning these patients. (67)

Traditional behavior management techniques currently used in dentistry may not encourage people with cognitive and behavioral disabilities, such as ASD, to tolerate simple in-office dental procedures consistently. (68) Hand-holding by a parent, tell-show-do, rewards, general anesthesia, and distraction were accepted at rates of 51% or greater. Efficacy for varying methods of protective stabilization was: parental restraint (46%); stabilization device (44%); and staff restraint (27%). (69) Applied behavior analysis (ABA) is a science in which procedures are based on the principles of behavior through systematic experimentation. (68) Unfortunately, ABA strategies are time-consuming, require professional training and their effectiveness has not been demonstrated in cost-benefit terms in the dental setting. The majority of published studies on this subject suggest that the process may be successful when the patient does not show resistance to sitting in the chair and allows oral examination to be performed. (70)
Oral premedication or procedural sedation is an advanced behavior management technique used to aid cooperation in children with behavioral disturbances. The use of moderate sedation or general anesthesia is often used in children with autism. (71) As there are few medical problems associated with autism that are related to sedation, sedation of this patient group is permissible with no increased medical risk over that experienced in the normal population. (72) The most acceptable advanced behavior management technique for CSHCN is general anesthesia (GA). (69) Although methods are generally considered safe, parents are often hesitant to expose their children to sedation, especially when it is not medically indicated. (72) ASD patients with higher caries severity, who were uncooperative or female, were more likely to require GA. (61) One chart review reports treatment under general anesthesia in the operating room was necessary in 37% of all patients when comprehensive care was required or difficult procedures were carried out. (60) A case control study shows more patients in the ASD group (37.2 %) than in the unaffected group (29.8 percent) required dental treatment to take place under general anesthesia (P = .03). (57)

Procedural sedation for CSHCN has a long history in medicine and dentistry. Significant effects on organ systems include: decrease in blood pressure, depressed ventilation (transient apnea, especially in combination with opioids), and a decrease in cerebral metabolic rate. It is very interesting to note that basic science research continues to try to elucidate the effect of anesthetics, including benzodiazepines, on the developing
brain and neurocognitive function. (73) Kopel originally suggests an anxiolytic regimen with hydroxyzine. An attempt is being made to bring the disruptive behavior under control slowly, to educate the patient to tolerate or accept dental procedures rather than proceeding with a completely uncommunicative child who has been placed in an almost somnolent state. (74) The use of barbiturates in autistic children is generally not advisable, as it may have a paradoxical stimulating effect. (75) Benzodiazepines are particularly useful for sedation in pediatric patients with developmental disabilities and neurologic disorders because of their useful range of therapeutic effects: sedation, anxiolysis, muscle relaxation, and anterograde amnesia. (73) Benzodiazepines also have anticonvulsant effects by enhancing the effect of the neurotransmitter gamma-aminobutyric acid (GABA) and are ideal for sedating children with epilepsy, a common comorbidity in ASD. (73) A case study of ketamine to midazolam shows it to be acceptable when given orally with flavored liquid and without paradoxical reaction in autistic patient. (76) Pentobarbital and fentanyl were the two most common medications used for moderate to deep sedation in medicine with no difference in mean dosages between children classified as “normal” or “developmental disability”. However, the patients classified as having developmental disability had a threefold increased incidence of hypoxia (11.9% versus 4.9%; P < .01). (73) Intramuscular and intravenous midazolam is effective in 89% of a convenience sample for dental procedures in patients with neurological and behavioral disturbances, but it was less effective for patients with autism (p<0.05). (77)
Intranasal drug administration for CSHCN has gained popularity due to its simplicity of delivery in spite of patient cooperation. The highly vascularized nasal mucosa and the olfactory tissue in direct contact with the central nervous system allow nasally administered drugs to be rapidly transported into the bloodstream and brain with onsets of action approaching that of intravenous therapy. First-pass drug metabolism via the liver is also avoided, resulting in high bioavailability of many medications. Delivery of intranasal medications is relatively painless, inexpensive, and easy to deliver with a minimum of training. (78)

