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BRIEF ARTICLE

Ketamine and midazolam sedation for pediatric gastrointestinal endoscopy in the Arab world

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Abstract

AIM: To evaluate the safety and effectiveness of intravenous ketamine-midazolam sedation during pediatric endoscopy in the Arab world.

METHODS: A retrospective cohort study of all pediatric endoscopic procedures performed between 2002-2008 at the shared endoscopy suite of King Abdullah University Hospital, Jordan University of Science & Technology, Jordan was conducted. All children were > 1 year old and weighed > 10 kg with American Society of Anesthesiologists class 1 or 2. Analysis was performed in terms of sedation-related complications (desaturation, respiratory distress, apnea, bradycardia, cardiac arrest, emergence reactions), adequacy of sedation, need for sedation reversal, or failure to complete the procedure.

RESULTS: A total of 301 patients (including 160 males) with a mean age of 9.26 years (range, 1-18 years) were included. All were premedicated with atropine; and 79.4% (239/301) had effective and uneventful sedation. And 248 (82.4%) of the 301 patients received a mean dose of 0.16 mg/kg (range, 0.07-0.39) midazolam and 1.06 mg/kg (range, 0.31-2.67) ketamine, respectively within the recommended dosage guidelines. Recommended maximum midazolam dose was exceeded in 17.6% patients [34 female (F):19 male (M), $P = 0.003$] and ketamine in 2.7% (3 M:5 F). Maximum midazolam dose was more likely to be exceeded than ketamine ($P < 0.001$). Desaturation occurred in 37 (12.3%) patients, and was reversible by supplemental oxygen in all except 4 who continue to have desaturation despite supplemental oxygen. Four (1.3%) patients had respiratory distress and 6 (2%) were difficult to sedate and required a 3rd sedative; 12 (4%) required reversal and 7 (2.3%) failed to complete the procedure. None developed apnea, bradycardia, arrest, or emergence reactions.

CONCLUSION: Ketamine-midazolam sedation appears safe and effective for diagnostic pediatric gastrointestinal endoscopy in the Arab world for children aged > 1 year and weighing > 10 kg without co-morbidities.

Key words: Pediatric endoscopy; Sedation; Ketamine; Arab

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INTRODUCTION

Although progress is being made in improving medical services in modern third world countries, limited financial resources are a critical concern. This environment necessitates effective but cost conscious approaches to medical care. Sedation for medical procedures is a potential area for intervention. For example, ketamine-based intravenous sedation has proven effective in suboptimal circumstances, such as the wartime battlefield, avoiding the need for general anesthesia[1-2].

Endoscopic procedures are frequently required for the diagnosis and treatment of gastrointestinal diseases in children. Since such procedures can cause considerable anxiety and distress, many children find the procedures worse than disease itself.

The goal of sedation is to provide a patient who is only lightly sedated, cooperative on demand, free from anxiety and amnesic after the procedure[3]. It must have a rapid onset, short duration of action, and should be safely administered by a non-anesthesiologist without significantly increased risk of potential complications[4]. Unfortunately, there is no ideal sedation protocol for gastrointestinal (GI) endoscopy that is agreed upon by pediatric gastroenterologists as confirmed by a recent survey by the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN)[5] and by another survey by the Francophone Pediatric Hepatology, Gastroenterology and Nutrition Group[6]. It appears that there is a wide variety of sedation techniques used by practicing pediatric gastroenterologists.

Although ketamine-based sedation provides many of the desired effects of an ideal sedative, it is not widely used in pediatric gastrointestinal endoscopy. There is limited published research regarding its efficacy and safety, particularly in developing countries. The aim of this study is to assess the safety and efficacy of ketamine + midazolam sedation for GI endoscopy in pediatric patients in Jordan.

MATERIALS AND METHODS

A retrospective cohort study of all pediatric endoscopic procedures done under intravenous sedation by a combination of ketamine and midazolam over a period of six years (August 1st, 2002 - July 31st, 2008) done at the endoscopy suite of King Abdullah University Hospital (affiliated with Jordan University of Science and Technology) in Jordan was conducted.

