Retrospective Comparisons of the Efficacy and Safety of Variable dosing of Midazolam with and without Meperidine for Management of Varying Levels of Anxiety of Pediatric Dental Patients: 35 years of Sedation Experience

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***Purpose**: This retrospective study compares the efficacy and safety of variable dosing of Midazolam (Mid) with and without Meperidine (Mep) combinations for managing varying levels of anxiety and uncooperative behavior of young pediatric dental patients over a thirty-five-year period. **Study design**: Reviews of the sedation logs of 1,785 sedation visits are compared with emphasis on what dosing proves both safe and effective for differing levels of challenging pediatric behavior. Variable dosing of midazolam with and without meperidine which spanned low-end, mid-range, and upper-end were judged making use of a pragmatic approach which defined sedation success as optimal, adequate, inadequate, or over-dosage. Behavioral and physiologic assessment was included with attention to readily observable analysis of the extent to which need for physical restraint occurred to control interfering behavior. Assessment of arousal levels requiring stimulation along with the frequency of alterations in oxygen de-saturation and adverse reactions were included as indications of safety. **Results:** Where Mep was used, success rates were consistently higher; working times were significantly prolonged and greater control was provided to avoid adverse reactions by virtue of reversal capability for both agents. **Conclusions**: Predictability and working time of Midazolam was enhanced by combination with narcotic for all levels of patient anxiety. Dosages of 0.7-1.0 mg/kg Mid combined with 1.0-1.5 mg/kg Mep offers the most effective and safe results to overcome need for restraint for moderate and severe levels of anxiety, respectively.*

Keywords: *Sedation,Midazolam, Meperidine*

INTRODUCTION

Selected for its potential to modify challenging and resistive child dental behaviors, and a capacity for reversal, midazolam has evolved as the most frequently used regimen for pediatric dental sedation in both advanced training programs and private practice. [1,2] Among sedative regimens utilized for the pediatric patient, although limited to short and ultrashort duration of action, midazolam is among the safest and most studied of agents for the pediatric dental patient. [3-16] The combination with meperidine has been proposed to extend working times, provide analgesia to enhance the quality of sedations for invasive and unpleasant dental treatment while offering double-edged capacity of reversal to avoid and manage adverse reactions should they arise. [17-20]

Before midazolam became available, the combination of CH-Hydroxyzine with Meperidine enjoyed great popularity in pediatric dental sedation from the mid 80's to 2000 and beyond. Inclusion of the narcotic enabled lowering the dosage of the sedative-hypnotic, lessened the occurrence of somnolence, and permitted longer duration of action. [21-24] The unpredictability of CH dosing and the absence of a reversal capability, lessened its comfort level and demand for use in training level applications. Substitution

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of midazolam for chloral hydrate hence emerged as a logical alternative providing an additional measure of reversibility. [25]

The objective of this retrospective study was to examine different doses of midazolam with and without meperidine for managing difficult young pediatric dental patients with varying levels of anxiety. While numerous reports have appeared in the literature that have compared differing dosages of midazolam, virtually all have involved undifferentiated levels of anxiety. In effort to specifically explore efficacy and dosing variation, the current study subdivided its study groups by anxiety levels. This aspect was considered valuable in an effort to differentiate the usefulness (or lack thereof) of varying dosing patterns when encountering differing levels of anxiety.

Background

Orally and parenterally administered midazolam as a pre-medication to general anesthesia for the pediatric patient has been and remains commonplace for going on 25 years. Medical and dental study is considerable.

Several medical trials compared the effects of oral and parenteral midazolam combined with meperidine. Bahal-O'Mara et al, [26] compared P.O. 2.0 mg/kg meperidine with 2.0 mg/kg meperidine plus 0.05 mg/kg IV midazolam in a randomized double-blind trial of 40 patients undergoing endoscopy. Success rates of 71 and 79%, respectively were reported although differences were not found statistically different; 23% of the meperidine alone showed evidence of amnesia compared to 78% receiving midazolam.

Marx *et al* [27] compared midazolam IV at 0.1 mg/kg plus meperidine 2.0 mg/kg vs midazolam 0.05 mg/kg and ketamine 1.5 mg/kg in a randomized, double-blind crossover study of 22 pediatric oncology patients. Those receiving ketamine experienced significantly less stress, rapid recovery, and fewer side effects; all subjects experienced amnesia. The greater potency of ketamine and its dissociative anesthetic trance-like state providing pain relief, profound sedation, and amnesia should not be surprising when comparisons with midazolam are performed.

