Original Article

Enhancing cooperation during pediatric ultrasound: Oral midazolam versus conventional techniques

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Abstract

Background and Aims: Ultrasound is a safe and non-invasive method for detecting numerous pathologies. Pediatric patients are often uncooperative which leads to decreased quality and increased time of scan. We compared the conventional means alone and combination of oral midazolam for the above cited purpose.

Material and Methods: This double blind prospective study (CTRI/2016/06/007030) was conducted after obtaining due approval from institutional ethical committee. One hundred Children aged 2-6 years belonging to ASA class 1 or 2, posted for high resolution ultrasonography of abdomen were included in the study. They were randomised to receive midazolam 0.3 mg/kg mixed in 20 mL of apple juice (Group I) or 20 mL of apple juice alone (Group II) 20 minutes prior to the procedure. The parameters assessed were level of cooperation, sonologist's satisfaction, total scan time, heart rate and SpO_2.

Results: Out of 100 patients, 44 patients of group I and 42 of group II were analysed. The cooperation score was significantly higher in Group I (35%) than Group II (19%). Likert scale revealed very satisfied and satisfied rating in 61.3% (Group I) and 21.4% (Group II). The time taken by sonologist and number of attempts were significantly less in Group I than Group II. There was no difference in discharge time between the groups. There was no reportable adverse event in either group.

Conclusion: Oral midazolam is a safe and effective agent to aid routine abdominal ultrasonography in pediatric patients.

Keywords: Oral midazolam, pediatric cooperation, pediatric sonography

Introduction

An ideal diagnostic imaging technique should be free from radiation, needle pricks and noise, simultaneously generating high quality image of all dimensions. This holds true for pediatric patients too.[1] Sonography, due to its lack of radiation and its non-invasive approach, should be considered as the initial pediatric imaging modality wherever feasible. High resolution, real-time duplex colour doppler sonography has emerged as the modality of choice for the evaluation of pediatric pelvis, gastrointestinal tract and urinary tract.[2,3] It permits direct visualization of the various mural layers of the gastrointestinal (GI) tract, adding a new dimension to the imaging of this body system. Many recent studies have mentioned the utility of ultrasound for the diagnosis of pediatric GI pathologies.[4,5]

For proper scanning, one requires a calm and quiet patient. Any effort of contracting abdominal musculature as in crying, hampers the quality of scan and increases the duration of scanning. Most children are managed through conventional means like adopting child friendly interiors, visual stimulation and toys. However, sedation is seldom used.

Till now, literature doesn't have any published studies regarding, use of medication to enhance the cooperation of child during routine ultrasound. Midazolam, a benzodiazepine group sedative

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and anxiolytic agent, has been approved by FDA for pediatric uses. It can be administered through various routes e.g. oral, intravenous, intramuscular, rectal, sublingual, intranasal, for sedation and induction of anesthesia.[6] Among all clinically used benzodiazepines, midazolam is the most lipid soluble *in vivo*. However, because of its pH dependent solubility, midazolam is water soluble only when formulated in a buffered acidic medium (pH 3.5). Oral midazolam undergoes significant intestinal absorption and first pass metabolism resulting in a bioavailability of 36% in pediatric patients.[7] In several studies, it fulfilled many criteria for an "ideal" sedation agent, with a rapid onset of action (around 12 minutes) and absence of serious side effects while simultaneously improving patient compliance.[7,8] Studies have shown that premedication with midazolam does not prolong discharge time and that it has minimal side effects.[9,10]

McMillan *et al.*[9] and Feld *et al.*[11] reported that the most effective and the safest dose of oral midazolam as 0.75 mg/kg. They concluded that the children could be separated easily from their parents by 10 minutes whilst the maximum effectiveness appeared in 20 to 30 minutes. The effect of oral midazolam is also reported to end in 45-60 minutes.[10]

The current study compared the conventional means alone and in combination of oral midazolam for the above cited purpose.