All procedures were performed in the endoscopy suite which is shared with adult gastroenterologists and pulmonologists and a part of a general university hospital. All procedures were performed by a single pediatric gastroenterologist. A registered nurse provided constant patient monitoring (before, during and after the administration of sedatives) including continuous cardiac monitoring, respiratory rate, pulse oximetry and blood pressure monitoring. During the study period, the same gastroenterologist performed all the procedures, calculated and administered the sedative medications. The operating physician and nursing staff assessed the adequacy of sedation and documented all the above. The operating physician is Pediatric Advance Life Support certified.

Pre-sedation risk assessment included a detailed history and complete physical examination, review of current medications and drug allergies as well as an assessment of the cardiopulmonary status. All patients in the study were at American Society of Anesthesiologists (ASA) class 1 or 2. Procedures in patients with a higher ASA class were excluded from the study and performed under general anesthesia[7,8]. General anesthesia was used in the following groups of patients: (1) children below the age of one year or weighing less than 10 kg; (2) patients underwent the therapeutic endoscopy (e.g. esophageal dilation, variceal treatment and polypectomy) under general anesthesia for their safety, the need to be motionless during the procedure as these procedures are typically associated with more pain and discomfort; (3) patients with known neurologic disorders (seizures), developmental delay (cerebral palsy), and psychiatric disorders (phobia); (4) increased intracranial pressure (hydrocephalus); and (5) patients known to have abnormal anatomy of the upper airways (Pierre Robin sequence).

All patients were premedicated with atropine at a dose of 0.01 mg/kg - 0.02 mg/kg (a minimum dose of 0.1 mg to avoid paradoxical bradycardia, and a maximum dose of 0.4 mg). Standard dosage guidelines for sedatives are: midazolam 0.05 mg/kg - 0.20 mg/kg and ketamine 0.5 mg/kg - 2.0 mg/kg used at each dose[4,8]. Midazolam was always administered first.

In our study, three types of endoscopic procedures were used: upper (U), lower (L), and combined upper and lower (U&L). If an upper and lower endoscopy was performed in the same sedation session, they were counted as a single sedation session. If the same procedure was repeated at a later time, it was counted as a separate sedation session.

Analysis of the data included demographic details (age, gender) weight, procedure (s) performed, doses of each medication/kg body weight, effectiveness of sedation, need for other sedatives, side effects and complications.

Sedation-related complications were defined as a drop in oxygen saturation to equal or less than 94%, respiratory distress (stridor or wheezes), apnea, bradycardia, cardiac arrest and emergence reactions. The operating gastroenterologist and nursing staff assessed the adequacy of sedation; this was defined as lack of agitation, ability to complete the procedure comfortably, and no need to add other sedatives. The need of an antidote for reversal medications was also included.

Table 1 Types of endoscopic procedures

	n (%)	Males	Females	Age range (yr)	Mean age (yr)
Upper (U)	218 (72.4)	106	112	1-18	8.86
Lower (L)	16 (5.3)	14	2	1-16	9.09
U & L	67 (22.3)	40	27	2-18	10.89
Total	301	160	141		

Table 2 Midazolam and ketamine doses

	Midazolam doses			Ketamine doses		
	All patients	Males	Females	All patients	Males	Females
Min dose (mg/kg)	0.07	0.07	0.07	0.31	0.31	0.46
Max dose (mg/kg)	0.39	0.32	0.39	2.67	2.00	2.67
Mean dose (mg/kg)	0.16	0.15	0.16	1.06	1.03	1.08

Table 3 Sedative doses

	Midazolam doses (mg/kg)			Ketamine doses (mg/kg)		
	Min	Max	Average	Min	Max	Average
Upper (U)	0.07	0.39	0.15	0.33	2.67	1.02
Lower (L)	0.07	0.32	0.17	0.60	1.84	1.12
U & L	0.08	0.27	0.18	0.31	2.11	1.17

Table 4 Distribution of patients receiving doses exceeding recommended max dose

Procedure	Midazolam		Ketamine	
	n (%)	% per specific procedure	*n* (%)	% per specific procedure
Upper (U)	30 (57)	14	4 (50)	1.8
Lower (L)	5 (9)	31	0 (0)	0
U & L	18 (34)	27	4 (50)	6
Total	53 (17.6)		8 (2.7)	

Table 5 Sedation failure

Sedative-related complications	*n* (%)
Desaturation < 94% in RA	37 (12.3)
Desaturation < 94% on supplemental O_2	4 (1.3)
Respiratory distress	4 (1.3)
Apnea	0 (0.0)
Bradycardia	0 (0.0)
Cardiac arrest	0 (0.0)
Emergence reaction	0 (0.0)
Difficult to sedate/third medication	6 (2.0)
Need for reversal medications	12 (4.0)
Need for overnight stay	1 (0.3)
Failure to complete the procedure	7 (2.3)

RA: Ruba abdelhadi.