In a double-blind study, Lee *et al* [28] prospectively compared Midazolam-Meperidine with and without dexmedetomidine (Dex) administered IV for endoscopy. Addition of Dex provided better sedation and safety, although the addition of Dex necessitated lower dosing of the midaz and meperidine.

Several pediatric dental trials have since explored the impact of adding meperidine to sedative-hypnotics and benzodiazepine medications. In general, the addition of meperidine was found to enhance predictability and safety of the sedations by providing analgesia potentiating the sedative effects of the benzodiazepine while reducing the incidence of somnolence during and following treatment, and reduce the need for high-end dosing of the primary agent.

Wilson *et al*,2000 [14] compared the effectiveness of three regimens using CH-Hydroxyzine vs CH-Hydroxyzine –Mep vs Midazolam. 300 subjects, ages 2-5 years, divided into three groups of 100 were reported to display significantly different behavioral and physiological responses between all groups. Subjects were prepped to make use of a restraint device as needed and received 50% Nitrous oxide (+ or – 10%). The CH-H-Mep group displayed quieter and sleeping behaviors. Unfortunately, dosing was not identified for any of the regimens to provide insight as to efficacy or explanation for why groups may have differed other than age and respective coping ability.

Nathan and Vargas [17] retrospectively compared patient responses from the sedation logs of 120 moderately to severely anxious and uncooperative subjects, aged 24-48 months, divided into six groups of 20 subjects. Subjects received midazolam in doses of 0.7 and 1.0 mg/kg with and without 1.0-1.5 mg/kg meperidine. When midazolam was used alone, use of 0.7 mg/kg produced the most agitation, required restraint most frequently and produced the shortest working times, (all $p<0.001$). Subjects receiving 1.0 mg/kg midazolam and meperidine proved the most effective, completing treatment objectives in 20/20 visits with no need for persistent restraint or adverse reactions ($p<0.001$). Use of 0.7 mg/kg midazolam and higher dose of meperidine permitted treatment in 18/20 visits. Combined higher doses of both agents demonstrated somnolence and over-sedation. The addition of meperidine significantly increased working time ($p<0.05$). It is noteworthy that a maximum 0.5 mg/kg Midazolam alone is considered commonplace in current advanced training programs, despite an underwhelming lack of success. [17] As such, use of a lower than therapeutic dosing of midazolam, for moderate and high levels of patient anxiety, (below 0.7 mg/kg with or without mep) may be expected to fall short of efficacious.

Sheroan *et al* [29] compared the behavioral and physiologic responses of 16 subjects, 24-54 months of age, to CH-H-Mep vs Mid –Mep-H. Dosages were not identified and the authors cited no significant differences in behavior or sedation effectiveness between the two regimens.

Musial and Wilson *et al* [30] evaluated the behavioral and physiologic responses of twenty subjects, 36-60 months of age identified as mildly to moderately apprehensive in a two-visit blind crossover. Group A received 1m/kg midazolam on visit one and midazolam 0.5 mg/kg with 1.0 mg/kg meperidine on the second visit. Group B received the same in the reverse order. 50% nitrous oxide and a papoose board was used for all subjects. No significant differences were detected between drug conditions and physiological measures other than to indicate that behaviors worsened and heart rate was elevated as the intensity and invasiveness of the visit increased. No mention of the potential confounding nature of fixed nitrous oxide or use of restraint was made. Nathan and Vargas [17] using no confounding nitrous oxide or restraining devices reported significantly enhanced sedation success and less physiologic arousal which might best be explained by the use of higher dosages of midazolam in their retrospective study.

Chowdhury and Vargas [31] retrospectively compared CH – H 25 mg/kg and 1 mg/kg , respectively, with Mep 1 mg/kg vs Midazolam 0.65 mg/kg of 116 sessions for ages 24-60 months using 50% nitrous oxide. CH-H-Mep was significantly more effective than Mid.

The specific objectives of the present study were to:

1. Explore the relative efficacy and safety of variable dosing of Midazolam with and without Meperidine
2. To explore the above with respect to the impact of varying levels of anxiety and uncooperative behavior.
3. Determine if the addition of Meperidine has potential to predictably prolong the duration of action/working time, (overcoming a well-known shortcoming of midazolam) when confronting various levels of anxiety and uncooperative behavior, without need for restraint.

