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Intranasal Midazolam with Lidocaine for Sedation in Pediatric Myringotomy and Tube Surgery: A Randomized Controlled Trial

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Abstract

Background & aims: Intranasal Midazolam (INM) sedation for children has been associated with side effects. This prospective, double-blind, placebo-controlled trial assessed whether the addition of Lidocaine to intranasal Midazolam (INM+L) affected efficacy or discharge time among pediatric patients undergoing elective bilateral myringotomy and tube placement (BMT).

Methods: This trial enrolled children aged 18 months to 7 years undergoing BMT, Physical Status class 1 or 2, in a single academic medical center. Interventions were

Placebo (intranasal saline); INM only (0.2mg/kg of INM concentration 5mg/ml); INM plus Lidocaine (INM+L; 0.2mg/kg INM plus Lidocaine 4% based on 25% of Midazolam volume). Outcomes included post-anesthesia care unit times, observed behavioral distress visual analog (OBD) scales (nurse and parent), and sedation scores (Certified Registered Nurse Anesthetist [CRNA] and Registered Nurse [RN]).

Results: Forty-two subjects were included, 14 in each group, with 52% female, 41% Physical Status 2 and average age 2.7 years. Post-anesthesia care unit times averaged 36.5 minutes (range 15-132 minutes), with no delay in discharge with INM or INM+L versus placebo (p=0.88). Verbal complaints were highest among INM+L at the time of administration (p=0.01). RN-scored OBD at 1-minute post-administration differed significantly across the three groups (p=0.01). Parental OBD scores did not differ across treatment groups. Agitation was greatest at time of induction of anesthesia in the placebo group (p=0.01).

Conclusions: The addition of Lidocaine to INM does not adversely influence time to discharge and does not reduce side effects, improve efficacy or change duration of action of INM.

Trial Registration: Clinicaltrials.gov, trial # NCT02356705

MeSH Keywords: Anesthesia; Intranasal administration; Pediatric anesthesia

Abbreviations: INM: Intranasal Midazolam; INM+L: Intranasal Midazolam+Lidocaine; RN: Registered Nurse; CRNA: Certified Registered Nurse Anesthetist; OR: Operating Room; PS: Physical Status; VAS: Visual Analog Scale; OBD: Observed Behavioral Distress; PACU: Post-Anesthesia Care Unit; MAD: Mucosal Atomization Device; SD: Standard Deviation; IQR: Interquartile Range; BMT: Bilateral Myringotomy and Tube placement; IN: Intranasal

Introduction

The ideal premedication for the pediatric patient remains controversial. Preoperatively, an agitated child is at risk for undesirable sequelae such as injury, anxiety and post-operative sleep disorders **[1-5]**. An ideal preanesthetic medication should reduce anxiety and allay parental separation fears while minimizing any delay in discharge **[6].** Untoward side effects should be minimized such as painful intramuscular injection, delayed onset via oral/rectal administration. Crying after Intranasal Midazolam (INM) administration has been described as a causative measure of discomfort from the drug **[7],** as well as nasal burning, bitter aftertaste **[8],** and mild epistaxis **[7].** A potential pitfall with orally administered Midazolam is low bioavailability **[9].** Bitter aftertaste is also detrimental to patient compliance and is cause for rejection of oral or sublingual administration of Midazolam **[7,9]** resulting in reduced efficacy. Other concerns for orally administered Midazolam include possible adverse effects on gastric pH and gastric volume **[10].** Administration of INM+L in an attempt to reduce side effects has been described **[8,11].** For years, the lead author has utilized readily available components at

the bedside for INM+L administration in a single atomization versus two separate atomizations in an effort to reduce patient discomfort. The current study was designed to investigate whether simple, convenient combination of Lidocaine and Midazolam could improve patient compliance and preoperative sedation in a timely, safe fashion while reducing unwanted side effects in 18 months to 7-year-old pediatric patients scheduled for BMT. All cases were performed under mask general anesthesia in a teaching hospital as outpatients. A secondary objective was to examine discharge times from the Post Anesthesia Care Unit (PACU) in patients receiving INM alone, INM+L, or placebo.