Failure of sedation was defined as: (1) The occurrence of sedative-related complications: (a) Oxygen desaturation < 94%; (b) Respiratory distress wheezes or stridor; (c) Apnea; (d) Bradycardia; (e) Cardiac arrest; and (f) Emergence reactions; (2) Difficult to sedate, as judged by the physician or nursing staff, requiring a third sedative medication; (3) The need for reversal medications; (4) Need for overnight stay because of sedation-related issues; and (5) Failure to complete the procedure.

RESULTS

A total of 560 procedures were performed over the study period (August 1st, 2002 - July 31st, 2008), 12 patients were excluded because of incomplete medical records. Of the 548, 247 were performed under general anesthesia, and 301 were done utilizing ketamine + midazolam. All 301 patients included in the study who had conscious sedation received combined midazolam and ketamine in addition to atropine. The sedatives were given in small boluses and titrated to achieve the desired effect. Not infrequently, patients required extra doses during the procedure; this was especially noted in longer procedures. For dosage calculations, we used the cumulative dose.

There were 160 males and 141 females (1.13:1), age ranged from 1 to 18 years, with a mean age of 9.26 years in males and 10 years in females. Among the three types of endoscopic procedures, upper endoscopy was the most frequently performed procedure (218 patients or 72.4%) followed by combined upper and lower (67 patients or 22.3%). Details are shown in Table 1.

The average dose of midazolam used in all procedures was 0.16 mg/kg, (range, 0.07 mg/kg - 0.39 mg/kg), while the average dose of ketamine was 1.06 mg/kg (range, 0.31 mg/kg - 2.67 mg/kg) (Table 2). There was no statistically significant difference in the average dose used between males and females for either of the two medications.

Analysis of sedative dosage according to the type of procedure is shown in Table 3. In general, patients require similar doses of sedatives regardless of the type of procedure.

Most patients received a dose within the recommended dosage guidelines of both medications (248 patients or 82.4%). The maximum dose for either medication was exceeded in 53 patients (17.6%) (Table 4).

The recommended maximum dose of midazolam was exceeded in 53 (17.6%) patients (19 M:34 F), which was more likely to be exceeded in females ($P = 0.003$). The recommended maximum dose of ketamine was exceeded in only eight patients (2.6% of all patients) (3 M:5 F). The dose of midazolam was more likely to be exceeded than ketamine ($P < 0.001$).

Maximum dose of midazolam was significantly exceeded in combined upper and lower endoscopic procedures when compared to upper endoscopies (27% *vs* 14%; $P = 0.02$). Maximum midazolam dose was also exceeded more in lower endoscopic procedures when compared to upper endoscopies (31% *vs* 14%), but the limited number of lower endoscopic procedures precluded sta-

Table 6 Effects of midazolam and ketamine dosing on development of desaturations

Procedure	Midazolam average dose (mg/kg)			Ketamine average dose (mg/kg)		
	Patients with desaturation	Patients without desaturation	*P* value	Patients with desaturation	Patients without desaturation	*P* value
Upper (U)	0.26	0.14	< 0.001	2.2	0.86	< 0.001
Lower (L)	NA	0.17	NA	NA	1.12	NA
U & L	0.24	0.168	< 0.001	2	1.01	< 0.001
n	37	264	NA	37	264	NA

NA: Not available.

tistical significance ($P = 0.126$). The maximum ketamine dose was also exceeded more in combined upper and lower endoscopies (6% *vs* 1.8%), but was not statistically significant ($P = 0.170$)

Sedation failure

Two hundred and thirty-nine patients (79.4%) had effective and uneventful sedation. Sedation failure is summarized in Table 5.

