Effectiveness of sedation using nitrous oxide compared with enteral midazolam for botulinum toxin A injections in children

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This randomized, double-blind, placebo-controlled study compared the efficacy of inhaled nitrous oxide (N_2O) with enteral midazolam for sedation of children with cerebral palsy (CP) undergoing botulinum toxin A (BoNT-A) injections. Fifty children (29 males, 21 females; mean age 8y 2mo [SD 4y 5mo]; range 1–16y) were randomized to sedation with N_2O (n=25) or midazolam (n=25). Groups were similar in type of CP (diplegia, 11; triplegia, three; quadriplegia, 16; hemiplegia, 16; other, three) and Gross Motor Function Classification System level (Level I, 4; II, 24; III, 4; IV, 13; V, 5). Both groups were equally sedated at time of injection (p=0.661), but those in the midazolam group were more sedated at time of discharge (p<0.001). N_2O was more effective in reducing pain compared with midazolam as measured using the Face, Legs, Activity, Cry, Consolability (FLACC) scale (p=0.010), parental estimate of pain (p=0.009), and nursing estimate of pain (p=0.007). Parents in the N_2O group rated it better than prior sedation with midazolam for BoNT-A injections (p=0.031). Physicians and nurses reported no difference in ease of procedure between the groups. One child in the midazolam group and eight in the N_2O group had adverse effects, all of which resolved promptly. N_2O appears to be an effective means of sedation for children undergoing outpatient BoNT-A injections.

Several studies have demonstrated the benefit of intramuscular botulinum toxin type A (BoNT-A) injections for the management of spasticity in children.[1–3] Although these studies addressed the technical aspects of BoNT-A injections as well as functional outcomes, little attention has been given to the procedural pain and distress that result from this procedure. Several reviews of BoNT-A injections in children note the lack of consensus between medical centers about use of preinjection interventions, ranging from no intervention, to topical anesthesia only, oral sedation, or general anesthesia.[4–6]

Inhaled nitrous oxide (N_2O) is a rapidly acting sedative with analgesic and amnesic properties. It has been used for a variety of medical procedures in children, including laceration repair, lumbar puncture, bone marrow biopsy, and upper endoscopy.[7–10] The safety and efficacy of N_2O for sedation of patients with intellectual disability for outpatient dental treatment has recently been demonstrated.[11] One study of N_2O plus a topical anesthetic in children noted complete absence of a clinical pain response to BoNT-A injections in 45% of patients.[12]

This randomized, double-blind, placebo-controlled study compared the efficacy of sedation with enteral midazolam to inhaled N_2O in children undergoing BoNT-A injections for spasticity. All children received some form of sedation. Those who were randomized to receive midazolam received oxygen as an inhaled placebo, and those who received N_2O received saline as an enteral placebo.

Method

This study had approval from the Institutional Review Board of the University of Minnesota. Parental informed consent was documented for each child. Assent was obtained from participants whenever possible.

PARTICIPANTS

Children and adolescents aged 1 to 17 years scheduled to receive BoNT-A injections for management of spasticity in the outpatient clinic of Gillette Children's Specialty Healthcare, Minnesota were eligible for this study. Children were excluded if they had specific contraindications to N_2O.[13] Topical anesthetic cream was applied to intended injection sites at least 30 minutes before injection in all participants.

MIDAZOLAM SEDATION

Midazolam was administered at a dose of 0.35 to 0.5mg/kg to a maximum of 10mg (one child weighing 35kg received an 8mg dose, and one child weighing 58kg received a dose of 15mg based on past sedation experience). Children randomized to N_2O sedation received an equivalent volume of saline enterally as placebo. Midazolam or placebo was administered either orally or rectally based on patient preference. Midazolam was administered rectally to all but one of the children randomized to this agent.

