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SHORT COMMUNICATION

Midazolam premedication in ileocolic intussusception: a retrospective multicenter study

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Abstract

Ileocolic intussusception is a common cause of bowel obstruction. When spontaneous reduction does not occur, non-operative management through enema reduction is necessary. Despite the evidence indicating that sedatives favor success in the reduction, their use is still not a common practice. To determine if midazolam (MDZ) before enema improves the rate of procedure success, we retrospectively reviewed charts of patients admitted to two Italian pediatric emergency departments. Outcome measures were the success rate of the enema, recurrence, and need for surgery. Patients were grouped according to the use of MDZ or not, before hydrostatic reduction attempt. We included 69 and 37 patients in the MDZ and non-MDZ groups, respectively. The two groups did not differ in demographics, clinical characteristics, and ultrasound findings. Intussusception reduction after the first enema attempt occurred in 75% (MDZ group) and 32.4% (non-MDZ group) of patients ($P < .001$); 27.9% (MDZ group) and 77.8% (non-MDZ group) of patients underwent surgery ($P < .001$). Among them, spontaneous reduction of intussusception during the induction of general anesthesia occurred in 31.6% and 42.9% of patients, respectively (P .43). Multivariate logistic regression analysis showed that only MDZ had a positive effect on the result of the enema (OR 7.602, 95%CI 2.669–21.652, $P < .001$).

Conclusion: Procedural sedation with MDZ for enema reduction of intussusception can increase the success rate and lead to a better management of patients.

What is Known:
• *Despite the evidence of the usefulness of sedatives in the reduction of intussusception, their use is still not a common practice.*

What is New:
• *Midazolam during enema reduction of intussusception can increase the success rate and consequently lead to better management of patients.*

Keywords Midazolam · Intussusception · Procedural sedation

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Abbreviations

CI	Confidence interval
ED	Emergency department
IN	Intranasal
IV	Intravenous
MDZ	Midazolam
OR	Odds ratio
PO	Oral
PSA	Procedural sedation and analgesia
SD	Standard deviation
US	Ultrasound

Introduction

Ileocolic intussusception is a common cause of bowel obstruction in pediatrics [1].

When spontaneous reduction does not occur, non-operative management through ultrasound (US) or radiography monitored air or liquid enema reduction is necessary [1, 2]. In cases of enema reduction failure or presence of contraindication, surgery is necessary [3].

Despite the evidence indicating that sedatives favor success in the reduction of intussusception by increasing the patient's cooperation, reducing procedure-associated anxiety and achieving amnesia of the stressful procedure and acting as muscle relaxant [4], their use for the reduction of intussusception is still not a common practice [3–9].

We aimed to study if premedication with midazolam (MDZ) could improve the success rate of enema reduction in children with ileocolic intussusception.

Methods

We retrospectively reviewed charts of patients (0-16 years) with an US diagnosis of ileocolic intussusceptions from January 2014 to June 2018. Patients were assessed in 2 pediatric emergency departments (ED) with a combined annual volume of 66,587 patients: Meyer Children's Hospital, Florence, with an approved procedural sedation and analgesia (PSA) protocol (implemented through simulation [10] and adhering to the consensus statement on PSA in ED [11], and S. Orsola Malpighi Hospital, Bologna, where PSA was not implemented (control group). Patients in critical condition or who directly underwent surgery were excluded.

At both hospitals, contrast agent was selected and then injected by a radiologist using a fluoroscopical guide under a surgeon's supervision. Patients were grouped according to whether MDZ was used before the enema (MDZ group and non-MDZ group). The MDZ group was composed exclusively of children enrolled in Florence where PSA was already in use, while the non-MDZ group was composed of patients enrolled in Bologna, where PSA was not implemented, and of patients enrolled in Florence who did not receive MDZ because the treating physician did not have full privileges for PSA.

Sonographic findings and enema images were reviewed by a pediatric radiologist at each center, in order to confirm the diagnosis. Reduction was defined as the radiological evidence of the contrast agent passing over the ileocecal valve with retrograde opacification of ileal loops [9]. In the case of unsuccessful reduction, charts were reviewed to investigate if a delayed repeated enema reduction was performed and to record data from surgical reports. Groups were compared for demographic and clinical characteristics, success rate of the enema, recurrence of intussusception, and need for surgery. The study was approved by the Ethics Committee at both institutions participating in the research.

Data analysis

Descriptive analyses are reported as number and relative percentages if categorical, whereas quantitative variables are presented as mean and standard deviation (SD). Groups were compared by chi-square tests to analyze the differences between categorical variables, while continuous variables were compared by the Student *T*-test for independent variable.