Sedative-related complications: (1) Desaturation < 94% in room air occurred in 37 (12.3%) patients, (26 U, 11 U&L, none of L). The average doses of both medications were higher than the maximum dose. The patients received a higher dose of both medications in comparison with the patients who did not develop desaturation; the difference was statistically significant (Table 6). Oxygen by nasal cannula was administered to these patients, and normal saturation was achieved in 33/37 (89%). In four patients, the oxygen saturation did not improve and the procedure was terminated and rescheduled under general anesthesia later; and (2) respiratory distress (stridor or wheezes) developed in four patients (1.3%) after termination of procedure. All four were U, one recovered spontaneously while the other three required Albuterol (Ventolin) nebulizer treatment. None of the patients who developed respiratory distress exceeded the recommended dose of either medication, and none of them developed desaturation. No apnea, bradycardia, cardia arrest or emergence reactions occurred in any patient.

Difficult to sedate: As judged by the physician or nursing staff, six patients (2%) (3 M, 3 F) required a third sedative medication and meperidine was given. Five were U&L, and one was L. The maximum dose of midazolam was exceeded in four but none of them exceeded the maximum dose of ketamine.

Need for reversal medications: During recovery, 12 (4.0%) patients were judged to be excessively sedated and required reversal of benzodiazepines using flumazenil (3 U, 8 U&L, 1 L). None of them had desaturation or respiratory distress. The average dose of midazolam in those patients was 0.23 mg/kg (range, 0.18 mg/kg - 0.27 mg/kg). The average dose of ketamine in those patients was 1.4 mg/kg (range, 0.80 mg/kg - 2.11 mg/kg).

Need for overnight stay: One.

Failure to complete the procedure: Seven (2.3%) patients failed to complete the procedure. Four patients had desaturation despite oxygen supplementation and all were U. The other three did not complete the procedure because of lack of cooperation of the patient.

DISCUSSION

Intravenous ketamine + midazolam sedation for gastrointestinal endoscopy is safe and effective in most patients. Routine use of general anesthesia for endoscopic procedures is not necessary, which increases cost and is often not readily available in some developing countries. According to a recent NASPGHAN survey, 23% of the respondents described the difficulties and inconvenience in the process of scheduling a procedure in the operating room[5]. Only half (55%) reported their endoscopy suites with general anesthesia equipment. In developing countries, cost is a detrimental factor. To the best of our knowledge, this is the first study that documents the safety and effectiveness of ketamine + midazolam sedation for pediatric gastrointestinal endoscopy in an Arab country.

Ketamine is a non-barbiturate dissociative agent with a rapid onset of action (peak intravenous concentrations occur within one minute) that induces profound sedation, analgesia and amnesia, with a short duration of action (15-30 min) which is adequate for routine diagnostic endoscopy, allowing fast recovery[9,10]. It induces functional dissociation between the limbic and the cortical systems. This cataleptic state impairs sensory recognition of painful stimuli and memory inducing a state referred to as "dissociative anesthesia"[9]. Protective airway reflexes are maintained during sedation with ketamine, with minimal cardiovascular and respiratory side effects. This paramount advantage over other categories of sedatives (narcotics) lies in maintaining airway reflexes with minimal cardiovascular and respiratory side effects[11].

The high therapeutic index of ketamine makes it useful in children with less predictable response to sedatives[12]. This might explain the low incidence of sedative-related complications in our study.

While midazolam has been used in procedural sedation in children extensively, ketamine has not. Mid-

azolam provides sedation and amnesia but it lacks any analgesic effect. The analgesic properties of small-dose ketamine have been rediscovered. Available data strongly suggest that the preemptive administration of ketamine can have profound effects on postoperative analgesic requirements with minimal risk and side effects[13,14]. The use of ketamine for procedural (endoscopic and other procedures) sedation is increasing in the developed countries[15]. There are only a handful of studies that looked at ketamine's value in the endoscopic sedation in children[13,16] but none of them in developing countries.

A prospective randomized study by Varadarajulu *et al*[17] evaluated the use of ketamine for endoscopic procedures and concluded that ketamine is a useful adjunct to conscious sedation in patients who are difficult to sedate. Its use results in better quality and depth of sedation with shorter recovery than in patients sedated using benzodiazepines and meperidine alone. This was confirmed in our study as patients who did not respond to midazolam + ketamine did not benefit from adding meperidine.

Endoscopy was completed in 97.7% (294/301) of our study patients, confirming that midazolam-ketamine is an effective sedation for such procedure. A third medication was mainly needed in the combined procedures (U&L); the ketamine dose could be increased rather than adding an additional sedative. It may be more prudent to maximize ketamine dose before adding a third medication. For example, five of the six patients who were difficult to sedate by the endoscopist and nursing staff, remained inadequately sedated even after adding a third sedative.