An issue of methodological relevance includes how sedation success is determined. There appears to be no universal consensus among pediatric dentists whether the use and need for physical restraint to permit completion of visit objectives is or is not a deterrent to concluding clinical success when sedation agents alone prove inadequate. To that extent many clinicians routinely anticipate and make use of passive or active forms of restraint (often referred to as protective stabilization) appears commonplace. A second distinction between existing sedation literature and this effort was focus on how sedation agents and dosing selection alone are sufficient to permit treatment on patients with varying degrees of anxiety without need for persistent or transient deployment of restraint. As mentioned later in this section, parental perceptions of the use and application of restraint appears to be moving in a direction of being unfavorable and counterproductive when assessing the success of sedative agents to achieve optimal results. [2,32-37]

METHODS

The present study offers a conceptual model in which to pragmatically define efficacy and safety of pediatric sedation visits. Subjects were randomly selected from a private practice setting on the basis of initial consultation, examination, and parental agreement/acceptance that treatment best considered the need for pharmacological assistance to minimize or eliminate the need for physical restraint. Subjects included those with a history of unpleasant experience or manifested uncooperative behavior on examination. For some, visits were reported by parents as having been aborted and deferred for sedation as result of the occurrence of persistent interfering behaviors. Within the private practice arena, the objective of completing treatment needs utilizing a pharmacologic approach to avoid need for general anesthesia or restraint was presented to parents as desirable outcomes.

Data was secured from sedation logs accumulated over a thirty five year period (1983-2018) of all visits in which entry level behavior and treatment needs were assessed. Behavioral anxiety was classified into one of three levels as described below. Visit intervals were identified as being of short or ultra -short duration, (<15 minutes), mid-range (20-40 minutes), or long-duration (>40 minutes). A sedation log developed by the author was used until one developed by the AAPD (2009-10) [38] and modified by the author was used to record behavioral and physiological responses at visit intervals (pre-administration of agents, latent periods, administration of local, intra- and post-operatively and when discharge criteria was satisfied. Pulse oximetry was maintained as well as qualitative and quantitative assessment of ventilation and tissue perfusion. Ratings by independent observers were made with respect to the relative success of sedative regimens to permit treatment with no need for restraint, transient application of restraint or persistent need for restraint. Capnography, while recognized as the most sensitive measure of ventilatory efficiency, was not used due to low nature with which consciousness was compromised in the study.

IRB approval (140402002) was granted by the University of Alabama, Birmingham for this retrospective review of 1,785 pediatric sedation visits. Random samples of subjects were selected to receive varying dosages of Midazolam with and without meperidine. Characteristic of formulations of meperidine have been recognized as possessing limited absorption (approximating 50%) due to extensive first pass metabolism. [38] Subjects receiving 50 mg dosing in actuality, absorbed 25 mg. An inherent benefit of both medications is the availability of reversal agents for the benzodiazepine (Flumazenil) and narcotic antagonist (Naloxone) for potential respiratory depression. Instances for which reversal was warranted included deeper than intended levels of sedation, somnolence, and diminished arousal intra-operatively and post-operatively. Need for reversal of either agent, however, occurred rarely (< 1%) in the study.

Additional Patient Selection criteria

Age range: 30-84 months; mean 48 months. Weight <70 lbs. Sufficient caries to warrant visits of 15-60 minutes

Inability to permit treatment without persistent application of restraint (as perceived by both parent(s) and clinician. Informed parent/guardian consent.

Nitrous oxide was excluded in its entirety to permit comparison of efficacy of primary drug conditions alone without confounding interpretation. Future studies may be considered which include subgroups receiving variable concentrations of nitrous oxide to assess potential adjunctive nature and opportunity to extend working times and potential to make use of lower primary agent dosing to further clarify efficacy and safety.

Statistical analyses included one-way ANOVA. Descriptive analysis of physiologic data was included.

Three experimental groups were identified by the relative level of anxiety and resistance manifested as falling into one of the below categories of mild, moderate, or severely anxious and resistive behaviors.

Definitions of what constituted varying levels of anxiety

Mild: Minimum levels where some form of restraint was needed to overcomeinterfering or harmful behavior.

