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Oral ketamine and midazolam for pediatric burn patients: A prospective, randomized, double-blind study

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Abstract

Purpose: The aim of this study was to compare the efficacy of oral midazolam and ketamine with oral midazolam, acetaminophen, and codeine in providing sedation and analgesia for wound care procedures in children with burns.

Methods: This is a prospective, randomized, double-blind study that includes patients 1 to 5 years old hospitalized between 2010 and 2011, with burns covering up to 10% of total body surface area that required bedside wound care. Group 1 received oral midazolam (0.5 mg/kg) and ketamine (5 mg/ kg). Group 2 received oral midazolam (0.5 mg/kg), acetaminophen (10 mg/kg), and codeine (1 mg/kg). Sedation was assessed using the University of Michigan Sedation Scale and pain using the CHEOPS scale.

Results: Sixty patients were enrolled and evenly distributed into the two groups. There were a higher percentage of well-sedated patients in Group 1, but this was not statistically significant. Patients in Group 2 reported lower levels of pain ($p=0.0245$). Adverse reactions were reported in both groups. The only parameter that had a statistical difference was nystagmus ($p=0.001$).

Conclusion: The combination of oral midazolam and ketamine provides better analgesia than the combination of midazolam, acetaminophen, and codeine for painful procedures in burned children.

Burns of variable severity are caused by physical, chemical, or biological agents. Burned children who require hospitalization are subjected to numerous painful wound care procedures. These procedures occur in the patient's room or operating room, depending on the severity of the burn, after administration of analgesic and sedating agents [1,2].

The use of pharmacological sedation and anxiolysis is a common practice in pediatric anesthesia and other pediatric procedures involving an unfamiliar environment, fear associated with separation from parents, and fear associated with pain [3-6]. The pharmacological characteristics of good sedation and analgesia include ease of application,

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rapid action, short duration of action, and lack of significant adverse reactions. Midazolam possesses these characteristics in its various forms of administration and is therefore the most commonly used premedication. It produces anterograde and retrograde amnesia, muscle relaxation, anxiolysis, and sedation. However, it lacks analgesic properties, and therefore good or excellent results have been found when the drug is used alone in only 60%–80% of cases [7]. Ketamine is an NMDA (*N*-Methyl-D-aspartate) receptor antagonist that dissociates the cortex from the limbic system, producing analgesia, sedation, and amnesia. Ketamine is a versatile compound that can be administered in various forms [8], parenteral administration being the most common. However, there are studies that support the oral administration of ketamine as an effective alternative with fewer adverse reactions [9-11,14]. Other authors have reported that the combination of midazolam and ketamine produces better premedication than either drug administered alone [11-14].

In terms of adverse effects of pain secondary to burns, we know that burns trigger a neurohumoral response including elevated catecholamines, insulin, growth hormone, antidiuretic hormone, aldosterone, glucagon, and interleukins, leading to a state of increased catabolism, oxygen consumption, glucogenolysis, lipolysis, and gluconeogenesis. The effects of this stress response result in a redistribution of proteins from the musculoskeletal tissue to the vital organs, which decreases immunological function and impairs healing [15]. In a study by Stoddard, 29% of patients aged between 12 and 48 months old developed acute stress symptoms such as re-experiencing, avoidance and arousal symptoms. Size of burn, heart rate, pain, and parental stress were risk factors that, via various pathways, influence the stress symptoms [4]. For these reasons, it is important to provide adequate management for pain and anxiety in burn victims.

The objective of this study is to compare the efficacy of oral ketamine and midazolam versus midazolam, acetaminophen and codeine in providing sedoanalgesia for bedside wound care procedures in burned children.

1. Materials and methods

A prospective, randomized, double-blind study was carried out in the Plastic Surgery and Burn Unit of Dr. Exequiel González Cortés Children's Hospital between November 2010 and March 2011. Patients 1 to 5 years of age, hospitalized with a diagnosis of burn covering up to 10% of total body surface area (TBSA), and requiring bedside wound care procedures were enrolled, after obtaining informed consent by parents. Bedside wound care procedures were either wound dressing or graft revision. Wound dressing refers to the procedure of wound cleansing with saline, debridement of necrotic tissue and dressing. Graft revisions included removal of staples, removal of necrotic tissue if present, and dressing. Patients with a history of allergic reaction to any of the study medications, cardiac insufficiency, or acute respiratory infection were excluded from the study.