Materials and Methods

Ethical approval for this study (Study # 1098) was provided by the Mary Imogene Bassett Hospital Institutional Review Board, Cooperstown, New York, USA (Chairperson David Strogatz, PhD) on January 6, 2015. This study was conducted in compliance with the ethical standards of this Institutional Review Board as well as with the Helsinki Declaration. Written informed consent was obtained by the child's parent or legally authorized representative. This study was registered prior to subject enrollment (on February 2, 2015), with clinicaltrials.gov, trial # NCT02356705 (Registered Trial Name: Intranasal Midazolam in Children as a Pre-Operative Sedative - Part 2).

Protocol

This study was prospective, double-blind, randomized, and placebo controlled. Eligible subjects were children aged 18 months-7 years, scheduled for BMT requiring mask anesthesia at Bassett Medical Center (between February 2015 and December 2017). All patients were seen in our ENT clinic and diagnosed with chronic bilateral otitis media and noted to be surgically naïve. Eligible subjects had to be classified as Physical Status (PS) Class 1 or 2 according to the American Society of Anesthesiologists. Furthermore, subjects were only eligible if a parent or legally authorized representative was willing and able to provide informed consent and had the ability to complete the behavioral Observed Distress (OBD) Visual Analog Scale (VAS). Children with Physical Status (PS) Class 3 or greater, with history of allergy to Midazolam or Lidocaine, or presence of acute respiratory infection at the time of surgery, were excluded. Eligible, consented study participants were randomly assigned to one of three treatment groups in a 1:1:1 ratio.

The treatment groups were as follows:

- Group 1 – Placebo – Patients received intranasal saline.
- Group 2 – INM: Nasal Midazolam Only – Patients received 0.2 mg/kg of intranasal Midazolam; Midazolam concentration 5mg/ml.
- Group 3 – INM+L: Midazolam Plus Lidocaine – Patients received 0.2 mg/kg intranasal Midazolam plus Lidocaine 4% in a dose based on 25% of the volume of the calculated Midazolam dose; Midazolam concentration 5mg/ml.

All individuals involved in the execution of the study, including investigators and administering staff, were blinded with the exception of the inpatient pharmacist. Preparation of the study drugs was carried out by this pharmacist. The drugs were prepared in two vials: Midazolam/placebo and Lidocaine/placebo, with instructions on how much to withdraw from each vial and mix in one syringe. Syringes were 3cc or 1cc (tuberculin) depending on the size of the dose. The volume of medication was shielded from investigators and administering staff to preserve blinding. The medication was administered into a naris using the LMA MAD Nasal™ Intranasal Mucosal Atomization Device **(Figure 1).**