N_2O SEDATION

Inhalation of N_2O or placebo (100% oxygen) was initiated a minimum of 10 minutes after rectal or 20 minutes after oral administration of midazolam or placebo. Inhaled medical gas was administered by a continuous flow device (Porter Instrument Company, Hatfield, PA, USA) which allows titration of N_2O concentration from zero to a

maximum of 70%, with oxygen as the remaining gas. Gas was administered through a disposable nasal hood (Accutron, Inc., Phoenix, AZ, USA) which fits comfortably over the nose of an older child or the nose and mouth of a toddler. Children randomized to N_2O received 70% N_2O/30% O_2 initially, with titration to a lower percentage of N_2O at the discretion of the sedation provider. Children randomized to midazolam received 100% oxygen throughout the procedure. Gas was administered for 2 to 3 minutes before initial injection. BoNT-A injections proceeded as per usual protocol. Distraction (e.g. storytelling, soothing discourse) was provided to all children throughout the procedure. After completion of injections, 100% oxygen was administered to all participants for 2 to 3 minutes. Throughout gas administration, children were monitored with continuous pulse oximetry and direct nursing observation. All children remained in the sedation area until they were in an appropriate state for discharge.[14]

RANDOMIZATION AND STUDY BLINDING

Before study initiation, a random number list was generated (1, N_2O; 2, midazolam) to determine sedation order. After informed consent was obtained, participants were added to this list in order of entry to determine the assigned sedative and corresponding placebo. Patients were added to the randomization list, midazolam and saline placebo doses were prepared, and N_2O or 100% oxygen placebo was administered by personnel who were not directly involved with the procedure nor with data collection for the study. Children, parents, physician staff administering BoNT-A, nursing staff, and the trained observer collecting data were blinded to sedation randomization. Mask placement and gas administration were initiated before entry of study personnel responsible for objective pain scoring.

LEVEL OF SEDATION

Level of sedation during and after the procedure was quantified using a modified University of Michigan level of sedation scale.[15] Numerical scoring of level of sedation corresponded to the following values: 0, awake, alert; 1, minimally sedated (tired/sleepy, appropriate response to verbal conversation and/or sound); 2, conscious: moderate (drowsy, eyes open or closed, but easily arouses to consciousness with verbal stimulus); 3, moderate: deep (arouses to consciousness with moderate tactile or loud verbal stimulus); 4, deep (arouses to consciousness with sustained painful stimulation).

OBSERVED AND ESTIMATED PAIN

Pain was measured by a trained observer using the Face, Legs, Activity, Cry, Consolability (FLACC) scale, a validated behavioral assessment pain scale scored from 0 to 10, based on observation of facial expression, leg movement, activity level, cry, and consolability with higher scores indicating increased distress.[16]

After the procedure, the trained observer asked parents and involved nursing staff to estimate the child's pain during injections on a 0 to 10 scale (0, no pain to 10, worst possible pain). Physicians administering BoNT-A and nursing staff assisting with the procedure were also asked to estimate the ease of the procedure on a 0 to 10 scale (0, completely easy to perform to 10, unable to complete injections).

SATISFACTION WITH SEDATION

Parents were asked to rate their satisfaction with their child's comfort for the procedure on a 1 to 10 scale (1, completely satisfied to 10, completely dissatisfied). Parents were also asked to compare the study sedation with prior sedation for similar procedures using a 5-point Likert-type scale (1, much worse; 2, worse; 3, same; 4, better; 5, much better).

ADDITIONAL DATA COLLECTION

Demographic information, verbal or non-verbal status, type of cerebral palsy (CP), Gross Motor Function Classification System level, previous experience of BoNT-A injection, and prior sedation for BoNT-A injections were noted for this study. The total number of intramuscular injections administered, site of injections, adverse effects of sedation, and time in department were recorded.

STATISTICAL ANALYSIS

Descriptive statistics and frequencies were performed using SPSS (version 14.0). These used patient characteristics, pain, parental satisfaction, ease of procedure, level of sedation, and adverse events. χ^2 calculations analyzed patient characteristics. Two-tailed Mann–Whitney U tests were then performed with the remainder of the measures to detect differences between the N_2O group and the midazolam group.