Reduction by enema attempt was entered as dependent variable in univariate logistic regression to analyze the risk factors for enema failure (Table S). A multivariate logistic regression was planned whether more than one univariate analysis resulted statistically significant with $P < 0.200$. Odds ratios (OR) were reported as point values and relative 95% confidence interval (CI).

Statistical significance was set at $P < 0.05$. Statistical analyses were performed using SPSS software (version 25; SPSS Inc., Chicago, IL).

Results

We retrieved data from 116 cases of ileocolic intussusception; 10 (8.6%) patients underwent surgery because of contraindications for enema reduction. We included 106 patients in the final analysis (Fig. 1). Mean age was 30.5 (SD 24.3) months. Children presented with abdominal pain (94, 88.7%), vomiting (45, 42.5%), and bloody stools (18, 17%). Sixty-nine (65.1%) patients received MDZ prior to enema: oral (PO) in 40 (58%) patients, intranasal (IN) in 26 (37.7%) patients, and intravenous (IV) in 4 (5.8%) at recommended doses according to administration route: 0.5 mg/kg, 0.3–0.4 mg/kg, and 0.1 mg/kg, respectively. The choice of administration route of MDZ was at the treating

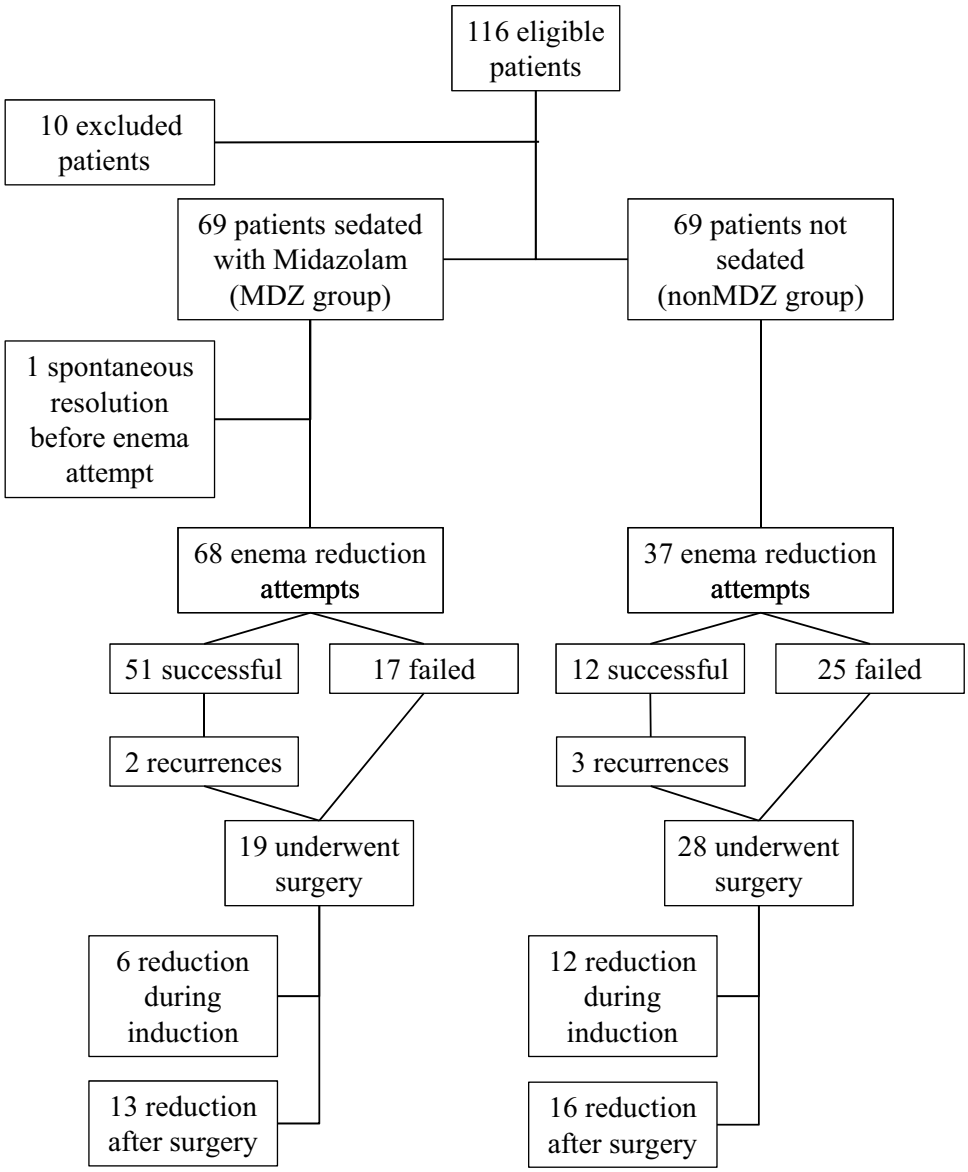

Fig. 1 Flow diagram of the study

physician's discretion. We found no difference in the rate of intussusception reduction among the three different routes of administration (75% each, $P = 1.00$). Comparing the enema outcome in the MDZ and non-MDZ groups, 51 (75%) and 12 (32.4%) patients, respectively, had a reduction after first enema ($P < 0.001$).

The success rate of reduction was 72.1% (57 patients) in the ED with PSA implemented, and 23.1% (6 patients) in the ED where sedatives were not used ($P < 0.001$). A subgroup analysis among patients who underwent enema reduction without MDZ revealed no difference between the two centers in terms of reduction of the intussusception (6, 54.5% in Florence and 6, 23.1% in Bologna, $P = 0.07$).

We analyzed the length of symptoms before referral to the ED in patients for whom this data was available (81, 69.8%). We found that in 22 cases, symptom onset occurred more than 36 h before the ED assessment. Of these patients, 12 received MDZ before enema, while 10 underwent enema reduction without sedation, with a significant difference of successful reduction of intussusception (9 and 3 patients, respectively) ($P = 0.046$).

The univariate logistic regression demonstrated 3 risk factors for enema failure (symptom duration > 48 h, > 3 lymph nodes in the intussusception at US, failure to use MDZ) (Table S). The latter was the only which remained statistically significant at the multivariate analysis (OR 7.602, 95%CI 2.669–21.652, $P < 0.001$).