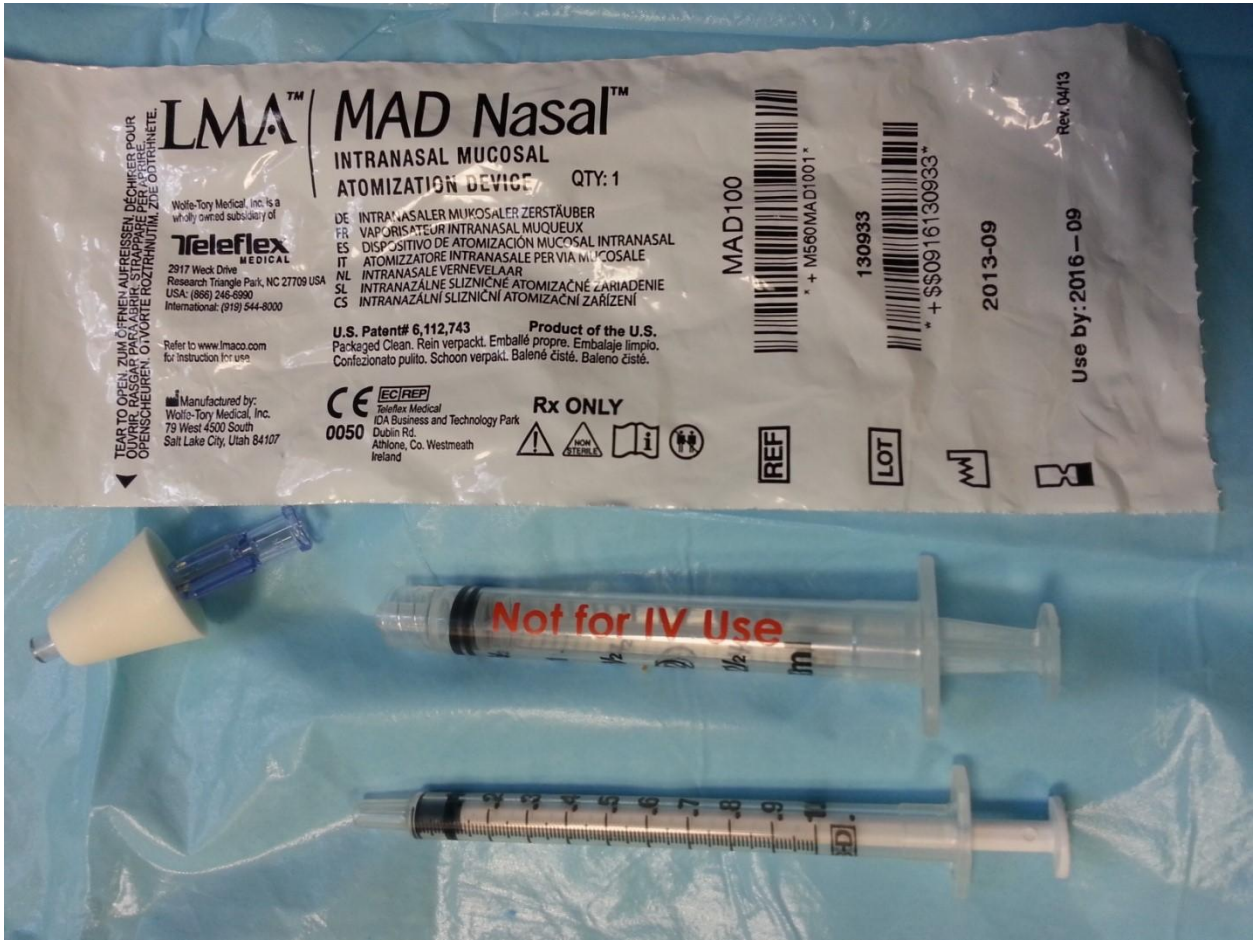

Figure 1: Intranasal Mucosal Atomization Device used for drug administration.

All patients had mask anesthesia, provided by a staff CRNA under medical direction of a staff Anesthesiologist with no additional analgesia administered in the PACU. All patients received a standardized mask anesthetic administration and maintenance consisting of Nitrous Oxide combined with either Sevoflurane or Desflurane. Acetaminophen 10mg/kg was administered per rectum after administration of anesthesia. The same administering RN enrolled patients and collected informed consent documentation from the parents pre-operatively in the ENT clinic. This RN collected the following data points within 10 minutes of transfer to the operating room: verbalized complaints at the time of study drug administration, 1 minute, and 5 minutes post-administration; any episodes of epistaxis; Observed Behavioral Distress Visual Analog Scale (OBD VAS) at 1 minute and 5 minutes post-administration; Sedation score [12] at 10 minutes and 15 minutes post-administration (measured as: agitated, alert, calm, drowsy, asleep). The accompanying parent completed the OBD VAS at 1 minute and 5 minutes post-administration. A staff CRNA assigned to the study room each day completed the sedation scale at the time of transport to the Operating Room (OR) and at time of induction of anesthesia. For the OBD VAS measures, the RN and accompanying parent were asked to "place a mark on the line to indicate how distressed you think the child is right now", with "0" indicating no distress and "10" indicating the most distress possible. One additional endpoint included time from the Post-Anesthesia Care Unit (PACU) using the Aldrete scoring system of at least 9 points, to discharge home.