Material and Methods

This prospective study was conducted after approval from institutional ethical committee and written informed consent, obtained from parents or legal guardian of the participating subjects. The trial was registered prior to patient enrolment at Clinical Trials Registry of India, www.ctri.nic.in (CTRI/2016/06/007030, Registered on 22nd June 2016). The study population consisted of 100 pediatric patients who were posted for abdominal and pelvic ultrasound. The site was the dedicated pediatric ultrasound room in a government medical college.

We followed a randomized double-blind study design. Eligible participants included children aged 2-6 years. These children were in American Society of Anesthesiology physical status (ASAPS) I (a normally healthy patient) or ASAPS II (patient with mild systemic disease).[12] Exclusion criteria consisted of any serious systemic disease, obesity, and any condition that contraindicates oral administration.

The sample size was derived using Slovin's formula,[13] $n = N/(1 + N e^2)$ applied to the mean number of cases performed in past three years. N represented the mean of number of pediatric sonography performed during the past three years and e the confidence interval (CI), which is kept 95% (an alpha level of 0.05). Power yield was 90% at standardized effect size of 0.46. The exact sample size was calculated to be 83 keeping in view of post-procedure exclusions, the sample size increased to 100, with 50 in each group. The study was undertaken between June 2016 and March 2017.

The trial used computer generated equal randomization. Randomisation and blinding was done by an investigator with no clinical involvement in the trial. The sonologist, data collectors who had administered the medication too, outcome assessors and data analysts were all kept blinded to the allocation. All cases were performed by the same sonologist who had experience of more than ten years in pediatric sonography.

All children were randomized to receive either midazolam (after nil per orally period of two hours for both solid and clear fluids) in the dose of 0.3 mg/kg mixed in 20 mL of apple juice (Group I) or 20 mL of apple juice (Group II) 20 minutes prior to the procedure by the anesthesiology team posted in the radiology department. Children of both the groups were offered colourful soft toys just before entry into the ultrasound room by the room attendant. In the room they were accompanied by a parent or family member or guardian. The procedure rooms were fully equipped with facilities of for emergency airway management.

The level of cooperation/sedation was assessed by a subjective 7 point scale, called as cooperation score subsequently.

- I (Agitated): Clinging to parent/crying
- II (Alert): Anxious, not clinging to parent, may whimper but not cry
- III (Calm): Sitting or lying comfortably with eyes open but not following commands
- IV (Cooperative): Eyes closed/open but actively following commands
- V (Light sleep): Eyes closed responding to minor stimuli. (Correspond to Ramsey sedation score 5)
- VI (Sleep): Eyes closed sluggish response to minor stimuli (glabellar tap)
- VII (Deep sleep) No response to light glabellar tap or loud auditory stimuli.

The primary outcomes were cooperation during the procedure and completing of the scan in a single sitting. Total scan time was also looked for, as also the sonologist's satisfaction rated on a Likert scale.[14]

Likert scale

1. Very Unsatisfied
2. Unsatisfied
3. Neutral
4. Satisfied
5. Very Satisfied.

Procedural abortions due to several factors like extremely agitated patient interfering with probe application, inability to accept full dose, serious adverse event were considered as failure of the allotted regimen and the child was rescheduled for rescan.

The patient's heart rate and oxygen saturation (SpO_2) were continuously monitored for 2 hours post administration of juice or till discharge in both groups, using a finger pulse oximeter probe. A lower limit of SpO_2 was set as 95% for administration of supplemental oxygen via venturi mask/nasal prongs at a flow rate of 4 Litre per minute. Patients were kept in post -procedure room of radiology department which is fully equipped with emergency facilities in the presence of anesthesia resident. Patients were discharged when they met the following criteria: stable cardiorespiratory function, satisfactory airway patency, cooperation score less than 4, talking and unaided sitting, absence of nausea and vomiting. It was assessed by the resident doctor once every 20 minutes after ultrasound scan.

The data was analyzed using Statistical Package for the Social Sciences (SPSS) software for Windows, version 22.0, IBM Corp., Armonk, NY, USA. Chi-square test was used for data analysis of qualitative variables and mean values were compared using independent z-test. Differences were considered significant at $P < 0.05$.