Minimizing drug volume while maximizing drug concentration, adequate dosing, use of both nostrils to double the absorptive mucosal surface, and use of atomized particles to enhance medication absorption all improve the effectiveness of medication delivered intranasally. Because of incomplete and slower absorption with nasal administration, higher medication doses than those given intravenously are also require to achieve similar efficacy. The recommended dosage is 0.4-0.5 mg/kg in the literature (79). Although there were no statistically significant differences in preoperative Frankl behavior ratings between oral and nasal routes of administration for typically developing 2- and 3-year olds, behavior ratings during administration were statistically better for the nasal spray. (80) The most common adverse effect noted is nasal burning and irritation after administration of midazolam. (81) Concentrated medications in a small volume (0.2-0.3mL per nostril) are ideal, whereas volumes in excess of 1mL per nostril are not reliably absorbed as a result of mucosal surface saturation and runoff from the nasal cavity. (80)
Emergency medicine studied intranasal midazolam for laceration repair in preschool-aged children and observed a dose range of 0.3-0.5mg/kg to be associated with adequate sedation in 80-100% of children. No vomiting or clinically significant oxygen desaturation was observed. (82) Lane and Schunk reviewed 205 cases of intranasal midazolam use for procedural anxiolysis among children who were 1-60 months and seen in the emergency department. They found that 95% of patients who were treated with intranasal midazolam achieved anxiolysis and required no additional sedative to complete the procedure. There were no adverse events among the 194 patients who received only intranasal midazolam. (83)

The dental literature uses more conservative doses intranasally. A dose of 0.2 mg/kg was studied as an adjunct for various restorative dental procedures on a group of mentally disabled patients under local anesthesia and nitrous oxide/oxygen analgesia. Ratings on a scale of 1-7 were noted as "markedly effective" and "effective" for 69.2% of those patients who received infiltration injection anesthesia, 93.8% under rubber dam, 76.2% during cavity preparation, 84.2% for restoration placement and 87.5% during pulpotomy procedures. (84)

OBJECTIVE

The specific aim is to conduct a pilot study to assess the benefit of intranasal midazolam for patients with ASDs in the context of preventive and diagnostic dental appointments. Secondary aims include measurement of caregiver satisfaction, post-operative complications, and diagnostic yield of radiographs as measures of patient benefit.
METHODS

A quality assurance database approved by the Nationwide Children’s Hospital (NCH) IRB was maintained and reviewed from 2009 to present. Patients included in the database were assessed as procedural sedation candidates during an initial examination visit, referred for sedation, and treated at NCH. A data subset was reviewed with the following inclusion criteria: a diagnosis of an autism spectrum disorder reported by the legal guardian, age 5-18 years, history of uncooperative behavior reported by guardian or record.

Each sedation visit followed the NCH Pediatric Dental Clinic protocol. The child’s identity is confirmed and weighed. Medical history, a review of systems, and limited physical exam are conducted to establish the risks and safety of procedural sedation for the patient. All children are fasting for 8 hours but given daily medications as prescribed with limited water. The legal guardian signs an informed consent for sedation and the procedures to be planned.

Patients were sedated with 0.5 mg/kg intranasal midazolam to a maximum of 15 mg using a Medication Atomizing Device. A papoose for protective stabilization was used if needed for patient safety with consent and the guardian remained in the room for duration of the appointment. Bitewing radiographs were taken using phosphor plates and a Snap-Array with lead apron for patient and operator and a lead hand shield to stabilize film. Prophylaxis was performed and scaling as indicated followed by a mirror and explorer clinical exam and fluoride application. Restorations or sealants were completed as the appointment permitted. Patients were discharged based on hospital criteria that
include return to baseline vital signs and ability to interact and maintain head posture. If further restorative treatment was diagnosed and not completed in the visit, appropriate referrals to general anesthesia or sedation were made. All treatment and assessment were performed by a single pediatric dental resident and attending. Caregivers of children were contacted by the study coordinator within 48 hours of discharge to assess recovery, complications, and satisfaction.