Results

Fifty participants were enrolled (29 males, 21 females; mean age 8y 2mo [SD 4y 5mo]; range 1–16y) with 25 children randomly assigned to each sedative group. There was no difference in patient characteristics between the two groups (Table I). Children in the N_2O group received more injections during the study visit; however, this did not reach statistical significance ($p=0.058$).

LEVEL OF SEDATION

There was no difference in maximum level of sedation between midazolam and N_2O sedation ($p=0.661$, Fig. 1). Most children (94%) in both groups remained in a minimally sedated state (score 0 or 1). One child reached a level of deep sedation after receiving rectal midazolam. This child regularly received valproate, aripiprazole, amphetamine/dextroamphetamine, and escitalopram. He was awake and alert at time of discharge. Only one other child regularly received valproate. This child, who received gabapentin and topiramate in addition to valproate, remained alert throughout midazolam sedation. Two children sedated with N_2O achieved a level of moderate sedation. One received only baclofen regularly, the other, atomoxetine, ibuprofen, methotrexate, and lansoprazole. Eighteen children received no regular medication. The remainder of the participants received a variety of medications including anticonvulsants, stimulants, and antispasticity medications.

The level of sedation score at time of discharge was higher for children sedated with midazolam than those sedated with N_2O ($p<0.001$, Fig. 1). There was no difference in time in clinic between the two groups.

PAIN AND PARENTAL PERCEPTIONS OF SEDATION

Pain during intramuscular injection of BoNT-A was significantly lower for children receiving N_2O compared with those given midazolam sedation for all three parameters measured: FLACC, parent estimate of pain, and nurse estimate of pain (Table II). Although there was no difference in parental satisfaction with sedation between the groups (midazolam median score 2 [minimum 0, maximum 10], N_2O median score 1 [minimum 0, maximum 10]; $p=0.10$), there was a significant difference between the midazolam and N_2O groups in parental comparison of study sedation to prior sedation experience ($p=0.031$, Fig. 2).

Table I: Comparison of midazolam and nitrous oxide groups

Characteristic	*Midazolam (n=25)*	*Nitrous oxide[a] (n=25)*
Age, y		
Mean (SD), y:m	8:7 (4:9)	8:6 (3:8)
Median, y:m	7:9	8:11
Range, y:m	1:11–16:9	2:10–16:6
Male:female	15:10	14:11
Verbal:non-verbal	13:12	15:10
Prior BoNT-A injections:no prior injections	23:2	24:1
Prior sedation with midazolam for BoNT-A injections:no prior sedation	24:1	23:2
Number of injections this visit		
Median	8	11
Range	2–17	3–24
Site of injection		
Gastrocnemius/Soleus	19	21
Hamstring	16	16
Hip	3	3
Wrist	5	11
Biceps	6	10
Other	4	5
Type of cerebral palsy		
Diplegia	5	6
Triplegia	0	3
Spastic quadraplegia	9	7
Hemiplegia	8	9
Other	3	0
GMFCS level		
I	0	4
II	13	11
III	3	1
IV	6	7
V	3	2

[a]One child in the N_2O group had a diagnosis of incomplete spinal cord injury. BoNTA, botulinum toxin type A; GMFCS, Gross Motor Function Classification System.

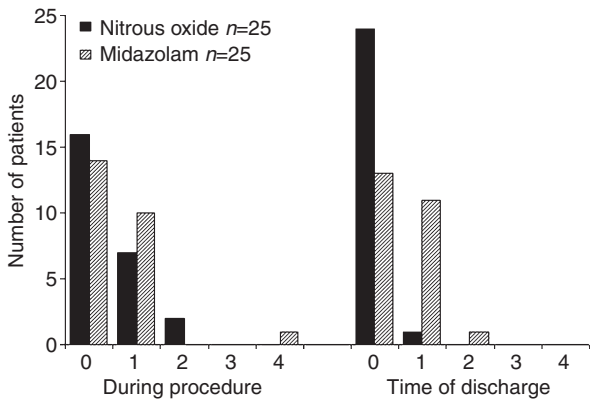

Figure 1: *Level of sedation score.*

EASE OF PROCEDURE

There was no difference in either physician estimate of ease of procedure ($p=0.387$) or nurse estimate of ease of procedure ($p=0.116$) between the sedative agents.