Subjects responsive to nitrous oxide alone for the control of behavior were excluded. Behavior which interfered with securing routine dental X-rays, resistance to local anesthetic showing limited ability to accept invasive procedures. Subjects satisfying Frankl -1 ratings minimally qualify for this group [40]

Moderate: Those behaviors above which included a higher degree of resistance to overcome interfering movement in a more than transient nature. Subjects falling between Frank -1 and -2 ratings.

Severe: Heightened resistance necessitating persistent application of physical restraint for administration of local and invasive restorative/surgical care reflecting Frankl -2 or worse ratings. For those in this category, the option of an unconscious technique was made available.

Determination of Clinical Success

Clinical success of a sedation regimen was judged by two independent raters at the conclusion of each visit as falling into one of the following classifications: Optimal, Adequate, Inadequate, or Over-dosage. Inter-rater reliability was found high; less than 10% of the visits necessitated operator input as a third judge to categorize the level of clinical success.

Optimal Level of Sedation obtained: Maintenance of responsiveness to verbal requests for cooperation without need for transient application of physical restraint; absolute minimal or no need for

restraint (exception might include passive parental hand-holding) to permit treatment to achieve visit objectives.

Adequate Success: Above with only transient need for physical restraint to offset or overcome interfering reflexive-type movement.

Inadequate : Unable to accomplish any or all treatment objectives due to persistent need for physical restraint.

Over-dosage: Subjects experiencing somnolence of a persistent nature; unresponsive to verbal stimulation intra- and post-operatively, with potential for loss of protective reflexes, frequent oxygen desaturation below 90%, necessitating noxious physical stimulation to cause awakening or arousal thereby eliminating the feasibility or appropriateness of declaring patient consciousness.

Latent Periods Observed

A standard or routine latent period observed for midazolam alone or in combination was 15-20 minutes for drug absorption. Recognized as a limitation of the oral route of administration is the impact of anxiety on GI motility, gastric emptying and drug absorption. NPO requirements that extend beyond 6 hours or longer, or the previous evening's meal does not guarantee gastric emptying and timely drug absorption. In some cases latent periods up to and exceeding 45 minutes were followed. Subjects manifesting no signs of sedation after such were directed accordingly to the discretion of both parent and operator for decisions how to proceed or abort treatment. Alternate strategies were discussed and made available to parents at this juncture.

RESULTS

Comparisons of midazolam combinations for MILD LEVELS of Anxiety

Table 1 compares the efficacy and safety of Midazolam at varying dosages currently advocated within institutional and clinical practice, with and without meperidine. Without meperidine, success rates for using less than 0.7 mg/kg Midazolam ranged between 40-58%; for 0.7 and 1.0 mg/kg, used alone success ranged from 65-75%, respectively.

The addition of meperidine enhanced success from 68% for 0.5 mg/kg and 75% for dosages of 0.7mg/kg, and 93% for 1.0 mg/kg. Significant differences at ($p<0.05$) occurred between dosages of midazolam alone when using a minimum of 0.7 mg/kg while differences were at the ($p<0.001$) comparing 0.7 and 1.0 mg/kg with the addition of meperidine. Working times were significantly enhanced by the addition of meperidine. Without meperidine, working times ranged between 5-10 minutes compared to 20-40 minutes with meperidine. Use of Midaz at 0.7 mg/kg combined with 1.0 mg/kg Mep was found to be most beneficial and safe for milder levels of anxiety.

There was no incidence of somnolence or adverse reactions (with the exception of few instances of brief oxygen desaturations) for any of the dosages with and without meperidine for subjects within this range of anxiety.

Comparisons of midazolam for MODERATELY APPREHENSIVE LEVELS of Anxiety

Table 2 illustrates similar findings to Table 1 observed where dosages of 0.3-0.5 mg/kg with or without meperidine proved inadequate necessitating the greatest need for persistent application of restraint. At the highest dosage of midazolam used alone, optimal / adequate success rates were at best 60-%.

Success rates for subjects using 0.7-1.0 mg/kg with meperidine proved significantly more efficacious ($p<0.05$). Success rates increased to 80% and 86%, respectively with 1.0 mg/kg Mep. With an increase from 1.0-1.5 mg/kg of meperidine, success rates increased from 90-94% ($p<0.05$). Two cases using the highest dosing demonstrated over-dosage.