A bitewing radiographic exam was attempted in each appointment. These radiographs were de-identified, printed from Dexis and reviewed by 3 independent calibrated examiners to quantify their diagnostic yield. A diagnostic yield point was assigned if the radiographs met criteria for caries, periodontal, or other oral pathology detection for a maximum score of 3 and automatic 0 if no radiographs were obtained. The reviewers were calibrated with 3 example radiographs printed with the rating criteria.
RESULTS

DEMOGRAPHICS

Data for this pilot study were collected from Nationwide Children’s Hospitals Post-Sedation Survey and selected from records for patients with an ASD given intranasal midazolam for a diagnostic and preventive appointment (n=29). Twenty-eight caregivers were successfully contacted after the appointment for a complete post-operative survey. Ninety percent (n=26) of patients were male. Ages were evenly distributed with 14% (n=4) 60-79 months of age, 10% (n=3) 80-99 months, 17% (n=5) 100-119 months, 21% (n=6) 120-139 months, 17% (n=5) 140-159 months, and 21% (n=6) 160 months or older. Caucasian patients were 76% (n=22) of the sample with the balance being African American (21%, n=6) and Hispanic (3%, n=1). Comorbidities include MRDD (17%, n=5), attention deficit hyperactive disorder (10%, n=3), asthma (7%, n=2), cerebral palsy (7%, n=2), obsessive compulsive disorder (7%, n=2), and unspecified other behavior disorders (14%, n=4). Twenty-one percent of patients were accompanied by one or more caregivers missing work for the appointment. Roundtrip distance recorded 45% (n=13) traveling 0-50 miles, 21% (n=6) 51-100 miles, 10% (n=3) 101-150 miles, and 24% (n=7) greater than 150 miles.

CHARACTERISTICS OF SEDATIONS

Weight distribution allowed 24% of patients to be given 0.5mg/kg doses with the remaining 76% above 30 kg and given lower doses due to the absolute maximum dosage of 15 mg. All but one patient required passive stabilization during the sedation. Ninety-three percent (n=27) of patients required 60 minutes or less from administration of
medication to discharge. Ninety-seven percent (n=28) of patients completed a prophylaxis, 93% (n=27) completed bitewing radiographs, and 14% (n=4) completed sealants or composite restorations. The operator rated 76% (n=22) of the sedations effective, 17% (n=5) somewhat effective, and 7% (n=2) ineffective. There were no incidences of over sedation. Caregivers rated 93% (n=26) of the sedations successful with 96% (n=27) satisfied with the procedure. When asked, 89% (n=25) would consent to sedation again if needed.

POST-OPERATIVE RECOVERY

Normal eating habits were observed by 68% (n=19) caregivers in less than 2 hours, 18% (n=5) in 2-4 hours, 4% (n=1) in 4-6 hours, and 11% (n=3) in greater than 4 hours. Normal play was observed by 43% (n=12) caregivers in less than 2 hours, 29% (n=8) in 2-4 hours, 14% (n=4) in 4-6 hours, and 14% (n=4) in greater than 4 hours. Normal sleeping habits were observed by 57% (n=16) caregivers in less than 2 hours, 21% (n=6) in 2-4 hours, 0% (n=0) in 4-6 hours, and 21% (n=6) in greater than 4 hours. These are summarized in Figure 6. Normal eating habits were observed in less than 2 hours in patients with mean weight 50.0 kg, in 2-4 hours with mean weight 37.9 kg, in 4-6 hours with mean weight 22.5 kg, and in greater than 4 hours with mean weight 27.2 kg. Normal play was observed in less than 2 hours in patients with mean weight 52.0 kg, in 2-4 hours with mean weight 40.0 kg, in 4-6 hours with mean weight 35.0 kg, and in greater than 4 hours with mean weight 40.2 kg. Normal sleeping habits were observed in less than 2 hours in patients with mean weight 50.6 kg, in 2-4 hours with mean weight 35.6 kg, and in greater than 4 hours with mean weight 37.0 kg. These are summarized in
Figure 7. Common side effects noted by caregivers were hiccups (32%, n=9) and nausea/vomiting (11%, n=3), which are higher the pediatric populations estimates of 3.9% and 5.4% respectively for oral midazolam. No paradoxical reactions were observed in study subjects, compared to 2% expected in for the pediatric population.