Patients were randomly assigned to one of two groups: group 1, which received oral midazolam (0.5 mg/kg) and ketamine (5 mg/kg) or group 2, which received oral midazolam (0.5 mg/kg), acetaminophen (10 mg/kg), and codeine (1 mg/kg).

The medications, liquid ketamine and midazolam tablets were prepared by the chemist–pharmacologist using a sweetened, orange-flavored syrup as the vehicle, with an equivalent volume of medication for both groups. If the medication was not ingested completely, the patient was excluded from the study.

Demographic data including age, sex, and weight were recorded, as well as type of burn according to Benaim's classification (Type A/ first degree; AB/second degree; B/ third degree), percentage of total body surface area burned, days of evolution of the burn, and procedure performed (wound dressing, graft revision). All patients were monitored for heart rate and oxygen saturation using a pulse oximeter, and the room was supplied with oxygen masks, oxygen, and a positive-pressure ventilation bag in case these were required.

The painful procedure was initiated 20 min after administration of the medications and was performed by a trained nurse. A blinded rater evaluated the patient's sedation using the University of Michigan Sedation Scale (Appendix 1) at 20, 25, 30, 45, and 60 min after administration of medication. For statistical analysis, the scale values were transformed into a three-category variable: insufficient sedation (level 0), adequate sedation (levels 1 and 2) or excessive sedation (levels 3 and 4). Pain was evaluated during the painful procedure using the CHEOPS scale (Appendix 2), by the same rater. This rater did not have any other responsibilities.

Statistical analysis was performed using SPSS v.19. Student's t-test was used for quantitative and chi-square test for qualitative variables. For patients that had more than one procedure, each procedure was analyzed separately as if they were from different patients. The results were unblinded by a person not otherwise involved with the study.

2. Results

The study enrolled 60 patients, distributed into 2 groups: 30 in group 1 and 30 in group 2. The two groups were comparable in terms of age, weight, sex, days of evolution of the burn, extent and depth of the burn, and procedure performed (Table 1).

2.1. Sedation

Twenty minutes after receiving the drugs, most of the children reached an adequate level of sedation. No patient lost consciousness. A larger percentage of children in group

Table 1 Demographic characteristics, diagnosis, time of evolution, and procedure performed, by group.

	Group 1	Group 2	p
Age (months)	23.83±12.50	22.93±10.39	0.832
Weight (kg)	13.65±2.76	13.13±2.50	0.617
Sex (F/M)	11/19	11/19	
TBSA (%) [a]	5.36±2.75	5.36±2.50	0.481
Type A (no/yes) [b]	21/9	22/8	0.774
Type AB (no/yes) [b]	0/30	2/28	0.150
Type B (no/yes) [b]	26/4	26/4	
Days evolution	8.83±4.90	9.10±6.50	0.858
Procedure (wound dressing/ graft revision)	28/2	24/6	0.129

Means±standard deviation.
p: p value.
[a] TBSA: Total body surface area.
[b] Benaim Classification: Type A equivalent to first degree burn, Type AB equivalent to second degree burn and Type B equivalent to third degree burn.

1 achieved an adequate level of sedation than in group 2, although this difference was not statistically significant (Table 2).

2.2. Evaluation of pain

Range of pain was equivalent in the two groups. The mean CHEOPS score was calculated for both groups, with a significant difference (p=0.0245) between them. The mean score in group 2 was 8.9 (range 4–13, confidence interval [CI] 95%) versus 7.4 for group 1 (range 4–12, CI 95%) (Fig. 1). As part of the evaluation protocol, the parents or guardians were asked their impression (better, worse, the same, or don't know) of the pain control for the wound care procedure performed in the emergency room with that performed under the study protocol. This interview was performed in only 16 cases, as the person who accompanied the child to his or her first wound care procedure was not necessarily the same person who was with the child in the second procedure (by study protocol). In group 1, there were 10 responses of "better", and in group 2, there were 6 responses of "better". There were 3

Table 2 Percentage of children adequately sedated at various time intervals.

	Group 1 n (%)	Group 2 n (%)	p
20 min	26 (86.66)	22 (73.33)	0.197
25 min	28 (93.33)	23 (76.66)	0.145
30 min	27 (90)	23 (76.66)	0.166
45 min	28 (93.33)	25 (83.33)	0.424
60 min	25 (83.33)	20 (66.66)	0.136

min: minutes; *p*, p value.