Randomization and sample size considerations

The randomization schedule was produced by the study statistician using SAS software with a randomized block design in blocks of random permutations of the numbers one, two and three. Based on pilot data, collected from February 2012 – January 2014, it was estimated that 15 subjects in each treatment group would provide adequate statistical power (power=0.824, two-tailed alpha of 0.05) to detect a 2-unit difference (estimated standard deviation=3.3 units) in RN observed visual analog behavioral distress scores at 1-minute post-administration. Due to limitations in the number of providers (attrition of one otolaryngologist) and low numbers of willing eligible patients during the two-year study period, recruitment was halted once 14 subjects were recruited in each treatment arm. This did not amount to a significant drop in statistical power (power=0.793).

Statistical Analysis

Comparisons between the three treatment groups were carried out using chi-square for categorical outcomes (e.g., verbalized complaints, sedation scores). The Kruskal-Wallis test was used to compare VAS scores and age across the three treatment groups. For three-group comparisons with overall $p<0.05$, pairwise relationships were

explored by first converting the data to ranks and then performing Scheffe's post hoc tests via parametric analysis of variance (ANOVA). Probabilities of less than 0.05 were considered statistically significant. All analyses were conducted using SAS 9.3 (Cary, NC).

Results

Pre-screening identified 105 pediatric subjects scheduled for BMT. Among those, ten were excluded due to ineligibility (unknown PS class, too young, guardian unable to give consent). Among 95 eligible subjects, eight had surgeries canceled and were therefore excluded. From the 87 remaining eligible subjects, 15 parents/guardians did not respond to the invitation to participate in the study, while 30 parents/guardians declined participation. A total of 42 subjects were included in this study, 14 in each of the INM alone, INM+L, and placebo groups (Figure 2). The study sample was 52% (N=22) female, 41%(N=17) PS Class 2, and 2.7 years old on average with a range of 18 months to 7 years old. There were no significant differences in these characteristics across treatment groups (Table 1).

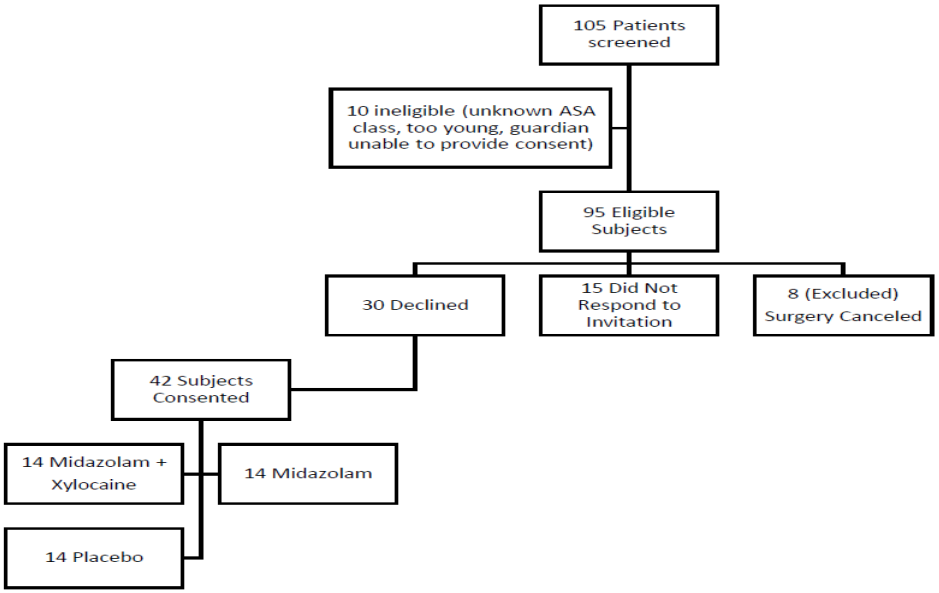

Figure 2: Flow diagram of included and excluded subjects.

Table 1: Demographic profile of participants, compared between Midazolam, Midazolam+Lidocaine, and placebo groups (n=42).