Results

This study enrolled 100 patients out of which 45 subjects of group I and 46 subjects of group II consumed the medication completely and were included for analysis [Figure 1]. The abdominal scan was not performed on one child of group I and 4 children of group II, as their parents demanded a different scan day because children were agitated and not lying on the couch. Hence they were also excluded from the study the resultant final number was 44 in group I and 42 in Group II. Both the groups were comparable in terms of demographic profile (Age, sex, weight, height) [Table 1]. Thirty minutes after administration of the drug or placebo, 35% of children in Group I were cooperative (score of 4)

Table 1: Demographic details

Feature	Group I (*n*=44)	Group II (*n*=42)	*P*
Sex (Male/female)	21/23	22/20	
Average Age (in years) (mean±2 SD)	3.8±1.0	3.6±1.0	0.324
Average Weight (in kg) (mean±2 SD)	17.8±2.3	18.1±2.8	0.320
Average Height (in cm) (mean±2 SD)	96.6±5.7	94.6±6.1	0.112

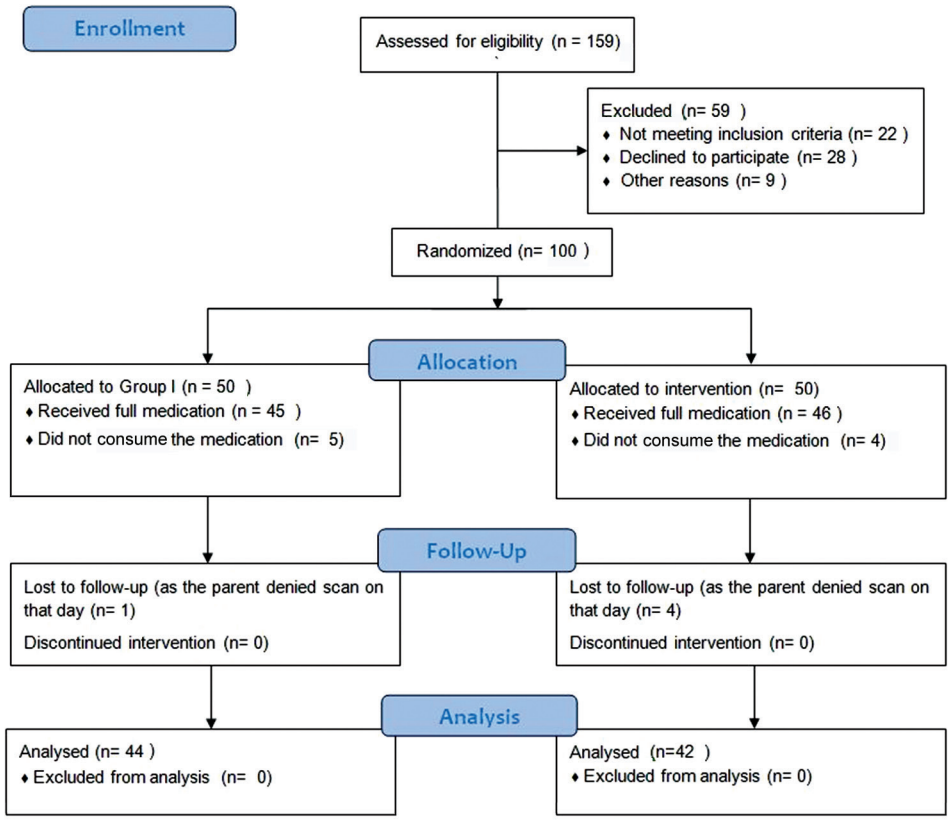

Figure 1: Consort flow diagram

Table 2: Comparative cooperation Score

Score	6 (Sleep)	5 (Light Sleep)	4 (Cooperative)	3 (Calm)	2 (Alert)	1 (Agitated)
Group I (n=44)	0	17	18	5	3	1
Group II (n=42)	1	8	9	12	9	3
P Value	--	0.045	0.051	0.04	0.05	0.14
		Cooperative Patients (Patients with score 4-6)				
Group I		35				
Group II		18				
P Value		0.038				