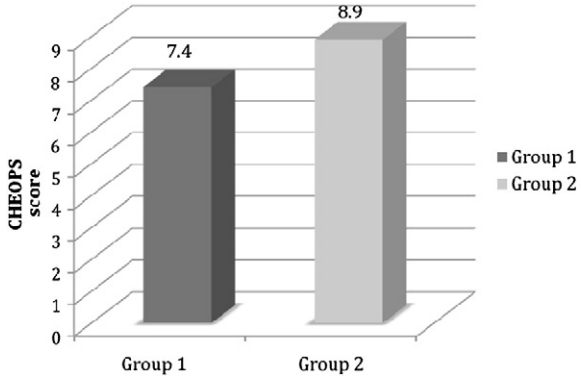

Fig. 1 CHEOPS score, by group.

"worse" responses in group 2 and there were no "worse" responses group 1. However, this difference was not statistically significant (p=0.06).

2.3. Adverse reactions

There were adverse reactions in both groups. Although the number of adverse reactions was significantly higher in group 1 (p=0.03), these reactions were of minor clinical significance and did not compromise patient stability. Five patients in group 2 presented with adverse reactions, including nystagmus (1), salivary hypersecretion (2), and irritability (2). In group 1, 16 patients presented with one or more adverse reactions, including nystagmus (13), salivary hypersecretion (2), irritability (1), and desaturation (1). The only parameter with a statistically significant difference between groups was nystagmus (p=0.001) (Fig. 2). There were no differences in heart rate or oxygen saturation between groups.

3. Discussion

Burns are a common cause of pediatric hospitalization, requiring repeated wound care procedures as part of the

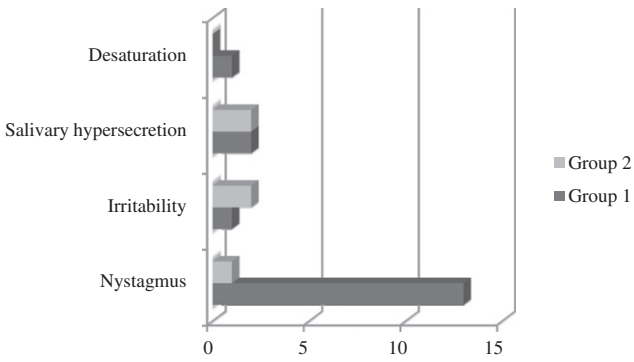

Fig. 2 Type of adverse reaction by group.

therapeutic plan. The pain associated with these procedures may disrupt recovery, interfere with the implementation of the procedures, and increase the likelihood of post-traumatic stress surrounding the accident [4–6]. Pain is associated with elevated heart rate and an elevated heart rate during hospitalization is associated with decreased social smiling and decreased vocalization at 1-month follow up [5]. In our hospital, the conventional premedication for procedures in children with burns is a combination of oral midazolam, codeine, and acetaminophen. However, we had observed poor sedation and analgesic response to these drugs in our burn patients, and, therefore, we designed the present study to evaluate other combinations of drugs that might provide a better option for our patients. Our study demonstrates that the combination of oral midazolam and ketamine provides better analgesia than the combination of oral midazolam, codeine, and acetaminophen in children with burns covering up to 10% TBSA. We also observed a tendency for higher sedation levels in group 1, although this finding was not statistically significant.

Previous studies have shown that the combination of midazolam and ketamine results in a better premedication than the administration of either drug by itself [7,12,13]. This finding indicates that there is a synergistic effect, improving efficacy and decreasing adverse reactions associated with the drugs when used separately, and therefore improving the pharmacological safety profile [11–13]. Beebe et al. carried out a study combining midazolam (0.5 mg/kg) and ketamine (3 mg/kg), finding a more satisfactory parental separation in the study group vs. the groups that received midazolam or ketamine alone [12]. Ozdemir et al. also studied the efficacy of the combination of midazolam and ketamine, comparing different administration routes — oral, intravenous, and rectal. This group found that efficacy is comparable for the various administration methods, but that hallucinations and prolonged sedation only occurred with intravenous administration [14].