Respiratory distress (stridor or wheezes) was rare (1.3%). This low rate of respiratory distress could be explained by the fact that both ketamine and atropine have a bronchodilator effect which adds another advantage in the pediatric age group where reactive airway disease is common.

Like any other sedatives, the sedative response to ketamine is not uniform and may be unpredictable; hence it is prudent to increase a small dose slowly, tittering to the desired effect (typically horizontal nystagmus). Dosing of ketamine has a wide safety margin. Reported unintentional administration of overdoses (up to ten times that of recommended dosage) has been followed by prolonged but complete recovery[1,12,18,19].

Bradycardia is a known side effect of sedatives and may be further augmented by vagal stimulation during upper endoscopy. The lack of bradycardia in our patients could be related to the fact that all patients received atropine prior to the procedure[20].

One of the major drawbacks of ketamine is the occurrence of emergence reactions (psychological manifestations vary in severity between pleasant dream-like state, vivid imaginary, hallucinations and emergent delirium). None of our patients developed any of these reactions. The explanation for that is probably multifactorial. First, emergence reactions are more common in adults than in children. Second, this phenomenon is more common in patients known to have psychiatric or neurological disorders. In our study, those were excluded and their endoscopies were done under general anesthesia. Third, these reactions are usually more pronounced if ketamine is used alone, in large doses and if rapidly administered[21]. All our patients received a combination of midazolam and ketamine; both medications were given slowly and in small boluses. They were observed for the development of emergence reactions for at least 2 h after the procedure. Our findings are supported by a recent study by Gilger *et al*[9]. In that study, the authors concluded that emergence phenomena were more common in those not receiving ketamine, and suggested that true ketamine-associated emergence phenomena are either rare or that midazolam does reduce the frequency of emergence reactions[9].

The biggest worry of the endoscopist administering ketamine is the lack of an antidote[12]. One reassuring fact about ketamine is its short duration of action of 15-30 min[1]. If a patient develops an unexpected adverse reaction, he can be managed by supportive care until the drug effect wears off. This was supported by our findings among the 301 patients; only one child required an overnight stay for observation due to over-sedation. In this particular patient, the recommended doses of midazolam and ketamine were exceeded and required meperidine.

Midazolam + ketamine is not routinely used in children at KAUH outside the operating room. This "procedural sedation phobia" by non-anesthesiologists is noted among other medical institutions in other parts of the world as there is still significant resistance to pediatric sedation techniques used outside the operating room by non-anesthesiologists , as reported in a recent study by Krauss *et al*[15]. The lack of familiarity with ketamine significantly affects the comfort level of the physicians and nursing staff and brings more hesitation to use it outside the operating room by non-anesthesiologists.

In conclusion, ketamine + midazolam is a safe and effective sedative regimen for diagnostic pediatric GI endoscopy in the Arab world for children over the age of one year and weighing more than 10 kg without comorbidities. Side effects of hypoxia and respiratory distress are uncommon. None of our patients developed a serious complication (apnea, bradycardia, cardiac arrest, or emergence psychosis). Pre-sedation risk assessment and proper patient evaluation and selection are of paramount importance and cannot be over-emphasized to minimize potential complications.

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COMMENTS

Background

Endoscopic procedures are frequently required for the diagnosis and treatment

of gastrointestinal diseases in children. Such procedures can cause considerable anxiety and distress, and many children find the procedures worse than disease itself. Ketamine-based sedation is not widely used in pediatric gastrointestinal endoscopy. There is limited published research regarding its efficacy and safety, particularly in developing countries.

Research frontiers

Ketamine-based intravenous sedation has been studied and proven to be effective when used in the emergency room for children requiring painful interventions.

Innovations and breakthroughs

This research focuses on the endoscopic sedation in a pediatric population using ketamine-based sedation avoiding the need for general anesthesia.

Applications

About 80% of children had effective and uneventful sedation using intravenous midazolam and ketamine. Side effects were uncommon and reversible, and there was no mortality associated with this type of sedation. This should encourage more clinicians to use this type of sedation, thus avoiding general anesthesia for pediatric endoscopic procedures.

Peer review

This research confirms the safety and efficacy of ketamine-based sedation for endoscopic procedures in a third world country.

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