	Total sample (n=42)	Midazolam Alone (n=14)	Midazolam + Lidocaine (n=14)	Placebo (n=14)	Probability
Male	20 (48%)	9 (64%)	4 (29%)	7 (50%)	0.16
Female	22 (52%)	5 (36%)	10 (71%)	7 (50%)	
PS Class 1	25 (59%)	9 (64%)	7 (54%)	8 (57%)	0.85
PS Class 2	17 (41%)	5 (36%)	6 (46%)	6 (43%)	
Age, mean (SD)	2.7 (1.6)	3.1 (1.5)	2.5 (1.7)	2.4 (1.7)	0.53
Median (IQR)	2.0 (1.0,3.0)	2.0 (2.0,5.0)	2.0 (1.0,3.0)	2.0 (1.0,3.0)	
Range	1-7	1-5	1-6	1-7	

There was no delay in discharge with INM or INM+L as compared to placebo (p=0.88). Patients stayed in the post-operative care unit for an average of 36.5 minutes (range 15-132 minutes). The average time from administration of study drug to induction of anesthesia was 22 minutes (range 12-87 minutes). There was no difference in time from drug administration to induction across treatment groups (p=0.19). Patient discomfort, as measured by verbal complaints, was highest among the INM+L group at time of administration (N=9,82%) compared to the INM group (N=6,43%) or placebo (N=3,21%) (p=0.01, **Table 2).** At one-minute post-administration, verbal complaints were reduced among the INM+L group and INM alone group, but were still significantly more frequent than in the placebo group (p=0.03). There were no verbal complaints reported at 5 minutes post-administration in any of the three groups. At one-minute post administration, OBD was scored by the RN observer differed significantly across the three groups (p=0.01, **Table 2**). Pairwise comparisons showed statistically significantly lower observed distress scores among the placebo group as compared to INM (p=0.03). The OBD score in the INM+L group was not statistically significant compared to placebo (p=0.05). At five minutes post-administration, the RN-scored OBD was higher among the INM group versus placebo, but not significantly so (p=0.08). Parental OBD scores were not statistically significantly different across treatment groups at either one minute or five minutes post-administration (p=0.20 and p=0.59, respectively). Sedation scores were generally more favorable among the INM group at the time of induction of anesthesia, with the most agitation observed in the placebo group (p=0.01). At 15 minutes post-administration, agitation was documented in the placebo group (21% of patients) whereas no agitation was seen in either INM or INM+L groups. No statistically significant differences were seen across treatment groups related to sedation scores at time of transport to the OR or 10 minutes post-administration **(Table 2).**

Table 2: Comparison of discharge times, patient complaints, observed behavioral stress, and sedation scores across treatment groups.

	Total sample (n=42)	**Midazolam Alone (n=14)**	**Midazolam + Lidocaine (n=14)**	**Placebo (n=14)**	**Probability**
Minutes post-op to discharge, mean (SD)	42.1 (24.0)	44.9 (31.7)	41.6 (18.1)	39.6 (21.8)	0.88
Median (IQR)	36.5 (29.0,45.0)	39.5 (22.0,50.0)	35.5 (31.0,45.0)	35.0 (29.0,44.0)	
Range	15-132	15-132	20-90	20-109	
Minutes drug admin to induction, mean (SD)	22.3 (11.8)	21.2 (4.9)	23.1 (18.6)	22.6 (8.1)	0.19
Median (IQR)	20.0 (18.0,22.0)	21.0 (19.0,23.0)	18.0 (17.0,20.0)	20.0 (18.0,22.0)	
Range	12-87	14-35	12-87	17-46	
Verbal complaint – administration	18 (46%)	6 (43%)	9 (82%)	3 (21%)	0.01
Verbal complaint – 1 minute †	9 (22%)	5 (38%)	4 (31%)	0	0.03
Observed Behavioral Distress Scores					
Parent Score 1 minute, mean (SD)	0.8 (1.9)	1.4 (2.9)	0.7 (1.3)	0.3 (0.7)	0.20
Median (IQR)	0.2 (0,0.5)	0.3 (0,0.5)	0.3 (0.1,0.5)	0.01 (0,0.3)	
Range	0-9.2	0-9.2	0-4.8	0-2.1	
Parent Score 5 minutes, mean (SD)	0.1 (0.3)	0.2 (0.4)	0.1 (0.2)	0.1 (0.4)	0.59
Median (IQR)	0 (0,0.1)	0.01 (0,0.2)	0 (0,0.05)	0 (0,0.01)	
Range	0-1.6	0-1.6	0-0.6	0-1.4	
RN Score 1 minute, mean (SD)	0.9 (2.0)	1.6 (3.0)	0.9 (1.6)	0.1 (0.1)	0.01
Median (IQR)	0.1 (0.01,0.4)	0.3 (0.1,0.6)	0.4 (0.01,0.6)	0.02 (0,0.1)	