Forty-seven (44.3%) patients underwent surgical reduction of intussusception after failure of enema reduction, 19 (27.9%) patients of the MDZ group and 28 (77.8%) of the non-MDZ group ($P < 0.001$).

Among patients who required surgery, spontaneous reduction during the induction of general anesthesia occurred in six (31.6%) and 12 (42.9%) patients in the MDZ and non-MDZ groups, respectively ($P = 0.43$).

Finally, we analyzed the population of children < 3 years (74, 69.8%) who most likely had idiopathic intussusception, and for which an enema reduction was initially planned. No meaningful differences were found between the MDZ (48, 64.9%) and non-MDZ (26, 35.1%) groups (Table 1). Reduction after enema was achieved in 35 (74.5%) patients of the MDZ group, and 9 (34.6%) patients of the non-MDZ group ($P = 0.001$).

Among patients < 3 years of age, 14 (29.8%) children who had sedation and 20 (76.9%) who did not receive MDZ underwent surgery ($P < 0.001$). All patients were discharged with good outcome either after observation in the ED or after admission. No adverse events due to MDZ administration were recorded during hospital stays.

Discussion

We examined the role of MDZ for a more effective reduction of intussusception. All patients who received MDZ were managed where PSA was implemented. However, only 65.1% of patients received MDZ before enema due to a lack of physicians credentialed for PSA.

The lack of recognition of pediatric emergency medicine as a formal subspecialty and other identified barriers contribute to hinder the adoption of PSA [12, 13].

Results confirm the scarce use of sedation before enema reduction of intussusceptions [6] and indicate that the use of sedatives could enhance the success of intussusception reduction. Patients sedated with MDZ before intussusception reduction had a higher success rate compared to patients who did not receive it, and therefore a lower recourse to surgery ($P < 0.001$). The same was documented in children < 3 years of age, who most likely have idiopathic intussusception ($P = 0.001$). MDZ was the only variable which seemed to have a positive effect on the result of the reduction of intussusception ($P < 0.001$).

A higher success rate of reduction of intussusception was demonstrated under general anesthesia [6] or deep sedation with propofol or ketamine [5, 7]. Both procedures come with a potential risk of intestinal perforation due to the loss of the Valsalva maneuver [5–8].

Several authors reported on the use of different sedation techniques for the reduction of intussusception reporting high success rate [8, 14] and shorter duration of the procedure [15].