DIAGNOSTIC YIELD

The operator was successful taking 2 bitewings on 93% (n=27) patients during the sedation appointment. Figure 8 demonstrates that of the 27 radiographic examinations, 41% (n=11) received 0-3 total diagnostic yield points from the 3 reviewers, 37% (n=10) received 4-6 points, and 22% (n=6) received 7-9 points. When scored by category, the mean diagnostic yield of caries was 17.7 points (sd=1.5), periodontal disease was 13.7 points (sd=5.0), and other pathology was 7.3 points (sd=4.0).
DISCUSSION

Twenty-nine records of 568 met the inclusion criteria of an ASD and intranasal midazolam sedation for diagnostic dental procedures. NCH Department of Pediatric Dentistry currently employs traditional behavior management, passive stabilization, and general anesthesia in addition to procedural sedation for the management of patients with ASDs. A patient may be sent to general anesthesia if there are visible carious lesions or if a radiographic examination is indicated and not completed for an extended period of time. A referral for procedural sedation is made when traditional behavior management and passive stabilization do not provide an adequate oral assessment and prophylaxis or the caregiver requests an alternative to reduce the patient’s anxiety during the procedure. Intranasal midazolam is an alternative to general anesthesia for uncooperative patients with ASDs that do not show clear clinical signs of extensive restorative needs. Oral midazolam syrup is a commonly used medication for pediatric conscious sedation, but it is not an ideal regimen for adolescents with ASDs. It requires cooperation for administration or syringing with protective stabilization. The bitter flavor is difficult to mask for typically developing children, and patients with ASDs are frequently aversive to flavors and textures.

The database is kept to record demographics, intraoperative and postoperative characteristics of sedations, and caregiver satisfaction. The reported gender ratio of 90% male is not consistent with the 4 to 1 ratio of males to female affected with an ASD in the general population. (11) This may reflect the small sample size or may be attributed to the different characteristics of males and females with ASDs. Females frequently have
more severe disabilities and comorbidities which may have selected them for general anesthesia. (10) The age distribution shows a modest trend of increased frequency with increased age. This is consistent with the initial indication for a procedural sedation that traditional behavior management and passive stabilization were initially inadequate. If patients do not desensitize or adapt to the routine of a dental appointment as they age and grow, their size becomes an additional challenge for the providers.

Comorbidities were either reported by caregiver or taken from the hospital chart. The findings do reflect some of the most common diagnoses associated with ASDs, but epilepsy is markedly absent. The rate of epilepsy in ASDs is typically defined as 30%, and no patient sampled had a seizure disorder. (46) Unlike the gender distribution, patients with seizures would not be excluded for their health condition alone as midazolam raises the seizure threshold. The reporting method was limited by caretaker recall and sophistication. Due to the changing nature of an ASD diagnosis, many caregivers only reported their child’s diagnosis as an ASD without providing the details of PDD-NOS, Autism Disorder, or Asperger’s Disorder. Mental Retardation Developmental Delay was inconsistently reported and some behavioral conditions, such as aggression, were given by family, but not diagnosed by a physician. Caregivers were instructed to maintain behavior drug regimens unless impossible to give with a limited volume of water to maintain baseline behavior. These were not specifically recorded in the database, but are part of the standard preoperative instructions.

Families of children with special healthcare needs (CSHCN) are more likely to report financial problems, need additional income for the child’s medical care, reduce or
stop work because of the child’s condition, spend 10 hours per week providing or coordinating care, and paid more than $1000 in the previous year for the child’s care. (64) Dental care is the most commonly unmet need for Children with Special Healthcare Needs. (63) Twenty-one percent of patients had one or more caregiver’s missing work for the sedation appointment. This does not reflect the burden of no longer being able to work because the child requires full time care or when patients were brought to the appointment by a caregiver from a facility who is working when bringing the patient to the appointment.

Midazolam is a benzodiazepine which enhances the inhibitory effect of GABA on neuronal excitability. This increases neuronal membrane permeability to chloride ions and hyperpolarizes the membrane. When administered intranasally for anxiolysis, the pediatric dosage is 0.5 mg/kg with a maximum dose of 15mg. It has a 4-8 minute onset and approximate duration of 15 minutes. (86) Nitrous oxide was not used to isolate the benefit to the midazolam and keep the patient in the category of anxiolysis requiring baseline, pre-operative and post-operative vital signs measurements rather than intermittent and continuous. Intranasal administration eliminates cooperation for full dosage.