Range	0-9.5	0-9.5	0-6	0-0.4	
RN Score 5 minutes, mean (SD)	0.2 (1.1)	0.6 (1.9)	0.02 (0.1)	0.1 (0.2)	0.08
Median (IQR)	0 (0,0.04)	0.02 (0,0.2)	0 (0,0.01)	0 (0,0.02)	
Range	0-7	0-7	0-0.2	0-0.6	
Sedation Scores					
10 minutes post-administration (RN)					0.09
Agitated	0	0	0	0	
Alert	22 (52%)	9 (64%)	4 (29%)	9 (64%)	
Calm	19 (45%)	4 (29%)	10 (71%)	5 (36%)	
Drowsy	1 (2%)	1(7%)	0	0	
15 minutes post-administration (RN)					0.01
Agitated	3 (7%)	0	0	3 (21%)	
Alert	15 (37%)	4 (29%)	3 (23%)	8 (57%)	
Calm	22 (54%)	9 (64%)	10 (77%)	3 (21%)	
Drowsy	1 (2%)	1 (7%)	0	0	
At OR Transport (CRNA)					0.39
Agitated	7 (17%)	1 (7%)	1 (7%)	5 (36%)	
Alert	7 (17%)	3 (21%)	3 (21%)	1 (7%)	
Calm	26 (62%)	9 (64%)	9 (64%)	8 (57%)	
Drowsy	2 (5%)	1 (7%)	1 (7%)	0	
At Induction of Anesthesia (CRNA)					0.01
Agitated	20 (48%)	3 (21%)	6 (43%)	11 (79%)	
Alert	5 (12%)	1 (7%)	3 (21%)	1 (7%)	
Calm	16 (38%)	10 (71%)	4 (29%)	2 (14%)	
Drowsy	1 (2%)	0	1 (7%)	0	