Dosing of Midaz at 0.7-1.0 mg/kg with Mep at 1.0 mg/kg appeared the most efficacious and safe for patients with more moderate levels of anxiety.

TABLE 1: COMPARISONS OF MIDAZOLAM WITH AND WITHOUT MEPERIDINE FOR MILD LEVELS OF APPREHENSION

REGIMEN (mg/kg)	N=	% THERAPEUTIC SUCCESS				% EASE OF AROUSAL AT END OF TX		% EASE OF AROUSAL AT DC		# OF CASES ABORTED	ADVERSE REACTIONS/COMPLICATIONS			
		OPTIMAL	ADEQUATE	INADEQUATE	OVERDOSAGE	VERBAL	PHYSICAL	VERBAL	PHYSICAL		pO2	AGITATION	RESPIR DEPRESS	LOSS OF PROTECTIVE REFLEXES
Midaz 0.3 mg/kg	50	22	18	60	0	100	0	100	0	35	0	0	0	0
Midaz 0.5 mg/kg	70	30	28	42	0	100	0	100	0	27	0	0	0	0
Midaz 0.7 mg/kg	70	35	32	33	0	100	0	100	0	24	0	0	0	0
Midaz 1.0 mg/kg	75	42	33	25	0	100	0	100	0	16	0	0	0	0
Midaz + Meper 0.5 mg/kg 1.0 mg/kg	75	33	40	27	0	100	0	100	0	12	0	0	0	0
Midaz + Meper 0.7 mg/kg 1.0 mg/kg	75	48	45	7	0	100	0	100	0	9	0	0	0	0
Midaz + Meper 1.0 mg/kg 1.0 mg/kg	75	63	32	5	0	94	0	100	0	4	4	0	0	0

Comparisons of midazolam with and without Meperidine for severely apprehensive levels of anxiety

Most revealing were the cases illustrated in Table 3 comparing the efficacy and safety of Midazolam with and without Meperidine for the most anxious of subjects.

Least effective was the use of midazolam alone, regardless of the dosage (40-91% inadequate). Even with the addition of meperidine at 1.0 mg/kg, optimal/adequate success was found at 36%. Only at upper range dosing of both midazolam and meperidine, effectiveness improved significantly ($p<0.05$). This did not occur without respective increased need for physical stimulation to induce wakefulness, occurrence of over-dosage, desaturations, respiratory depression, and loss of protective reflexes to warrant diligent scrutiny if not reticence to make use of upper end dosing.

This latter point reinforces concerns related to expectations for success when attempting to overcome heightened levels of anxiety and resistance with oral sedative regimens. Search for regimens with a predictable capacity to overcome this degree of resistance

TABLE 2: COMPARISONS OF MIDAZOLAM WITH AND WITHOUT MEPERIDINE FOR MODERATE LEVELS OF APPREHENSION

REGIMEN (mg/kg)	N=	% THERAPEUTIC SUCCESS				% EASE OF AROUSAL AT END OF TX		% EASE OF AROUSAL AT DC		# OF CASES ABORTED	ADVERSE REACTIONS/COMPLICATIONS			
		OPTIMAL	ADEQUATE	INADEQUATE	OVERDOSAGE	VERBAL	PHYSICAL	VERBAL	PHYSICAL		pO2	AGITATION	RESPIR DEPRESS	LOSS OF PROTECTIVE REFLEXES
Midaz 0.3 mg/kg	25	10	10	80	0	100	0	100	0	28	0	24	0	0
Midaz 0.5 mg/kg	50	11	11	78	0	100	0	100	0	30	0	18	0	0
Midaz 0.7 mg/kg	75	20	32	48	0	100	0	100	0	26	0	14	0	0
Midaz 1.0 mg/kg	75	32	28	40	0	100	0	100	0	20	0	10	0	0
Midaz + Meper 0.5 mg/kg 1.0 mg/kg	75	15	18	67	0	100	0	100	0	10	0	12	0	0
Midaz + Meper 0.7 mg/kg 1.0 mg/kg	75	38	42	20	0	100	0	100	0	4	0	6	0	0
Midaz + Meper 1.0 mg/kg 1.0 mg/kg	75	52	34	14	0	98	2	100	0	4	0	4	0	0
Midaz + Meper 0.5 mg/kg 1.5 mg/kg	70	17	25	58	0	96	4	100	0	2	0	4	0	0
Midaz + Meper 0.7 mg/kg 1.5 mg/kg	75	44	46	10	0	94	6	98	2	4	0	0	0	0
Midaz + Meper 1.0 mg/kg 1.5 mg/kg	75	58	36	6	0	96	4	98	2	4	2	0	2	0