ADVERSE EVENTS

Nine children experienced adverse events. One in the midazolam group developed oxygen saturation less than 92% pre-procedure which resolved with administration of oxygen. Eight participants in the N_2O group experienced adverse events. One developed nausea during N_2O administration and one developed headache and pallor after the procedure. Four children vomited during N_2O administration. One of these children, who was non-verbal and fought the mask, also developed oxygen saturation less than 92% which resolved promptly with discontinuation of N_2O and application of 100% oxygen. Two others developed brief oxygen saturation less than 92% which resolved without incident. No patient experienced upper airway obstruction or apnea. Parents of five of the eight children who experienced adverse effects of N_2O rated the sedation experience either better or much better than prior sedation experiences.

Table II: Procedural pain for midazolam and nitrous oxide group

	Midazolam	*n*	*Nitrous oxide*	*n*	*p[a]*
FLACC scale[b c]					
Median	6	24	4	25	0.010
Range	0–10		0–10		
Parent estimate of pain[b]					
Median	4	25	2	25	0.009
Range	0–10		0–10		
Nursing estimate of pain[b]					
Median	4	25	1	25	0.007
Range	0–10		0–8		

[a]Mann–Whitney *U* test. [b]All scales 0–10, with 10 representing maximum pain. [c]FLACC, Face, Legs, Activity, Cry, Consolability.

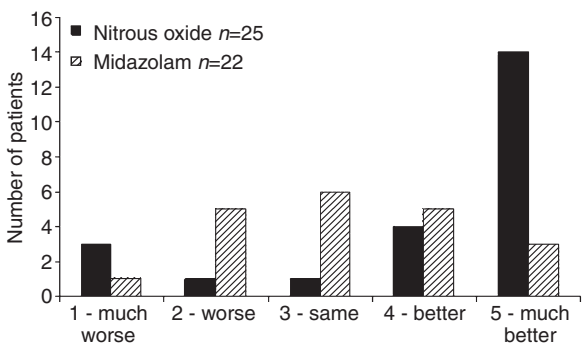

Figure 2: *Parental comparison with prior sedation.*

All children received verbal distraction during the procedure from the provider who was handling the mask for the administration of N_2O or oxygen. Although there was not a specific assessment of the effectiveness of these distraction techniques, we found that they were more effective at holding the child's attention when combined with N_2O rather than with midazolam.

DISCUSSION

The negative consequences of inadequate analgesia on children's future experience with painful procedures has been well studied.[17,18] In children who require repeated painful procedures, such as intermittent lumbar punctures for treatment of leukemia, pain experienced during the initial procedure significantly influences pain scores and distress with subsequent procedures.[19] Children undergoing BoNT-A injections for spasticity often receive multiple intramuscular injections at regular intervals.[20] A recent report from our institution indicated that parents are concerned about the pain associated with the procedure but find that the benefits of BoNT-A injections outweigh this concern.[21] Pain with injection, however, has been cited as a reason for discontinuation of BoNT-A injections in children.[22]

Several articles refer to midazolam sedation as a method to mitigate the discomfort of BoNT-A injections.[1,4,6] Although midazolam may provide a degree of sedation and amnesia for the procedure, its usefulness is tempered by its lack of analgesia. By contrast, N_2O provides analgesia in addition to procedural sedation and amnesia. This analgesic aspect may be responsible for the lower pain scores seen with N_2O compared with enteral midazolam in the current study, as the level of procedural sedation was comparable between the two groups. The lower pain scores are particularly notable in light of the fact that children sedated with N_2O for this study received more injections than those sedated with midazolam.