‡ times in row headings refer to time in minutes from study drug administration

Discussion

The use of Intranasal (IN) premedication was described by Wilton et al. [12] in 1988. The dose utilized for INM of 0.2 mg/kg has been previously described [9,12]. Chiaretti et al. [8] described the combination of INM+L to be efficacious in children while reducing side effects, but unfortunately it was not a controlled or blinded study. In 2008 Manley et al. [11] reported using a standardized IN preparation of Midazolam 40 mg/ml and Lidocaine 20 mg/ml prepared exclusively by their pharmacy. We utilized readily available and inexpensive drugs easily prepared at the bedside for this study. When utilizing INM it is critical to keep the nebulized volume as low as possible to avoid excess drug being introduced in the hypopharynx or gastrointestinal tract [13]. We utilized Midazolam 5 mg/ml and preservative free Lidocaine 4% to achieve a final concentration of Midazolam 0.2 mg/kg and a volume of Lidocaine equivalent to 25% the volume of the Midazolam volume for a final nebulized mixture. The use of aerosolized INM has been well described using the Mucosal Atomization Device (MAD) to improve bioavailability while reducing the amount of drug introduced into the gastrointestinal tract [7,11]. One notable disadvantage of oral and INM "syringe only" administration is that patients have been reported to spit out the administered drug thereby reducing available drug [7]. Karl et al. [7] reported these phenomena with lNM delivered by "syringe only" technique. Efficacy of the MAD for IN administration of drugs has been previously reported [7,8,14,15], as well as the MADgic atomizer for airway topicalization [15]. We utilized a five-point sedation scale previously well described [12] to quantify sedation efficacy as classified by the blinded CRNA and RN evaluator. We also elected to have the parents participate in the evaluation of their own child's level of distress in addition to direct observed patient response and a blinded, trained RN evaluator. Patient discomfort was directly measured by evaluating patient verbal complaints and patient signs of distress. Verbal complaints were in fact highest in the INM+L group at the time of administration compared to both INM and placebo ($p=0.01$). At one-minute verbal complaints were highest among the INM group but the INM+L group also reported more discomfort compared to placebo ($p=0.03$). In this study, it appears there was no benefit adding Lidocaine and in fact it appears to worsen complaints at the time of administration. Our findings are consistent with O'Connell et al. [16] who reported that pain and distress were comparable when IN Lidocaine was administered before or concurrently with INM, but that IN Lidocaine alone also caused significant pain and distress. A combined dose would allow a single atomized dose compared to causing distress from two doses. It would be interesting to compare a single dose versus multi dose IN atomization in future studies. The addition of INM+L in this study was not associated with any epistaxis. Whether it contributed to subjective complaints of nasal stinging is unclear since this symptom was not specifically captured. INM+L was associated with higher frequency of patient complaints at the time of administration, but rapidly resolved by 5 minutes. Whether this was a surrogate for stinging is uncertain. No symptoms of neurotoxicity were documented in any patient during hospital stay. Sedation scores were favorable in the INM group compared to placebo at the time of induction of anesthesia. At 15 minutes post-administration, both INM and INM+L groups had better sedation scores versus placebo. Interestingly, OBD was increased in the INM and INM+L groups compared to placebo as reported by RN observation and the INM+L may in fact exacerbate patient complaints compared to placebo. Sedation may be "adequate" in the INM group with no definitive advantage or disadvantage with

INM+L. Nonetheless, both seem less favorable than placebo in affecting patient distress and comfort during IN sedation. Based upon sedation scores in this study, at 10 minutes post administration 100% of subjects were alert, calm or drowsy; at 15 minutes, 7% of subjects were agitated **[17].** It would appear that the optimal time after administration for separation from the parents is 10 minutes. Unfortunately, we did not examine response to sedation based upon sex or age group. While no statistically significant differences were observed in delay of onset or discharge times, the INM+L group had a lower mean time to discharge compared to the INM group. If this difference was attributed to altering the bioavailability of INM because of adding Lidocaine, a corresponding difference in levels of sedation and onset times might have been expected. We acknowledge that this study was limited by the small number of subjects. As demonstrated in **Figure 2**, the patient population was difficult to reach, a factor further exacerbated by the attrition of an otolaryngologist during the course of study recruitment.

Conclusions

In summary, the current study suggests that convenient "at the bedside" preparation of INM+L via MAD used as a premedication in children undergoing BMT resulted in more verbal complaints after administration than placebo and also caused higher behavioral distress in the PACU. INM+L via atomization offers potential for rapid onset, precise delivery of administered drug and no effect on time to discharge. However, the addition of Lidocaine as described in this study offers no clear advantage in patient comfort compared to INM alone and may statistically lower patient acceptance. Our data shows that at induction of anesthesia, INM premedication with addition of lidocaine offers no definitive advantage over INM alone. As a rural teaching hospital, our patient base was limited requiring a fairly broad age range. We also acknowledge another weakness was this study was a single center study with limited sample size. Further randomized and controlled studies with a larger study group and variable Lidocaine dose would help elucidate the utility of adding Lidocaine to INM. It is unclear if the addition of 4% Lidocaine in a volume of 25% of the Midazolam volume is efficacious in reducing side effects or enhancing patient acceptance.

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Informed Consent

Written informed consent was obtained by the child's parent or legally authorized representative. All consenting protocols were approved by the Mary Imogene Bassett Hospital Institutional Review Board.

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