TABLE 3: COMPARISONS OF MIDAZOLAM WITH AND WITHOUT MEPERIDINE FOR SEVERE LEVELS OF APPREHENSION

REGIMEN (mg/kg)	N=	% THERAPEUTIC SUCCESS				% EASE OF AROUSAL AT END OF TX		% EASE OF AROUSAL AT DC		# OF CASES ABORTED	ADVERSE REACTIONS/COMPLICATIONS			
		OPTIMAL	ADEQUATE	INADEQUATE	OVERDOSAGE	VERBAL	PHYSICAL	VERBAL	PHYSICAL		pO2	AGITATION	RESPIR DEPRESS	LOSS OF PROTECTIVE REFLEXES
Midaz 0.5 mg/kg	25	5	4	91	0	100	0	100	0	80	0	75	0	0
Midaz 0.7 mg/kg	50	12	20	68	0	100	0	100	0	69	0	60	0	0
Midaz 1.0 mg/kg	75	24	30	46	0	100	0	100	0	40	0	30	0	0
Midaz 1.5 mg/kg	75	30	30	40	0	100	0	100	0	35	0	25	0	0
Midaz + Meper 0.5 mg/kg 1.0 mg/kg	75	16	22	62	0	100	0	100	0	28	0	20	0	0
Midaz + Meper 0.7 mg/kg 1.0 mg/kg	100	35	32	33	0	100	0	100	0	20	0	12	0	0
Midaz + Meper 1.0 mg/kg 1.0 mg/kg	100	48	38	14	0	100	0	100	0	12	0	4	0	0
Midaz + Meper 1.5 mg/kg 1.0 mg/kg	75	52	34	12	2	96	4	98	2	4	6	8	0	2
Midaz + Meper 1.5 mg/kg 1.5 mg/kg	60	46	30	20	4	94	6	94	6	10	8	8	4	2
Midaz + Meper 1.0 mg/kg 2.0 mg/kg	70	46	28	24	2	90	10	86	14	10	10	8	2	2
Midaz + Meper 1.5 mg/kg 2.0 mg/kg	60	36	34	26	4	86	14	88	12	10	12	8	4	2

continues; success to complete treatment objectives may not surprisingly include more frequent induction of deeper planes of depressed consciousness. The importance of the availability of reversal for both agents is paramount under these circumstances.

The impact of meperidine addition to working time and ability to complete treatment objectives

Differences in working times were significant across all levels of apprehension ($p<0.05$) by the addition of meperidine. Use of midazolam alone limited duration of action to 10 minutes. Abortion of visits significantly increased as anxiety levels intensified. To the contrary, addition of meperidine enhanced working times 2X for lower dosing of midazolam and up to 4X with higher-end dosing.

Parental Perspectives

Parental attitudes over the past decades have evolved from what was once a passive acceptance of what the dental professional advocated as an authoritarian approach to definitive concerns and preferences regarding how they expect management of their children to occur. Clinician attitudes have similarly changed. While some advocate use of restraint to facilitate patient cooperation and compliance, and make use of such in an arbitrary manner, others appear to reject their use.

All parents were surveyed at the conclusion of visits prior to discharge regarding their perceptions of comfort level, safety, and willingness to consider sedation techniques for future visits. Assessments ranged from "no hesitation" to consider it for future events to "never again."

Enthusiasm for future use diminished with the need for restraint, occurrence of somnolence and increasing recovery periods. The vast majority of sentiment was that sedation was safe and preferable to having witnessed restraint of their child against his/her will. Approximately 25% expressed that they remained apprehensive about its use but were in agreement that it benefitted their child. For subjects in which persistent use of restraint was needed to complete treatment objectives, sentiment was mixed. Approximately half indicated they would give serious consideration to selecting an unconscious technique or deferring treatment altogether. Half would consider all instances in which persistent restraint of their child occurred as being preferable to resorting to an unconscious technique. This topic is considered important and is expanded in another paper. What emerges here is a question of how both clinicians and parents perceive the role and appropriateness of "protective stabilization" when assessing the success or lack thereof of sedative techniques.