Patient comfort, however, must be weighed against patient risk. Children with CP may be at increased risk of complications from general anesthesia because of poor handling of oropharyngeal secretions and/or gastroesophageal reflux, factors that may also place them at increased risk of sedation.[23] Laryngeal reflexes have been shown to remain intact with N_2O sedation, albeit in healthy volunteers. Maintenance of airway reflexes is particularly important with N_2O sedation as nausea and vomiting are the most common side effects, a finding reflected in the current study. Although vomiting occurred in four children sedated with N_2O, none experienced clinical aspiration (e.g. change in respiratory status, persistent oxygen desaturation). The small number of participants in the current study precludes specific conclusions about the safety of N_2O; however, the safety of N_2O sedation in patients with intellectual disability was recently demonstrated.[11] In the largest study of N_2O safety, serious adverse events were seen in fewer than 0.1% of over 35 000 administrations.[24]

An appealing aspect of N_2O is its rapid onset and short half-life. N_2O sedation has an onset of action within 5 minutes of initiation of inhalation. Return to baseline level of function occurs within 5 minutes of N_2O discontinuation. By contrast, midazolam requires 10 to 20 minutes for onset of sedation and has a half-life of over 2 hours. Time to maximum sedation and level of sedation achieved are similar whether midazolam is given orally or rectally.[25] The rapid onset of N_2O sedation allows it to be more precisely targeted to the time of BoNT-A injections, minimizing the amount of time the child experiences sedative effects. If adverse events occur, the rapid cessation of sedation with N_2O allows the child to return expeditiously to baseline function. Because the current study was constructed to allow adequate time for onset of effect of midazolam for all participants and to allow sufficient time for the topical anesthetic cream to be effective, it is not surprising that time in clinic was the same between the N_2O and midazolam groups. Although there was no difference in time in clinic for the two groups, only about half of the children who received midazolam had returned to a fully awake state at the time of discharge compared with all but one who received N_2O. In addition to limiting exposure to sedative effects, it could be surmised that more rapid return to baseline function with N_2O may also translate into less time away from normal activities for children sedated with this agent and, potentially, less time away from work for their parents.

Although 94% of participants fell into a minimal sedation category, the fact that two children who received N_2O reached a level of moderate sedation and one child who received rectal midazolam was deeply sedated reinforces the need for adequate preparedness whenever children receive procedural sedation. The children in this study who reached higher levels of sedation did not regularly receive any unique medications compared with the remainder of the other participants. Patients with CP, however, may be regularly receiving medications (e.g. benzodiazepines, anticonvulsants), which can have additive effects with procedural sedatives and/or affect bioavailability of enterally administered sedatives, such as midazolam, which undergo first-pass metabolism. The American Academy of Pediatrics 'Guidelines for monitoring and management of pediatric patients during and after sedation for diagnostic and therapeutic procedures' stress the importance of preparation for a level of sedation deeper than intended.[14] Equipment for oropharyngeal suction should be readily available whenever N_2O sedation is administered, in recognition of the incidence of nausea and vomiting associated with this agent.

Because children receiving N_2O are minimally sedated, age and developmentally appropriate distraction techniques are valuable adjuncts to optimal use of this agent. Guided imagery, storytelling, and softly spoken encouragement all serve to focus the child's attention away from the site of injection. It is possible that the importance of adjunctive distraction may limit the efficacy of N_2O in patients who have severe cognitive deficits.

CONCLUSION

N_2O produced a level of procedural sedation comparable to enteral midazolam in this randomized, double-blind, placebo controlled study of children and adolescents with CP receiving BoNT-A injections in an outpatient setting. However, those who received N_2O were less sedated at the end of the clinic encounter. N_2O was more effective in reducing pain than midazolam based on objective and subjective measures. Parents were satisfied with both types of sedation, but those in the N_2O group rated it better than prior sedation experience with midazolam.

N_2O appears to be an effective means of sedation for children undergoing outpatient BoNT-A injections. Further study of adverse events, ease of procedure, and duration of clinical encounter as a result of using this method is warranted.

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