Table 3: Likert Scale

		Group I (44)	Group II (42)	*P*
I	Very Unsatisfied	01	5	0.08
II	Unsatisfied	03	10	0.02
III	Neutral	13	18	0.19
IV	Satisfied	19	08	0.015
V	Very Satisfied	08	01	0.016
Satisfied + Very satisfied Rating				
Group I (44)	27			
Group II (42)	9			
P Value	0.012			

Table 4: Mean scan time; Patients requiring >1 sittings for completion of scan and Patients requiring supplemental oxygen

Criteria	Group I (n=44)	Group II (n=42)	*P*
Time Required for sonography (in min)	12.48±4.12	18.94±5.14	0.017
Number of patients requiring >1 sitting for completion of scan	2	8	0.035
Patients requiring supplemental oxygen (SPO_2 Level <95%)	2 (4.54%)	1 (2.38%)	0.183

compared to 19% in Group II, the difference as calculated using z score was significant statistically (*P* 0.045) [Table 2]. If we consider patients with score (IV-VI) as cooperative, 79.5% (35 patients) of group I and 42.8% (18 patients) of group II patients can be labelled as cooperative, the difference was statistically significant. Surprisingly, one patient in group II had a cooperation score of VI and none of the group I patients exhibited this score. At the same time, none of the patients of either group scored VII on the cooperation scale. Analysis of Likert scale [Table 3] revealed statistically significant difference in very satisfied and satisfied rating which was present in 61.3% of group I and 21.4% of group II. If we combine the very satisfied and satisfied rating, the difference was found to be statistically significant.

Oxygen supplement was required in 2 (4.54%) patients in group I and 1 (2.38%) in group II, the difference was not significant. The time taken by sonologist to perform case was significantly less in group I in comparison to group II [Table 4]. The time required for scan was 12.48 ± 4.12 minute in group I and 18.94 ± 5.14 minute in group II P=0.017. In group I [Table 4], only 2 patients (4.54%) required more than one attempt for completion of the scan, while in group II, 8 (19.04%) children required more than one attempt P=0.035.

None of the patients from either group reported any side effect like vomiting, nausea, excitability, irritability. All children of either group achieved the discharge criteria within 60 minutes post scan.

Discussion

Ultrasound has the advantage of being fast, non-invasive and cost effective with no threat of ionizing radiation; this all makes it an ideal mode of imaging especially in pediatric patients.[15,16] Though ultrasound is non-invasive, pediatric population has intrinsic fear of hospital which makes them difficult to handle. Currently, in most of the countries, these evaluations are performed on OPD basis using conventional method for distracting child's attention. Behaviour management techniques such as voice control, intimidation or restraints, toys, offering chocolates are commonly adopted distraction methods for pediatric ultrasound. Though they are effective, many, if not all sonologists often face difficulty in doing this. As the number of diagnostic and therapeutic procedures performed in children that require cooperation, lack of movement, anxiolysis, fear reduction, reduced awareness, and analgesia are growing it has increased the demand for safe pediatric procedural sedation and analgesia (PSA) by anesthesiologists.[17] It is important to decide in collaboration with the child and family whether nonpharmacological techniques, local or regional anesthesia, systemic analgesia, sedation or general anesthesia (or combinations of these) are the most appropriate technique for a given child and procedure.

Hence, the purpose of this study was to evaluate the role of oral midazolam for OPD sedation in children undergoing high resolution sonography. Midazolam HCL is a short-acting,

water soluble benzodiazepine drug that acts by facilitating GABA (-y -amino butyric acid). It has anxiolytic, sedative, hypnotic, anticonvulsant, muscle-relaxant, and anterograde amnesic effects. It has been proved in previous studies that midazolam is a safe agent for pediatric sedation.[18-20] As only 15-30% of the oral dose makes it to systemic circulation due to profound first pass hepatic metabolism the oral dose should be approximately double or triple of intravenous dose to achieve similar clinical effects. An oral dose ranging between 0.3-0.75 mg/kg is recommended commonly, and is to be given 20-30 minutes prior to the procedure.[21] Though oral preparations of midazolam are widely available, we used the injection form of midazolam mixed in apple juice to make it soluble (as pH of apple juice is acidic), palatable and comparable with placebo without altering the taste and volume of medication used.