Table 1 Demographic, clinical, and sonographic characteristics of the included patients

	All patients			Patients < 3 years		
	NO-MDZ ($n = 37$)	MDZ ($n = 69$)	*P*	NO-MDZ ($n = 26$)	MDZ ($n = 48$)	*P*
Female—*n* (%)	12 (32.4)	20 (29.0)	.71	8 (30.7)	15 (31.3)	.97
Median age (IQR) [months]	21.63 (13.39–38.38)	24.57 (14.3–43.49)	.37	17.1 (8.5)	18.9 (8.7)	.60
Median weight (IQR) [kg]	11.25 (9.075–13.75)	12 (10–15)	.43	10.4 (2.1)	10.8 (2.4)	.39
Clinical presentation						
Crampy like abdominal pain/crying—*n* (%)	32 (86.5)	62 (89.9)	.60	21 (80)	43 (89.6)	.29
Median duration of symptoms (IQR) [hours]	24 (8.25–48)	14 (7–42)	.55	24 (8.75–48)	14 (6–30)	.29
Fever—*n* (%)	6 (16.2)	14 (20.3)	.61	4 (15.4)	11 (22.9)	.44
Vomit—*n* (%)	16 (43.2)	29 (42.0)	.90	13 (50.0)	25 (52.1)	.86
Diarrhea—*n* (%)	6 (16.2)	17 (24.6)	.32	6 (23.1)	23 (47.9)	.85
Bloody stools—*n* (%)	7 (18.9)	11 (15.9)	.70	6 (23.1)	11 (22.9)	.99
Ultrasound findings						
> 3 lymphonodes—*n* (%)	23 (62.1)	54 (85.5)	.07	14 (53.8)	36 (75)	.56
Abdominal free fluid—*n* (%)	11 (29.7)	6 (8.7)	.002	8 (30.8)	2 (4.1%)	.002
Localization of intussusception			.09			.04
Right lower quadrant—*n* (%)	11 (35.5)	20 (64.5)		7 (26.9)	11 (22.9)	
Right flank—*n* (%)	4 (57.2)	3 (42.8)		3 (11.5)	2 (4.2)	
Right upper quadrant—*n* (%)	14 (25)	42 (75)		9 (34.6)	32 (66.7)	
Mesogastrium—*n* (%)	4 (57.2)	3 (42.8)		4 (15.4)	3 (6.2)	
Left upper quadrant—*n* (%)	1 (50)	1 (50)		1 (3.9)	0 (0)	
Left flank—*n* (%)	0 (0)	0 (0)		0 (0)	0 (0)	
Left lower quadrant—*n* (%)	2 (100)	0 (0)		2 (7.7)	0 (0)	

MDZ midazolam, *IQR* nterquartile range

Esposito et al. reported a higher success rate of reduction of intussusception by using a premedication with IV betamethasone, OS or IN MDZ, and OS ranitidine [9]. The higher success rate could be due to the anti-edematous effect of betamethasone, or just to the exclusion of patients with intussusception due to pathological leading points.

Only two studies directly evaluated the use of sedation with MDZ (intrarectal or IV) on intussusceptions, finding a positive correlation between its use and the successful reduction with no complications (success rate 93.8% and 74%) [3, 4]. The small sample size [3] and the not statistically significant result [4] do not allow a generalization of these findings.

Considering that patient's collaboration may improve the outcome of the intussusception reduction, PSA seems to be necessary. Unfortunately, as reported in our cohort, PSA is not always available in the ED. These clinically relevant findings have several implications. The use of benzodiazepines could reduce anxiety and post-traumatic stress related to the enema [16] and could contribute to increase the success rate of non-surgical treatment of intussusceptions [3, 4].

We acknowledge limitations. MDZ was used only in one center, thus likely affecting the low success rate of enema attempts in the center which did not use PSA; the different modalities to perform the enema by radiologists could affect the result of the reduction; pain associated with intussusception and procedure was not assessed.

Conclusion

The procedural success is not a complete perspective as a sedation outcome. Future perspective studies considering PSA for intussusception should explore variables such as pain control, patient tolerance, and acceptance for all step of PSA. Our results suggest a role of PSA before reduction of ileocolic intussusception. MDZ as sedative agent before enema reduction of ileocolic intussusception can contribute to a significant success rate and potentially to a better treatment of patients and allocation of resources.

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Availability of data and material The authors confirm that the data supporting the findings of this study are available within the article and/or its supplementary materials.

Code availability Not applicable.

Declarations

Ethics approval The study was approved by the Ethical Committee at both institutions.

Consent to participate Informed consent to participate in the study was obtained from parents.

Consent for publication Parents of retrospectively enrolled patients consented both to participate in the study and to have their data (reported as aggregated data) published in a journal article.

Conflict of interest The authors declare no competing interests.

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