Traditionally, ketamine has been administered parenterally, but numerous studies support the use of oral ketamine as an effective alternative with fewer adverse reactions. Humphries, Melson and Gore (1997) compared patients who received ketamine with a group that received a combination of acetaminophen, codeine, and diphenhydramine. They observed higher levels of sedation and analgesia in the ketamine group [9]. In 1992, Gutstein randomized 45 children into 3 groups, one of which received oral ketamine at a dose of 3 mg/kg, another which received oral ketamine at a dose of 6 mg/kg, and a third that received only a placebo. The study found that the dose of 6 mg/kg provided a uniform and predictable sedation in 20 to 25 min, without respiratory depression, tachycardia, or oxygen desaturation [10]. In our study, we found that 25 min after administering the drugs, 93.33% of patients in group 1 had achieved adequate sedation, 10% more than in group 2. We also found no adverse reactions that compromised patient stability.

There are no commercially available oral ketamine preparations. Some studies have prepared capsules, and others have used oral administration of a vial of liquid ketamine. Pharmacokinetic studies of oral ketamine were performed using liquid ketamine [16,17]. Our study used liquid ketamine, administered in combination with midazolam in a sweetened, flavored vehicle.

Evaluating pain in pediatric patients is difficult, as infants and small children are unable to verbally report their experiences. This problem has led to the development of many tools and scales for pediatric pain evaluation [18]. Pain can be evaluated in children by observing behavior, movements, and posture that suggest pain, or, in older children, by self-report. Self-report measures are generally used in children over the age of 4 years, but these require adequate cognitive and language development for accurate results [19]. We restricted enrollment to patients aged 1 to 5 years, so that we could use two scales validated for children of the same age group — one to evaluate sedation and the other to evaluate analgesia. The University of Michigan Sedation Scale is a reliable instrument for quickly and simply evaluating changes in depth of sedation in patients receiving a sedative for diagnostic and/or therapeutic procedures [20,21]. The CHEOPS has adequate inter-rater reliability and is effective for evaluating pain in patients aged 1 to 5 years [22].

A limitation of our study is the small number of patients. It is likely that with a larger number of patients, it would be possible to demonstrate the superiority of midazolam administered with ketamine in providing sedation for painful procedures.

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Appendix 1. University of Michigan Sedation Scale.

Score		
0	Awake/Alert	
1	Minimally Sedated	Tired/sleepy, appropriate response to verbal conversation and/or sounds.
2	Moderately Sedated	Somnolent/sleeping, easily aroused with light tactile stimulation.
3	Deeply Sedated	Deep sleep, arousable only with significant physical stimulation.
4	Unarousable	

Appendix 2. Children's Hospital of Eastern Ontario Pain Scale

	FINDING	Points	
CRY	No cry	1	Child is not crying
	Moaning	2	Child is moaning or quietly vocalizing silent cry
	Crying	2	Child is crying but the cry is gentle or whimpering
	Screaming	3	Child is in a full-lunged cry; sobbing may be scored with or without complaint
FACIAL	Smiling	0	Score only if definite positive facial expression
	Composed	1	Neutral facial expression
	Grimace	2	Score only if definite negative facial expression
CHILD VERBAL	Positive	0	Child makes positive statement or talks about other things w/o complaint
	None	1	Child not talking
	Complaints other than pain	1	Child complains but not about pain (”I want Mommy; I am thirsty”)
	Pain complaints	2	Child complains about pain
	Both pain and non-pain complaints	2	Child complains about pain and other things (”It hurts, I want Mommy”)
TORSO	Neutral	1	Body (not limbs) at rest, torso inactive
	Shifting	2	Body in motion, in a shifting or serpentine fashion
	Tense	2	Body is arched or rigid
	Shivering	2	Body is shuddering or shaking involuntarily
	Upright	2	Child is in an upright or vertical position
	Restrained	2	Body is restrained
TOUCH	Not touching	1	Child is not touching or grabbing at wound area
	Reach	2	Child is reaching for but not touching wound
	Touch	2	Child is gently touching wound or wound area
	Grab	2	Child is grabbing vigorously at wound
	Restrained	2	Child’s arms are restrained
LEGS	Neutral	1	Legs in any position, but relaxed; includes gently swimming
	kicking	2	Definitive uneasy or restless movements and/or striking out
	Drawn up, tense	2	Legs tensed and/or pulled up tightly and kept there
	Standing	2	Standing, crouching, or kneeling
	Restrained	2	Child’s legs are being held down

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