As the scan time is dependent on multiple factors principle being ultrasonologist experience, quality of machine and cooperation of patient, all the cases were performed by a single and experienced sonologist on same machine (Philips HD 11 XE) so as to eliminate subjective bias.[22]

The results of our study suggest that oral midazolam (0.3 mg/kg) effectively reduces the anxiety associated with sonography and enhances the cooperation as suggested by better cooperation and sedation score. The duration of effect of oral midazolam is around 60-90 minutes, which correlates well with the scan time and all children were discharged within 90 minutes of procedure.[11]

For assessing cooperation and sedation together we devised a subjective and easy to interpret score, we scored 1 as agitated crying child; score 6 is given to those who got light sleep and correspond to Ramsay sedation score of 1. Although this scoring is not published in psychometric data, it is easy to apply and can be employed in OPD procedures. As the aim of the study was to make child cooperative rather than being sedated, so we used 0.3 mg/kg dose of midazolam. In such low doses respiratory depression is seldom encountered. In the current study too, we didn't encounter a single event of respiratory depression (SpO_2 < 90%). In only two patients out of 44 SpO_2 dropped below 95% and responded immediately to nasal prongs/mask. In one patient of group II also SpO_2 dropped to 94% which can be explained if the scan period corresponds to the normal sleeping period of the child, in that case also saturation increased after oxygen supplementation. Better cooperation describes the lesser scan time in midazolam group compared with placebo; this also explains the better Likert scale rating of sonologist. Midazolam administration aided completion of almost all scans in single sitting.

With the current regimen, we achieved cooperation (score 4) in 79.5% of patients. The same findings were reported by Coté, *et al.* who concluded that an oral dose of 0.25 to 0.33 mg/kg (maximum, 20 mg) generally results in a.very compliant child who will separate from parents without crying.[8] One patient of group II exhibited cooperation score of 6 which can be explained by rare chance that his natural sleep time got synced with scan time.

In the past, Ghajari *et al*.[23] had studied the sedation efficacy of 0.3 mg/kg and 0.5 mg/kg oral midazolam for 3-6 year old uncooperative children undergoing dental treatment and they found that although 0.5 mg was slightly superior to 0.3 mg/kg in terms of sedation efficacy but the differences were not significant and the treatment success was not significant either.

Chloral hydrate, sodium pentobarbital are the other drugs that can be used for sedating pediatric patient.[24-26] Oral chloral hydrate is the most frequently used drug for pediatric sedation in many pediatric centres, however the drug has many known adverse effects such as nausea, vomiting, agitation, ataxia, prolonged sedation, delayed apnea events, gastric irritation, potential carcinogenicity, and genotoxicity which makes it unsuitable for OPD sedation.

Ashrafi *et al*.[27] compared oral midazolam and oral chloral hydrate for sedating pediatric patients undergoing EEG and concluded that both chloral hydrate 5% (1 ml/kg) and oral midazolam (0.5 mg/kg) could be administered as a pre medication agent for EEG recording in children. Fallah *et al*.[28] compared oral chloral hydrate and intranasal midazolam for sedation during computerized tomography, they used midazolam in the dose of 0.2 mg/kg and reported oral chloral hydrate to be a better sedating agent, they however attributed this to the low dose. In both the studies, sedation was assessed by Ramsay sedation score and neither cooperation nor anxiolysis was assessed.

Radhika *et al*.[29] assessed efficacy of midazolam as oral premedication in children and compared it with triclofos sodium and reported both the drugs to produce successful separation from parents, and the children were very cooperative during induction. The adverse effects of triclofos were mild and included dizziness, irritability, and vomiting.[30]

Anxiety is age dependent and peaks in 3-5 year old children, more extensive study would be required to evaluate the comparative efficacy of oral midazolam in different age groups of children. Further, the cooperation score adopted in the current study is not a validated score, hence being a limitation of the current study.

Conclusion

Oral midazolam is a safe yet effective agent to aid routine abdominal sonography in the pediatric patients.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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