DISCUSSION

The availability of a sedative regimen with the capacity to obtund moderately and severely apprehensive and interfering child dental behaviors with highly predictable efficacy for variable durations of length is a valuable asset. Possession of reversal capabilities adds insurmountable benefit from the perspective of both efficacy and safety. Both benzodiazepines and narcotics have such and serves as qualities unmatched by other traditional pediatric sedative combinations. Lastly, inclusion of an amnesic component further represents an advantage of this combination. Unlike Chloral Hydrate, which lacks capacity for reversal, excessive effects of midazolam can be promptly terminated. Without sacrificing behavioral modifying capacity or adversely affecting respiratory or circulatory function, midazolam offers a distinct safety advantage.

Regarding expectations for midazolam used alone, higher –end dosing can be expected to produce more effective levels of sedation for more highly anxious subjects. Age related differences with respect to behavioral expectations and adaptation to stress can be expected to play a role in dosage determination between pre-cooperative subjects and those above 36 months of age. Children below the age of reason may require deeper levels of depressed consciousness to permit invasive procedures whereas older subjects more experienced in coping with stress and greater capacity to learn from experience, and differing temperament, may need lower dosing and lesser degrees of depressed consciousness.

Under conditions where the duration of action of midazolam can be safely extended by the addition of the narcotic while retaining the capacity to reverse adverse effects should an unintended deeper level of depression occur; the use of this regimen poses significant advantage. Prospective study to yield evidence-based support for both efficacy and safety seems warranted. To circumvent problems associated with long-acting and dose-related somnolence midazolam has emerged as a potential alternative to chloral hydrate because of its rapid onset, potency to obtund difficult patient resistance, and perceived range of safety.

The impact of anxiety level on both agent and dosing choices appears to suggest future study includes variable degrees of apprehension when identifying the rationale for dosing of individual agents. Much of the existing literature has sought to reduce efficacy and safety of a given agent for anxiety and resistance in general to avoid adverse reaction. Comparisons that differentiate between mild vs moderate vs heightened patient resistance can be expected to offer greater insights for the clinician. Subtleties that offer distinction between when low-end dosing vs higher-end dosing are indicated ultimately contribute to safer and more effective use of pharmacologic agents. This author finds the distinctions between parent preference for restraint over general anesthesia where conditions are most controlled to be worthy of exploration. Parental reticence to make use of general anesthesia or a sedative technique appear based on numerous variables. Need for persistent restraint to overcome or control interfering behavior from an acceptance point of view for some may relate more to cost or its prohibitive nature.

Safety considerations

The full intent of selecting a sedative strategy to overcome interfering behavior is predicated on the ability to accomplish treatment visit objectives without inadvertently inducing unsafe and deeper planes of depressed consciousness. Rendering a subject during intra- and post-operative periods to a state where responsiveness and arousal necessitates physical or noxious stimulation, results in agitation, recurrent oxygen desaturation, respiratory depression, or loss of protective reflexes all of which refutes the conclusion that sedation was both safe and successful. Comparisons seen in Tables 2 and 3 witnessed such when dosages of 1.5 mg/kg and 2.0 mg/kg meperidine were included for the most challenging levels of anxiety. The extent to which use of 2.0 mg/kg meperidine necessitated physical arousal to awaken 10-14% of severely anxious subjects, and 4-6% of moderately apprehensive subjects receiving 1.5 mg/kg

suggests the need to avoid higher-end dosing of narcotic, regardless of midazolam dosages used.

Alternatively, comparisons between all dosages of midazolam used alone manifested the lowest frequencies of optimal/ adequate levels of success. Dosages of 0.3 – 0.5 mg/kg midazolam proved inadequate 68-91% of the time. Elevation to 0.7 mg/kg proved failure in 48-68% of visits for moderately and severely apprehensive subjects respectively. Interestingly, a majority of advanced training programs reportedly advocate and limit the use of dosage range <0.7 mg/kg where midazolam is the only agent permitted for its oral sedations. [1,2]

Hypothetically, if a reasonable goal could be expected to be in the range of 80% optimal/adequate success, the data suggests that use of midazolam (0.7-1.0 mg/kg) in combination with meperidine (1.0-1.5 mg/kg) might best be considered.an appropriate range for the pediatric patient. Selection of the upper vs lower end of dosing might be determined by the extent of the anxiety manifested. Training programs that restrict dosing to sub-therapeutic ranges (<0.7 m,g/kg Midaz may consider upward revisions in their dosing protocols to monitor such increases on efficacy. Future prospective study of these comparisons seems warranted.