This sample of patients was older than the pre-cooperative, typically developing children sedated for operative dentistry, therefore their weights required the maximum dosage rather than pediatric dose by weight in 76% (n=22) of cases. The provider recorded the sedation “effective” if radiographs were taken and the patient appeared calmer than baseline. The sedation was considered “somewhat effective” if there was
progress such as scaling or prophylaxis that had not been completed without the sedation.

“Ineffective” sedations were those in which the patient never calmed as reflected in vitals or reported behavior. In spite of the dose limitation and the variable metabolism of the pediatric population, only 7% (n=2) were categorized ineffective by the provider.

Protective stabilization was used for 97% of patients. The Papoose was used for a number of indications beyond behavior management during the sedation. Unless the patient was particularly small, they were placed in the Papoose with the help of the caregiver for administration of the midazolam. This prevented movement during administration that could reduce the delivered dosage or resulted in an eye injury to the patient or providers. If the medication was administered in the Papoose, the patient remained for the duration of the procedure. Pressure is a calming stimulation for patients with neurobehavioral disorders and it has been empirically observed as a benefit to patients with ASDs. This also prevented injury as the medication took effect reduced the number of operators remaining in the room during radiograph exposure.

The decision to keep caregivers in the room during the procedural sedation was based on the nature of the treatment and benefit to the patient. Caregivers were given an opportunity to see in the patient’s mouth, observe clinical pathology, and receive oral hygiene instructions, as a typically developing child would during outpatient hygiene appointments.

The duration of intranasal midazolam sedation is shorter than oral regimens because of its short onset time (4-8 seconds) and briefer than general anesthesia because of its effect time (15 minutes) and rapid recovery. Ninety–three percent of patients were
discharged in 60 minutes or less from time of midazolam administration. This improves access since a provider can see more patients in a unit time and reduces the time burden on the family as compared to alternative pharmacological behavior management.

Caregivers rated 93% (n=26) of the sedations successful with 96% (n=27) satisfied with the procedure. When asked, 89% (n=25) would consent to sedation again if needed. The database did not provide factors for satisfactions, but reducing anxiety associated with dental appointments, avoidance of general anesthesia, and presence in the room may all contribute.

In less than 2 hours, normal eating habits were observed by 68% (n=19) caregivers normal play was observed by 43% (n=12) caregivers and normal sleeping habits were observed by 57% (n=16). The patients that returned to baseline most rapidly also had the highest mean weight but the trend did not appear linear as seen in Figure 3. The recovery may also be influence by BMI, concurrent medications, or baseline agitation which were not measured in this database. Sleep disturbances are commonly noted in the literature for children with ASDs, but not clearly observed here. The question used to assess baseline sleep may be the weakness in this finding since these children are above the age for midday naps and the questions only covered daytime sleeping. Common side effects noted by caregivers were hiccups (32%, n=9)) and nausea/vomiting (11%, n=3). No paradoxical reactions were observed supporting the benefits with low risk associated with intranasal midazolam.

Ninety-seven percent (n=28) of patients completed a prophylaxis, 93% (n=27) completed bitewing radiographs, and 14% (n=4) completed sealants or composite
restorations. Previous studies report 50% of patients with an ASD able to complete radiographs with traditional behavior management (55). The 93% recorded here are of the half that were unable to complete radiographs unaided and allowing the balance of children with an ASD to have the same standard of preventive and diagnostic care as typically developing children without the additional burden, risk and cost of general anesthesia.

The sealants and restorations were diagnosed and treatment planned from the successful examinations. They are examples of diagnostic yield, which we describe as diagnostic information gained from the procedure. The radiographs taken were further assessed for their own diagnostic yield. If caries, periodontal disease, or other pathology were detected, the radiograph was given a point. This was in an effort to recognize the variation in radiograph quality still contributed to the patients overall care. More stringent radiographic assessments exist, but do not capture contributions from imperfect radiographs. Figure 8 demonstrates 77% of radiographs had high or moderate diagnostic yield. This is clinically significant for patients that otherwise would forgo radiographs until general anesthesia. Reviewers gave higher diagnostic yield scores in caries diagnosis. The lowest were for oral pathology. The radiographs were taken with a Snap array to provide an extraoral point of stability. This reduced the periodontal tissues captured in the film if a larger film was not used. Reviewers were least consistent in the oral pathology diagnostic yield due to the ambiguity of the definition and the limited view of a bitewing radiographs.
As a pilot study, there were many limitations. The sample size was small and cannot demonstrate statistically significant trends, but clinically significant observations were possible. The lack of controls and blinding were the greatest weakness in the dataset. Great efforts were made to make each appointment valuable to the patient and caregiver, so using the last recall as a control allows for too many variables to isolate intranasal midazolam as the determinant of success. The caregiver observations of the patient returning to baseline allowed for ambiguity in findings and were very subjective. Greater clarification of diagnostic yield criteria will be gained from the pilot assessment.

Given the limitations of the pilot study, the results support the use of intranasal midazolam for diagnostic and preventive dentistry appointments as a safe and effective adjunct for children and adolescents with Autism Spectrum Disorders, and provide the foundation for an Investigational New Drug application for novel use of intranasal midazolam in the future.
REFERENCES


APPENDIX A: SEDATION SURVEY

The Postoperative Management of
Children Undergoing Oral Sedation
for Dental Rehabilitation

Zip Code:________
Name:________________________________________
Phone:________________________________________
Weight(kg):_______   Med Hx: (circle) Autism   Asthma   Respiratory-Illness   Prematurity
Other:________________
Race: Caucasian   AA   Hispanic   Asian   Other:________________
Was interpreter needed: (circle) Yes or No
Language:________________
Sedation Regimen Given:________________________(circle) Cup   Syringe   Nasal
Duration of Procedure (from time meds given until pt’

discharge):_______________________________________
Effectiveness of Sedation
Ineffective
Did anyone miss work? Somewhat effective
Y/N Effective
How many__________ Overly effective

Restraints: Papoose Lead Apron Other: Local Anesthetic Y/N
Parents in room: Yes or No Block or Infiltration
Xray attempted: Yes or No Achieved: Yes or No Local
Anesthetic:________________
Next Visit: GA Sedation Hygiene CC All Scheduled work complete? Yes or No
Resident:________________________

Please list procedures in chart below:

<table>
<thead>
<tr>
<th>Max Arch</th>
<th>Pulp</th>
<th>SSCs Kinder</th>
<th>Ext</th>
<th>Resin Amal</th>
<th>Strip Crown</th>
<th>Mand Arch</th>
<th>Pulp</th>
<th>SSCs Kinder</th>
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<th>Resin Amal</th>
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Other work completed: -
Analgesics required (circle) Yes or No
If yes, please write the name of the drug dosage, date and time. Please include every time analgesic was given:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Date/Time</th>
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</table>

Nausea or vomiting? (Circle)  Yes or No
Lip biting? (Circle)  Yes or No
Cheek biting? (Circle)  Yes or No
Tongue biting? (Circle)  Yes or No
Hiccups? (Circle)  Yes or No  Intraoperative or Postoperative
Other problems? (Circle)  Yes or No
If yes, please describe:

How long after the procedure was your child:

<table>
<thead>
<tr>
<th></th>
<th>&lt;2hrs</th>
<th>2-4 hrs</th>
<th>4-6 hrs</th>
<th>&gt;6hrs</th>
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<tbody>
<tr>
<td>Eating Normally</td>
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<td>Playing Normally</td>
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<tr>
<td>Sleeping Normally</td>
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Did you consider that the sedation was successful? (Circle) Yes or No
If no, why not?
Are you satisfied with the outcomes of the procedure? (Circle)  Yes or No
If necessary would you choose sedation for your child again? (Circle)  Yes or No

How long after were parents contacted:  <24 hrs  48-72 hrs
                                        24-48 hrs  >72 hrs
APPENDIX B: RADIOGRAPH ASSESSMENT FORM