Limitations and Implications for future study

There remains little disagreement that retrospective comparisons of sedation regimens do not match the methodological design strength of prospective studies from an evidence-based perspective. That said, where selection samples are immense, differentiation between detection of subtle and more obvious variations in effect becomes more easily discerned. Among the challenges associated with pediatric sedation studies begins with subject selection. Both definition and selection of subjects with adequate levels of anxiety and limited coping skills presents difficulty. This would appear especially problematic where sample sizes are small. Selection is often limited to a certain degree of subjectivity to parental (and investigator) perceptions and interpretation of the child's cooperative ability. Rarely have valid and defined subject selection criteria been offered to enable sufficient sample sizes to be included. The ability to draw conclusions regarding drug efficacy, experimental groups must show statistical uniformity from the outset. The magnitude of the sample size in the current study is projected as sufficient to enable comparisons between both drug conditions and varying levels of apprehension. Heart rate elevations while an indication of heightened emotional response, often calls for subtle and difficult interpretation at best. Elevations can be expected to occur during more stressful components of a visit, but may not be demonstrative with respect to behaviors, either cooperative or otherwise. Where alterations in vital functions such as respiratory distress, persistent oxygen desaturations, or loss of protective reflexes occur, however, conclusions of over-dosage or drug inadequacy become somewhat clear.

From a clinician's perspective, pragmatic use of a scale that defines clinical success by the extent to which a sedation regimen prevented the need for transient or persistent application of restraint, seems logical and sufficient in which to clarify which agents and dosing prove effective and safe.

Future studies are advisably encouraged to make comparisons of a prospective nature; the addition of further control groups that include the use of variable concentrations of nitrous oxide to identify its adjunctive potential to primary agents to enhance the quality of sedations, permit reduced dosing of primary agents, and its impact on working time seem warranted. Among findings that the addition of meperidine to primary agents like midazolam or chloral hydrate show improved quality of sedations while permitting use of lower dosing, such evidence suggests enhanced safety to be a beneficiary component. Lessening the use of high-end dosing by combining meperidine can reasonably be hypothesized to contribute to safer use of pharmacologic approaches. While use of sedative techniques are viewed as desirable to lessen the selection of unconscious techniques, they are by no means a panacea. Intensity and severity of anxiety and treatment need may warrant use of general anesthesia. Training programs with a high reliance on general anesthesia due to highly limited success using low-end sedation dosing may need to reassess their sedation dosing protocols.

Study of additional agents such as triazolam, lorazepam, diazepam, and ketamine, with and without meperidine and/or nitrous oxide are suggested. Dexmeditomidine is beginning to raise attention as a potential sedative for children. A recent study,[40] explored aspects of safety, yet no data has yet emerged with respect to its efficacy in a pediatric dental context. Combination with hydroxyzine may also be considered as a potentiating agent for midazolam and meperidine due to mild sedative qualities it possesses. Such may be useful to broaden the range of the arsenal of agents for safe and effective in-office and out-patient child management.

CONCLUSIONS

1. The addition of meperidine to midazolam has the potential to enhance the quality, predictability and safety of pediatric sedations for mildly, moderately, and severely apprehensive young children.
2. The addition of meperidine can be expected to lengthen if not double the working time of midazolam for children with all levels of anxiety
3. Except for simple tasks of short and ultrashort duration for the mildly anxious pediatric dental patient, use of midazolam alone may prove inadequate.
4. A potential advantage of low-end dosages of midazolam combined with meperidine may permit management of some non-pulpal procedures without local anesthetic.
5. Dosages of 0.3-0.5 mg/kg midazolam alone or in combination with meperidine should not be expected to sufficiently sedate moderately (or more severe) anxious young pediatric dental patients.
6. Dosages of 0.7 mg-1.0 mg/kg of Midazolam combined with Meperidine 1.0-1.5 mg/kg appear to offer the most successful results to overcome need for physical restraint and use of higher vs lower end dosing may best be guided by the level of anxiety encountered.

Disclaimer:

Use of the agents described in this manuscript requires advanced training and clinical expertise in pediatric dentistry, proficiency and skills in airway and emergency medical management. Use by the novice is not recommended.

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