Circle the answer

1. Can the radiographs confirm the absence or presence of caries?
   Yes or No

2. Can the radiographs confirm the absence or presence of periodontal disease?
   Yes or No

3. Can the radiographs confirm the absence or presence of other oral pathology?
   Yes or No

**Calibration Criteria:**

**Yes:**
Contacts in 2 or more quadrants have no more than half enamel thickness of overlap or Radiographic decay detected in any tooth

**Yes:**
Alveolar crestal bone present in 2 or more quadrants or Radiographic signs of bone loss in a single quadrant

**Yes:**
Can you visualize the entire crown and the coronal root third of the primary maxillary and mandibular first molars or permanent first premolars? or Oral pathology found
<table>
<thead>
<tr>
<th>Gender</th>
<th>% of Patients</th>
<th>Roundtrip Distance</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>26 90%</td>
<td>0-50 miles</td>
<td>13 45%</td>
</tr>
<tr>
<td>Female</td>
<td>3 10%</td>
<td>51-100 miles</td>
<td>6 21%</td>
</tr>
<tr>
<td>Total</td>
<td>29</td>
<td>101-150 miles</td>
<td>3 10%</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Age (months)</th>
<th>% of Patients</th>
<th>Did Someone Miss Work for Apt?</th>
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<tbody>
<tr>
<td>60-79</td>
<td>4 14%</td>
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<tr>
<td>80-99</td>
<td>3 10%</td>
<td>Total 29</td>
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<tr>
<td>100-119</td>
<td>5 17%</td>
<td>Mother 2 7%</td>
</tr>
<tr>
<td>120-139</td>
<td>6 21%</td>
<td>Father 2 7%</td>
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<tr>
<td>140-159</td>
<td>5 17%</td>
<td>Both 2 7%</td>
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<td>160+</td>
<td>6 21%</td>
<td>Relative 0 0%</td>
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<td>Total =</td>
<td>29</td>
<td>Other 0 0%</td>
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<tr>
<th>weight (kg)</th>
<th>% of Patients</th>
<th>Comorbidities</th>
<th>% of Patients</th>
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<tbody>
<tr>
<td>10-20.</td>
<td>2 7%</td>
<td>No 23 79%</td>
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<td>20-30</td>
<td>5 17%</td>
<td>Asthma 2 7%</td>
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<td>30-40</td>
<td>7 24%</td>
<td>ADHD 3 10%</td>
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<td>40-50</td>
<td>5 17%</td>
<td>MRDD 5 17%</td>
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<td>50+</td>
<td>10 34%</td>
<td>OCD 2 7%</td>
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<tr>
<th>Race</th>
<th>% of Patients</th>
<th>Comorbidities</th>
<th>% of Patients</th>
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<tbody>
<tr>
<td>Caucasian</td>
<td>22 76%</td>
<td>CP 2 7%</td>
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<tr>
<td>AA</td>
<td>6 21%</td>
<td>other 4 14%</td>
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<td>Hispanic</td>
<td>1 3%</td>
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<td>Asian</td>
<td>0 0%</td>
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<td>Other</td>
<td>0 0%</td>
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<td>Don't Know</td>
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<td>Total =</td>
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**Table 1: DEMOGRAPHICS**
APPENDIX D: FIGURES

Figure 1: AGE (MONTHS)

Figure 2: ROUNDTrip DISTANCE TRAVELED
Figure 3: FREQUENCY OF COMORBIDITIES

- Asthma: 2
- ADHD: 3
- MRDD: 5
- OCD: 2
- CP: 4
- Other: 6

Figure 4: OPERATOR RATED EFFECTIVENESS OF SEDATION

- Effective: 76%
- Somewhat Effective: 17%
- Ineffective: 7%
- Overly Effective: 0%
Figure 5: DOSAGE

Figure 6: DURATION OF PROCEDURE
Figure 7: DISTRIBUTION OF NORMAL EATING, PLAYING, AND SLEEPING

Figure 8: TIME TO BASELINE BEHAVIORS

44
Figure 9: DISTRIBUTION OF DIAGNOSTIC YIELD

Figure 10: DIAGNOSTIC YIELD BY CATEGORY